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REVIEW ARTICLE

Bioactive integration and stimuli-responsive therapeutic regulation in additively manufactured metallic orthopedic implants

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Abstract

Additive manufacturing (AM) has accelerated the evolution of metallic orthopedic implants from passive structural substitutes toward multifunctional therapeutic platforms. Leveraging the geometric freedom and compositional flexibility of AM, bioactive substances can be integrated into metallic implants through multiple strategies to regulate the peri-implant microenvironment and enhance tissue regeneration. This review summarizes recent advances in bioactive integration and responsive therapeutic release in additively manufactured metallic orthopedic implants. First, major biofunctionalization strategies are discussed, including surface modification, bulk alloying, and structurally integrated reservoirs. These approaches enable the incorporation of antibacterial, osteogenic, angiogenic, and immunomodulatory functions through localized delivery of antibiotics, bioactive ions, peptides, growth factors, and small-molecule therapeutics. Subsequently, recent progress in stimuli-responsive release systems is reviewed, including endogenous stimuli such as pH, enzymes, and reactive oxygen species, as well as exogenous stimuli such as light, magnetic fields, and electrical stimulation, which enable on-demand and microenvironment-adaptive therapy. The relationships among implant architecture, bioactive integration, and dynamic therapeutic regulation are further discussed to highlight the unique advantages of AM in constructing multifunctional implants. Finally, current challenges associated with multifunctional AM metallic implants are discussed, particularly the need to achieve synergistic biofunctionality, maintain structural and mechanical integrity under process constraints, ensure predictable therapeutic release, and establish reliable process–structure–property relationships. This review provides insights into the development of intelligent metallic implants that simultaneously provide mechanical support and actively regulate therapy.

Keywords: Additive manufacturing; Metallic implants; Biofunctionalization; Surface modification; Stimuli-responsive release

1. Introduction

With the increasing prevalence of aging populations, trauma, tumor resection, and infection-associated bone defects, bone repair has become one of the most challenging clinical problems in modern orthopedics.[1,2] Unlike soft tissues, bone regeneration requires not only tissue reconstruction but also the restoration of long-term mechanical stability and load-bearing capacity. Consequently, for large-volume defects, load-bearing injuries, and complex osteoarticular reconstruction, intrinsic healing alone is often insufficient to achieve satisfactory clinical outcomes.[3,4] Autografts and allografts remain widely used in clinical practice, yet their limitations have become increasingly evident. Autografts are restricted by donor-site morbidity, limited tissue availability, and prolonged surgical procedures, whereas allografts may lead to immune rejection, pathogen transmission, and long-term integration failure.[5-7] Meanwhile, conventional bioceramics and polymeric materials, despite exhibiting some bioactivity, generally suffer from brittleness, insufficient mechanical strength, and limited long-term stability.[8] Therefore, the development of advanced orthopedic implants that combine desirable mechanical performance, biocompatibility, and active therapeutic functionality has emerged as a major research focus in bone repair.

An ideal orthopedic implant should not merely provide structural support but also function as a dynamic therapeutic platform that actively participates in tissue regeneration and regulates the peri-implant microenvironment (Figure 1). First, implants must possess mechanical properties compatible with native bone, including an appropriate elastic modulus, high strength, and excellent fatigue resistance, to minimize stress shielding and maintain long-term stability.[9-11] Second, implant surfaces and interfaces should exhibit favorable biocompatibility to support cell adhesion, proliferation, and osteogenic differentiation while avoiding severe inflammatory responses, toxic ion release, or uncontrolled corrosion.[12,13] However, the mere fulfillment of biomechanical compatibility and biocompatibility is no longer sufficient to meet increasingly complex clinical demands. Postoperative infection, chronic inflammation, insufficient vascularization, and failed osseointegration remain major causes of implant failure and revision surgery.[14,15] Consequently, the research focus of orthopedic

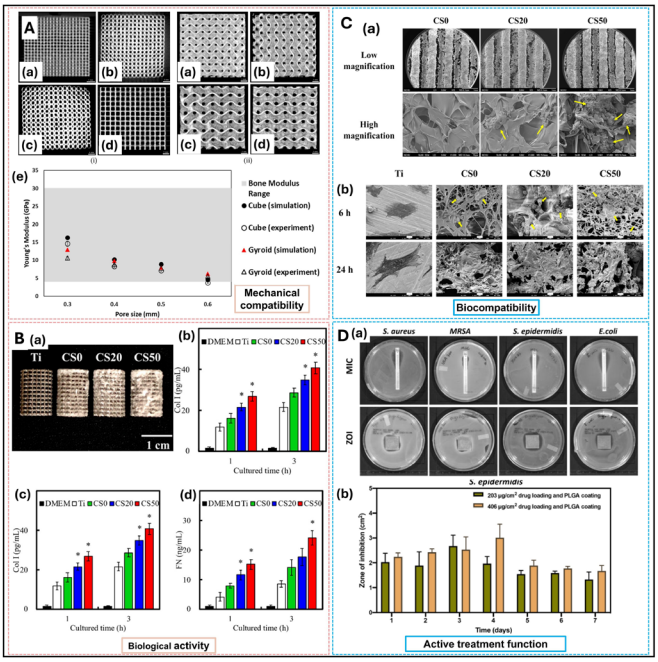

Figure 1. Characteristics of ideal bone implants. (A) Mechanical compatibility: Computed tomography images of cubic and gyroid scaffolds with different pore sizes (i, ii, a–d). (e) Comparison of simulated and measured Young's modulus within the bone range. Scale bar: 1 mm. Reprinted from Zaharin *et al.*[16] (B) Biological activity: (a) Mg–CS/CH bioactivation of AM Ti–6Al–4V scaffolds; (b) Col I and (c) FN secretion by WJMSCs, and (d) their adsorption on the coated surface. Scale bar: 1 cm. Reprinted from Tsai *et al.*[17] (C) Biocompatibility: (a) Scanning electron microscopic images of the coated scaffold surface and (b) WJMSCs adhered after 6 and 24 hours. Scale bar: 10 μm. Reprinted from Tsai *et al.*[17] (D) Active treatment function: (a) MICs and inhibition zones of coated implants against four bacteria; (b) 7day antibacterial durability against *S. epidermidis*. Reprinted from Zhang *et al.*[18]
Abbreviations: AM: Additive manufacturing; CH: Chitosan; Col I: Collagen type I; CS: Calcium silicate; FN: Fibronectin; MIC: Minimum inhibitory concentration; Mg: Magnesium; WJMSCs: Wharton's jelly mesenchymal stem cells.

implants has gradually shifted from passive structural replacement toward active therapeutic regulation. Within this paradigm, implants are increasingly engineered with multifunctional bioactivities, including antibacterial, anti-inflammatory, osteogenic, angiogenic, and localized drug-delivery capabilities, thereby enabling dynamic intervention throughout the bone-healing process. This transition marks the evolution of orthopedic implants from conventional inert devices toward therapeutic implants.

Metallic materials occupy an irreplaceable position in load-bearing bone repair owing to their excellent mechanical strength, fatigue resistance, and long-term stability.[16,19] Commonly used metallic biomaterials for orthopedic implants include stainless steels, cobalt–chromium alloys, titanium and titanium alloys, magnesium-based alloys, and zinc-based alloys (Table 1). Stainless steels and cobalt–chromium alloys provide high strength and wear resistance but may suffer from ion release and stress-shielding effects during long-term implantation.[20-22] Titanium and titanium alloys have become the most widely used orthopedic metals because of their favorable corrosion resistance, biocompatibility, and relatively low elastic modulus.[23-25] In contrast, biodegradable magnesium- and zinc-based metals have attracted increasing attention in recent years due to their ability to gradually degrade after bone healing, thereby reducing the need for secondary surgery.[26-29] Despite their excellent mechanical properties, however, conventional manufacturing approaches often struggle to simultaneously achieve complex structural fabrication, patient-specific customization, and multifunctional integration.[30] In particular, traditional casting, forging, and machining techniques are limited in their ability to precisely fabricate individualized implants with interconnected porosity and graded architectures, which restricts efficient biological integration between implants and host bone.

Table 1. Summary of major metallic material systems for orthopedic implants

Material type	Advantages	Limitations	Application	References
Ti & Ti-based alloys	Excellent corrosion resistance, high biocompatibility, relatively low elastic modulus	Stress shielding; inherently bio-inert surface	Load-bearing, permanent or long-term implants	[31-33]
Stainless steels	High mechanical strength, good ductility, cost-effective, easy to process	High elastic modulus causing severe stress shielding; risk of toxic ion (Ni, Cr) release during long-term implantation	Temporary fixation, cost-sensitive applications	[34,35]
Co–Cr alloys	Superior wear resistance, excellent high-temperature strength, good corrosion resistance	Extremely high elastic modulus; potential release of toxic heavy metal ions leading to hypersensitivity or metal poisoning	High-wear applications (articulating surfaces in hip/knee joint replacements); resists mechanical friction	[36,37]
Mg-based alloys	Elastic modulus is close to that of human cortical bone; degradation avoids the need for secondary removal surgery; osteo-inductive	The degradation rate in physiological environments is too rapid; localized hydrogen gas evolution can hinder tissue healing	Temporary load-bearing implants; degrade *in vivo*	[38-40]
Zn-based alloys	A more appropriate degradation rate than Mg; favorable biocompatibility and intrinsic antibacterial activity	Inferior mechanical strength and ductility compared to standard load-bearing	Temporary implants; degrade at a moderate rate	[41,42]

Abbreviations: Co–Cr: Cobalt–chromium; Cr: Chromium; Mg: Magnesium; Ni: Nickel; Ti: Titanium; Zn: Zinc.

The rapid development of additive manufacturing (AM) has provided a new technological route to address these challenges. Unlike conventional subtractive manufacturing, AM fabricates structures layer by layer from digital models, thereby enabling the production of patient-specific implants with highly complex geometries.[43-45] More importantly, AM enables precise control over porosity, pore size, lattice architecture, and internal channels, thereby improving the balance among mechanical performance, nutrient transport, and tissue ingrowth.[44,46-49]

Current AM technologies for metallic orthopedic implants mainly include powder bed fusion, inkjet printing, and extrusion-based printing. Among these, selective laser melting (SLM)[50-52] and electron beam melting (EBM),[53,54] as representative powder bed fusion technologies, have been extensively applied to the high-precision fabrication

of titanium and cobalt–chromium alloys. Inkjet printing exhibits advantages in low-temperature processing and complex internal structure construction, making it attractive for certain biodegradable metal systems,[55,56] whereas extrusion-based printing is better suited to producing metal scaffolds with high structural integrity.[57] The emergence of AM has therefore not only transformed the manufacturing process for implants but also the design concept: implants are no longer just machined metal devices but integrated therapeutic systems in which structure, composition, and function can be engineered together.

With continued advances in the field, strategies based solely on structural optimization have gradually revealed their limitations. Although porous architectures and surface topographies can enhance bone ingrowth and improve biomechanical compatibility, their capacity to actively regulate complex pathological microenvironments remains limited. For instance, postoperative infection may result in bacterial biofilm formation and impaired osseointegration; chronic inflammation can suppress osteogenesis and induce fibrotic encapsulation; and insufficient local vascularization may hinder tissue regeneration.[58] These challenges indicate that future implants must possess not only structural compatibility but also therapeutic capability. Against this background, the integration and release of bioactive substances have emerged as central themes in the development of AM metallic implants. By incorporating antibiotics, therapeutic metal ions, growth factors, peptides, immunomodulatory molecules, and responsive nanomaterials, implants can actively regulate the peri-implant microenvironment to achieve antibacterial activity, immune modulation, angiogenesis, and bone regeneration.[59,60]

A large number of valuable review studies have emerged, providing important references for the development of different technical approaches. However, the existing literature remains fragmented. For instance, Jing *et al.*[61] systematically reviewed functionalization strategies for three-dimensional (3D)-printed titanium alloys, focusing primarily on long-term stability and anti-infection, with limited discussion of therapeutic regulation. Vyavahare *et al.*[62] and Kechagias *et al.*[63] concentrated on porosity design and mechanical optimization, overlooking how implants can assume active therapeutic functions. Li *et al.*[64] and Akay *et al.*[65] provided comprehensive overviews of antibacterial and osteogenesis coatings yet often separated surface modification from structural design and biological response. Meanwhile, reviews on stimulus-responsive materials, such as that by Zhang *et al.*,[66] typically emphasized single triggers without integrating these strategies into the broader design logic of additively manufactured metallic implants. Moreover, with the development of AM technologies, bioactive integration strategies in implants have gradually expanded from simple surface loading toward more complex functionalization modes. The role of implants is also transitioning from traditional passive load-bearing structures toward therapeutic platforms capable of achieving localized treatment, stimuli-response, and microenvironmental regulation. However, existing studies still tend to focus on specific material systems, individual functional modules, or localized release behaviors, while discussions on dynamic release regulation from the perspective of bioactive integration remain relatively limited. Therefore, this review reexamines the development of AM metallic orthopedic implants from the viewpoint of therapeutic implants and bioactive integration, and summarizes recent advances in bioactive integration and dynamic therapeutic regulation.

This review focuses on bioactive integration and therapeutic functionalization in AM metallic orthopedic implants. Unlike reviews that focus on isolated aspects such as structural design, surface coatings, or single-stimulus responses, this review centers on the integration of bioactive substances. It primarily focuses on AM orthopedic implants, particularly titanium and Ti6Al4V systems, as they represent the most extensively studied and clinically relevant metallic platforms in current orthopedic applications. Other metallic systems, including stainless steels, cobalt–chromium alloys, magnesium-based alloys, and zinc-based alloys, are discussed when directly relevant to specific functionalization strategies. Within this scope, this review summarizes recent progress in research on the bioactive integration and therapeutic regulation of AM metallic orthopedic implants (Figure 2). First, strategies for introducing biofunctions through bulk alloying, structural reservoirs, and surface functionalization are discussed, with emphasis on antibacterial activity, osteogenic and angiogenic promotion, and localized therapeutic delivery. Subsequently, stimulus-responsive systems designed to regulate therapeutic release in response to pathological microenvironments or exogenous physical cues are reviewed, including endogenous stimulus-responsive platforms triggered by pH, enzymes, and reactive oxygen species (ROS), as well as exogenous regulation approaches based on light, magnetic fields, and electrical stimulation. Finally, current challenges associated with multifunctional AM metallic implants are discussed, particularly the need to achieve synergistic biofunctionality, maintain structural and mechanical integrity under process constraints, ensure predictable therapeutic release, and establish reliable process–structure–property relationships.

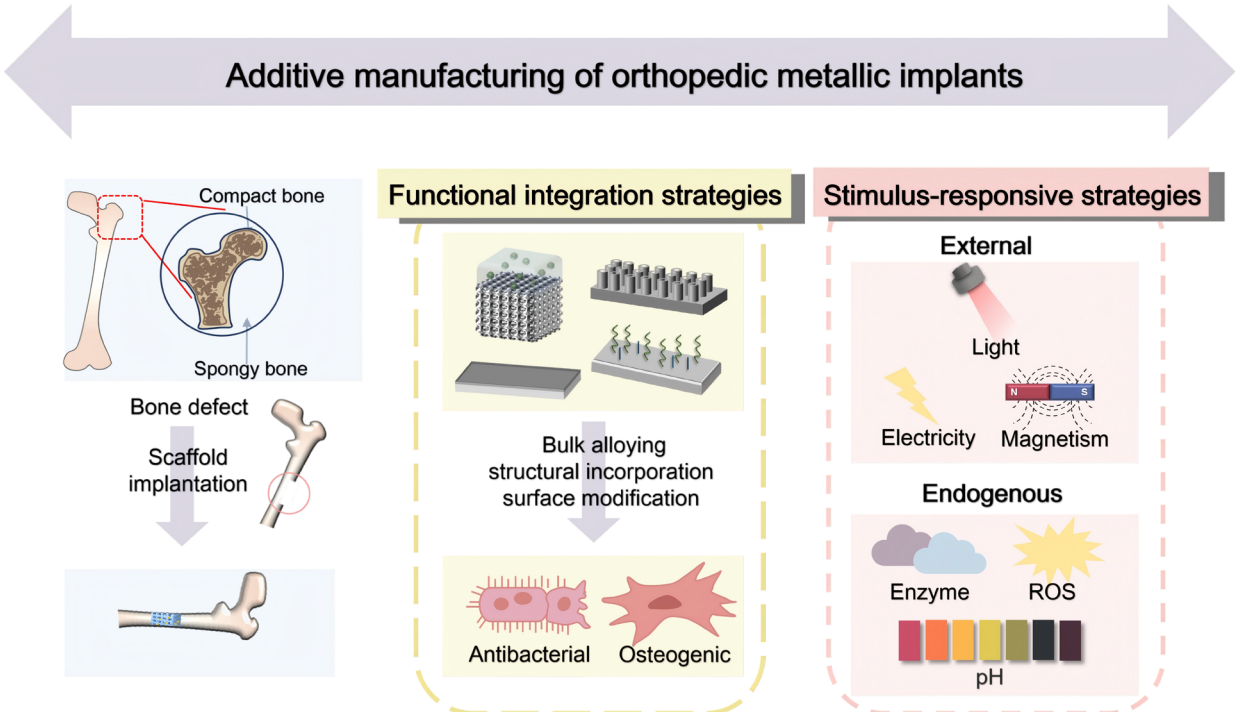

Figure 2. Conceptual framework for bioactive integration and stimuli-responsive therapeutic release in additive-manufactured metallic orthopedic implants. Created with Microsoft PowerPoint.

2. Functional integration strategies for additive-manufactured metallic implants

Additive manufacturing offers unique advantages for integrating bioactive substances into metallic orthopedic implants. The layer-by-layer fabrication process allows flexible control over the geometry, surface characteristics, internal cavities, and composition of implants, thereby providing versatile platforms for incorporating functional bioactive substances. Based on the integration mode, bioactive substances can be integrated into AM metallic implants through three main strategies: surface modification, bulk alloying, and structural reservoirs. This section summarizes the types of bioactive substances, fabrication approaches, and biomedical applications associated with these strategies.

2.1. Types of bioactive substances

The integration of various bioactive substances aims to actively endow implants with the ability to combat postoperative complications and promote tissue regeneration, mainly focusing on two directions: antibacterial/anti-inflammatory effects and osteogenic/angiogenic promotion (Table 2).

2.1.1. Antibacterial/anti-inflammatory effects

Among postoperative complications, implant-associated infection remains one of the major causes of implantation failure and revision surgery. Accordingly, localized delivery of antibacterial agents has become a widely adopted strategy for constructing a biological defense barrier at the implant–tissue interface. Conventional antibiotics, including vancomycin (Van), gentamicin (Gen), and rifampicin, remain the most widely used antibacterial agents in implant systems.[67] Van, a glycopeptide antibiotic effective against Gram-positive bacteria, is frequently incorporated into implants to suppress *Staphylococcus aureus* infection. Gen is an aminoglycoside antibiotic composed of four major components (C1, C1a, C2, and C2a) together with a minor component, C2b.[68] Owing to its broad antibacterial spectrum and good thermal stability, Gen has become one of the most widely used antibiotics in antimicrobial coatings. Rifampicin exhibits potent dose-dependent bactericidal activity against Gram-positive bacteria.[69] Mechanistically, this semisynthetic antibiotic selectively inhibits bacterial RNA synthesis by targeting the β subunit of RNA polymerase.[70,71] More importantly, rifampicin demonstrates pronounced anti-biofilm capability and intracellular antibacterial activity, making it particularly important in the treatment of periprosthetic joint infection.[72]

In addition to conventional antibiotics, naturally derived antibacterial materials have attracted growing

interest owing to their improved biocompatibility and lower risk of inducing bacterial resistance. Chitosan (CS), a polycationic natural polymer obtained through partial or complete alkaline deacetylation of chitin derived from crustacean shells,[73] has been widely investigated in therapeutic delivery systems, antimicrobial coatings, tissue-engineering scaffolds, and wound dressings because of its biodegradability, low cytotoxicity, and broad-spectrum antimicrobial activity.[74] Its antibacterial effect is primarily attributed to electrostatic interactions between positively charged polymer chains and negatively charged bacterial cell-wall components, which disrupt membrane integrity and induce leakage of intracellular substances.[75] In addition, low-molecular-weight CS can penetrate bacterial cell walls and interfere with intracellular DNA replication or transcription. CS can also chelate environmental metal ions and essential nutrients, thereby further inhibiting bacterial proliferation.[76]

Antimicrobial peptides (AMPs), another important class of bioactive antibacterial agents, are widely present in innate immune systems and exhibit broad-spectrum antimicrobial activity and potent anti-biofilm activity at relatively low concentrations.[77] Compared with traditional antibiotics, AMPs show a substantially lower tendency to induce bacterial resistance.[78] Their antibacterial activity is largely attributed to their cationic nature, which enables membrane disruption through electrostatic interactions with bacterial surfaces. In addition, AMPs can inhibit DNA, RNA, and protein synthesis while simultaneously regulating host immune responses.[79] Importantly, AMPs can eliminate not only planktonic bacteria but also those embedded in biofilms.[80]

Inorganic antibacterial agents, including silver/silver nanoparticles (Ag/AgNPs), copper/copper oxide nanoparticles, and zinc/zinc oxide nanoparticles, have also been extensively explored because of their long-term antibacterial stability.[81,82] These metallic ions or nanoparticles exert bactericidal effects mainly by interacting with negatively charged bacterial membranes, thereby inducing membrane perforation and intracellular leakage. Some ions can additionally bind to bacterial proteins, enzymes, or DNA, leading to metabolic dysfunction and cell death.[83,84] Furthermore, antibacterial metallic ions can be incorporated into coatings alongside osteogenic ions, such as Sr^{2+} [85] and Zn^{2+},[86] thereby enabling the coatings to exhibit both antibacterial and osteogenic properties.

Beyond bacterial infection, excessive inflammatory responses can also compromise osseointegration and long-term implant stability. Therefore, increasing attention has been paid to incorporating immunomodulatory agents that regulate the local inflammatory microenvironment. Most anti-inflammatory strategies are based on promoting macrophage polarization from the pro-inflammatory M1 phenotype toward the pro-regenerative M2 phenotype. Representative agents include anti-tumor necrosis factor-alpha therapeutics such as infliximab, adalimumab, and the fusion protein etanercept, as well as interleukin-4, luteolin, curcumin, and certain bioactive metallic ions. By modulating macrophage behavior, these agents can suppress the expression of pro-inflammatory cytokines, including interleukin-1β, interleukin-6, and tumor necrosis factor-α, thereby alleviating chronic inflammation and creating a more favorable microenvironment for tissue repair and regeneration.[87,88]

2.1.2. Osteogenic/angiogenic promotion

Effective bone defect repair requires not only strong osteoinductive stimulation but also sufficient vascularization to supply nutrients and oxygen. To this end, various osteogenic and angiogenic agents have been widely applied in implant functionalization strategies. Among them, growth factors are considered some of the most potent bioactive regulators. Bone morphogenetic proteins (BMPs), particularly BMP-2 and BMP-7, can effectively promote the osteogenic differentiation of mesenchymal stem cells (MSCs) and stimulate new bone formation.[89,90] In addition, transforming growth factor beta has been widely investigated for its important roles in extracellular matrix remodeling.[91]

Meanwhile, angiogenic growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2, and platelet-derived growth factor, have been reported to play roles in either angiogenesis or osteogenesis, thereby contributing to vascularized tissue regeneration and bone formation.[92,93] Notably, some of these factors may also influence both processes, highlighting the close interplay between vascularization and bone formation during tissue repair.

In addition to growth factors, bioactive ions such as strontium and silicon ions, as key components of bioactive glass or doped coatings, can continuously stimulate osteoblast activity and promote bone mineralization during sustained release.[94] In addition, small-molecule drugs such as dexamethasone, icariin (ICA), and zoledronic acid (ZOL) have also shown considerable potential in regulating the peri-implant microenvironment. Dexamethasone and ICA can promote osteogenic differentiation and vascularization by modulating osteogenesis- and angiogenesis-related signaling pathways. ZOL primarily suppresses osteoclast-mediated bone resorption and peri-implant osteolysis, thereby improving osseointegration and implant stability.

Collectively, the integration of antibacterial, immunomodulatory, osteogenic, and angiogenic agents enables metallic implants to actively modulate the peri-implant microenvironment, thereby improving infection control, immune regulation, vascularized bone regeneration, and ultimately long-term implant integration.

Table 2. Representative bioactive substances incorporated into metallic implants for infection control, immunomodulation, and vascularized bone regeneration

Functional category	Representative substances	Main mechanisms	Biological functions	References
Antibiotics	Van, Gen, rifampicin	Inhibition of bacterial cell wall, protein, or RNA synthesis	Antibacterial therapy of implant-associated infection	[68-72]
Natural antibacterial polymers	CS	Electrostatic interaction with bacterial membranes; membrane disruption; interference with intracellular DNA replication/transcription; nutrient chelation	Broad-spectrum antibacterial activity and improved biocompatibility	[73-75]
Antimicrobial peptides	AMPs	Membrane disruption; inhibition of DNA/RNA/protein synthesis; immunomodulation	Antibacterial and anti-biofilm activity against planktonic and biofilm-embedded bacteria	[77-80]
Inorganic bioactive ions	Ag, Cu, Zn, Sr (released as ions)	Membrane disruption, ROS generation, intracellular leakage, and metabolic dysfunction (antibacterial); regulation of osteoblast activity and mineralization-related pathways (osteogenic)	Relatively long-lasting antibacterial activity; promotion of bone mineralization and bone regeneration	[81-86]
Immunomodulatory agents	Infliximab, adalimumab, etanercept, IL-4, luteolin, curcumin, bioactive metallic ions	Regulation of macrophage polarization; suppression of inflammatory signaling	Reduction of excessive inflammatory responses and establishment of a pro-regenerative microenvironment	[87]
Osteogenic growth factors	BMP-2, BMP-7, TGF-β	Regulation of osteogenic differentiation and extracellular matrix remodeling	Promotion of MSC osteogenic differentiation and new bone formation	[89-91]
Angiogenic growth factors	VEGF, FGF-2, PDGF	Regulation of endothelial cell migration, proliferation, and neovascularization	Promotion of vascularized tissue regeneration	[92,93]
Small-molecule bioactive drugs	Dex, ICA, ZOL	Modulation of osteogenesis-, angiogenesis-, and bone-remodeling-related signaling pathways	Promotion of bone regeneration, vascularization, and suppression of peri-implant osteolysis	[95-99]

Abbreviations: Ag: Silver; AMPs: Antimicrobial peptides; BMP: Bone morphogenetic protein; CS: Chitosan; Cu: Copper; Dex: Dexamethasone; FGF: Fibroblast growth factor; Gen: Gentamicin; ICA: Icariin; IL: Interleukin; MSC: Mesenchymal stem cell; PDGF: Platelet-derived growth factor; ROS: Reactive oxygen species; Sr: Strontium; TGF-β: Transforming growth factor beta; Van: Vancomycin; VEGF: Vascular endothelial growth factor; Zn: Zinc; ZOL: Zoledronic acid.

2.2. Surface modification strategies

Surface functionalization represents one of the most versatile post-fabrication approaches for endowing AM metallic implants with biological and therapeutic functions. By constructing bioactive interfaces on implant surfaces or within porous architectures, surface functionalization enables localized regulation of cell behavior, antibacterial activity, osseointegration, and therapeutic delivery while largely preserving the bulk structural properties of the substrate.

Depending on the formation mechanism and interfacial characteristics of the functional layer, current surface

functionalization strategies can be broadly classified into four categories: solution-deposited functional coatings, interfacial molecular functionalization, *in situ* electrochemical conversion coatings, and vapor-deposited inorganic films (Figure 3). Solution-deposited functional coatings mainly serve as reservoirs for therapeutic agents and bioactive ions; interfacial molecular functionalization introduces biological signaling motifs at the molecular scale without markedly changing surface morphology; *in situ* conversion coatings generate substrate-derived oxide or ceramic layers with strong interfacial adhesion; and vapor-deposited inorganic films provide dense, durable protection while enabling long-term biological functionality.

2.2.1. Solution deposited functional coatings

Solution-deposited functional coatings are among the most direct and widely used surface engineering strategies to enable localized therapeutic functions in AM metallic implants. This method introduces an independently existing functional phase onto implant surfaces or within porous structures via dip coating, sol–gel reactions, or *in situ* hydrogel gelation.

Such coatings generally exhibit good biocompatibility and biodegradability, serving as reservoirs for drugs, growth factors, or bioactive ions, thereby providing active therapeutic effects in antibacterial activity, osteogenesis, and angiogenesis. This solution-based strategy is applicable to virtually all metallic materials used in orthopedic implants, yet the design rationale differs between non-degradable and biodegradable substrates. For non-degradable metals, the coating primarily serves as a therapeutic reservoir, imparting antibacterial, osteogenic, or anti-inflammatory properties to an otherwise bioinert surface. Here, coating stability and sustained release are the main concerns. In the case of biodegradable metals, the coating can also regulate degradation kinetics and prevent sudden release of metal ions. This dual function complicates the coating design. Depending on the coating composition, these systems can be categorized primarily as polymer/hydrogel coatings and bioactive ceramic coatings.

Polymer and hydrogel-based coatings represent a major category. Thermosensitive or ionically crosslinked hydrogels physically loaded onto implants are widely used. In this approach, drug- or ion-containing hydrogel precursor solutions are directly infused into the interconnected pores of AM porous metal scaffolds, where a temperature-triggered phase transition or ion-mediated

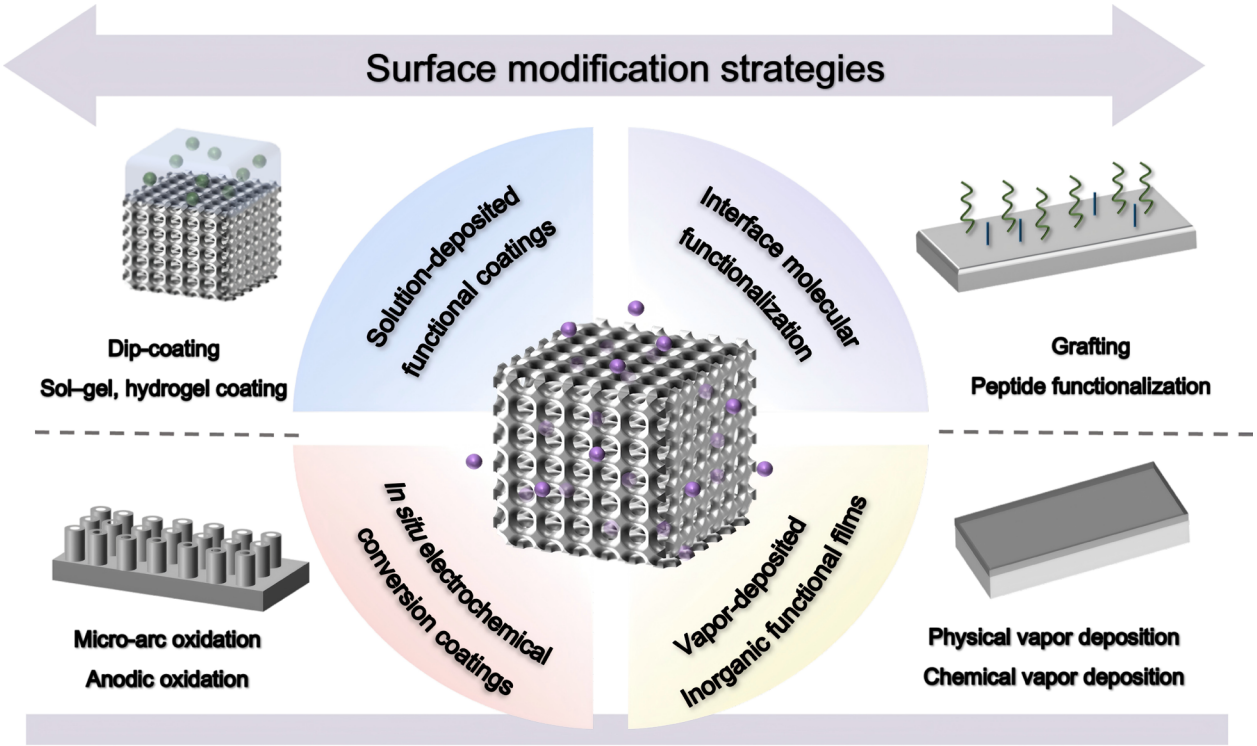

Figure 3. Classification of surface modification strategies for additive manufacturing of metallic implants, including surface-deposited functional coatings, interfacial molecular functionalization, *in situ* electrochemical conversion coatings, and vapor-deposited inorganic functional films. Created with Microsoft PowerPoint.

crosslinking induces *in situ* gel formation, thereby enabling localized, sustained release of bioactive substances. Bai *et al.*[95] mixed ZOL with a poloxamer 407 hydrogel precursor and infused the mixture into electron-beam-melted porous Ti6Al4V scaffolds, forming a ZOL/gTi composite system. Gelation at 37 °C immobilized the drug within the scaffold, enabling sustained ZOL release (≈63% cumulative release over 28 days). *In vitro* results showed enhanced osteogenic differentiation of human bone marrow MSCs (hBMSCs) and downregulation of osteoclast-related genes, while in an osteoporotic rabbit model the system significantly improved osseointegration and interfacial stability. Zhu *et al.*[96] loaded ICA into a thermosensitive CS hydrogel on EBM porous Ti6Al4V scaffolds, achieving sustained ICA release for over 17 days and significantly enhancing in vivo osseointegration. Beyond single-factor delivery, multifunctional hydrogel systems can also coordinate osteogenesis and angiogenesis. Sheng *et al.*[100] developed a strontium-functionalized alginate–mineralized collagen hydrogel integrated into porous titanium scaffolds. Sustained Sr^{2+} release (≈88% over 28 days), combined with mineralized collagen, upregulated osteogenic gene expression (alkaline phosphatase, *BMP2*, runt-related transcription factor 2) in hBMSCs and enhanced angiogenic activity of human umbilical vein endothelial cells (HUVECs) via phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin signaling, resulting in simultaneous osteogenic and angiogenic enhancement in a rabbit femoral defect model. Li *et al.*[97] further loaded ICA into a low-molecular-weight alginate/mineralized collagen composite hydrogel, which was combined with AM porous Ti6Al4V scaffolds, forming AMCI/PTi dual-functional scaffolds. Coordinated hydrogel degradation and drug diffusion enabled sustained ICA release (≈77% over 28 days), promoting both osteogenic differentiation of bone marrow stem cells and angiogenesis in HUVECs, resulting in significant bone regeneration in a rabbit radial defect model. Chu *et al.*[98] fabricated a gelatin methacryloyl/polyacrylamide interpenetrating hydrogel on titanium alloy surfaces via ultraviolet-initiated polymerization and then loaded it with ZOL. Arginine-glycine-aspartic acid motifs from gelatin methacryloyl promoted early adhesion and proliferation of hBMSCs, whereas ZOL was slowly released (≈64.1% over 21 days), synergistically promoting osteogenesis while inhibiting osteoclast activity. Although the above examples focused on non-degradable Ti6Al4V, polymer coatings are equally important for biodegradable metals. Wang *et al.*[101] immersed alkali-treated, negatively charged AM magnesium–zinc–calcium scaffolds into a pH 5 collagen solution. Through electrostatic adsorption and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide crosslinking, a stable ~25 μm-thick coating was formed. Acting as a physical barrier, it precisely regulated the 24-hour Mg^{2+} release concentration from 10.69 mmol/L to 5.23 mmol/L—falling within the optimal therapeutic window (2–10 mmol/L) for osteogenesis and angiogenesis. *In vitro*, the coating promoted HUVEC migration and tube formation and upregulated osteogenic gene expression in MC3T3-E1 cells.

Bioactive ceramic coatings, such as hydroxyapatite (HA) and calcium phosphate, are widely used due to their compositional similarity to the inorganic phase of bone. In addition to their intrinsic osteoconductivity, porous or nanostructured ceramic coatings can serve as carriers for functional ions, thereby combining structural bioactivity with sustained-release capability.[102] Knaislová *et al.*[103] used a sol–gel dip-coating technique to fabricate Ag and HA-doped TiO_2 composite coatings on AM porous Ti6Al4V structures. The coating provided nearly 100% antibacterial activity against *Escherichia coli*, while HA promoted apatite formation. Notably, gyroid porous structures exhibited approximately fivefold higher Ag^{+} release than solid rods due to larger specific surface area, highlighting the amplifying effect of AM porous architectures on surface modification and release behavior. Tabia *et al.*[104] fabricated 316L stainless steel lattice structures by SLM and dip-coated them with a 58S bioglass suspension. A silica pre-layer was optionally applied to improve adhesion. After heat treatment, the coating formed a uniform layer on the porous struts. In simulated body fluid, the coating induced the formation of a homogeneous apatite layer within seven days, confirming its bioactivity. Ye *et al.*[105] deposited a strontium-doped octacalcium phosphate/strontium hydrogen phosphate (Sr-OCP/$SrHPO_4$) nanocomposite coating onto SLM-fabricated porous JDBM magnesium alloy scaffolds. Acting as a barrier-supply-integrated system, the dense coating slowed Mg degradation and the burst release of Mg^{2+} while continuously supplying osteogenic Sr^{2+}, Ca^{2+}, and PO_4^{3-} ions, thereby better matching degradation to new bone formation.

2.2.2. Interface molecular functionalization

Interfacial molecular functionalization refers to the direct presentation of bioactive motifs at the implant interface via molecular-scale modifications. Unlike macroscopic coatings, this approach preserves the original surface topography and bulk mechanical properties while enabling precise regulation of cell adhesion, differentiation, and immune responses. Moreover, since binding peptides can be selected for different metal substrates, this approach is applicable not only to titanium alloys but also to other clinically relevant alloys such as cobalt–chromium–molybdenum (CCM), provided that suitable anchoring

strategies are available. Depending on the mode of molecule–surface interaction, two main strategies are commonly employed: non-covalent adsorption via material-binding peptides and covalent grafting via silane chemistry.

The non-covalent strategy uses material-binding peptides identified via phage display that spontaneously bind to specific metal surfaces through electrostatic, hydrophobic, and van der Waals forces. These peptides can be fused with functional motifs and immobilized via a simple one-step immersion process. A representative example of this strategy was reported by Zhao *et al.*,[106] who designed chimeric peptides comprising a titaniumbinding peptide (minTBP1) and osteogenic (W9) or angiogenic (PR1P) motifs. The minTBP-1 domain enabled rapid, specific immobilization on AM titanium surfaces within five minutes without any chemical coupling agent. The molecular coating promoted cell migration, tube formation, and upregulation of osteogenic and angiogenic markers via BMP-2/Smad and VEGF/protein kinase B/extracellular signal-regulated kinase pathways. A rigid $(GP)_4$ linker further enhanced bioactivity by maintaining domain separation. In a rat calvarial defect model, the modified implants increased bone volume and new bone formation at 12 weeks. Beyond titanium, this molecular functionalization paradigm can be extended to other metallic biomaterials by identifying substrate-specific binding motifs. Migita *et al.*[107] screened a 12mer peptide (CCMBP04) from a phagedisplay library that exhibits high binding affinity to CCM alloy, a material widely used in coronary stents and artificial joints. This peptide binds equally well to cast CCM and to CCM fabricated by SLM. By fusing CCMBP04 with the celladhesive RGDS motif, the resulting fusion peptide was immobilized onto SLM CCM surfaces via a simple 30-minute immersion, enhancing endothelial cell attachment under both serum-containing and serum-free conditions. To address postoperative infection without compromising osseointegration, Cui *et al.*[108] designed a novel fusion peptide that incorporated minTBP-1, AMP KR-12, and the cell-adhesive peptide GFOGER into a single molecular chain (Figure 4). A stable molecular layer was formed on AM titanium implants through a simple immersion process. This one-step modification simultaneously conferred over 90 % antibacterial efficiency against *E. coli* and *S. aureus* and significantly enhanced osteogenic activity, which was associated with activation of focal adhesion and phosphoinositide 3-kinase/protein kinase B signaling pathways.

The covalent strategy relies on silane chemistry to form stable molybdenum–oxygen–silicon bonds between silane coupling agents (e.g., 3-aminopropyltriethoxysilane, APTES) and hydroxyl-rich metal oxide surfaces, introducing reactive groups for subsequent conjugation of bioactive molecules via crosslinkers such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide or maleimide-thiol chemistry. Covalent grafting offers superior long-term stability compared to physical adsorption. For instance, Lei *et al.*[109] functionalized 3D-printed Ti6Al4V scaffolds by first immobilizing APTES to create an amino-rich interface, followed by covalent conjugation of E7 peptides and umbilical cord mesenchymal stem cell-derived exosomes, significantly enhancing osteoporotic bone repair and multi-stage osseointegration *in vivo*. Collectively, interfacial molecular functionalization offers a simple, multifunctional platform to enhance the bioactivity of AM metallic implants.

2.2.3. In situ electrochemical conversion coatings

Electrochemical surface modification involves applying an electric field in a controlled electrolyte environment to induce *in situ* electrochemical conversion reactions on metal substrates, leading to the growth of oxide ceramic layers or ordered nanostructures that are metallurgically bonded to the underlying matrix.[110] This strategy is primarily applicable to valve metals and their alloys (e.g., titanium, tantalum, magnesium). When an anodic voltage is applied in an electrolyte, these metals inherently form a dense, high-resistance oxide film, which serves as the physical basis for subsequent micro-arc discharges or the self-organized growth of nanostructures. By tuning the electrolyte composition, electrical parameters, and treatment duration, one can not only generate micro- and nanoscale porous topographies but also incorporate bioactive elements (e.g., calcium, phosphorus, silicon, strontium) into the growing layer, thereby achieving synergistic structural regulation and chemical biofunctionalization.[111] Among the representative techniques, micro-arc oxidation (MAO) and anodic oxidation stand out. Both yield functional layers that originate from substrate-derived conversion growth, thus exhibiting favorable interfacial adhesion and long-term stability. These advantages make them highly attractive for promoting osseointegration, regulating the degradation behavior of biodegradable metals, and serving as versatile platforms for subsequent functional loading.

Micro-arc oxidation is typically conducted under voltages exceeding the dielectric breakdown threshold, generating localized micro-arc discharges and transient high-temperature, high-pressure conditions that oxidize the substrate and drive reactions with electrolyte species. The resulting coatings are typically rough, porous TiO_2-

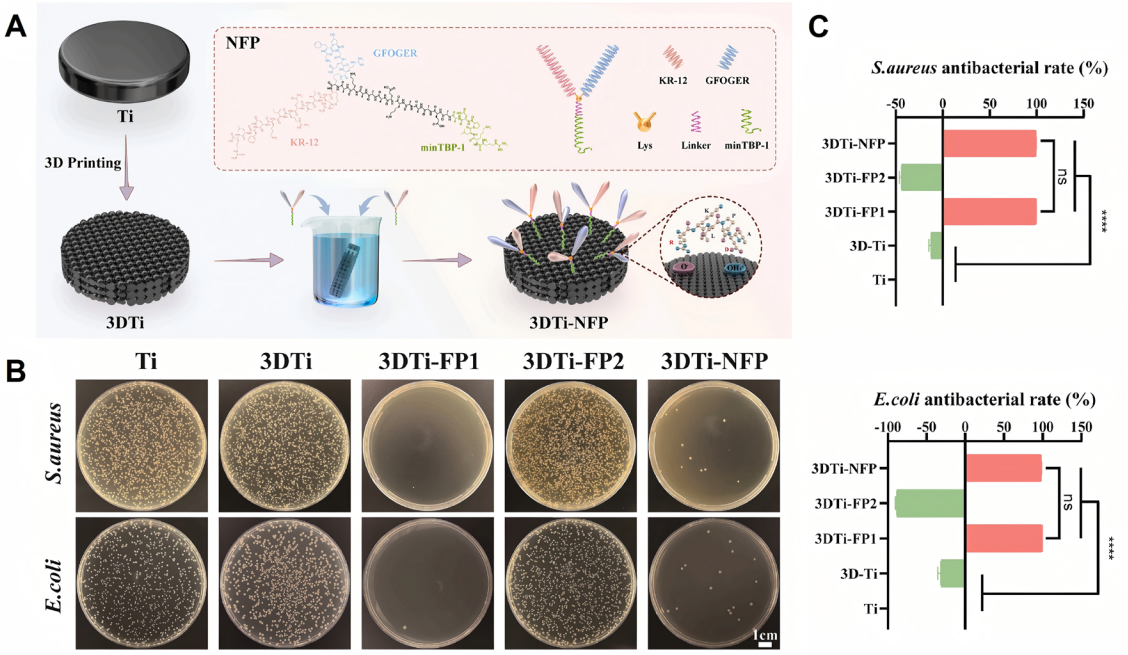

Figure 4. Peptide-mediated bio-specific functionalization. (A) Schematic of the fabrication process for three-dimensional (3D) titanium (Ti) implants functionalized with the multifunctional fusion peptide. (B) Representative images of *E. coli* and *S. aureus* colonies on different groups of modified Ti substrates. Scale bar: 1 cm. (C) Antibacterial rate (%) against *E. coli* and *S. aureus* of different groups. Reprinted from Cui *et al.*[100]

based ceramic layers enriched with bioactive elements. Sun *et al.*[112] combined MAO with hydrothermal treatment to fabricate a calcium phosphate bioactive coating with hierarchical micro- and nanotopography on AM Ti6Al4V interbody fusion cages, significantly enhancing hBMSC adhesion, proliferation, and osteogenic differentiation, and improving spinal fusion outcomes *in vivo*. Xiu *et al.*[113] directly applied MAO to AM porous Ti6Al4V scaffolds, producing a calcium–phosphorus-rich microporous TiO_2 layer that markedly improved bone ingrowth. Yang *et al.*[114] performed MAO on EBMed low- to medium-modulus Ti-24Nb-4Zr-8Sn porous scaffolds, forming a ceramic layer containing Nb_2O_5 and SnO_2. This treatment increased surface hydrophilicity and roughness while synergistically promoting osteogenic differentiation of hBMSCs and polarization of macrophages toward the anti-inflammatory M2 phenotype, resulting in favorable osseointegration both *in vitro* and *in vivo*. MAO can also generate bioactive coatings with *in vitro* mineralization activity on AM magnesium alloys. Yue *et al.*[115] performed MAO on SLM AZ91D magnesium alloy at 350 V for 30 minutes. The $Mg_3(PO_4)_2$ phase was formed *in situ* by reaction of PO_4^{3-} with Mg^{2+} released from the substrate. After 21 days of immersion in simulated body fluid, Fourier transform infrared spectroscopy spectra detected PO_4^{3-}, CO_3^{2-}, and OH^- groups, confirming the formation of an apatite-like layer on the coating surface and providing direct evidence of its *in vitro* mineralization capability and potential osseointegration bioactivity.

Beyond osteogenic regulation, MAO-derived oxide layers can also serve as multifunctional platforms for incorporating antibacterial agents. By embedding therapeutic ions or nanoparticles into the oxide matrix, these coatings can achieve sustained antibacterial activity while maintaining favorable osteocompatibility. Fazel *et al.*[116] combined MAO with hydrothermal treatment to fabricate AgNP- and HA-containing multifunctional coatings on porous SLM Ti6Al4V scaffolds, enabling sustained Ag^+ release for up to 28 days, effectively inhibiting *S. aureus* biofilm formation, and enhancing osteogenic activity. Similarly, van Hengel *et al.*[117] incorporated AgNPs into MAO layers on selectively laser-melted porous titanium implants using a calcium/phosphorus-based electrolyte. Compared with geometrically comparable solid implants, the interconnected porous architecture released approximately fourfold higher Ag^+ concentrations and exhibited enhanced antibacterial efficacy without detectable cytotoxicity. Interestingly, HA formation was observed only on the porous implants after MAO treatment, further suggesting that AM-enabled porous architectures can synergistically amplify the biological functionality of electrochemically generated coatings.

Anodic oxidation is another representative

electrochemical conversion strategy widely applied to titanium and its alloys.[118] Through a self-organized growth mechanism, anodization can generate highly ordered titania nanotube arrays whose diameter, length, and wall thickness can be tuned by adjusting the applied voltage, electrolyte composition, and oxidation duration. This nanotubular architecture substantially increases the specific surface area and provides nanoscale reservoirs for drugs, proteins, or bioactive ions, while the nanoscale topography itself can also regulate cell adhesion and differentiation. Zhang *et al.*[119] fabricated Ta_2O_5 nanotube arrays on SLM porous tantalum scaffolds via electrochemical anodization. The nanotubular surface transformed the substrate from hydrophobic to superhydrophilic and enhanced protein adsorption. *In vitro* results demonstrated that the modified scaffolds promoted adhesion, spreading, and osteogenic gene expression (*Osterix*, *Runx2*, *COLI*) of MC3T3-E1 preosteoblasts. In a rabbit femoral implantation model, more new bone ingrowth and collagen fiber formation were observed in the modified group as early as two weeks post-implantation, confirming that this hierarchical nanostructure effectively promotes early-stage osseointegration. Zhao *et al.*[120] further constructed ordered TiO_2 nanotube arrays on selectively laser-melted Ti6Al4V scaffolds using a two-step anodization process, followed by loading with mesoporous bioactive glass. This composite structure enabled the sustained release of Ca^{2+} and Si^{4+} ions, thereby improving hydrophilicity and cytocompatibility and providing a stable supply of bioactive ions for long-term bone regeneration.

2.2.4. Vapor deposition inorganic functional films

Vapor deposition techniques, including physical and chemical vapor deposition, enable the formation of dense inorganic functional films on metallic implants, with thicknesses ranging from nanometers to micrometers. In contrast to degradable drug-loading coatings, these films are primarily designed to provide durable mechanical and chemical protection, thereby improving wear and corrosion resistance while limiting unwanted ion release. When doped with Ag, copper, or other functional elements, they can also impart long-lasting antibacterial or osteogenic activity. Because of their dense interfacial architecture, vapor-deposited films are particularly valuable for load-bearing and long-term implantation scenarios, although conformal coverage in deep, porous structures may still be limited by line-of-sight deposition characteristics. Vapor-deposited inorganic films are applicable to high-melting-point metals. These techniques require elevated temperatures (typically >300 °C) and high vacuum, making them unsuitable for low-melting-point metals, which may melt, oxidize, or degrade during deposition.

Ran *et al.*[121] deposited a tantalum coating onto porous SLM-fabricated Ti6Al4V scaffolds via chemical vapor deposition. The coating not only suppressed the release of potentially toxic vanadium ions from the substrate but also significantly promoted stem cell osteogenic differentiation and *in vivo* osseointegration. Guo *et al.*[122] applied arc ion plating to deposit TiCu/TiCuN multilayer coatings on porous SLM Ti6Al4V scaffolds. The release of Cu^{2+} activated the stromal cell-derived factor-1α/chemokine receptor type 4 axis and related signaling pathways, effectively enhancing BMSC recruitment, adhesion, and osteogenic differentiation. Hu *et al.*[123] employed filtered cathodic vacuum arc to deposit Ag-doped diamond-like carbon coatings on SLM Ti6Al4V joint implants. Diamond-like carbon coatings are known for their extremely high hardness, low friction coefficient, and chemical inertness. With Ag incorporation, the coating maintained desirable wear resistance (friction coefficient reduced by ~16.7%) and strong interfacial adhesion (increased by ~55%), while also providing durable, broad-spectrum antibacterial properties and good cytocompatibility. This highlights the advantage of vapor deposition techniques in integrating mechanical protection with biological functionality.

Overall, different functionalization strategies offer distinct pathways for implementation and application, collectively advancing AM metallic implants from passive structural replacements toward active therapeutic platforms (Table 3). Solution-deposited functional coatings offer the greatest flexibility in integrating and controlling the release of drugs and bioactive factors, making them suitable for constructing temporally regulated therapeutic microenvironments; however, their long-term interfacial stability still requires further improvement. Interface molecular functionalization, by contrast, relies on precise regulation at the molecular scale and can modulate cell behavior and immune responses without altering the macroscopic structure, yet the persistence of its function is limited by the availability of surface binding sites and the stability of functional molecules. *In situ* electrochemical conversion coatings combine morphological regulation with chemical activation, and because the functional layer originates from the *in situ* transformation of the substrate, they exhibit strong bonding strength and long-term stability, offering notable advantages for promoting osseointegration and regulating the degradation of biodegradable metals. Vapor-deposited inorganic functional films primarily provide long-lasting mechanical and chemical protection by forming dense interfacial layers that enhance wear and corrosion resistance, and can also introduce long-term, stable antibacterial or osteogenic properties. While a single strategy is insufficient to meet complex clinical demands, multi-technology coupling

is becoming an important direction for development. By integrating structurally stable interfaces with release-capable functional layers or molecular functionalization, synergistic optimization of mechanical performance, biological activity, and therapeutic function can be achieved.

Table 3. Comparison of surface modification strategies for integrating bioactive substances into additive-manufactured metallic implants

Surface strategy	Applicable metallic substrates	Carrier matrix for active substances	Integrated active substances	Core implementation mechanism
Solution-deposited functional coatings	Virtually all metallic frameworks (Ti6Al4V, 316L stainless steel, and biodegradable Mg alloys)	Polymer/Hydrogel: Poloxamer 407, CS, alginate, GelMA, and collagen. Bioactive ceramics: HA, CaP, and 58S bioglass	Exogenous therapeutic drugs (ZOL, ICA), growth factors, and bioactive ions (Sr^{2+}, Ag^{+})	Introduces an independent physical functional phase into porous architectures via dip coating, sol–gel, or *in situ* gelation, serving as a versatile reservoir for bioactive substance release
Interface molecular functionalization	Primarily applied to (Ti) and extendable to other clinical alloys via substrate-specific screening	No macroscopic physical film: A molecular-level interface composed of self-assembled monolayer/few-layer material-binding peptides (e.g., minTBP-1, CCM BP04, NFP)	Bio-specific functional motifs (osteogenic W9, angiogenic PR1P, cell-adhesive RGD/RGDS, and antimicrobial KR-12)	Employs material-binding peptides (via phage display) for noncovalent adsorption or silane-based covalent grafting to engineer the interface at the molecular scale while preserving the original topography
In situ electrochemical conversion coatings	Primarily used for valve metals and their alloys, such as Ti6Al4V, low-modulus Ti-24Nb-4Zr-8Sn, Ta, and biodegradable Mg alloys	Substrate-derived, in situ grown oxide ceramic layers (e.g., TiO_2, Ta_2O_5, $Mg_3(PO_4)_2$) or highly ordered self-organized nanotube arrays	Electrolyte-derived doping elements (Ca, P, Si, Sr) and post-loaded functional nanostructures (e.g., AgNPs, mesoporous bioglass)	Applies a controlled electric field to trigger micro-arc discharges or self-organized anodization, yielding functional conversion layers with exceptionally strong metallurgical bonding while coupling topographic and chemical modifications
Vapor deposition of inorganic functional films	High-melting-point alloys; strict	Nano to micro scale dense inorganic protective films fabricated via PVD or CVD (e.g., pure Ta coatings, TiCu/TiCuN multilayers, and carbon films)	Long-lasting therapeutic metallic elements (e.g., Cu, Ag) incorporated directly into the film lattice	Deposits a highly dense, high-hardness barrier layer in a vacuum or vapor phase, prioritizing wear resistance and corrosion protection while physically suppressing the hazardous release of substrate metal ions

Abbreviations: Ag: Silver; AgNPs: Silver nanoparticles; BP: Binding peptide; Ca: Calcium; CaP: Calcium phosphate; CCM: Cobalt–chromium–molybdenum; CS: Chitosan; Cu: Copper; CVD: Chemical vapor deposition; GelMA: Gelatin methacryloyl; HA: Hydroxyapatite; ICA: Icariin; Mg: Magnesium; minTBP-1: Minimal titanium-binding peptide 1; NFP: Novel fusion peptide; P: Phosphorus; PR1P: Promotif-derived peptide 1; PVD: Physical vapor deposition; RGD: Arginine-glycine-aspartic acid; RGDS: Arginine-glycine-aspartic acid-serine; Si: Silicon; Sr: Strontium; Ta: Tantalum; Ti: Titanium; ZOL: Zoledronic acid.

2.3. Bulk alloying strategies

Bulk alloying represents a source-level strategy for constructing functional metallic implants by directly integrating bioactive elements into the metallic matrix during alloy preparation. In AM, this is typically achieved through pre-alloyed powders or *in situ* mixing of elemental powders prior to processing. Compared with surface modification strategies, bulk alloying enables metallurgical incorporation of therapeutic elements within the host matrix, thereby providing intrinsic bioactivity and improved long-term stability. Importantly, the biological mechanisms of bulk-alloyed systems strongly depend on material stability. In biodegradable alloys, therapeutic effects are closely coupled with matrix degradation, ion release, and microstructural evolution. By contrast, in chemically stable systems such as titanium–tantalum and titanium–niobium alloys, biological responses are more frequently mediated by surface oxide chemistry, wettability, and interfacial immune regulation rather than extensive ionic release. Owing to the absence of coating/substrate interfaces, bulk alloying can also avoid delamination and

interfacial instability commonly observed in surface-coated systems, making it particularly attractive for long-term orthopedic applications requiring durable osseointegration, immune regulation, and antibacterial functionality.

2.3.1. Stable therapeutic alloy systems for osteoimmunomodulation

Among stable therapeutic alloy systems, tantalum and niobium have received extensive attention because of their favorable biocompatibility and immunomodulatory potential. Tantalum is well known for its osteoconductivity, corrosion resistance, and chemical stability. Alloying tantalum with titanium aims to combine titanium's favorable processability with tantalum's biological affinity. Brodie *et al.*[124] fabricated Ti25Ta and Ti65Ta alloys via SLM using mixed elemental powders. Compared with conventional Ti6Al4V, both alloys enhanced early osteogenic differentiation and mineralization of hBMSCs, indicating that osteogenic functionality can be introduced through compositional regulation alone. To further improve compositional uniformity, Li *et al.*[125] developed pre-alloyed TaTi spherical powders and fabricated a series of TaTi alloys via SLM. The resulting Ta55 alloy exhibited a favorable balance between mechanical strength and elastic modulus. More importantly, the Ta_2O_5/TiO_2 mixed oxide layer formed on the alloy surface effectively suppressed pro-inflammatory signaling and promoted macrophage polarization toward the reparative M2 phenotype, thereby establishing an immune microenvironment favorable for bone regeneration.

Beyond tantalum-containing systems, niobium alloying has emerged as another effective route for osteoimmunomodulation. Liang *et al.*[126] fabricated porous titanium–niobium scaffolds through *in situ* alloying of titanium and niobium powders during SLM processing. The incorporation of niobium altered the composition of the surface oxide layer by forming Nb_2O_5 and simultaneously improved surface hydrophilicity. More importantly, Nb_2O_5-rich surfaces effectively promoted macrophage polarization toward the anti-inflammatory M2 phenotype, leading to increased expression of osteogenic and angiogenic factors, including BMP-2 and VEGF. *In vivo*, Ti-25Nb scaffolds generated substantially greater bone formation than pure titanium scaffolds in a rabbit bone defect model. These findings collectively suggest that stable bulk-alloyed systems can regulate osseointegration not only through direct osteogenic stimulation, but also through modulation of the peri-implant immune microenvironment.

2.3.2. Biodegradation-coupled therapeutic alloy systems

For biodegradable metallic systems, therapeutic functionality is closely associated with degradation behavior and ion-release dynamics. Among these systems, zinc–magnesium alloys have attracted increasing attention because incorporating magnesium can simultaneously regulate mechanical performance, corrosion behavior, and biological activity. Liu *et al.*[127] and Qin *et al.*[128] demonstrated that SLM-fabricated zinc–magnesium alloys, including zinc–0.4 magnesium and zinc–1 magnesium, exhibited significantly improved overall performance after magnesium addition. Mechanistically, magnesium incorporation modifies microstructure, phase constitution, corrosion-product formation, and local electrochemical behavior, thereby affecting both degradation kinetics and mechanical stability. Concurrently, Mg^{2+} released during degradation can serve as an osteogenic cue to promote osteoblast proliferation and differentiation. Qin *et al.*[128] further reported that porous zinc–1 magnesium scaffolds maintained compressive properties comparable to cancellous bone while achieving a favorable balance between degradation rate and osteogenic activity. These studies highlight a defining feature of biodegradable bulk alloying strategies: biological functionality is dynamically coupled with degradation-induced microstructural and chemical evolution.

2.3.3. Alloy-enabled anti-infective functionality

Incorporating antibacterial elements directly into metallic matrices represents an effective strategy for constructing long-lasting anti-infective implants. Among various antibacterial alloying elements, copper has attracted particular attention because of its combined antibacterial, anti-inflammatory, and pro-angiogenic activities. Xu *et al.*[129] fabricated Ti6Al4V–copper alloys via SLM for osteoporotic bone repair applications. The alloy exhibited homogeneous copper distribution and sustained low-concentration Cu^{2+} release. The released Cu^{2+} inhibited osteoclast differentiation, suppressed pro-inflammatory M1 macrophage activation, and promoted extracellular matrix synthesis by osteoblasts, thereby simultaneously alleviating inflammation and enhancing osteogenesis under osteoporotic conditions.

In dental restoration applications, Xu *et al.*[130] further alloyed 6 wt.% copper into Ti6Al4V to develop an antibacterial crown material. The Ti6Al4V–6 copper alloy maintained favorable mechanical properties and corrosion resistance while exhibiting pronounced antibacterial

activity against *Streptococcus mutans*. In addition to inhibiting biofilm formation, the alloy also downregulated bacterial virulence-associated gene expression without compromising cytocompatibility. These findings demonstrate that alloy-enabled antibacterial functionality can provide durable anti-infective capability while preserving the structural integrity of metallic implants.

2.3.4. Machine learning-driven alloy design and manufacturing

Although bulk alloying strategies offer advantages in long-term functional stability, their primary challenge lies in complex trade-offs under multi-objective constraints: the type and concentration of functional elements must simultaneously satisfy cytotoxicity thresholds, biological activity requirements, mechanical support capability, corrosion and degradation rates, and AM processability. Traditional experience-based trial-and-error alloy development approaches are inefficient for optimization in high-dimensional composition and processing spaces. Consequently, machine learning (ML) is emerging as an important tool for compositional design and process optimization of functional bulk alloys.[131-133] By integrating databases and establishing predictive learning models, ML enables the construction of efficient multi-objective performance optimization frameworks (Figure 5).

At the materials design level, ML primarily focuses on uncovering high-dimensional coupling relationships among composition, processing, and performance. Peng *et al.*[134] employed Bayesian optimization combined with explainable ML to successfully design a new biodegradable magnesium alloy with desirable overall performance. Their framework navigated a nine-dimensional design space and, through Shapley additive explanation analysis, revealed that processing parameters and zinc content were the key drivers. For titanium alloys targeting low elastic modulus, Marković *et al.*[135] applied an extra trees regression model that not only accurately predicted Young's modulus but also innovatively identified specific heat capacity as a key influencing factor. Monte Carlo simulations were further used to predict promising multicomponent alloy compositions. Mukherjee *et al.*[136] systematically compared multiple ML algorithms in analyzing element–property relationships in magnesium alloys, providing clear data-driven guidance for simultaneously tuning strength and degradation rates through elemental combinations.

Machine learning is therefore driving the transition of bulk alloying from experience-based exploration toward data-driven design, progressively establishing a manufacturable design space for functional alloys. In the future, incorporating degradation kinetics, ion release behavior, and cellular responses into unified multiscale models may enable fully intelligent design workflows spanning alloy composition design, AM process optimization, and prediction of *in vivo* functional performance, thereby accelerating the development of actively therapeutic metallic implants.

Overall, bulk alloying introduces bioactive elements directly at the material scale, providing implants with long-term functionality without the need for additional carriers. This strategy avoids interfacial instability issues such as coating delamination; however, it also faces intrinsic trade-offs because the biological windows of different elements

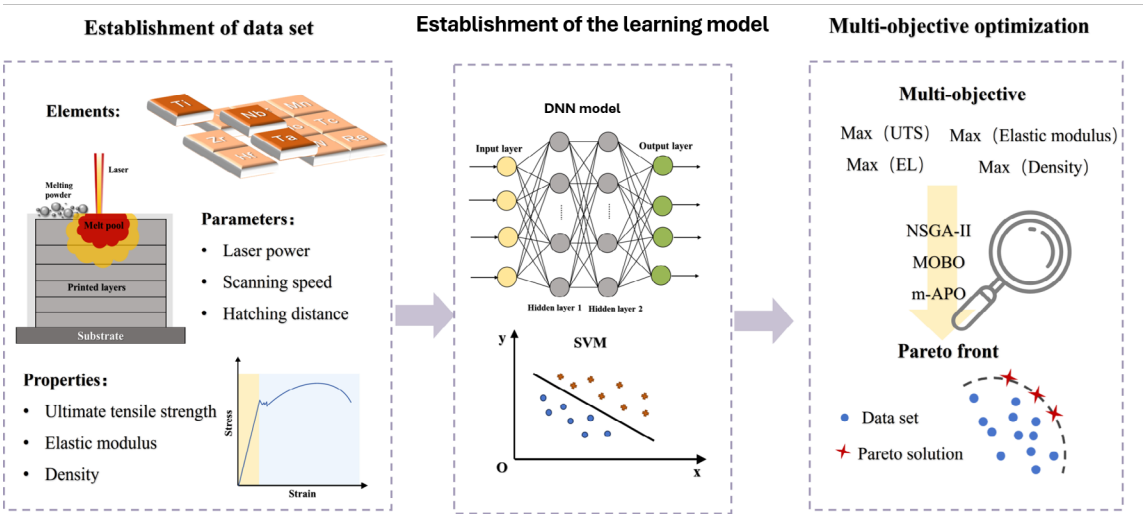

Figure 5. Workflow for machine learning-based multi-objective optimization in alloy design and manufacturing. Created with Microsoft PowerPoint. Abbreviation: DNN: Deep neural network.

may overlap or conflict, and the desired therapeutic effect must be balanced against mechanical integrity, corrosion behavior, and processability

2.4. Structural integration strategies

Structurally integrated therapeutic reservoirs represent a unique strategy enabled by the geometric freedom of AM, in which internal cavities, microchannels, or functionally partitioned architectures are directly incorporated into implants to achieve localized drug storage and release. Unlike surface-based loading approaches, therapeutic functionality in this strategy is embedded within the implant architecture itself, thereby enabling spatial separation between load-bearing and drug-delivery regions while preserving the overall mechanical integrity of the implant.

Within dense or partially dense implants, closed or semi-closed cavities (reservoirs) and micrometer-scale channels connecting to the surface can be directly printed to create built-in storage spaces. Šalandová *et al.*[137] used SLM to fabricate interconnected subsurface reservoirs and surface microchannels inside Ti6Al4V implants (Figure 6). After loading the reservoirs with a hydrogel containing AMPs, the openings were sealed using a poly(lactic-co-glycolic acid) film. An exogenous alternating magnetic field was then applied to induce eddy-current heating within the implant, thereby causing a thermal phase transition and rupturing the poly(lactic-co-glycolic acid) film, thereby enabling remote, on-demand drug release. Following alternating magnetic field triggering, the system achieved rapid, efficient release, with 99% released within 20 hours. Moreover, systematic cell experiments confirmed that the loaded AMPs exhibited good biocompatibility at their minimum bactericidal concentration and did not significantly interfere with macrophage polarization or early osteogenic marker expression in pre-osteoblasts. Karavasili *et al.*[138] further demonstrated that structural parameters can directly regulate release kinetics. They designed and fabricated hollow reservoirs with different surface pore patterns in Ti6Al4V pedicle screws. Systematic comparisons confirmed that pore size, number, and spatial distribution are key variables in programming drug-release behavior. A lattice-like helical pore design with larger pore size exhibited a higher initial burst release due to its greater exposed surface area, whereas a central channel design with smaller rhombic pores was more favorable for sustained long-term release. These studies collectively demonstrate that AM-enabled internal architectures are not merely passive structural features, but can function as programmable therapeutic reservoirs whose release behavior is governed by geometrical parameters such as pore topology, channel connectivity, and diffusion path length.

Structurally integrated strategies highlight the unique capability of AM to integrate therapeutic functionality directly into implant architectures. Compared with conventional surface loading approaches, these systems enable higher drug-loading capacity, programmable release behavior, and spatial separation between mechanical support and therapeutic delivery. Nevertheless, their release profiles are still largely predetermined by structural geometry and diffusion pathways established during fabrication. Further development therefore requires more adaptive release systems capable of responding to the dynamically evolving biological microenvironment.

Overall, current strategies for integrating bioactive substances into AM metallic implants can be broadly categorized into surface modification, bulk alloying, and structurally integrated strategies (Table 4). Surface modification primarily regulates interfacial bioactivity and localized therapeutic delivery through coatings or molecular functionalization. Bulk alloying introduces intrinsic, long-term functionality directly at the material level through the metallurgical incorporation of therapeutic elements. Structurally integrated reservoirs exploit the geometric freedom of AM to achieve spatially programmable drug storage and release.

Collectively, current bioactive integration strategies have enabled AM metallic implants to evolve from passive structural substitutes toward localized therapeutic platforms. However, most existing systems still rely on pre-programmed therapeutic release profiles determined during fabrication, where the timing, dosage, and duration of release are largely fixed in advance. Such static therapeutic paradigms remain insufficient for addressing the dynamically evolving peri-implant microenvironment, in which infection progression, inflammatory fluctuations, oxidative stress, and tissue regeneration continuously change over time. Therefore, the next developmental stage of therapeutic metallic implants is shifting from integrated bioactivity to adaptive therapeutic regulation, in which implants are expected not only to carry therapeutic agents but also to actively sense pathological changes and dynamically modulate therapeutic responses in real time.

3. Stimuli-responsive release strategies for bioactive substances of metallic implants

Conventional sustained release systems generally rely on drug diffusion, concentration gradients, or the gradual degradation of carrier materials to achieve prolonged delivery of bioactive substances. Such strategies have significantly advanced local therapy in orthopedic implants. However, their release behaviors are typically

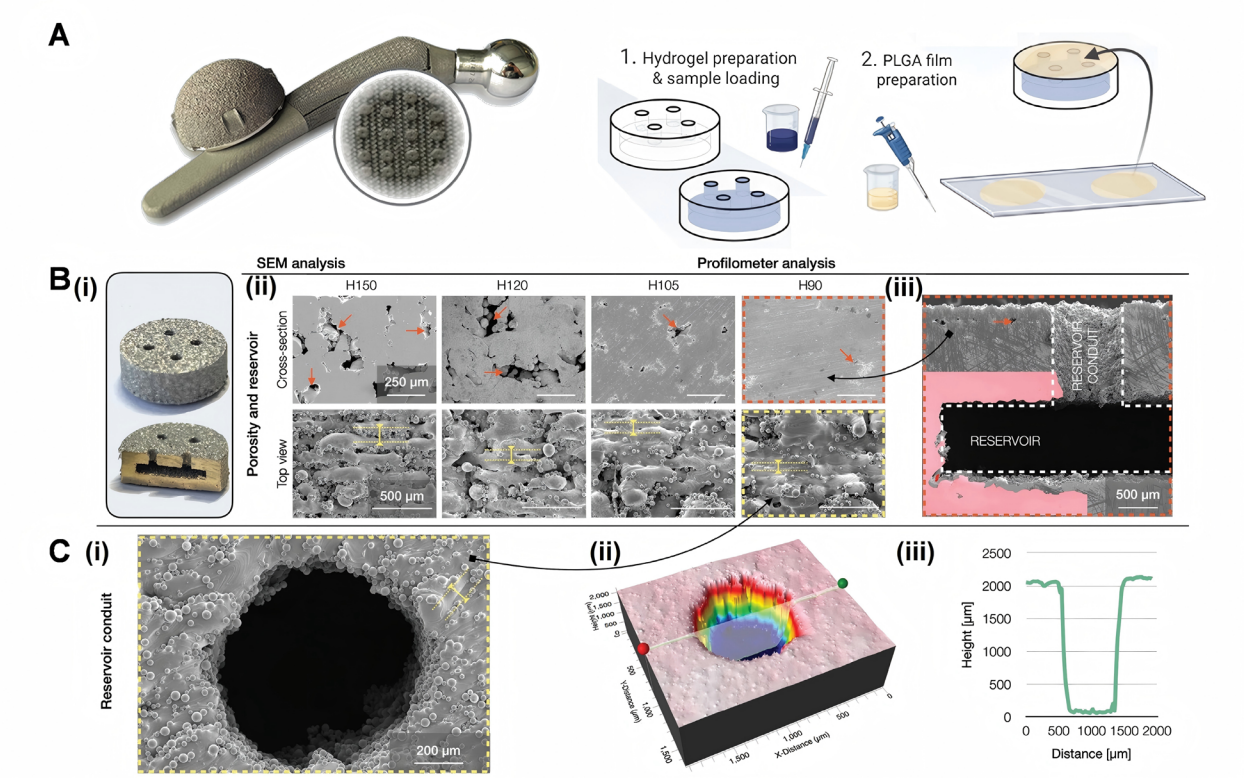

Figure 6. Structural integration strategy. (A) Real-scale implant and preparation process for hydrogel dye-loaded samples with a poly(lactic-co-glycolic acid) film. (B) Morphology and structural optimization of the three-dimensional-printed samples: (i) macroscopic image and cross-section; (ii) trend of pore formation (red arrows) with decreasing hatching distance from 150 µm to 90 µm (scale bars: 250 µm, 500 µm); (iii) cross-sectional view of a sample printed with the final parameters, showing the integrated reservoir and delivery conduit (scale bar: 500 µm). (C) Microstructural and topographical characterization of the reservoir and conduit (final parameters): (i, ii) images obtained by scanning electron microscopy (SEM) and optical profilometry, respectively (scale bar: 200 µm); (iii) depth line profile of the reservoir measured by the profilometer. Reprinted from Šalandová.[137]

Table 4. Comparison of therapeutic integration strategies in additive manufactured metallic implants

Strategy	Functional mechanism	Advantages	Limitations
Surface modification strategies	Functionalization through coatings, material-binding peptides, *in situ* electrochemical conversion layers, or vapor deposited films on implant surfaces	High versatility; convenient post-processing; tunable release behavior; suitable for multifunctional integration	Limited long-term interfacial stability; possible coating delamination or burst release
Bulk alloying strategies	Intrinsic incorporation of bioactive elements into the metallic matrix through metallurgical alloying	Long-term stable functionality; uniform elemental distribution; avoids coating-related instability	Trade-offs among cytocompatibility, mechanics, and processability; limited flexibility after fabrication
Structural integration strategies	Drug storage and release enabled by additive manufacturing-designed internal cavities, channels, or partitioned architectures	High loading capacity; programmable release kinetics; spatial separation of mechanical and therapeutic functions	Fabrication complexity; sealing reliability; risk of channel blockage or incomplete release

predetermined at the time of implantation, making it difficult to dynamically adapt to the continuously changing *in vivo* pathological microenvironment. In comparison, controlled release places greater emphasis on regulating the release process itself, including the tunability of the release rate, timing, dosage, and responsiveness. However, the microenvironment surrounding implants is highly dynamic. Pathological events such as bacterial infection, aggravated inflammation, and oxidative stress imbalance are often unpredictable, and conventional pre-programmed sustained-release strategies may therefore be insufficient to meet therapeutic demands at different stages.

To overcome this limitation, research has increasingly shifted toward the development of stimuli-responsive implants that use pathological microenvironmental signals *in vivo* or exogenous physical fields as triggers to initiate, accelerate, or regulate the on-demand release of therapeutic agents. Within this framework, endogenous or exogenous stimuli do not act as therapeutic agents themselves but serve as regulatory input signals to control the timing and dosage of active substance delivery. According to the source of triggering signals, these approaches can be further categorized into endogenous stimuli-responsive strategies and exogenous stimuli-responsive strategies, each with characteristics in triggering mechanisms, controllability, and clinical implementation challenges.

3.1. Endogenous stimuli-responsive release strategies

The core of this strategy lies in exploiting the inherent biochemical differences between diseased sites and normal physiological environments as triggers, thereby enabling targeted, spontaneous therapeutic activation. By mimicking the body's natural feedback-regulation mechanisms, this responsive mode avoids the systemic side effects of continuous drug release and the complexity of external intervention, thereby enhancing therapeutic safety and specificity.

Endogenous responsive systems use biochemical changes in the local pathological microenvironment as intrinsic triggers for therapeutic activation. These triggers typically include pH variations, elevated expression of specific enzymes, abnormal ROS levels, and changes in inflammation-related molecules (Figure 7). Because their activation depends on disease-associated signals, such systems exhibit a degree of biological specificity and

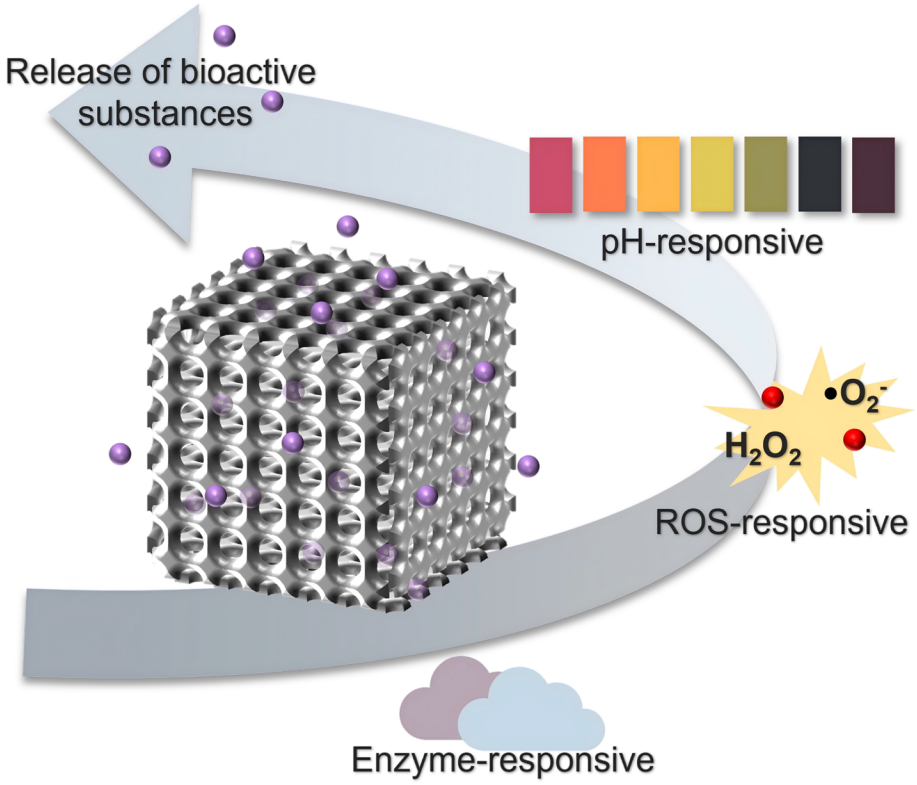

Figure 7. Schematic of endogenous stimuli-responsive release strategies, including pH, enzymes, and reactive oxygen species (ROS). Created with Microsoft PowerPoint.

autonomous regulation without external intervention.

3.1.1. pH-responsive release strategies

Pathological processes such as infection, inflammation, and tumors often lead to acidification of the peri-implant microenvironment, providing a specific signal for stimuli-responsive activation. pH-responsive systems incorporate chemical bonds or polymers that are sensitive to proton concentration, enabling degradation or conformational changes in drug carriers under acidic conditions, thereby accelerating the release of therapeutic molecules. Their core advantage lies in distinguishing diseased tissues from healthy ones, thus minimizing off-target toxicity to normal cells.

In response to different clinical challenges, pH responsiveness has demonstrated diverse design strategies. For integrated bone tumor therapy, Fan *et al.*[139] developed a composite material (TS@PAP) based on an AM titanium scaffold. This system used acid-labile acetal bonds to link a paclitaxel prodrug, enabling rapid, burst-release (85.33% within 72 hours) in a simulated tumor acidic microenvironment (pH 6.5), while maintaining slow release at physiological pH (~11.28%). This design achieved highly selective killing of residual tumor cells while preserving a therapeutic window for subsequent bone regeneration.

In the prevention of implant-related infections, Pereira *et al.*[140] constructed a pH-sensitive thin film based on poly(methacrylic acid) on titanium implant surfaces. Protonation of carboxyl groups in acidic environments caused contraction of polymer chains, thereby regulating tetracycline release from the underlying drug-loaded multilayers. This system not only effectively inhibited various biofilms but also promoted the activity of cells involved in soft tissue repair, demonstrating the dual potential of smart surface coatings in infection control and tissue integration. Furthermore, Zhou *et al.*[141] utilized the conformational transition of silk fibroin from α-helix to β-sheet under acidic conditions, which transformed originally dense coatings into looser structures, thereby accelerating the release of loaded Ag^+ and AMPs and enabling an infection-triggered intelligent antibacterial "switch." Zhang *et al.*[142] designed a pH-responsive adaptive coating based on a quaternary ammonium–carboxyl copolymer. In this coating, antibacterial quaternary ammonium centers were electrostatically shielded by negatively charged carboxyl groups under physiological pH, exhibiting good biocompatibility and promoting osteogenesis. Under acidic infection conditions, the quaternary ammonium centers became exposed, disrupting bacterial membranes via electrostatic interactions and enabling on-demand antibacterial activation.

With the development of AM, pH-responsive mechanisms have been deeply integrated with the macroscopic structural design of implants, enabling more complex therapeutic logic. Zeng *et al.*[143] fabricated titanium alloy implants with integrated funnel-shaped drug reservoirs using SLM. By combining osmotic pressure differences induced by pH reduction with protonation-driven swelling of drug-loaded gelatin microspheres, the system achieved adaptive feedback between infection severity and drug release rate. Similarly, Baek *et al.*[99] developed a pH-responsive hydrogel based on an injectable ABA triblock copolyether and loaded it into drug-storage cavities of SLM-printed titanium implants. This hydrogel underwent a sol–gel transition in acidic inflammatory environments, enabling controlled release of dexamethasone and achieving on-demand local anti-inflammatory therapeutic delivery.

For diseases such as osteoporosis accompanied by complex metabolic abnormalities, Li *et al.*[144] integrated a rapamycin-loaded polyvinyl alcohol–carboxymethyl CS–agarose/Ag nanowires hydrogel onto the surface of AM porous titanium alloy implants, constructing a hydrogel coating responsive to both pH and competitive molecules. This system relied on a dynamic boronate ester covalent network that underwent reversible gel–sol transitions in acidic and high-metabolite microenvironments, thereby enabling controlled rapamycin release to activate autophagy pathways in osteoporosis-derived stem cells and promote osteogenic differentiation. Meanwhile, Ag nanowires provided baseline long-term antibacterial activity, demonstrating synergistic responsiveness and therapeutic effects toward multidimensional pathological signals.

3.1.2. Enzyme-responsive release strategies

Enzyme-responsive systems use specific enzymes that are overexpressed during disease progression or healing processes as biological triggers. By designing peptide or polymer chains that can be specifically cleaved by these enzymes, localized and temporally controlled drug release can be achieved. This strategy typically exhibits high biological specificity, with therapeutic activation closely linked to the pathological process itself.

Among various endogenous stimuli-responsive strategies, hyaluronic acid has become an ideal material for constructing enzyme-triggered release platforms due to its unique biological properties. First, hyaluronic acid is a natural component of the extracellular matrix, exhibiting favorable biocompatibility and biodegradability. Second, its strong hydrophilicity and negative charge

enable the formation of hydration layers and electrostatic repulsion, providing broad-spectrum antibacterial adhesion capability. Hyaluronic acid can be specifically degraded by hyaluronidase (HAase) secreted by various pathogenic bacteria, such as *S. aureus*. When infection occurs at the implant site, bacterial enzymes rapidly degrade the hyaluronic acid matrix, enabling rapid release of therapeutic agents.

Sutrisno *et al.*[145] constructed a HAase-sensitive CS/sodium hyaluronate–lauric acid multilayer film on the surface of titanium nanotubes loaded with the osteogenic factor BMP-2. When early infection occurred, HAase secreted by pathogenic bacteria degraded the hyaluronic acid matrix, simultaneously releasing the embedded natural antibacterial agent lauric acid, which functions by disrupting bacterial membranes and inhibiting virulence factor expression, as well as BMP-2. This strategy enabled early antibacterial action while initiating osseointegration without relying on traditional antibiotics, effectively interrupting the vicious cycle in which infection and bone healing inhibit each other.

Similarly, Yuan *et al.*[146] assembled multilayer films of catechol-functionalized hyaluronic acid and CS on Van-loaded titanium dioxide nanotube arrays. This coating also responded to HAase secreted by bacteria, triggering the intelligent release of Van and achieving an *in vitro* antibacterial rate exceeding 86%. In addition, catechol groups upregulated integrin gene expression, enhancing osteoblast adhesion and osseointegration. Furthermore, Yu *et al.*[147] combined enzyme responsiveness with angiogenic regulation by constructing hyaluronic acid–Gen multilayer films on deferoxamine-loaded titanium nanotubes. HAase triggering enabled the simultaneous release of Gen and deferoxamine, thereby synergistically suppressing infection and promoting the formation of a bone-repair microenvironment.

Such enzyme-responsive systems establish a closed-loop therapeutic logic, from infection sensing to drug release and subsequent promotion of healing. By avoiding systemic toxicity and antibiotic overuse, they effectively interrupt the vicious cycle between infection and impaired bone healing, providing a design paradigm for multifunctional integration in implants.

3.1.3. Reactive oxygen species-responsive release strategies

Pathological conditions such as chronic inflammation, diabetes, and osteoporosis are often accompanied by abnormally elevated local ROS levels. ROS-responsive systems incorporate materials containing ROS-sensitive chemical bonds, such as thioketal or selenium-based linkages, that cleave upon exposure to high ROS levels, thereby releasing the loaded therapeutic agents. This strategy not only intervenes in the primary disease but also actively alleviates the negative effects of excessive oxidative stress on surrounding tissue repair.

Chen *et al.*[148] exploited the fine-tuning potential of ROS-responsive systems to treat comorbid pathological conditions and developed a functional coating (titanium/DNAzyme-zinc oxide nanoflowers/polydopamine-naringenin) for titanium implants in osteoporotic environments. When ROS levels increased due to osteoporosis-associated inflammation at the implantation site, thioketal bonds in the coating cleaved, sequentially releasing naringenin and DNAzyme-zinc oxide nanoflowers. Nar promoted angiogenesis by activating the endothelial nitric oxide synthase/nitric oxide pathway, while DNAzyme-zinc oxide nanoflowers specifically degraded the mRNA of the inflammation-related gene *STING* that was overexpressed intracellularly. This dual synergistic mechanism aimed to redirect disordered angiogenesis in pathological conditions toward H-type vessel formation that supports osteogenesis, thereby improving the osseointegration microenvironment in osteoporotic conditions at the level of gene regulation.

3.2. Exogenous stimuli-responsive release strategies

In addition to endogenous pathological signals, externally applied physical fields provide important means for achieving spatiotemporally precise control over the release of therapeutic agents. Unlike microenvironment-responsive systems that rely on disease-induced biochemical changes, exogenous stimuli can be applied on demand according to clinical needs, with flexible adjustment of intensity and duration. This section focuses on exogenous physical stimuli used to regulate the release behavior of preloaded therapeutic agents. These strategies convert externally supplied energy into physical or chemical changes within the carrier materials (such as localized heating, structural transitions, or enhanced molecular diffusion), thereby enabling controllable, noninvasive, and repeatable regulation of therapeutic delivery. Representative exogenous triggers include light irradiation, magnetic fields, and electrical stimulation, each of which enables remote control over therapeutic release through distinct mechanisms (Figure 8).

3.2.1. Light-responsive release strategy

Light irradiation, with precisely controllable wavelength, intensity, and duration, has been widely applied in implant-related therapeutic strategies. In therapeutic delivery platforms for implants, light is increasingly used as a remote regulatory signal to modulate therapeutic

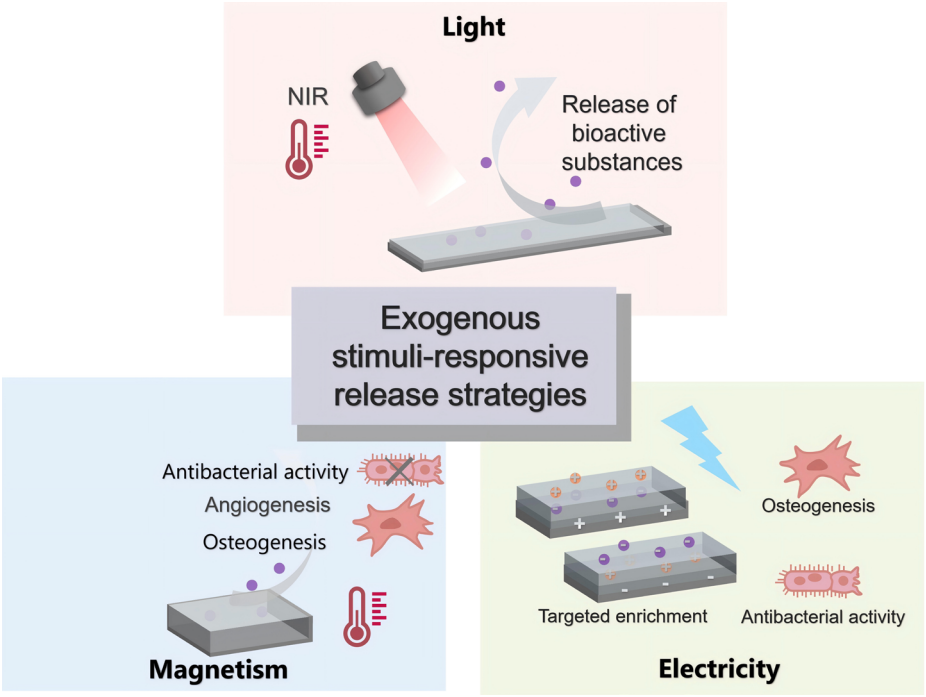

Figure 8. Schematic of exogenous stimulus-responsive release strategies, including light, magnetic, and electrical stimuli. Created with Microsoft PowerPoint.
Abbreviation: NIR: Near-infrared.

release via photothermal conversion or photoresponsive structural changes. Near-infrared (NIR) light is particularly important due to its strong tissue penetration capability. Photothermal materials integrated into coatings or carrier matrices can convert NIR irradiation into localized heating, thereby inducing polymer softening, structural relaxation, or enhanced molecular diffusion, thereby promoting the release of preloaded active agents.[149-152]

In early studies, the photothermal effect was used to directly treat implant surfaces, laying the foundation for employing light as a remote-control tool. Wang *et al.*[153] constructed a nano-TiO_2 coating on SLM-printed Ti6Al4V implants, thereby extending its photoresponsive activity into the 808 nm NIR region and reducing potential photodamage to biological tissues. Under NIR irradiation at 0.8 W/cm^2, the coating temperature rose to 46.9 ± 0.32 °C within 15 minutes. Through the synergistic effects of photothermal therapy (PTT) and physical nanostructure puncture, antibacterial rates against *S. aureus* and *E. coli* both exceeded 90% (Figure 9).

Furthermore, photothermal effects have been integrated with drug-controlled release and enhanced osseointegration for multifunctional therapy. Ji *et al.*[154] constructed an NIR-triggered cascade release system on SLM-printed porous titanium scaffolds. Upon 808 nm laser irradiation, PTT (~54 °C) was first induced, leading to rapid degradation of a thermosensitive hydrogel at the surface and the release of Mg^{2+}, curcumin, and paclitaxel, thereby achieving early postoperative antitumor, antibacterial, and anti-inflammatory effects. Meanwhile, zinc oxide loaded within the scaffold matrix provided long-term Zn^{2+} release, supporting prolonged antibacterial and osteogenic effects. Cai *et al.*[155] demonstrated a sequential therapeutic strategy combining photothermal ablation with long-term therapeutic delivery. A wide-bandgap TiO_2/titanium(III) phosphide photothermal coating was applied to EBM-printed Ti6Al4V scaffolds, and the pores were infused with a gelatin/hyaluronic acid release system loaded with the antiresorptive drug alendronate. Under NIR irradiation, PTT directly ablated residual osteosarcoma cells, while alendronate was continuously released (approximately 78% over 28 days), effectively promoting osteogenic differentiation of bone marrow mesenchymal stem cells and *in vivo* osseointegration. Zhang *et al.*[156] developed a rare earth-doped TiO_2/quercetin/L-arginine composite coating on titanium implants. Under 1,060 nm NIR irradiation, the system heated to 48 °C and generated ROS that synergized with L-arginine in the coating to produce angiogenesis-promoting nitric oxide *in situ*. This enabled integrated antibacterial, anti-inflammatory, osteogenic, and angiogenic functions, achieving efficient synergistic therapy.

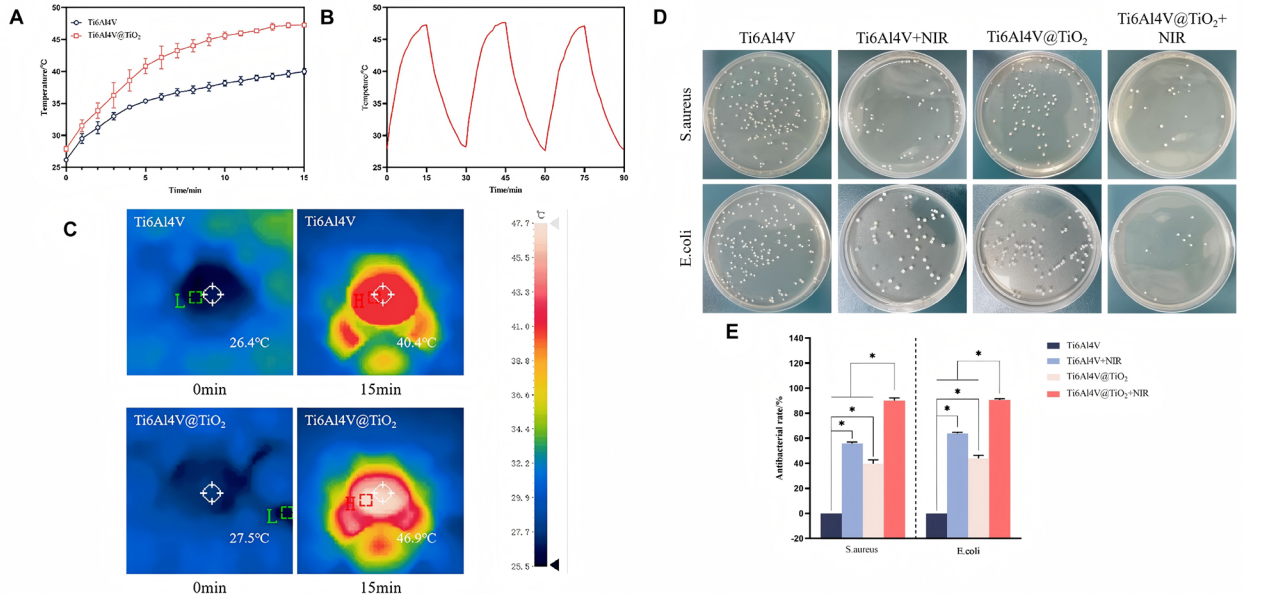

Figure 9. Light-responsive strategy of the nano-TiO_2 coating. (A) Temperature change in 1 mL of phosphate-buffered saline under 808 nm near-infrared (NIR) irradiation (0.8 W/cm^2). (B) Temperature variation during on/off illumination cycles. (C) Infrared thermal images of the sample. (D) Bacterial colonies of *E. coli* and *S. aureus* with or without NIR irradiation. (E) Corresponding antibacterial rates under different conditions. Reprinted from Wang *et al.*[153]

3.2.2. Electrically-responsive release strategy

Electrically-responsive strategies construct conductive coatings on implant surfaces, such as polypyrrole and polyaniline. By applying safe external voltages, reversible and precise regulation of surface properties or the state of loaded molecules can be achieved.[157,158]

Liao *et al.*[159] prepared a polypyrrole coating co-doped with chondroitin sulfate and the AMP OP-145 on Ti-5Al-2.5Fe implants. By switching the polarity of the applied voltage (+0.50 V vs. −0.50 V), functional molecules with different charges could be directionally enriched at the coating surface. Under anodic conditions, OP-145 dominated the surface, providing contact-based antibacterial activity; under cathodic conditions, chondroitin sulfate was exposed, promoting osteoblast adhesion, spreading, and differentiation. This design enabled the same implant to switch between functional modes noninvasively in response to external electrical signals, according to postoperative stage requirements.

3.2.3. Magnetically-responsive strategies

Magnetically-responsive strategies primarily use superparamagnetic nanoparticles, such as Fe_3O_4, to generate magnetic hyperthermia in an alternating magnetic field. This mechanism is similar to PTT, but magnetic fields are less affected by optical scattering and can penetrate deep tissues. However, achieving efficient energy conversion under clinically safe field strengths remains challenging.[160] In addition, magnetic particles can generate magneto-mechanical effects in magnetic field gradients, directly disrupting bacterial biofilm structures. Static magnetic fields themselves have also been shown to promote bone healing by influencing membrane receptors and ion channels.[161] The greatest advantage of magnetic responsiveness is the ability to noninvasively and remotely manipulate implants at virtually any depth within the body.[162]

Zeng *et al.*[163] constructed an AM-porous polymer scaffold integrated with Fe_3O_4 nanoparticles and loaded with a drug-loaded thermosensitive hydrogel. This system initially employed NIR-triggered PTT to achieve rapid antibacterial activity and drug release. After infection control, an externally applied static magnetic field was used to promote endothelial cell tubule formation and migration, enhancing angiogenesis and thereby coupling vascularization with bone tissue regeneration.

Overall, exogenous physical-field-triggered systems offer important strategies for achieving spatiotemporally precise regulation of therapeutic release from implants. Unlike endogenous microenvironment-responsive systems that depend on pathological signals, exogenous stimuli such as light, magnetic fields, and electrical stimulation can be applied on demand and dynamically adjusted in intensity and duration according to clinical

needs. By converting externally supplied energy into localized physical or chemical changes in carrier materials, these strategies enable noninvasive, repeatable control of therapeutic delivery.

4. Conclusion

Overall, AM is driving metallic orthopedic implants from traditional passive load-bearing devices toward multifunctional therapeutic platforms that actively participate in bone repair. The significance of this transition lies not only in the geometric flexibility and manufacturing freedom provided by AM, but also in its ability to integrate structural design, bioactive substances, and therapeutic regulation within a single implant system. In this review, major strategies for bioactive integration, including bulk alloying, structural reservoir integration, and surface functionalization, are systematically summarized. These approaches enable implants to achieve antibacterial activity, immunomodulation, osteogenesis promotion, angiogenic regulation, and localized therapeutic delivery through distinct material and structural pathways. Furthermore, recent advances in controlled-release systems are discussed, particularly stimulus-responsive platforms that respond to endogenous pathological cues or exogenous physical stimuli. Collectively, these developments indicate that the design logic of AM metallic implants is gradually shifting from static structural replacement toward dynamically regulated therapeutic systems.

Despite substantial progress, several important challenges still limit the further development of bioactive-integrated AM metallic orthopedic implants. Achieving effective coordination among multiple therapeutic functions remains difficult. Antibacterial activity, osteogenesis promotion, angiogenic regulation, immunomodulation, and controlled release often require different activation periods, concentration ranges, and release kinetics. However, many current systems still rely on simple functional superposition rather than truly coordinated regulation. Similarly, highly porous structures that favor drug loading and tissue ingrowth may simultaneously accelerate degradation or compromise mechanical stability. Therefore, one of the central challenges is achieving biologically rational coordination among therapeutic efficacy, release behavior, structural stability, and biosafety within a single implant system.

Additionally, the intrinsic characteristics of AM processes introduce additional complexity to bioactive integration systems. Layer-wise fabrication can generate heterogeneous microstructures, surface roughness variations, partially melted particles, and internal defects, all of which may influence coating uniformity, interfacial bonding stability, corrosion behavior, and release consistency. In complex porous architectures, irregular transport pathways and local microenvironment differences may further result in nonuniform loading distribution and unpredictable release behavior. In addition, post-processing procedures may alter surface chemistry and, in turn, affect biological performance. As a result, the interactions among printing parameters, structural features, surface properties, and therapeutic functions remain insufficiently understood.

Future development of AM metallic orthopedic implants will likely focus on the transition from single-function enhancement toward spatiotemporally coordinated therapeutic systems. Rather than simply integrating multiple bioactive components into a single implant, future strategies should aim to achieve sequential, environment-adaptive regulation across the different stages of bone healing. For example, early-stage antibacterial activity may need to be combined with sustained promotion of osteogenesis and angiogenesis at later stages. Therefore, future implant design may increasingly emphasize therapeutic timing, spatial distribution, and functional coordination.

Structural design is expected to play a more active role in therapeutic regulation. AM enables precise control over pore geometry, hierarchical architecture, and internal transport pathways, allowing structural features to directly influence diffusion behavior, local mass transport, and therapeutic distribution. Consequently, future AM metallic implants may evolve from drug-loaded structures toward structure-mediated therapeutic systems, in which architecture itself participates in therapeutic regulation.

The integration of computational and data-driven approaches is another important direction. Computational simulation, degradation prediction, and artificial intelligence-assisted parameter optimization may help establish quantitative relationships among material composition, structural configuration, release behavior, and biological response, thereby improving the design and optimization of multifunctional implants.

Overall, future AM metallic implants will increasingly rely on the synergistic integration of material composition, structural architecture, and therapeutic regulation, enabling next-generation implants to actively participate in complex bone-repair processes.

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Conflict of interest

Both Chee Kai Chua and Liqiang Wang serve the Editorial Board of this journal as Editor-in-Chief and Editorial Board Member, respectively, but they were not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Visualization: Yi Mao, Yihong Li
Writing–original draft: Yi Mao, Yihong Li
Writing–review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

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