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Mesoporous silica nanoparticles and osteoporosis

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Nanomedicine

The application of nanotechnology in medicine has given rise to a new discipline: nanomedicine, which, as we can imagine, is a multidisciplinary field where many main actors take part: engineers, physicists, chemists, biologists, doctors and even legislators[1]. Nanomedicines are so popular today among the scientific community due to a series of factors, among which we would highlight the control over the pharmacokinetic profile, the protection of transported therapeutic agents against possible degradation within the organism, the possibility of developing targeted therapies towards specific tissues, the possibility of including different therapeutic agents in the same transporter and even the possible inclusion of contrast agents to have a biomedical image for diagnosis. In this sense, among the possible systems of drug release, nanoparticles have acquired great prominence since they present great versatility from the point of view of their composition, shape, size, and external surface[2].

This makes them the focus of a large number of biomedical researches for either the treatment of certain diseases, their prevention, diagnosis, or even in tissue engineering.

Mesoporous silica nanoparticles

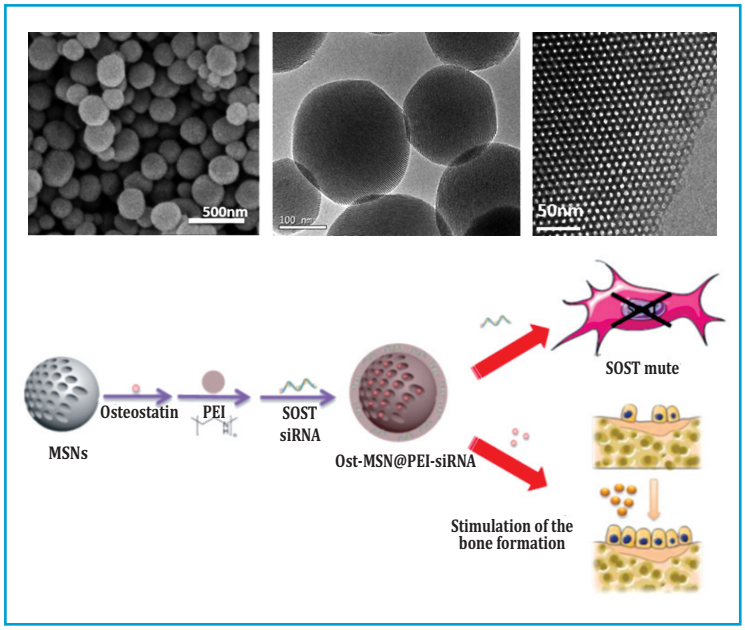
Among all the nanoparticles used in the field of nanomedicine, whether organic or inorganic, mesoporous silica nanoparticles (MSNs) are being widely studied in recent years as transport vectors for therapeutic agents[3].

Their notoriety could be attributed their robustness, their porous system's very high load capacity, their ability to protect drugs against possible degradation and the ease with which their outer surface can be modified[4]. The synthesis of these nanoparticles is based on the combination of 3 methods: the sol-gel process, in which the hydrolysis and condensation of the silica precursors that will form the three-dimensional web of SiO_2 takes place; the use of surfactants as directing agents of the structure as templates, so that the silica condenses around the structures created by these surfactants which, after their elimination, will prompt a network of cavities or mesoporous structures; and the use of high dilution conditions, as proposed by the Stöber method, which allows to obtain spherical shaped nanoparticles of very defined diameters, between 100 and 150 nm, and with pores of around 2 nm, available to be loaded with therapeutic agents. In this sense, the concept of introducing drugs inside the pores of mesoporous materials to later be released into the organism was first proposed by Professor María Vallet-Regí in 2001. This has inspired considerable research conducted by different groups around the world[5]. In this sense, our research group has worked hard in recent years to develop MSNs capable of accumulating in different tissues in a specific way and releasing loaded drugs in response to different stimuli[6] (figure 1).

Treatment of osteoporotic situations

Among all the possible applications, an interesting example in which we have worked on in recent years is the use of mesoporous silica nanoparticles for the possible treatment of osteoporosis[7,8].

Figure 1



Top: Scanning and transmission electron microscopy images of mesoporous silica nanoparticles. Bottom: Strategy to coat the nanoparticles with a cationic polymer to transport the siRNA that will silence the SOST gene and stimulate new bone formation.

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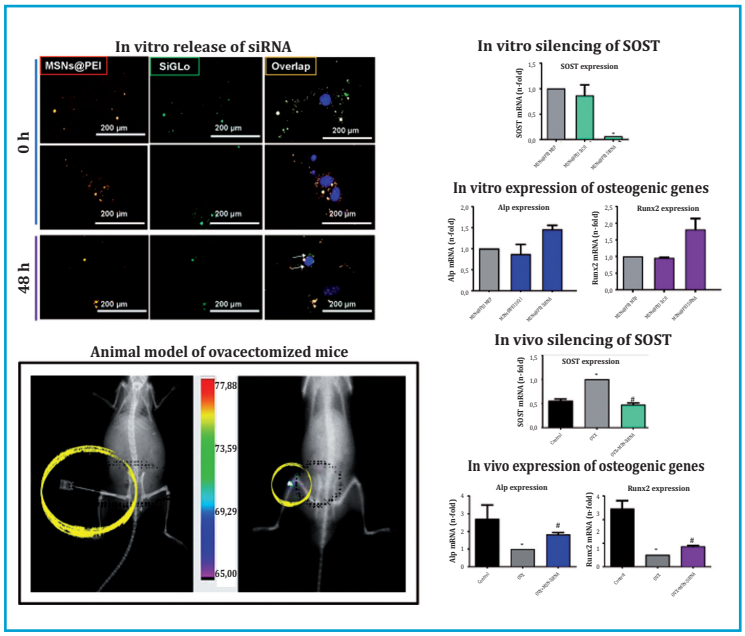
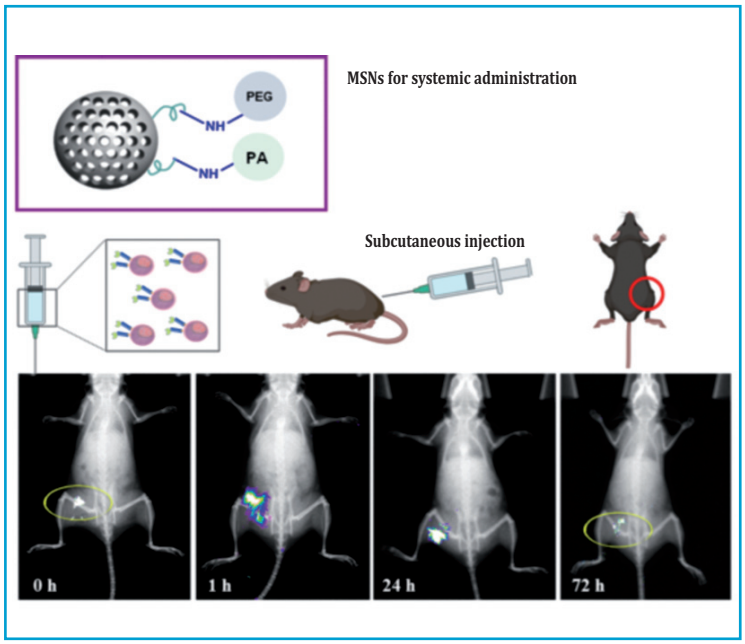
Figure 2



Top: Release and in vitro silencing studies of the SOST gene and the expression of other osteogenic genes. Bottom: Administration of the nanoparticles by femoral bone marrow injection in an osteoporotic female mice model and subsequent in vivo studies of SOST gene silencing and expression of other osteogenic genes.

Figure 3



Top: Design of the nanoparticles for systemic administration by subcutaneous injection. Bottom: Images at different times of the injected animal where the permanence of the nanoparticles in the area up to 72 hours after injection can be noticed.

In an osteoporotic setting, the WNT/β-catenin signaling pathway, which normally participates in the differentiation of mesenchymal stem cells to osteoblasts, is inhibited. This happens due to the overexpression of the sclerostin protein, which is encoded by the SOST gene. The consequence of this inhibition is the reduction of osteoblastic differentiation and, as a consequence, the reduction of bone formation and loss of bone mass so characteristic in osteoporosis. Our working hypothesis has been based on the possibility of silencing the SOST gene using a small interfering RNA (siRNA), in order to reduce sclerostin expression and to be able to reactivate the WNT/β-catenin cycle, and thus reactivate osteoblastic differentiation and consequently increase bone formation, so important in osteoporotic scenarios. However, siRNAs have very short life spans and very poor ability to penetrate cell membranes, so their biggest problem is their administration, and that is where our nanoparticles acquired great relevance. We coated our MSNs with a cationic polymer capable of retaining the siRNA on their surface to be later released, silencing the SOST gene and causing increased bone formation.

After optimizing the system in terms of siRNA design and loading, we found that our nanoparticles were capable, not only, of releasing siRNA inside cells, but also of reducing SOST expression in vitro and increasing other osteogenic factors' SOST expression, such as alkaline phosphatase (ALP) and RUNx2 (figure 2).

We also had very positive results by injecting our nanoparticles into the bone marrow of the femur in osteoporotic female mice, observing the reduction in the expression of the SOST gene and the consequent increase in the expression of certain osteogenic genes.

Taking into account the difficulty of an administration by injection into the bone marrow of the femur could entail in a future clinical application, we decided to redesign the system. To do so, MSNs with high affinity for bone tissue were developed by anchoring bisphosphonates on their surface, which are molecules with a high affinity for the inorganic content of bone, in order to administer them by subcutaneous injection, a much easier method, so the nanoparticles themselves preferentially accumulate in bone tissue. In fact, we observed that after 72 hours of injection, the nanoparticles were still in the area (figure 3).

After different treatments lasting 2 to 3 weeks with successive subcutaneous injections every 72 hours, real-time PCR analysis of the different gene expressions in the bone tissue of osteoporotic animals revealed that we were able, not only of silencing the gene SOST, but also of increasing the expression of various osteogenic genes, such as Runx2, Alp, Osterix and Osteoprotegerin, as well as increasing vascular endothelial growth factor (VEGF), which relates to an increase in vascularization, all this factors pointing at the formation of new bone tissue (figure 4).

In line with the results obtained, the microcomputed tomography analysis revealed significant increases in bone mineral density and bone mineral content, which, together with the quality of the new bone formed, similar

to healthy bone as revealed by trabecular thickness and trabecular separation, gave us significant results in terms of new bone formation and quality in an in vivo model of osteoporotic female mice (figure 5).

This way, this brilliant investigation showed the skills of mesoporous silica nanoparticles in a possible treatment of osteoporosis, proving their capacity to load, transport, protect and intracellularly release a particular type of nucleic acid: a siRNA to silence a specific gene responsible for a malfunction in bone tissue development. These results open the doors for this type of MSNs to be used for carrying a large number of nucleic acids, including all types of RNAs or DNAs, with a wide variety of final applications within the biomedicine of the future.

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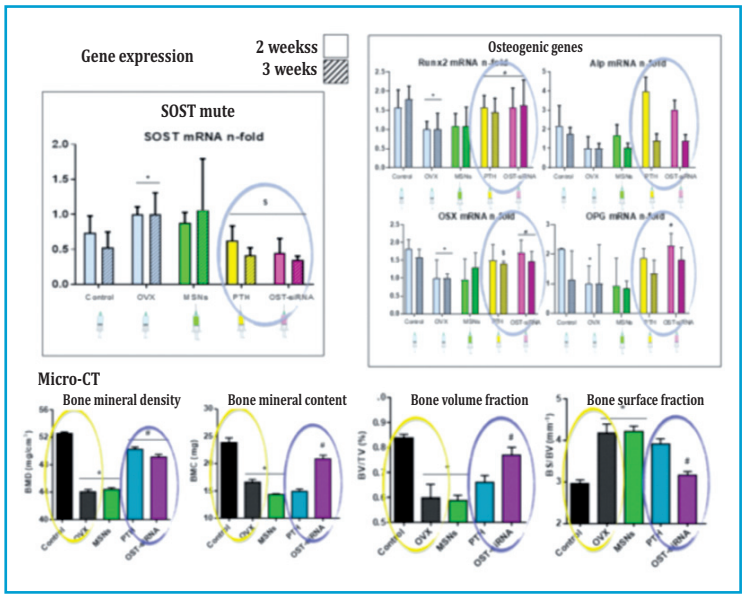
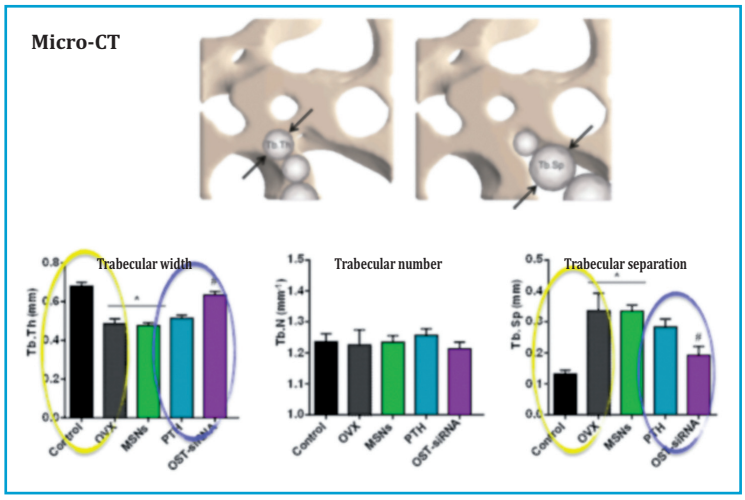
Conflict of interests: The authors declare no conflict of interest.

Figure 4



Top: Gene expression results in vivo after administration of the nanoparticles. Bottom: in vivo micro-CT results after administration of the nanoparticles.

Figure 5



In vivo micro-CT results after administration of the nanoparticles

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