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Mesoporous Silica Nanoparticles in Biomedicine: Advances and Prospects

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Mesoporous Silica Nanoparticles (MSNs) represent a versatile platform in biomedicine thanks to their unique structural properties and functional versatility. These nanoparticles are at the forefront, offering exceptional biocompatibility, tunable pore sizes, and surface functionalization to enhance drug loading and controlled release. On top of that, stimuli-responsive MSNs can be designed to respond to specific triggers such as pH, temperature, or light. These smart MSNs further optimize drug delivery by ensuring targeted release and minimizing side effects. Beyond drug delivery applications, mesoporous materials are increasingly utilized in tissue regeneration, providing scaffolds that promote cell growth and integration. In bone-related pathologies, these materials exhibit significant potential, enhancing mineralization and facilitating the repair of osseous defects. Future perspectives focus on advancing the multifunctionality of MSNs, integrating imaging, therapeutic, and diagnostic capabilities into single platforms. The remarkable adaptability of MSNs ensures their continued evolution, paving the way for innovative solutions to complex biomedical challenges.

1. Introduction

From a historical perspective, the development of mesoporous silica materials (MSMs) dates back to the early 1990s, when Kuroda and co-workers in Japan and Mobil Oil Corporation researchers in the United States first reported the synthesis of these silica-based materials using surfactant molecules as templates.[1–4] Recognized for their outstanding textural properties that will be bellow described, these materials were initially explored for applications in catalysis and adsorption.[5,6] The potential of MSMs for biomedical applications was first proposed in 2001 by Vallet-Regí and colleagues, who introduced the concept of using ordered mesoporous silica as drug delivery systems.[7,8] This innovation marked a turning point, as it will detailed in this review, shifting the focus of silica-based mesoporous materials research toward biomedicine.

Considering that nanotechnology has emerged as a groundbreaking field in modern medicine, the translation of mesoporous materials to the nanoscale led to the development of mesoporous silica nanoparticles (MSNs), which offered improved dispersibility, controllable particle sizes, and enhanced biocompatibility. In fact, among the diverse nanomaterials developed for biomedical applications, MSNs have gathered significant attention due to their unique physicochemical properties, biocompatibility, and versatility.[9–15]

As displayed in **Figure 1**, over the subsequent decades, MSNs have shown suitability for potentially addressing some critical challenges in biomedicine. As an example. engineering stimuli-responsive MSNs enabled control on the cargo release, which fueled their application as versatile platforms for drug delivery, imaging, and tissue engineering.[16–19]

MSNs are characterized by their ordered pore structures, high surface area, tunable pore size, and remarkable loading capacity for therapeutic and imaging agents.[20] These features make them ideal candidates for a wide array of biomedical applications, including cancer therapy,[21] bone tissue engineering,[] and infection treatment,[23] as it will be reviewed throughout this manuscript. Additionally, MSNs offer the flexibility to incorporate functional modifications at their surface, enabling targeted delivery of a plethora of biomedical molecules, controlled release of therapeutic agents, and stimuli-responsive behavior.[24] Such attributes have propelled MSNs to the forefront of nanomedicine, presenting opportunities to overcome limitations of conventional therapies, such as systemic toxicity, poor drug solubility, and limited bioavailability.[25] However, and despite these promising attributes, the clinical translation of MSNs faces several hurdles, including the need for standardized synthesis protocols,[26] comprehensive safety evaluations, and optimization of biodistribution and clearance profiles.

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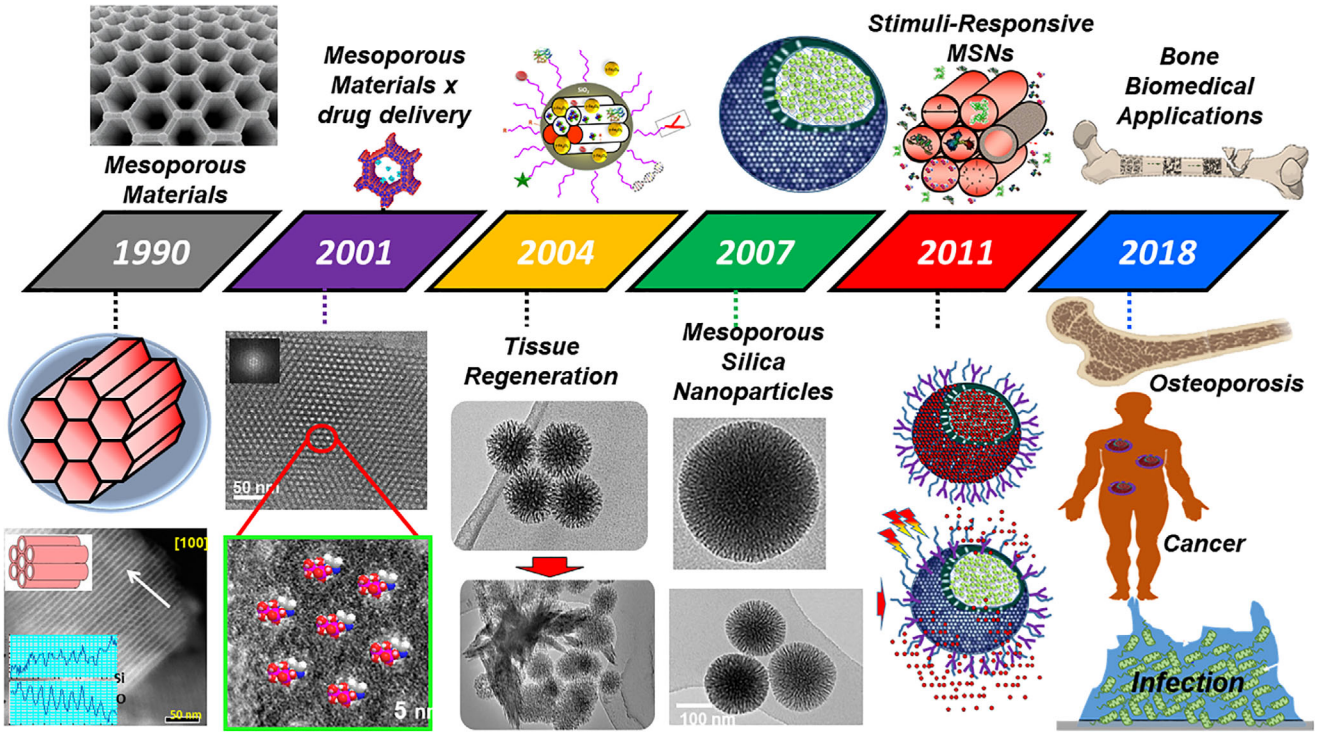

Figure 1. Timeline of the key milestones of MSNs for biomedical applications.

Additionally, MSNs have emerged as promising candidates for addressing various challenges in bone biomedical applications, including the treatment of bone infections, osteoporosis, and bone cancer.[27,28] They are ideal platforms for the delivery of therapeutic agents, such as antibiotics, anti-inflammatory drugs, and osteogenic factors, directly to bone tissue, enhancing bone regeneration and repair. Today, MSNs are recognized as one of the most promising materials for addressing challenges in personalized medicine, owing to their stimuli-responsive properties, surface functionalization capabilities, and capacity for targeted and controlled therapeutic delivery.[29,30]

The aim of this review is to provide a comprehensive overview of the development, properties, and biomedical applications of MSNs, highlighting their role as a versatile platform in nanomedicine. By exploring their structural features, such as high surface area, tunable pore sizes, and functionalization capabilities, the review emphasizes their potential in drug delivery, tissue engineering, and regenerative medicine. Furthermore, it addresses the challenges and opportunities associated with the clinical translation of MSNs, including their biocompatibility, biodegradability, and safety. In addition, this review aims to highlight the profound potential of MSNs in overcoming complex biomedical challenges and driving progress in the field of personalized medicine through an in-depth examination of recent advancements and pioneering initiatives, such as the VERDI project.

2. Order Mesoporous Materials

The history of mesoporous materials is strongly linked to the advancements in material science and catalysis during the late 20th century. Initially, efforts to develop porous materials were largely focused on porous glasses and disordered silica gels for catalysis and adsorption applications, but the discovery of silica-based mesoporous materials in the early 1990s marked a turning point in the field. The first ordered MSMs were independently discovered by Kuroda's group[1,2] and the Mobil Oil Corporation researchers.[3,4] These novel materials presented highly uniform pore structures, large surface areas, and tunable pore sizes thanks to the concept of supramolecular chemistry of surfactants as templates. The Mobil research team, in particular, gained wide recognition for their work on MCM-41 and MCM-48, which showcased hexagonal and cubic mesostructures, respectively. Their seminal publications not only described the unique properties of these materials but also introduced the concept of liquid crystal templating, a novel mechanism for structuring highly ordered porous networks.

The synthesis of MSMs represents a significant milestone in materials science, combining innovative chemistry with precise structural control. In this sense, the discovery of surfactant-templated processes introduced a new paradigm for creating mesostructured materials, using surfactant micelles as templates to organize silica precursors into ordered mesostructures.[31–33] The synthesis of mesoporous materials involves three main steps:[8]

1) *Creation of the mesostructure*, that is achieved through the self-assembling of surfactants into micelles at a certain concentration, the so-called critical micelle concentration. These micelles can be spherical, rod-shaped, cubic, or lamellar, depending on different conditions such as concentration or temperature. In this sense, the synthesis conditions strongly influence

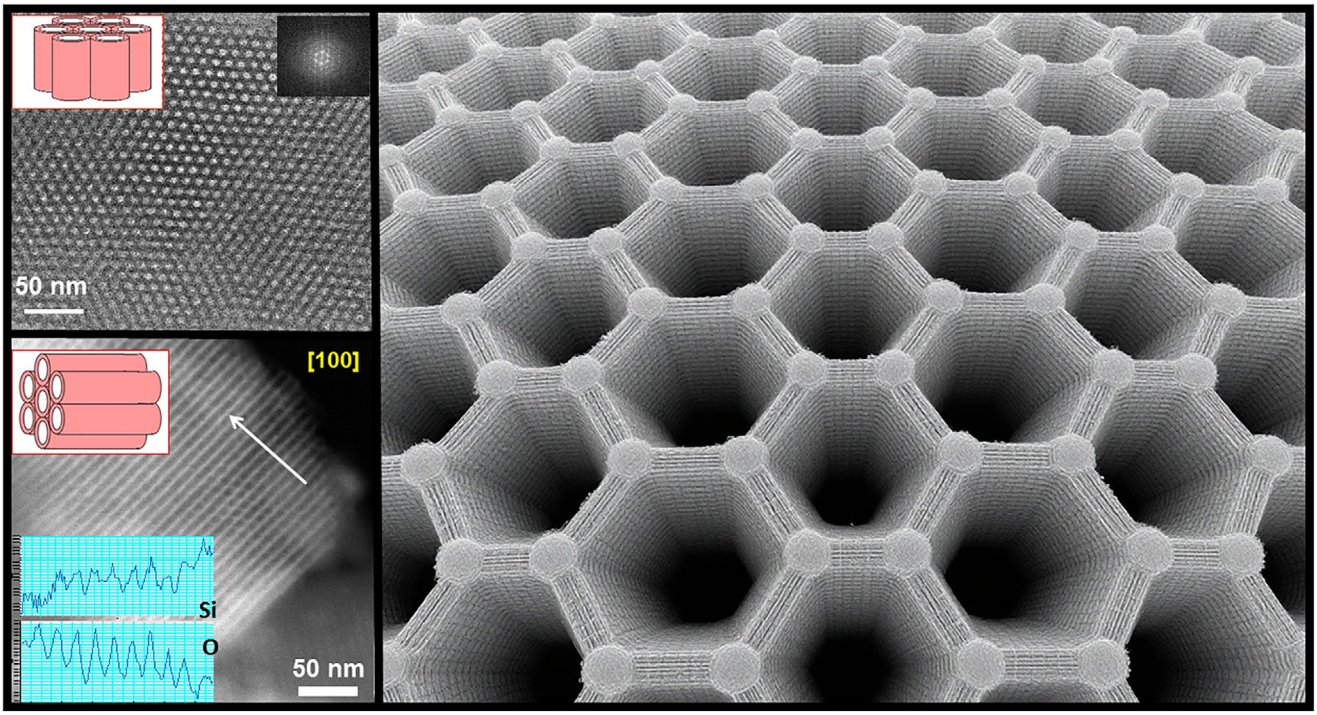

Figure 2. Left: Transmission Electron Microscopy (TEM) images of MCM-41 mesoporous material (adapted from ref. [34]). Right: Schematic representation of the mesostructure of ordered mesoporous materials.

the final material properties, including pore size, wall thickness, and particle morphology. For example, MCM-41, SBA-15, and MCM-48 are synthesized using varying surfactants and pH conditions to produce hexagonal, cubic, or lamellar pore structures. These micelles or liquid crystalline phases in solution would act as templates for the formation of the mesostructure in the subsequent processes.

2) *Silica precursors condensation*, where the silicates condense around these micelles under a wide range of different conditions to form an ordered structure. Conventionally, silica precursors would undergo hydrolysis and condensation around the surfactant micelles. The interaction between the surfactant micelles and silica species would lead to the formation of a composite material with an ordered mesostructure. Electrostatic interactions, hydrogen bonding, and van der Waals forces play important roles in the formation of a silica-surfactant composite material with an ordered arrangement of mesopores.
3) *Template removal*. Once the mesostructure is formed, the next step is to remove the surfactant template to create the porous silica framework. The template removal is achieved upon elimination of the organic surfactant templates either by calcination or solvent extraction, leaving behind a 3-Dimensional network of mesopores, as it can be observed in **Figure 2**.

In addition to these basic synthetic stages, the surface of mesoporous silica materials can be functionalized with a plethora of organic or inorganic groups to tailor the material for specific applications and enabling the creation of multifunctional mesoporous silica materials.[35,36] This adaptability is particularly valuable in the field of drug delivery, as it will be reviewed below, where the interaction between the carrier material and the therapeutic molecules plays a critical role in determining the efficiency of the system. By modifying the surface properties, researchers can improve drug loading, retention, and controlled release, while also addressing biocompatibility and biodegradation requirements.[37] The incorporation of inorganic species into the silica framework provides an avenue for enhancing the matrix properties. For example, doping silica with elements such as calcium, iron, or manganese can influence its degradation behaviour in physiological environments, as well as its bioactivity.[38] On the other hand, the grafting or incorporation of organic groups onto the silica surface provides a means to fine-tune the interaction between the carrier and the drug molecules.[39]

Mesoporous silica materials exhibit exceptional properties, including their highly ordered porous structures, with pore sizes ranging between 2 and 50 nm, and high surface area and pore volume, which make them excellent candidates for applications requiring significant adsorption or catalytic activity.[40] Their uniform pore size ensures precise control over molecular interactions, while the presence of silanol groups on the surface enables versatile functionalization with organic or inorganic molecules, enhancing their adaptability for various chemical processes. Additionally, mesoporous silica, such as SBA-15 and MCM-41, are known for their robust thermal and mechanical stability, allowing them to maintain structural integrity under very different and demanding conditions. The combination of these characteristics make mesoporous silica an important class of materials in modern technological science and engineering.

The main features of mesoporous materials make them ideal for applications requiring controlled molecular interactions,

such as in catalysis, adsorption, and biomedical fields. In catalysis, their large pore volumes and uniform pore distribution allow for efficient support of catalytic species, enhancing reaction rates and selectivity.[41] In environmental science, mesoporous materials are employed for adsorption and removal of pollutants due to their capacity to capture contaminants effectively.[42] Additionally, their customizable surface chemistry enables the development of advanced materials for energy storage and conversion, such as in batteries and super capacitors.[43] Other applications include sensor development, separation processes, and as carriers for active agents in chemical and industrial processes. The adaptability and multifunctionality of mesoporous materials continue to drive innovations in both fundamental research and practical applications.

In recent years, the field of biomedical research has demonstrated increasing interest in ordered mesoporous silica due to their promising potential in drug delivery systems[44,45] and tissue engineering[46] particularly in bone tissue regeneration.[47,48] This growing interest is largely attributed to the unique mesoporous structure of these materials, as well as their exceptional chemical composition and textural properties, which make them highly suitable for various biotechnological applications.[49] Nowadays, one of the primary application of mesoporous materials lies in drug delivery systems, where they serve as carriers for controlled and targeted release of therapeutic agents.

3. Mesoporous Materials for Drug Delivery

The biopharmaceutical industry constantly demands improved delivery systems for biomolecules, designed to provide localized and sustained release over time while protecting biopharmaceutical agents from degradation.[50–52] These systems should maintain drug concentrations at precise target sites within the body, ensuring they remain within the optimum therapeutic range and below toxicity thresholds, thereby enhancing therapeutic efficacy and minimizing adverse effects. In this regard, inorganic silica is an appealing material due to its excellent biocompatibility, low cytotoxicity, adjustable surface charge, and extensive potential for organic functionalization. In particular, MSMs exhibit unique mesostructures and porosities that make them highly effective as drug delivery systems.[53] The significant impact of these materials in biotechnological research raises from their exceptional properties: their high pore volume, that enables the confinement of substantial amounts of drugs or biologically active species; their large surface area, that provides excellent potential for drug adsorption; their well-ordered pore distribution, that ensures homogeneity and reproducibility during drug adsorption and release; and their high density of surface silanol groups, that allows for easy chemical modification of the pore walls, offering precise control over drug loading and release.[54]

The journey of using mesoporous materials as potential drug delivery systems began with a bold question: "Is it possible to introduce drugs into the porous network of mesoporous materials?" This pivotal question, rooted in materials science and pharmaceutical technology, catalyzed a groundbreaking revolution in drug delivery research, as observed in the number of publications in this topic in the last few years.[55] During the 90s, conventional drug carriers were limited in their ability to provide sustained and localized release while protecting therapeutic agents from physiological degradation.[56] However, the large pore sizes and pore volume inspired the use of mesoporous materials as carriers capable of encapsulating drug molecules.[57]

The initial breakthrough came in the early 2000s when Prof. Vallet-Regí and her team demonstrated the feasibility of loading ibuprofen, a model drug, into the pores of MCM-41, an ordered mesoporous silica with a 2D hexagonal pore arrangement.[7] This pioneering work provided direct evidence that MSMs could effectively adsorb and release drugs with predictable kinetics, thereby establishing a new class of drug delivery systems.[45,58] The innovative concept of using mesoporous materials as therapeutics carriers capitalized on their unique textural properties, including high surface area, large pore volume, and a robust silica framework. These features allowed not only the efficient encapsulation of small drug molecules but also the potential to host larger biomolecules, laying the foundation for subsequent advancements in the field.

The adsorption of biologically active species into the pores of MSMs begins with selecting an appropriate matrix for hosting each specific drug.[45] This process requires considering the size of the molecule to be confined alongside the textural properties of the host material, particularly the mesopore diameter, which determines the size of the molecule that can be accommodated. If the molecule is smaller than the mesopore cavity, it will be confined within the inner mesopores, whereas larger molecules, exceeding the mesopore diameter, will only adsorb onto the external surface of the material. Therefore, the pore diameter serves as a critical size-selective parameter for adsorption. When the molecule to be loaded is significantly smaller than the pore diameter, most of the drug molecules are not retained inside the pores, as only a fraction can directly interact with the pore walls, while the rest remain unconfined. In such cases, the specific surface area of the matrix becomes the primary factor determining the amount of retained molecules. Additionally, pore volume plays a crucial role in loading large-volume molecules, such as proteins, and is also a key factor when high quantities of adsorbed molecules are needed. This can be achieved through repeated and consecutive impregnations, which ultimately lead to the complete filling of the pore volume. Functionalization of the MSMs is a valuable strategy to enhance adsorption capacity or control the release kinetics of adsorbed molecules. Molecular adsorption in MSMs is predominantly a surface phenomenon governed by chemical interactions between silanol groups and the functional groups of guest molecules. These interactions can be tailored by functionalizing the silica walls, which have a high density of silanol groups. Grafting alkoxysilanes with various organic groups enables precise tuning of the surface's chemical properties. Furthermore, functionalization can modify the hydrophobicity of the matrix surface, influencing the conformation of adsorbed biomolecules or proteins.

The textural properties of MSMs also play a significant role in modulating the release kinetics of biologically active species, particularly pore diameter.[59] Smaller pore diameters resulted in slower drug release rates. Therefore, the release kinetics of drugs can be effectively controlled by tailoring the mesopore diameter. The specific surface area of the matrix is also a critical factor influencing both the retention and release kinetics of molecules.[60] A higher surface area increases molecular retention by providing more sites for host–guest interactions, which not only enhances

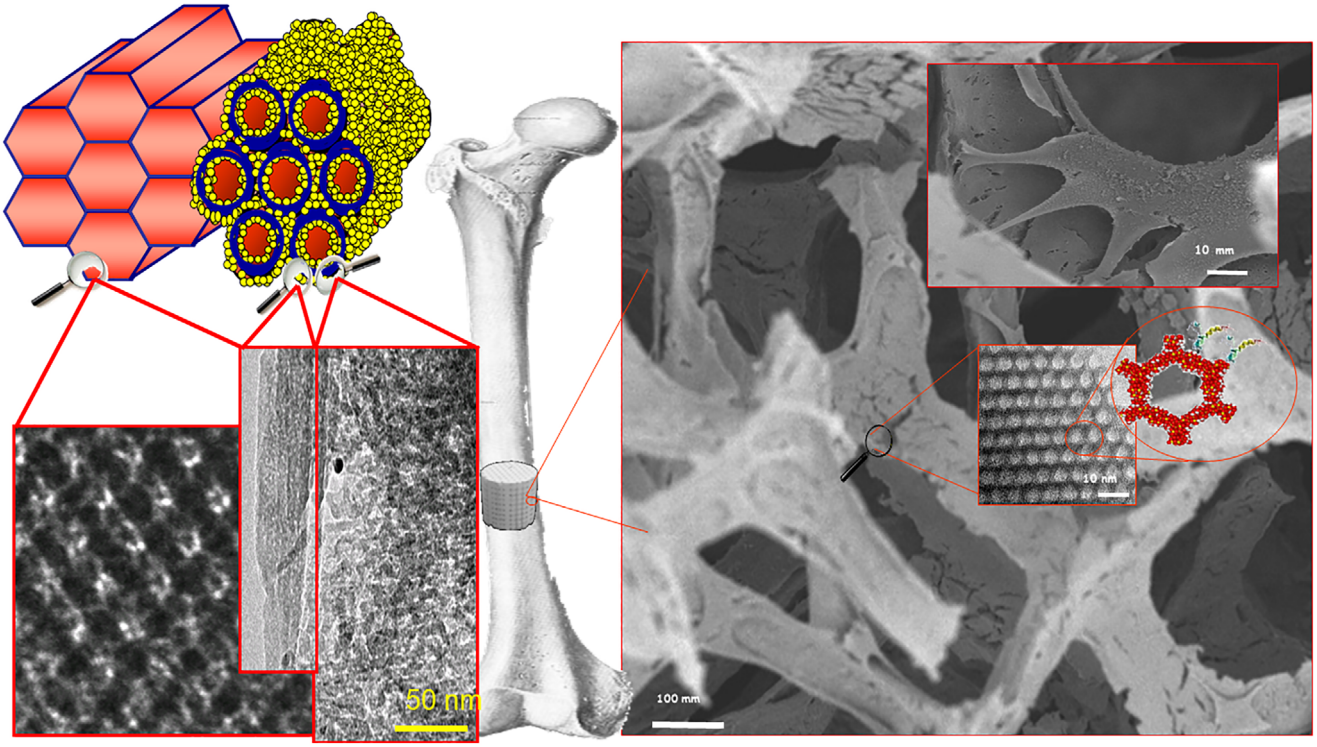

Figure 3. Schematic representation and TEM images of MSMs surface exposed to physiological fluids that form nanoapatite coatings with crystallinity comparable to biological apatites (left) and the possibility to load bioactive agents to help in the bone tissue healing process (right).

molecule uptake but also slows the release process. This retention effect significantly impacts the overall release kinetics, making surface area a key parameter in designing effective delivery systems. Additionally, the release of molecules from mesoporous silica can be effectively controlled through appropriate organic functionalization. Functional groups are selected to promote specific host–guest interactions with the chemical groups of the drug or biologically active agent, enhancing drug loading and significantly slowing release by retaining the drug within the matrix. Among all investigated matrices, functionalization has proven to be the primary factor governing drug release kinetics.[54] Therefore, when designing mesoporous silica materials, the choice of functionalization must be carefully tailored to the specific properties of the drug or active agent to be confined within the mesopores.

4. Mesoporous Materials for Tissue Engineering

When artificial materials were being implanted into bone defects, they were typically encapsulated by fibrous tissue to isolate them from the surrounding biological environment. However, Hench and colleagues demonstrated that certain glasses within the Na_2O–CaO–SiO_2–P_2O_5 system, known as Bioglasses, could spontaneously bond to living bone without the formation of fibrous tissue.[61] Currently, biomedical materials are designed with careful consideration of the interactions between the material and the biological system, which primarily occur at the surface of the biomaterial.[62] In this context, the silanol groups at the surface of silica-based ordered mesoporous materials can play a critical role in mediating interactions with physiological fluids. Notably, the chemical surface of these materials resembles that of Bioglasses, which are well-established as bioactive materials.[63–65] Due to their chemical composition, ordered mesoporous silicas exhibit similar behavior to Bioglasses; specifically, when exposed to physiological fluids, they are likely to form nanoapatite coatings with crystallinity comparable to biological apatites (**Figure 3**).[48,49] This property enables the material to bond with living bone, making ordered mesoporous silicas particularly appealing for applications in bone regeneration technologies. Besides, the unique textural properties of ordered mesoporous silicas above mentioned together with their straight and well-defined channels facilitate the controlled diffusion of the adsorbed drugs, a process influenced by factors such as pore size, surface functionalization, and particle morphology.[66] The combination of these advantageous textural properties with their bioactive chemical composition has driven their application in bone regeneration technologies.[67] Specifically, these materials can be loaded with targeted drugs and implanted into damaged bone regions, enabling localized and controlled drug release to support the healing process. In this sense, it is possible to develop scaffolds made from MSMs, which are characterized by their interconnected porous networks, high surface area, and tunable pore sizes, which allow them to mimic the extracellular matrix and facilitate cellular adhesion, proliferation, and differentiation. Moreover, the mesoporous structure enables the incorporation and controlled release of bioactive molecules, such as growth factors, drugs, or ions, that promote tissue repair and regeneration. The surface of mesoporous silica scaffolds can also be

functionalized with various chemical groups to enhance their bioactivity, biocompatibility, and osteoconductive properties. Additionally, their mechanical properties can be tailored to match those of natural bone, providing structural support during the healing process. These unique features make mesoporous silica scaffolds a versatile and effective platform for advancing biomedical applications in tissue repair and regeneration.

As it has been mentioned above, the key advantage of mesoporous materials lies in their tunable physicochemical properties. Their porous structure allows the encapsulation and release of biomolecules, such as growth factors, peptides, and drugs, in a sustained and controlled manner. The high density of silanol groups on their surfaces enables surface functionalization, facilitating interactions with cells and biomolecules. Additionally, their biocompatibility and mechanical stability ensure their integration into biological environments without eliciting adverse effects, making them an excellent choice for tissue engineering applications.

5. Mesoporous Silica Nanoparticles for Tissue Regeneration

A milestone in mesoporous materials technology was the transition from bulk mesoporous silica materials (MSMs) to mesoporous silica nanoparticles (MSNs), which offered unique advantages in the nanoscale dimension, particularly in biomedical and drug delivery applications,[10] as stated throughout this manuscript. Bulk MSMs, with their uniformly distributed pores, high surface area, and robust structural properties, are ideal for applications requiring significant adsorption and catalytic activity. However, their large size limits their versatility within biological systems, particularly for drug delivery or tissue engineering. In contrast, MSNs, as nanoscale derivatives of MSMs, retain the key structural features of bulk materials, such as tunable pore sizes and high surface areas, but offer enhanced functionality due to their smaller size and higher dispersibility.

Unlike bulk materials, MSNs have a smaller particle size and higher dispersibility, enabling better cellular uptake and more efficient delivery of therapeutic agents to target sites. Their nanoscale dimensions also allow for improved penetration into tissues and enhanced interaction with biological systems. Additionally, MSNs provide a higher surface-area-to-volume ratio, which increases drug loading capacity and facilitates controlled and sustained release profiles of bioactive molecules, such as growth factors, peptides, and drugs, which are essential for promoting tissue repair and regeneration, as it will be detailed in the following sections. Moreover, MSNs can act as scaffolds, providing structural support and guiding cellular growth while delivering osteogenic or angiogenic factors to stimulate bone or vascular tissue formation. Their ability to integrate with other materials, such as polymers or hydrogels, for composite scaffolds further enhances their versatility.

Mesoporous Bioglass Nanoparticles (MBGNs) are a particular type of mesoporous nanoparticles that represent a highly advanced and versatile class of biomaterials in regenerative medicine, combining the bioactivity of bioglasses with the structural benefits of MSNs.[68,69] These MBGNs are composed primarily of silica, calcium oxide, and phosphorus pentoxide, and they exhibit exceptional bioactivity by forming a hydroxycarbonate apatite layer on their surface when in contact with body fluids, as observed in **Figure 4**. This layer closely resembles the mineral phase of natural bone, making bioglass nanoparticles highly effective in promoting osteogenesis and enhancing bone regeneration. Additionally, these nanoparticles possess a hierarchical porous structure, enabling efficient loading and sustained release of therapeutic agents, such as drugs, growth factors, and ions (e.g., calcium, silicon, and phosphate), which are critical for tissue regeneration. The mesoporous architecture also enhances their bioactivity due to the increased surface area for interaction with biological fluids, facilitating the formation of hydroxycarbonate apatite on their surface, and accelerating the bone tissue integration.

The synthesis of MBGNs involves a variety of methods, each offering unique advantages and limitations depending on the desired properties and applications.[70] The sol-gel method is one of the most widely used techniques due to its ability to produce highly porous nanostructures with a large surface area and controlled morphology. Similar to the synthesis of MSMs, this method involves the hydrolysis of precursors, followed by gelation and thermal treatment to form nanobioglass particles.[71] Variations, such as the use of acidic or template-based sol-gel processes, allow further customization of particle size and bioactivity. Melt quenching is another commonly employed method, which involves melting high-purity precursors and rapidly cooling them to form glass.[72] Although simpler and faster, this method typically results in particles with lower surface area compared to sol-gel-derived materials. Emerging techniques, such as spray pyrolysis and flame synthesis, enable the production of nanobioglasses with uniform size and shape through rapid thermal decomposition of precursors. Additionally, microwave-assisted and ultrasound-assisted methods offer time-efficient and energy-saving alternatives, producing nanobioglasses with enhanced bioactivity and reduced agglomeration. Each method can be further optimized by incorporating ion doping, which enhances specific properties such as osteogenesis, angiogenesis, and antibacterial activity, making nanobioglasses highly versatile for biomedical applications.

The nanoscale size of MBGNs offers several advantages over their bulk counterparts. Their high surface-area-to-volume ratio enables faster ion exchange and improved bioactivity, which accelerates tissue healing and integration with host tissues. Additionally, MBGSNs can be easily incorporated into scaffolds, hydrogels, or coatings to enhance the mechanical properties and bioactivity of these materials. These MBGNs have been added to different types of polymers, including collagen, chitosan, and gelatin, to create hybrid biomaterials with improved mechanical, biological, and antibacterial properties. These composites have demonstrated significant potential in tissue engineering applications, such as the development of scaffolds for bone, cartilage, nerve, and skin regeneration. The advantage of using MBGNs relays into their capacity of releasing therapeutic agents, including drugs, peptides, and growth factors, enabling targeted and sustained delivery for precision medicine. Advanced applications, such as bioglass-based nerve conduits, myocardial repair patches, and wound healing materials, further emphasize the versatility of bioglass in addressing complex biomedical challenges. Furthermore, bioglass nanoparticles are highly versatile and can be

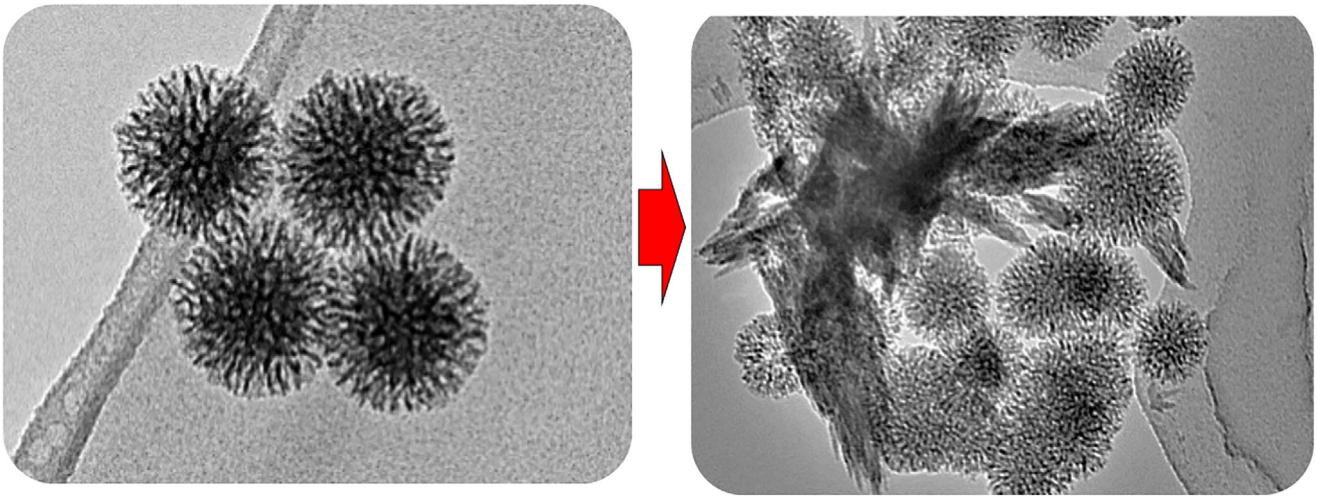

Figure 4. TEM images of MBGNs before (left) and after (right) being in contact with simulated body fluids, where hydroxycarbonate apatite layer newly formed can be observed.

functionalized or doped with trace elements like magnesium, zinc, or silver to promote specific biological responses, such as antibacterial activity or enhanced angiogenesis. Their biocompatibility, biodegradability, and ability to stimulate cell proliferation and differentiation make them an ideal candidate for a wide range of applications, including bone and dental repair, wound healing, and even soft tissue regeneration.

6. Mesoporous Silica Nanoparticles

The transition from bulk mesoporous materials to mesoporous silica nanoparticles MSNs represents a significant advancement in nanotechnology, particularly for biomedical applications. As it has been mentioned above, bulk MSMs were synthesized using self-assembled surfactant molecules as templates, resulting in materials with uniformly distributed pores, high surface areas, and bioactive properties due to the presence of silanol groups.[73] However, even if these bulk materials demonstrated great potential in applications such as drug delivery and tissue engineering, their size limited their versatility within biological systems. To address this, researchers began scaling down the dimensions of MSMs to the nanoscale, leading to the development of MSNs.[8] In this context, it should be highlighted that nanoparticles have emerged as a transformative innovation across various scientific disciplines. Their small size and high surface-to-volume ratio impart unique physical, chemical, and biological properties that differ significantly from their bulk counterparts. Therefore, the newly prepared MSNs retained the key structural features of bulk MSMs, such as tunable pore sizes and high surface areas, while offering enhanced functionality.[74]

The first spherical and monodisperse silica particles at the micron scale were developed by Stöber.[75] In fact, this approach has been widely recognized as the Stöber method and it is based on using very dilute concentrations of the silica precursor during the sol-gel process. Over time, numerous modifications have been introduced to refine the method, enabling the production of monodisperse, structurally ordered silica nanoparticles. The synthesis of MSNs can be conducted under basic, acidic, or neutral conditions, with systematic variation of reaction parameters facilitating precise control over particle morphology and size. The first significant modification to the Stöber synthesis employed a cationic surfactant as a templating agent to direct the formation of a spherical mesoporous silica structure yielding spherical MCM-41 with physicochemical properties comparable to those obtained via alternative synthetic routes.[76] Continuous advancements in research have led to a broad spectrum of variations in synthesis conditions and methodologies, ultimately enhancing the stability and monodispersity of MSNs (**Figure 5**). They can be synthesized with controlled diameters ranging from a few nanometers to hundreds of nanometers, allowing them to operate effectively in biological environments. This nanoscale adaptation has enabled MSNs to serve as highly efficient carriers for drug delivery and imaging agents, with the added benefit of surface nanoparticle functionalization to access to targeted and stimuli-responsive therapies. Thus, the shift to MSNs has expanded the possibilities of mesoporous materials in modern medicine.[77,78]

In the biomedical domain,[79,80] all types of nanoparticles have revolutionized drug delivery, diagnostics, and therapeutics by enabling targeted treatment, controlled drug release, and minimally invasive imaging techniques.[81] In this sense, MSNs have emerged as innovative nanomaterials with immense potential for biomedical applications.[82] In fact, the development of MSNs was inspired by the need for highly efficient drug delivery systems and advanced biomedical tools, making them an essential focus of nanomedicine research. Their tunable physicochemical properties and ability to interact intimately with biological systems have established MSNs as versatile nanocarriers for targeted therapies and diagnostics.[83]

MSNs are synthesized through sol-gel processes using surfactants as structure-directing agents, which guide the formation of uniform and ordered mesopores. This method allows precise control over particle size (ranging from 50 to 300 nm), pore size (2–30 nm), and surface area (up to 1000 $m^2\ g^{-1}$). These structural features enable MSNs to host and release a diverse array of therapeutic agents It should be highlighted that by tuning

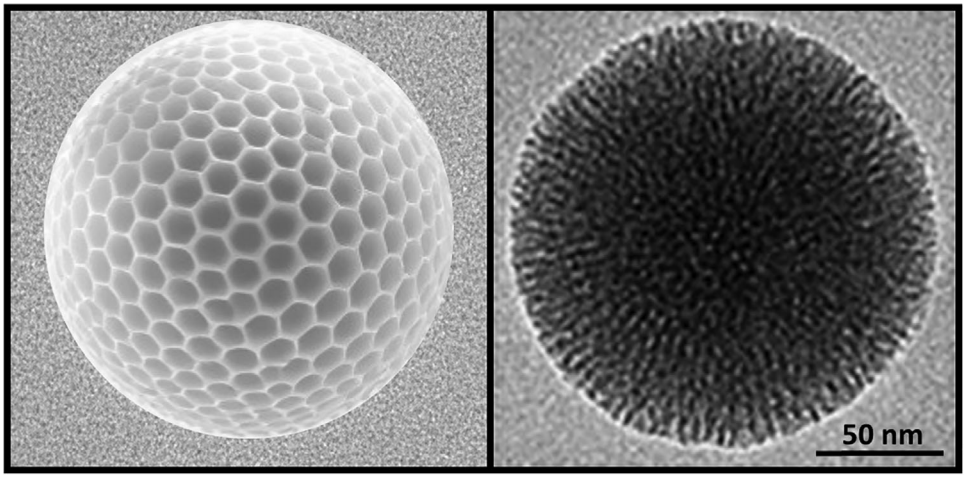

Figure 5. Schematic representation (left) and TEM image (right) of a MSN.

synthesis conditions, researchers can fabricate MSNs with specific textures, such as hexagonal, cubic, radial, or worm-like pore arrangements, further enhancing their adaptability. Moreover, the high density of silanol groups on their surface provides opportunities for functionalization with organic or inorganic groups, ensuring compatibility with different biomedical applications and/or enhancing their interaction with biological systems. As an example, and in the context of tissue regeneration as commented below, this functionalization enables the coupling of osteoinductive agents, such as peptides, hormones, or growth factors, which act as signals for cellular differentiation and proliferation.

The above-mentioned textural parameters of MSNs, such as particle size, pore size, pore volume, and surface area, have a profound influence on the nanoparticles biological performance. Particle size determines cellular uptake, biodistribution, and clearance pathways; thus, smaller particles than 100 nm are more efficiently internalized by cells and can circulate longer in the bloodstream, while larger particles tend to be uptake by the reticuloendothelial system. Also, as commented for bulk mesoporous materials, pore size and volume affect drug loading and release kinetics, with larger pores enabling higher loading capacity and facilitating the delivery of larger biomolecules, such as proteins or nucleic acids. Additionally, a high surface area provides more active sites for interaction with the drug molecules and functionalization, enhancing the performance as drug delivery systems, similarly to what happens with bilk mesoporous materials. Finally, the morphology of MSNs influences their interaction with biological membranes and their ability to evade immune detection.[30] Therefore, the optimization of these parameters is essential to improve therapeutic efficacy, minimize toxicity, and ensure effective clearance from the body.

7. Biomedical Applications of MSNs

Regarding the application of MSNs in biomedicine, they have been explored as drug delivery systems to fight many different diseases, agents of imaging and diagnosis, and as nanoparticles of interest for tissue engineering and bone tissue regeneration, whether on their own or as additives to engineered scaffolds, as below commented.[84] In the context of regenerative medicine, MSNs have emerged as a groundbreaking tool in tissue regeneration due to their unique structural features and functional versatility.[85] Their high surface area, tunable pore sizes, and biocompatibility make them suitable for hosting and releasing bioactive agents that promote cellular growth and tissue repair. MSNs are particularly valuable in addressing some complex challenges in regenerative medicine, such as bone regeneration, by providing controlled delivery of osteogenic molecules, growth factors, and genetic material. In this sense, bone regeneration has been a primary focus area for mesoporous materials in tissue engineering. MSNs are often integrated into 3D-scaffolds to mimic the natural extracellular matrix (ECM) of bone.[86] These hybrid scaffolds combine the mechanical strength of traditional biomaterials with the drug delivery and bioactivity of mesoporous materials. The mesoporous structure serves as a reservoir for osteogenic agents, such as bone morphogenetic proteins, osteostatin, and calcium ions, which are essential for promoting osteoblast differentiation and bone formation. Furthermore, mesoporous bioactive glasses have also demonstrated the ability to stimulate hydroxyapatite deposition, enhancing bone regeneration in defect sites. For instance, mesoporous materials have been embedded into polymeric or ceramic scaffolds to create constructs that support both the structural and biochemical needs of the regenerating tissue.[87–89] Such systems can co-deliver multiple agents, such as antibiotics and growth factors, to simultaneously promote healing and prevent infection.

Cartilage repair is another area where mesoporous materials have shown promise. Cartilage injuries are challenging to treat due to the tissue's avascular nature and limited self-repair capacity. Mesoporous materials loaded with chondrogenic growth factors, such as transforming growth factor-beta, can enhance chondrocyte proliferation and extracellular matrix deposition. When incorporated into hydrogels or 3D scaffolds, these materials provide both mechanical support and a controlled release of therapeutic agents, creating a conducive environment for cartilage regeneration.[90–92]

In their role as nanocarriers, MSNs have revolutionized drug delivery due to their ability to load significant quantities of therapeutic molecules within their mesopores. These nanocarriers provide controlled and sustained drug release profiles, reducing

premature drug degradation and side effects. Additionally, stimuli-responsive MSNs, designed to respond to pH, redox conditions, or external triggers such as light or magnetic fields, offer precise spatiotemporal control over drug release, as detailed in the next section. This adaptability is particularly advantageous for cancer therapy, where MSNs can selectively release cytotoxic agents within tumor tissues while sparing healthy cells.

MSNs could also serve as effective imaging agents due to their capacity to incorporate dyes, contrast agents, and fluorescent molecules within their pores.[93] This multifunctionality allows MSNs to act as both diagnostic and therapeutic tools, so-called theranostics, enabling simultaneous disease detection and treatment. For example, MSNs can be engineered for fluorescence imaging, magnetic resonance imaging, or computed tomography, providing comprehensive insights into disease progression and treatment efficacy.

Beyond drug delivery, MSNs could play a crucial role in tissue engineering and bone-related therapies. Their bioactive properties, derived from their silanol groups and structural similarity to bioactive glasses, promote cell adhesion and proliferation. As mentioned before, MSNs have also been incorporated into three-dimensional scaffolds for tissue engineering, mimicking the natural extracellular matrix of bone and aiding in the repair of osseous defects.[22] These hybrid scaffolds combine the controlled release capabilities of MSNs with the structural support needed for cell adhesion and proliferation. By integrating osteoinductive agents into the scaffold, these materials provide sustained signals for bone regeneration while maintaining their mechanical integrity. Such systems have shown promise in accelerating healing and improving outcomes in bone defects. Furthermore, their ability to deliver growth factors, minerals, and therapeutic agents to bone tissue makes them highly effective in treating bone-related pathologies such as osteoporosis and bone cancer.

Chronic bone infections, often associated with biofilm formation and antibiotic resistance, pose a significant challenge in clinical settings. MSNs have also been engineered to address this challenge by delivering antimicrobial agents directly to the infection site.[94] Functionalized MSNs with antimicrobial properties, such as those loaded with levofloxacin, have shown efficacy in preventing bacterial adhesion and biofilm formation. Additionally, the stealth properties of MSNs, achieved through surface modifications like pseudo-zwitterionic coatings, reduce macrophage uptake and enhance their therapeutic potential in infection management.[95]

8. Stimuli-Responsive MSNs

Stimuli-responsive nanoparticles have revolutionized the field of drug delivery research by enabling precise, controlled, and targeted release of therapeutic agents in response to specific physiological or environmental triggers, ensuring that therapeutic agents are released only when and where they are needed.[96] These nanoparticles are designed to respond to various stimuli, such as pH changes, temperature, light, enzymes, or redox conditions, which are often distinct in diseased tissues like tumors or inflamed areas. This functionality addresses key challenges in drug delivery, such as minimizing side effects and improving therapeutic efficacy. For instance, elevated levels of reactive oxygen species in the tumor environment can act as triggers for the release of encapsulated drugs, ensuring that the therapeutic effect is localized to the target site while minimizing off-target side effects. This approach not only enhances drug efficacy but also reduces systemic toxicity, making therapies safer for patients. Additionally, stimuli-responsive systems can accommodate complex drug release profiles, such as sustained, pulsatile, or on-demand delivery, which are essential for treating chronic diseases or conditions requiring precise dosing. The versatility and adaptability of these nanoparticles make them invaluable for advancing personalized medicine and improving outcomes in challenging therapeutic areas like cancer, neurological disorders, and infectious diseases.[97]

Internal stimuli, such as pH, redox potential, and enzymatic activity, are often exploited in stimuli-responsive MSNs because they reflect the microenvironment of specific pathological tissues (**Figure 6**).[98] For example, tumor tissues typically exhibit a more acidic pH than healthy tissues due to lactic acid production during fast glycolysis. Taking this difference into account, MSNs functionalized with pH-sensitive polymers release their cargo only in acidic environments. Similarly, redox-sensitive MSNs are designed to release drugs in response to elevated glutathione (GSH) levels, which are prevalent in cancer cells.[99]

External stimuli, including magnetic fields,[100] ultrasound, and light, offer the advantage of remote control over drug release. Magnetic fields, for instance, can generate localized heating when applied to magnetic nanoparticles embedded in MSNs.[101] This heat induces structural changes in thermoresponsive polymers, triggering the release of therapeutic agents. Similarly, ultrasound-triggered MSNs use sound waves to disrupt polymer coatings or cleave specific bonds, enabling targeted drug release with non-invasive techniques.[102]

9. Safety and Biodegradability

The biocompatibility and biodegradability of MSNs are critical to their biomedical success.[103,104] In this sense, one of the challenges that could limit their clinical use is their biodegradability, which could lead to bioaccumulation and potential biosafety concerns.[105] MSNs are primarily composed of silica, which degrades into biocompatible byproducts, such as orthosilicic acid ($Si(OH)_4$), under physiological conditions. The biodegradation of MSNs primarily occurs through a hydrolytic process, where hydroxyl groups in aqueous environments interact with the silica framework, converting it into dissolvable silicic acid, which is biocompatible and naturally excreted through urine.[106] This process is influenced by factors such as the specific surface area, particle morphology, pore size, particle diameter, the silicon-oxygen network's condensation degree and functionalization.[107,108] Smaller MSNs tend to degrade faster due to their higher surface-to-volume ratio, while surface functionalization, such as polyethylene glycol coating, can slow the degradation process by protecting the silica framework, enhance circulation time and reduce immune recognition, while maintaining stability in physiological environments.[109,110] Controlled biodegradation is essential to ensure that MSNs are cleared from the body after delivering their therapeutic or diagnostic payload, minimizing the risks of long-term accumulation.

The specific surface area plays a critical role in determining the biodegradation rate of MSNs.[111] Studies have shown

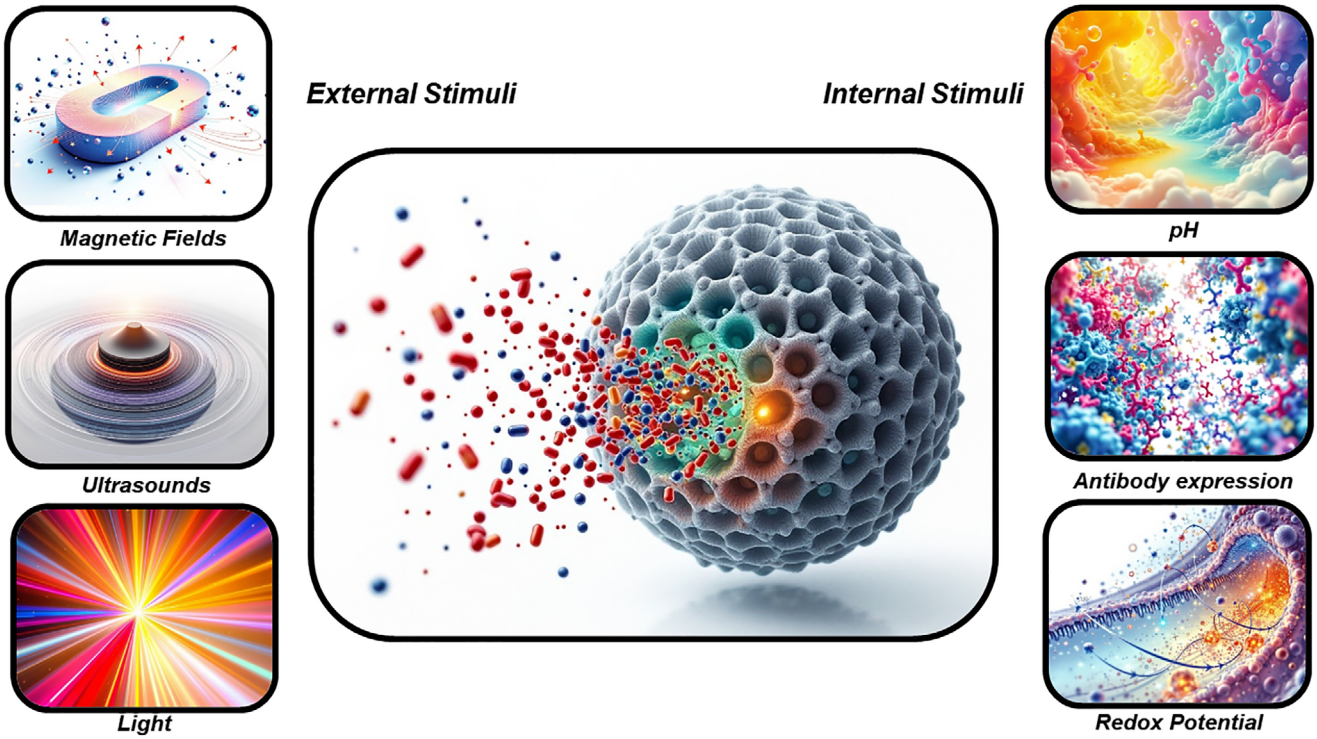

Figure 6. Schematic representation of the different external and internal stimuli employed to trigger the drug release from smart MSNs.

that MSNs with larger surface areas degrade more rapidly due to the increased availability of hydrolysis-active sites. Similarly, particle morphology significantly affects the degradation process; spherical MSNs exhibit faster degradation compared to rod-shaped or other morphologies, as the latter often have higher aspect ratios that hinder hydrolysis. Furthermore, the pore size of MSNs also contributes to their biodegradation behavior, with larger pore sizes facilitating greater interaction between water molecules and the particle surface, thus accelerating the hydrolysis process. Another key factor is the condensation degree of the silicon-oxygen (—Si—O—Si—) network. MSNs with a lower condensation degree exhibit faster biodegradation as they have more hydrolysis-prone sites. For instance, calcined MSNs, which have a highly condensed —Si—O—Si— network, degrade more slowly compared to uncalcined counterparts. Additionally, doping MSNs with metal ions such as manganese, iron, strontium, or calcium has been shown to enhance their biodegradability.[112] These dopants weaken the silica network by introducing metal-oxygen bonds, which are more susceptible to hydrolysis in acidic or reductive environments, typical of tumor microenvironments.

Despite their promising biodegradability, potential toxicity remains a concern, particularly at high doses or with improper surface modifications. The toxicity of MSNs is primarily attributed to their surface silanol groups, which can interact with cell membranes, causing oxidative stress, inflammation, and cell lysis. Studies have shown that MSNs can induce dose- and size-dependent cytotoxicity, with smaller particles exhibiting a higher likelihood of causing oxidative damage due to their increased surface area. Functionalization strategies, such as amination or PEGylation, have been employed to reduce MSN cytotoxicity by neutralizing surface silanols and improving colloidal stability. Evaluating the safety of MSNs is crucial for their progression from preclinical studies to clinical applications.[113,114] The safety of MSNs is influenced by factors such as their size, shape, surface chemistry, porosity, and, as mentioned above, their biodegradability. These characteristics determine the interaction of this type of nanoparticles with biological systems, including their biodistribution, metabolism, and clearance.[115] Many studies have shown that MSNs are generally safe when used within specific parameters, but potential risks, such as cytotoxicity and bioaccumulation, must be carefully assessed.[116]

Additionally, MSN biodistribution studies have revealed that nanoparticles tend to accumulate in the liver, spleen, and lungs due to uptake by the reticuloendothelial system (RES). While this is beneficial for targeting certain diseases, excessive accumulation can overload these organs, potentially leading to adverse effects. Immunotoxicity is another area of concern, as MSNs can interact with immune cells, triggering the release of pro-inflammatory cytokines. Neurotoxicity and genotoxicity are less studied but are critical areas for future research, especially for MSNs that cross the blood-brain barrier or interact with DNA.

The metabolism and excretion of MSNs primarily occur through two routes: the renal (kidney) and hepatobiliary (liver) systems. MSNs with diameters below 10 nm are typically renally cleared, which reduces the likelihood of long-term tissue accumulation. Conversely, larger particles are often cleared through the hepatobiliary route, which involves metabolism in the liver and excretion via bile or feces. The surface charge of MSNs also impacts their interaction with proteins in the bloodstream, influencing their clearance. For instance, positively charged MSNs tend to bind more readily to serum proteins, leading to faster clearance, whereas neutral or negatively charged particles display

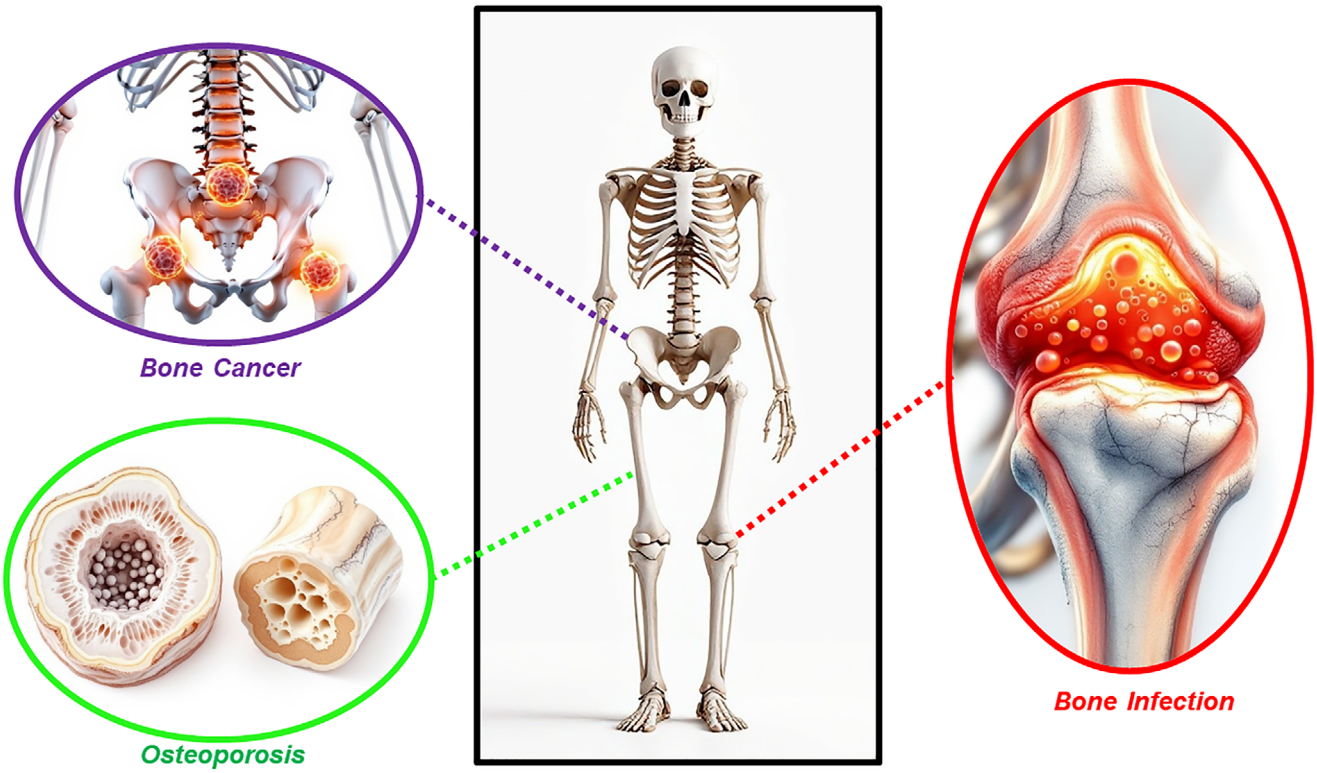

Figure 7. Schematic representation of the bone pathologies tackled by the VERDI project.

prolonged circulation times. These factors collectively highlight the need to optimize MSN design to enhance their safety profile.

One significant consideration in the safety of MSNs is protein corona formation, wherein proteins from biological fluids adsorb onto the surface of the nanoparticles. This phenomenon can alter the nanoparticles' physicochemical properties, including their biodistribution and cellular interactions. The formation of a "hard corona" (stable protein layer) versus a "soft corona" (transient protein layer) affects the recognition of MSNs by the immune system. In some cases, this can lead to rapid clearance by phagocytic cells in the liver, spleen, and lungs. Studies have shown that strategies such as polyethylene glycol coating can minimize protein adsorption, thereby improving the biocompatibility and circulation time of MSNs.

The size and shape of MSNs also play a critical role in their safety. Spherical MSNs are generally cleared more rapidly than rod-shaped particles, which tend to have longer retention times in the body due to reduced uptake by the reticuloendothelial system. For example, rod-shaped MSNs have demonstrated slower renal clearance and prolonged circulation compared to their spherical counterparts. This prolonged retention, however, raises concerns about potential bioaccumulation, especially in long-term applications. Therefore, selecting the appropriate size and shape of MSNs based on their intended application is essential to minimize toxicity risks.

Long-term in vivo studies and clinical trials have provided valuable insights into the biocompatibility of MSNs. Evidence from preclinical studies suggests that MSNs exhibit minimal toxicity even after chronic administration. For instance, oral and intravenous administration of MSNs in animal models, at doses up to 2000 mg kg^{-1}, showed no significant adverse effects on major organs. Additionally, clinical trials, such as those involving Cornell Dots and other silica-based formulations, have demonstrated excellent safety profiles in humans.

Despite these promising findings, further research is required to investigate the effects of prolonged exposure to MSNs, particularly on sensitive biological barriers such as the blood-brain barrier and gastrointestinal tract. Comprehensive preclinical and clinical evaluations are necessary to ensure the safe and effective use of MSNs in a wide range of biomedical applications.

10. Mesoporous Materials for Bone-Related Pathologies: Verdi Project

The VERDI project, "Polyvalent Mesoporous Nanosystems for Bone Diseases", funded by the ERC Advanced Grant program, was designed to address critical challenges in treating bone-related pathologies—such as osteoporosis, bone infections, and bone cancer—particularly in aging populations (**Figure 7**).[117] The project aimed to develop a versatile and clinically translatable nanoplatform for targeted, stimuli-responsive drug delivery based on MSNs, thanks to the previously mentioned properties in the biomedical arena[118] This approach targeted to improve some therapeutic outcomes while minimizing systemic side effects, tackling issues like co-delivery of therapeutics, biofilm penetration, tumor targeting, and gene therapy, areas where current treatments, like chemotherapy and antibiotics, often fall short due to limited specificity and severe side effects.[119]

The VERDI project explored innovative approaches using MSNs for cancer treatment,[120–122] focusing on their ability to address challenges in targeting and treating aggressive tumors like osteosarcoma and metastatic bone cancer.[123,124] MSNs were engineered for selective drug delivery through functionalization with bone-specific agents, such as bisphosphonates,[125] and tumor-targeting ligands like RGD peptides, enhancing accumulation in bone tissue and tumor cells.[126–129] These nanoparticles were also designed for controlled drug release triggered by tumor-specific stimuli, such as pH or enzymes, minimizing damage to healthy tissues.[130–135] To overcome drug penetration barriers in dense tumor extracellular matrices, the project developed collagenase-coated MSNs and UVA-sensitive nanosystems that release enzymes upon light activation, improving deep tumor access while reducing off-target effects.[136–139] In general, the project developed a toolbox of components (e.g., targeting agents, responsive linkers, therapeutic molecules) that could be combined to create tailored nanomedicines. In a different approach, Biohybrid systems based on using bacteria as carriers for drug-loaded MSNs, enabled deep penetration into tumor tissue. Non-pathogenic *E. Coli* were engineered to deliver doxorubicin-loaded MSNs, achieving higher tumor penetration than conventional nanocarriers, and 80% destruction of cancer cells in dense collagen matrices.[140,141]

Bone infections, especially those involving biofilms, are highly resistant to conventional antibiotics. The VERDI project developed functionalized MSNs for co-delivery of antibiotics and antimicrobial metal ions, achieving over 90% bacterial eradication in rabbit models of osteomyelitis while promoting bone healing.[142] Additionally, stimuli-responsive MSNs and implant coatings were designed to disrupt biofilms, deliver antibiotics locally, and support bone regeneration, offering a dual-action approach to infection management.[133,143–147] The VERDI project has also achieved significant progress in developing novel therapies for the potential treatment of osteoporosis,[148,149] which remains a significant challenge due to the limitations of current treatments. MSNs can provide a platform for the localized delivery of anti-resorptive drugs, such as bisphosphonates, and anabolic agents, such as osteostatin or bone morphogenetic proteins[150] targeting the underlying causes of osteoporosis and stimulating bone regeneration. Small interfering RNA (siRNA) targeting the SOST gene, which inhibits bone remodeling, has also been co-delivered,[151,152] suppressing a key inhibitor of bone formation and stimulating osteoblast activity, demonstrating potential as a therapeutic platform for osteoporosis.[153] When testing this therapeutic innovation in vivo in ovariectomized mice, a recognized model for postmenopausal osteoporosis, the nanosystem demonstrated: increased expression of osteogenic markers, meaning that new bone was starting to be formed; significant improvements in bone microarchitecture; and restoration of bone density to levels approaching healthy controls, representing osteoporosis remission.[154] This nanosystem offers a scalable and targeted approach to osteoporosis treatment, reducing the systemic side effects associated with current therapies, which require high doses due to poor bone vascularization.

Advanced formulations for bone tissue engineering and targeted therapies have also been explored during this project. Magnetic colloidal formulations[155] and mesoporous bioactive glasses loaded with osteoinductive peptides or silver nanoparticles showed promise in promoting bone regeneration and fighting infections.[156,157] Additionally, biomimetic MSNs coated with preosteoblastic cell membranes demonstrated selective migration to bone defects, optimized drug delivery, and controlled release, highlighting their potential for personalized nanomedicine in bone-related diseases.[158]

11. Non-Bone Biomedical Applications of MSNs

Nanoparticles hold immense potential for revolutionizing cancer treatment by addressing the limitations of conventional therapies, including poor drug targeting, systemic toxicity, and multidrug resistance. In particular, MSNs have demonstrated significant potential in various non-bone biomedical applications due to their unique physic-chemical properties and excellent biocompatibility. One of the most prominent applications of MSNs is in cancer therapy, where they serve as efficient carriers for chemotherapeutic agents.[29] Their large surface area, tunable pore size, and high porosity enable efficient loading of both hydrophilic and hydrophobic drugs, protecting them from premature degradation, improving drug solubility and bioavailability and reducing their toxicity to healthy tissues. MSN can be chemically functionalized to enhance tumor targeting through active and passive mechanisms, such as ligand-based targeting (e.g., folic acid, RGD peptides) and exploiting the enhanced permeability and retention effect.[159] These nanoparticles also provide controlled and sustained drug release, reducing premature drug leakage and minimizing systemic side effects. MSNs have been effectively utilized for the delivery of chemotherapeutic agents like doxorubicin, paclitaxel, and cisplatin, as well as for combination therapies involving siRNA or photodynamic and photothermal approaches.[160] Their biocompatibility and ability to overcome multidrug resistance through endocytotic uptake and gene silencing strategies further highlight their potential.

Recent developments in MSN-based catalytic nanomedicines have demonstrated significant potential for cancer treatments thanks to the combination of tumor-specific biochemical environments and innovative catalytic mechanisms.[161–163] MSNs have been engineered to enable targeted delivery and catalysis-based therapeutic interventions. One notable application involves iron-catalyzed ascorbate oxidation for tumor chemotherapy. Specifically, ascorbate can be encapsulated within Fe-engineered hollow MSNs, where its release in the tumor microenvironment initiates pro-oxidation reactions, leading to substantial hydrogen peroxide production.[164] Subsequently, Fenton reactions between Fe^{2+} and H_2O_2 generate hydroxyl radicals, which induce oxidative stress and selectively eliminate cancer cells. The acidity-responsive degradation of the MSN framework facilitates the controlled release of Fe^{3+} and ascorbate, thereby reducing off-target toxicity and enhancing therapeutic specificity. Yang et al. introduced a novel concept of intratumoral coordination reactions and reacting oxygen species (ROS) generation designing Fe-engineered hollow MSNs loaded with gallate to facilitate the co-release of Fe^{3+} and gallate in acidic tumor environments.[165] This enables the formation in situ of nanocomplexes with a strong ligand field, promoting oxygen reduction reactions to generate hydrogen peroxide and subsequent hydroxyl radicals through Fenton-like reactions. This approach exploits the strong metal–ligand exchange coupling between

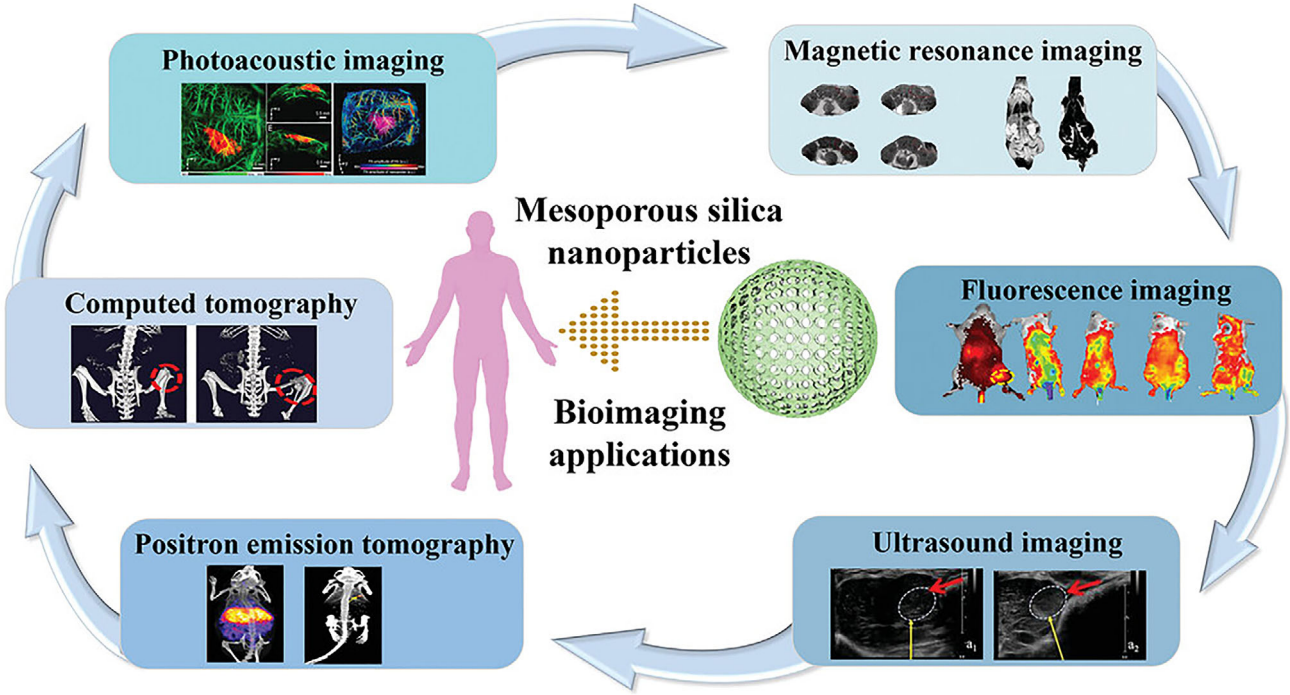

Figure 8. Schematic representation of different applications of MSNs as bioimaging agents, from.[173]

Fe centers and gallate ligands to enhance catalytic efficiency within tumors while minimizing systemic side effects. In a related approach, Yang et al. engineered Mn-doped hollow MSNs loaded with dopamine for tumor-specific chemotherapy.[166] This nanoplatform takes advantage of the coordination between Mn^{2+} and dopamine to form a binary complex that catalyzes oxygen reduction to hydrogen peroxide and dopamine oxidation to dopamine-o-quinone. Both dual catalytic reactions generate highly oxidizing hydroxyl radicals, thereby promoting oxidative stress in cancer cells and depleting intracellular glutathione, which disrupts the antioxidative defense of cancer cells and amplifies oxidative damage.

Gene therapy involves delivering nucleic acids such as DNA, siRNA, or microRNA to alter gene expression for therapeutic purposes. However, challenges such as the instability of nucleic acids, short half-life, and limited cellular uptake hinder their effective delivery. MSNs can address these issues by providing a protective environment that shields nucleic acids from enzymatic degradation and facilitates their controlled release at the target site.[30] Furthermore, the surface of MSNs can be functionalized with cationic polymers like polyethyleneimine or amination to enhance electrostatic interactions with negatively charged nucleic acids, significantly improving loading capacity and cellular uptake.[30]

Recent advancements in MSN-based gene delivery systems have demonstrated their potential for treating drug-resistant cancers and other genetic disorders. Similarly, MSN systems with large mesopores have been developed to accommodate larger genetic materials, such as plasmids, while ensuring efficient delivery and transfection. These systems often incorporate stimuli-responsive features, such as pH-sensitive linkers, to achieve precise gene release in the acidic tumor microenvironment. Moreover, multifunctional MSNs can co-deliver therapeutic genes and anticancer drugs, offering a synergistic approach for cancer treatment. This dual delivery allows siRNA to silence resistance-related genes while the loaded drug exerts cytotoxic effects, enhancing therapeutic outcomes.[167] These innovations highlight the versatility of MSNs in overcoming the challenges of gene therapy and their potential for clinical translation.

Mesoporous silica nanoparticles are emerging as innovative platforms in vaccine development because they can efficiently encapsulate and deliver antigens, adjuvants, and other immunostimulatory molecules while protecting them from premature degradation. MSNs have shown great potential in enhancing immune responses by facilitating antigen delivery to antigen-presenting cells like dendritic cells.[168] Their mesoporous structure allows for controlled and sustained antigen release, providing prolonged immune stimulation and enabling the generation of robust and long-lasting immunity. As mentioned above, the surface of MSNs can be functionalized with targeting ligands, to enhance the uptake of antigens by antigen-presenting cells, further improving the potency of vaccines.[169]

Mesoporous silica nanoparticles have also demonstrated exceptional potential as imaging agents due to their unique structural properties and ability to integrate diagnostic functionalities (**Figure 8**). Their network of cavities allows for the efficient loading of imaging agents such as fluorescent dyes, quantum dots, and magnetic contrast agents, enabling their use in various imaging modalities, including fluorescence imaging, magnetic resonance imaging, and positron emission tomography.[170] Furthermore, the biocompatibility and stability of MSNs ensure that these agents remain functional during in vivo imaging without

causing significant toxicity. MSNs can be functionalized with targeting ligands, such as antibodies, to enhance imaging specificity by directing the nanoparticles to disease sites, such as tumors, thereby improving diagnostic precision.[171,172]

Mesoporous silica nanoparticles have shown significant advances in tissue engineering due to their ability to deliver bioactive molecules, promote cell adhesion, and stimulate tissue regeneration.[22] Their above mentioned physico-chemical properties and biocopatibility enable them to serve as effective carriers for growth factors, proteins, and other bioactive agents essential for tissue repair and regeneration. MSNs can be functionalized with specific surface groups to enhance their interaction with cells, facilitating processes such as osteogenesis, angiogenesis, and wound healing. In fact, and beyond bone regeneration, MSNs have demonstrated their utility in soft tissue engineering and wound healing. For example, MSNs loaded with gentamicin and incorporated into hydrogels have been used to eradicate pathogenic bacteria in diabetic wounds, promoting efficient healing.[86] These nanoparticles can also serve as scaffolds to mimic the extracellular matrix, providing structural support for cell growth and differentiation. Functionalization with polymers, such as chitosan, further enhances MSN biocompatibility and mechanical properties, making them ideal candidates for applications in both hard and soft tissue engineering. The versatility of MSNs in carrying and delivering bioactive agents while maintaining structural integrity highlights their potential in advancing tissue engineering strategies and improving clinical outcomes.[174]

12. Global Innovations in MSNs

The remarkable versatility of MSNs has driven innovation across a wide range of fields beyond biomedicine, including environmental science, agriculture, materials engineering and catalysts.

Regarding environmental science, MSNs have demonstrated significant potential, particularly for applications such as water purification, air quality improvement, pollutant remediation and heavy metal adsorption. Functionalized MSNs, such as those modified with amine, thiol, or sugar groups, have been widely applied for the removal of heavy metals like arsenic, mercury, chromium, and cadmium through electrostatic interactions or chelation mechanisms.[175] Their high surface area, tunable pore sizes, and chemical stability make them ideal for removing contaminants like volatile organic compounds,[176] and hazardous gases.[177] For instance, MSNs functionalized with amine groups are effective in capturing airborne aldehydes and CO_2, while phenyl- or n-octyl-functionalized silica excels in adsorbing hydrophobic VOCs like toluene.[178,179] Additionally, MSNs are used as templates for synthesizing porous carbon[180] or metal oxides,[181] which further enhance their utility in catalyzing pollutant degradation and improving energy efficiency in environmental processes.

Additionally, the development of composite materials, such as magnetic mesoporous silica nanoparticles with iron oxide cores, enhances their environmental utility by enabling efficient pollutant adsorption and magnetic recovery.[182] MSNs also serve as effective catalysts for environmental processes,[183] including catalytic emission abatement of nitrogen oxides and volatile organic compounds, and renewable energy production through biomass conversion.[184]

In modern agriculture, mesoporous silica materials are ideal candidates for addressing critical agricultural challenges, such as enhancing crop productivity, improving stress resistance, and reducing environmental harm from conventional fertilizers and pesticides.[185,186] Studies have demonstrated the efficacy of MSNs as carriers for fertilizers, herbicides, and pesticides, enabling targeted and controlled delivery of agrochemicals.[187] This reduces the required quantities of chemical inputs, minimizes off-target effects, and enhances nutrient uptake by crops. For instance, MSNs loaded with urea and other nutrients have shown improved soil nutrient retention and controlled nutrient release, leading to enhanced crop growth and productivity while mitigating environmental run-off. In addition to nutrient delivery, MSNs can play a significant role in mitigating biotic and abiotic stresses in crops.[188] They can act as nanocarriers for bioactive compounds, such as antimicrobial agents, to enhance plant resistance to pathogens. Furthermore, MSNs improve plant tolerance to abiotic stresses, including drought, salinity, and heavy metal toxicity. As a sustainable agricultural technology, MSNs also leverage green synthesis approaches using agro-waste materials, such as rice husk and sugarcane bagasse, to produce eco-friendly nanoparticles with reduced toxicity.[189] This integration of MSNs into agriculture also could, therefore, promote environmental sustainability by reducing the ecological footprint of agricultural practices while addressing food security concerns.

Mesoporous silica nanoparticles have also emerged as highly versatile catalytic supports due to their well-defined pore structures, large surface areas, and thermal stability.[190] These attributes make them ideal for hosting and stabilizing metal or metal oxide nanoparticles, which are critical in various catalytic applications.[190] MSNs enhance the dispersion of active catalytic species, prevent sintering at elevated temperatures, and improve catalytic efficiency by offering controlled access to active sites. For instance, noble metal nanoparticles such as platinum, palladium, and gold have been immobilized on MSNs for hydrogenation, oxidation, and coupling reactions. The tunable pore sizes of MSNs allow for selective catalysis by restricting the diffusion of larger molecules, thus improving reaction specificity.[191] Additionally, the chemistry and technology of MSNs allows for embedding catalytic nanoparticles within the silica matrix to further enhance the stability and activity of the catalysts. Techniques such as core-shell structuring and intercalation of metal nanoparticles into the silica walls have demonstrated significant improvements in catalytic performance and resistance to sintering. Furthermore, MSNs have been utilized in reactions such as CO oxidation, water-gas shift reactions, and biodiesel production, showcasing their versatility across industrial and environmental applications.[192] In general, their ability to incorporate multiple functional groups and active metals enables the design of multi-functional catalysts for complex chemical transformations, opening the gates for more sustainable and efficient catalytic processes in the near future.

Machine learning has the potential to revolutionize the design and optimization MSNs by enabling data-driven insights into their complex synthesis and functionality.[193] Traditionally, MSN design relies on trial-and-error experiments to optimize parameters such as pore size, particle size and surface area, which are

critical for applications in drug delivery, diagnostics, and catalysis. However, machine learning algorithms streamline this process by analyzing vast datasets, identifying patterns, and predicting outcomes based on synthesis variables like pH, surfactant concentration, reaction time, stirring conditions and temperature. By employing models such as neural networks, random forests, or regression-based approaches, researchers can optimize synthesis protocols to achieve precise control over MSN properties. Moreover, machine learning is expected to predict interactions between MSNs and biological systems, such as drug loading efficiency, release profiles, celular internalisation and biocompatibility, thus expediting the development of tailored nanocarriers.[194] In this sense, machine learning-guided approaches have the potential to improve reproducibility, scalability, and quality control, thereby expediting the translation of MSNs into industrial and clinical applications, the challenges of which are detailed in the following section.

13. Clinical Translation of MSNs

The clinical translation of MSNs is hindered by significant challenges related to biosafety, regulatory requirements, and manufacturing scalability. FDA/EMA regulatory considerations primarily focus on ensuring safety, efficacy, and quality, which necessitates extensive data on long-term toxicological profiles, particularly concerning chronic exposure and different routes of administration.[195] This involves rigorous evaluation of MSN interactions with biological systems, including effects on immune response, hemotoxicity, and accumulation in organs such as the liver and spleen. Regulatory bodies also demand comprehensive studies on biodistribution, clearance mechanisms, and potential tissue accumulation to ensure biosafety. Additionally, MSNs must be designed with tunable biodegradability to break down into non-toxic byproducts, such as silicic acid, which can be eliminated via renal or hepatobiliary pathways. This can be achieved through modifications in surface chemistry or incorporating biodegradable organic groups.[114] Manufacturing-related challenges further complicate clinical translation. MSNs face hurdles in demonstrating batch-to-batch reproducibility, a critical requirement for meeting good manufacturing practice standards. The lack of standardized synthesis and characterization methods exacerbates this issue, as variations in particle size, surface chemistry, and porosity can significantly influence biological behavior. To meet these demands, optimization of physicochemical properties—such as size (50–200 nm), shape (spherical or rod-like), and surface functionalization (e.g., PEGylation or lipid coatings)—is crucial to enhance circulation time, reduce rapid uptake by the reticuloendothelial system, and ensure effective targeting of diseased tissues. Moreover, limited clinical data on advanced MSN formulations highlights the need for further preclinical and clinical studies.

The lack of robust scale-up methods and reliable manufacturing processes are slowing the pace of MSN translation to the clinic. Standardized manufacturing protocols that ensure scalability, reproducibility, and cost-effectiveness are necessary for regulatory approval and commercialization. In this sense, scalability of MSNs remains a significant challenge in their clinical translation, primarily due to the complexity of maintaining uniform physicochemical properties during large-scale production.[196] Key parameters such as particle size, pore structure, surface area, and functionalization must remain consistent across batches to ensure reproducibility and efficacy. Traditional laboratory-scale synthesis methods, such as sol-gel and template-directed approaches, are difficult to scale due to the sensitivity of these processes to reaction conditions, including temperature, pH, and precursor concentrations. Additionally, removal of surfactants or templates—critical for reducing toxicity—often requires time-intensive and costly steps, such as calcination or refluxing in acidic solutions. In this sense, cost-effectiveness of MSNs is hindered by complex synthesis processes, including the use of expensive surfactants, functionalization steps, and energy-intensive purification methods. Scalable techniques like continuous flow reactors and cost-efficient alternatives for surfactants could be developed to reduce production costs. Emerging techniques, like microwave-assisted methods, could also offer promising routes for scaling up production and maintaining particle homogeneity. In fact, automation and high-throughput manufacturing systems could further enhance scalability by reducing batch-to-batch variability. These combined strategies, alongside compliance with regulatory standards and robust pharmacokinetic studies, will pave the way for the successful clinical translation of MSNs.

Silica nanoparticles are undergoing clinical trials for a range of biomedical applications, showcasing their versatility and potential in drug delivery, diagnostics, and therapeutic interventions.[195] In drug delivery, silica nanoparticles have been tested for improving the bioavailability of poorly water-soluble drugs. For example, silica–lipid hybrid formulations have enhanced the pharmacokinetics of ibuprofen and simvastatin, showing a 1.95-fold and 3.5-fold increase in bioavailability, respectively, compared to existing commercial formulations.[197,198] Similarly, MSNs were used to improve the bioavailability of fenofibrate by 54%, demonstrating their capacity to overcome solubility and stability challenges in oral drug delivery.[199] These studies highlight the potential of silica nanoparticles to revolutionize drug delivery systems by enhancing therapeutic efficacy and reducing required doses.

In diagnostics and therapy, silica nanoparticles are being utilized for advanced imaging and treatment modalities. Ultrasmall silica nanoparticles, such as Cornell dots, have been deployed in clinical trials for imaging tumors, including melanoma and brain cancer. Functionalized with tumor-targeting ligands and fluorescent dyes, these nanoparticles allow for real-time imaging with high specificity and minimal side effects.[200] Importantly, their size (6–10 nm) ensures renal clearance, mitigating concerns about long-term accumulation in the body. Additionally, hybrid silica–gold nanoparticles have been explored for photothermal ablation therapy in cancers such as prostate, head, and neck tumors. These particles accumulate at tumor sites via the enhanced permeability and retention effect and convert near-infrared light into heat, enabling precise and minimally invasive tumor ablation.[201]

Silica nanoparticles have also been tested for cardiovascular applications, such as plasmonic resonance therapy. In a phase I clinical trial, silica–gold nanoparticles successfully reduced coronary atherosclerosis while maintaining a favorable safety profile.[202,203] Other ongoing studies are exploring silica nanoparticles for theragnostic applications, combining therapeutic and

diagnostic functionalities in a single platform. Despite these advancements, challenges remain in achieving robust batch-to-batch reproducibility, scalable manufacturing, and long-term safety validation. Addressing these issues could accelerate the translation of MSNs to the clinic.

14. Next Generation of MSNs

The future of MSNs in biomedicine lies in the development of multifunctional and adaptive nanoplatforms that integrate diverse therapeutic and diagnostic capabilities into a single system.[204] A promising conceptual framework for these next-generation MSNs involves the use of computational design and machine learning to optimize nanoparticle properties.[205] In this sense, the use of predictive algorithms could simulate the effects of pore size, morphology, and surface functionalization on drug loading, release profiles, and biodistribution. This data-driven approach would enable the rational design of MSNs tailored for specific medical applications, including personalized medicine. For example, integrating machine learning with high-throughput experimentation can facilitate the identification of optimal surface chemistries for selective targeting of disease-specific biomarkers while minimizing off-target effects. This framework ensures that MSN development is not only efficient but also highly customizable, paving the way for precision nanomedicine.

15. Directions and Conclusion

Mesoporous silica nanoparticles MSNs have emerged as transformative tools in biomedicine, particularly in tissue engineering and regenerative medicine. Their ability to mimic the extracellular matrix, combined with their high surface area, tunable pore sizes, and bioactive surfaces, makes them ideal for supporting cellular adhesion, proliferation, and differentiation. MSNs enable the encapsulation and controlled release of biomolecules like growth factors and peptides, which are essential for tissue repair. In bone regeneration, MSNs show promise by delivering osteoinductive agents and ions to promote osteogenesis while offering structural support. These features position MSNs as a cornerstone for advancing tissue engineering technologies.

Despite their potential, several challenges hinder the clinical translation of MSNs. Issues such as scalability, manufacturing reproducibility, and production costs remain significant hurdles. The production of MSNs with consistent properties at an industrial scale is complex, and variability in synthesis protocols can impact reproducibility. Additionally, achieving controlled biodegradation that aligns with therapeutic timelines is vital to avoid bioaccumulation or long-term toxicity. Regulatory requirements further demand comprehensive studies on the biosafety, biodistribution, and clearance profiles of MSNs to ensure their safe and effective use in clinical settings.

The integration of advanced technologies, such as machine learning and computational design, offers a promising pathway for optimizing MSN development. Machine learning can analyze vast datasets to predict the impact of synthesis parameters on properties like pore size and drug release profiles, accelerating the design of tailored nanoplatforms for specific applications. Furthermore, the ability of MSNs to integrate multiple capabilities, such as drug delivery and diagnostic imaging (theranostics), positions them as versatile tools for personalized medicine. Stimuli-responsive MSNs, designed to respond to environmental or pathological triggers, offer precise control over drug release, enhancing therapeutic efficacy while minimizing side effects.

The future of MSNs lies in scaling up production and developing multifunctional, adaptive nanoplatforms that combine therapeutic, diagnostic, and imaging capabilities. Ensuring regulatory compliance of MSNs could revolutionize modern medicine, offering innovative solutions for drug delivery, diagnostics, and tissue regeneration. Their adaptability and potential to support personalized therapies highlight their pivotal role in tackling complex biomedical challenges.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] T. Yanagisawa, T. Shimizu, K. Kuroda, C. Kato, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 988.
[2] T. Yanagisawa, T. Shimizu, K. Kuroda, C. Kato, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1535.
[3] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710.
[4] J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T. W. Chu, D. H. Olson, E. W. Sheppard, S. B. McCullen, J. B. Higgins, J. L. Schlenker, *J. Am. Chem. Soc.* **1992**, *114*, 10834.
[5] U. Ciesla, F. Schüth, *Microporous Mesoporous Mater.* **1999**, *27*, 131.
[6] A. Taguchi, F. Schüth, *Microporous Mesoporous Mater.* **2005**, *77*, 1.
[7] M. Vallet-Regi, A. Rámila, R. P. Del Real, J. Pérez-Pariente, *Chem. Mater.* **2001**, *13*, 308.
[8] M. Vallet-Regí, F. Schüth, D. Lozano, M. Colilla, M. Manzano, *Chem. Soc. Rev.* **2022**, *51*, 5365.
[9] I. Slowing, J. Vivero-Escoto, C. Wu, V. Lin, *Adv Drug Deliv Rev* **2008**, *60*, 1278.
[10] F. Tang, L. Li, D. Chen, *Adv. Mater.* **2012**, *24*, 1504.
[11] Z. Li, J. C. Barnes, A. Bosoy, J. F. Stoddart, J. I. Zink, *Chem. Soc. Rev.* **2012**, *41*, 2590.
[12] Y. Wang, Q. F. Zhao, N. Han, L. Bai, J. Li, J. Liu, E. X. Che, L. Hu, Q. Zhang, T. Y. Jiang, S. L. Wang, *Nanomed.:Nanotechnol. Biol. Med.* **2015**, *11*, 313.
[13] M. Manzano, M. Vallet-Regí, *Adv. Funct. Mater.* **2020**, *30*, 1902634.

[14] R. Fatima, P. Katiyar, K. Kushwaha, *Front. Nanotechnol.* **2025**, *7*, 2025.
[15] L. Kremer, J. Aguilera-Correa, Y. Tasrini, M. Gisbert-Garzarán, A. Boulay, T. Carvalho, F. Blanchet, M. Vallet-Regí, *Nat. Comm.* **2025**, *16*, 7388.
[16] A. Rahikkala, S. A. P. Pereira, P. Figueiredo, M. L. C. Passos, A. Araújo, M. Saraiva, H. A. Santos, *Adv. Biosyst.* **2018**, *2*, 1800020.
[17] A. Baeza, M. Manzano, M. Colilla, M. Vallet-Regí, *Biomater. Sci.* **2016**, *4*, 803.
[18] R. R. Castillo, D. Lozano, B. González, M. Manzano, I. Izquierdo-Barba, M. Vallet-Regí, *Expert Opin. Drug Delivery* **2019**, *16*, 415.
[19] C. Iriarte-Mesa, F. Kleitz, *New J. Chem.* **2025**, *49*, 10018.
[20] M. Bouchoucha, M. F. Côté, R. C-Gaudreault, M. A. Fortin, F. Kleitz, *Chem. Mater.* **2016**, *28*, 4243.
[21] Y.-T. Lee, S.-H. Wu, C.-H. Wu, Y.-H. Lin, C.-K. Lin, Z.-A. Chen, T.-C. Sun, Y.-J. Chen, P. Chen, C.-Y. Mou, Y.-P. Chen, *ACS Appl. Mater. Interfaces* **2024**, *16*, 61787.
[22] L. Chen, X. Zhou, C. He, *Wiley Interdiscip Rev Nanomed Nanobiotechnol* **2019**, *11*, 1.
[23] M. Colilla, M. Vallet-Regí, *Int. J. Mol. Sci.* **2020**, *21*, 8605.
[24] A. Noureddine, A. Maestas-Olguin, L. Tang, J. I. Corman-Hijar, M. Olewine, J. A. Krawchuck, J. Tsala Ebode, C. Edeh, C. Dang, O. A. Negrete, J. Watt, T. Howard, E. N. Coker, J. Guo, C. J. Brinker, *ACS Nano* **2023**, *17*, 16308.
[25] M. Manzano, M. Vallet-Regí, *J. Mater. Sci. Mater. Med.* **2018**, *29*, 65.
[26] J. Chen, Z. Xu, M. Zhang, Z. Ju, Z. Niu, Y. Ma, Z. Xu, T. Zhang, F. Shi, *Mater. Today Chem.* **2024**, *42*, 102426.
[27] M. Gisbert-Garzarán, M. Manzano, M. Vallet-Regí, *Pharmaceutics* **2020**, *12*, 83.
[28] P. Pan, Q. Yue, J. Li, M. Gao, X. Yang, Y. Ren, X. Cheng, P. Cui, Y. Deng, *Adv. Sci.* **2021**, *8*, 2004586.
[29] S. Yousefiasl, M. Ghovvati, A. Alibakhshi, M. Azizi, P. Samadi, A. Kumar, A. Shojaeian, E. Sharifi, E. N. Zare, A. D. Dey, M. Chehelgerdi, P. Makvandi, *Small* **2025**, *21*, 2408898.
[30] T. B. Huq, P. A. Kumar Jeeja, S. K. Dam, S. S. Das, J. L. Vivero-Escoto, *Adv. Healthcare Mater.* **2025**, 2404781.
[31] A. Berggren, A. E. C. Palmqvist, K. Holmberg, *Soft Matter* **2005**, *1*, 219.
[32] M. Kruk, *Acc. Chem. Res.* **2012**, *45*, 1678.
[33] L. Duan, C. Wang, W. Zhang, B. Ma, Y. Deng, W. Li, D. Zhao, *Chem. Rev.* **2021**, *121*, 14349.
[34] M. Vallet-Regí, M. Manzano, J. M. González-Calbet, E. Okunishi, *Chem. Commun.* **2010**, *46*, 2956.
[35] F. Hoffmann, M. Cornelius, J. Morell, M. Fröba, *Angew. Chem., Int. Ed.* **2006**, *45*, 3216.
[36] C. Trayford, S. van Rijt, *Biomater. Sci.* **2024**, *12*, 5450.
[37] P. Yang, S. Gai, J. Lin, *Chem. Soc. Rev.* **2012**, *41*, 3679.
[38] H. Zhu, K. Zheng, A. R. Boccaccini, *Acta Biomater.* **2021**, *129*, 1.
[39] S. Giret, M. Wong Chi Man, C. Carcel, *Chem.– Eur. J.* **2015**, *21*, 13850.
[40] T. Asefa, M. J. MacLachlan, N. Coombs, G. A. Ozin, *Nature* **1999**, *402*, 867.
[41] A. Corma, *Chem. Rev.* **1997**, *97*, 2373.
[42] P. Zhang, M. M. He, W. Teng, F. K. Li, X. Y. Qiu, K. X. Li, H. Wang, *Green Energy Environ.* **2024**, *9*, 1239.
[43] W. Li, J. Liu, D. Y. Zhao, *Nat. Rev. Mater.* **2016**, *1*, 16023.
[44] M. Vallet-Regí, F. Balas, D. Arcos, *Angew. Chem., Int. Ed.* **2007**, *46*, 7548.
[45] M. Manzano, M. Vallet-Regí, *J. Mater. Chem.* **2010**, *20*, 5593.
[46] I. Izquierdo-Barba, L. Ruiz-González, J. C. Doadrio, J. M. González-Calbet, M. Vallet-Regí, *Solid State Sci.* **2005**, *7*, 983.
[47] M. Vallet-Regí, *Chem.-Eur. J.* **2006**, *12*, 5934.
[48] P. Horcajada, A. Rámila, K. Boulahya, J. González-Calbet, M. Vallet-Regí, *Solid State Sci.* **2004**, *6*, 1295.
[49] M. Vallet-Regí, L. Ruiz-González, I. Izquierdo-Barba, J. M. González-Calbet, *J. Mater. Chem.* **2006**, *16*, 26.
[50] R. S. Langer, N. A. Peppas, *Biomaterials* **1981**, *2*, 201.
[51] T. M. Allen, P. R. Cullis, *Adv. Drug Delivery Rev.* **2013**, *65*, 36.
[52] S. Mitragotri, T. Lammers, Y. H. Bae, S. Schwendeman, S. De Smedt, J.-C. Leroux, D. Peer, I. C. Kwon, H. Harashima, A. Kikuchi, Y.-K. Oh, V. Torchilin, W. Hennink, J. Hanes, K. Park, *J. Controlled Release* **2017**, *246*, 183.
[53] M. Manzano, M. Colilla, M. Vallet-Regí, *Expert Opin. Drug Delivery* **2009**, *6*, 1383.
[54] P. Horcajada, A. Rámila, G. Férey, M. Vallet-Regí, *Solid State Sci.* **2006**, *8*, 1243.
[55] M. Manzano, *Pharmaceutics* **2021**, *13*, 2179.
[56] T. M. Allen, P. R. Cullis, *Science* **2004**, *303*, 1818.
[57] M. Manzano, M. Vallet-Regí, F. Balas, M. Colilla, A. Nieto, *Microporous Mesoporous Mater.* **2008**, *116*, 4.
[58] I. Izquierdo-Barba, E. Sousa, J. C. Doadrio, A. L. Doadrio, J. P. Pariente, A. Martínez, F. Babonneau, M. Vallet-Regí, *J. Solgel Sci. Technol.* **2009**, *50*, 421.
[59] P. Horcajada, A. Rámila, J. Pérez-Pariente, M. Vallet-Regı´, *Microporous Mesoporous Mater.* **2004**, *68*, 105.
[60] F. Balas, M. Manzano, P. Horcajada, M. Vallet-Regi, *J. Am. Chem. Soc.* **2006**, *128*, 8116.
[61] L. L. Hench, J. Wilson, *Science* **1984**, *226*, 630.
[62] A. López-Noriega, D. Arcos, I. Izquierdo-Barba, Y. Sakamoto, O. Terasaki, M. Vallet-Regí, *Chem. Mater.* **2006**, *18*, 3137.
[63] L. L. Hench, J. M. Polak, *Science* **2002**, *295*, 1014.
[64] M. Vallet-Regí, C. V. Ragel, A. J. Salinas, *Eur. J. Inorg. Chem.* **2003**, *2003*, 1029.
[65] M. Vallet-Regí, *Dalton Trans.* **2006**, 5211.
[66] M. Vallet-Regí, A. J. Salinas, in *Bioactive Glasses: Fundamentals, Technology and Applications* (Eds.: A. R. Boccaccini, D. S. Brauer, L. Hupa), The Royal Society Of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge CB4 0WF, UK **2016**.
[67] A. J. Salinas, M. Vallet-Regí, *J. Non-Cryst. Solids* **2016**, *432*, 9.
[68] C. Vichery, J. M. Nedelec, *Materials* **2016**, *9*, 288.
[69] N. Gómez-Cerezo, D. Lozano, A. J. Salinas, M. Vallet-Regí, *Adv. Healthcare Mater.* **2025**, https://doi.org/10.1002/adhm.202502201.
[70] L. Krishnan, P. Chakrabarty, K. Govarthanan, S. Rao, T. S. Santra, *Int. J. Biol. Macromol.* **2024**, *277*, 133073.
[71] X. Chatzistavrou, O. Tsigkou, H. D. Amin, K. M. Paraskevopoulos, V. Salih, A. R. Boccaccini, *J. Eur. Ceram. Soc.* **2012**, *32*, 3051.
[72] L. L. Hench, *J. Am. Ceram. Soc.* **1991**, *74*, 1487.
[73] R. Narayan, U. Y. Nayak, A. M. Raichur, S. Garg, *Pharmaceutics* **2018**, *10*, 118.
[74] B. G. Trewyn, Slowing I. I., S. Giri, H. T. Chen, V. S. Lin, *Acc. Chem. Res.* **2007**, *40*, 846.
[75] W. Stöber, A. Fink, E. Bohn, *J. Colloid Interface Sci.* **1968**, *26*, 62.
[76] M. Grün, I. Lauer, K. K. Unger, *Adv. Mater.* **1997**, *9*, 254.
[77] C. C. Zhang, H. Y. Xie, Z. Y. Zhang, B. J. Wen, H. Cao, Y. Bai, Q. S. Che, J. Guo, Z. Q. Su, *Front. Pharmacol.* **2022**, *13*, 829796.
[78] T. M. Albayati, S. M. Alardhi, A. H. Khalbas, Z. J. Humdi, N. S. Ali, I. K. Salih, N. M. C. Saady, S. Zendehboudi, M. A. Abdulrahman, *ChemistrySelect* **2024**, *9*, 202400450.
[79] P. Lavrador, V. M. Gaspar, J. F. Mano, *J. Controlled Release* **2018**, *273*, 51.
[80] X. Zhou, E. J. Cornel, S. He, J. Du, *Mater. Chem. Front.* **2021**, *5*, 6735.
[81] O. C. Farokhzad, R. Langer, *ACS Nano* **2009**, *3*, 16.
[82] M. I. Grini, C. Benbayer, S. Saidi-Besbes, A. Elaissari, *Microporous Mesoporous Mater.* **2025**, *391*, 113603.
[83] J. M. Rosenholm, C. Sahlgren, M. Lindén, *Nanoscale* **2010**, *2*, 1870.
[84] B. Xu, S. Li, R. Shi, H. Liu, *Signal Transduction Targeted Ther.* **2023**, *8*, 435.
[85] M. Vallet-Regí, E. Ruiz-Hernández, *Adv. Mater.* **2011**, *23*, 5177.

[86] J. L. Pablos, D. Lozano, M. Manzano, M. Vallet-Regí, *Mater. Today Bio* **2024**, *29*, 101342.
[87] C. Rinoldi, E. Kijeńska-Gawrońska, M. Heljak, J. Jaroszewicz, A. Kamiński, A. Khademhosseini, A. Tamayol, W. Swieszkowski, *ACS Mater. Au* **2023**, *3*, 636.
[88] Y. Cui, S. Hong, W. Jiang, X. Li, X. Zhou, X. He, J. Liu, K. Lin, L. Mao, *Bioact. Mater.* **2024**, *34*, 436.
[89] L. Suamte, A. Tirkey, J. Barman, P. J. Babu, *Smart Mater. Manuf.* **2023**, *1*, 100011.
[90] T. Shi, J. Zhao, K. Long, M. Gao, F. Chen, X. Chen, Y. Zhang, B. Huang, D. Shao, C. Yang, L. Wang, M. Zhang, K. W. Leong, L. Chen, K. He, *Biomaterials* **2023**, *303*, 122366.
[91] P. L. Cui, P. P. Pan, L. Qin, X. L. Wang, X. D. Chen, Y. H. Deng, X. L. Zhang, *Bioact Mater.* **2023**, *19*, 487.
[92] R. Singla, S. M. S. Abidi, A. I. Dar, A. Acharya, *J. Biomed. Mater. Res. Part B* **2019**, *107*, 2433.
[93] D. L. Ni, W. B. Bu, E. B. Ehlerding, W. B. Cai, J. L. Shi, *Chem. Soc. Rev.* **2017**, *46*, 7438.
[94] M. Vallet-Regí, D. Lozano, B. González, I. Izquierdo-Barba, *Adv. Healthcare Mater.* **2020**, *9*, 2000310.
[95] Y. H. Zhu, H. S. Sundaram, S. J. Liu, L. Zhang, X. W. Xu, Q. M. Yu, J. Q. Xu, S. Y. Jiang, *Biomacromolecules* **2014**, *15*, 1845.
[96] S. Mura, J. Nicolas, P. Couvreur, *Nat. Mater.* **2013**, *12*, 991.
[97] Z.-A. Chen, C.-H. Wu, S.-H. Wu, C.-Y. Huang, C.-Y. Mou, K.-C. Wei, Y. Yen, I.-T. Chien, S. Runa, Y.-P. Chen, P. Chen, *ACS Nano* **2024**, *18*, 12716.
[98] C. Chen, W. Sun, W. Yao, Y. Wang, H. Ying, P. Wang, *RSC Adv.* **2018**, *8*, 20862.
[99] N. Song, Y. W. Yang, *Chem. Soc. Rev.* **2015**, *44*, 3474.
[100] E. Ruiz-Hernández, A. Baeza, M. Vallet-Regí, *ACS Nano* **2011**, *5*, 1259.
[101] S. Payamifar, Y. Khalili, A. Foroozandeh, M. Abdouss, M. Hasanzadeh, *RSC Adv.* **2025**, *15*, 16050.
[102] H. Mekaru, J. Lu, F. Tamanoi, *Adv. Drug Delivery Rev.* **2015**, *95*, 40.
[103] Q. J. He, J. L. Shi, *J. Mater. Chem.* **2011**, *21*, 5845.
[104] S. E. Moya, R. R. Hernández, P. C. Angelomé, *Adv Nanobiomed. Res.* **2024**, *4*, 2400005.
[105] Q. J. He, Z. W. Zhang, Y. Gao, J. L. Shi, Y. P. Li, *Small* **2009**, *5*, 2722.
[106] J. L. Paris, M. Colilla, I. Izquierdo-Barba, M. Manzano, M. Vallet-Regí, *J. Mater. Sci.* **2017**, *52*, 8761.
[107] E. Bindini, Z. Chehadi, M. Faustini, P.-A. Albouy, D. Grosso, A. Cattoni, C. Chanéac, O. Azzaroni, C. Sanchez, C. Boissière, *ACS Appl. Mater. Interfaces* **2020**, *12*, 13598.
[108] L. Li, T. Liu, C. Fu, L. Tan, X. Meng, H. Liu, *Nanomedicine* **2015**, *11*, 1915.
[109] V. Cauda, A. Schlossbauer, T. Bein, *Microporous Mesoporous Mater.* **2010**, *132*, 60.
[110] J. S. Souris, C.-H. Lee, S.-H. Cheng, C.-T. Chen, C.-S. Yang, J. A. Ho, C.-Y. Mou, L.-W. Lo, *Biomaterials* **2010**, *31*, 5564.
[111] Y. Hu, S. Bai, X. Z. Wu, S. W. Tan, Y. J. He, *Ceram. Int.* **2021**, *47*, 31031.
[112] X. Guo, H. Shi, W. Zhong, H. Xiao, X. Liu, T. Yu, C. Zhou, *Ceram. Int.* **2020**, *46*, 11762.
[113] J. Lu, M. Liong, Z. Li, J. I. Zink, F. Tamanoi, *Small* **2010**, *6*, 1794.
[114] A. Lérida-Viso, A. Estepa-Fernández, A. García-Fernández, V. Martí-Centelles, R. Martínez-Máñez, *Adv. Drug Delivery Rev.* **2023**, *201*, 115049.
[115] S. Mukhopadhyay, H. Veroniaina, T. Chimombe, L. Han, W. Zhenghong, Q. Xiaole, *RSC Adv.* **2019**, *9*, 35566.
[116] T. I. Janjua, Y. Cao, F. Kleitz, M. Linden, C. Yu, A. Popat, *Adv. Drug Delivery Rev.* **2023**, *203*, 115115.
[117] E. Álvarez, B. González, D. Lozano, A. L. Doadrio, M. Colilla, I. Izquierdo-Barba, *Pharmaceutics* **2021**, *13*, 2033.
[118] E. Álvarez, M. Estévez, C. Jiménez-Jiménez, M. Colilla, I. Izquierdo-Barba, B. González, M. Vallet-Regí, *Acta Biomater.* **2021**, *136*, 570.
[119] M. Martínez-Carmona, Q. P. Ho, J. Morand, A. García, E. Ortega, L. C. S. Erthal, E. Ruiz-Hernandez, M. D. Santana, J. Ruiz, M. Vallet-Regí, Y. K. Gun'ko, *Inorg. Chem.* **2020**, *59*, 10275.
[120] J. L. Paris, P. de la Torre, M. V. Cabañas, M. Manzano, A. I. Flores, M. Vallet-Regí, *Acta Biomater.* **2019**, *83*, 372.
[121] M. Gisbert-Garzarán, D. Lozano, K. Matsumoto, A. Komatsu, M. Manzano, F. Tamanoi, M. Vallet-Regí, *ACS Appl. Mater. Interfaces* **2021**, *13*, 9656.
[122] M. Manzano, A. Gabizón, M. Vallet-Regí, *Pharmaceutics* 1483, **2022**, *14*,.
[123] G. Villaverde, A. Alfranca, Á. Gonzalez-Murillo, G. J. Melen, R. R. Castillo, M. Ramírez, A. Baeza, M. Vallet-Regí, *Angew. Chem., Int. Ed.* **2019**, *58*, 3067.
[124] S. Montalvo-Quiros, G. Aragoneses-Cazorla, L. Garcia-Alcalde, M. Vallet-Regí, B. González, J. L. Luque-Garcia, *Nanoscale* **2019**, *11*, 4531.
[125] M. Martínez-Carmona, D. Lozano, M. Colilla, M. Vallet-Regí, *Acta Biomater.* **2018**, *65*, 393.
[126] V. López, M. R. Villegas, V. Rodríguez, G. Villaverde, D. Lozano, A. Baeza, M. Vallet-Regí, *ACS Appl. Mater. Interfaces* **2017**, *9*, 26697.
[127] R. R. Castillo, D. Lozano, M. Vallet-Regí, *Bioconjug. Chem.* **2018**, *29*, 3677.
[128] G. Villaverde, V. Nairi, A. Baeza, M. Vallet-Regí, *Chem.-Eur. J.* **2017**, *23*, 7174.
[129] J. L. Paris, G. Villaverde, M. V. Cabañas, M. Manzano, M. Vallet-Regí, *J. Mater. Chem. B* **2018**, *6*, 2785.
[130] A. Baeza, E. Guisasola, E. Ruiz-Hernández, M. Vallet-Regí, *Chem. Mater.* **2012**, *24*, 517.
[131] E. Guisasola, A. Baeza, L. Asín, J. M. de la Fuente, M. Vallet-Regí, *Small Methods* **2018**, 1800007.
[132] J. L. Paris, C. Mannaris, M. V. Cabañas, R. Carlisle, M. Manzano, M. Vallet-Regí, C. C. Coussios, *Chem. Eng. J.* **2018**, *340*, 2.
[133] J. L. Paris, G. Villaverde, S. Gómez-Graña, M. Vallet-Regí, *Acta Biomater.* **2020**, *101*, 459.
[134] J. L. Paris, P. De La Torre, M. V. Cabañas, M. Manzano, M. Grau, A. I. Flores, M. Vallet-Regí, *Nanoscale* **2017**, *9*, 5528.
[135] J. L. Paris, M. Manzano, V. Cabañas, M. Vallet-Regi, *Nanoscale* **2018**, *10*, 6402.
[136] V. M. Moreno, A. Baeza, M. Vallet-Regí, *Acta Biomater.* **2021**, *121*, 263.
[137] M. R. Villegas, A. Baeza, A. Usategui, P. L. Ortiz-Romero, J. L. Pablos, M. Vallet-Regí, *Acta Biomater.* **2018**, *74*, 430.
[138] M. R. Villegas, A. Baeza, M. Vallet-Regí, *ACS Appl. Mater. Interfaces* **2015**, *7*, 24075.
[139] V. M. Moreno, C. Meroño, A. Baeza, A. Usategui, P. L. Ortiz-Romero, J. L. Pablos, M. Vallet-Regí, *Pharmaceutics* **2021**, *13*, 499.
[140] C. Jiménez-Jiménez, V. M. Moreno, M. Vallet-Regí, *Nanomaterials* **2022**, *12*, 288.
[141] V. M. Moreno, E. Álvarez, I. Izquierdo-Barba, A. Baeza, J. Serrano-López, M. Vallet-Regí, *Adv. Mater. Interfaces* **2020**, *7*, 1901942.
[142] J. J. Aguilera-Correa, M. Gisbert-Garzarán, A. Mediero, R. A. Carias-Cálix, C. Jiménez-Jiménez, J. Esteban, M. Vallet-Regí, *Acta Biomater.* **2022**, *137*, 218.
[143] D. M. Dereje, A. García, C. Pontremoli, B. González, M. Colilla, M. Vallet-Regí, I. Izquierdo-Barba, N. Barbero, *Microporous Mesoporous Mater.* **2024**, *372*, 113096.
[144] C. Carucci, J. L. Pablos, J. A. Romero-Antolìn, B. González, M. Colilla, I. I. Barba, A. Salis, M. Monduzzi, M. Vallet-Regí, *Microporous Mesoporous Mater.* **2024**, *363*, 112810.
[145] F. Rizzi, E. Fanizza, M. Giancaspro, N. Depalo, M. L. Curri, B. González, M. Colilla, I. Izquierdo-Barba, M. Vallet-Regí, *Microporous Mesoporous Mater.* **2025**, *383*, 113414.

[146] A. Aguilar-Colomer, C. Jiménez-Jiménez, B. González, J. Esteban, M. Vallet-Regí, M. Colilla, I. Izquierdo-Barba, *Nanoscale Adv.* **2025**, *7*, 3414.
[147] J. J. Aguilera-Correa, M. Gisbert-Garzarán, A. Mediero, M. J. Fernández-Aceñero, D. de-Pablo-Velasco, D. Lozano, J. Esteban, M. Vallet-Regí, *Acta Biomater.* **2022**, *154*, 608.
[148] G. Luengo-Alonso, B. Bravo-Gimenez, D. Lozano, C. Heras, S. Sanchez-Salcedo, L. Benito-Garzón, M. Abella, M. Vallet-Regi, D. Cecilia-Lopez, A. J. Salinas, *Biomolecules* **2024**, *14*, 143.
[149] D. Lozano, B. Leiva, I. S. Gómez-Escalonilla, S. Portal-Núñez, A. R. de Górtazar, M. Manzano, M. Vallet-Regí, *Pharmaceutics* **2023**, *15*, 658.
[150] P. Mora-Raimundo, M. Manzano, M. Vallet-Regí, *AIMS Bioeng.* **2017**, *4*, 259.
[151] D. Lozano, M. Manzano, J. C. Doadrio, A. J. Salinas, M. Vallet-Regí, E. Gómez-Barrena, P. Esbrit, *Acta Biomater.* **2010**, *6*, 797.
[152] A. Imanpour, H. Kolahi Azar, D. Makarem, Z. Nematollahi, R. Nahavandi, M. Rostami, N. Beheshtizadeh, *Sci. Rep.* **2023**, *13*, 18185.
[153] P. Mora-Raimundo, D. Lozano, M. Manzano, M. Vallet-Regí, *ACS Nano* **2019**, *13*, 5451.
[154] P. Mora-Raimundo, D. Lozano, M. Benito, F. Mulero, M. Manzano, M. Vallet-Regí, *Adv. Sci.* **2021**, *8*, 2101107.
[155] M. Estévez, M. Cicuéndez, M. Colilla, M. Vallet-Regí, B. González, I. Izquierdo-Barba, *J. Colloid Interface Sci.* **2024**, *664*, 454.
[156] L. García-Lamas, D. Lozano, V. Jiménez-Díaz, B. Bravo-Giménez, S. Sánchez-Salcedo, J. Jiménez-Holguín, M. Abella, M. Desco, M. Vallet-Regi, D. Cecilia-López, A. J. Salinas, *Acta Biomater.* **2024**, *180*, 104.
[157] B. Dumontel, C. Jiménez-Jiménez, M. Vallet-Regí, M. Manzano, *Mater Today Bio* **2023**, *23*, 100850.
[158] C. Jiménez-Jiménez, A. Moreno-Borrallo, B. Dumontel, M. Manzano, M. Vallet-Regí, *Acta Biomater.* **2023**, *157*, 395.
[159] A. Barkat, S. Beg, S. K. Panda, K. S. Alharbi, M. Rahman, F. J. Ahmed, *Semin. Cancer Biol.* **2021**, *69*, 365.
[160] J. M. Rosenholm, C. S., M. Linden, *Curr. Drug Targets* **2011**, *12*, 1166.
[161] D. Manoharan, L.-C. Wang, Y.-C. Chen, W.-P. Li, C.-S. Yeh, *Adv. Healthcare Mater.* **2024**, *13*, 2400746.
[162] X. Wu, Y. Li, M. Wen, Y. Xie, K. Zeng, Y.-N. Liu, W. Chen, Y. Zhao, *Chem. Soc. Rev.* **2024**, *53*, 2643.
[163] L. Wang, M. Huo, Y. Chen, J. Shi, *Biomaterials* **2018**, *163*, 1.
[164] B. Yang, J. Shi, *J. Am. Chem. Soc.* **2020**, *142*, 21775.
[165] B. Yang, H. Yao, H. Tian, Z. Yu, Y. Guo, Y. Wang, J. Yang, C. Chen, J. Shi, *Nat. Commun.* **2021**, *12*, 3393.
[166] Y. Bowen, G. Yuedong, W. Yuemei, Y. Jiacai, Y. Heliang, S. Jianlin, *CCS Chemistry* **2021**, *4*, 1499.
[167] Y. Zhou, G. Quan, Q. Wu, X. Zhang, B. Niu, B. Wu, Y. Huang, X. Pan, C. Wu, *Acta Pharm. Sin. B* **2018**, *8*, 165.
[168] K. T. Mody, A. Popat, D. Mahony, A. S. Cavallaro, C. Yu, N. Mitter, *Nanoscale* **2013**, *5*, 5167.
[169] T. L. Nguyen, B. G. Cha, Y. Choi, J. Im, J. Kim, *Biomaterials* **2020**, *239*, 119859.
[170] B. G. Cha, J. Kim, *WIREs Nanomed. Nanobiotechnol.* **2019**, *11*, 1515.
[171] C. Caltagirone, A. Bettoschi, A. Garau, R. Montis, *Chem. Soc. Rev.* **2015**, *44*, 4645.
[172] J. E. Lee, N. Lee, T. Kim, J. Kim, T. Hyeon, *Acc. Chem. Res.* **2011**, *44*, 893.
[173] Y. Feng, Z. Liao, M. Li, H. Zhang, T. Li, X. Qin, S. Li, C. Wu, F. You, X. Liao, L. Cai, H. Yang, Y. Liu, *Adv. Healthcare Mater.* **2023**, *12*, 2201884.
[174] J. M. Rosenholm, J. Zhang, M. Linden, C. Sahlgren, *Nanomedicine* **2016**, *11*, 391.
[175] Z. Ezzeddine, I. Batonneau-Gener, G. Ghssein, Y. Pouilloux, *Water (Switzerland)* **2025**, *17*, 669.
[176] S. Hu, C. Li, K. Li, W. Teng, F. Li, P. Zhang, H. Wang, *Environ. Sci. Nano* **2024**, *11*, 4666.
[177] S. E. Lehman, S. C. Larsen, *Environ Sci Nano* **2014**, *1*, 200.
[178] A. Nomura, C. W. Jones, *ACS Appl. Mater. Interfaces* **2013**, *5*, 5569.
[179] B. Dou, Q. Hu, J. Li, S. Qiao, Z. Hao, *J. Hazard. Mater.* **2011**, *186*, 1615.
[180] J. Ren, J. Ding, K.-Y. Chan, H. Wang, *Chem. Mater.* **2007**, *19*, 2786.
[181] D. Gu, F. Schüth, *Chem. Soc. Rev.* **2014**, *43*, 313.
[182] R. Nicola, S.-G. Muntean, M.-A. Nistor, A.-M. Putz, L. Almásy, L. Săcărescu, *Chemosphere* **2020**, *261*, 127737.
[183] S. N. Kothawade, V. V. Pande, *Mesoporous Silica Nanoparticles: Drug Delivery, Catalysis and Sensing Applications*, De Gruyter, Berlin, Boston, **2024**.
[184] N. Linares, A. M. Silvestre-Albero, E. Serrano, J. Silvestre-Albero, J. García-Martínez, *Chem. Soc. Rev.* **2014**, *43*, 7681.
[185] P. Goswami, J. Mathur, N. Srivastava, *Heliyon* **2022**, *8*, 09908.
[186] A. Rastogi, D. K. Tripathi, S. Yadav, D. K. Chauhan, M. Živčák, M. Ghorbanpour, N. I. El-Sheery, M. Brestic, *3 Biotech* **2019**, *9*, 90.
[187] X.-P. Kong, B.-H. Zhang, J. Wang, *J. Agric. Food Chem.* **2021**, *69*, 6735.
[188] J. Du, B. Liu, T. Zhao, X. Xu, H. Lin, Y. Ji, Y. Li, Z. Li, C. Lu, P. Li, H. Zhao, Y. Li, Z. Yin, X. Ding, *J. Nanobiotechnol.* **2022**, *20*, 197.
[189] S. Sankar, S. K. Sharma, N. Kaur, B. Lee, D. Y. Kim, S. Lee, H. Jung, *Ceram. Int.* **2016**, *42*, 4875.
[190] S.-H. Wu, C.-Y. Mou, H.-P. Lin, *Chem. Soc. Rev.* **2013**, *42*, 3862.
[191] M. Davidson, Y. Ji, G. J. Leong, N. C. Kovach, B. G. Trewyn, R. M. Richards, *ACS Appl. Nano Mater.* **2018**, *1*, 4386.
[192] U. Chadha, S. K. Selvaraj, H. Ashokan, S. P. Hariharan, V. M. Paul, V. Venkatarangan, V. Paramasivam, *Adv. Mater. Sci. Eng.* **2022**, *2022*, 1552334.
[193] L. F. Ferreira, G. F. Giordano, A. L. Gobbi, M. H. O. Piazzetta, G. R. Schleder, R. S. Lima, *ACS Sens.* **2022**, *7*, 1045.
[194] X. Wu, J. Wang, W. Shi, Y. Ding, Y. Li, *Nanoscale* **2025**.
[195] T. I. Janjua, Y. Cao, C. Yu, A. Popat, *Nat. Rev. Mater.* **2021**, *6*, 1072.
[196] R. R. Castillo, L. de la Torre, F. García-Ochoa, M. Ladero, M. Vallet-Regí, *Int. J. Mol. Sci.* **2020**, *21*, 7899.
[197] A. Tan, N. G. Eskandar, S. Rao, C. A. Prestidge, *Drug Deliv. Transl. Res.* **2014**, *4*, 212.
[198] T. R. Meola, A. Y. Abuhelwa, P. Joyce, P. Clifton, C. A. Prestidge, *Drug Delivery Transl. Res.* **2021**, *11*, 1261.
[199] K. Bukara, L. Schueller, J. Rosier, M. A. Martens, T. Daems, L. Verheyden, S. Eelen, M. Van Speybroeck, C. Libanati, J. A. Martens, G. Van Den Mooter, F. Frérart, K. Jolling, M. De Gieter, B. Bugarski, F. Kiekens, *Eur. J. Pharm. Biopharm.* **2016**, *108*, 220.
[200] D. K. Zanoni, H. E. Stambuk, B. Madajewski, P. H. Montero, D. Matsuura, K. J. Busam, K. Ma, M. Z. Turker, S. Sequeira, M. Gonen, P. Zanzonico, U. Wiesner, M. S. Bradbury, S. G. Patel, *JAMA Network Open* **2021**, *4*, 211936.
[201] A. R. Rastinehad, H. Anastos, E. Wajswol, J. S. Winoker, J. P. Sfakianos, S. K. Doppalapudi, M. R. Carrick, C. J. Knauer, B. Taouli, S. C. Lewis, A. K. Tewari, J. A. Schwartz, S. E. Canfield, A. K. George, J. L. West, N. J. Halas, *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 18590.
[202] A. N. Kharlamov, J. A. Feinstein, J. A. Cramer, J. A. Boothroyd, E. V. Shishkina, V. Shur, *Future Cardiol.* **2017**, *13*, 345.
[203] A. N. Kharlamov, A. E. Tyurnina, V. S. Veselova, O. P. Kovtun, V. Y. Shur, J. L. Gabinsky, *Nanoscale* **2015**, *7*, 8003.
[204] O. Adir, M. Poley, G. Chen, S. Froim, N. Krinsky, J. Shklover, J. Shainsky-Roitman, T. Lammers, A. Schroeder, *Adv. Mater.* **2020**, *32*, 1901989.
[205] B. McLean, I. Yarovsky, *Small* **2024**, *20*, 2405299.

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