Nanoparticles: a promising new therapeutic platform for bone regeneration?

“Addressing these existing challenges will open up new avenues for the effective utilization of CaPn as drug delivery systems in bone tissue engineering and regeneration.”

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Nanomedicine is an emerging field of research for the treatment of a number of diseases. This editorial will concentrate on the application of nanotechnology in the treatment of skeletal-related disorders. Bone is a dynamic tissue that plays a biomechanical role in locomotion and a chemical role in mineral homeostasis. Unlike most tissues, bone is capable of continuous regeneration without formation of scar tissue through its unique biological structure and components [1]. However, this ability is only limited to the repair of simple and small structural disruption. From a clinical standpoint, treatment of bone defects brought on by trauma (fractures), diseases (infection and cancer) and age (osteoporosis) remains a formidable challenge [2].

Osteoporosis is a bone disease that reduces bone mineral density, often leading to osteoporotic fracture at an incidence of 9 million per year and costing the health sector billions of dollars worldwide [3]. Bisphosphonates (BPs) are one of the most effective pharmaceutical treatments available [4]. However, the problem remains in the targeted delivery of the drug at therapeutic levels. Osteomyelitis (bone infection) is another formidable medical challenge that can be lethal particularly for large bone defects [5]. Osteomyelitis is recognized as a global health problem by

WHO [6]. The major cause of osteomyelitis is bacterial infections by *Staphylococcus aureus* introduced during a severe bone injury or fixation surgeries. Standard treatments for infected bone defects include surgical removal of the infected bone, local or systemic administration of antibiotics and use of bone grafts. However, these treatments remain suboptimal in controlling the infection [7]. Therefore, there is a pressing need for an effective technology that can simultaneously eliminate the infection and accelerate new bone formation. Cancer is known as the main cause of death worldwide, and it is speculated to be the leading cause of death for 24 million individuals by 2030 [8]. Although primary bone cancer is rare, bone metastasis is common as a type of bone cancer due to the close interaction between cancer cells and the bone marrow environment [9]. Current treatment for bone cancer involves surgical resection, radiotherapy, chemotherapy or a combination of these methods. However, these treatments have several limitations, including the resistance of cancer cells to anticancer drugs, dose-related side effects due to non-targeted drug treatment, cancer recurrence at the site of tumor resection, limb loss in the case of aggressive cancers (osteosarcoma) and poor ability for new bone formation at the resection site.

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Nanomedicine: a paradigm shift in bone regeneration

Richard Feynman was the first to present the vast potential of the nanoscale domain, whereby he introduced the top-down nanotechnology approach during his lecture, 'There's Plenty of Room at the Bottom', in 1959 [10]. Since then, enormous progress has been made in the development of nanomaterials and their applications in various sectors, such as electronics, construction, environmental sciences, transportation, energy and medicine. Nanoparticles constitute the main pillar in nanomedicine, offering a range of unique properties including a high surface area to volume ratio, as well as unique optical properties and chemical characteristics. Nanomedicine research is actively being applied to oncology, infectious diseases, and diseases of the CNS and cardiovascular system [11]. Around 80% of research publications in nanomedicine are focused on drug delivery by nanoparticles [12]. Medical nanoparticles can be divided into two categories: hard and soft particles. Soft nanoparticles include liposomes (nanoparticles with the longest history of use in medicine), dendrimers, micelles and polymeric particles. Hard nanoparticles include inorganic and metallic particles, such as silica and gold, quantum dots and carbon nanotubes [13]. The cellular uptake and biodistribution of nanoparticles can be controlled by altering their size, shape, surface charge and porosity [14]. Nanoparticles, such as mesoporous silica, gold, magnetic iron oxide, calcium phosphates, layered double hydroxides, poly(lactic-co-glycolic) acid and chitosan are continually explored for their use in targeted delivery and sustainable release of drugs, or as inhibitory factors of signaling pathways for the treatment of bone diseases [15]. One attractive strategy is to utilize nanoparticles for the treatment of osteoporosis, by developing a drug delivery system that specifically binds to osteoporotic bone. Using BPs as a linker agent between nanoparticles and bone minerals is an alternative option for developing a targeted delivery system for bone, due to the high affinity of BPs for calcium phosphates [16]. Another strategy is to control the function of bone cells using nanoparticles loaded with specific inhibitors for osteoclasts (bone resorbing cells) and promoters for osteoblasts (bone forming cells) to prevent the progression of osteoporosis. Nanoparticles functionalized with BPs can be developed for targeted drug delivery to metastasized bone, in an attempt to increase the therapeutic efficacy of the drug and to reduce the side effects on nontargeted areas. A large amount of research is being conducted in developing nanoparticles for clinical use, such as poly(lactic-co-glycolic) acid, hyaluronic acid and chitosan, in the targeted delivery of drugs, growth factors or genes

to an osteoarthritic joint [17]. Conjugation of these nanoparticles with cartilage targeting molecules, such as chondroitin sulfate and chondrocyte-affinity peptide, has enabled the targeted delivery of inflammatory inhibitors. One of the effective strategies in treating osteomyelitis is to incorporate drugs with both osteo-inductive and antibacterial effects into nanoparticles as a codelivery configuration incorporation of multiple drugs into nanoparticles can be achieved through the combination of various techniques, including internal encapsulation, chemical binding, surface adsorption and surface coating methods.

Bone repair is a complicated process, where significant challenges remain in the lack of blood vessel formation and slow rate of bone mineralization. For decades, the focus in the research community has been on the delivery of a single growth factor, particularly members of the bone morphogenetic protein family or VEGF [18]. The use of nanoparticles can be an effective approach for dual or multiple drug delivery systems to facilitate bone healing. However, limitations of these approaches include the lack of synergistic effects in dual delivery of the drugs, and inability to achieve controlled release for more than one drug which leads to a risk of overdose and toxicity. Therefore, it is imperative to fully optimize a multidelivery system, by investigating the appropriate combination of drugs or growth factors and using the correct dosage to maximize bone healing.

Currently, the approval process for medical nanoparticles in humans is regulated by the US FDA. This process is the same as for traditional drugs and biologics, meaning that the clinical use of nanoparticles is subject to extensive preclinical and clinical validation. The entire process is estimated to take approximately 12 years, with preclinical tests involving animal studies to demonstrate safety and efficacy of the product. A total of 51 products comprising nanoparticles and drugs, biologics or imaging agents are FDA approved, and 77 products are now in clinical trials [19]. Polymeric nanoparticles, micelles and liposomes, as well as inorganic nanoparticles are the main categories for these products. Despite the availability and frequent use of these nanoparticles, an ideal delivery vehicle with the ability to transport multiple drugs or bioactive molecules to a specific target in bone has not yet been developed. The main hurdle in advancing the development of such products is a lack of understanding of pharmacokinetics and complexity of the *in vivo* environment, compared with the simplified *in vitro* environment where physiochemical validations are typically conducted. Calcium phosphate (including hydroxyapatite and β -tricalcium phosphate) nanoparticles (CaPn) represent an ideal platform for bone-specific drug delivery due to their biocompatibility, biodegradability

and biological activity [20]. A significant advantage of using CaPn is that they are found throughout the body as the major constituent of bone and tooth enamel. Unlike soft nanoparticles, the degradation products of CaPn are calcium and phosphate ions that are abundantly found in bloodstream, and hence do not trigger an immune response. Moreover, CaPn do not undergo enzymatic cleavage and have a pH-dependent degradation, exhibiting stability at pH 7.4 and increased solubility at reduced pH. Among CaPn, hydroxyapatite nanoparticles undergo dimensional changes in buffer solutions, while β -tricalcium phosphate nanoparticles can retain their original shape and size, making them interesting candidates in nanomedicine. Future progress in utilizing CaPn to treat bone diseases needs to explore the development of nano- or mesoporous CaPn to maximize their drug-loading capacity and retention. Addressing these existing challenges will open up new avenues for the effective utilization of CaPn as drug delivery systems in bone tissue engineering and regeneration. Another interesting strategy is to combine nanoparticles with bone scaffolds to obtain a multifunctional scaffold. The scaffold can serve as both a support structure for cells and a drug carrier. The incorporation of nanoparticles into scaffolds can be an effective approach for achieving multidrug delivery.

This will allow for sustainable delivery of a range of drugs at different release profiles.

Future perspective

Our belief is that the future of nanomedicine in the bone health sector will rely on nanoparticles that combine active targeting, diagnosis, responsive multidrug release and imaging. The development of ideal nanomaterials capable of triggering the bone regeneration process remains to be a primary challenge in the field. In the near future, it is anticipated that technological advances will lead to the development of nanoparticles with ideal properties and propel their translation into the clinic, ultimately leading to improved therapeutic outcomes in patients with skeletal-related disorders.

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References

- Gusić N, Ivković A, VaFaye J *et al.* Nanobiotechnology and bone regeneration: a mini-review. *Int. Orthop.* 38(9), 1877–1884 (2014).
- Pilia M, Guda T, Appleford M. Development of composite scaffolds for load-bearing segmental bone defects. *Biomed. Res. Int.* 2013, 1–15 (2013).
- Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos. Int.* 15(11), 897–902 (2004).
- Fazil M, Baboota S, Sahni JK, Ameduzzafar, Ali J. Bisphosphonates: therapeutics potential and recent advances in drug delivery. *Drug Deliv.* 22(1), 1–9 (2014).
- Nandi SK, Bandyopadhyay S, Das P *et al.* Understanding osteomyelitis and its treatment through local drug delivery system. *Biotechnol. Adv.* 34(8), 1305–1317 (2016).
- Lu H, Liu Y, Guo J, Wu H, Wang J, Wu G. Biomaterials with antibacterial and osteoinductive properties to repair infected bone defects. *Int. J. Mol. Sci.* 17(3), 1–18 (2016).
- Snoddy B, Jayasuriya AC. The use of nanomaterials to treat bone infections. *Mater. Sci. Eng. C Mater. Biol. Appl.* 67, 822–833 (2015).
- Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *Lancet Oncol.* 13(8), 790–801 (2012).
- Buenrostro D, Mulcrone PL, Owens P, Sterling JA. The bone microenvironment: a fertile soil for tumor growth. *Curr. Osteoporos. Rep.* 14(4), 151–158 (2016).
- Feynman R. There's plenty of room at the bottom. *Eng. Sci.* 23(5), 22–36 (1960).
- Zazo H, Colino CI, Lanao JM. Current applications of nanoparticles in infectious diseases. *J. Control. Release* 224, 86–102 (2016).
- James K, Highsmith J, Highsmith J. Nanotechnology market – nanotechnology markets in healthcare & medicine. *Drug Dev. Deliv.* 11(12), 43–45 (2014).
- Kannan RM, Nance E, Kannan S, Tomalia DA. Emerging concepts in dendrimer-based nanomedicine: from design principles to clinical applications. *J. Intern. Med.* 276(6), 579–617 (2014).
- Saptarshi SR, Duschl A, Lopata AL. Interaction of nanoparticles with proteins: relation to bio-reactivity of the nanoparticle. *J. Nanobiotechnology* 11(1), 26 (2013).
- Gong T, Xie J, Liao J, Zhang T, Lin S, Lin Y. Nanomaterials and bone regeneration. *Bone Res.* 3, 15029 (2015).
- Cole LE, Vargo-Gogola T, Roeder RK. Targeted delivery to bone and mineral deposits using bisphosphonate ligands. *Adv. Drug Deliv. Rev.* 99, 12–27 (2016).
- Holyoak DT, Tian YF, van der Meulen MC, Singh A. Osteoarthritis: pathology, mouse models, and nanoparticle injectable systems for targeted treatment. *Ann. Biomed. Eng.* 44(6), 1–14 (2016).

- 18 Farokhi M, Mottaghitalab F, Shokrgozar MA, Ou KL, Mao C, Hosseinkhani H. Importance of dual delivery systems for bone tissue engineering. *J. Control. Release.* 225, 152–169 (2016).
- 19 Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm. Res.* 33(10), 2373–2387 (2016).
- 20 Bose S, Tarafder S. Calcium phosphate ceramic systems in growth factor and drug delivery for bone tissue engineering: a review. *Acta Biomater.* 8(4), 1401–1421 (2012).