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Opinion paper

Our contributions to applications of mesoporous silica nanoparticles

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ABSTRACT

Our contributions to mesoporous silica materials in the field of biomedicine are reported in this article. This perspective article represents our work in the basics of the material, preparing different ranges of mesoporous silica nanoparticles with different diameters and with varied pore sizes. We demonstrated the high loading capacity of these materials. Additionally, the possibility of functionalizing both internal and external surface with different organic or inorganic moieties allowed the development of stimuli-responsive features which allowed a proper control on the administered dose. In addition, we have demonstrated that these carriers are not toxic, and we have also ensured that the load reaches its destination without affecting healthy tissues.

Statement of significance

This paper presents my personal opinion and background on a hot topic as mesoporous silica nanoparticles for drug delivery. To this aim it provides a comprehensive and historical overview on the innovative contributions of my research group to this rapidly expanding field of research.

1. Main

In recent years, nanomedicine has been at the cutting edge of nanotechnology, bringing about huge prospects in the biomedical field. Researchers are developing innovative nanoparticles both for diagnosis via imaging technology and treatment through drug delivery technologies. Among the different kinds of nanoparticles, inorganic mesoporous silica nanoparticles (MSNs) have recently entered into this landscape, taking advantage of their exclusive and outstanding characteristics to achieve breakthroughs in the knowledge and development of personalized and regenerative biomedicine [1–4]. Late advances include the synthesis of MSNs and their application as nanocarriers for drug delivery, as well as the most recent developments in this type of nanoparticles for modern medicine applications, underlining the significant repercussion that this technology may have in the forthcoming future [5–7].

1.1. Origins of mesoporous silica materials

Reviewing the history of mesoporous silica materials, I must begin by emphasizing that research on mesoporous materials is in the spotlight, as it resulted in important work in chemical synthesis, accounting for the high number of impressive practical applications for the welfare of society. From catalysis to medicine and nanotechnology applications, there are numerous materials developed since the discovery of mesoporous solids. And, in such discovery, there are three main players to highlight: Prof Kuroda group, Mobil Oil Corporation group and Prof. Terasaki.

In chronological order, the creators and pioneers of mesoporous materials synthesis in early 1990s are the Japanese research group headed by Yanagisawa et al. [8,9] and Mobil Oil Corporation headed by Kresge et al. [10,11] and, subsequently, Prof. Inagaki et al. [12,13], who performed the complex structural characterization of these materials given their high sensitivity to the electron beam. This outstanding characterization effort allowed us to have knowledge of the performance of these materials and to envisage them in innovative and relevant applications.

After pioneering work by the Japanese and American groups, research on mesoporous solids has increased dramatically over

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the past twenty-seven years. Under certain circumstances, advanced materials arise through the development of state-of-the-art synthesis pathways such as mesoporous solids. Mesoporous silica materials are synthesized by the self-assembly of amphiphilic molecules in water, and further studies have been reported on self-organized structures in amphiphile-water systems that were the key to understanding unique structural types.

Following the advent of mesoporous materials at the beginning of the 1990s, numerous research groups became interested in the synthesis and fundamental study of mesoporous materials' formation mechanisms; unique reaction routes were found, resulting in more complicated nanostructures and broader range of compositions. The investigation of the structural and porous properties of these materials relies heavily on recently developed characterization methods; electron crystallography is a crucial tool in this field [14–19].

1.2. Applications of mesoporous silica materials

Therefore, ordered mesoporous silica became a major breakthrough and triggered the research interest worldwide. Consequently, the number of potential applications expanded dramatically, finding many uses in fields ranging from catalysis to nanomedicine. This is evidenced by the publications focused on these materials that can be found at present in Web of Knowledge (more than 20,000 publications).

The initial design of mesoporous silica materials catered for catalysis applications; but it was evidenced shortly after that their adequacy in a wide range of research areas, for instance magnetism, sensors, optical materials, photocatalysis, fuel cells, thermoelectrics and even in healthcare research. Albeit the provenance of these mesoporous silica ceramics principally is the catalysis industry, they have found promising applications in the medical field thanks to their porosity and composition, which favors their drug delivery abilities, and tissue engineering capacity.

1.3. Mesoporous silica materials for drug delivery

In our pioneering work in 2001, these materials were proposed *for the first time as drug delivery systems* [20]. Previously, these materials were proposed for the sequestration and release of proteins [21]. A mesoporous matrix of ceramic material, used until then to convert alcohol in gasoline, was hereby used for the adsorption and release pharmaceutics. However, any material proposed as a drug delivery system must be unambiguously non-toxic; hence [22], the work of Lu et al. [23] was crucial ascertaining the biocompatibility of these materials, providing the toxicological profiles and biodistribution of MSNs upon injection in mice. They found that the maximum tolerated dose was 1 mg per mouse and, what is more important, 4 days after the injection, all the silica was excreted out [23].

Ordered mesoporous silica materials are increasingly studied within the field of bioceramics as a promising biomaterial, thanks to their ability to host diverse guest molecules. The design of these materials as drug delivery systems involves host-guest interactions between the silanol groups covering the mesoporous silica surface and the functional groups of the drug molecule. The textural and structural characteristics of the porous host determine to a large extent the intended drug adsorption and release processes.

These hybrid systems are increasingly complex when aimed at specific clinical needs. It is usually essential to modify the mesoporous silica surface through the covalent grafting of functional groups. Such functionalization process produces hybrid mesoporous materials that can behave as host matrices of many different drugs through weak interactions [24–27].

The functionalization of the mesoporous silica walls could be needed for several aims. For instance, if the pharmaceutical species to be loaded is highly hydrophobic, it will not load properly into the hydrophilic silica matrix. The functionalization using hydrophobic moieties allows to load diverse hydrophobic drugs [28,29].

A similar approach is performed to slow down the release of particular drug molecules from the mesopores to the aqueous medium, as a result of the diminution of the wettability degree of the matrix surface.

There are other scenarios, however, where the pharmaceutical agents can be directly loaded onto the mesopores. But even in these cases, it is possible to achieve higher loads and slower release rates if the mesoporous silica matrix is functionalized with diverse organic functions Among them, the functionalization with amino groups has been extensively reported [30–32]. In this case, the functionalization of the silica walls with amino groups changes the surface charge of the walls, from the negatively charged silanol groups towards the positively charged amino groups. This is of capital importance in terms of favoring the retention of certain charged cargo molecules, such as amino acids, peptides and a whole variety of biomolecules.

1.4. Mesoporous silica nanoparticles for biomedicine

A significant advantage of these ordered mesoporous materials is their versatile synthesis pathway: the material can be produced in bulk form, as microcapsules or even as nanoparticles, depending on its final application.

When Kuroda and Kresge research groups discovered this unique material, with considerable applications in catalysis, little could they imagine that it would also become an outstanding weapon in medicine and nanomedicine. For example, magnetic nanoparticles have already been encapsulated into MSNs for application in cancer therapy; these smart nanosystems are playing a simultaneous double function, releasing cytotoxic agents in a controlled fashion and producing heat (hyperthermia). The stimuli-responsive effect can be used for on-demand delivery of the drug.

The silanol groups covering the silica surface permits the reaction with alcohols and organosilanes capable of stabilizing suspensions in non-aqueous media, and also providing groups for the anchorage of specific ligands.

A difficult challenge to address is the gene transport and release by magnetic conjugates; in order to reach the cell nucleus from the extracellular environment, DNA fragments must bypass several biological barriers. A hopeful strategy to develop magnetic force-assisted transfection *in vitro* is the covalent attachment of dendrimer moieties to magnetic nanoparticles. In these systems, the magnetic part facilitates a close contact between cell culture and gene vectors, thus providing a reduction of transfection times.

Many different fields of research are currently expecting original solutions thanks to the development of these advanced multifunctional materials. In this sense, recent research advances in the biomedical field are opening up possibilities for future personalized treatments and diagnostic methods thanks to a previously unattainable selectivity.

Powerful advances in the preparation and characterization techniques of nanotechnology products are allowing to produce devices that can establish a close interaction with the biological world. This fact denotes an accurate control over the release of therapeutic agents, and brings up a chance to enhance the specificity of the therapeutic action and also to reconsider some of the more powerful drugs for different diseases that were discarded due to their low levels of tolerance.

The targeting capability of these innovative nanodevices should lead to custom-made dosing regimen, significantly reducing severe

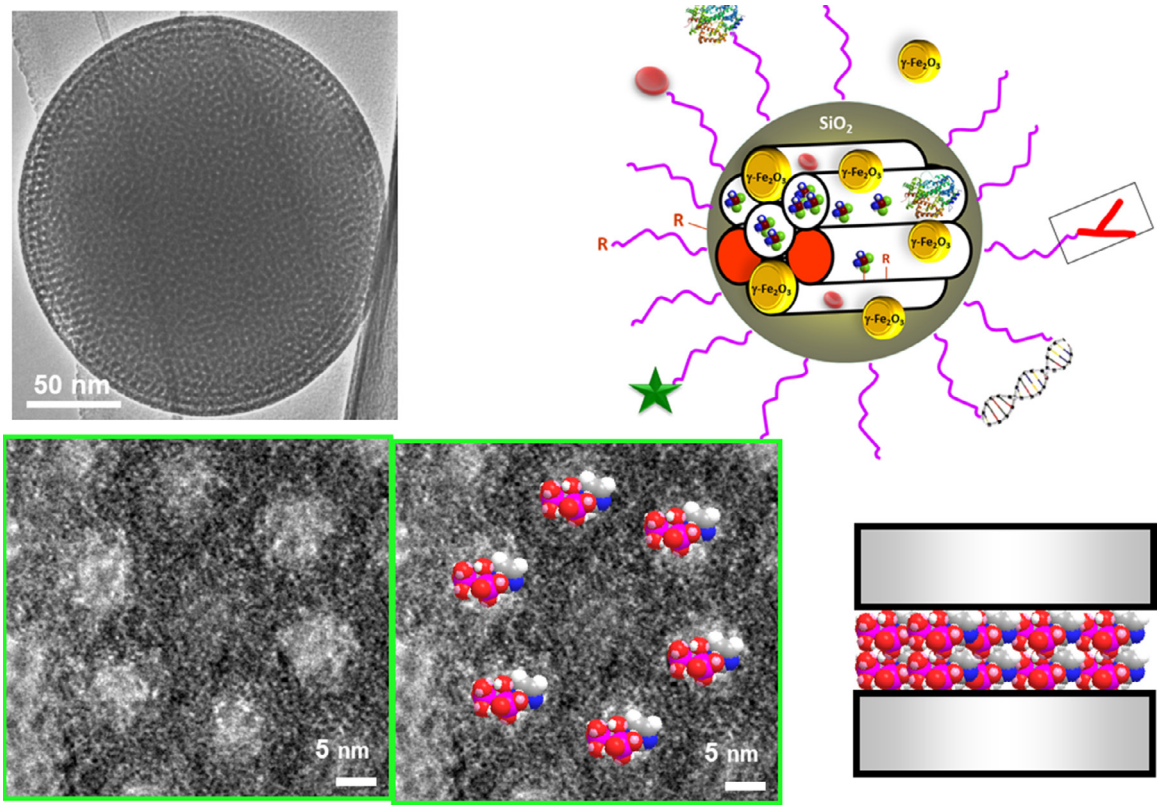

Fig 1. Schematic illustration of drug loading into the mesopores of Mesoporous Silica Nanoparticles (MSNs). Top left image: Transmission electron micrograph of MSN. Top right illustration: Schematic depiction of a MSN showing its role as a versatile multifunctional nanoplatform: different drugs can be loaded into the mesopores; premature cargo release can be avoided by grafting of different stimuli-responsive nanocaps as pore blockers that allow smart drug release under exposure to external or internal stimuli; its outermost surface can be grafted of hydrophilic polymers to provide it of stealth properties, and different targeting agents, imaging moieties, genetic material, etc. can be also incorporated. Bottom left image: Enlargement of the above image where the ordered hexagonal arrangement of the pores to be loaded is clearly seen. Bottom center: depiction of drug molecules loaded into mesoporous channels; Bottom right: schematic representation of a horizontal perspective of silica channel loaded with drug molecules.

side-effects related to some diseases, such as cancer, and would also ultimately produce a more proficient distribution of health-care resources. Hence, the application of such engineered products may permit to combine the therapeutic capacity and diagnosis at the nanoscale with little tissue invasiveness. In many of such situations, MSNs are being applied.

1.5. Our contribution to the field

In the specific case of my group's research in this field, I would like to point out that it all started with the idea of an unusual application of mesoporous silica nanomaterials, thinking that it would be possible to introduce drug molecules into their pores and then devise an efficient and effective way to release them. This idea was pioneering in the scientific world and today there are many research groups working in this brand-new field of nanomedicine (Fig. 1), which has led to important advances in personalized and regenerative biomedicine.

Although ordered mesoporous materials can be used to develop imaging systems for developing diagnostic systems for a variety of diseases [33–36], the contributions from our research group were focused on drug delivery technologies, as it can be observed in the sequential advances bellow.

2. Sequential advances

The *FIRST ADVANCE* was the unique nanotechnological application of controlled release of drug molecules that had been previously loaded into the pores of these nanoparticles. The size of the nanoparticles is about 100 nm and each nanoparticle has about 1400 pores. Since drug molecules measure around the nanometer, the loading capacity of these nanoparticles is immense [20,37,38].

The *SECOND ADVANCE* has been to ensure that the cargo is not lost along the way and arrives safely at its destination in its entirety. In order to achieve this, it was important to design molecular gates that would avoid precipitate release of the cargo earlier it reached its destination. The initial proof of concept was to develop the strategy of, once loaded with the drug, keeping it inside the pores by chemically designing molecular gates to prevent the cargo from leaving the nanoparticle before reaching its destination. Our first test was to synthesize the gates with magnetic nanoparticles and attach them to the silica nanoparticles using complementary conjugated DNA strands. Once the drug was locked inside the pores the next step was to get the gates to open upon reaching the tumor [39].

To achieve this, it was necessary to design intelligent systems that responded to stimuli that could be both external and internal, depending on how and where one wanted this absolutely controlled release to occur, managing not to lose drug along the way and to get 100% of the load to the chosen destination [40]. This application is extremely interesting in cases of cancerous tumors since, being these tissues the targets to be reached, avoiding losses of cytotoxins in healthy tissues, it would represent an extraordinary alternative to chemotherapy. In the case of magnetic nanoparticles, we managed to make them capable of opening on demand when they reach the tumor by applying an external stimulus (magnetic in this case).

Many intelligent systems can be designed using stimuli from external body, which are those that can be activated by the physician. One of the gains of these types of sensitive nanosystems is that the release can be turned on and off as needed, which can lead to intermittent responsive release structures. In addition, some of these stimuli can be enforced in the vicinity at the disease site, which increase the precision of treatment by improving efficacy and efficiency [41].

We have studied and tuned smart mesoporous silica nanoparticle systems where we have used as stimuli light, ultrasound, ultraviolet, heat, pH, enzymes, etc. and this constitutes the *THIRD ADVANCE* [42–46].

But the therapy of multifaceted disorders such as cancer complications requires, in many cases, the simultaneous administration of different drugs in order to increase the efficacy of the treatment and this is very complicated. This objective was brought to our attention when we collaborated with oncologists who informed us of the serious problem they had with treatments where the patient had to be given two very aggressive treatments in two successive stages, leaving time for the patient's partial recovery between them. The oncologists thought that if the two cytotoxic drugs could be loaded in the same nanoparticle it would be a considerable solution to improve the treatment and recovery of the patient in less time. Therefore, we initiated the design of a nanocarrier accomplished of performing controlled release of proteins and small molecules reply to a discontinuous magnetic field acting as a stimulus. This nanosystem is produced on MSNs with iron oxide nanocrystals condensed within the silica matrix and functionalized on the surface with a thermoresponsive polyethylenimine-b-polyisopropylacrylamide (PEI/NIPAM) copolymer. This proof-of-concept allows to solve the problem of loading two different species which in turn can be released with different kinetics, at different times. So this nanodevice constitutes a *FOURTH ADVANCE* in this extraordinary range of unique personalized biomedical possibilities [47,48].

The *FIFTH ADVANCE* was the design of an alternative pathway to molecular gating to prevent premature release of the load. This unusual pathway is the coating of the loaded nanoparticle by a polymer layer. But that polymer must have certain features. We chose it to be thermosensitive. In this way we were able to design an intelligent ultrasound response MSNs nanocarriers loaded with drugs and protected by a copolymer to avoid their early release. The nanoparticles are coated at low temperature (4 °C), taking benefit of the exposed conformation of the polymer under these circumstances. At 37 °C the copolymer collapses, finishing the pore entries and thus permitting the nanosystems to transport the cargo at 37 °C without early release. This element is critical when loading cytotoxic medicines such as in the case of tumor approaches. When irradiated with ultrasounds, the polymer variates its hydrophobicity and its conformation unlocks, activating the pores opening and the consequent liberation of the drug. These hybrid nanosystems have been displayed to be non-cytotoxic and internalize into LNCaP cells while keeping their ultrasound responsiveness in the cytoplasm of these cells. Furthermore, these hybrid nanocarriers based on MSNs loaded with doxorubicin-loaded were exposed to LNCaP cell line, demonstrating their ability to produced cytotoxicity only when the nanocarrier had been exposed to ultrasound. These MSN-hybrids can be activated by remote stimuli, which is of paramount significance for upcoming approaches in cytotoxic delivery and cancer treatment [49,50].

The *SIXTH ADVANCE* in these mesoporous silica nanoparticle systems was found while looking for a way to direct the loaded and protected nanoparticles to their final destination, the tumor. And what better than to find an already available transport for them. Indeed, it is known that, in cases of breast cancer, mesenchymal cells travel towards the tumor tissue in an attempt to provide solutions. Therefore, we discussed the possibility of using these mesenchymal cells as transport for our charged nanoparticles. Thus, we designed an original platform consisting of MSNs that are transported by mesenchymal stem cells (Fig. 2).

The ultrasound-sensitive nanocarriers based on MSNs are covered with polyethylene to improve their efficient internalization by decidua-derived mesenchymal stem cells. *In vitro* and *in vivo* studies demonstrated the release capacity of theses nanosystems. Moreover, this capacity is preserved within the cells used as vehicles. The ability of the nanocarrier-cell system towards mammary tumors was evaluated *in vitro*. The efficiency of this complex nanosystem for antitumor treatment is demonstrated in mammary tumor cells by producing doxorubicin release only when the cell carriers are in contact with ultrasounds [51–55].

And one more step leads us to the *SEVENTH ADVANCE*, improving the penetration of nanomedicines. We have studied how to increase the penetration of nanocarriers into extracellular matrices, which is a general problem to be solved with all nanomedicines. We designed a nanodevice capable of transporting proteolytic enzymes loaded with a pH-responsive polymeric nanocapsule. This degradable coating defends the enzyme hosts against proteolytic attack while triggering its release below acidic environments, generally related to numerous tumor tissues. These enzymes have been encapsulated and bound to mesoporous silica nanoparticle surface, showing significantly higher penetration than nanoparticles without this strategy, which may increase the healing efficiency of existing nanomedicines, permitting a more standardized and deeper distribution of therapeutic nanocarriers in tumoral tissues [56].

To avoid damage to healthy tissues by premature release of the load we have seen two solutions, molecular gating and polymer coating. In both cases the use of a stimulus permits the liberation of the load upon reaching its target. But there is a third solution, loading the MSNs with a prodrug, which is non-toxic until activated, so that if some cargo is lost on the way to its target it will not produce adverse effects to healthy tissues. Based on this strategy, we designed an unfamiliar functionalized mesoporous silica nanosystem, which carried both a non-toxic prodrug (indol-3-acetic acid) and the enzyme (horseradish peroxidase), which is the responsible for its conversion into cytotoxic compounds, namely, reactive oxygen species (ROS) that lead to specific killing of cancer cells via membrane and DNA damage [57]. This nanocarrier is capable of generating *in situ* toxic species once accumulated in the tumor cell. Enzymes are sensitive macromolecules that can undergo denaturation in biological media due to the existence of proteases or additional destructive mediators. Enzymes can be direct attached to the silica surface to decrease their action through conformational variations or blocking of active sites. With this background, to produce a forceful structure capable of working in lifeforms, we pre-coated the enzymes with a protective polymer layer and chemically attached it to the nanoparticle surface conserving its action. The efficiency of this hybrid nanocarrier for antitumor applications was analyzed with various human tumor cells such as neuroblastoma and leukemia displaying significant efficiency (Fig. 3). This makes this nanosystem an interesting candidate for advance *in vivo* studies for cancer treatment and constitutes the *EIGHTH ADVANCE* [58–60].

An additional modification of mesoporous silica nanoparticle systems, which would be the *NINTH ADVANCE*, attempts to solve one of the main problems regarding the use of chemotherapy for cancer treatment: the lack of selectivity of the cytotoxic drugs used to kill cancer cells and the subsequent high toxicity. To this end, an advanced synthetic strategy has been developed to graft drug-loaded MSNs on the outer surface of certain bacteria in order to transport these drugs to hard-to-reach areas in solid tumors. The obtained conclusions confirm that nanoparticles could be trans-

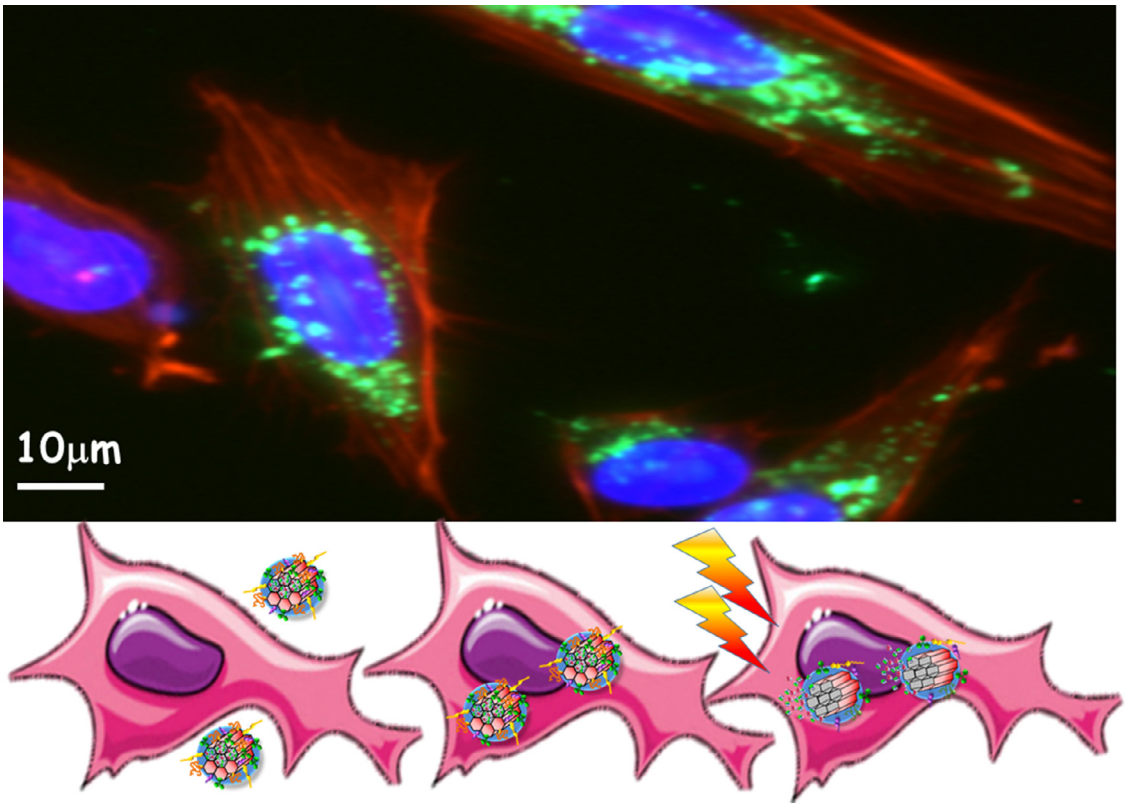

Fig. 2. Top: Mesoporous Silica Nanoparticles (MSNs) internalized into mesenchymal stem cells (green dots represent aggregates of MSNs labelled with fluorescein). Bottom: Schematic representation of MSNs internalized and triggered drug release. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

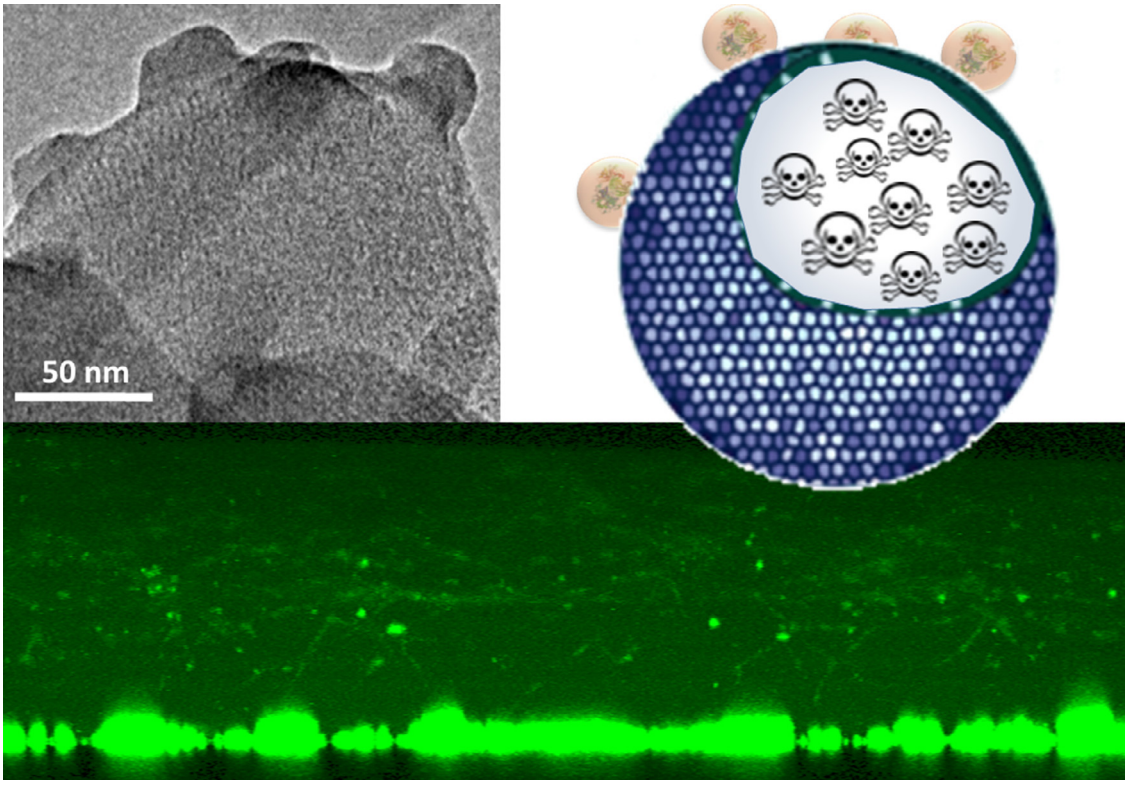

Fig 3. Mesoporous Silica Nanoparticles (MSNs) decorated with capsules that contain collagenase. Top image: Transmission electron micrograph of MSN decorated with capsules that contain collagenase. Bottom image: penetration of fluorescently labelled MSNs on the 3D collagen gel seeded with osteosarcoma HOS cells. This 3D tumoral tissue model was prepared in order to study the MSN penetration in a more representative model which takes into account the influence that could exert the presence of tumoral cells embedded within the matrix.

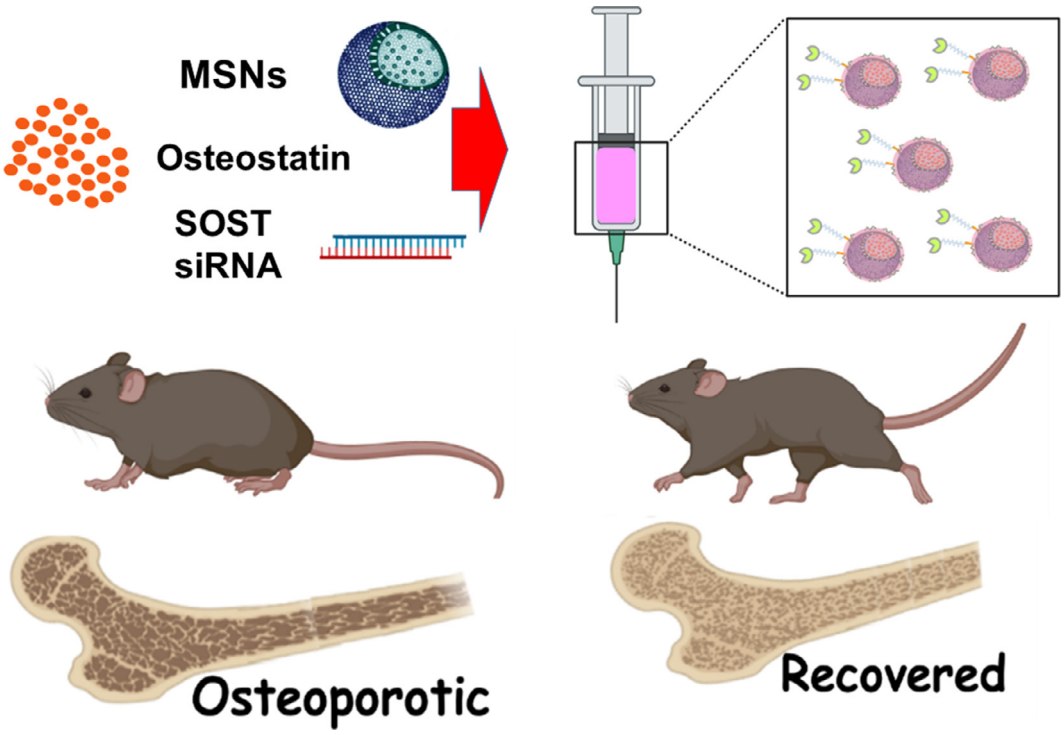

Fig 4. Representation of Mesoporous Silica Nanoparticles (MSNs) loaded with SOST siRNA and osteostatin (osteogenic peptide) injected in bone tissue of osteoporotic mice. SOST gene inhibits the Wnt signaling pathway reducing osteoblast differentiation. The nanoparticle administration produced an increase expression of osteogenic related genes improving the bone microarchitecture. The osteoporotic mice that were treated with those MSNs recovered values of healthy animals approaching to osteoporosis remission.

ported by these bacteria through tissues and can destroy almost 80% of tumor cells. These findings provide a glimpse of an alternative and potentially powerful approach for the treatment of cancer by enabling a homogeneous distribution of the selected drugs in malignant neoplasia [61].

However, MSNs do not only have applications in cancer, but also in the treatment of osteoporosis and infection. Osteoporosis is a very common disease involving bone degeneration due to lack of bone mass. Today, clinical treatments cannot offer a satisfactory curative response, so more efficient treatments are being sought. Gene silencing employing silencing RNA (siRNA) has received considerable attention as an alternative treatment for certain bone diseases. In this regard, the SOST gene is known to inhibit the Wnt signaling pathway through the reduction of the differentiation process of osteoblastrs. Thus, SOST genes with a specific siRNA can be explored as an option for the treatment of a disease such as osteoporosis. However, one of the pitfalls of this approach could be the short half-life of siRNAs, together with their variable capacity of transfection. These drawbacks could be overtaken through the use of an effective carrier. We proposed for this role MSNs loaded with osteostatin, an osteogenic peptide. With all this information and possibilities, we have designed a nanocarier based on MSNs decorated with polyethylenimine that can efficiently release SOST, siRNA and osteostatin in the cytoplasm of cells, with the subsequent increase of certain osteogenic markers thanks to their synergistic effect (Fig. 4). With this system we demonstrated the potential employment of MSNs to co-release different biomolecules and thereby promote the formation of bone, thus constituting a promising alternative for the potential treatment of osteoporosis. And we are already at the *TENTH ADVANCE* achieved in silica mesoporous systems [62,63]. Additionally, it is also possible to improve the treatment of osteoporosis, loading MSNs with drugs used in the clinic as therapeutic strategies to limit bone loss and prevent fracture. Among the antiresorptive drugs (that target osteoclasts) MSNs could be loaded with bisphosphonates, raloxifene or a humanized monoclonal anti-RANKL. As for anabolic drugs (osteoblast stimulation), recombinant human parathyroid hormone or growth factors like bone morphogenetic proteins could be used. In this sense, MSNs can be loaded with several of these drugs at the same time or combine them with the use of SiRNAs or miRNAs [64].

And let's move on to the *ELEVENTH ADVANCE*, bone regeneration. It is possible to synergistically combine inorganic and organic components in a similar way as our bones do. MSNs are able to interact with certain organic molecules to perform variable roles. An example of this are the weak interactions of the mesoporous silica host matrices with the different molecules loaded into their network of cavities allow these systems to be employed as controlled release matrices. In addition, three-dimensional (3D) scaffolds used for tissue engineering could be fabricated with those hybrid systems [65–67]. Also different osteoinductive agents, such as peptides, hormones or growth factors, can bind tightly to the matrix surface to act as bone cell attracting signals to promote the bone regeneration process. These nanoparticles could be employed in a wide range of different medical applications: controlled drug release, tissue engineering and gene transfection among others [68].

Another breakthrough of these nanosystems, the *TWELFTH ADVANCE*, is the possibility of dual targeting to treat bone tumors. We designed a dual targeting system capable of recognizing diseased bone tissue, and once the nanocarrier might be there, a hidden secondary target might be activated due to the overexpression of an enzyme, cathepsin K, in the tumor tissue, allowing the recognition of cancer cells. This approach can be applied to conjugate drugs and/or to improve the efficiency of bone cancer treatments [69,70].

Another important advance, the *THIRTEENTH ADVANCE*, can be put down to the possibilities of using silica nanoparticles to solve infection problems. Chronic bone infection has been considered as a dangerous infection involving the development of a biofilm.

The observed recurrent and resistant behavior, the subsequent high morbidity, together with the prolonged hospitalization and costly health care expenses have fueled the research on this area aiming modern therapies. In the last few years, there has been an intense debate on the treatment of this type of infection for establishing consistent and agreed guidelines in the different national health systems. In this regard, the scientific research in the last few years has been oriented towards the development of anti-infective biomaterials for both prevention and cure. Those biomaterials must present certain properties, such as better anti-infective performance and good compatibility, which would guarantee the proper integration of the implant within the surrounding bone tissue. Thus, nanocarriers based on MSNs have proven useful in multiple cases. The design of any drug delivery system must take into account first its biocompatibility for proper performance. Mesoporous silica nanoparticle surfaces were decorated with two types of groups: $-NH_3^{\oplus}$ and $-PO_3^{\ominus}$, capable of providing a pseudo-zwitterionic nature under physiological pH conditions. Those MSNs were evaluated in terms of surface properties, low adhesion ability and cellular adsorption compared to PEGylated MSNs. The results confirmed that both mixed-charged pseudo-zwitterionic MSN and PEG-MSN show significantly reduced serum protein binding and macrophage uptake in comparison to unmodified MSNs. In fact, this reduction was up to 70-90% for protein adsorption and *ca.* 60% for cellular uptake when both groups ($-NH_3^{\oplus}$ and $-PO_3^{\ominus}$) were present. This so-called *pseudo-zwitterionic* modification was aimed for the potential local treatment of bacterial infections through the synergistic effect of the antimicrobial effect of system and the release of levofloxacin. These promising findings might bring some expectations on the treatment of certain bacterial infections thanks to the use of macrophage-stealthy mixed-loading pseudo-zwitterionic MSNs with antimicrobial properties [71–75].

And the *FOURTEENTH ADVANCE* focuses on the use of silica nanoparticles as nanomotors [76]. It was a self-propelled nanodevice capable of motion, load transport and target recognition. The system was based on a mesoporous motive particle that was functionalized asymmetrically by attaching a single-strand of DNA on one side, and a catalase on the other side. This enzyme catalyzes the decomposition of H_2O_2 into O_2 and H_2O, providing energy necessary for the movement of the system. Additionally, those particles were capable of capturing and transporting other cargo particles decorated with a non-complementary single-strand DNA, exclusively when a specific oligonucleotide sequence was present in the surroundings. Thus, this hybrid nanomotor device was based on mesoporous materials capable of capturing and transporting a specific charge by a self-assembly process. The movement is enzymatically driven by the formation of O_2 bubbles in a H_2O_2 solution.

3. Conclusions

All of the above confirms the scientific importance of MSNs within the field of nanotechnology and the tremendous advances in personalized and regenerative biomedicine that are being achieved with them. If we look from the clinical perspective to the problems that need a solution, the research on MSNs should follow the next path: (1) check that the developed nanocarrier might not be toxic; (2) achieve the maximum possible loading of the pharmaceutical cargo into the carrier to develop an efficient system; (3) achieve a proper targeting of the nanocarrier, ensuring that the load reaches the targeted tissue or cell without affecting other healthy tissue in the body; (4) achieve certain control in the release kinetics, which could be done thanks to the stimuli-responsive approach above mentioned; (5) optionally, it could be interesting developing nanocarriers with autonomous propulsion thanks to the nanorobots technology that has been developed within these MSNs.

A variety of different approaches have been investigated for the potential treatment of different pathologies, such as bone infection or osteoporosis, where MSNs have produced very promising results [6,77,78]. However, their application to the clinic is still far away and more research in this area is needed.

This article presents my personal opinion and background on a hot topic as mesoporous nanoparticles for drug delivery. The aim of this manuscript was also to offer a historical viewpoint on the notable scientific achievement of introducing drugs into the pores of mesopores materials for developing drug delivery systems. This achievement fueled the research on this topic, as it can be observed in the manuscript, and entailed a boom in the number of publications in this topic. I honestly believe that we had to look back and remember how everything started.

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.

CRediT authorship contribution statement

María Vallet-Regí: Conceptualization, Writing – original draft.

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