

Review

Zinc-Based Biomaterials for Regeneration and Therapy

Yingchao Su,¹ Irsalan Cockerill,¹ Yadong Wang,² Yi-Xian Qin,³ Lingqian Chang,^{1,*} Yufeng Zheng,^{4,*} and Donghui Zhu^{1,*}

Zinc has been described as the ‘calcium of the twenty-first century’. Zinc-based degradable biomaterials have recently emerged thanks to their intrinsic physiological relevance, biocompatibility, biodegradability, and pro-regeneration properties. Zinc-based biomaterials mainly include: metallic zinc alloys, zinc ceramic nanomaterials, and zinc metal–organic frameworks (MOFs). Metallic zinc implants degrade at a desirable rate, matching the healing pace of local tissues, and stimulating remodeling and formation of new tissues. Zinc ceramic nanomaterials are also beneficial for tissue engineering and therapy thanks to their nanostructures and antibacterial properties. MOFs have large surface areas and are easily functionalized, making them ideal for drug delivery and cancer therapy. This review highlights recent developments in zinc-based biomaterials, discusses obstacles to overcome, and pinpoints directions for future research.

Metallic Biomaterials for Regeneration and Therapy

Conventional metallic biomaterials, including titanium alloys, stainless steels, and cobalt–chromium alloys, have been widely used clinically for load bearing hard tissue reconstruction and regeneration. They have superior mechanical properties, machinability, and durability, but are considered nondegradable, and long-term clinical complications may occur, necessitating a second removal surgery [1]. To overcome such drawbacks, novel **biodegradable metals** (see Glossary) have been developed to degrade gradually *in vivo* while promoting complete healing of local tissues. Thus, the subsequent removal surgery is avoided [2].

The three main biodegradable metals are: magnesium (Mg), zinc (Zn), and iron (Fe). Mg materials generally degrade too quickly (within 1–4 months), and are accompanied by harmful hydrogen gas evolution. Fe materials typically degrade too slowly (over 2–3 years), and the degradation products are retained in tissues for a long time. Zn materials have degradation rates between those of Mg and Fe, and their degradation products are fully bioresorbable without hydrogen gas evolution [3]. Ionic Zn has also been described as ‘the calcium of the twenty-first century’ because of the increasing awareness of its significant functional roles in physiological and biological systems [4]. Therefore, Zn is a better choice for biodegradable metallic materials than Mg and Fe, with a better *in vivo* biodegradation rate and biocompatibility for tissue regeneration and therapy (Figure 1, Key Figure).

Zn-based ceramic nanomaterials have been extensively applied in the emerging field of theranostics, including drug delivery, tissue targeting, bioimaging, and cancer therapy [5–7] (Figure 1). They have unique physical and chemical properties, such as large surface/volume

Highlights

Zn-based biomaterials have promising applications in tissue regeneration, theranostics, and treatments.

Zn-based biomaterials have desirable biological features for regeneration and therapy, including biocompatibility, osteogenesis, and antibacterial, antifungal, and anticancer properties.

Zn-based biodegradable metals have good degradation rates and biocompatibility, and their mechanical strength and ductility can be enhanced through alloying, thus making them promising for cardiovascular and orthopedic applications.

Zn-based ceramic biomaterials are being developed as synergistic nanocomposite platforms capable of combined cancer targeting, bioimaging, and responsive drug delivery.

Strategies for controlled release of degradation products from biodegradable Zn-based biomaterials are necessary to ensure their biosafety when optimizing their therapeutic and treatment effects.

¹Department of Biomedical Engineering, University of North Texas, Denton, TX, USA

²Nancy E. and Peter C. Meinig School of Biomedical Engineering, Cornell University, Ithaca, NY, USA

³Department of Biomedical Engineering, Stony Brook University, Stony Brook, NY, USA

⁴Department of Materials Science and Engineering, College of Engineering, Peking University, Beijing, China

*Correspondence: Lingqian.chang@unt.edu (L. Chang), yfzheng@pku.edu.cn (Y. Zheng), and Donghui.Zhu@unt.edu (D. Zhu).

ratio, photoluminescence, antibacterial activity, good biocompatibility, and pH-responsive nanostructure. Zn-based organic biomaterials, mainly **metal–organic frameworks (MOFs)**, also have large surface/volume ratios and pH responsiveness, making them promising materials for drug delivery, bioimaging, and cancer therapy [8].

Zn-based biomaterials have attracted increasing attention recently, but articles summarizing their features, applications, and potential are still infrequently published [9,10]. This review provides a timely overview of Zn-based biomaterials, briefly covering the biological roles of Zn in mammalian systems, as well as describing the properties and biological performance of various Zn-based biomaterials and the challenges and perspectives in this rapidly developing field.

Physiological Role of Zn

Zn is the second most abundant micronutrient in living organisms [11], and is fundamental to cell biology, human anatomy, and physiology. It is necessary for hundreds of enzymatic reactions, affecting development, maturation, proper immune function [12], numerous disease states, and cancer. In humans, average daily zinc intake is 4–14 mg/day, and normal plasma levels range from 70 to 120 $\mu\text{g/dL}$, whereas plasma levels $<60 \mu\text{g/dL}$ are considered low [13]. Zn deficiency can be observed in growth failure, but Zn toxicity is rarely a concern as ingestion of ten times the recommended daily dose leads to few symptoms [13].

Zinc finger proteins (ZFPs) and Zn receptors (Box 1), including Zn transporters (ZnTs) and Zrt/Irt-like proteins (ZIPs), are the predominant cellular transport mechanisms for Zn ions. ZFPs represent the largest and most diverse family of DNA binding transcription factors, as they can bind to DNA, RNA, and other proteins with high specificity. ZnTs, ZIPs, and ZFPs have demonstrated relevance in important aspects of health, ranging from epigenetic changes via **DNA methylation** [14,15], to development [15–18], cancer progression/repression [19–27], bone remodeling/mineralization, and atherosclerosis.

Zn plays a pivotal role in preventing and treating various pathophysiological conditions, including cardiovascular, skeletal, and neurological diseases, as well as cancer. One example is atherosclerosis, the most prevalent cardiovascular disease; it is characterized by breakdown in endothelial cell integrity, and Zn can exert cardioprotection through preserving the endothelium [28,29]. In addition, Zn is required for bone formation and mineralization, stimulating osteoblasts while inhibiting bone resorbing **osteoclasts** [30]. To take advantage of the therapeutic features of Zn in various disorders, Zn can be functionalized and incorporated into numerous biomaterials (Figure 1), such as biodegradable stents or porous bone implants, to support, nourish, and stimulate regeneration of damaged blood vessels and new bone formation. Furthermore, Zn nanomaterials and Zn-MOFs can be manipulated to specifically target cancer cells or tissues with overexpressed cancer-specific proteins in a slightly acidic microenvironment, act as bioimaging contrasts, and deliver therapeutic agents (Figure 1). Given these impressive attributes, combined with its fundamental physiological roles, Zn is quickly becoming a primary choice for biomedical applications.

Zinc-Based Biodegradable Metallic Biomaterials

Degradation and Mechanical Properties

Zn has been recently proposed as a novel biodegradable metal thanks to its essential physiological and biological roles (as discussed previously), and its promising *in vivo* degradation rate [3]. The **standard electrode potential** of Zn (-0.76 V/SCE) is between that of Mg (-2.37 V/SCE) and Fe (-0.44 V/SCE), so the degradation rate of Zn is slower than that of Mg but

Glossary

α 2-macroglobulin: a plasma protein with a wide variety of functions, produced by macrophages, fibroblasts, and liver and adrenocortical cells.

Albumin: a transport protein in human blood plasma that also regulates osmotic pressure.

Alzheimer's disease: the most common cause of dementia; it affects memory, cognition, and behavior.

Bacteriolysis: the rupture of a bacterial cell by chemical or physical interactions.

Biodegradable metal: a metal or alloy that degrades in the body.

Biphasic cellular responses: two separate and distinct responses of cells to different signals.

Cell viability assay: an assessment of the ability of a cell to remain viable in the presence of a foreign material.

Chondrocyte differentiation: the differentiation of mesenchymal stem cells (MSCs) to chondroblasts with the secretion of cartilage extracellular matrix.

DNA methylation: the process of adding a methyl group to DNA, which serves as an important regulatory mechanism in epigenetic repression or activation of target genes.

Luminescence: cold-body emission of light from a source.

Metal–organic frameworks

(MOFs): organic–inorganic hybrid materials formed by organic ligands linked to metal ions or clusters.

Osteoclast: a type of multinucleated bone cell that breaks down bone tissue by secreting acid to facilitate maintenance, restoration, and remodeling of bone.

Photoluminescent: emission of light due to absorption of photons.

Photoluminescent quantum yield: emission efficiency from a given photon absorption.

Quantum dots: nanoscale semiconductor particles that have unique electrical and optical properties.

Reactive oxygen species (ROS): chemically reactive species of oxygen, such as hydroxyl radical, superoxide, or singlet oxygen.

Reendothelialization: the migration of endothelial cells and attraction of endothelial progenitor cells to repair

faster than that of Fe. It has been clinically demonstrated that Mg alloys degrade too quickly and Fe alloys degrade too slowly [2], but the behavior of Zn alloys is more likely in line with clinical demand. For example, the *in vivo* degradation behavior of a pure Zn stent in a rabbit abdominal aorta model showed localized corrosion (Figure 2A) [31]. In another study, implants into the abdominal aorta of a Sprague Dawley rat (Figure 2B) exhibited uniform corrosion with degradation rates of ~ 0.05 mm/year after 6 months [3,32], which is promising for biodegradable cardiac stents. The degradation products mainly included insoluble Zn-based compounds, including ZnO , Zn(OH)_2 , $\text{Zn}_3(\text{PO}_4)_2 \cdot 4\text{H}_2\text{O}$ [3,31]. In addition, Ca^{2+} from body fluids could react with zinc phosphate and precipitate as calcium phosphate or Zn-doped calcium phosphate [31,33]. These compounds have lower solubility in aqueous solution and may detached from implants together with substrate particles, which could be resolved or degraded in the physiological environment.

The mechanical properties of Zn and its alloys in comparison to biodegradable stent benchmarks are summarized in Figure 2C. Compared to Mg alloys and Fe alloys, one of the main factors limiting the extensive clinical application of Zn and its alloys is their lower mechanical strength [10]. While it can be improved through alloying with different elements (such as Mg, Ca, Sr, Mn, Cu, or Li), and plastic deformation processing techniques [34], low mechanical strength still remains an important challenge, and more effort is required to obtain a series of alloys with reproducible mechanical strength and ductility. These techniques can also affect the degradation behavior of Zn-based alloys [35,36].

Localized corrosion is easily induced at the interface of the surrounding Zn matrix because of galvanic coupling. Due to homogenization, wrought alloys exhibit more uniform corrosion behavior than cast alloys, and thus superior corrosion resistance. Nevertheless, the effects of various post-treatments for specific alloys on their mechanical and degradation behaviors are still largely unknown. The mechanical integrity during the *in vivo* degradation process should be closely monitored.

In Vitro Biocompatibility

The *in vitro* cytocompatibility of pure Zn shows interesting results [32,37,38], which could possibly result from **biphasic cellular responses** of different Zn ion concentrations [39,40]. This is a concentration-dependent phenomenon, whereby low concentrations of Zn ion are beneficial to cells, while high concentrations are harmful. Zn-1X (X = Ca, Sr, Mg) alloys significantly improved cell viability and proliferation compared to pure Zn (Figure 2D) [41–43]. To test the *in vitro* biocompatibility of biodegradable metallic materials, an extraction medium diluted by a factor of 6:10 for is recommended to obtain reliable and consistent results [44]. A surface oxide film is important for the degradation and biocompatibility behavior of Zn and its alloys [45]. Surface modifications with collagen [37], preincubation in simulated body fluid (SBF) [46], or cell culture medium [47], was also suggested for designing *in vitro* experiments. Therefore, surface modification could be a new strategy to provide programmable biocompatibility and tunable degradation rates [48]. Moreover, the surfaces of orthopedic and dental implants should ideally inhibit bacterial colonization, and concomitantly promote osteoblast functions through its interactions with proteins, bacteria, and cells. For example, a Zn–Cu alloy inhibits biofilm formation better than pure Zn or pure Ti (Figure 2E) [36].

In Vivo Biocompatibility

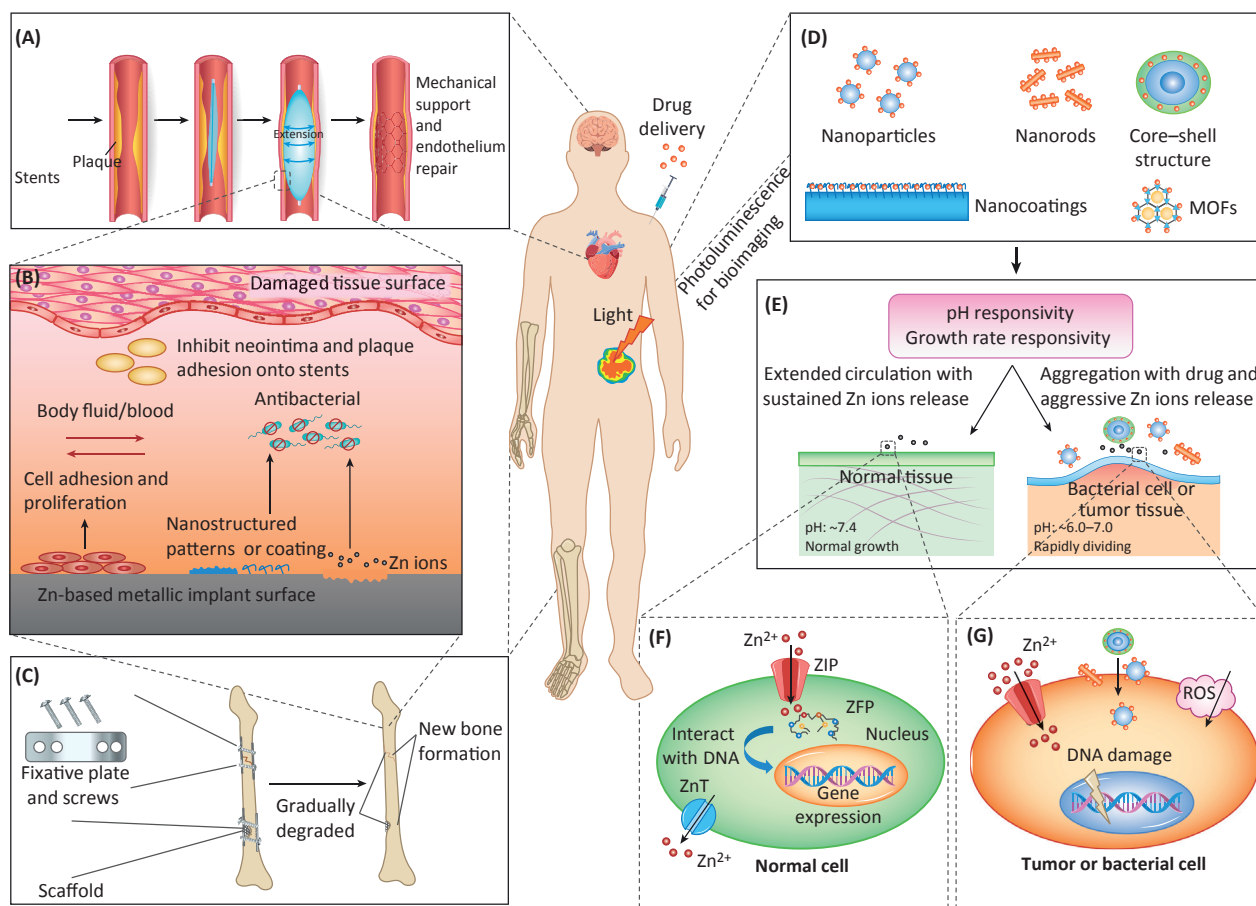
When biodegradable metallic implants corrode, the released degradation products ideally should not induce local or systemic toxicity, but instead promote remodeling and healing of local tissues. A recent study demonstrated there was no severe inflammation (Figure 2F),

a damaged blood vessel following stent implantation.

Standard electrode potential: the electric potential difference measured between a metal and the standard hydrogen electrode, which is set to 0 volts. It tells how easily an element can be oxidized or reduced, and it is associated with the likelihood for electrochemical corrosion/ degradation reactions to occur.

Thrombosis formation: restriction of blood through a blood vessel resulting from a blood clot.

Key Figure

Zn-Based Biomaterials and Their *In Vivo* Interactions with Different Tissues and Cells for Tissue Regeneration and Therapy

Trends in Biotechnology

Figure 1. (A) Metallic Zn-based coronary stents provide mechanical support to the vascular wall, and help repair the endothelium by removing plaque to avoid thrombosis and stent restenosis. (B) *In vivo* interactions of a Zn-based metallic implant surface with damaged tissues: an ideal nanostructured pattern or coating on the surface, and the release of Zn ions from the degradation process may promote cellular adhesion and proliferation while inhibiting the adhesion of bacterial cells or other subjects (such as smooth muscle cells and plaque for a stent). (C) Metallic Zn-based orthopedic implants (fixative plates, screws, and porous scaffolds) provide temporary mechanical support for bone tissue regeneration in a parallel process of implant biodegradation and new bone formation. (D) Nanostructured Zn-based ceramic and organic biomaterials provide high surface/volume ratios for drug delivery and excellent photoluminescence for *in vivo* bioimaging. (E) Nanostructured Zn-based ceramic and organic biomaterials have sensitive responses to pH and cell growth rate, differentiating their circulation or aggregation behaviors on normal tissues, bacterial cell, or tumor tissues. (F) Relatively low concentrations of Zn ions have no adverse, and sometime beneficial, effects on normal cells. (G) High concentrations of Zn ions, aggressive Zn ion release, cellular surface aggregation of Zn-based nanomaterials, and induced ROS, can damage the cell surface and DNA in tumors or bacterial cells. Abbreviations: MOFs, metal-organic frameworks; ROS, reactive oxygen species.

Box 1. Cellular Handling of Zn

Zn is essential for all cellular functions, and has been identified in over 3000 human proteins [19]. Human adults contain approximately 2–3 grams of Zn; 60% is stored in skeletal muscle, 30% is stored in bone, 5% in the liver and skin, and the remaining 2–3% is located in other tissues [19]. Approximately 80% of serum zinc is bound to **albumin** and 20% to **α 2-macroglobulin**. Severe Zn deficiency manifests as anemia, growth retardation, hypogonadism, and mental exhaustion [19]. It does not require a redox reaction like iron or copper, so the precise localization of ZnTs and ZIPs is crucial to proper maintenance of Zn. Ten ZnTs [20], known collectively as the solute carrier family (SLC30), have been identified as responsible for transporting Zn out of the cytosol into the extracellular space, or into lumens of intracellular structures such as the Golgi apparatus, endosomes, or synaptic/secretory vesicles (Figure I) [11]. ZnT1 is primarily localized to the plasma membrane. There are 14 ZIP transporters located at the phospholipid bilayer responsible for the cellular uptake of Zn. ZIP1 is expressed universally in the human body and closely regulates Zn hemostasis. In response to increased cytosolic Zn, metallothionein (MT) protein expression surges to lower the intracellular Zn concentration within appropriate bounds. ZnT and ZIPs are accountable for maintaining functional levels of Zn and protecting the cell from excess influx of Zn, such as during ischemia or during times of Zn deficiency.

Zn finger proteins (ZFPs) can bind to DNA, RNA, and, to a lesser extent, proteins with high specificity. They represent the largest and most diverse family of DNA binding transcription factors. The most characterized and well known is the C2H2 class, which comprises ~700 human proteins, 50% of which contain a Krüppel-associated box (KRAB) domain [21]. Their function is largely unknown, but a few have been shown to suppress transposable elements in embryonic stem cells (ES) through cofactor tripartite motif-containing 28 (TRIM28) [21,22]. ZFP binding to DNA induces conformational and methylation changes in regulatory regions, which influence epigenetic mechanisms and lead to gene silencing or transcription. The eight classes of ZFP include Class 1 Cys2His2 (C2H2), Gag knuckle, Treble clef, Zn ribbon, Zn2/Cy6, TAZ2 domain like, Zn binding loops, and MT [23].

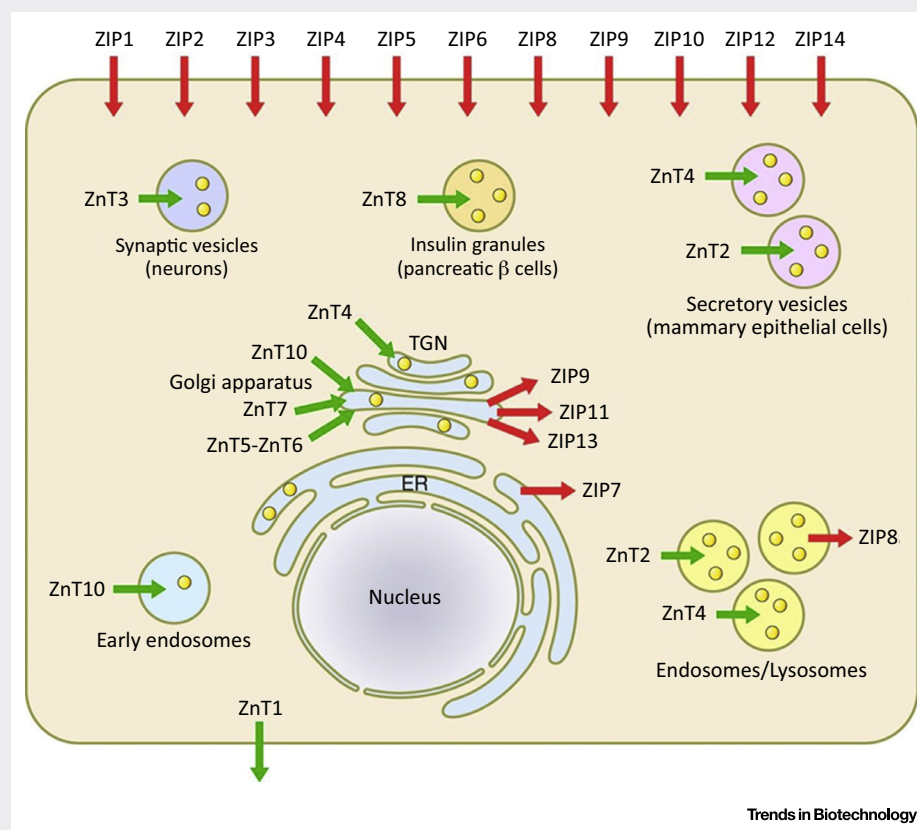


Figure I. Cellular Receptors and Channels of Zn. Reproduced, with permission, from [11].



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platelet aggregation, **thrombosis formation**, or obvious intimal hyperplasia observed during the first 12 months of implantation of Zn in the abdominal aorta of rabbits [31]. In another study, Zn-1X (X = Mg, Ca, Sr) alloys were implanted in femoral shaft from the distal femur of 3-month-old C57BL/6 mice to evaluate the tissue compatibility [41]. Figure 2G shows representative histological cross-sections of implanted pins under fluorescent microscopy. Compared to the control group, the Zn-1X alloys promoted more new bone formation at the periosteum, with the Zn-1Sr alloy exhibiting the most promising osteogenic potential [41]. In contrast, the Zn-Al alloys induced intense inflammatory response due to a high density of mononuclear cells present at the tissue interface surrounding the implants in the abdominal aorta wall of adult Sprague Dawley rats [49].

Cardiovascular Therapy

Zn plays critical roles in maintaining cardiac function, and Zn deficiency is associated with cardiovascular disease [50]. As described previously, the mechanical integrity and good biocompatibility of pure zinc wire provides strong evidence for its promising potential in cardiovascular stents [3,31]. Although the mechanical strength of pure Zn might be insufficient for a biodegradable stent (Figure 2C) [3,9,10], extruded Zn-Cu alloys, and hot rolled Zn-Mn-Cu and Zn-Li alloys, have sufficient mechanical strength and elongation to meet clinical requirements [43,51,52]. Another issue is potentially unstable behavior during *in vivo* degradation, which was assumed to be influenced by the **reendothelialization** process, leading to potentially harmful localized degradation (Figure 2A). However, uniform degradation was also observed during 6 months of implantation *in vivo* (Figure 2B) [3]. Clearly, more *in vivo* studies in larger animals for a longer term are needed to fully ascertain the potential of zinc biomaterials for cardiovascular stent applications.

Orthopedic Regeneration

Zn ion is well known for its roles in bone growth through promoting osteoblast and **chondrocyte differentiation** (cells responsible for new bone generation), while inhibiting osteoclast (cells responsible for bone absorbance) differentiation and resorption [30]. Pure Zn has insufficient strength to act as a load-bearing orthopedic implant (natural bone has a compressive yield strength of 130–180 MPa), but its strength can be significantly improved through alloying. There are many options for fabricating wrought Zn-based alloys, with different alloying elements, including Mg, Ca, Sr, Li, and Cu, beneficial to improve the mechanical properties and bone health [41,53,54]. Nonetheless, so far there are few reports on the *in vivo* implantation of Zn-based alloys in orthopedic applications. The feasibility of novel Zn-hydroxyapatite (HA) composites was explored recently in the form of orthopedic implants with tunable degradation rates, enhanced bone formation ability, and effective antibacterial properties [55]. Compared with Mg and its alloys, the higher density and slower degradation rates of Zn make it more suitable as porous scaffolds for bone, tooth, cartilage, tendon, and spinal regeneration, with potentially more functionalization possibilities (e.g., for drug loading and delivery).

Zinc-Based Ceramic Biomaterials

The richness of structures and properties of the Zn-based nanostructure family endows these materials with diverse functionalities. Zn-based ceramic materials, including zinc oxide (ZnO),

Ca, Sr) alloy after 1 day of culture [41]. (E) Biofilm formation on Zn-4Cu alloy compared to Ti-6Al-4 V after incubation with *Staphylococcus aureus* for 1 day, illustrated by live/dead staining [36]. (F) Representative immunofluorescence staining images of macrophage antibody during implantation, and the corresponding number of macrophages per strut [31]. (G) Representative histology of cross-sections of a mouse distal femoral shaft from Zn-1Mg, Zn-1Ca, and Zn-1Sr implanted pins, and a sham control group, observed under fluorescent microscopy at week 8 post-implant, with green fluorescence indicating new bone formation [41]. Reproduced, with permission, from the indicated references. Abbreviation: mo., months.

Table 1. Major Methods, Characteristics and Biomedical Applications of Zn-Based Ceramic Biomaterials

Category	Methods	Characteristics	Potential biomedical applications	Refs
ZnO	Hydrothermal Sol-gel Vapor-liquid-solid Physical vapor deposition Chemical vapor deposition Biosynthesis	Easy fabrication Antibacterial pH-responsive Large surface/volume ratio Wide band gap Efficient excitonic blue and near-UV emission Phototoxic effect Good biocompatibility	Orthopedic regeneration Drug and gene delivery Bioimaging Cancer therapy	[57] [58,59] [60–63] [64]
ZnS	Hydrothermal/solvothermal One pot synthesis Sol-gel Ultrasonic assisted Microwave assisted	Antibacterial Wide band gap Highly luminescent High transmittance in the visible region High thermal and photochemical stabilities Large surface/volume ratio Good biocompatibility	Drug delivery Bioimaging Cancer therapy	[65,66] [67,68] [69]
ZnSe	Hydrothermal/solvothermal One pot synthesis Solid state reaction Ultrasonic assisted Microwave assisted Chemical vapor deposition	Wide band gap Characteristic emission profile in the UV-blue region High thermal and photochemical stabilities Good biocompatibility	Bioimaging	[70,71]
Zn ₃ (PO ₄) ₂	Hydrothermal Biomimetic Solid state reaction Chemical conversion coating	Good corrosion resistance Excellent biocompatibility	Orthopedic regeneration	[72,73]
ZnAl ₂ O ₄	Hydrothermal Sol-gel Ultrasonic assisted Microwave assisted	Wide band gap High thermal and chemical stability Low sintering temperature High quantum yields Excellent biocompatibility	Orthopedic regeneration Bioimaging	[74] [75]

zinc sulfide (ZnS), zinc selenide (ZnSe), zinc phosphate [Zn₃(PO₄)₂], and zinc aluminate (ZnAl₂O₄), have been extensively explored in a variety of biomedical applications [7,56]. The major methods, characteristics, and biomedical applications of Zn-based ceramic biomaterials are summarized (Table 1) and discussed in the following sections [57–75].

Antibacterial and Biocompatibility

The Zn²⁺ ions released from Zn-based ceramic materials could potentially interact with bacterial surfaces, altering charge balance and inducing cell deformation and **bacteriolysis** [76]. Theoretically, all Zn-based biodegradable materials can potentially have antibacterial abilities. Apart from these antibacterial mechanisms, photocatalytic and nanoantibiotic mechanisms predominate through generation of **reactive oxygen species (ROS)** and specific nanostructures, respectively [56]. Therefore, nanostructured Zn-based ceramic materials, especially the photocatalytic ZnO and ZnS, exhibit unique antibacterial properties. The cytotoxicity of ZnO nanoparticles to various mammalian cell types is mainly due to increased intracellular Zn²⁺ ions as a result of ZnO solubility. Other Zn-based nanoparticles or **quantum dots** may also have similar issues under certain physicochemical and environmental conditions [77]. However, other nanostructures (e.g., nanowires and nanorods) or thin films have been reported with significantly improved cytocompatibility [78,79], especially when composited with other inorganic and organic agents [80], which is another potential direction for Zn-based nanomaterials.

Skeletal Repair and Regeneration

Due to their inherent antibacterial properties, Zn-based nanomaterials have attracted much attention, but there are few reports for tissue regeneration applications so far. However, incorporating Zn into various biomaterials, including calcium phosphates [81], bioactive glasses [82], and titanium dioxide (TiO₂) [30,57], could greatly enhance bone formation through inhibiting osteoclasts while stimulating osteoblastic differentiation. TiO₂ has been extensively studied as a biocompatible coating on Ti implants for orthopedic regeneration [83], but TiO₂ nanoparticles can induce significant oxidative DNA damage and apoptosis in human liver cells, even at a concentration of 1 µg/ml [84]. Nanostructured ZnO/TiO₂ hybrid nanofibers show enhanced cell adhesion, proliferation, and spreading behavior (Figure 3B) [57]. This provides a new promising direction for biodegradable coatings with Zn-based ceramic biomaterials. For example, Zn₃(PO₄)₂ and ZnAl₂O₄ coatings have demonstrated excellent cytocompatibility [73,74]. In addition, because of the released Zn ions, Zn-containing composites could potentially provide antibacterial properties for orthopedic implants to decrease or eliminate bacterial infections and the subsequent complications in the orthopedic surgery.

Drug Delivery

Nanoparticles have been studied extensively as drug delivery systems due to their outstanding merits (e.g., high stability, big surface area, and easy fabrication and incorporation), to target specific cells and control drug release in different microenvironments [85]. ZnO and ZnS nanoparticles have been studied as a type of pH-responsive drug carrier to target tumor cells, which have significantly lower pH values than normal cells and tissues [5,58]. Traditionally, ZnO and ZnS nanoparticles, or quantum dots, have been used as cappers to cover the pores of mesoporous silica nanoparticles (MSNs), or one component in the nanocomposites [58,65,86]. Because of the adsorption and nondegradability of MSNs, nanocomposites are preferred for drug delivery systems. *In vitro* and *in vivo* active tumor targeting is possible using microwave-assisted synthesized water-dispersed NIR Cd composite with degradability, rapid pH response, and stable **luminescence** in an aqueous solution. This system ensures the stability and accuracy of the drug release is safe for normal tissues, and can be monitored during the drug delivery process (Figure 3A) [58].

Bioimaging

The inherent **photoluminescent** properties and good compatibility of Zn-based ceramic nanomaterials make them superior bioimaging agents over traditional organic fluorescent dyes and commonly used CdSe and CdTe QDs. Therefore, most of the Zn-based nanomaterials in Table 1, including ZnO, ZnS, ZnSe, and ZnAl₂O₄, have been studied for their bioimaging applications. Surface modification using certain polymeric or silica ligands to form a core-shell or core-shell-shell structure is a key method for achieving chemical stability and high **photoluminescent quantum yield** in aqueous solutions, especially circulating blood [56]. In *in vivo* animal imaging, because the animal body cannot be penetrated by UV excitation when using ZnO QDs, a dual modal imaging ZnO-based nanoprobe incorporated with radionuclide (e.g., ⁶⁴Cu), or rare earth elements (e.g., Gd³⁺ and Yb³⁺), was used to achieve good tumor targeting and image contrast [56]. Similar results were found with ZnS, ZnSe, and ZnAl₂O₄ QDs doped with Ag, In, and Cr [67,68], but the biosafety of these doping elements is a concern. Thus, Fe and Mn could be alternatives with improved biocompatibility [63,71]. *In vivo* bioimaging of **Alzheimer's disease** was also achieved through targeted biolabeling fluorescent ZnO nanoclusters, which are biosynthesized and specifically accumulate in the hippocampus [62]. Similar results with high spatiotemporal dual-modality bioimaging (i.e., magnetic resonance and fluorescence imaging) were obtained in a subsequent study through the combined

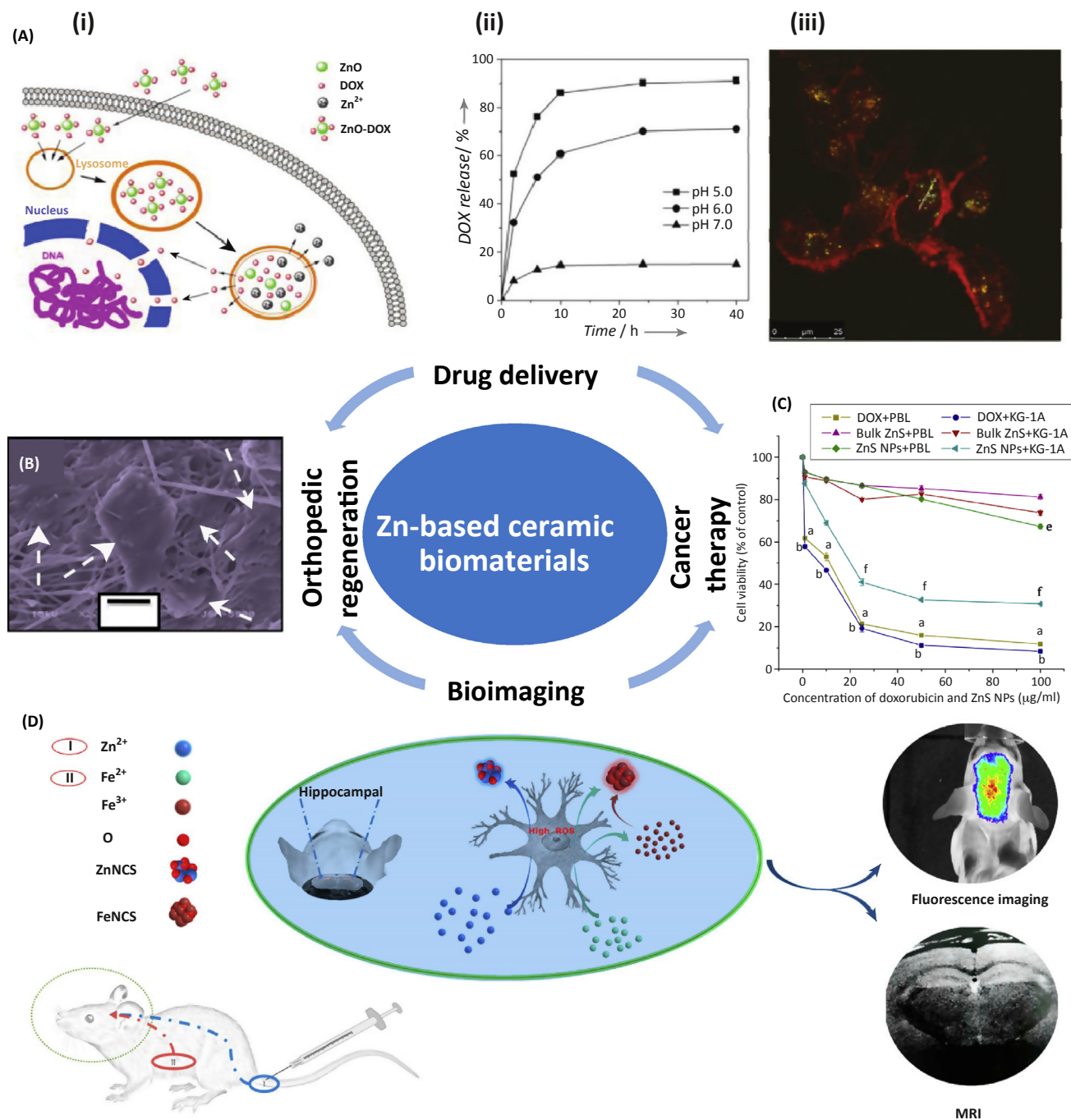


Figure 3. Potential Clinical Applications of Zn-Based Ceramic Biomaterials. (A) Multifunctional ZnO@polymer-DOX composites for drug delivery: (i) schematic delivery process into the cells, (ii) drug release profiles at different pH values, and (iii) CLSM images of U251 cells after 3 h incubation with the composites and lysotracker. The green emission is from the lysotracker; the red emission is from the composites [58]. (B) SEM images of the cellular spread pattern (white arrows) of C2C12 cells after 72 h incubation on electrospun ZnO/TiO₂ nanofibers [57]. (C) **Cell viability assay** of peripheral blood lymphocytes (PBL) and KG-1A cell (leukemic C2C12 cells) after 72 h incubation on electrospun ZnO/TiO₂ nanofibers [57]. (D) **Bioimaging** applications of Zn-based ceramic biomaterials. (Figure legend continued on the bottom of the next page.)

injection of ferrous chloride solution post-stomach, and Zn gluconate solution post-tail vein, into Alzheimer's model mice, as shown in Figure 3D [63].

Cancer Therapy

One of the timeliest clinical applications for drug delivery and bioimaging is cancer therapy. A key goal is to construct a synergistic nanoplatform for combined cancer targeting, bioimaging, and responsive drug delivery [87]. Multifunctional ZnO@polymer-DOX nanocomposites (Figure 3A) [58], including surface modifications with targeting moieties (e.g., folic acid [88]), are typical examples. In addition to smart drug delivery nanocarriers and bioimaging agents, ZnO and ZnS based composite nanoparticles show a strong preference to kill tumor cells [64,69]. Different cell types and their manner of proliferation could influence the cytotoxic and genotoxic properties of Zn-based ceramic nanoparticles, which induce generation of higher levels of ROS in rapidly dividing cells compared to noncancerous cells [89]. The selective cytotoxic effect of ZnS nanoparticles was observed in leukemic cells and human normal lymphocytes, resulting from the different internalization of Zn²⁺ ions in these two cells, as shown in Figure 3C [69]. Similar selective antiproliferative performance of ZnO nanoparticles were observed in a coculture mode of C2C12 myoblastoma cancer cells and 3T3-L1 normal cells [64].

Zinc Organic Biomaterials

MOFs are being utilized in many biotech applications, including drug delivery systems, bioimaging, and cancer therapy [8,90]. High surface area and pore volume, in combination with facile modification and chemical functionalization, have made them attractive tools in biomedical engineering. Zeolitic imidazolate MOF-8 (ZIF-8), formulated for cancer therapy and tested on HepG2 cells, exhibited slow release profiles (<15% over 24 h) under neutral conditions, and accelerated release (>50%), when under pH 6.0 [91]. Similarly, temperature and pH responsive Zn-MOFs increase drug release with increasing temperature and pH. MOFs can also be used as coatings to regenerate bone in tissue engineering applications. For example, nano ZIF-8 thin films have been applied to surfaces of porous titanium to improve osteogenic activity and antibacterial effect [92].

Concluding Remarks and Future Perspectives

The significant physiological and biochemical roles of zinc have been illustrated by a great number of studies describing its biological functions, health implications, and pharmacological targets. The progressive understanding of multifunctional Zn could facilitate the development of Zn-based biomaterials. Compared to Mg and Fe, Zn-based alloys have more desirable degradation characteristics for cardiovascular therapy and orthopedic regeneration. Zn-based ceramic biomaterials, in the form of nanoparticles, coatings, or other nanomaterials, are promising in the emerging field of theranostics, including drug delivery, tissue targeting, bioimaging, and cancer therapy. In addition, other Zn-containing nanomaterials and organic materials (e.g., MOFs) show various biofunctional properties and have great potential as smart materials for drug delivery, bioimaging, and cancer therapy.

Inspired by the promising results of Zn alloys in bone fixation and vascular stents, more Zn-based implants or devices could be developed for other clinical applications. For example, Zn wire seems to be suitable for fixation of comminuted fractures and tension fixation in

Outstanding Questions

What properties and functions of Zn-based biomaterials are optimal for the regeneration and therapy of specific tissues?

How to functionalize Zn-based biomaterials for the regeneration and therapy of specific tissues?

How to tune the biodegradation rate of Zn-based implants *in vivo* and maintain the mechanical and biofunctional support long enough for complete healing during degradation?

How to minimize the unwanted toxicity of Zn-based biomaterials, while maximizing their antimicrobial, anticancer, and other desirable features, for applications in tissue regeneration and therapy?

How feasible are therapeutic Zn-based microscale or nanoscale medical devices in the future?

cells) when cultured with DOX, bulk zinc sulfide powder, and ZnS nanoparticles for 24 h [69]. (D) Schematic illustration of *in vivo* dual-modality bioimaging of modeled Alzheimer's mice brains, through biosynthesized zinc and iron oxide via the combined injection of ferrous chloride solution post-stomach, and zinc gluconate solution post-tail vein [63]. Reproduced, with permission, from the indicated references.

intercondylar fractures, as well as medical sutures in wound closure. Zn-based staples/clips are also good candidates for gastrointestinal anastomosis applications. Additionally, highly porous Zn-based scaffolds filled with different soft materials containing growth factors and cells could be useful as bone graft substitutes for segmental or large bone defects.

Based on the clinical requirements for controllable degradation rate, prolonged stability and excellent biocompatibility, discovering and implementing new strategies to improve the targeting, mechanical features, degradation pace, or biocompatibility, will enhance the usefulness of Zn-based biomaterials for regeneration and therapy (see Outstanding Questions). Reproducible and improved mechanical profiles of Zn-based alloys could be obtained by proper alloying and post-treatments, and changes to the mechanical integrity *in vivo* during degradation could be modeled by *in vitro* tests in appropriate SBFs under dynamic conditions. Surface modifications, composites, or porous structures could be applied to create multifunctional designs for Zn-based nanomaterials. This approach will help to construct a synergistic nanoplatform for combined cancer targeting, bioimaging, and responsive drug delivery, or to obtain a selectively cytotoxic or cytocompatible effect on bacterial cells, tumor cells, or normal mammalian cells.

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