Nanoparticles for the potential treatment of osteoporosis

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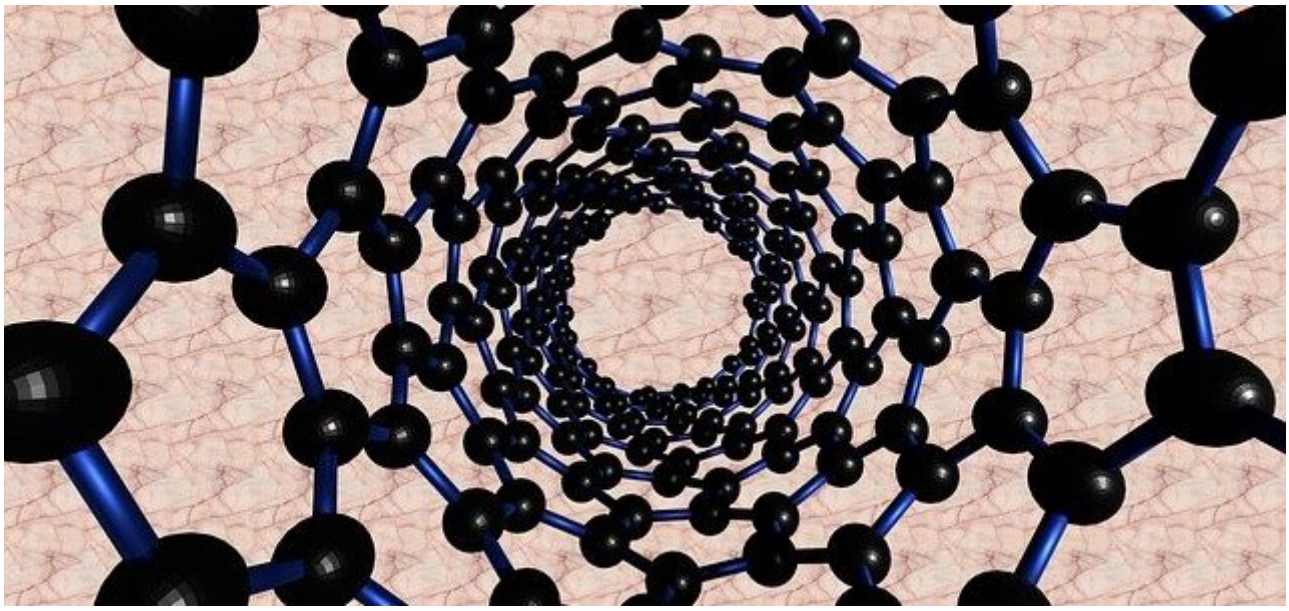
BONE REGENERATION DRUG DELIVERY OPINION OTHER THERAPEUTICS



In this original editorial piece, María Vallet-Regí, Patricia Mora-Raimundo, Daniel Lozano and Miguel Manzano (all at the Universidad Complutense de Madrid, Spain) discuss the use of nanoparticles for the potential treatment of osteoporosis, in light of some of their recently published work in the field.

In the last few decades, the global life expectancy has risen considerably, which has consequently increased the impact of skeletal diseases, such as osteoporosis. In this sense, osteoporosis is defined by the WHO as a 'progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture' [1].

The bone remodeling process is governed by the action of osteoclasts, which resorb old bone, and osteoblasts, which subsequently stimulate new bone formation. Current conventional therapies are limited to two main groups: antiresorptive drugs, which slow down bone resorption and include bisphosphonates, denosumab, estrogen or raloxifene, among others, and anabolic drugs, which stimulate bone formation, such as teriparatide. Although these conventional drugs are effective in reducing the fracture risk and increasing bone mineral density , they present some limitations and side effects, which restrict their long-term administration and reduce treatment adherence.

Recognition of signaling pathway targets has led to the development of new antiosteoporotic agents. As a consequence, new therapeutic approaches have been proposed for osteoporosis treatments, such as cathepsin K inhibitors, antisclerostin antibodies, parathyroid hormone analogs or therapies based on gene expression modification by the application of small interfering RNAs (siRNAs) [2]. The main drawback of these therapies is their short half-lives due to degradation by different enzymes – proteases in the case of peptides and nucleases in the case of nucleic acids. Further, due to the complexity of diverse diseases such as osteoporosis, it has become increasingly clear that drugs administered alone, targeted to specific molecular pathways, present limitations. Therefore, another possible approach considered for increasing treatment efficacy is the combined use of several drugs, known as combination therapy.

Over the last few years, nanoparticles have been found to be promising systems for efficient therapeutic delivery in bone disease therapy. The development of nanoparticles for bone regeneration in osteoporosis patients seems to be ideal, since bone itself is a nanocomposite. In addition to this dimensional similarity, nanoparticles can offer several benefits. First, they can enhance therapeutic delivery and increase tissue specificity, boosting therapy efficiency. They also provide drug protection from biodegradation and improve drug pharmacokinetics, pharmacodynamics, biodistribution and targeting, decreasing doses without sacrificing treatment efficacy [3]. Additionally, nanoparticles could also reduce exposure of the therapeutic agent to non-target cells, minimizing its potential side effects and improving the life quality of patients. Moreover, regarding combination therapy, nanoparticles could also play a key role in this field, offering the possibility of loading several drugs and transporting them to the target tissue. In this way, the number of medications required to be administered would be reduced and adherence could be potentially improved.

In the frame of nanomedicine and, more specifically, in the field of osteoporosis treatment, different nanoparticles have been developed, such as liposomes, dendrimers, polymeric nanoparticles, iron oxide or gold nanoparticles, and mesoporous silica nanoparticles (MSNs), among others. Compared with other types of particles, MSNs present higher robustness due to their silica framework [4]. They are mechanically, thermally and chemically stable, allowing harsh reaction conditions for their modifications. MSNs have been used for the delivery of osteoporotic conventional drugs, such as alendronate, calcitonin or zoledronic acid, however, they could also be functionalized for the transport of nucleic acids, presenting a potential alternative method for delivering siRNAs to target cells. The mesoporous structure of the nanoparticles also allows the loading of several drugs and, therefore, empowers a dual treatment.

In our recent work [5], which was carried out in the context of the Advanced Grant VERDI (polyvalent mesoporous nanosystem for bone diseases) from the European Research Council (Brussels, Belgium), the purpose was to co-deliver two therapeutic agents – *SOST* siRNA and osteostatin – inside cells using MSNs as nanocarriers. The employed siRNA was selected to silence *SOST*, which is responsible for the expression of sclerostin, overexpression of which reduces osteoblast formation and differentiation through inhibition of the Wnt/β-catenin pathway. Thus, silencing *SOST* with a specific siRNA in osteocytes could represent an effective alternative treatment approach. Additionally, the network of cavities from MSNs allowed loading an osteogenic peptide, osteostatin – a parathyroid hormone–related peptide that has been observed to stimulate osteoblastic cell growth and differentiation.
The developed platform was able to transport, co-deliver and transfect *SOST* siRNA and osteostatin, maintaining their activity and achieving an effective silencing effect. Surprisingly, the combination of *SOST* siRNA with the osteogenic peptide in ovariectomized mice resulted in a synergy – not only knocking down the selected gene, but also increasing the expression of early markers of osteogenic differentiation. This system has demonstrated remarkable efficacy for an intrabone marrow injection. In consequence, this system will constitute a potential candidate as a platform for gene therapy in osteoporosis treatment and might lead to further investigations.

Taking everything stated above into consideration – and regarding the promising results obtained in our work – it could be concluded that nanoparticles and, more precisely, MSNs, present huge potential in the frame of osteoporosis treatment. However, there is still a huge amount of effort and research that needs to be done before translating this research into the clinic to improve patients' conditions in the fight against osteoporosis.

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Disclosures:
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