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Bisphosphonate-incorporated coatings for orthopedic implants functionalization

Jiaxin Zhang [a], Haotian Bai [a], Miao Bai [b], Xiaonan Wang [a], ZuHao Li [a], Haowen Xue [a], Jincheng Wang [a], Yutao Cui [a], Hui Wang [a], Yanbing Wang [a], Rongqi Zhou [a], Xiujie Zhu [a], Mingwei Xu [a], Xin Zhao [a,*], He Liu [a,**]

[a] Orthopedic Institute of Jilin Province, Orthopedic Medical Center, The Second Hospital of Jilin University, Changchun 130041, PR China
[b] Department of Ocular Fundus Disease, Ophthalmology Center, The Second Hospital of Jilin University, Changchun 130041, PR China

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ABSTRACT

Bisphosphonates (BPs), the stable analogs of pyrophosphate, are well-known inhibitors of osteoclastogenesis to prevent osteoporotic bone loss and improve implant osseointegration in patients suffering from osteoporosis. Compared to systemic administration, BPs-incorporated coatings enable the direct delivery of BPs to the local area, which will precisely enhance osseointegration and bone repair without the systemic side effects. However, an elaborate and comprehensive review of BP coatings of implants is lacking. Herein, the cellular level (e.g., osteoclasts, osteocytes, osteoblasts, osteoclast precursors, and bone mesenchymal stem cells) and molecular biological regulatory mechanism of BPs in regulating bone homeostasis are overviewed systematically. Moreover, the currently available methods (e.g., chemical reaction, porous carriers, and organic material films) of BP coatings construction are outlined and summarized in detail. As one of the key directions, the latest advances of BP-coated implants to enhance bone repair and osseointegration in basic experiments and clinical trials are presented and critically evaluated. Finally, the challenges and prospects of BP coatings are also purposed, and it will open a new chapter in clinical translation for BP-coated implants.

1. Introduction

Due to the outstanding development of bioengineering, orthopedic implants are extensively used for bone fixation and joint replacement [1,2]. Although these surgeries have achieved remarkable health outcomes for decades, approximately 10% of implants fail prematurely within the first 10–20 years, and tens of thousands of patients must undergo revision annually [3,4]. Long-term success of orthopedic implants is largely determined by osseointegration, which is the direct contact between living bone and the implant [5]. The quality and amount of osseointegrated bone around the implant may affect the osseointegration [6]. Physiological imbalances in bone homeostasis lead to metabolic diseases, including osteoporosis, osteopetrosis, and Paget's disease, which have adverse effects on osseointegration and eventually lead to implant loosening [7]. Osteoporosis (OP) can be divided into two categories: postmenopausal osteoporosis occurs after menopause, while senile osteoporosis occurs in both men and women [8]. OP is a systemic disease characterized by bone loss exceeding bone formation, resulting in diminished bone mass, degeneration of bone microarchitecture, and fracture susceptibility [9,10]. In pathological states, osteoclasts (OCs) are influenced by a variety of pro-inflammatory osteoclastogenic cytokines that can stimulate their activity [11]. Among them, the receptor activator of nuclear factor κ B ligand (RANKL) is a major osteoclastogenic cytokine that stimulates OC differentiation by binding to its receptor RANK on OC precursors [12]. Thus, activation and hyperactivation of the osteoprotegerin (OPG)/RANKL/RANK signaling pathway can mediate the process of bone erosion and affect the microstructure of cancellous bone such as trabecular thickness and spacing.

Bisphosphonates (BPs) are a component of standard pharmaceutical therapy for osteoporosis and osteoporotic fracture prevention [13]. Through binding to exposed hydroxyapatite (HA) crystals, BPs are incorporated into the bone matrix when administered orally or intravenously [14]. BPs belong to the typical OC inhibitor used to treat osteoporosis [15]. In addition to the effect on OCs, BPs can promote

* Corresponding author.
** Corresponding author.
E-mail addresses: xzhao@jlu.edu.cn (X. Zhao), heliu@jlu.edu.cn (H. Liu).

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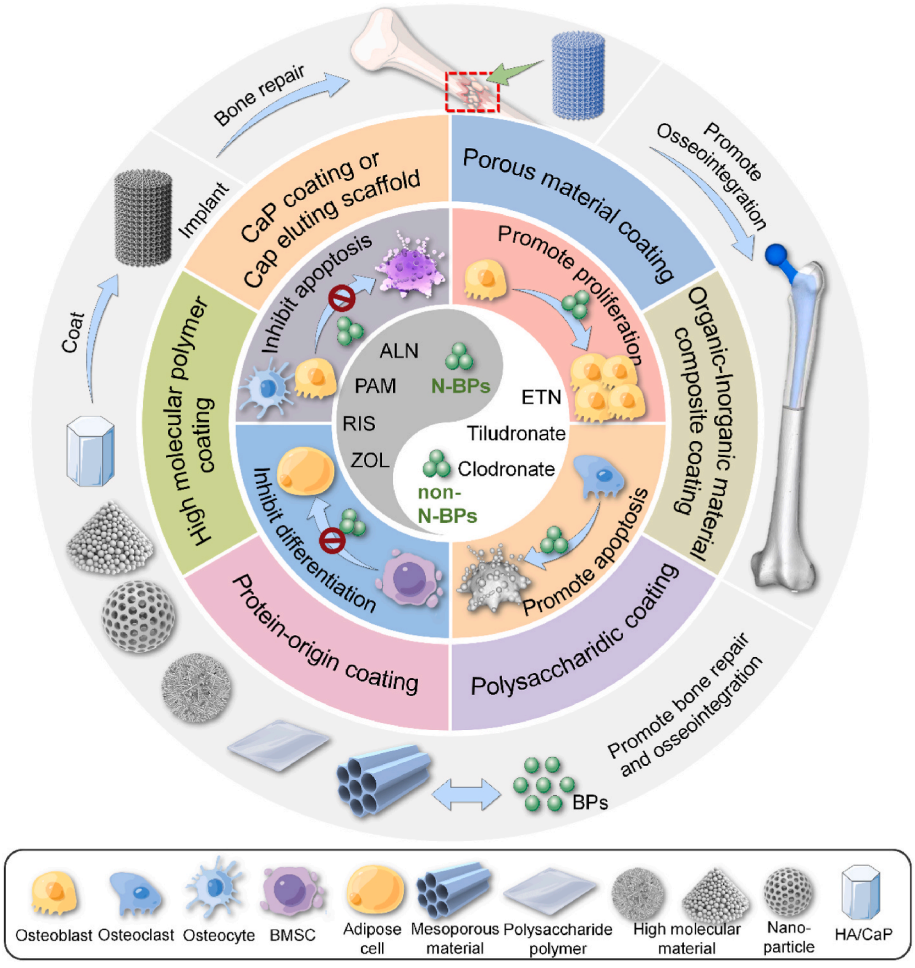
osteoblasts (OBs) proliferation and differentiation to accelerate bone regeneration [16]. BPs also inhibit the excessive growth of fibroblasts and induce apoptosis of fibroblasts, which prevent the excessive proliferation of fibers around the implant and improve implant stability [17]. Despite its established efficacy of treatment for OP, there are several adverse effects by administering orally or intravenously. For instance, oral BPs can lead to upper gastrointestinal problems and the absorption by the gastrointestinal tract can reduce drug efficacy [18]. Meanwhile, intravenous BPs may cause a series of complications such as jaw necrosis, nephrotoxicity, and increased risk of venous thrombosis [19]. An alternative to oral or intravenous administration is the development of a local delivery system by combining drugs with implants, which assures sustained release of BPs and maintains a localized effect without affecting healthy bone tissue [20]. Thus, the local application of BPs has been proposed as an interesting strategy to enhance treatment efficiency, reducing side effects, and promoting osseointegration of implants in humans.

Implant surface modifications and functionalization play an important role in constructing a local delivery system to regulate the release profile of drugs [21]. Currently, the surface coating is the most widely used value-added strategy for surface modification [22]. BPs are characterized by a strong affinity for the calcium component of both natural and synthetic HA bone minerals [23]. Therefore, using BPs-based functional coating implants enable them to play a role in manipulating the osteogenesis-osteoclastic balance around the implant, as well as targeting bone tissue to further improve osseointegration. However, recent reviews in related fields do not highlight or elaborate on the construction method of BPs-based multifunctional coating and their current application in bone formation [24,25]. We aimed to provide a summary of the mechanism of BPs regulating bone homeostasis at the cellular and molecular biological levels. Meantime, a comprehensive summary of the ideal concentration of BPs for localized release has been presented. In addition, the principle of constructing BPs-based coating was analyzed. Furthermore, we highlight the application of different kinds of BP-based coatings to promote osseointegration. The present review provides a theoretical and novel perspective on clinical therapy (Scheme 1).

2. Mechanism of BPs in regulating bone homeostasis

A variety of cells belong to the skeletal lineage responsible for maintaining and repairing bone during homeostasis and injury (Fig. 1). This lineage of cells includes OBs and osteocytes, which are primarily responsible for bone formation [26,27]. OCs originate from the monocyte/macrophage lineage and are responsible for bone resorption [28]. Bone mesenchymal stem cells (BMSCs) can also differentiate toward mature OBs [29]. A delicate balance between the function of OBs and OCs maintains bone homeostasis. During the aging process, especially among postmenopausal women, overall bone remodeling is increased and OC activity surpasses that of OBs, leading to bone loss [30]. In this section, we discuss the differences in molecular structure and pharmacological activity between various BPs, and the mechanisms of BP modulation of a variety of cells involved in the process of bone remodeling to enhance osseointegration.



Scheme 1. BPs are coated on the surface with organic and inorganic materials to form the functionalized surface of implants, promoting bone formation and osseointegration.

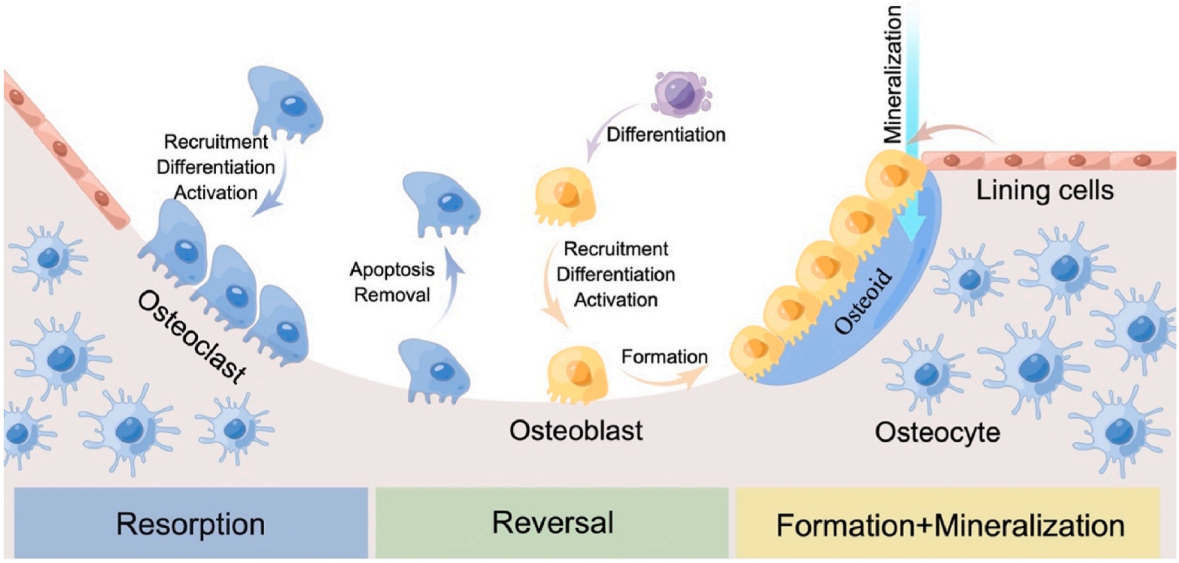


Fig. 1. The function of various cells (OCs, OBs, osteocytes, and BMSCs) in maintaining bone homeostasis and regulating bone remodeling (By Figdraw.).

2.1. Classification of BPs

BPs, stable analogs of naturally occurring pyrophosphates, are used to regulate the process of calcification and bone resorption, in that the P–*O*–P bond of pyrophosphates (PPi) is replaced by a P–C–P bond to resist chemical or enzymatic hydrolysis (Fig. 2A). The P–C–P group binds to HA as strongly as PPi, which makes these compounds highly attractive bone targeting agents [31]. Individual BPs are characterized by the R1 and R2 side chains bound to the central carbon [32]. BPs have better affinities for the bone mineral, where the R1 groups are responsible for targeting bone, and R2 groups play a vital role in the biological functions of BPs [33]. According to the existence of nitrogen in their side chain, BPs are classified into nitrogen-containing BPs (N-BPs) and non-nitrogen-containing BPs (non-N-BPs) [34]. Although both N-BPs and non-N-BPs can bind to HA, N-BPs have higher bone affinity and excellent bone resorption resistance [35]. In clinical use, BPs are classified according to their chemical structures. The first generation of BPs includes molecules that have no nitrogen atoms are called non-N-BPs (etidronate and clodronate). This generation is characterized by small substituent chains or groups, such as hydrocarbon groups. Due to their chemical structures, this generation have a relatively low ability to inhibit osteoclasts [36].

The second and third generations of BPs comprise a nitrogen atom in their side chains, normally referred to as N-BPs (Fig. 2B). Because N-BP contains nitrogen atoms, they can block the mevalonate pathway in addition to ATP synthesis, thus achieving a stronger osteoclast inhibitory effect [37]. The major drugs belonging to the second generation of BPs include pamidronate (PAM), alendronate (ALN), and neridronate. The third-generation products, including zoledronate (ZOL) and risedronate (RIS), introduce more complex N-heteroaromatic groups, which are more active, resistant to bone resorption, efficient, and have a wider therapeutic range [38]. In comparison with older generations of BPs, ZOL and RIS have a 1000- to 10,000-fold higher antiresorption potency [39]. In the subsections, we summarize the potential mechanisms by which BPs regulate bone tissue homeostasis and promote osseointegration via targeting bone tissue and subsequently modulating OCs, osteocytes, OBs, and other cells.

2.2. Biochemistry and cellular targets of BPs

Biological molecular mechanisms for regulating OC activity are associated with BP structure (Fig. 3). Non-N-BPs are metabolized to a cytotoxic analog of ATP, adenosine-5′-(β,γ-dichloroethylene)-triphosphate, which inhibits the mitochondrial adenine nucleotide translocase (ANT) and eventually trigger OC apoptosis [40]. N-BPs inhibit bone resorption through the mevalonate pathway, which is required for protein prenylation [41]. Lack of protein prenylation affects the OC cytoskeletal organization and cell morphology, reducing cell activity and inducing apoptosis. It has been shown that the molecular target of N-BPs is farnesyl pyrophosphate synthase (FPPS), a vital mevalonate pathway enzyme [42]. Okamoto et al. [43] indicated that inhibition of FPPS upregulates the levels of cytotoxic ATP analogs, including isopentenyl pyrophosphate and triphosphoric acid 1-adenosine-5′-yl ester 3-(3-methylbut-3-enyl) ester (ApppI), which can restrain ANT and induce OC apoptosis through the same mechanism as non-N-BPs. Compared with the initial two generations of BPs, the third generation BPs exhibit the most potent inhibition of FPPS and demonstrate the capacity to stabilize the conformational alteration of its inhibitory effect [44]. Additionally, the third-generation BPs display the highest mineral binding constant, signifying their efficacy and prolonged duration in inhibiting OCs [45].

2.3. Potential effect of BPs on osteoclasts

BPs can preferentially adsorb to the bone surface upon release, thus acquiring close contact with OCs (Fig. 4A). During bone resorption, the proton pump in the OC trap produces an acidic environment, which significantly increases the association of BPs with HA crystal [46]. OCs take up the released BPs via liquid phase endocytosis [47]. Thompson et al. [48] used fluorescent labeling to localize the entry of BPs into the intracellular vesicles and indicated that the drug migrates from the intracellular vesicles into the cytoplasm and other organelles in the acidified environment, where they exert a biological effect at the cellular level. Numerous investigations have demonstrated that N-BPs impede bone resorption resulting from OCs differentiation and functional enhancement through the interruption of the RANKL/RANK pathway [49,50]. N-BPs hinder the differentiation of OCs by suppressing the expression of RANKL and TNF and diminishing the expression of RANK [51]. The N-BPs can also inhibit the differentiation of OCs by modulating the non-canonical Wnt/Ca2+/calmodulin dependent protein kinase II pathway [52]. However, the ability of non-N-BPs to inhibit bone resorption was achieved through the indirect reduction of RANKL release and RANK activation, which is accomplished by inhibiting the activity and function of OC precursors [53]. Furthermore, BPs can affect

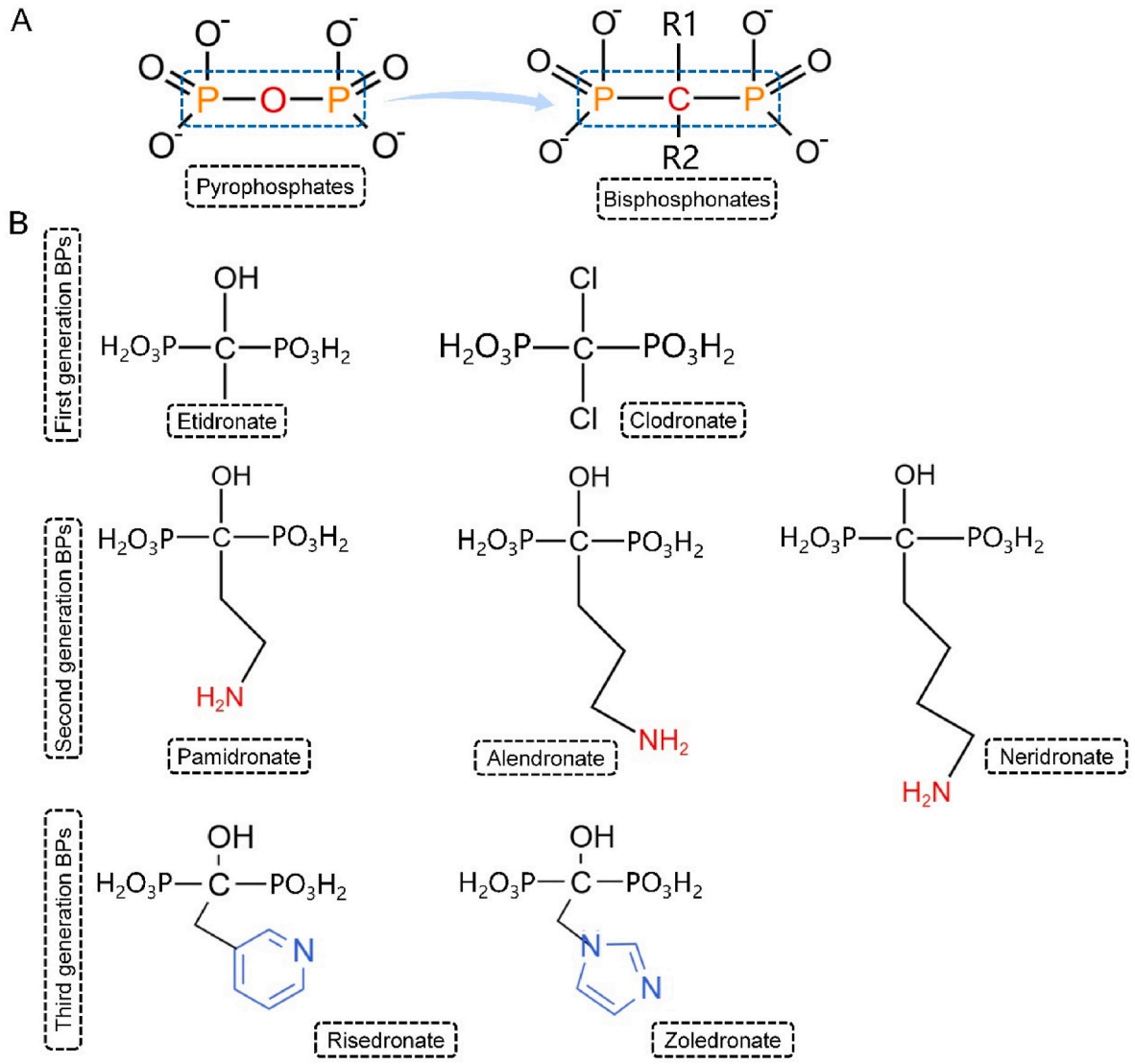


Fig. 2. Chemistry structures of BPs. A) Structural similarities and differences between PPi and BPs. B) Structures of the different generations of BPs used in clinical applications.

OC-induced morphological changes, such as lack of the ruffled border and disruption of actin rings, which may lead to apoptosis of mature OCs and macrophages [54,55]. The above characteristics enable BPs to interact with relevant cellular sites of action, especially OCs, but also osteocytes, OBs, and BMSCs.

2.4. Potential effect of BPs on osteocytes

Previous study has shown that osteocytes regulate cell communication and bone remodeling by exchanging information with OBs and OCs via tubules and dendrites [56]. The regulatory effect of BPs on osteocyte function has also been demonstrated (Fig. 4B). Due to the enormous surface area of osteocytes in an organism [57], BPs can access osteocytes by different means, which depend mainly on the mineral affinity and intrinsic properties of BPs. Fluorescein labeled BP analogs are ingested by the canalicular compartment, which is bathed in extracellular fluid, allowing the BPs to enter the osteocytes [58]. In addition, Weinstein et al. [59] indicated that osteocytes undergo apoptosis in the environment of glucocorticoids, micro-damage, and weightlessness. Lower concentrations of BPs can prevent the pro-apoptotic effect of glucocorticoids and cyclic mechanical loading on OBs [60]. The molecular mechanism of the anti-apoptotic effect of BPs on osteocytes involves the opening of the connexin (Cx)-43 hemichannels followed by activation of the kinase Src and extracellular signal-regulated kinase (ERK) [61]. Therefore, the ability of BPs to induce apoptosis in OCs contrasts with their ability to inhibit apoptosis in osteocytes.

2.5. Potential effect of BPs on osteoblasts

BPs have been shown to activate the proliferation, differentiation, and bone-forming ability of pre-osteoblasts and OBs [62], as well as affect bone metabolism by regulating OCs and OBs (Fig. 4B) [63]. The bone tissue is continuously repaired and maintained in a homeostatic state by osteoclastic bone resorption and growth of osteoblastic bone [64]. It has been shown that BPs cause a decrease in bone resorption and a proportional decrease in bone formation, thereby retarding bone repair [65]. However, in the bone remodeling process, OBs can work independently. Therefore, a reduction in OC activity can be expected to shift the balance between formation and resorption toward increased net bone formation [24,66].

Generally, a low concentration of BPs increases the gene expression of essential molecules for OBs growth (TGF-β1, TGF-βR, and VEGF). TGF-β1 has been shown to stimulate OBs differentiation while inhibiting the RANKL gene expression of OBs to block the RANK/RANKL/OPG

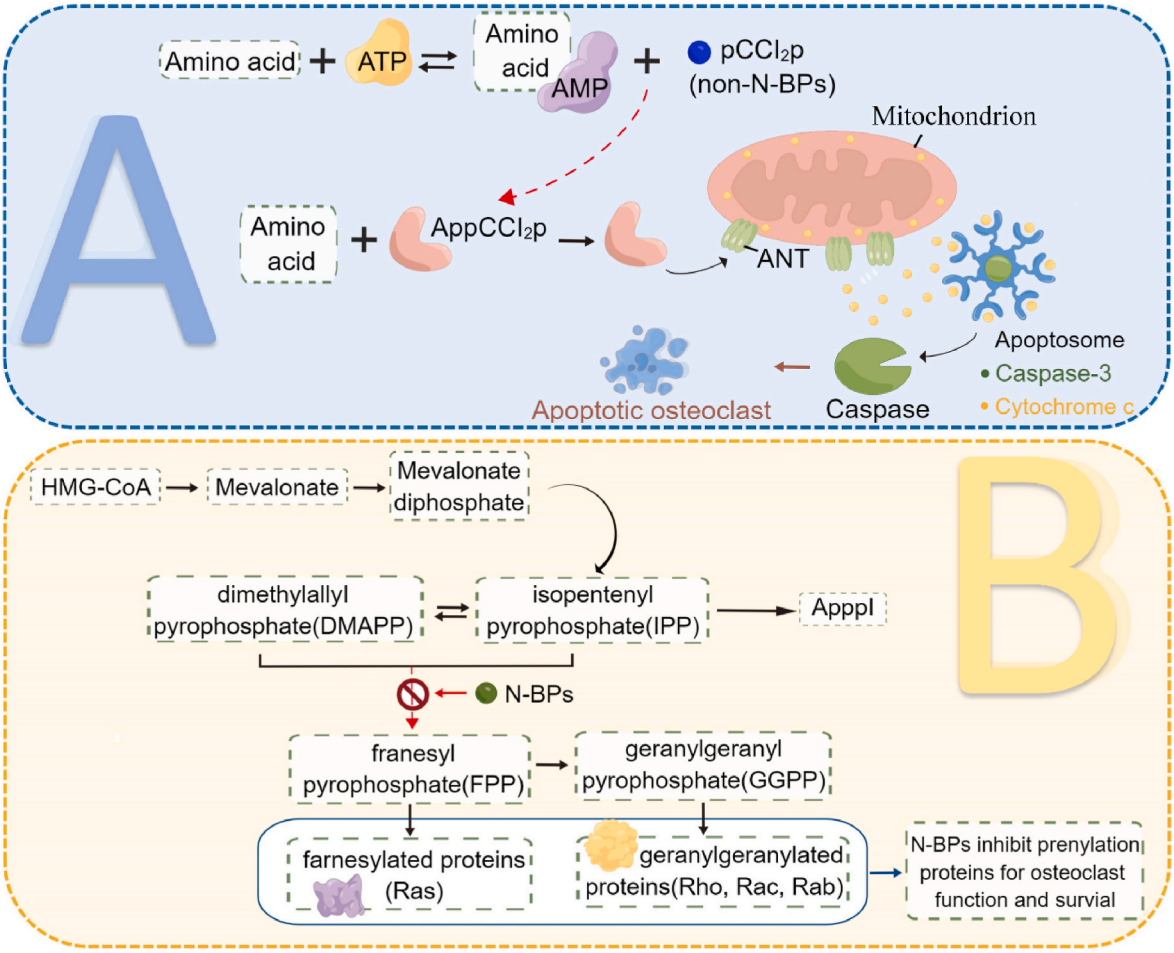


Fig. 3. BPs display different mechanisms of inhibiting OC function and promoting OC apoptosis at the molecular level (By Figdraw.). A) Non-N-BPs, such as etidronate (ETN) and clodronate, are metabolized to cytotoxic analogs of ATP in OCs, which eventually induce OC apoptosis. B) The N-BPs inhibit FPPS in the biosynthesis of mevalonate to restrain the function of OCs and survival, while increasing the accumulation of the ATP analog ApppI and, therefore, induce apoptosis.

system, which is responsible for osteoclastic activation [67]. Hence, BPs promote OBs action while indirectly limiting OCs formation and bone resorption [68]. McLaughlin et al. [69] indicated that BPs have no effect on VEGF receptor mRNA levels but up-regulate VEGF expression manifesting a potential osteogenic regulatory pathway. Internalized BPs also can increase alkaline phosphatase activity (ALP) and upregulate the expression of genes for BMP-2, type-I collagen, and osteocalcin (OCN), which are involved in the formation, metabolism, and regeneration of bone tissue [70,71]. Mulcahy et al. [72] showed that BPs promote OB differentiation by inhibiting the mevalonate pathway. Moreover, similarly to the effect on osteocytes, BPs open the hemichannel of CX43, which activates upstream Src and leads to the release of ERK to prevent OB apoptosis [73].

2.6. Potential effect of BPs on other cells

The OB precursors can internalize BPs, and the deposition of drugs in the cells is time-dependent [74]. The internalized BPs induce the cyclin-dependent kinase (CDK) inhibitor p21 expression and upregulate the gene expression of OCN [75]. The CDK inhibitor p21 plays a crucial part in regulating OB differentiation and interacts with procaspase-3 on the mitochondria to inhibit caspase-3 activation and resist Fas-mediated cell deaths. BPs act on BMSCs to modulate their differentiation by inhibiting adipogenic differentiation and enhancing osteogenic differentiation (Fig. 4C). The potential mechanism is the activation of ERK and c-Jun NH2-terminal kinase (JNK), followed by the increase in Runx2 transcription activity and the decrease in peroxisome proliferator-activated receptor γ2 (PPARγ2) transcription activity [76]. The PPARγ2 is the most essential studied transcription factor in adipogenesis [77].

3. Optimal concentration of BPs for osseointegration

The suitable concentration of BPs in the desired area has important implications for promoting osseointegration of drug-releasing implants [78]. Li et al. [79] found that BPs exhibited a significant inhibitory effect on OCs formation at the concentration of 10^{-6} M, which was further augmented at the concentration of 10^{-5} M. However, the inhibitory effect of zoledronic acid diminished at a concentration of 10^{-4} M, with no additional dose-dependent increase observed. Simultaneously, at concentrations of 10^{-10} M, BPs exhibit a promoting effect on the formation of osteoclast-like cells [80]. Additionally, the low concentrations of BPs have the potential to enhance OBs proliferation and promote osteogenic differentiation, whereas high concentrations have a notable inhibitory effect on OBs activity [81]. In a study conducted by Im et al. [82], found that BPs facilitated the expression of osteogenic genes and cell proliferation at concentrations $<10^{-7}$ M, with the most pronounced osteogenic effects observed at concentrations of 10^{-8} M. In contrast, BPs demonstrate an inhibitory effect on OBs proliferation at concentrations exceeding 10^{-4} M. According to the findings of Von Knoch and Lei et al. [83,84], the concentration of 10^{-8} M BPs stimulates both proliferation and viability of BMSCs, whereas at concentration ranging from 0.5–1 × 10^{-5} M inhibited the proliferation and osteogenic differentiation of BMSCs. At the same time, BPs at various concentrations ranging from

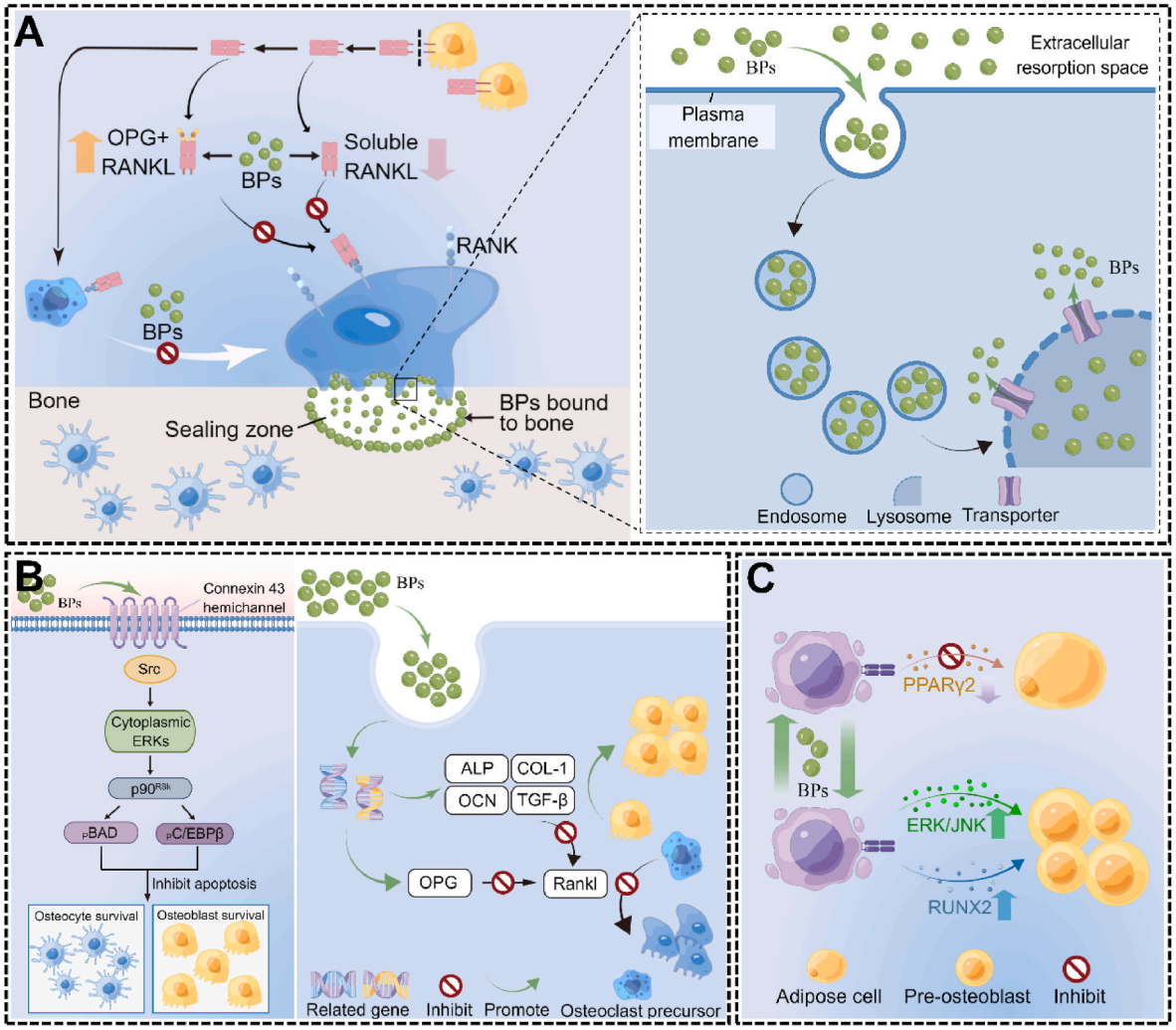


Fig. 4. Effects of BPs on multiple cell types at the cellular level (By Figdraw.). A) BPs regulate OC activity via manipulating the OPG/RANKL signal pathway, and OCs also take up BPs to exert an intracrine action. B) The BPs can promote various cells (osteocyte and OB) survival, induce the osteogenic differentiation of mesenchymal stem cells, facilitate the expression of osteogenic genes, and inhibit the recruitment and differentiation of OCs precursor cells through multiple different mechanisms. C) BPs promote osteogenic differentiation and inhibit adipogenic differentiation of BMSCs.

10^{-8} M to10^{-7} M enhance bone mineralized deposition by BMSCs [85]. On the contrary, this drug inhibited bone nodule formation at the concentration of 10^{-4} M [86]. Wang et al. [87] have determined that adipose derived stem cells (ADSCs) undergo osteogenesis promotion in the presence of BPs, with an optimal concentration range of 0.5–1 × 10-7 M, while concentrations exceeding 10-4 M result in inhibition. The aforementioned dual effect can be partially attributed to the downregulation of osteogenic genes, including Col, ALP, OCN, and RUNX, as BPs concentration increased [88]. Notably, the reduction in ALP expression can impede the mineralized deposition process. Hence, the suitable drug concentration can efficaciously impede the generation of OCs, stimulate the proliferation and differentiation of OBs and stem cells, and consequently augment the osseointegration potential of implants.

4. Methods of fabricating BP-coated implants

The appropriate drug release profile is the main factor in maintaining local drug concentrations and enhancing osseointegration in the desired area [89]. The condition of drug release depends on a combination of factors, such as the drug properties and the method and materials of loading BPs. Thus, the multivalent interactions between BPs and supported materials have paramount importance for osseointegration [90]. To understand the interactions, it is essential to have detailed knowledge on the mechanisms of constructing BP-coated implants. Improved bonding of BPs to the implant requires pretreatment of the surface. Using the surface modification of physical deposition technique and wet chemical deposition technique to form the calcium phosphate (CaP) or HA coatings is a very attractive approach because BPs have a marked affinity to the substances [91]. Alternatively, the polymer coatings, including layer-by-layer (LBL), polymer brushes, dip coating, Langmuir–Blodgett, spin, and plasma-based coating methods, are also capable of loading BPs [92,93]. In this section, we focus on the mechanism of fabricating BP-coated implants (**Table 1**).

4.1. Chemical bonding

HA is a form of CaP and the substance that makes up a major inorganic bone component, which has been an excellent delivery medium for drugs [94,95]. BPs are constantly combined with a substrate of CaP or HA coating, to form a bio-functional coating which possesses the ability to promote new bone formation and osseointegration with the host tissue (Fig. 5A) [96]. Alghamdi et al. [97] indicated that compared to direct adsorption of BPs on the implant surface, the construction of CaP/BP-coated implants could increase peri-implant bone contact (BIC) and volume (BV). Moreover, the newly formed bone can be clearly distinguished from the old bone in the bone/implant interfacial area.

Table 1
Methods of fabricating BP-coated implants.

Description	Advantages	Challenges	Typical example
Chemical Bonding			
Implant surface is coated with CaP, HA, and materials containing Ca^{2+}, which allows for the adsorption of BPs onto the surface via weak van der Waals forces.	No complicated implant surface modification. The release performance of BPs is commendable.	Uncontrolled adsorption and release from the surface.	The complete release of BPs (adsorbed onto calcium titanate) upon exposure to bodily fluids has been demonstrated [132].
Physical Adsorption			
BPs are adsorbed onto the implant surface via non-covalent interactions, including electrostatic adsorption and hydrophobic interaction.	The methodology of preparation is comparatively uncomplicated.	The binding force may be relatively weak, and attention should be paid to stability and persistence	The titanium surfaces immobilized with BPs demonstrated a protracted discharge of varying BPs concentrations, contingent upon the initial concentration of BPs [109].
Covalent Attachment			
Cross-linking agents or their precursors are coated on the surface, which subsequently react with BPs to establish a durable covalent cross-linked architecture.	The stable binding of BPs to the interface can be achieved.	BPs may be released incompletely *in vivo*. This approach necessitates intricate chemical manipulation and regulation, thereby augmenting the intricacy and expenditure.	The covalent grafting of amino groups on implant surface results in an approximately two-fold increase in ALN adsorption [115].
Carrier Systems (Porous materials and Organic material films)			
Porous materials (Mesoporous materials, nanoparticles, and nanotubes) and organic material films (CHI, PCL, and PLGA) are employed as carriers for coating the BPs on the implant surface.	The systems exhibit a substantial specific surface area, encapsulation capacity, and regulatory potential, thereby providing more binding sites, facilitating sustained and controlled release effects of BPs.	The generation of a local acidic microenvironment resulting from porous materials or organic materials degradation will impact biocompatibility.	The mesoporous SiO2 coating of implant surface leads to an approximately three-fold increase in BPs adsorption [126].

Currently, it is commonly used in combination with BPs to construct bio-functional coatings with well-crystalized, noncarbonated HA [$Ca_{10}(PO_4)_6(OH)_2$]. The type of HA presents two different coordination environments of calcium ions depending on the various amounts of oxygen-coordinated spheres: Ca (1) (nine oxygen coordination spheres) and Ca (2) (six oxygen coordination spheres). The ≡Ca–OH has been proven to be the functional group that binds to BPs [98]. Briefly, BPs have a strong affinity to HA crystals by the following mechanisms: 1) BPs strongly coordinate to HA via a bidentate chelating bond between phosphonate groups and calcium ions [99]; 2) BPs can bind specifically to the bone mineral by the R1 and R2 groups that branch from the quaternary carbon of BPs [100]. The R1 group can coordinate with calcium ions to enhance affinity with bone. Moreover, the R2 group not only determines the biological function of BPs but also directly binds to the HA surface hydroxyl group through its hydrogen bond [101]. The electrical charges of BPs are influenced by the nitrogen atom in the R2 group, which plays a vital role in pharmacological properties, including their effects on HA [102]. The binding of BPs to HA would confer a charge at the mineral surface through the nitrogen present in the R2 side chain, thereby leading to a discernible alteration in zeta potential [103]. The alterations in zeta potential have an impact on the subsequent attachment of electrically charged molecules and the overall quantity of BPs that can be adhered to the HA surface. Russell et al. [104] indicated that ALN, ZOL, and ibandronate could induce a more positive zeta potential on the HA surface at PH 7.4, and thereby may attract additional BPs with negatively charged phosphonate moieties. The binding of RIS can generate a more negative zeta potential on HA surface, which may limit the further accumulation of BPs, and lessen the maximum binding capacity on the crystal surface. Therefore, studies are needed to find the optimal type of BPs for immobilization on the surface.

4.2. Physical adsorption

To construct BP-carrying coatings, organic compounds, such as amino and carboxyl groups, can be incorporated into the implant's surface to introduce active functional groups and change the surface charge properties. In comparison with the formation of covalent bonds, the electrovalent bonds from electrostatic interaction between BPs and implant surfaces are simple to manipulate and are favorable to maintain the bioactivity of drugs and proteins. Well known as a natural anticoagulant, heparin belongs to pentosan, which is synthesized by the liver, mucous membranes, and lungs [105]. Due to its carboxyl groups and negative charge, heparin has a high affinity with many bioactive substances. In particular, the negatively charged heparin can adsorb positively charged drugs through electrostatic interaction [106]. To impart the amine groups for the implant surface, the implant must be pre-treated with dopamine (DOPA) [107]. Subsequently, heparin is grafted onto the aminated implant's surfaces by chemical conjugation with the carboxyl group in heparin [108]. The net charge of BPs can transition from a negative charge to a positive charge in an acidic environment (Fig. 6A) [109]. Therefore, heparinized implants exhibit direct integration with BPs in an acidic buffer environment with a pH of 5.6, thereby ensuring optimal drug loading capacity. Meanwhile, the stable electrostatic interaction between BPs and the heparinized implants also slows the release rate of drugs. The heparinized coating method reduces the initial burst release of BPs and ensures the superior sustained release profile [110,111].

4.3. Covalent attachment

Multilayer fibrinogen films are also utilized to functionalize implant surfaces with immobilizing N-BPs. Glutaraldehyde is bound to 3-aminopropyltriethoxysilane (APTES) coated implant surfaces to serve as an anchor for fibrinogen attachment. The multilayers of fibrinogen are then conjugated to the implant surface via the 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide/N-hydroxysuccinimide (EDC/NHS) coupling reaction (Fig. 5B). The carboxyl group on the surface of EDC-activated fibrinogen then binds to the amino group of N-BPs, causing the N-BPs to be stably bound to the implant surface [112]. The reason for using EDC/NHS crosslinked multilayers of fibrinogen is to increase the mechanical stability of the BP containing film, possibly increasing the number of carboxyl groups in which BPs can be immobilized, and protect the significant components of coatings from rapid enzymatic cleavage [113]. In addition, amino-silane coupling agent 3-aminopropyltrimethoxysilane (APTMS) is used to graft amino groups on the implant surface [114]. Subsequently, N-BPs can combine with the amino-modified implant surface by the strong chemical interaction between the phosphonate groups in N-BPs with the amine groups (Fig. 5C) [115].

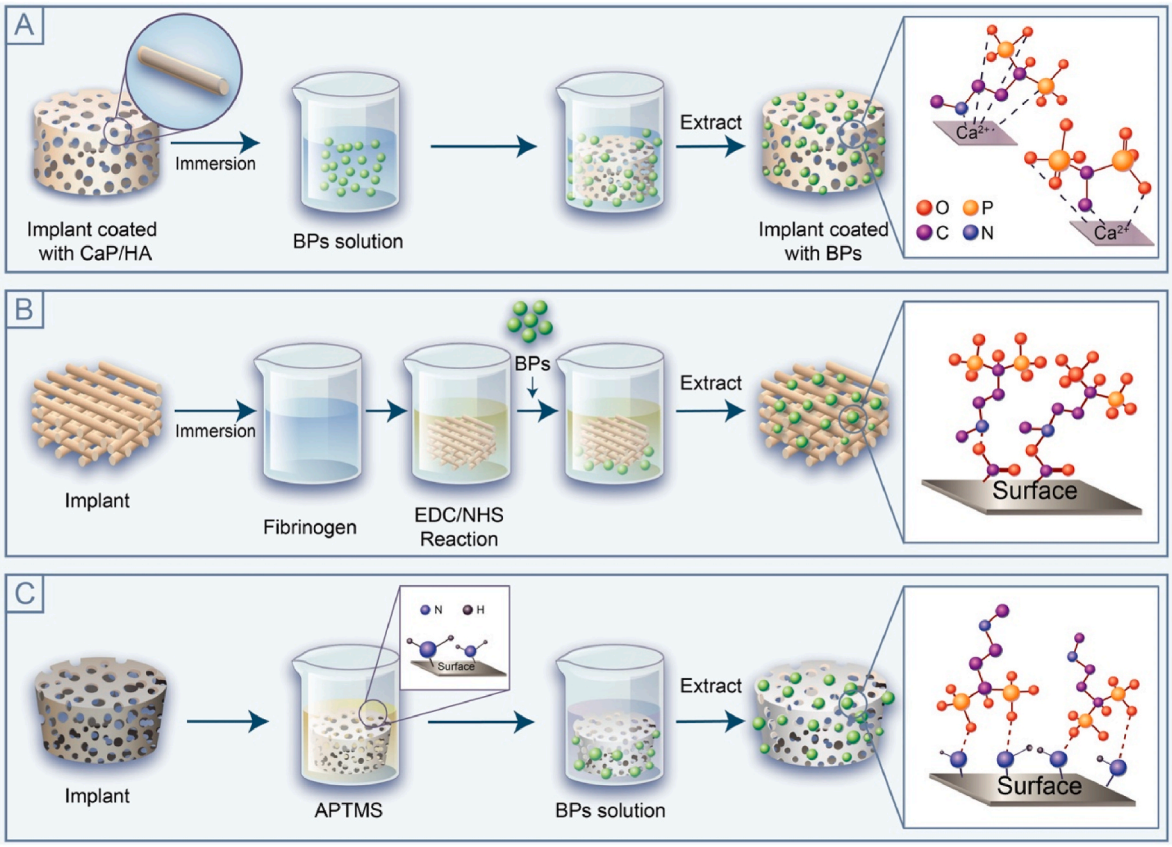


Fig. 5. BP-coating strategies. A) Binding materials containing calcium ions to the implant surface and immersing in BPs solution. B) EDC/NHS activated carboxylic group of fibrinogen surface binds to the amino group of N-BPs to form the BP coating. C) BPs coated on the implant by combining with the surface modified by APTMS.

4.4. Carrier systems

4.4.1. Porous materials

Porous materials, which have been investigated as drug-delivery carriers for more than a decade, may provide a more advantageous alternative to achieving controlled and localized drug delivery (Fig. 6B). Using porous materials in drug delivery increases drug efficiency and safety, overcomes the drug's pharmacokinetic and pharmacodynamic limitations, enhances the bioavailability, increases drug stability, optimizes doses, and reduces side effects [116,117]. According to the International Union of Pure and Applied Chemistry (IUPAC), porous materials are classified into three categories by their pore sizes. That is, microporous when the pore size is below 2 nm, mesoporous (2–50 nm), and macroporous (>50 nm) [118]. Among them, mesoporous titanium oxide (TiO_2) [119], silicon oxide (SiO_2) [120], and mesoporous bioactive glasses [121] are the most studied coating materials, due to their biocompatibility and low toxicity without any pH value decreases. Moreover, the large specific surface area of mesoporous materials can be selectively modified to ensure higher drug loading into the framework for sustained release ability [122].

Mesoporous material coatings can be fabricated by a sol–gel process using pluronic copolymers to template the mesopore formation on planar and three-dimensional metal, which has been studied extensively [123]. As water-soluble drugs, BPs can enter the empty space of mesoporous material coatings by simple diffusion, which can be used as a drug-delivery system (i.e., as an ideal drug-storage matrix that can locally deliver drugs over a suitable duration after implantation). Depending on the material properties and the concentration difference between BPs and coating materials, the release rate can be tuned [124]. Moreover, the adsorption of BPs can be effectively controlled by the appropriate variation of the functionalization degree of the surface of mesopores [125]. Balas et al. [126] covalently grafted amine groups to the silanol groups on the mesoporous SiO_2 surfaces, and the BPs adsorption increased almost three-fold, which subsequently improved the local drug concentration. Therefore, a well-designed mesoporous structure and surface functionalization degree could control the adsorption and release of BPs. Although the excellent performance of loading BPs of mesoporous material coatings has been achieved, some challenges remain. For example, the implant coating with mesoporous materials is usually synthesized using the redispersion method, resulting in the coating easily falling off [126]. Low efficiency of loading BPs is another major challenge. Many drugs remain in the solution without entering the mesoporous interior, resulting in drug waste. Future studies should focus on overcoming these hurdles.

4.4.2. Organic material films

Except for the above-mentioned methods, organic materials can also incorporate BPs to form a thin layer on the implant's surface, working as a functional coating (Fig. 6C). Organic materials such as high-molecular materials or polysaccharides polymers have many advantages including low toxicity, suitable biocompatibility, and hemocompatibility, which have been studied for loading BPs [127]. Korn et al. [128] prepared a functionalized surface via coating the Ti implant surface with chitosan (CHI) that incorporated ZOL in its matrix. This ZOL-CHI composite coating significantly increased the peri-implant bone formation and enhanced the stability of the implant. The striking feature of this drug-material composite coating method is that the synthesis process is simple and has versatile surface functionalization. After the BP-loaded film was combined with the surface of the implants, the conjugated interactions were disrupted due to progressive degradation of the coating

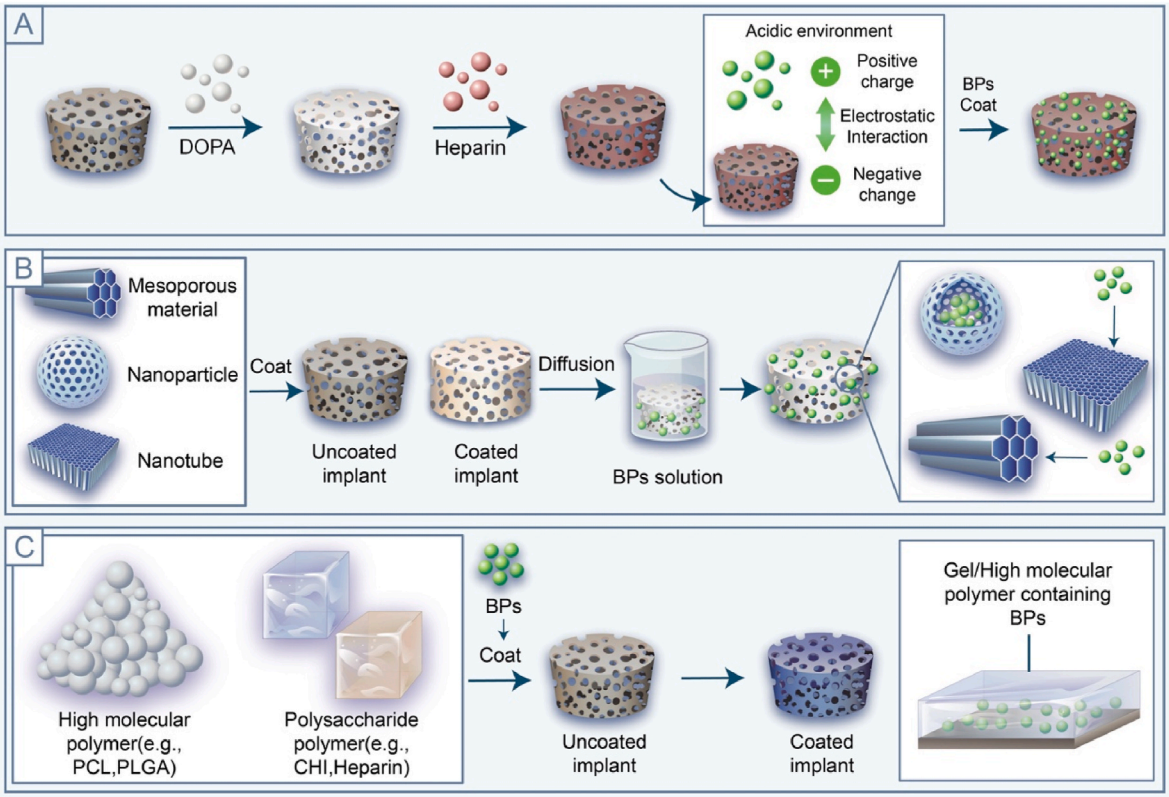


Fig. 6. BP-coating strategies. A) In an acidic environment, BPs that present a positive charge are coated on the negatively charged surface by electrostatic interaction. B) BPs can incorporate into porous materials, including mesoporous materials, nanotubes, and nanoparticles, to form drug coatings. C) High-molecular polymer and polysaccharide polymers encapsulate BPs to form composite coatings on the implant surface.

materials. For instance, polycaprolactone (PCL) films have a long degradation period, resulting in sustained drug release for months in cases where polymer matrix degradation is the cause of drug release [129]. However, some kinds of organic polymers present a fast degradation rate, which causes an initial burst release from the composite coating implant [130,131]. Therefore, future trials should aim to improve the drug release properties by effectively controlling the coating material profiles, such as coating thickness and degradation kinetics.

5. Role of BPs as coatings to promote osseointegration

BPs are loaded on the implant surface in various coating strategies, which are employed to effectively improve the binding stability of orthopedic implants and promote bone regeneration and osseointegration. Thus, ideal BPs coatings need to possess good osteogenesis, osteoinductivity, and osteoconductivity [133,134]. The coating materials used to load BPs are mainly divided into inorganic materials (e.g., HA, CaP, TiO_2, and SiO_2), and organic materials, such as chitosan (CHI), fibrinogen, gelatin, and poly (DL-lactic acid) (PDLLA). In addition, the organic-inorganic hybrid materials that load BPs are also utilized to promote osseointegration. In this section, we summarize the different kinds of BP coatings and discuss their loading strategies, release profiles, and the regulation of bone formation. Furthermore, we discuss the osseointegration ability of BP-coated scaffolds.

5.1. BP-coated with inorganic materials

Most inorganic materials (e.g., CaP or HA) are similar to the inorganic part of human mineralized tissues, which can form a stable combination with BPs via bidentate structure connections. Moreover, several porous materials (e.g., mesoporous TiO_2, nanotube TiO_2, and mesoporous SiO_2) can adsorb BPs through suitable pore sizes (**Table 2**).

5.1.1. CaP

CaP or HA are bioactive materials that possess a chemical composition akin to that of natural bone tissue, predominantly comprising phosphate and calcium ions [135]. These materials are non-immunogenic and do not elicit significant rejection responses. The tunable microstructure and pore characteristics of CaP and HA enable the promotion of cellular adhesion, proliferation, elongation, and mineralization process [136]. Due to these excellent biocompatibility, bioactivity, and biodegradability, CaP and HA coatings have been utilized for bone regeneration and osseointegration [137]. However, long-term use if HA-coated implants leads to adverse effects on the bone matrix, and a consequent inflammatory response, which induces implant loosening [138]. In osteoporotic conditions, the osteolysis phenomenon is further intensified. Applying BP-CaP composite coatings could inhibit peri-implant osteolysis, and increase peri-implant bone formation, bone mineralization, and the mechanical stability of the implants [139]. Bigi et al. [140] directly deposited ALN to modify HA thin films on Ti substrates, which could promote OB differentiation and inhibit OC proliferation. Some *in vivo* studies had indicated that the ALN-HA composite coating can reduce peri-implant high bone turnover, improve bone-implant integration and implant stability, and simultaneously inhibit particle migration [139,141].

Because BPs have different affinities for minerals (ZOL > ALN > Ibandronate > RIS > ETN > clodronate) [142], the selection of BPs for drug coatings affects the osseointegration. According to Niu et al. [143], ALN-HA composite coatings increase BIC ratios, bone mass augmentation, bone mineral density (BMD), and implant stability in the peri-implant region, which is more potent on peri-implant bone. Furthermore, RIS-HA composite coatings, which have a significant systemic effect, are more effective on non-*peri*-implant bone, particularly

Table 2
BP-coated with inorganic materials.

Material	Type of BP	BP delivery system	Experimental trial	Most important contributions	Ref.
HA	ZOL	ZOL chemically bonded with HA coated on Ti intramedullary nails	*In vivo* (rat)	The mean bone area in the peri-implant bone region was significantly greater. The average peak pullout force was greater.	[96]
HA	ZOL	ZOL chemically bonded with HA-coated Tantalum	*In vivo* (canine)	The mean extent of bone ingrowth was significantly higher in the ZOL coated group.	[139]
HA	ALN	ALN chemically bonded with HA-coated Ti	*In vitro*	Promoted osteogenic gene expression. Reduced OCs proliferation.	[140]
HA	ALN	ALN chemically bonded with HA-coated Ti	*In vivo* (rabbit)	ALN-HA coating reduced peri-implant high bone turnover, improved bone-implant integration, bone quality, and implant stability.	[141]
HA	ALN/RIS	BPs combined with HA-coated Ti alloy	*In vivo* (rabbit)	ALN-HA coating induced higher BIC ratio, bone mass augmentation, BMD, and implant stability in the peri-implant region.	[143]
HA	ZOL/PAM/ Ibandronate	BPs chemically bonded with HA-coated Ti	*In vivo* (Ovariectomized [OVX] rat)	BPs promoted bone/implant integration and bone formation around implants.	[144]
HA	ZOL	ZOL chemically bonded with HA-coated Ti	*In vitro* and *in vivo* (OVX rat)	Appropriate concentration could increase the mechanical fixation of the coated implants.	[146]
HA	ALN	ALN chemically bonded with HA-coated Ti	*In vitro*	HA-ALN significantly promoted apoptosis of OC-like cells.	[149]
Material	Type of BP	BP delivery system	Experimental trial	Most important contributions	Ref.
HA	ALN	ALN + Fe_3O_4 combined with HA nanocrystal coated PCL substrate	*In vitro* and *in vivo* (OVX rat)	Inhibited osteoclastic activity, promoted OBs proliferation and differentiation, enhanced implant osseointegration and bone remodeling.	[173]
HA	ZOL	ZOL chemically bonded with HA-coated Ti	*In vivo* (OVX rat)	ZOL coated groups promoted bone healing around the implant.	[174]
HA	ALN	ALN chemically bonded with HA-coated Ti	*In vivo* (dog)	Local elution of ALN increased peri-implant bone.	[175]
CDHA[a)]	ALN	ALN chemically bonded with CDHA coated Ti alloy	*In vitro*	ALN/CDHA coating played a significant role, and optimum ALN content in the local area benefited OBs proliferation.	[176]
HA	ZOL	ZOL/HA + Sr/HA-coated Ti substrate	*In vitro*	Enhanced extracellular matrix deposition and reduced OCs proliferation.	[177]
nCaP	ALN	ALN chemically bonded with nCaP coated Ti	*In vivo* (OVX Rat)	ALN/nCaP composite coating increased BIC and BV[b)]	[97]
CaP	ALN	ALN chemically bonded with CaP-coated Ti	*In vitro*	Suppressed fibroblast proliferation, enhanced OB proliferation and ALP activity.	[151]
CaP	ZOL	ZOL chemically bonded with CaP-coated Mg–Sr alloy	*In vitro*	ZOL-CaP coating could regulate the crosstalk of OBs-OCs and increased the ratio of OPG/RANKL.	[178]
CaP	ALN	ALN chemically bonded with CaP-coated Tantalum	*In vivo* (rabbit)	The percentage of the length of implant that was in contact with new bone in the BPs coating group was increased by an average of 804%.	[179]
Mesoporous TiO2 film	ALN	ALN adsorbed into mesoporous TiO2 coated Ti	In vitro	ALN was reserved for a long time in the vicinity of the implant and improved the mechanical fixation of the bone anchored implant.	[155]
Material	Type of BP	BP delivery system	Experimental trial	Most important contributions	Ref.
Mesoporous TiO_2 film	ALN	ALN adsorbed into mesoporous TiO2 film coated Ti	*In vivo (rabbit)*	ALN/TiO2 composite coating enhanced apatite formation and increased bone density.	[158]
TiO_2 film	ALN	ALN adsorbed into TiO_2 coated Ti substrate	*In vitro*	ALN/TiO2 composite coating surface enhanced the biocompatibility of Ti.	[180]
Mesoporous TiO_2 film	ALN	ALN adsorbed into mesoporous TiO2 film coated Ti	*In vitro*	When ALN was released from the coating, the surface became completely covered with apatite.	[181]
Nanotube TiO_2	Ibandronate	Ibandronate adsorbed into nanotube TiO2 coated Ti	*In vivo (rat)*	Ibandronate coating significantly improved the degree of osseointegration.	[159]
Nanotube TiO_2	Ibandronate	Ibandronate adsorbed into nanotube TiO2 coated Ti alloy	*In vivo (rat)*	A higher level of BV/TV, trabecular thickness and separation, more increased bone contact, and larger percentage of the bone area were presented.	[182]
MSNs/HA	ZOL	ZOL adsorbed into MSNs/HA-coated Kirschner wire substrate	*In vitro*	The loading capacities of ZOL increased almost eight-fold, and MSNs retarded ZOL release to achieve sustained release and exerted an inhibitory effect on OCs.	[163]
TiO2/CaP	ALN	ALN adsorbed into TiO2 nanoporous/CaP-coated steel	*In vivo (rat)*	Surface immobilized ALN showed a better osseointegration than systemically delivered.	[153]
CPC	ALN	ALN is chemically bonded with CPC to form surface coating	*In vitro* and *in vivo* (OVX rat)	The relatively low dose of ALN increased bone formation in the peri-defect region.	[16]
Material	Type of BP	BP delivery system	Experimental trial	Most important contributions	Ref.
BCP	ALN	ALN was chemically bonded with BCP scaffold to form surface coating	*In vitro*	ALN-eluting BCP scaffolds exhibited increased ALP activity, calcium deposition, and gene expression.	[168]
PDD	ALN	ALN was anchored inside PDD	*In vitro* and *in vivo* (rat)	ALN-PDD enhanced MSC migration and osteogenic differentiation and inhibited the formation and function of OCs.	[172]

[a] Carbonated calcium deficient hydroxyapatite, CDHA.
[b] Bone volume, BV.

the lumbar vertebrae. Additionally, ibandronate coatings obviously increase the number of trabecular and connectivity density, while ZOL has more striking effects on increasing trabecular thickness, bone volume, and osseointegration [144].

There are several possible explanations for this mechanism. One is a nitrogen-containing ring on the side chain, leading to the high affinity of N-BPs to CaP, which may be responsible for this mechanism. The second is that N-BPs, especially ZOL, are more effective than ibandronate and PAM in converting the bone turnover in osteoporosis to a positive balance of bone formation and bone resorption [145]. Moreover, the loading amount of BPs by the implant surface coatings have an essential influence on implant osseointegration. In an *in vivo* trial, the maximal pullout force was reduced for the implants loaded with 16 μg ZOL compared to the 2.1 and 8.5 μg implant [146].

The bone condition in the drug release area is also one of the factors affecting the action of BP-HA coatings. Compared to normal bone, osteoporosis provides a larger region to be exposed to the BP-HA coating; the local resorption and osteoclastic activity at the implantation site are also stronger [147]. In this condition, immobilized BPs not only reduce the implant loosening associated with particulate debris, but also inhibit the osteolysis and osteoporotic bone loss at the peri-implant area, to alter the dynamic equilibrium of bone metabolism that favors the formation of stronger bone [97]. Synthetic crystalline nano-HA crystals (nHA) are beneficial materials due to their specific physicochemical properties (e.g., increased specific surface area, biodegradability, and available surface ionic sites), and improved biological affinity in terms of favorable cell proliferation because of their similarity with biological cells (Fig. 7A and B). *In vivo*, the nHA-ALN composite coatings enhanced osseointegration and accelerated bone remodeling in osteoporotic conditions (Fig. 7C) [148]. Thus, the combination of nHA with BPs and subsequent deposition on the surface as a coating on implants represents an approach with high potential to improve implant fixation and osseointegration [149].

In addition to regulating OB-OCs homeostasis, BP-HA composite coatings have regulatory effects on other cells to promote implant osseointegration. The aggressive fibroblasts at the bone surface can produce pro-inflammatory osteoclastogenic cytokines to activate osteoclast-genesis, suppress OBs functions, and create an inflammatory microenvironment, which may subsequently induce osteolysis and implant aseptic loosening [150]. Hu et al. [151] found that BP-CaP coatings, especially the highly potent N-BP coating, can inhibit fibroblast proliferation and increase apoptosis. With progressive apoptosis of fibroblasts induced by the ALN release from coatings, the cells on the Ti–CaP-ALN substrates were predominantly OBs after co-culture. Thus, the BPs and inorganic materials coated surface have excellent potential to reduce fibrous encapsulation and provide another positive effect on

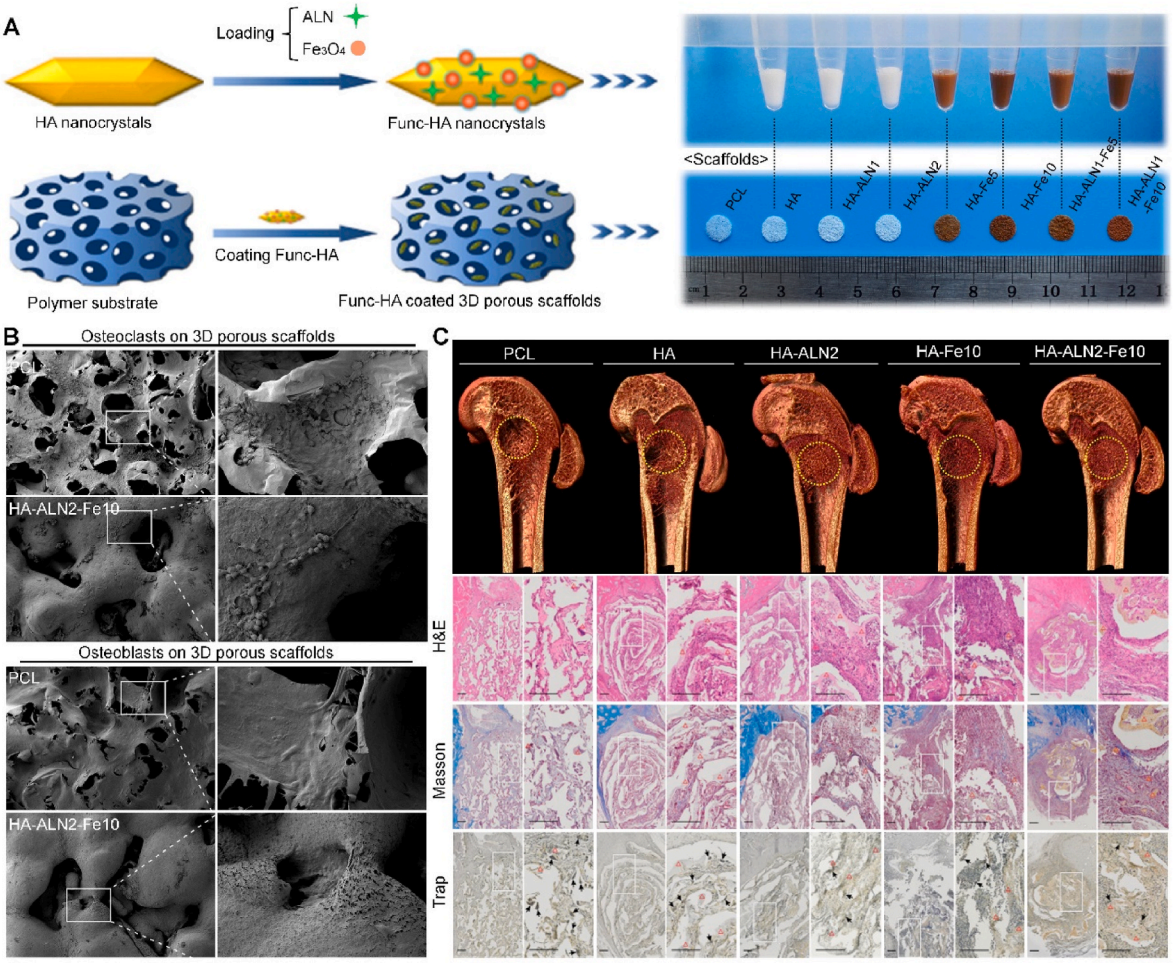


Fig. 7. ALN functioned HA nanocrystals coated on the 3D porous scaffold for osteoporotic bone reconstruction. A) Preparation of func-HA nanocrystals and func-HA added 3D porous scaffolds. B) scanning electron microscope (SEM) photographs of OBs and OCs cultured on uncoated and functioned HA-ALN-coated scaffolds at seven days. (Left image, scale bar = 100 μm; right image, scale bar = 10 μm). C) Three-dimensional reconstructed images of mineralized bone formation and hematoxylin and eosin (H&E), Masson's trichrome, and Trap staining analysis of cavity defects at 4 weeks post-surgery (Red triangle, implanted scaffolds; black arrows, OCs.). Reproduced with permission from Ref. [148] (Copyright 2018, ACS Applied Materials Interfaces). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

osseointegration.

5.1.2. Porous materials

Porous materials, especially mesoporous materials, have been utilized to effectively control BP delivery and release; their high pore volume and large surface area guarantee a high BP-loading capacity, and the ordered porous network enables the fine control of BP loading and release kinetics [152]. Chemically inert mesoporous oxides are suitable to develop drug coatings because they can easily bind to low molecular substances. Therefore, the mesoporous TiO_2 [153], mesoporous SiO_2 [154], and mesoporous bioactive glasses [155] are the most studied coating materials. Karlsson et al. [156] deposited mesoporous TiO_2 thin films onto Ti implants and subsequently loaded with ALN. In that study, Raman spectroscopy demonstrated that a concentration of 0.1 mg/mL of ALN completely hindered biomineralization at the surface (Fig. 8A–C); therefore, 0.1 mg/mL of ALN is too high a concentration to achieve the desired therapeutic outcome.

When ALN was loaded into the mesoporous coating, the appropriate concentration of ALN was provided to the surroundings, allowing the formation of apatite. Additionally, bone tissue with ALN was overall more mature than without ALN, and the bone formed was almost identical to the native bone after 4 weeks of healing. Due to its long half-life (in the order of years) at random sites in the skeleton, systemic distribution of high doses of ALN may be detrimental [157]. The distribution in the skeleton is also uneven, with the least in the middle of long bones and the highest localization at bone growth plates. Harmankaya et al. [158] loaded 14C labeled ALN into the mesoporous TiO_2, and cross-sections of the implant/bone interfaces were examined *ex vivo* using autoradiography, which confirmed that the distal transport of released 14C-ALN was extremely low.

The empty space within the TiO_2 nanotube (TNT) coatings can also be used as a BP-delivery carrier that can accelerate osseointegration by

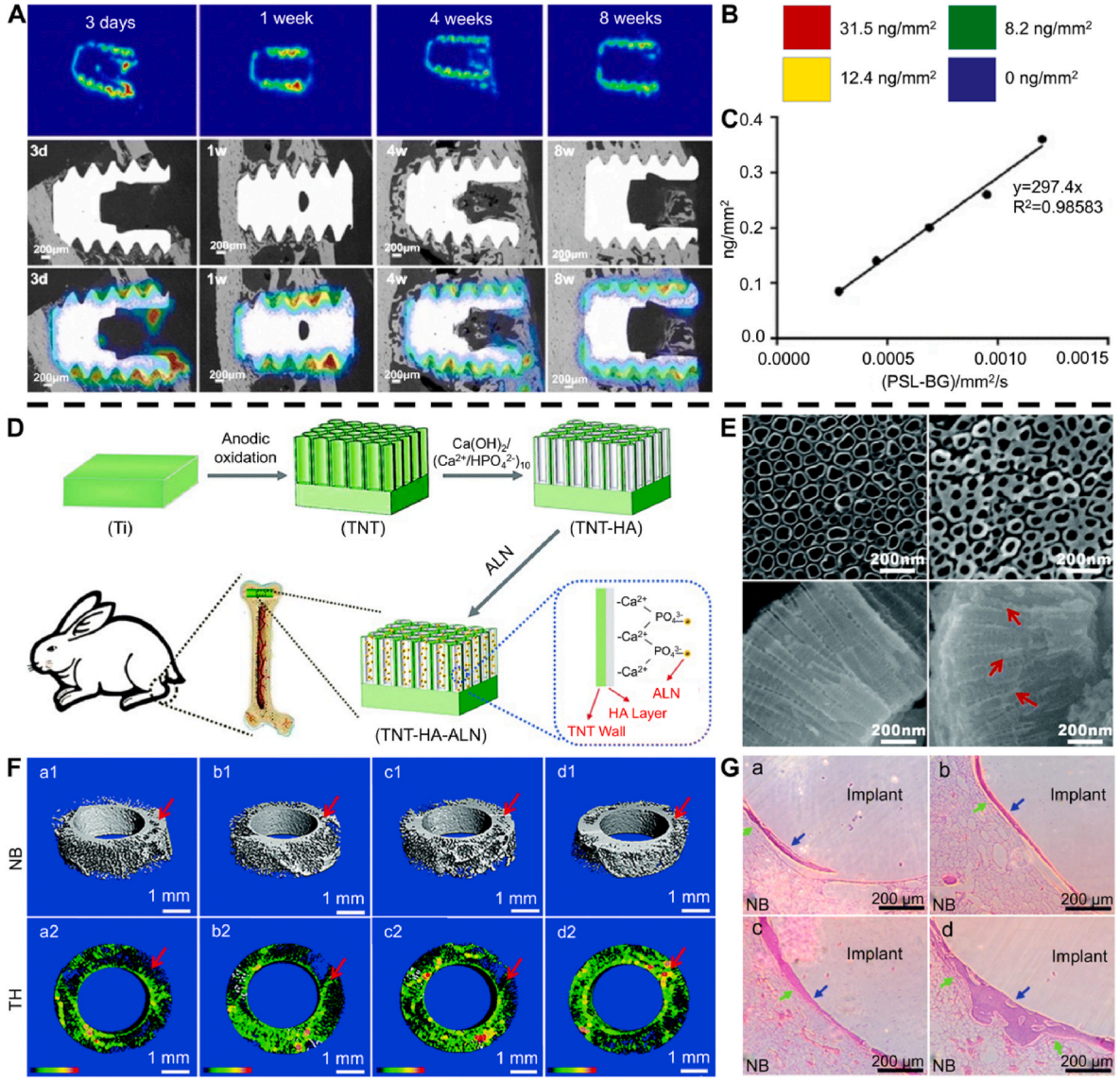


Fig. 8. TiO_2 porous materials loaded BP-coated implants for improving bone formation. A) Timeline of autoradiographic images with the different time points of bone formation. B) Color scale of autoradiographic images. C) Curve indicating a correlation between radioactivity and the amount of ALN (ng/mm^2). Reproduced with permission from Ref. [156] (Copyright 2015, Journal of Materials Science). D) ALN-loaded HA-TiO_2 nanotubes improve local femoral epiphysis osseointegration. E) Surface morphology images of SEM for different substrates. F) Micro-CT images of new bone formation (a1–d1) and trabecular thickness (a2–d2) around different implants (a gradual increase from black to red). G) H&E staining analysis of uncoated and coated implants after surgery for 3 months (NB, natural bone; blue arrows, newly formed bone; green arrows, transitional region). Reproduced with permission from Ref. [162] (Copyright 2016, Journal of Materials Chemistry B). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

promoting osteoblastic functions as well as by suppressing OC activities [159]. The removal torque, BMD, and degree of bone-formation marker expression increased after ibandronate was adsorbed into an anodized implant with a nanotube structure. Due to the moderate corrosion resistance, porous structure, and good wear resistance, micro-arc oxidation (MAO) has been widely used to modify implant surfaces [160]. The ETN-MAO coating significantly improves the cytocompatibility and osteogenic performance due to the biological functions of ETN and the improved corrosion resistance [161]. Besides, the ALN-loaded HA and TiO_2 nanotubes (TNT-HA-ALN) hybrid coatings can facilitate the interactions between cells and materials, and improve the ALN loading amount and effectively regulate its release (Fig. 8D and E) [162].

When the TNT-HA-ALN implant was inserted into an osteoporotic rabbit, the surface nano-geometry and nano-HA layers facilitated OB proliferation or differentiation, while the over secretion of organic acids by OCs would accelerate the release of ALN from the TNT-HA-ALN implant, locally inhibiting the maturation of OCs and promoting osseointegration in the osteoporotic condition (Fig. 8F and G). Zhu et al. [163] employed a novel procedure to develop a mesoporous SiO_2

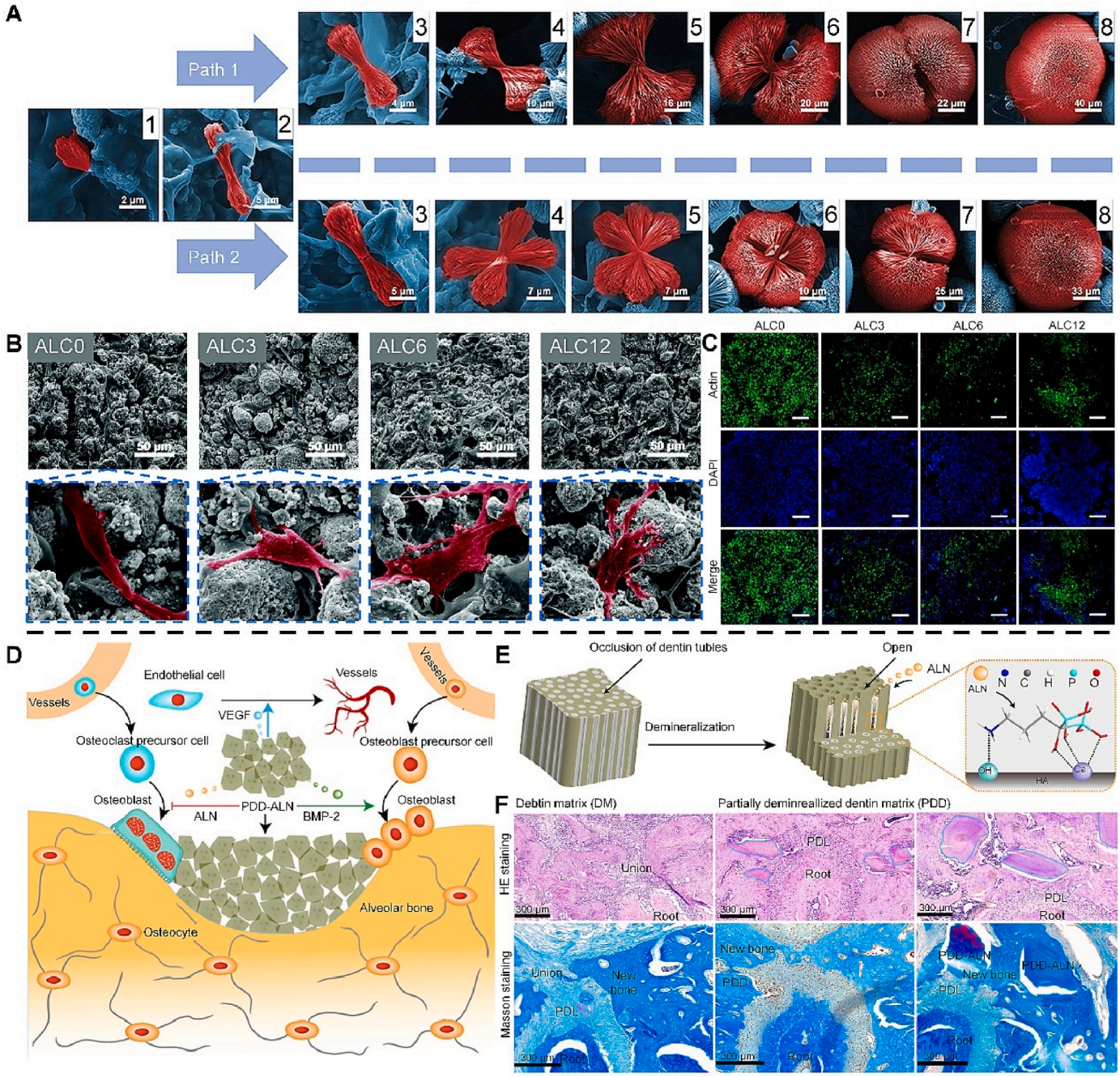


Fig. 9. BPs coated the eluting implants for bone formation. A) Composite scaffolds grow crystals in ALN solution in two different ways. B) Cell adhesion and spreading of adipose-derived stem cells cultured on different coated scaffolds. C) The inhibiting effects of coated composite scaffolds on the osteoclastogenic differentiation of RAWs cultured with a RANKL-containing medium. Reproduced with permission from Ref. [169] (Copyright 2020, Journal of Materials Chemistry B). D) Adsorption of ALN on the surface of PDD to form a drug coating could promote OB differentiation and inhibit OC differentiation. E) Mechanism illustration of the PDD-ALN fabrication process. F) H&E and Masson staining analysis showed that PDD-ALN coating has more obvious bone formation and repair ability. Reproduced with permission from Ref. [172] (Copyright 2021, Applied Materials Today).

nanoparticles and HA (MSNs/HA) hybrid coating onto stainless Kirschner wire substrates, which was used to load ZOL. The MSNs/HA composite coating presented a severe initial burst release of ZOL during the first day, which accounted for approximately 50% of the total loaded from the coatings. Subsequently, another 30% ZOL dose was released comparatively sustainably and lasted for more than ten days. Bone turnover during the initial stages of callus formation exhibits a rapid rate. The premature remodeling of the callus due to stress shielding or disuse can lead to the removal of the callus prior to the formation of bone bridging [164]. According to Greiner et al. [165], a high concentration of BP in the early stage could delay the removal of the early callus and thus avoid precocious removal of the primary callus, so that the volume and strength of callus in the bone remodeling stage was increased. As the decrease of release rate and drug diminution, the inhibitory effect is alleviated, thereby restoring bone remodeling to normal state, and facilitating the process of implant osseointegration. Prolonged suppression of the callus remodeling phase may result in postponed bone healing. Therefore, it is crucial to choose the suitable initial drug loading concentration and release duration to facilitate osseointegration.

5.1.3. BP-eluting inorganic scaffold

In addition to constructing drug and inorganic materials to coat implants, inorganic scaffolds can also directly incorporate BPs to form drug-coated implants and act as a catalyst for osseointegration (**Table 2**). Calcium phosphate cement (CPC) scaffold is a three-dimensional structure used to replenish bone defects and possess the osteo-regenerative properties for regenerative bone treatment [166]. ALN chemically binds to the surface of the CPC scaffold to form a drug elution coating, which presents a suitable compressive strength and a controllable ALN release rate [16]. The osteoporotic model showed that a relatively low dose of ALN coated on the CPC scaffolds obviously increased bone formation in the peri-defect region. Biphasic calcium phosphate (BCP) possesses good biocompatibility and osteoconductivity properties for bone tissue repair, with various ratios of beta-tricalcium phosphate (β-TCP) and HA [167]. However, due to the lack of intrinsic osteoinductivity, the new bone formation that occurs after osteoconduction is limited. Thus, the ALN-coated BCP scaffold can serve as a local delivery system to improve osseointegration.

Kim et al. [168] indicated that the ALN-coated BCP scaffold affects the three stages of OB differentiation (proliferation, extracellular matrix maturation, and mineralization) in a dose-dependent manner. Moreover, the BP-coated HA composite scaffold could grow crystals in a specific direction and fabricate rod-like morphologies (Fig. 9A) [169]. The duration of co-culturing BP and HA composite scaffolds (0, 3, 6, and12 h) can influence the integrin expression levels on the surface of ADSCs, which are crucial for facilitating cell adhesion and surface signal transduction. The expression of integrin in ADSCs is significantly increased when the composite scaffolds are co-cultured with BPs for 6h and 12h. The cells morphology exhibits a flat cell body and an increased number of pseudopods, suggesting that the composite scaffolds (6h and 12h) are more conducive to cell adhesion and spreading (Fig. 9B). Meantime, BP-coated HA scaffold manipulated local bone homeostasis by inhibiting osteoclastogenic differentiation (Fig. 9C). Partially demineralized dentin matrix (PDD) possesses excellent osteogenic differentiation potential [170], and displays a high specific surface area, indicating the potential to be a drug carrier [171]. The PDD implant with ALN coating improves osseointegration via three synergistic effects: 1) PDD-ALN enhanced mesenchymal stem cells (MSCs) migration and their osteogenic differentiation related to the BMP/SMAD signaling pathway; 2) NF-κB, p38, and ERK1/2 signaling pathways are crucial in inhibiting the formation and function of OCs; 3) PDD-ALN can enhance angiogenesis via the VEGFA/VEGFR2 signaling pathway (Fig. 9D–F) [172].

In summary, BPs can form a drug-material composite coating on the implant through the formation of chemical bonds or physical adsorption. Furthermore, the local BP-delivery system can regulate the balance between OCs and OBs and exert a pro-angiogenic effect to improve osseointegration in osteoporotic conditions.

5.2. BP-coated with organic materials

Several organic materials have been approved as promising BP-delivery platforms due to their excellent biocompatibility, low cytotoxicity, and biodegradability. Current organic coating materials are classified into four types (**Tables 3 and 4**): (i) synthetic high-molecular polymers; (ii) protein-origin polymers; (iii) polysaccharidic polymers; and (iv) other materials.

5.2.1. Synthetic high-molecular polymers

Synthetic high-molecular polymers, including PDLLA and polylactic-co-glycolic acid (PLGA), are classified as hydrophilic polymers with high cell affinity and promote cell adhesion [183,184]. Previous *in vitro* studies investigated the effect of locally released ZOL from PDLLA coating on OBs and OCs [185]. A dose-dependent promoting effect on OBs and a decrease in OC formation and osteoclastic resorption activity could be shown. In addition, a time-dependent effect of the ZOL-PDLLA coating on OCs was seen [186]. In the short incubation period, the cell vitality and TRAPiso-5b synthesis showed a downward trend in all investigated ZOL groups and the only PDLLA group. However, OCs were further inhibited only in the high ZOL concentration group with the prolonged incubation period. The time-dependent and dose-dependent effects of BPs that are released from the coating have been validated. Cindy et al. [187] described a novel ultrasonic spray coating method to sustain the release of ALN encapsulated in PLGA film as a carrier. The ALN and PLGA hybrid coating significantly improved the formation of new bone in a rat critical size defect model (160% increase compared to the control group). Moreover, the condition of BP release also has a crucial impact on long-term bone remodeling. The controlled and continuous release of ZOL was achieved by polylactide (PLA)-BP hybrid coatings and the CaP film in the outermost layer (Fig. 10A). This drug-delivery system could regulate bone remodeling during fracture healing (Fig. 10B). In addition, the localized ZOL release promoted new bone formation and inhibited excessive bone adsorption. Such systems therefore are superior alternatives for bone reconstruction in the osteoporotic condition (Fig. 10C) [188].

There are several important factors regarding the influence of synthetic high-molecular polymer and BP composite coatings on the regulation of the osseointegration process. The time point of application and the method of implant fixation are decisive for the effect of BPs in osseointegration. Thus, the enhancement of implant stabilization by BPs appears to depend on contact with the surrounding bone and maybe even a press fit position [189]. Especially in implants fixed by the press fit method, the bone tissue next to the implant may become necrotic and prone to resorption by OCs. This resorption could be inhibited by BPs, causing an enhanced implant fixation. Back et al. [190] indicated that a PDLLA/ZOL coating cannot promote the osseointegration of non-press fit inserted implants. Thus, choosing an appropriate insertion method for the implant is also crucial for the osteogenesis-promoting effect of the drug coating.

5.2.2. Protein-origin polymers

Protein-based polymers have the advantage of combining biological properties, such as mimicking the extracellular matrix, and directing the migration, growth, and organization of cells [191]. Inspired by such properties of the protein-based polymers, scientists started to utilize natural macromolecules for delivery of drugs and nutrients. Currently, the protein-origin polymers used for BP loading and local release mainly contain fibrinogen, gelatin, and others.

5.2.2.1. Fibrinogen. Fibrinogen can be stably combined with the

Table 3
BP-coated with organic materials.

Material	Type of BP	BP delivery system	Experimental trial	Most important contributions	Ref.
PDLLA	ZOL	ZOL and PDLLA coated Ti Kirschner wire	*In vitro*	ZOL showed a significant decrease in OC-like cell formation.	[185]
PDLLA	ZOL	ZOL and PDLLA coated TCP block	*In vitro*	TCP coated with ZOL stimulated osteogenic gene, expression in OB-like cells.	[186]
PLGA	ALN	ALN and PLGA coated sandblasted screws	*In vivo* (Rat)	Coated screws significantly improved BIC, BMD, and BV.	[187]
PDLLA	ZOL	ZOL and PDLLA coated Ti Kirschner wire	*In vivo* (Rat)	There was no significant enhancement of osseointegration for all groups.	[190]
Fibrinogen	PAM Ibandronate	BPs combined with fibrinogen coated stainless-steel screw	*In vivo (rat)*	28% higher pullout force and 90% increased pullout energy for the BP-coated screws.	[113]
Fibrinogen	ZOL	ZOL combined with fibrinogen coated Ti	*In vivo (rabbit)*	Both the bone volume fraction and the pullout force were significantly higher.	[192]
Fibrinogen	PAM Ibandronate	PAM covalently linked and Ibandronate adsorbed to fibrinogen to coat steel screw	*In vivo (rat)*	The bone remodeling took place around the implant in the BPs coating group.	[193]
Fibrinogen	PAM Ibandronate	PAM covalently linked and Ibandronate adsorbed to fibrinogen to coat steel screw	*In vivo (rat)*	BPs improved osseointegration by increasing the amount of surrounding bone.	[194]
Fibrinogen	ZOL	ZOL combined with fibrinogen coated Ti	*In vivo (rabbit)*	ZOL coating increased bone-to-screw contact and bone volume.	[196]
Gelatin	ALN	Incorporation of ALN and NG into the gelatin to coat PLGA scaffold	*In vivo (rat)*	The composite coating presented inhibitory impact on OCs activity to promote rat calvarial defect repair.	[204]

Material	Type of BP	BP delivery system	Experimental trial	Most important contributions	Ref.
RGD peptides	BP	BP covalently bond with RGD-peptide to coat Ti	*In vitro*	The composite coating improved adhesion, spreading of OB-like cells, and mineralization compared to uncoated Ti.	[207]
Heparin	ALN	ALN (amine group) combined with Heparin (carboxyl group) coated Ti implant	*In vitro*	ALN-coated implant enhanced ALP and calcium content, and inhibited OCs differentiation.	[109]
CHI	ZOL	CHI/ZOL to form coatings on Ti implant	*In vitro* and *in vivo* (rat)	ZOL coating was able to improve BA/TA around the implant.	[128]
CHI acetic acid solution	ZOL	ZOL-conjugated with CHI acetic acid to coat Mg alloy	*In vitro*	The ZOL-coated implant could be easily and efficiently used in clinic.	[212]
CMCHI[a]	ALN	ALN (amine group) combined with CMCHI (carboxyl group) to coat Mg alloy	*In vitro*	ALN coating could stimulate the proliferation and differentiation of OBs.	[214]
CHI/Gelatin	ALN	ALN (amine group) was coupled to HA (carboxyl group) and deposited on the CHI/Gelatin to coat Ti	*In vitro* and *in vivo* (rabbit)	The composite-coated implants effectively promote osseointegration at an early stage.	[215]
Az-CHI	ALN	Az-CHI mixed with ALN to coat bone fixation plate	*In vivo (rat)*	Sustained delivery of ALN showed a significantly higher volume of newly formed bone.	[223]

Material	Type of BP	BP delivery system	Experimental trial	Most important contributions	Ref.
APTMS	ALN	ALN was coupled to the chain of the surface of N-BGS (amine group)	*In vitro* and *in vivo* (OVX Rat)	The amount of ALN were improved by amino modification. Proper concentration promoted osteogenic differentiation.	[115]
PDIB	ZOL	PDIB contained ZOL to coat bone graft	*In vivo (rat)*	PDIB was a viable delivery method for ZOL delivery to enhance the bone-forming.	[218]
PEC	RIS	PEC loaded RIS to adhesive Ti alloy	*In vitro*	RIS coating promoted bone mineral formation after 24 h, while reducing the number of MSC after 48 h due to cell toxicity of RIS.	[219]
DOPA	ZOL	ZOL chemically bond with DOPA coated Ti implant	*In vivo (OVX rat)*	The greater extent of bone formation and osseointegration around the coated implant than control.	[221]

[a] Carboxymethyl chitosan, CMCHI.

Table 4
BP-coated with organic materials (clinical trials).

Material	Year	Type of BP	BP delivery system	Number of patients	Follow-up time	Outcome variable	Most important contributions	Ref.
Fibrinogen	2012	PAM Ibandronate	BPs chemically bond with fibrinogen coated Ti implant	N = 16	2 and 6 months	ISQ and radiographic marginal bone level	The average difference in the increase in ISQ, and effect size. The margin of implant showed less bone resorption both at 2 and 6 months.	[197]
Fibrinogen	2016	PAM Ibandronate	BPs chemically bond with fibrinogen coated Ti implant	N = 14	5 years	Radiographic marginal bone levels	The BP-coated implant showed even less resorption and enabled the preservation of the marginal bone.	[198]
Fibrinogen	2019	ZOL	ZOL chemically bond with fibrinogen coated Ti implant	N = 16	2–8 weeks	ISQ and radiographic marginal bone level	No statistically significant differences were observed in ISQ values between coated and uncoated implants. There was a less marginal bone loss at the ZOL-coated implant.	[199]
Fibrinogen	2013	ZOL	ZOL chemically bond with fibrinogen coated pin	N = 20	8–15 weeks	Extraction torque	This trial could not show any improved cortical fixation.	[200]

implant via the EDC/NHS reaction to possess a functional carboxylic group, which provides binding sites to BPs. Therefore, the excellent biocompatibility and biochemical characteristics of fibrinogen-based materials ensured the finding of applications in the field of BP delivery with special focus. Roshan-Ghias et al. [192] coated implants with multilayer fibrinogen incorporating ZOL (150 ng/cm^2) to assess the ability to promote osseointegration in the implant/bone poor contact area (Fig. 11A). Eleven weeks after implantation, the bone volume

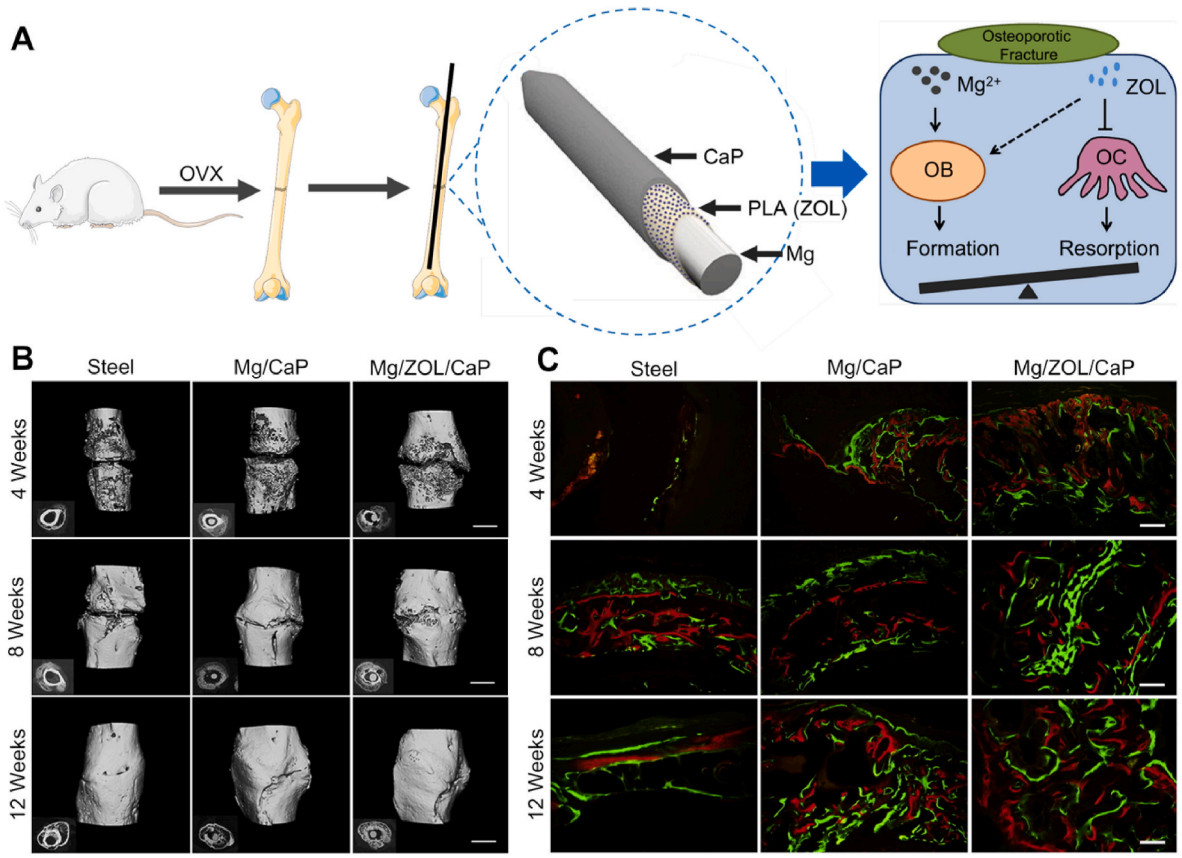


Fig. 10. ZOL-PLA coating on Mg alloy (Mg/ZOL/CaP) implants to treat osteoporotic fractures. A) Schematic of the modulation effect of the ZOL coating implant. B) Micro-CT images to determine the fracture-healing capacity of intramedullary pins after implantation. C) Calcein/alizarin red labeling in rat femurs at 4, 8, and 12 weeks after implantation to assess bone remodeling. Reproduced with permission from Ref. [188] (Copyright 2018, Acta Biomaterialia). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

fraction and pullout force were significantly higher in the trabecular region of the fibrinogen-ZOL coating group (Fig. 11B). In an earlier study, fibrinogen, without BPs, displayed an adverse effect on removal torque and bone contact [193]. However, with the incorporation of BPs into fibrinogen coating, these negative effects were obviously counteracted [194].

Compared with the HA and BP composite coatings, the use of fibrinogen to load BPs to promote osseointegration is different. HA by itself leads to a very strong attachment of the bone to the implant surface, which could increase bone and implant surface friction. However, this does not necessarily imply better fixation, because the fixation of implants is dependent upon the strength of the surrounding bone at a certain distance from the implant surface, rather than on bone–implant surface friction [193]. In contrast to HA coatings, the fast-degrading fibrinogen coating can release the BP completely within a few days. During this period, bone formation is characterized by an inflammatory response in which MSC and immune cells dominate the scene [195]. Thus, MSC may uptake the BP to an even higher extent. The attracted cells improve the formation of fibro-mesenchymal tissue and resulted in membranous bone formation [196]. The amount of fibro-mesenchymal tissue generated around the fibrinogen-ZOL coating implant is statistically significantly higher than that observed in a control group. Moreover, peri-implant osteogenesis was higher overall ($P < 0.05$) in a fibrinogen-ZOL coating group compared to a control group. Agholme et al. [194] also indicated that BP and fibrinogen coated implants improve osseointegration by increasing the amount of surrounding bone tissue, while HA-coated implants mainly promote bone to attach to the implant (Fig. 11C).

Several clinical trials have been conducted **(Table 3)** showing that implants coating BPs possess better osteointegration [197]. PAM and ibandronate-coated implants can increase the implant stability quotient (ISQ), which serves as a proxy for the stiffness of the implant-bone construct. In addition, x-rays show less bone resorption at the margin of the implant at 2 months ($P = 0.012$) and at 6 months ($P = 0.012$) after surgery. Abtahi et al. [198] note that BP-coated implants possess even less resorption (median 0.20 mm) and enable prolonged preservation of the marginal bone. Moreover, BPs and fibrinogen composite coatings can change marginal bone levels (Fig. 11D) and enhance implant stability (Fig. 11E) [199]. Thus, the fibrinogen coating containing suitable amounts of BPs improved early implant fixation with an effect maintained five years after functional loading. In another clinical trial, the marginal bone loss for the controls was minor (0.21 mm) and close to zero for the ZOL-coated implants (with a 0.17 mm difference). However, in proximal tibial correction osteotomy patients, the fibrinogen-ZOL coating implants enabled metaphyseal fixation similar to HA coatings, with no difference from uncoated pins in cortical bone [200]. Therefore, more clinical trials are needed to further clarify the capability of promoting osteointegration of BP-coated implants.

5.2.2.2. Gelatin. Natural polymers such as gelatin, derived from the partial hydrolysis of collagen, have many outstanding properties, including low cost and resemblance to natural extracellular matrix components [201]. Gelatin is commonly used for pharmaceutical and medical applications because of its biodegradability and biocompatibility in the physiological environment [202]. For delivery applications, the drug is either encapsulated or immobilized on the polymer, then released into the target site by diffusion or desorption [203]. Zhu et al. [204] incorporated ALN and naringin (NG) into the gelatin coating to

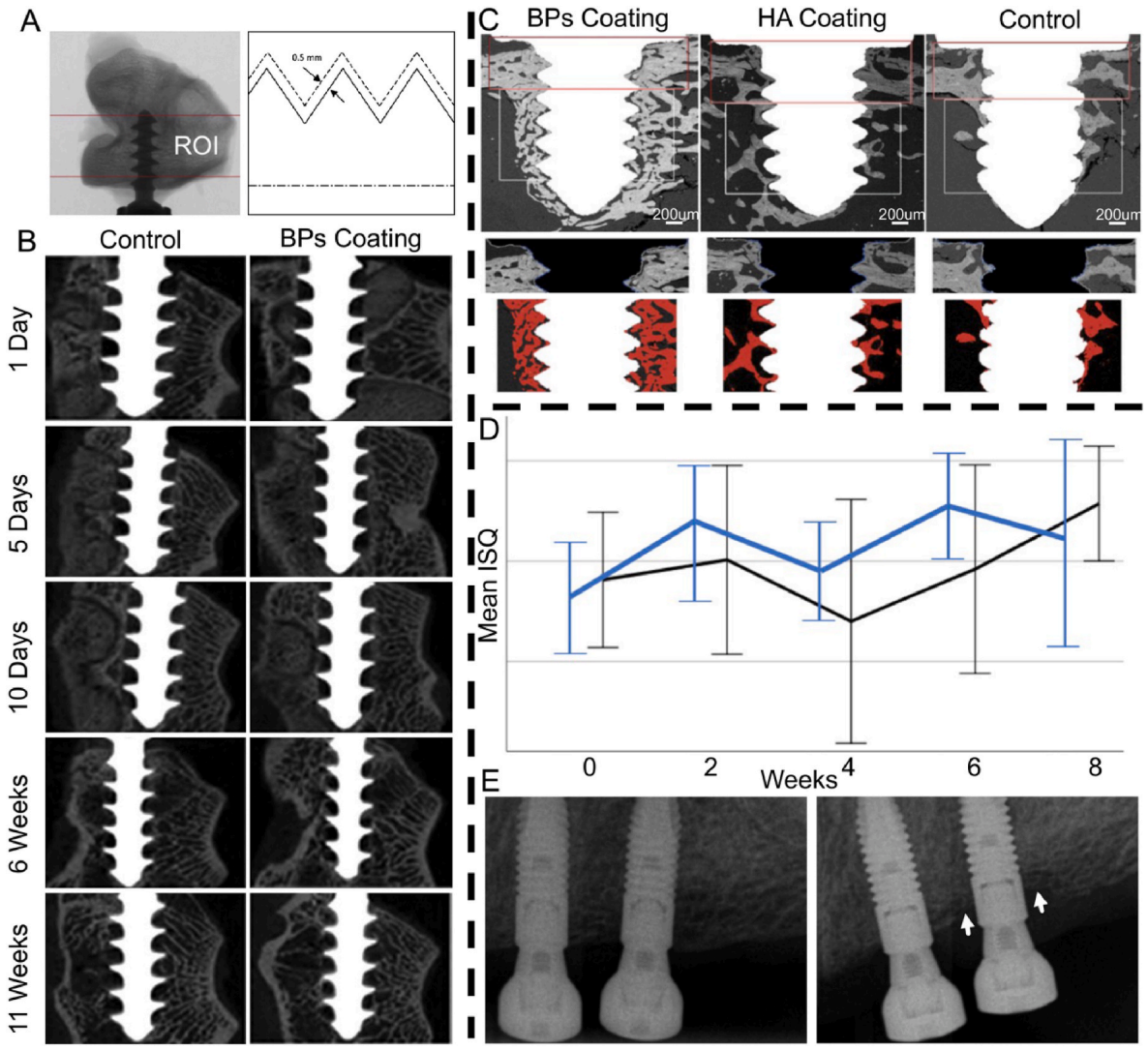


Fig. 11. BP-fibrinogen-coated implants enhance bone formation in base experiments and clinical trials. A) Region of interest (ROI) in a distal screw. B) Transverse slices of the distal femur from each time point. Reproduced with permission from Ref. [192] (Copyright 2011, Clinical Biomechanics). C) Backscatter electron images presenting BV/TV and implant to bone contact. Cortical ROI (red box) and cancellous ROI (white box). Reproduced with permission from Ref. [194] (Copyright 2012, Materials in Medicine). D) Implant stability quotient (ISQ) of control implants (blue) and BPs-coated implants (black) after insertion. E) Radiograph indicating BP-coated implant (left) and control implant (right) 8 weeks after insertion. Reproduced with permission from Ref. [199] (Copyright 2018, Clinical Oral Implants Research). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

repair rat calvarial defects (Fig. 12A). In that trial, apart from the improved properties (e.g., mechanical strength and hydrophilicity) of the gelatin coating, ALN suppressed bone resorption by inhibiting the activity of OCs, and NG positively facilitated bone regeneration by promoting the proliferation of OBs. After composite-coated scaffold implantation into the critical defects of rats, this coated scaffold exerted excellent osteogenic ability, indicating it could be a promising alternative to the conventional scaffold for clinical application (Fig. 12B and C).

5.2.2.3. Other polymers. Because amino acid (aa) composition varies from tens to thousands of residues, proteins and peptides serve different functions. Peptides are small molecules typically consisting of less than 50 aa, while any peptide larger than 50 aa is considered a protein [205]. Among them, arginylglycylaspartic (RGD) peptides (arginine, glycine, and aspartic acid), derived from fibronectin, are widely used to facilitate cell attachment to synthetic materials [206]. Due to the main role of the RGD sequence in cell adhesion, in one study RGD peptides were coupled to BPs used as an anchor system and chemically adsorbed on Ti disks to favor adhesion and spreading of OB-like cells and mineralization [207]. However, the adhesion layer between the Ti substrate and RGD peptides is weak and tends to crack and disintegrate. To overcome this problem, new coating strategies to reduce weak bonds should be developed.

5.2.3. Polysaccharide polymers

Polysaccharides are a class of biopolymers produced from living organisms or functionalized from sugar-based materials possessing a biological effect on organisms [208]. The functional groups on the chains of polysaccharidic polymers serve as anchoring sites for chemical modifications, fabricating BP coating implants of great significance in promoting osseointegration.

5.2.3.1. Chitosan. CHI serves as a biodegradable, biocompatible, and non-toxic polysaccharides biopolymer that has been utilized to fabricate complex coatings with BP [209]. Several studies have modified CHI to obtain various functions, such as hydrophilic and enhanced adsorption capacity [210,211]. An Mg alloy was coated with ZOL and CHI acetic acid solution via dip coating technology, which aimed to promote bone formation while inhibiting excessive resorption due to the degradation

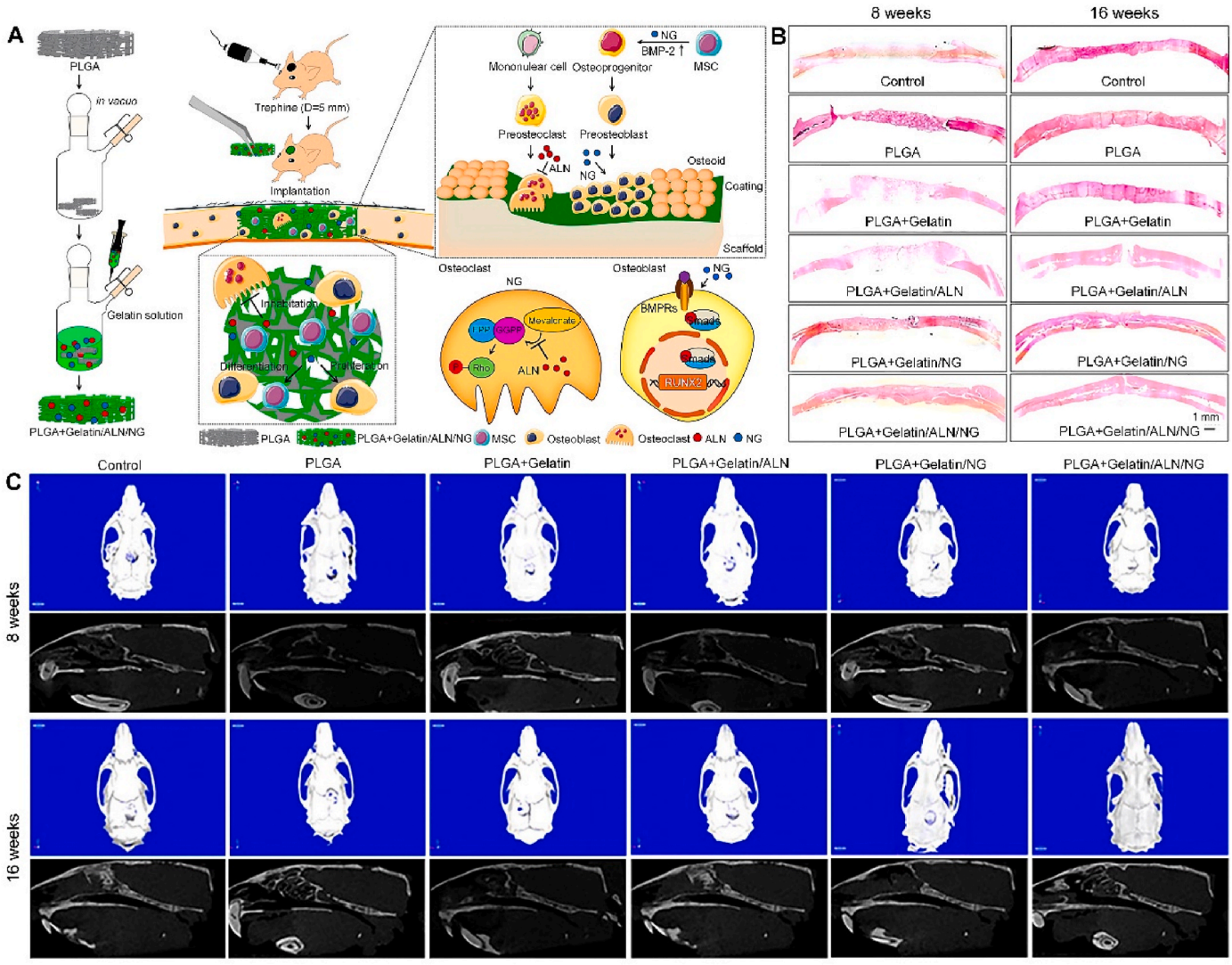


Fig. 12. Gelatin/ALN coating 3D PLGA scaffolds for synergistic bone regeneration. A) The PLGA scaffolds + Gelatin/ALN/NG coating exerted a synergistic effect to repair calvarial defects via regulating the balance between OBs and OCs. B) H&E staining images 8 and 16 weeks after implanting the coated scaffolds into rat calvarial defects. C) Three-dimensional reconstructions and sagittal images assessed bone repair outcomes 8 and 16 weeks after implantation. Reproduced with permission from Ref. [204] (Copyright 2019, ACS Biomaterials Science & Engineering).

of the Mg alloy [212]. For chitosan-based materials, the drug release rate is usually controlled by the chemical crosslinking method, using an agent such as glutaraldehyde, epichlorohydrin, and glyoxal [213]. However, this process requires a considerable reaction time in an aqueous environment, which may degenerate the mechanical properties of the implant, originally needed for bone fixation. In contrast, Azidobenzoic acid-modified chitosan (Az-CHI) could form a crosslinked network via UV irradiation in a short period (5 min) to achieve the prolonged release of BP [214], which significantly improved the new bone volume. For better osseointegration, polysaccharide and protein-origin polymers could be co-administered to load BPs. Shen et al. [215] constructed a CHI and gelatin hybrid network on implants that could mimic the extracellular microenvironment, and load HA-ALN/BMP-2 nanoparticles (Fig. 13A). This multilayer coating displayed superiority in maintaining the bioactivity of loaded BMP2, which is more beneficial to stimulate new bone formation. On the other hand, the ALN molecules in the HA-ALN/BMP-2 nanoparticles efficiently inhibit OC development, which in turn contributes to bone formation (Fig. 13B–D). This coating strategy introduced a flexible method to effectively promote osseointegration at an early stage between the implant and the native osteoporotic bone to prevent implant loosing and rejection.

5.2.4. *Heparin*

Heparin is a water-soluble and highly negatively charged sulfated polysaccharide belonging to the glycosaminoglycan family, which possesses critical biological functions [216]. Moon et al. [109] incorporated chemically active functional groups on implants by a grafting reaction with heparin; subsequently, implants were coated by immobilizing ALN onto the heparin-grafted surface. The ALN-coated implant significantly improved ALP and calcium content. In addition, TRAP analysis confirmed that RANKL-induced OCs differentiation of RAW264.7 cells was inhibited with the ALN-heparin coated implant. Interactions between heparin and BPs are based on the ionic interactions between the positive charge of BPs and the negative charge of heparin. To effectively transfer the drug to the defect area, the gelatin/heparin and BPs form a composite coating on the porous scaffold, and the negative charge of heparin is used to control release the BPs in the local area [217]. The polysaccharide polymer and BP coating show excellent osteogenic differentiation and bone formation (Fig. 14). In conclusion, polysaccharide polymers are a promising BP loading material, and provides an improved coating strategy to modify implants and ensure

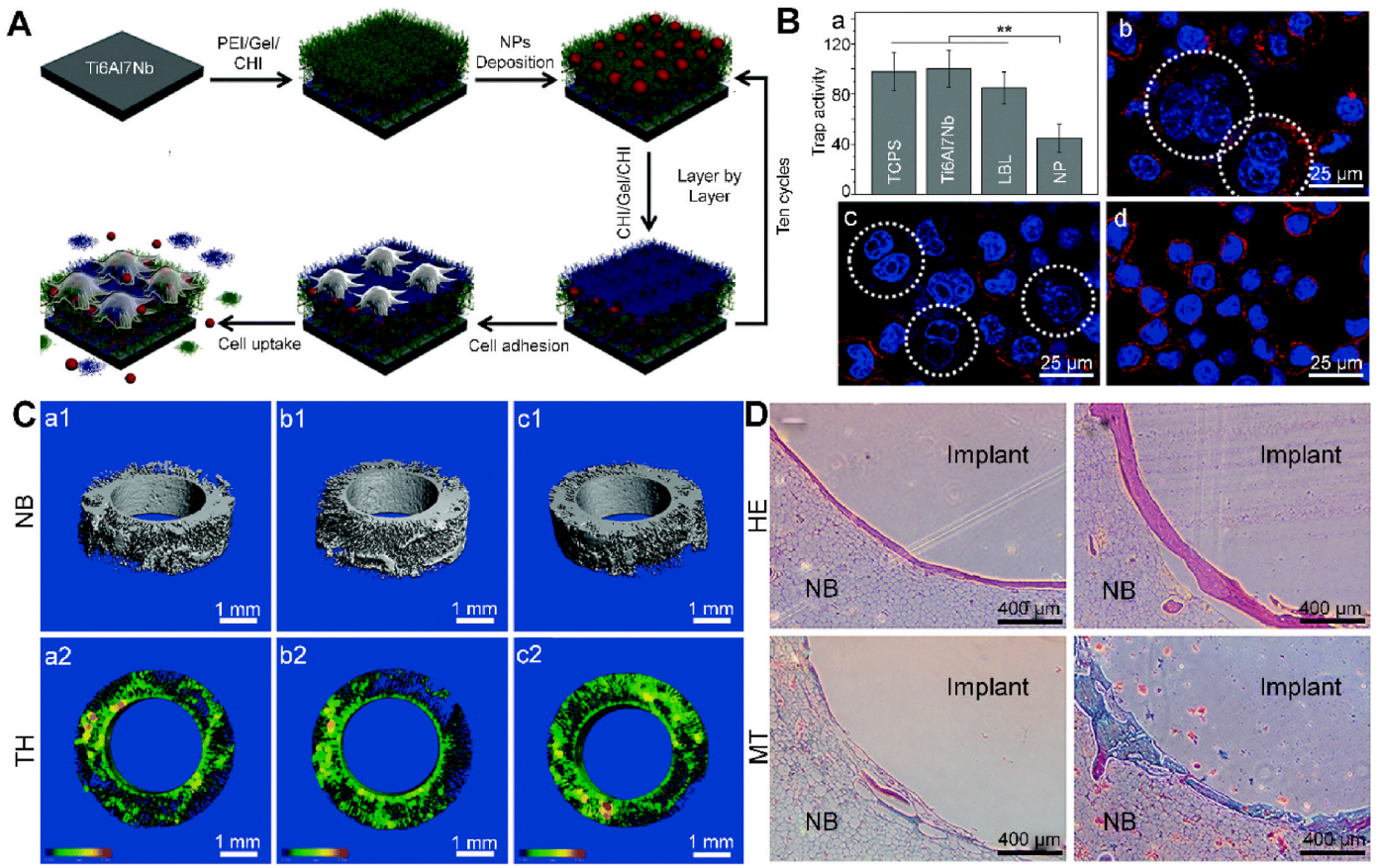


Fig. 13. Hybrid multilayer coating mediated local bone remodeling. A) Illustration of the fabrication of the BP composite coating for osteoporotic applications. B) Different kinds of composite coatings are applied to OCs. a) Trap activity of OCs grown on different substrates. b) Representative fluorescence images of OCs cultured on different composite coatings. C) Micro-CT images of new bone formation (a1–c1) and trabecular thickness (a2–c2) around different implants. D) H&E and Masson's trichrome staining images of different implants. Reproduced with permission from Ref. [215] (Copyright 2016, Journal of Materials Chemistry B).

osseointegration in osteoporosis conditions.

5.2.5. Other organic materials

Researchers have also used other organic materials to combine with BPs to form a composite coating, such as polycondensed deoxyribose isobutyrate ester (PDIB) polymer [218] and polyelectrolyte complex (PEC) [219]. These BP composite coatings have also presented excellent osteogenic properties.

APTMS, as a silane coupling agent, can be co-constructed with the implant to form an amino-modified scaffold [220]. Due to the strong polarity between the NH_2-covered implant surface and ALN, ALN released from the implant is slower than that from uncoated scaffolds [115]. Moreover, a morphometric analysis showed significantly greater BMD, BV/TV, and Tb. Th detected in the ALN coated group compared with the uncoated group. In addition, the DOPA and ZOL composite coating implants can enhance the removal torque values 8 weeks after implantation and improve the BIC value, indicating a higher degree of osseointegration [221]. Because both DOPA and ZOL regulate osseointegration mainly by inhibiting OC activity, the synergistic effect of osseointegration is limited [222]. Hence, BPs coating should be used in combination with materials with osteogenic effects—rather than materials that inhibit bone resorption—to exert a synergistic effect and obtain the desired osseointegration.

In summary, organic materials load BPs to form a composite coating on the implant that can increase drug loading capacity and control the release of BPs, which changes as the organic materials degrade. The BPs and organic materials composite coatings can improve osseointegration and mechanical stability by interlocking between the bone tissue and implant surface.

5.3. BPs composite coating with organic-inorganic materials

Although inorganic material coatings, such as CaP, can successfully load BPs, the effectiveness of the local drug-delivery system is still lacking due to the initial burst release phenomenon. This may cause a rapid depletion of the drug supply and cannot provide a sustainable local delivery condition [224]. Moreover, the organic coating materials show great potential in promoting bone formation, because they are biocompatible, occlusive, and space-maintaining, but lack osteoconductivity [225]. Thus, co-construction of organic materials, inorganic materials, and BPs as a composite coating can be utilized as a very effective method to control drug release and improve osseointegration [226].

Bose et al. [227] constructed a PCL, HA, and ALN composite coating, which could minimize the burst release of the drug. After 24 h, samples without PCL coating released >75% of ALN, and those with the PCL coating released approximately 50%. Moreover, composite coatings composed of CDHA, polylactic acid (PLA), and ALN were deposited on implants via electrospraying, which can control the slow release of ALN and promote osteogenesis [93]. Due to the prevention of the initial burst release of the PCL coating, the TCP-ALN-PCL composite coating scaffolds inhibited OC activity and promoted higher bone formation [228]. Thus, the initial controlled release played a critical role in early bone formation, which is crucial for rapid bone healing and implant–host tissue integration. In addition, most composite coatings of organic-inorganic materials loaded with drugs can carry both BPs and other drugs or bioactive factors to further synergistically promote osseointegration. A co-delivery system (TNT/Ral/LBL-ALN) has been presented, in which TNT arrays were used as the nano-reservoirs for raloxifene (Ral) and

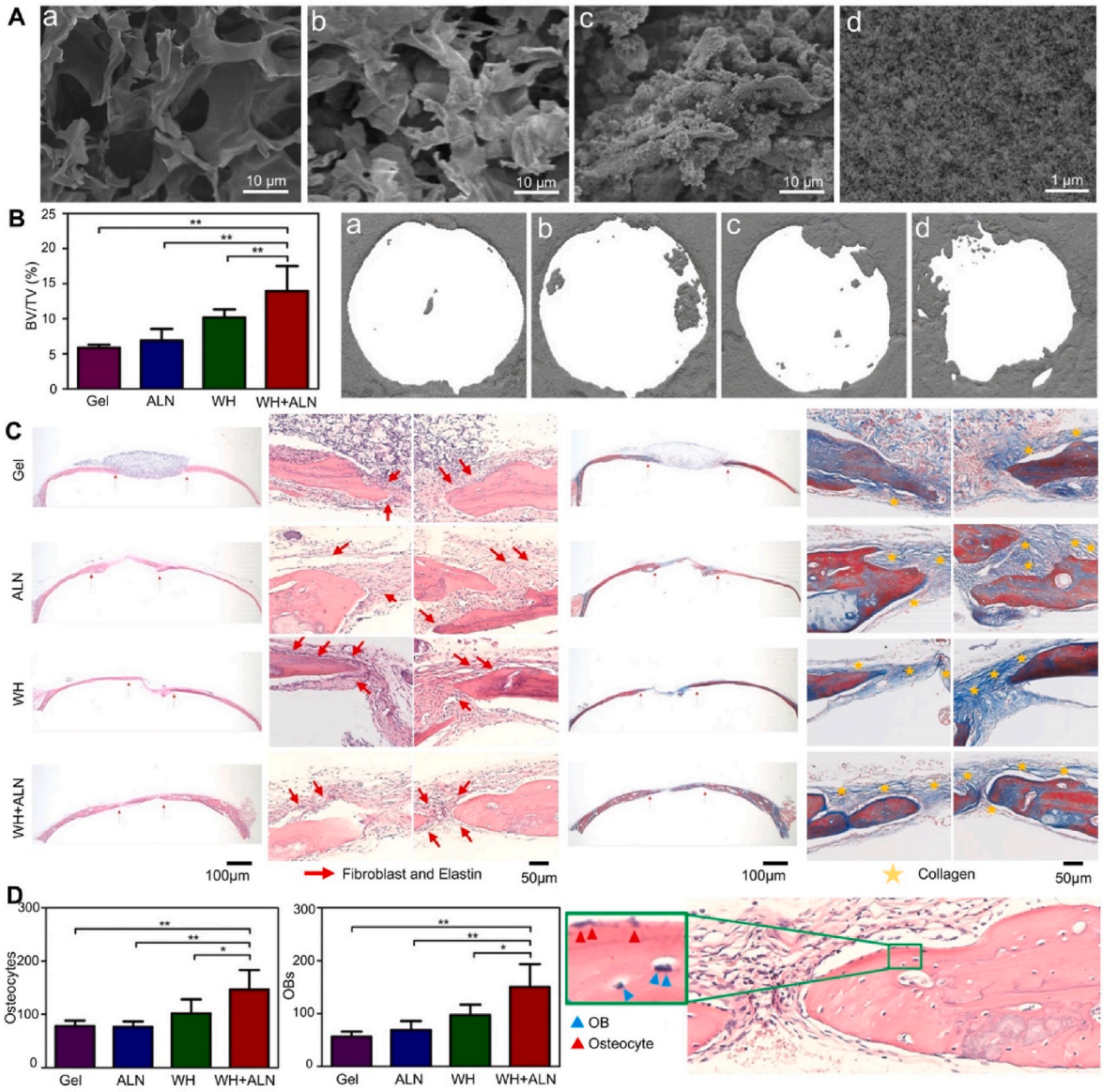


Fig. 14. Heparin/WH scaffolds combined with ALN to promote bone regeneration. A) SEM images of the composite scaffolds. B) Reconstructed CT images of the bone defect area and the percentage of BV/TV. C) H&E and Masson's trichrome staining analysis five weeks after implantation with different scaffolds into the bone defect area. D) H&E staining analysis measured the number of OBs and osteocytes in the defect area. Reproduced with permission from Ref. [217] (Copyright 2022, Tissue Engineering and Regenerative Medicine).

then coated with ALN grafted hyaluronic acid multilayers via a spin-assisted LBL technique. This improved osteogenic proliferation and differentiation, as well as effectively inhibited the maturation and differentiation on OCs *in vitro* [229]. The higher osteoinductive performance of the composite coating was also further proven *in vivo*. By considering the different phases of osseointegration, Zheng et al. [230] developed a degradable hybrid coating consisting of ALN-loaded nano-HA deposited on PEEK. Interleukin-4 (IL-4) was subsequently grafted onto the outer surface of the hybrid coating (Fig. 15A). In the early stage after implantation, the cascade of IL-4, a small amount of ALN, and calcium ions created an osteo-immunomodulatory microenvironment (Fig. 15B). In the following weeks, the steady release of ALN promoted osteogenesis and suppressed osteoclastogenesis continuously, contributing to new bone formation at the bone-implant interface with high quantity and quality (Fig. 15C and D).

In summary, there is increasing interest in combining BPs with organic and inorganic materials, which can exert the advantages of complementary and synergistic effects of two different materials and allow BPs to promote osseointegration further. This type of composite coating scaffold can load more than two drugs to enable dynamic modulation according to the stage of osseointegration. Additionally, we summarize the advantages and challenges of different types of BPs coatings, to build more ideal drug-loaded coatings (**Table 5**).

6. Conclusion and perspectives

Orthopedic implants, such as Ti and Mg alloys, are widely used in orthopedic surgery, but the lack of osseointegration is a barrier to their application, especially in osteoporotic conditions. BPs have traditionally been used in the clinic to inhibit excessive bone resorption. The appropriate BPs concentration of implant surfaces possess an excellent ability to promote osseointegration with host bone tissue, which correlates with the ability of BPs to induce OC apoptosis and inhibit bone resorption, upregulate osteogenic gene expression, and inhibit OB and osteocytes apoptosis through relevant molecular signaling pathways. Systemic administration of BPs can lead to severe complications, while

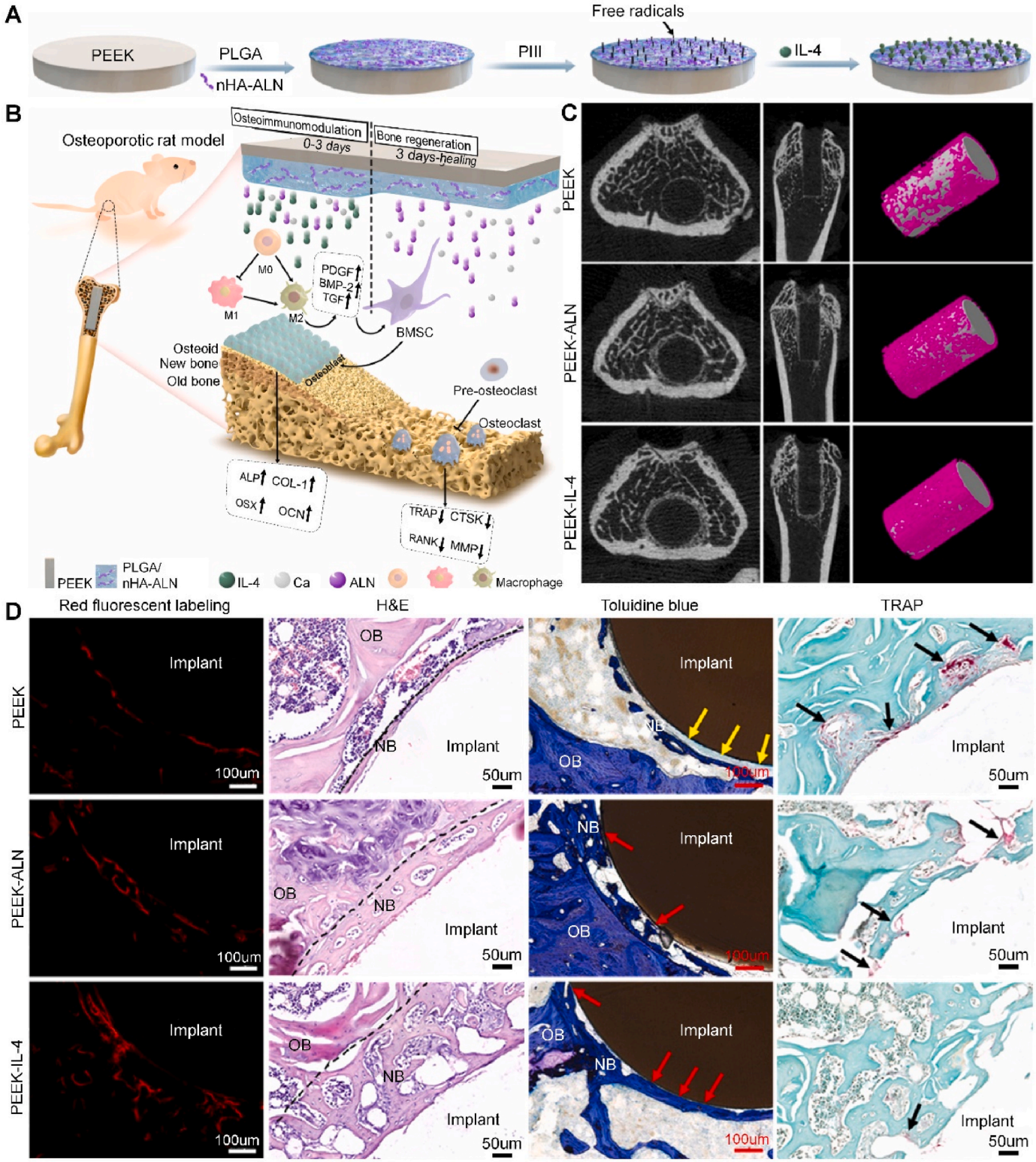


Fig. 15. PLGA/HA/ALN composite-coated scaffolds dictated osseoimmunomodulation and bone regeneration to achieve ameliorative osseointegration under osteoporotic conditions. A) Schematic illustration of coating preparation. B) Cell morphology after culturing RAW 264.7 cells for 24 h. C) Composite-coated scaffolds promote bone regeneration through multiple mechanisms. D) Reconstructed transverse, coronal, and 3D micro-CT images of defect areas four weeks after implantation. E) Red fluorescent labeling, H&E staining, and histological observation of new bone formation surrounding implants (yellow arrows, fibrous capsule; red arrows, contact between new bone and implants; black arrows, $TRAP^{+}$ cells). Reproduced with permission from Ref. [230] (Copyright 2022, Bioactive Materials). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 5
Advantages and challenges of materials loaded with BPs coating.

Type	Subgroup	Advantages	Challenges
Inorganic Materials	i. Cap or HA ii. Porous materials iii. Eluting scaffolds	i. Chemical composition akin to natural bone tissue, bioactivity, and non-immunogenic, ii. High pore volume and large surface area, iii. Excellent osteoinductive and mechanical properties.	i. Lack of control over drug release capability, ii. Controlling the drug loading capacity can be challenging.
Organic Materials	i. Synthetic high-molecular polymers ii. Protein-origin polymers iii. Polysaccharide polymers iv. Other organic materials	i. Excellent low cytotoxicity and biodegradability ii. Resemblance to natural extracellular matrix, iii. Ideal drug loading capacity, iv. Controllable drug release capability.	i. Controlling the degradation rate is challenging, ii. The degradation of certain materials can lead to adverse changes in the local microenvironment, iii. The preparation process for coating is intricate.
Organic-inorganic Materials	Co-construction of organic materials and inorganic materials	Harnessing the strengths of each component of Organic-inorganic materials, leading to coatings with enhanced properties, versatility, compatibility, and tunability.	i. High requirements for preparation techniques, ii. Issues with material compatibility, iii. The difficulty of translation to clinical application is increased.

the suitable concentration of BPs locally in the bone repair area will affect the osseointegration of the bone/implant surface. Thus, local administration of BPs in combination with implants has the potential to provide BPs at the proper concentration, improve bioavailability, reduce adverse effects, and promote osseointegration. Among these, the BP-coating strategy offers a very interesting direction to exert long-term and stable drug release within a lesion. Currently, inorganic (e.g., CaP, porous materials) or organic materials (e.g., high-molecular polymers, protein-origin polymers, and polysaccharidic polymers) are coated on the implants, and the coated implants are loaded with BPs by several methods, such as forming chemical bonds, physical adsorption, and encapsulation. Base experiments and clinical trials have confirmed the efficacy of BPs and material composite coatings in promoting bone/implant surface osseointegration.

Studies have confirmed the usefulness of BP coatings in promoting bone formation, and osseointegration, but some critical theoretical and technical areas need to be addressed or improved further. For example, the choice of coating materials, coating method, and the number of coating layers to carry BPs may have drastic effects on the regulation of osseointegration. These issues are worth further exploration and optimization. Previous studies have validated the release kinetics of BPs *in vitro* and used this to predict the release of BPs *in vivo* [231,232]. However, we should not overlook that the release kinetics of BPs *in vivo* may differ from what has been discovered *in vitro*. Thus, quantifying the actual *in vivo* release kinetics of BPs by establishing methods to explore its pharmacokinetics/

Pharmacodynamics *in vivo* may serve as a powerful tool to develop BP coatings.

To construct the BP and material composite coatings, studies generally start with inorganic or organic materials coating the implant surface and subsequently load BPs. Promoting osseointegration by BPs relies primarily on resistance to bone resorption; therefore, using coating materials with synergistic (e.g., osteogenesis-promoting) effects to construct composite coatings can further promote the osseointegration of implants. In addition, further studies will be necessary to clarify if the mechanism of action of the BP and material composite coatings will lead to improved osseointegration in a press fit implant fixation model, and if a coating with delayed release of the substance would lead to different findings in osseointegration.

Partially coated implants promote osseointegration by increasing the friction between the bone/implant surface, which is not a critical factor for excellent osseointegration. The osseointegration of the bone/implant surface depends not only on the friction, but also on the quality, quantity, and maturity of the new bone formed at a certain distance from the implant surface. Although several clinical trials have been conducted on BP-material composite coatings, the number of patients and the follow-up duration are relatively limited. Substantially increased support for sustained basic and clinical research is required to advance BP coating technology towards clinical translation. Despite current challenges, the incredible pace of progress in this field indicates that BP coating approaches may play a vital role in promoting osteointegration.

Declaration of competing interest

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.

Data availability

No data was used for the research described in the article.

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