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Mesoporous silicas in materials engineering: Nanodevices for bionanotechnologies

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ABSTRACT

In this review, the most valuable opportunities offered by mesoporous silica nanoparticles in the field of development of nanodevices for bionanotechnology applications are reviewed. The state of the art is critically discussed with particular emphasis on cancer-related application, paying attention to all the aspects of the design and development of the process that engineers the selective administration of an anticancer agent to cancer tissues. The analyses of the critical factors that limit this process are taken into account and the technical solutions proposed to face these factors are discussed. Furthermore, targeting to difficult tissues and forefront applications such as cancer immunotherapy, diagnostic, theranostic, and gene therapy are considered. Lastly, the authors provide their opinion on the reasons according to which the translation of this generation of nanodevices from laboratory research into practical clinical and eventually into the market is possible.

1. Introduction

In the nanotechnology era, the materials scientist is obliged to adopt a new, broader, concept of material that includes not only the need to characterize it, to understand its composition for having an exhaustive knowledge of its properties, but also the detail of its design at the nanoscale to the aim of obtaining the desired nanostructures and, consequently, the expected performance. Materials engineering is the emerging ability to create the matter at the nanoscale that makes possible to produce new materials that are themselves devices.

A pure engineering problem is the optimization of a process. The administration of an anticancer drug and its diffusion in a living organism are processes whose optimization become crucial and very urgent due to the toxicity of the drug. The optimization of the overall process of administration of an anticancer drug aims to reduce its toxicity and maximize its therapeutic efficacy. What is the better way to improve the administration of a drug? The ideal drug administration should concern, as more as possible, ill tissues and rapidly dividing normal cells should be

distinguished from tumor cell. The drug, to this purpose, can be modified or supported or encapsulated, but, if its fate in the organism has to be planned in detail, it has to became part of a nanostructured devices that is biomimetic and, in many cases, able to respond to stimuli.

Several types of nanomaterials have been studied and tested to improve the chemotherapy outcomes but a more complete set of potentialities is achieved if the Drug Delivery Device's nanostructure is designed at the nanoscale. In general, different materials are suitable for the combination with a drug and the so-obtained systems produce, after administration, a modified drug release if compared to the administration of the corresponding free drug. These systems will be generically indicated as nanocarriers specifying that they can present very different levels of development and engineering. They are classifiable in two main groups: organic and inorganic. The firsts (mainly liposomes and polymeric micelles but also dendrimers and carbon nanotubes) in some cases have reached the market and clinical use after approval by FDA. Amongst the seconds, mesoporous silica nanoparticles have gained increasing attention as promising tools for nanomedicine applications for their

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biosafety, versatility and multi-functionality properties.

Mesoporous silica nanoparticles (MSNs), introduced in the early 1990s, generated firstly expectations in the typical applicative fields of porous materials such as catalysis and separations. In the following decade the first hypotheses and studies appeared to employ these amorphous-silica nano-honeycombs to entrap drugs (mostly NSAIDs, Non-Steroidal Anti-Inflammatory Drugs) for the purpose of modifying or prolonging the diffusion of the same drug after administration (usually oral) [1,2]. At that time, it was still not evident that the greater opportunity was considering the mesoporous silica not the final material for the application but the starting architecture for the development of the best device to manage the release of a drug.

MSNs are, indeed, solid inorganic nanoparticles with advantageous structural properties including tunable pore size and morphology, high surface areas and chemically active surfaces [3,4]. Interestingly, the porous structure and high surface area allow to establish host–guest interactions of high interest for drug delivery purposes improving their pharmacokinetic, stability, safety and efficacy. Moreover, their inorganic nature provides considerable benefits if compared to the organic nanoparticles such as an increased loading capacity, chemical and thermal stability of the guest molecules [5]. Consequently, their employment as inert scaffold for the delivery of therapeutics have been extensively pursued and continue to be actively investigated. MSNs are commonly synthetized by hydrolysis and condensation of silica precursors such as tetraethylorthosilicate (TEOS) or tetramethylorthosilicate using surfactants as template agents. The choice of the surfactant with a defined chain length and structure is the main factor affecting mesoporous nanostructure. Many different surfactants were employed in the synthesis of silica materials as drug delivery systems (DDS) [6]. Therefore, depending on the templating agent used, nanoparticles with various mesoporous structures, symmetry, pore size and morphology can be obtained [7,8]. The large availability of template agents offers the possibility to select the more suitable surfactant for the desired therapeutic purpose. Among the MSN advantageous properties, very outstanding is the large availability of hydroxyls on MSN surface, responsible of surface reactivity, stands out. Silane chemistry ensures an easy MSNs functionalization using different kind of molecules to improve their biocompatibility, colloidal stability, targeting ability and cellular uptake [9–12].

The most disruptive potentiality is that MSNs may be selectively functionalized on the external particle surface and on the silica internal pore wall using two or more different functions (molecules).

Specifically, external surface is commonly conjugated with targeting molecules to achieve a selective recognition of a specific target cell. Instead, internal functionalization is accomplished to control drug loading and release kinetics. This strategy is widely exploited through the grafting of stimuli responsive molecules able to prevent premature drug leakage during blood circulation and trigger the cargo release under specific stimuli. Various compound sensitive to physical [13–15] (e.g. magnetic field, electric field, ultrasound, temperature and osmotic pressure), chemical [16,17] (e.g. pH, ionic strength and glucose) and biological [18] (enzymes and endogenous receptors) stimuli have been reported. Surface tailoring strategy allows, also, engineering MSNs in multiple ways and optimizing them in a more personalized manner for the use in precision medicine.

With these premises, it seems clear how mesoporous silica nanoparticles represent the best candidates for developing nanostructured functional materials as nanodevices able to smartly administer a drug to cancer cells. We reported this approach for the development of multifunctional materials for the first time in 2007, when we were envisioning this potential [19]. After that, and still today, the number of the publication on this subject became so high to be practically unmanageable. Several multifunctional devices based on MSNs have been developed for various biomedical applications including targeted cancer therapy [20], bioimaging [21], theranostic [22], immunotherapy [23] and gene therapy [24] (Fig. 1). Meanwhile, due to the increased background of
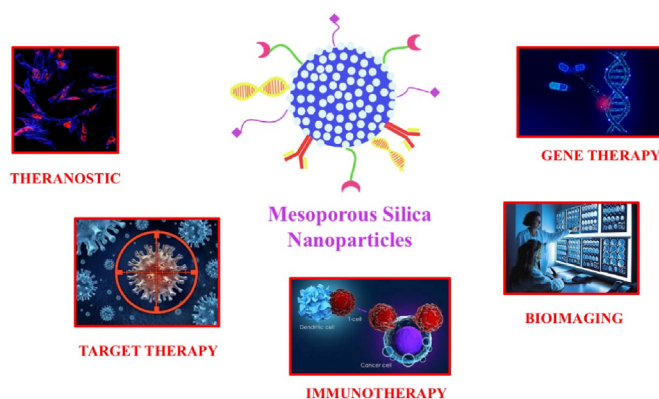

Fig. 1. Applications of MSNs in nanomedicine.

knowledge acquired, new trends first emerged, then new strategies appeared. For instance, among the trends is noteworthy to cite the development of devices able to provide multi-stimuli responsive drug delivery and the combined chemo-photothermal therapy [25–27], while, among the new strategies, the photothermal and photodynamic therapies and, more generally, nanodynamic therapies generating free radicals and Reactive Oxygen Species (ROS) have gradually become attractive cancer treatment strategies [28–30].

Bioinspired nanomachines have been developed bearing nanomotors moved by a catalytic self-propulsion mechanism that exhibits a directional movement, which drives the engines toward biological targets, consequently showing potentialities towards biosensing, diagnostics, and therapeutics applications [31].

Also, complex processes such as drug delivery into the lungs, limited by the anatomical, physiological and immunological barriers of the respiratory system, have been extensively investigated [32].

Nanomedicine employing mesoporous silica nanoparticles can be useful in overcoming these pulmonary barriers and providing insights for the rational design of future nanoparticles to improve lung treatments.

The potential applications of engineered mesoporous silica in bionanotechnologies today, and in perspective, define a very broad field that also includes bacterial properties or hormones delivery for plant growth and, more generally, an approach to nanostructured sensors not limited to mesoporous silica as starting architecture [33–36].

This review mainly focuses on nanodevices developed starting from mesoporous silica nanoparticles. The main aspects related to the development of a new drug administration will be considered, from the design to the most frequent problems, where the drug is not, as usually happens, an active principle but an engineered device that should be able to smartly administer the active principle.

2. The multifunctional project using MSNs

The development of specific, effective and safe devices able to increase drug selectivity and therapeutic index is the main challenge of the last years. To this aim, several approaches have been employed alone or in combination to target drug delivery to the desired site. MSNs can be engineered to possess multifunctional features:

- Physicochemical properties that allow a prolonged blood circulation and ability to accumulate at the target site;
- Drug release triggered by internal or external stimuli after cellular internalization;
- Active recognition of target cell.

Below we will provide a wide explanation of these aspects and an exhaustive collection of recent investigations.

2.1. Influence of physicochemical properties on MSNs biodistribution

Some of the main factors to be considered in the rational design of smart MSNs for drug delivery are physicochemical parameters (Fig. 2). Several physicochemical properties including size, shape and morphology significantly influence targeting, adhesion, clearance, uptake mechanisms and *in vivo* biodistribution [37,38]. Consequently, it is needed to fine-tune nanocarrier size, shape, and surface chemistry to enhance circulation times and direct the biodistribution of the drug within the organism. Some recent studies reported below have been focused on the correlation between MSNs physicochemical properties and their biodistribution to support the rational design of nanomedicines.

MSN physicochemical proprieties depend on the synthesis method used for their preparation. Sol-gel method and hydrothermal method have been widely used to produce MSNs with various mesostructures, morphologies and sizes. Sol-gel technique, also known as Stober synthesis vedi, takes place through the hydrolysis and condensation polymerization of a silica source such as tetraethylorthosilicate (TEOS), to obtain controlled size and monodispersed silica nanoparticles.

The main factor influencing the physicochemical features of nanoparticles is the choice of the surfactant that plays the role of template agent by directing the architectural characteristics of MSNs since at a specific concentration forms micelle structures on whose surface silica condenses. Similarly, hydrothermal synthesis involves the use of a template agent and a silica source, but the reaction takes place at elevated temperature and pressure [39]. An alternative method was recently developed by García-Muñoz and collaborators [40] that proposed to use as structure-directing agents drugs able to co-assemble with silica or to form biocompatible surfactant molecules by modifying the drug with an appropriate chain molecule. The employment of these drug-structured-directing agents such as ʟ-Dopa, octenidine dihydrochloride resulted in the reduction of the number of steps in MSN preparation and in a significant improvement of drug loading rates [41,42].

Imine groups embedded within the silica framework have been recently introduced to the aim of obtaining easier degradation in aqueous media [43]. The obtained materials showed fast degradation in both acidic and neutral aqueous solutions, at a rate depending on the pH value and particularly at acid pH where MSN are usually stable.

Recently, green methods based on the use of waste products as the silica source have been also developed. For instance, hexagonal and ordered mesoporous structures were designed by Abburri et al. employing hexafluorosilicic acid, waste from the fertilizer industry, as the silica source in the absence of a template [44]. Other innovative silica sources proposed in recent years are also rice husk [45], banana peels [46], fly ash [47] and coir pith [48].

Among the physicochemical characteristics, nanoparticle sizes primarily influence biodistribution. Typically, nanoparticles with diameter greater than 200 nm activate the complement system and are quickly removed from the bloodstream, accumulating in the liver and spleen, while particles with diameter smaller than 10 nm are rapidly removed by kidneys [49]. Consequently, tailoring MSN size allows to achieve the required accumulation in the target tissue and to avoid the rapid clearance from the bloodstream by the mononuclear phagocyte and the reticuloendothelial system. In this sense, Zhao and co-workers [50] optimized the size of multifunctional MSNs to improve their anticancer activity *in vivo*. Specifically, nanoparticle with three different size (48 nm- 72 nm-100 nm) were synthetized and after their *in vivo* administration their tissues distribution was evaluated by inductively coupled plasma mass spectrometry (ICP-MS) to quantify the concentration of Si element in each organ. Obtained results highlighted that the increasing MSN size led to a decreased accumulation in tumor while an increased localization in liver and spleen was observed. An improved biodistribution was also associate with a better *in vivo* therapeutic efficacy compared to free drug and non-targeted nanoparticles suggesting the great potential in cancer treatment. Moreover, the *in vivo* distribution of MSNs largely depends on their morphology. In the years, a lot of mesostructures such as hexagonal ("Mobil Composition of Matter number 41"-MCM-41 and Santa Barbara Amorphous type number 15"-SBA-15) [51,52], cubic (MCM-48) [53], lamellar (MCM-50) [54], stellate [55], hollow [56] and random structure (Michigan State University type number 1-MSU-1) [57] have been developed by the researchers for various application in nanomedicine. Anyway, there is still an increasing demand to explore new synthetic procedures to obtain MSNs with different morphological characteristics and investigate their *in vivo* behavior.

Mesoporous porosity and morphology can indeed be properly tailor-made varying reaction conditions during synthesis process [58]. Recently, asymmetric particles have been emerged as a promising tool for drug delivery applications since they exhibit better endocytosis rate and endosomal escape ability [59,60]. An example of the better performance of asymmetric MSNs has been reported by Yang and collaborators in 2021 [61]. With the aim to develop MSNs with innovative morphological properties, a new rosin-based template agent, a molecule with surfactant-like properties, has been employed in different amount (40 mg MSN-40; 60 mg MSN-60; 80 mg MSN-80) in synthetic process. The researchers observed that a rosin increase resulted in a decrease of micelle curvature and, thus, a more disordered structure. Despite the irregular morphology, a best cellular uptake and cytotoxic effect was observed for MSN-80 loaded with Doxorubicin (Dox). Their results proved that asymmetric nanoparticles were better internalized by cells compared to spherical nanoparticles. Similar results were also obtained by Zhao et al. in the same year [62]. They synthesized a series of multi-morphology mesoporous carbon@mesoporous silica nanoparticles (MC@MSs) by employing TEOS as silica source, CTAB and F127 as the templates and glycerol trioleate (GTO) as a swelling agent in alkaline solution. Performed experiments demonstrated that every single component influenced the topography of MC@MSs and varying ethanol concentration, solution polarity, CTAB amount, CTAB and ethanol/water (E/W) volume ratios, various asymmetric morphologies have been obtained. In addition to a better cellular uptake, the anisotropic mesoporous particles developed in this research also exhibited a reduced agglomeration during high-temperature annealing process, high biocompatibility and high affinity for hydrophobic drugs.

Cylindrical nanoparticles have emerged, instead, as appealing tools for lung application since they hold aerodynamic parameters suitable for inhalation and the ability to delay macrophage uptake and, consequently, allow a sustained residence time of the formulation in the lungs. This type of MSNs has been used by Schneider and co-workers [63] to deliver curcumin and a specific siRNA to reduce tumor necrosis factor alpha (TNF-α) secretion in the inflammatory process. A significant inhibition effect was observed by the authors depicting the potential for future applications of such carrier system in the treatment of diseases in which macrophages play central roles in inflammation (e.g., COVID-19) or even bacterial infections such as tuberculosis.

Fig. 2. Schematic illustration of tunable physicochemical properties of MSNs.

Particularly interesting was also the work done by Zhao et al. [64] in 2017 that developed MSNs with a virus-like topological structure via an epitaxial growth process. Virus commonly invade cells thanks the presence on their rough surface of spike proteins able to bind strongly cell membranes. Inspired by this mechanism, the authors proposed to engineer silica material in order to have a virus biomimetic morphology and, so, enhance the cellular internalization. From TEM and SEM analysis, the obtained MSNs had an interior spherical mesoporous silica core and separated peripheral silica nanotubes perpendicular to the core surface. This unique morphology conferred to MSNs a much faster cellular uptake, higher cancer cell killing efficiency, extended blood circulation and a unique internalization pathway compared to conventional MSNs. The same strategy was adopted more recently by Xu and collaborators [65] that designed novel virus-like hollow MSNs (VH-MSNs) using a self-consuming perovskite template to enhance immune system activity. These tools with a unique surface topology were able indeed to interact with immune system cells and activate or amplify the immune process *in vitro* and *in vivo*. The anti-tumor efficacy of the devices with virus-like surface topography was amplified by Dox loading, achieving a combination of chemotherapy and immunotherapy and a significant tumor killing effect.

Recently, Tomè and collaborators [66] compared the efficacy of different shaped MSN grafted with S-glycoside porphyrins (Pors) as carrier of photosensitizers (PSs) into tumor tissues during photodynamic therapy (PDT). Specifically, researchers employed sphere-shaped MSNs and rod-shaped mesoporous silica nanorods (MSNRs) grafted with PS1 or PS2 that differ for the presence of glucose and galactose moiety as tumor targeting ligand, respectively. Data obtained highlighted that spherical MSN had a higher phototoxic effect compared to MSNR and better uptake in two bladder cancer cell lines, HT-1376 and UM-UC-3 when PS2 was grafted on the external surface.

Surface charge and serum protein absorption represent also critical factors affecting MSN biodistribution. Generally, nanocarriers are recognized as foreign particles, so they are quickly removed from the blood circulation by the immune system. Specifically, protein absorption on MSNs surface can activate enzymatic cascades leading to thrombosis or make them suitable for uptake by the mononuclear phagocyte system. Typically, a higher uptake is observed in serum-free medium for positively charged nanoparticles due to electrostatic interactions with the negatively charged cell surface. In the presence of serum proteins, changes in MSN surface charge upon protein adsorption occur influencing particles uptake.

A common strategy used to reduce protein absorption and improve MSN blood circulation involves the covalent attachment of a hydrophilic polymer, PEG, on particles surface. Recently, Kleitz and co-workers [67] investigated the effect of different PEGylation methods on grafting efficiency and protein absorption. Researchers grafted PEG using different linkers such as amine-NHS, thiol-carboxylate, thiol-maleimide, epoxy-amine, isocyanate-amine and PEG-silane coupling agent. From performed studies, the most favorable PEGylation methods resulted to be the thiol-maleimide coupling or the use of PEG-silanes since they present the best performance in terms of high coupling efficiency and low serum protein adsorption, which may be desired properties in targeted drug delivery. Nevertheless, adsorption of certain proteins on the particle surface could, in some cases, be advantageous in terms of targeting/cell specificity.

For instance, Linden et al. [68] have studied the influence of particle surface charge on the specificity of active targeting of antibody-tagged MSNs, with particular attention to the influence of protein adsorption on targetability. The results show that serum protein adsorption can play an important role in enhancing the specificity of nanoparticle uptake, which may be a combination of multivalent serum protein and targeting ligand mediated nanoparticle-cell interactions and/or a "passive" enhancement of cellular internalization kinetics due to the presence of adsorbed proteins on the nanoparticle surface. The authors have also discussed the influence of serum protein adsorption on blood-circulation

times of nanoparticles *in vivo*, and an effective targeted drug delivery using nanoparticulate vectors. Lastly, they suggest that optimization should concern a long enough blood circulation time and the kinetics of cellular internalization of the particles by the target cells.

Cristini and co-workers [69] investigated the combined effects of size, surface chemistry and routes of administration on biodistribution and clearance kinetics of radiolabeled MSNs in healthy rats. The authors observed that the increasing of particle size from ~32- to ~142-nm results in a decrease in systemic bioavailability, irrespective of route of administration, with corresponding accumulation in the liver and spleen. Moreover, surface-positive MSNs and surface-exposed charged molecules (amines) had reduced circulation compared to identical-sized MSNs due to rapid sequestration in the liver and spleen.

Based on these papers, it is important to note that MSN physicochemical properties affect *in vivo* biodistribution and, so, their clinical efficacy. Therefore, design of MSNs with tailor-made features must be considered in the development of an advanced drug delivery platform.

2.2. Smart chemotherapies

2.2.1. Stimuli responsiveness

In the development of smart nanodevices for targeted cancer therapy, considerable attention has been addressed to tumor microenvironment. Metastatic diseases typically exhibit physiological features significantly different from normal cells such as acid pH [70], higher redox potentials [71] and overexpression of specific enzymes that can work as trigger [72]. These factors, therefore, can be successfully used as stimuli to induce drug release from the devices and achieve a target-specific delivery.

MSNs can be built, in fact, to experience rapid changes in their structure in response to endogenous or exogenous stimuli. Endogenous stimuli are related to biological changes in tumor tissue and provide a spontaneous, intrinsic and site-selective controlled release. Conversely, exogenous triggers are extrinsic and externally applied from outside providing a high temporal and spatial control of drug release at the targeted site. Moreover, because of the coexistence of different conditions in tumor microenvironment, the employment of multiple combined stimuli to further targeting efficiency has been advanced [73]. Drug release control is commonly achieved through functionalization with specific linkers or compounds able to cap particle pores acting as gatekeepers and disassembling in response to different stimuli. Specifically, these molecules can be used in three different ways, i.e., particle pore gating, coating of external particle surface and internal pore modification. Recent strategies for controlled release based on internal and external stimuli are described below [74,75]. Enzymes can also be used as functional components in the gating ensemble [76].

2.2.1.1. Internal stimuli. One of main endogenous stimuli exploited in the design of cancer-targeted MSNs takes advantage of the acidic tumor microenvironment. Considering pH difference between normal and tumor tissues, and between the intra- and extra-cellular environments, pH-responsive nanoplatforms are promising tools to avoid the unspecific drug release in systemic circulation and enhance it only at the desired site. PH-responsivity was typically attempted by researchers through the functionalization of MSN surface with molecules linked via pH-sensitive bonds. Common pH-sensitive bonds used to achieve a pH triggered drug release mainly include hydrazone, acetal, imine or ester bonds involved [77,78] (Fig. 3).

For instance, Wagner et al. proposed the conjugation on particle surfaces of biotin, able to form a strong complex with avidin, to the nanoparticle surface of a MSN-based nanocarrier of the anticancer immunostimulant R848 (resiquimod), through an acetal linker [79]. This bond was stable at neutral pH while it was cleaved at acidic pH causing the detachment of gatekeeper from particle surface and the pore opening. This strategy allowed to control drug release and localize it in the
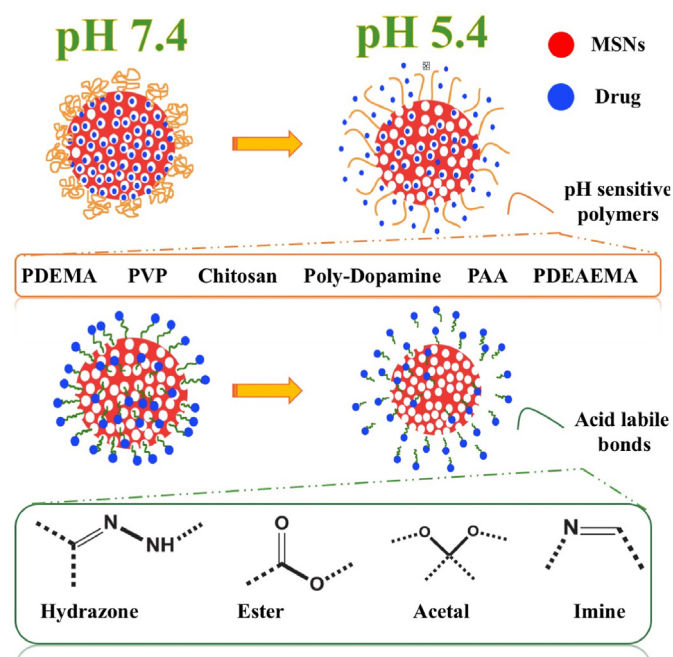
Fig. 3. Schematic representation of pH-sensitive DDS based on MSNs. Two main strategies are used in the design of pH-sensitive MSNs. The first involves the capping of nanoparticle surface with pH-responsive polymers. The second involves the conjugation of molecules to MSNs via pH-sensitive bonds.

intracellular acid environment of cancer tissues. *In vivo* studies, in fact, highlighted that the developed pH-sensitive system improved the pharmacokinetic profile of R848 increasing 6-fold its half-life and reducing the non-specific systemic release. A further approach to obtain pH-sensitive devices involves the capping of pH-sensitive polymers on particle surface. Several polymers have been used to confer pH-responsivity such as poly (2-(diethylamino) ethyl methacrylate) (PDEAEMA) [80], polydopamine [81], chitosan [82] and poly(2-vinylpyridine) (PVP) [83] (Fig. 3). For instance, Beagan et al. [80] proposed the coating of magnetic MSNs with PDEAEMA. The pH-sensibility of the obtained devices was highlighted by size changes evaluated by dynamic light scattering at different pHs. Indeed, nanoparticles hydrodynamic size increased from about 350 nm in basic environment to 750 nm in acid media due to the protonation of amino groups of PDEAEMA polymer resulting in swelling due to repulsion between like charges. These results were in accordance with *in vitro* drug release studies that confirmed a significant higher drug release in acid environment. Polydopamine (PDA) was also widely used by different research groups to confer pH-sensibility to MSNs. Indeed, PDA is able to form a cohesive layer on MSN surface in weak alkaline conditions, blocking the particle pores and slowing drug diffusion over a long period. In acidic conditions, instead, the disassembly of coating layer occurred, unlocking the channels of nanostructure and inducing drug release [84, 85].

Another particularly promising design strategy was proposed in a study conducted in 2021 by Zhang and co-workers [86] that engineered MSNs for a synergistic delivery and a dual-pH-responsive sequential release of two different drug. To this aim, the authors coated MSNs surface with a double layer, the first based on polyacrylic acid (PAA) with a responsivity to pH 5 and the second consisting of pH-sensitive lipid (PSL) with responsivity to pH 6.5. Arsenic trioxide (ATO) was loaded into the pores of MSNs, while Paclitaxel (PTX) was incorporated into the lipid bilayer. This engineered nanostructure made it possible to obtain a sequential drug release profile: PTX within PSL was firstly released at pH = 6.5 in extracellular tumor microenvironment, while ATO was released mainly at endosome/lysosome pH (pH = 5).

This approach, so, enables the co-delivery of different chemotherapeutics agents and the use of lower doses of each agent reducing drug toxicity and, consequently, increasing therapeutics efficacy.

In another recent work [87], MSN were coated with partially-carboxylated chitosan to give the system pH-responsiveness and regulate drug release kinetics. The partial carboxylation of chitosan coated on MSNs enabled modulation of drug release kinetics leading to a significantly greater extent of release in a shorter duration of time and allowed the conjugation of EGFR and HER2 aptamers (targeting agents) which led to improved tumor-specificity, enhanced uptake and cytotoxicity in both TNBC and HER2 positive breast cancer cells.

Instead, He at al. [88] coated amino-functionalized MSN with a pH-sensitive lipid layer made up of soybean phosphatidylcholine (SPC), cholesterol (Chol) and 9 alkyl-spiropyran (SP-C9). At the acidic pH of tumor microenvironment, the hydrophobic SP-C9 is converted into the amphiphilic 9 alkyl-merocyanine (MC-C9) leading to a significant decrease in the entire particle size for enhanced intratumoral penetration.

Extensive studies have also been performed in developing redox-responsive MSN-based nanocarriers. The redox-responsive mechanism is based on the difference in glutathione (GSH) concentration between extracellular (~10 μM) and intracellular environment (1–10 mM) [89]. Furthermore, in many cancer cells this difference resulted to be 3-fold higher than that in normal cells and so it can be exploited for targeted cancer therapy [90]. The introduction of cleavable disulfide bonds in nanosized platforms for drug delivery has been pursed as the main strategy to develop redox responsive devices.

Hu and al. [91] proposed the conjugation of Transferrin (Tf) to MSN surface via redox-cleavable disulfide bonds, acting as both a capping agent and a targeting ligand, to improve anticancer efficacy of Doxorubicin (Dox). *In vitro* release experiments demonstrated a rather slow drug release in the absence of GSH, while a higher amount of Dox was released from the MSNs once in the presence of GSH due to disulfide bond cleavage and Tf detaching from surface. The authors also found that drug release was dependent on GSH concentration due to the difference in the degrees of cleavage by various disulfide reducing agent concentrations. Another in-depth study devoted to evaluating of how density of disulfide bonds in nanostructure affects drug release was carried out by Wang and collaborators [92]. The authors prepared redox-responsive MSNs via conjugation of PEG, used as capping agent, to nanoparticle surface via disulfide bonds. In particular, three different types of MSNs with different grafting density were prepared using increasing concentrations of 3-Mercaptopropyltrimethoxysilane (0.5–1.5 mL) in the initial functionalization step to develop $M_{0.5}$-SS-PEG, M_1-SS-PEG, $M_{1.5}$-SS-PEG. The obtained results have shown no differences in drug release in presence and absence of GSH for $M_{0.5}$-SS-PEG, indicating that a small grafting density of PEG was not sufficient to confer redox-responsivity. A similar effect was observed for $M_{1.5}$-SS-PE and, in this case, the independence of drug release on GSH could be due to an excessive amount of PEG that led to a decrease in pore size and to difficulties in drug-loading process, thus limiting capping ability. On the contrary, an important drug release triggered by GSH was observed for M_1-SS-PEG for which a drug release equal to 25% and 60% was observed in absence and presence of GSH, respectively.

An additional tumor targeting redox-responsive DDS was constructed by immobilizing peptide-based amphiphile C12-CGRKKRRQRRRPPQRGDS (defined as ADDA-TCPP) onto the MSNs as an end-capping nanovalve. ADDA-TCPP consists of two main segments: a hydrophobic alkyl chain ADDA and a hydrophilic amino acid sequence containing a Tat48-60 peptide sequence with a thiol terminal group and an arginine-glycine-aspartic acid (RGD) targeting ligand grafted via a disulfide bond for redox-triggered intracellular drug delivery. The anticancer drug Dox is encapsulated in the MSN pores, the resulting system DOX@MSN-ss-ADDA-TCPP exhibited no drug release in the absence of GSH. The presence of GSH, instead, causes the breakage of disulfide bonds with consequent removal of the nanovalves and accelerated Dox

release. After internalization of the system into tumor cells, via the receptor-mediated endocytosis, the surface peptide-amphiphile nano-valve is detached due to the cleavage of disulfide bonds triggered by GSH in cellular cytoplasm, inducing a fast drug release inside tumor cells [93].

A similar strategy was also adopted by Zhang et al. [94] that modified MSN surface with alkyl chain stearic acid with a thiol terminal group via a disulfide bond in order to establish hydrophobic interactions with an amphiphilic peptide containing the RGD sequence by acting as gate-keeper collectively.

Conversely, Sil and co-workers [95] proposed an innovative strategy to develop nanoplatforms responsive to GSH based on the conjugation of gold nanoparticles (GN) on amine surface of MSNs via a relatively weak gold–nitrogen bond. This linkage was easily broken by exchange with sulfur containing molecules like GSH, removing the GN coating and inducing a sustained drug release.

Dysregulation of enzyme expression is commonly observed in many disease–associated microenvironments. Consequently, the development of enzyme-responsive MSNs has also been investigated to improve tumor accumulation of therapeutic agents.

Matrix metalloproteinase (MMPs) enzymes are a family of protease upregulated in disparate tumor types and associated to metastasis, tumor invasiveness, and angiogenesis. Focusing on this overexpression, the research group driven by Verma [96] fabricated MSNs for Cisplatin delivery capped with a dense layer consisting of collagen type1 as MMP-responsive gatekeeper. *In vitro* experiments indicated that pore capping inhibited the premature leakage of Cis into the systemic circulation, while in the cancerous environment the "on demand" drug release enhanced due to collagen degradation triggered by the presence of MMP enzymes.

Telomerase, an enzyme responsible for maintaining telomere length by adding guanine-rich repetitive sequences, is a useful biomarker for cancer cells that could be employed in the design of smart MSNs. In this regard, Ju and co-workers [97] developed telomerase-responsive MSNs to track intracellular telomerase activity. For this purpose, a telomeric repeated complementary sequence was linked to MSN surface as biogate preventing Fluorescein (Fluo) entrapped in the mesopores of MSN. High levels of telomerase in cancer cells led to DNA detachment from MSNs surface and release of fluoresceine for fluorescent imaging of intracellular enzyme activity.

Furthermore, enzyme responsivity has been emerged as interesting strategy to achieve colon targeted drug delivery due to the over-expression, at this site, of enzymes able to cleavage glycoside bonds. In fact, polymers with this type of bonds such as gelatin [98], hyaluronic acid (HA), starch [99], lactose [100] were widely employed in the design of enzyme-responsive MSNs. In a recent work [101], guar gum, a natural carbohydrate polymer, was used as a capping layer, sensitive to colonic enzymes, of MSN surface to localize 5-fluoruracile (5-FU) release in colon cancer cells.

Recently, a lung-targeted MSN-based nanocarrier loaded with rhodamine B (RhB) or dexamethasone (Dex), and coated with a peptide that targets TNFR1 receptor in macrophages, has been developed for the treatment of Acute lung injury (ALI).

After intravenous (i.v) injection of the nanoparticles in mice, TNFR-gated nanodevices are preferentially internalized by pro-inflammatory M1 macrophages, which overexpresses the TNFR1 receptor, and are able to release the cargo after the enzymatic hydrolysis of the capping peptide. Besides, TNFR-Dex-MSNs nanoparticles reduce cytokine levels *in vitro* in activated pro-inflammatory M1 macrophages and *in vivo* in an ALI mouse model [102].

Based on the fact that senescent cells accumulate in multiple aging-associated diseases, the elimination of these cells has recently emerged as a promising therapeutic approach. The high lysosomal β-galactosidase activity of senescent cells has been exploited for the design of a drug delivery system (Ga1NP) based on the encapsulation of diagnostic or therapeutic agents with galactooligosaccharides to deliver them preferentially to diseased tissues with a large content of senescent cells. Ga1NP consists of a mesoporous silica scaffold (MCM-41) that is loaded with different cargoes encapsulated by a coat of 6-mer β(1,4)-gal-actooligosaccharides.Gal-encapsulated cytotoxic drugs targeted senescent tumor cells and enhanced tumor xenograft regression in combination with palbociclib in a model of chemotherapy-induced senescence, furthermore, gal-encapsulated cytotoxics that targeted senescent cells, reduced collagen deposition and restored pulmonary function in a model of pulmonary fibrosis in mice [103].

Martínez-Máñez and collaborators, instead, reported the use galactohexasaccharide-capped MSNs for *in vivo* detection of cellular senescence using a NIR fluorophore. The system is able to release Nile Blue (NB), an *in vivo* imaging agent, in senescent cells due to the hydrolysis of the capping oligosaccharide in the presence of β-galactosidase.

Furthermore, the combined use of Palbociclib, a senescence inducer [104], with the senolytic agent navitoclax encapsulated within oligosaccharide-capped MSNs, produced inhibited tumor growth, reduced metastases, and a reduction in the systemic toxicity of navitoclax in an immunocompetent orthotopic mouse model of the aggressive triple negative breast cancer subtype [105].

2.2.1.2. External stimuli. External stimuli have been widely exploited to control cargo release at desired target site (Table 1) because they are non-invasive, have better spatiotemporal control and have the potential to overcome interpatient variability. Temperature is commonly used in the development of smart devices for on-demand drug delivery. The development of temperature responsive DDS involves the incorporation into the nanocarrier structure of temperature-sensitive materials that undergo morphology changes in response to temperature variations. A wide array of polymers have been used to induce thermo-responsivity such as poly(N-isopropylacrylammide) (pNIPAM) [106], Poly(NIPAM-co-propylacrylic acid) (p(NIPAAm-co-PAA) [107], poly[2-(2-ethoxy) ethoxyethyl vinyl ether] (p-EOEOVE) [108]. These polymers, at a specific temperature known as "low critical solution temperature" (LCST), undergo a transition from a hydrophilic state (random coil) to a hydrophobic state (spherical and aggregated state) destabilizing the nanocarrier structure and causing drug release. LCST can be fine-tuned controlling polymer length, composition, and hydrophilicity. An interesting example of temperature-sensitive tools based on MSNs has been developed by Kim and collaborators [109] that functionalized MSN surface with the poly(ethylene

Table 1
Representative endogenous and exogenous stimuli-responsive MSNs for programmed site-specific release.

Stimuli	Molecule	Drug	Target	Reference
pH	• PDA	Dox	MCF7/ MDA-MB-231	[112, 113]
	• PVP	Dox	T24	[114]
	• Imine bond	Dox	HepG2	[115]
	• ε-polylysine	prednisoloney	LS 174T	[116]
	• Hydrazone linkage	Ru(II) complexes	B16F1	[117]
	• BSA	Dox Bilirubin	HCT-116	[118]
Enzymes	• HA	Dox	MGC-803	[119]
	• Guam guar	5-FU	HT-29	[120]
GSH	• Cyclic peptide	Dox	H1299 A549	[121]
	• Disulfide linked PEG	MTX	MCF-7	[122]
	• AuNPs	Bis-lawsone derivative	MCF-7	[123]
Temperature	• PNIPAM	Dox	HeLa	[124]
	• DNA	Dox	MCF-7	[125]
	• Poly-benzyl-L-glutamate peptide	Dox	A549	[126]
Light	• Azobenzene	Dox	MCF-7	[127]
	• Polypyrrole	Dox	PANC-1	[128]

glycol)/poly(epsiloncaprolactone) (PEG/PCL) multiblock copolymer with dense crystalline structure. At physiological temperature, PEG/PCL was swollen and its compact crystalline structure limited drug release. Instead, heating the copolymer to about 45 °C caused the loss of the crystalline structure resulting in the release of the drug. In response to heating, a significant cytotoxicity was observed in A549 cells suggesting the potentiality of this device in the treatment of heat shock sensitive diseases, such as cancer and inflammatory conditions. An advanced temperature-sensitive device has also been developed by Asgari et al. [110] that combined thermo-responsivity of the poly(N-isopropylacrylamide-co-acrylic acid (P(NIPAAm-co-AAc)) polymer with the application of magnetic field. For this purpose, the authors developed a core-shell structure consisting of Fe_3O_4 nanoparticles as the core and mesoporous silica as the shell capped with thermo-responsive gatekeeper. The exposure to the magnetic field induces, in fact, the vibration of the magnetic core of silica nanoparticles and the heating of the system and, thus, a greater transition of polymer chains and a higher release rate. As a result, an enhanced and quick drug release was observed when the devices were exposed to alternating magnetic field, suggesting considerable potential for targeted cancer therapy.

An innovative strategy for designing temperature-sensitive MSNs has been advanced by Yu and co-workers [111] that proposed the use of a single-stranded DNA as gatekeeper. DNA, due to its negative nature, was adsorbed on the positive MSN surface via electrostatic interactions that blocked the pores and resulted in the "off" state. The increase of temperature destroyed the weak electrostatic interactions leading to the "on" state and the drug release from the nanocarrier. This mechanism was reversible, and the DNA valves could return to the original state. The drug release temperature can be controlled by adjusting the length of DNA valves, the authors achieved an ideal release temperature (39 °C) when 15-base DNA was used as the valve. Hence, the temperature induced on/off release offers new opportunities for the design of on-command DDS.

In addition, light can be used to control the site and time of cargo release during drug delivery. The use of photoswitchable molecules as gatekeepers has been widely employed to obtain light-sensitive MSNs due to their ability to undergo a reversible light-triggered conversion between their stable and metastable isomers resulting in pore opening and drug release (Fig. 4).

Photoactivatable MSNs have been developed according to an approach based on click chemistry by Cattoen et al. [127]. Azobenzene moieties as nano-impellers and a folic acid derivative were conjugated on MSN surface via click-chemistry for targeting of cancer cells. The azobenzene group, in fact, is able to obstruct the pores of the nanoparticles in the dark while, when irradiated, the *trans*-to-cis photoisomerization

Fig. 4. Schematic representation of light-triggered release from MSNs grafted with azobenzenes. UV irradiation at 365 nm converts azobenzene to the *cis* form, resulting in pore opening and drug release. The *cis* isomer of the azobenzene molecules transforms into the *trans* isomer under visible-light irradiation (450 nm), leading to pore closing.

enables the diffusion of the molecules loaded in the pores. This novel bifunctional system showed promising performance in dye release experiments, with interesting cancer cell killing performance with *in vitro* Dox delivery at low doses in the MCF-7 cancer cell lines.

Polypyrrole (PPy) is a promising photothermal agent for cancer therapy that has attracted increasing attention in the design of smart MSNs thanks to its good biocompatibility and excellent near-infrared light response property. Wang and collaborators [128] reported the polymerization of PPy on the external surface of magnetic Dox-loaded MSNs (Fe_3O_4@MSN@PPy-PVP@DOX). The obtained devices, in *in vitro* and *in vivo* experiments, showed a good inhibition of cancer cell growth due to the synergism of photothermal-, chemo- and chemodynamic therapy.

Recently, Shao and co-workers [129] developed red light-responsive MSNs by introducing ROS-cleavable diselenide-bonds into the silica framework for synergistic chemo-photodynamic therapy. The authors co-loaded in the carrier Dox and methylene blue that was able under red light irradiation to produce ROS that cleaved the diselenide-bridged silica backbones, leading to matrix degradation and methylene blue release for further ROS generation and Dox release responsible for tumor cells killing.

Responsivity to ultrasound represent, also, a promising opportunity to control drug release on demand at the tumor site without any harmful effects in healthy tissues. In a recent work, Bakowsky and co-workers [130] designed ultrasound-responsive MSNs by loading a responsive compound, perfluoropentane (PFP), into the mesoporous structure and coating MSN surface with a lipid layer. PFP, in fact, possess a lower boiling point of 28 °C and consequently can be easily converted to vapors by the thermal and mechanical effect induced by ultrasound treatment. The larger volume of gas produced inside the pores, so, determined a pressure able to break the lipid layer, inducing drug release. As expected, the authors observed a minimum drug leakage in the absence of ultrasound, while a fast drug release after ultrasound exposure provided the evidence that PFP introduction in nanostructures is a successfully way to develop tools with ultrasound triggered release features. Instead, Wang et al. [131] developed MSNs with a reversible ultrasound responsivity and an on/off release pattern by grafting on the particle surface a layer of sodium alginate cross-linked by $CaCl_2$. Dynamic metal coordination bonds formed between sodium alginate carboxyl groups (COO^-) and calcium ions (Ca^{2+}) resulted be cleavable when ultrasound was turned on and reformed after ultrasound was turned off. This research, so, represents an effective method to achieve an on-demand drug release pattern and build up efficacious tools for advancing future therapeutic applications.

X-ray radiation can also be used to trigger drug release thanks to its high tissue penetration capability and the possibility to perform the on-demand drug release by modifying X-ray dose and duration [132].

An X-ray-responsive nanomedicine for controlled NO (nitric oxide) release has been developed by Shi and collaborators [133] with application in the gas therapy of cancer [134]. The nanosytem (PEG-UCNP@MSN-SNO), obtained by engineering UpConversion Nano-Particles (UCNPs) with Pegylated S-nitrosothiol (SNO)-grafted mesoporous silica, successfully provided the X-ray dose-controlled NO release through the cleavage of the S–N bond of SNO *in vitro* and *in vivo*.

2.2.1.3. Multi-stimuli responsive MSNs. MSNs responsive to both internal and external stimuli have important drawbacks that limit their clinical efficacy. For instance, external stimuli-responsive MSNs shows a low targeting capability and selectivity, while multiple factors can induce dynamical changes of internal stimuli-responsive MSNs affecting response speed *in vivo* and limiting their use. In an effort to further fine-tune and improve drug release performance, novel dual and multi-stimuli responsive MSNs which can combine the advantages and overcome the limitations of single stimulus, have been intensively pursued (Table 2). Responsivity could take place simultaneously in the same site or
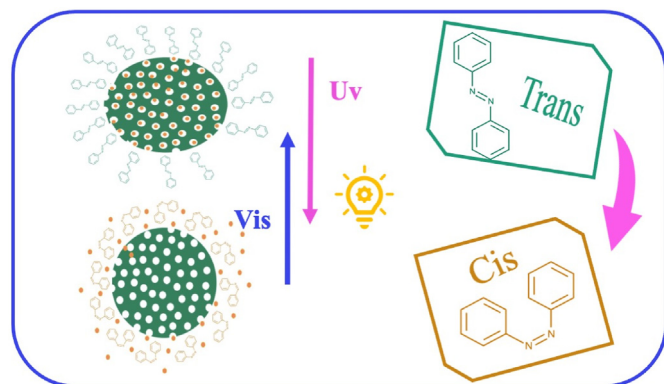
Table 2
Recent advances in multi-stimuli responsive MSNs based on several combinations of internal and external stimuli.

Multi-stimuli	Drug	Cells	Ref
Temperature/redox	Dox	SK-BR-3	[140]
Temperature/pH	Dox	MCF-7	[136]
Temperature/ultrasound	5-FU	HeLa	[141]
pH/redox/NIR	Dox	4T1	[142]
pH/enzymatic/redox	Dox	A549	[143]
GSH/pH/light	Dox	HeLa, MCF-7, 4T1	[138]

sequentially in different compartments. Specifically, external stimuli such as temperature, light, magnetic fields, and ultrasound can be applied directly to the target tissues to induce drug release allowing a high temporal and spatial control of the drug release and minimizing side effects in the surrounding healthy tissue. Internal stimuli responsivity, instead, is used to enhance drug release in tumor cells after internalization. Then combination of these two types of strategies would effectively provide a precise release to target tissues, cells and organelles and an enhanced release when multiple stimuli are applied simultaneously (Fig. 5). These dual and multi-stimuli responsive devices, therefore, might provide unprecedented smart release with a specific spatiotemporal control for cancer therapy and consequently a higher anti-cancer efficacy *in vitro* and/or *in vivo*.

Several stimuli combinations have been proposed by nanotechnology researchers. For instance, temperature and H_2O_2 dual stimuli-responsive nanocarriers were designed by Liu et al. [124] modifying simultaneously MSNs with ferrocene and a β-cyclodextrin-poly(N-isopropylacrylamide) (β-CD-PNIPAM) star-shaped polymer. Ferrocene (Fc), a hydrophobic molecule, resulted able to form host guest interactions with β-CD. H_2O_2 induced the oxidization to ferrocene ions (Fc+) which resulted in β-CDPNIPAM dissociation from the particle surface. A further destabilization of the composite was also triggered by increasing the temperature above the LCST of PNIPAM. This dual control allowed to localize drug release in the pathological site and enhance anti-cancer activity against HeLa cells as highlighted by results of the *in vitro* cytotoxic studies.

In another work [135], temperature dependence of PNIPAM was combined with ROS responsivity by grafting 4-(benzyl acrylate) phenylboronic acid pinacol ester (BAPAE) into the polymer backbone via free-radical polymerization method. Specifically, the authors took advantage of the temperature responsiveness for drug loading and, instead, of the ROS responsivity for drug release. From the analysis

Fig. 5. Schematic illustration of multi-stimuli responsive MSNs upon systemic administration. External stimuli may combine with internal stimuli and occur one-by-one or simultaneously to achieve a localized therapeutic agent release in pathological tissues.

performed, the resulting thermo- and H_2O_2-sensitive copolymers (ROSP) showed a LCST of 37 °C and below this temperature (4 °C) were in the hydrophilic form and silica particles pores were opened allowing drug diffusion into mesoporous structure. When the temperature was risen at 37 °C, polymers on particle surface blocked pores and, thus, prevented drug leaking out. The drug release was instead triggered by ROS stimuli. In fact, the exposure to high H_2O_2 levels induced the oxidation of hydrophobic monomers embedded in the copolymer into hydrophilic acrylate, which lead to an increase of LCST above 37 °C causing nanogates opening at physiological temperature.

Biocompatible dual stimuli-responsive MSNs were developed by Porrang et al. [136] using the rice husk, an agricultural waste byproduct, as silica bio-source for cancer therapy. In order to improve targeted Dox release, the authors modified the silica surface with p(NIPAAm-co-PAA) a temperature and pH-responsive polymer. The resulting nanoparticles exhibited an excellent thermo/pH dependent drug release. In fact, at pH 7.4 and 37 °C similar to physiological condition, Dox release was about 8.8% after 24 h. On the contrary, Dox release resulted to be about 75% in 24 h, at pH 5.4 and 40 °C similar to tumor microenvironment conditions. Dual targeting approach allows, thus, to increase release efficiency in the target tissue limiting drug leakage in systemic circulation responsible of side toxic effects of traditional chemotherapy.

A smart platform with dual stimuli responsivity (pH and redox stimuli) has been developed by Cheng et al. [137] to increase Dox cytotoxic efficacy against human cervical carcinoma (HeLa) cells. To this purpose, researchers conjugated 2,3-dimethylmaleic anhydride (DMA) to both a tumor-targeted fusion peptide (DTCPP) and a therapeutic peptide (DTPP) and grafted both polymers on MSN surface via a disulfide bond. DMA conjugation conferred to the nanocarrier pH- sensibility due to its stability under neutral and alkali conditions and easy degradation in acidic media. After the degradation of external layer, the positive nature of MSNs enhanced cellular internalization into the cytoplasm where the high GSH levels triggered the release of both Dox and therapeutic peptide, inducing an important toxic effect of HeLa cells. It is important to note that multistage targeting approach provides considerable opportunities to enhance therapeutic efficacy of anticancer drugs.

Additionally, very interesting results have been reported by Li et al. [138] that designed MSNs with stealth and charge-reversal property in the acidic tumor microenvironment. To this aims, MSNs were linked to β-cyclodextrin (β-CD) via redox-responsive bonds and further decorated with citraconicanhydride-functionalized poly-L-lysine (PLL(cit)) via host−guest interaction. Original MSNs were negative charged and showed a prolonged circulation time in bloodstream. Once accumulated in acidic tumor environment via EPR effect, the cleavage of the pH-sensitive citraconic amide bonds occurred, which led to the transformation of the carboxyl groups into amino groups. Consequently, the conversion into positive charged nanoparticles enhances their internalization in cancer cells where the high GSH concentration removed β-CD from the particle surface triggering drug release. The reported experiments confirmed an enhanced cellular uptake together with an important degree of depression for tumors growth in 4T1 breast-cancer-bearing mice and low systemic toxicity. Therefore, this could account as an efficient and safe nanomedicine for cancer therapy.

An interesting multi-stimuli approach has been proposed by Sun and co-workers [139]. Triple-stimuli (GSH, pH and light irradiation) responsive MSNs were developed for the co-delivery of Dox and a photosensitizer hematoporphyrin (HP). CeO_2 nanoparticles have been used both as quencher for Dox fluorescence and as redox and pH-sensitive gatekeeper. At the same time, light irradiation induced HP conformational change and the generation of $^1O_2$ to achieve a PDT synergism. A remarkable increase in drug release in acidic environment with reduced GSH and light irradiation has been observed compared to that in neutral environment suggesting the benefits of triple control-release. These outcomes open new opportunities in the design of effective platforms for targeted cancer therapy.
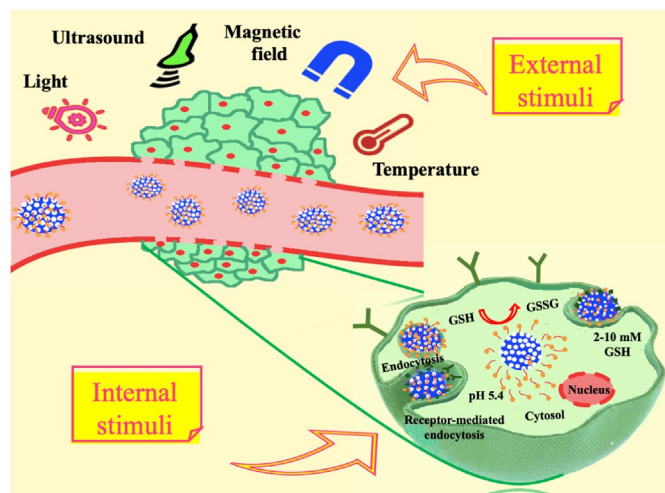
2.2.2. Active targeted MSNs

Active targeting is a common strategy employed in targeted cancer therapy to increase the ability of therapeutic nano-platforms to differentiate between disease and normal cells. This approach, in fact, is based on the conjugation of a targeting molecule on the carrier surface having a selective affinity for recognizing and interacting with a specific receptor overexpressed in cells, tissue or organ in the body [144]. A large number of ligands able of recognizing specific disease-associated biomarkers has been identified and studied as targeted agents including aptamers, small molecules, proteins, peptides, antibodies, carbohydrates or glycoproteins (Fig. 6, Table 3).

One of the most employed receptor-specific ligands is folic acid (FA) because of its low cost, small size, non-immunogenicity, stability, and easy availability. Its receptors are overexpressed in several solid tumors while are absent or present at very low levels in the corresponding normal tissues [145]. This makes folic acid an exceptional targeting moiety for tumors. In this regard, it is noteworthy that FA has been used by our group to improve the targeting capability of MSNs loaded with Cisplatin [146]. We observed that the obtained nanoparticles were more internalized by FR expressing cancer cells (HeLa cells) as compared to normal cells bearing only low receptor levels. This improved internalization resulted also associated with a much stronger toxic effect of smart
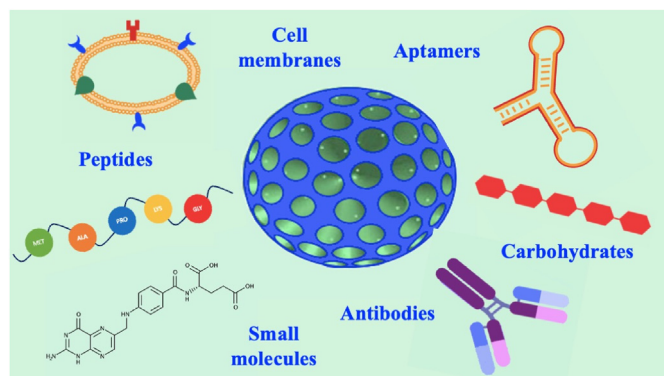

Fig. 6. Schematic illustration summarizing the main biological ligands employed for active targeting of MSN-based nanocarriers.

Table 3
Examples of common ligands used in MSNs active targeting strategies.

Ligand	Target	Cell type	Drug	Ref.
Anti-B220 antibody	B220	AML LCS	Daunorubicin	[152]
Anti-glypican-1 (GPG1) antibody	GPG1	PANC-1	Gemcitabine Ferulic acid	[153]
Anti-carbonic anhydrase IX antibody	Carbonic anhydrase IX	4TI	Dox	[154]
Intercellular adhesion molecule 1 antibody	Intercellular adhesion molecule 1	MDA-MB-231	Dox	[155]
F56 peptide	Tumor vascular endothelial cells	MCF-7	Arsenic trioxide PTX	[156]
PBA	Sialic acid	MCF-7	Bis-lawsone derivative	[95]
FA	FR	MCF-7	Anastrozole	[147]
FA	FR	LN 18	Cisplatin	[157]
Tf	Tf receptors	A2780	Titanium (IV) compound Organotin (IV) compound	[158]
TPP	Mithocondria	LNCaP	Topotecan	[159]
HA	CD44 receptors	4T1	Dox ICG	[160]
MT2-MP peptide	MT2-MP	H1299	Dox	[161]

MSN compared to the free drug. Similarly, a breast cancer targeted smart pH-responsive drug delivery system based on chitosan-folate coated MSNs has been developed to enhance anticancer activity of Anastrozole (AZT) [147]. The obtained MSN device showed considerable tumor suppressing activity of ATZ *in vitro* and *in vivo*. Several small molecules (<1000 Da) have been researched as targeting agents as they present unique advantages such as the stability, non-immunogenicity, easy conjugation at high densities, high bioavailability, and many of them already have FDA approval for use in other therapies [148].

For instance, bisphosphonates have been studied as bone-targeting molecules for the treatment of bone-related diseases thanks to their calcium-chelating properties. In a recent preliminary study from our research group, in fact, hybrid mesoporous silica-based particles were functionalized on the external surface using Alendronate, a drug of the bisphosphonate series able to interact with hydroxyapatite, the main inorganic component of bone tissue. The authors studied the tendency of the material to interact with hydroxyapatite as well as the possibility of loading it with a pharmacologically active molecule, specific for bone-targeted therapy [149]. Very interesting was the approach used by Day and collaborators [150] that, for the first time, proposed the employment of Tamoxifen (TAM), an estrogen receptor modulator widely used in the treatment of breast cancer (BC), as a targeting molecule to selectively direct MSNs towards estrogen receptors (ER)-overexpressing breast cancers.

TAM was conjugated to MSN surface using a pH-sensitive polymer, poly-L-histidine (PLH), as linker in order to combine active targeting with stimuli-responsivity in the same device. The results of physico-chemical characterization of the novel platform developed in this preliminary work have been excellent and have suggested the need to future investigation aimed at studying the *in vitro* and *in vivo* targeting ability. Another example of the use of small molecules as targeting ligands was reported by Hou et al. [151] that reported the conjugation of glycyrrhizin on the surface of chitosan-coated, lysine-embedded MSNs to develop a novel hepatocyte-targeted delivery carrier for liver regeneration. The developed system showed excellent performance in *in vitro* experiments with long-term delivery of lysine and the improvement of hepatic functions.

Carbohydrates are also used in active targeting approaches and Narayan et al. [162] proposed the use of glucuronic acid as targeting ligand, to specifically deliver MSNs to lectin receptors overexpressed on colorectal cancer cells (CRC). Glucuronic acid was conjugated to chitosan-coated MSNs for the pH-responsive targeted delivery of 5-fluorouracil (5-FU) The chitosan-glucuronic acid polymer capped on MSNs, in addition to trigger drug release at pH 5.5 similar to that of the tumor microenvironment, was found to enhance cellular internalization in HCT 116 colon cancer cell lines compared to the non-capped systems.

Hyaluronic acid (HA) has also been widely studied as potential biological ligand in active targeting delivery systems. Notably, HA is a natural, biocompatible, and non-immunogenic polysaccharide able to selectively recognize CD44 receptors overexpressed in many types of cancers associated with tumor progression, infiltration, and metastasis.

Recently, Lu and collaborators [160] proposed the grafting of a dopamine-modified HA (DA-HA) into a mesoporous structure to confer CD44 receptor targeting ability. The resulting nanoparticles showed a higher cell uptake ability in 4T1 cells with CD44 receptor overexpression compared to 293T cells with no receptor expression and a stronger cytotoxic effect.

Chen et al. [163] reported a tumor efficacy comparison of MSN-based vectors coated with several glycosaminoglycans such as HA, heparin (HP) and heparin sulfate (HS) and they found that HP and HS-coated MSNs were internalized by Hep G2 cells faster and released drug more efficiently respect HA-coated MSN.

Colilla and co-workers [164] reported, instead, the functionalization of MSNs with the plant lectin concanavalin A (ConA), to selectively recognize and bind several cell-surface glycans, such as sialic acids (SA)-overexpressing the human osteosarcoma cells (HOS). *In vitro* assays

suggested that the presence of ConA improved the MSN ConA selective internalization in HOS cells where the sialic acid levels were 6-fold increased, while no uptake was observed by non-tumor MC3T3-E1 cells that non-overexpressed sialic acid. Moreover, the enhanced internalization ability of the devices allowed to significantly reduce the amount of Dox able to induce antitumor efficacy compared to the free drug.

In recent years, antibodies have emerged as one of the most promising ligands used in the design of tumor targeted nanoparticles. The main advantage of antibodies is the high specificity and affinity for a target, which make them interesting therapeutic tools. The functionalization of MSN with anti-glypican-1 (GPC1) antibodies was proposed by Estevão [165] and collaborators to improve targeting and delivery of gemcitabine and ferulic acid to human pancreatic cancer (PANC-1) cells. Biological studies confirmed the antibody specificity towards the target cells and the increasing cytotoxicity due to the simultaneous activity of ferulic acid and gemcitabine. Recently, the discovery of a new antibody provided new insights for Triple Negative Breast Cancer (TNBC) treatment. TNBC is the most aggressive kind of breast cancer since it lacks the most common receptors, and it is untreatable with targeted therapies. Recently, it appeared that intercellular adhesion molecule1 (ICAM-1) is overexpressed in TNBC cell lines and it seems to be related to the development and metastasis of TNBC. In order to achieve TNBC targeted therapy, Teng et al. [155] developed an ICAM-1-targeted drug delivery system. In vivo experiments on TNBC cells showed higher accumulation of the obtained system loaded with Dox and better therapeutic effects compared to the control groups, suggesting a promising strategy for TNBC treatment.

Compared to antibodies, aptamers, single-stranded oligonucleotides, represent a more interesting class of active targeting ligands because of the advantageous features, such as low immunogenicity, small size, structural flexibility, and high chemical/thermal stability. Accordingly, Bagheri et al. [166] proposed the introduction in mesoporous structure of two different aptamers, MUC1 and ATP aptamers able to recognizes the MUC1 receptors overexpressed in several cancer cell lines and interact with ATP expressed in high levels in cancer tissues. Nanodevices uptake in cancer cells via MUC1 receptor-mediated endocytosis was confirmed by fluorescence microscopy that highlighted a cellular internalization of the nanodevices only in MUC1$^+$ cancer cells, such as MCF-7 and C26 cells. Moreover, a higher cytotoxicity of targeted MSNs was observed in MCF-7 and C26 cells, while a low anticancer activity was reported in CHO MUC1$^-$ cancer cells.

A further suitable alternative to antibodies are peptides that have several advantages, such as low production costs, good stability, low immune system activation and alteration of MSNs physicochemical properties [167]. For instance, Gisbert-Garzarán et al. [168] modified MSN surface with a versatile and polyvalent peptide containing biotin (HAVAB) able to target biotin receptors overexpressed in several cancer cells. For the first time, nanoparticles uptake via active targeting strategy has been demonstrated in 2D and 3D tumor models. In fact, a positive effect of HAVAB in enhancing accumulation in biotin-receptor-positive cells rather than in healthy cells and better cytotoxic profile has been observed.

Recently, a specific Membrane-type 2 matrix metalloproteinase (MT2-MP) has been identified for its critical involvement in growth, progression, and metastasis of lung tumor. Ren and co-workers [161] decorated fluorescent Dox-loaded MSNs with MT2-MP-targeting peptide to construct a nanomaterial with targeting, therapeutic and diagnostic functions. The biocompatible nanocarrier exhibited good tumor-targeting and accumulating effects in vitro and in vivo, thereby demonstrating its potentiality in cancer detection and therapy. A recent advance has been reported by Wang and collaborators [169] that developed a dual targeted MSNs by grafting on the same device FA and RGD peptide able to target FA and αvβ3 integrin receptors respectively

both overexpressed in MCF7 cancer cells. The dual-targeted MSNs increased cytotoxicity of PTX in cancer cells, suggesting new insights in the future clinical application.

As the materials scientists demonstrated the great potential of nanostructuring the matter, they then pursued more ambitious goals. In fact, they did not limit to the design of a single-targeted smart chemotherapy, but they conceptualized a double target, including the intracellular organelles, acting as a target inside a target.

Nucleus is the exact site where conventional chemotherapeutics play their role. Therefore, nuclear-targeted delivery of such drugs is required to improve therapeutic efficacy inducing apoptosis of cancer cells. Nucleus-targeted MSNs have been developed for the first time by Shi and collaborators [170] via grafting of transactivator of transcription peptide (TAT) on particle surface. These peptides are recognized by the nuclear pore complex, ensuring the transport of the TAT-conjugated nanocarrier to the nucleus. Regardless, TAT showed important drawbacks, such as low specificity to target cancer cells and unspecific delivery in some living cells, limiting their efficacy. To overcome these limitations, researchers proposed to combine simultaneously nuclear targeting and cancer cell targeting. Hence, nucleus-targeted ligand is temporally masked, and nanoparticles first bind cellular receptors, ensuring internalization in tumor microenvironment. Once inside the tumoral cell, nuclear target ligand drives the MSNs into the nucleus, releasing the drug and inducing cytotoxic effect (Fig. 7).

Zhao and co-workers [171] improved anticancer efficacy of TAT-targeted MSN by the simultaneous grafting of YSA peptides that specifically bind to EphA2 receptors overexpressed in some types of tumor cells. Another combination to design cancer-cell-specific nuclear-targeted delivery system based on MSN has been developed by Quiao et al. [172]. The authors grafted on MSN surface FA and Dexamethasone, a potent glucocorticoid able to bind nuclear glucocorticoid receptor (GR). The resulting MSNs enabled to enhance Dox anticancer efficacy on Hela cells and to reduce toxic side effects on healthy cells. Therefore, the dual-targeting ligand modification of MSNs successfully achieves a cell-nucleus sequential targeting and great anticancer effect.

More recently, a promising nuclear targeting approach has been reported by Huang et al. [173] using CRISPR-dCas9 technology. CRISPR-dCas9 specifically targets telomere-repetitive sequences at chromosomes tips. Consequently, the conjugation of CRISPR-dCas9 on MSN surface enhanced the specific delivery of the nanosystem to the nucleus, improving cancer treatment efficiency.
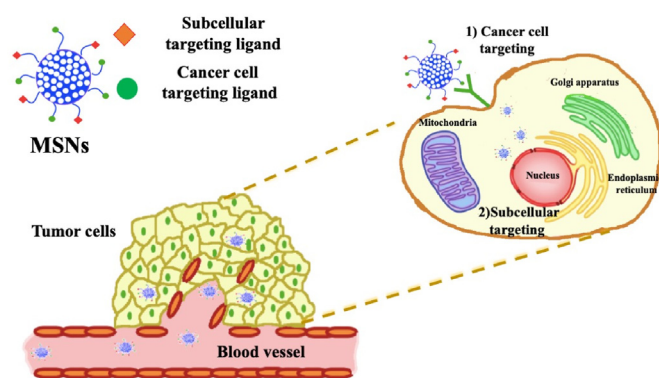

Fig. 7. Schematic representation of multistage targeting strategy for cancer therapy. MSNs were delivered to the tumor tissue through EPR effect and internalized via endocytosis thanks to interactions between a targeting moiety and the receptor overexpressed in tumor cells. MSNs were, then, localized to specific intracellular compartments driven by organelle-targeting moieties on their surface.

Mitochondria are organelles that play a critical role in metabolism of living cells, supplying most of the chemical energy and controlling the programmed cell death. They are also involved in many diseases, especially cancer. Consequently, the targeting of mitochondria has attracted great attention in the treatment of several diseases. Targeting approaches are mainly based on the significant difference in mitochondrial membrane potential and plasma membrane potential that enhance the accumulation of positively charged molecules. Common mitochondria-targeting molecules are triphenylphosphonium (TPP)-based conjugates that are directly linked to nanoparticle surface. In a very fascinating paper, Vallet-Regi et al. [159] reported the development of Janus mesoporous silica particles asymmetrically decorated with two targeting molecules, one for specific target of folate membrane cell receptors (FA) and the other for binding the mitochondria membrane (triphenylphosphine, TPP). The asymmetric decoration of each side of the particle allows fine control in the targeting process. After the folic acid-driven internalization process in cancer cell, the nanocarrier is driven close to mitochondria by the action of the TPP molecule.

In a further study, Ibragimova and collaborators [174] proposed for the first time the non-covalent surface modification of MSN with triphenyl-phosphonium cation, hexadecyltriphenylphosphonium bromide (HTPPB). This strategy was successfully achieved thanks to the self-assembly properties of the lipophilic phosphonium cation. An effective intracellular mitochondria uptake was reported using fluorescence microscopy of MSN@HTPPB loaded with Rhodamine B, suggesting a satisfying penetration capability toward HeLa cells compared to non-targeted nanoparticles.

2.23The. biomimetic stimulating function

Recently, a new strategy in the design of nanotherapeutic devices for drug delivery is based on the coating of nanocarriers with natural cell membranes. These biomimetic particles offer several advantages compared to traditional carriers such as an extended blood circulation time, immune escape capabilities and homologous targeting ability when cancer cells were used. This novel approach has been adopted by Peng et al. [175] that realized the envelopment of MSNs surface with red blood cell (RBC) membrane to improve MSN biodistribution. Specifically, the authors investigated the effect of various surface modifications ($-COOH$, $-SH$, $-NH_2$) in the coating process whose efficacy is crucially affected by surface characteristics. Performed analysis highlighted that surface functionalization including carboxyl group (-COOH) possessed a better RBC membrane coating efficiency and this coating layer showed remarkably longer blood circulation time compared to uncoated nanoparticles. Another approach to increase the biocompatibility of MSNs was pursued by Amin and collaborators [176] trough the design of MSN coated with phospholipid bilayers. These lipid-coated MSNs take advantage of the low toxicity and immunogenicity of liposomes along with the ability to act as a barrier and slow down drug release, avoiding leakage during blood circulation. The coating was carried out through electrostatic interactions of a positively charged liposome (DPPC:Cholesterol:DOTAP, 85:12:3 M mass ratio) on a negatively charged mesoporous silica core. *In vitro* release studies demonstrated that this coating effectively slowed down the drug release, resulting 5 times lower compared to naked MSNs. A higher internalization of lipid-coated MSNs and cytotoxic effect were also observed in SKBR-3 cells due to more biocompatible protocell nature of lipid layer which enhanced cellular uptake thanks to the interactions between cationic liposomes and cell membranes.

Mesenchymal stromal cells (MSC) have been proposed as alternative cancer-targeting agents due to their capacity to selectively and actively migrate to tumors in addition to their safety profile. This approach has been adopted by Flores and collaborators [177] that chose MSC derived from the decidua (DMSC) of human placenta that show target ability to cancer well as an intrinsic anticancer activity. Specifically, authors engineered DMSC to produce the antiangiogenic protein endostatin and simultaneously carry Dox-loaded MSNs for combined chemo- and anti-angiogenic therapy. The anticancer activity of designed devices has been studied using a multicellular 3D spheroid model formed by the co-culture of tumoral and endothelial cells and a significant decrease in spheroids viability was detected only for the combined approach, highlighting that the antiangiogenic effect of endostatin and the cytotoxic effect of Dox synergically work for cancer treatment prospective. Biomimetic approach has gained increasingly high interest and its combination with other targeting strategy has been pursued to improve the specificity of therapeutic platform for cancer therapy. A synergistic combination was proposed by Cai et al. [178] that associated biomimetic and magnetic hyperthermia properties in the same mesoporous silica structure. To this purpose, the authors prepared MSNs loaded with superparamagnetic ferroferric oxide and PTX and, then, coated their surface with MDA-MB-231 cell membranes. Cellular uptake studies demonstrated an internalization of CSiFePNs 3.76-fold higher compared to the free PTX and these results confirmed the homotypic targeting ability of coating layer. In addition, cell membrane-coated MSNs also showed a cytotoxicity 3-fold higher than the uncoated particles. This significant toxic effect is due to both apoptotic effect of PTX on cancer cell and the apoptosis induced by the increasing temperature of cancer cells after magneto-caloric reaction of Fe_3O_4 core in mesoporous structure.

2.3. Multifunctional MSNs

In the last years, a lot of effort has been addressed in using multifunctional MSNs, nanodevices with the ability of targeting multiple molecular pathways, providing valuable solutions for cancer therapies. Smart delivery systems which incorporate multiple complementary targeting strategies, including passive, active, and stimuli responsive targeting in the same systems, have been emerging as safe and effective tools for antitumor therapy (Table 4). The combination of two or more targeting approaches represents, in fact, an advanced way to maximize therapeutic outcomes.

For instance, Chen and collaborators [179] designed a highly selective nanomedicine for the hepatocyte carcinoma (HCC) therapy combining in the same device internal-, external-stimuli responsivity and active targeting. To achieve this goal, researchers grafted β-cyclodextrin (β-CD) on MSN surface via redox-sensitive disulfide bonds and an azobenzene/galactose-modified polymer (GAP) via host-guest interactions. GAP showed the ability to direct MSNs to hepatocellular carcinoma (HepG2) cells because of the presence of the asialoglycoprotein receptor-specific ligand (ASGPR). The presence of azobenzene in GAP structure, instead, conferred it light sensitivity inducing the polymer dissociation from particles surface after UV irradiation. The engineering process of UV- and GSH-responsive mesoporous nanostructure proposed by the authors allowed to efficiently deliver and release Dox after receptor-mediated internalization in HepG2 cells, reducing side toxic effects on healthy tissues.

In 2021, Narayan et al. [180] combined the pH-responsivity of chitosan with the ability of glucuronic acid to target lectin receptors over-expressed on tumor cells. To this purpose, glucuronic acid was chemically grafted on chitosan backbone via carbodimmide chemistry and then the resulting chitosan-glucuronic acid conjugate (CHS-GCA) was used to coat MSNs. *In vitro* studies displayed that CHS-GCA coated MSNs showed a pH dependent release, higher uptake and cytotoxicity in HCT 116 cell lines compared to uncoated particles. Furthermore, the researchers observed in *in vivo* studies a significant decrease in the diameter and number of the tumors, a reduction in the dysplastic features, and an improvement in the blood parameters, with low toxicity in other organs when coated CHS-GCA capecitabine-loaded MSN was used in comparison to free drug. These results highlighted that the dual-targeting approach allowed a site-specific release, enhancing efficacy in colorectal cancer therapy.

Table 4

Summary of recent representative multifunctional MSNs for targeted therapeutic delivery. Abbreviations: P(FBEMA-*co*-DMAEMA)-*b*-PTEGMA) Poly(2-(4-formylbenzoyloxy)ethylmethacrylate-co-2-(dimethylamino)ethyl methacrylate)-block-poly(triethylene glycol methyl ether methacrylate); PBA phenylboronic acid pinacol ester; HA-CD cyclodextrin-modified hyaluronic acid conjugate; CHI-g-CD chitosan-graft-β-cyclodextrin; Ad-GRGDS adamantane-glycine-arginine-glycine-aspartic acid-serine peptide; mPEG-CHO methoxy poly(ethylene glycol) benzaldehyde; ICG indocyanine green.

Gatekeeper	Responsiveness	Stimuli	Targeting	Coating	Tumor	Drug	Ref.
-	Disulfide bonds	GSH	Glucosamine	PEG	MC38GFP	HE	[181]
						Sulfo-cyanine	
Amino-β-cyclodextrin	Disulfide bonds	GSH pH	FA	PEG	MDA-MB-231	Dox	[182]
β-CD	Benzoic imine bond	pH	HA	–	4T1	Dox	[183]
	Disulfide bonds	GSH					
P(FBEMA-*co*-DMAEMA)-*b*-PTEGMA)	Disulfide bonds	GSH	–	PPy	HeLa	Dox	[184]
		Light pH					
Ferrocene	–	NIR	–	β-CD	HeLa	ICG	[185]
-	–	NIR	FA	PEG	MCF7	MTX iron NPs	[186]
						1-methyl-D-tryptophan	
PBAP	–	pH	HA	HA-CD	4T1 cells	Dox	[187]
		H$_2$O$_2$					
-	–	pH	RGD	PDA	CT26 cells	Dox	[188]
		NIR		PEG		NH4HCO3	
		Temperature					
CHI-g-CD mPEG-CHO	Benzoic imine bond	pH	Ad-GRGDS peptide	PEG	4T1 cells	Dox	[189]
PMASH	Disulfide bonds	GSH	Tf	–	A549 cells	PTX	[203]
–	–	pH	FA	Fe$_3$O$_4$ NPs	HCT-116 cells	Quercetin	[196]

Recently, Ma and co-workers [190] designed pH-responsive and dual-targeting antitumor nanodevices by coating MSNs with poly(N-isopropylacrylamide)-co-acrylic acid and calcium phosphate (MSCNs) and decorating the nanoparticle surface with Tf and the tripeptide arginine RGD. Compared to free Dox and Dox-MSNs, Dox-Tf/RGD-MSCNs showed a stronger inhibitory effect towards tumor cell growth than free Dox and Dox delivered by unmodified MSNs and higher biocompatibility.

In another study [191], an oleic acid-modified mesoporous silica-based therapeutic nanoplatform (OA-MSNs) conjugated with bovine α –lactalbumin (BLA), a complex resembling bovine α-lactalbumin made lethal against tumor cell (BAMLET) formed on the external MSN surface, was prepared. The so-obtained MSN-BAMLET complex with oleic acid modifications showed high docetaxel (DTX) loading efficiency.

Compared to OA-MSNs/DTX, the obtained MSN-BAMLET/DTX with a sustained and pH-responsive drug release behavior, exhibited good biocompatibility and enhanced cytotoxic effect against cancer cells due to a higher cellular uptake and a stronger inhibitory effect on the cell migrations of the BLA conjugated nanocomposite.

Another interesting combination was performed by Shao and collaborators [192] that designed biomimetic mesoporous nanoparticles with X-ray and ROS responsivity. This dual responsivity was pursued trough introduction in mesoporous structure of diselenide bonds acting as gatekeeper of the mouth of the pores. The resulting devices were also coated with 4T1 breast cancer cell membrane (CM) to achieve tumor-targeted and immune-evasive Dox delivery. *In vivo* studies, carried out in mice bearing 4T1 orthotropic mammary tumors, demonstrated a greater tumor accumulation of CM coated MSNs compared to uncoated systems. The anticancer efficiency of these nanoparticles was then further improved combining this strategy with a PD-L1 immune checkpoint inhibitor. Chemo-immunotherapy treatment led to pronounced anti-tumor immune response, greater inhibition of tumor growth, and pulmonary metastasis than chemotherapy alone, suggesting the potentiality of the designed devices to achieve efficient and safe chemo-immunotherapic effects in the clinic.

Multi-engineered smart MSNs were developed by Gong et al. [193] to increase chemotherapeutic efficacy and reducing adverse effects of Dox in BC treatment. FA and cRGD have been conjugated via disulfide bonds to MSN surface, subsequently coated with PDA, and coupled with PNEM polymer, creating a nanosystem possessing long circulating time, redox-sensitive and active targeting properties. The obtained formulation exhibited an enhanced cellular internalization and high selective killing effect on tumor cells saving the normal cells, suggesting a real potentiality in clinical treatments.

Our group is reporting, in a submitted paper, the development of a nanodevice (FOL-MSN-BTZ) able to work as a smart chemotherapy releasing Bortezomib in FR positive Myeloma cells as a response to a pH-sensitive stimulus [194]. The starting MSU-type MSNs used have been obtained at room temperature, neutral pH and without mineralizing agent and present a defective structure of amorphous mesoporous silica rich in hydroxyl groups susceptible to be degraded by hydrolysis into smaller oligomers. The external surface of MSU-type MSNs was functionalized with a specific targeting ligand FA (MSN-FOL), while the internal surface was linked to bortezomib via a pH-sensitive cyclic boronate ester as shown in Fig. 8.

The engineering details of this development show how the performance *in vitro* depends on the location and concentration of the different molecules that constitute the nanodevice. The developed nanodevice is a delicate balance of its components at the nanoscale and only this balance allows it to work as expected. The optimized composition when tested *in vivo*, after an accurate evaluation of the drug contained in the suspension, showed increased therapeutic efficacy and reduced toxicity if compared to the free drug administration.

A higher silicon accumulation was detected in liver tissues of mice treated with FOL-MSN-BTZ compared to same tissue of mice treated with free BTZ, probably due to the role of liver as the primary organ of nanoparticles detoxification [195]. Conversely, no significant difference
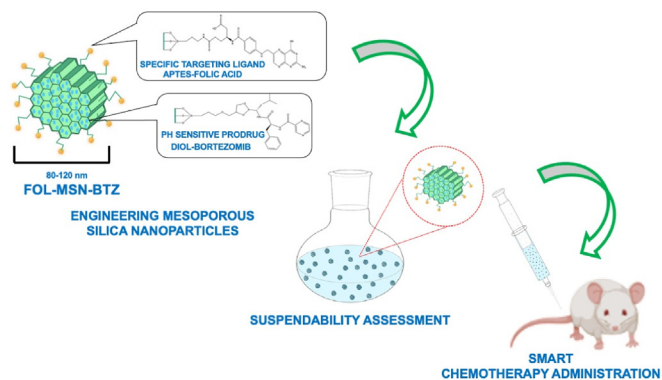

Fig. 8. Schematic representation of the strategy developed by Pasqua et al. [194] to improve Bortezomib delivery.

(*p > 0.05) in silicon accumulation was recorded in kidney of mice untreated (CTR TUM), treated with FOL-MSN-BTZ, and FOL-MSN.

A novel dual-functionalized Janus nanoparticle with active targeting and charge reversal capacity was synthesized [196]. Based on the Pickering emulsion interface method, each side of mesoporous silica was successfully modified separately producing a system having a tumor-targeting ligand (HA) modified on one side and a charge reversal group (2,3-dimethylmaleic anhydride, DMMA) on the other side. In general, the obtained HA-JMSN/Dox-DMMA could take the synergistic effect of active targeting and charge reversal to deliver drug in tumor cells killing them efficiently, thus representing a promising antitumor nanodrug.

In a recent paper [197], a new class of Ru(III) prodrugs that are bioreducible into highly active ruthenium(II) drugs, in response to high intracellular glutathione level, was engineered in a multifunctional nanodrug. The reduced compound (drug) is capable of tumor apoptosis through synergistic intercalation that blocked DNA replication, and coordination that cleaved nuclear DNA. The multifunctional nanodrug (Ru-MSN-PLip) was developed by integrating prodrug-loaded mesoporous silica nanoparticles (Ru-MSN) with a fusion protein-incorporated liposome (PLip) to achieve multiple targeting and eGFP-based fluorescence imaging of non-small cell lung cancer. Ru-MSN-PLip achieved sequential delivery and greater antitumor activity. In addition, Ru-MSN-PLip exhibited long-term blood circulation and selective accumulation in tumors, leading to significantly limited tumor growth *in vivo* without notable toxicity. The Ru-MSN-PLip achieved fluorescence imaging and hierarchically targeting delivery of the Ru(III) prodrugs by fusion protein-mediated cell membrane recognition and Ru(III) prodrug-mediated nuclear DNA targeting, enhancing antitumor activity.

With the combination of chemotherapy, magnetic hyperthermia and homotypic targeting ability, Zhou and co-workers [178] obtained superior *in vitro* toxicity in MDA-MB-231 cell membranes, suggesting a new treatment modality for tumor therapy. The aim of the work was to develop MSNs co-loaded with PTX and superparamagnetic ferroferric oxide able to accumulate at the tumors site thanks to the homotypic binding characteristics of cancer cells membranes coated on MSN surface. Indeed, the MSNs coated with MDA-MB-231 cells showed antiproliferative effects under alternating magnetic field (AMF) stronger than both that of non-coated MSNs irradiated by AMF and coated MSNs without any magnetic irradiation. In summary, the proposed multifunctional MSNs perfectly represents the concept that combination of several cancer targeting approaches may improve therapeutic activity of common anticancer drugs.

A novel class of MSN with a dendritic pore structure denoted as DMSN was engineered by Deng et al. [198] to develop a smart platform for PTX delivery. The formulation was optimized to improve colloid stability and tumor targeting ability assembling on the particle surface, via disulfide bond, a poly (methacrylic acid) thiol (PMAsh) multilayer shell functionalized with Tf whose receptors are overexpressed in many kinds of tumor cells. *In vitro* and *in vivo* studies demonstrated a specific accumulation of the developed MSNs on tumor cell and a significant inhibition of tumor growth and prolonged survival time of tumor-bearing mice, suggesting the promising role of these nanocarriers in the delivery of hydrophobic drug for cancer therapy.

Particular advantageous was the approach developed by Wang et al. [199] that proposed the design of a multifunctional device for cancer therapy modifying the mesoporous silica nanostructure using a single substance with multiple properties. This strategy allows to overcome the difficulty to graft several different moieties with effective concentrations on MSN surface. To this purpose, the authors chose HA since has several interesting properties to obtain a smart tool for target therapy. First, HA is a biocompatible polymer able to enhance blood circulation time and can be degraded by hyaluronidases (HAase) ensuring an enzyme-responsive release after being endocytosed by cancer cells. Moreover, HA is a ligand used in active targeting approach since is able to bind CD44 receptors overexpressed in several cancer cell lines.

Researchers, so, introduced HA into the mesoporous nanostructure, grafted via disulfide linkage, in order to further confer redox-responsivity. To investigate the dual stimuli responsivity of MSNs, drug release studies were performed in presence of GSH and HAase. Obtained results demonstrated that drug release was very low in absence of GSH and HAase while a markedly increase of drug release was observed upon the addition of GSH or HAase. Moreover, the release was further accelerated in the simultaneous presence of GSH and HAase. An increased cellular uptake and cytotoxic effect was observed in CD44 receptor over-expressed HCT-116 cells suggesting the real potentiality of engineered devices for cancer therapy.

Similarly, Kim et al. [200] have demonstrated the double potential of cyclic peptide as gatekeeper, for not only active targeting but also stimuli-responsive intracellular drug release.

The cyclic peptide, in addition to present targeting ability of aminopeptidase N (APN), a receptor overexpressed in tumor endothelial cells and in various tumor cell lines, resulted able to undergo a conformational transformation in presence of GSH due to the reduction of intramolecular disulfide bond of the peptide, inducing drug release. Consequently, MSNs functionalized with cyclic peptide exhibited a controlled drug release and greater uptake of the nanocarrier in H1299 cells (high APN expression) suggesting that this strategy using dual functional stimuli would be valuable to prepare MSNs with enhanced therapeutic efficacy by targeting cancer cells.

Besides, Ca^{2+} introduction in mesoporous framework has been employed by researchers in the design of carriers for cancer therapy thanks to its multiple advantages. Specifically, calcium presence enhances particle biodegradation via acid-triggered release mechanism and improves drug loading for its chelating effect [201]. Furthermore, Ca^{2+} ions possess an intrinsic anticancer activity inducing cell apoptosis and, consequently, can be combined with other drugs for synergic cancer therapy. This strategy was used by He et al. [202] that in a work combined the advantages of Ca^{2+} ions with the presence of disulfide bonds in the mesoporous framework to obtain a redox- and pH dual-responsive biodegradable MSN (BTCa-MSN). The biodegradation of BT-Ca-MSN was investigated in different media and characterized by TEM and ICP-OES in order to detect Si and Ca contents and evaluate the time-dependent structural evolution. A complete degradation and disintegration of BT-Ca-MSN was observed after 48 h in a concurrent reductive and acidic environment due to the simultaneous disulfide bond breakage and Ca^{2+} release. Moreover, the authors investigated Dox release from the devices in the same conditions and the obtained results were in accordance with biodegradation studies, suggesting that the drug release was controlled by carrier degradation. Particularly interesting was the intrinsic cancer cell killing activity of blank BT-Ca-MSN that was ehnanced by Dox loading in mesoporous structure as a consequence of the synergic activity of Dox and Ca^{2+}.

In summary, these papers have reported various combinations of targeting strategies and shown exciting results in preclinical studies, demonstrating their potential in the development of therapeutics carriers. The wide versatility in engineering MSNs may provide several insights into the rational design of nanomaterials as successful tools for achieving personalized medicine.

3. Recent field of applications

As follows, we report an exhaustive collection of the most recent and representative applications of multi-functional devices based on engineered mesoporous silica in precision medicine, such as cancer immunotherapy, diagnostic, brain targeting, theranostic, gene therapy.

3.1. Cancer immunotherapy

Cancer immunotherapy is one of the most promising fields of application of engineered MSNs thanks to their ability to stimulate antitumor immunity by the activation of specific immune cells, providing a long-

lasting and broader immune response than conventional immuno-therapy. MSNs possess physical properties suitable for immune activation and may transport antigens, cytokines, and antibodies allowing them to preferentially accumulate in key antigen presenting cells (APCs), such as dendritic cells. Consecutively, this accumulation activates CD8$^+$ cyto-toxic T lymphocytes (CTLs) that recognize and kill tumor cells through interactions between T cell receptors and major histocompatibility complex (MHC). Physico-chemical features of nanoparticles are crucial factors affecting the activation of immune response, therefore, the opti-mization of these parameters must be considered in the design of MSNs as platform for vaccine delivery. Hong et al. [203] deeply investigated the effect of MSN pore size on the eliciting immune response. Commonly, immune activation involves an *in vivo cascade* of four steps as shown in Fig. 9: the uptake by dendritic cells (DCs), the drainage to lymph nodes, the maturation DCs and the presentation of the peptide via MHC I to CD8$^+$ T cells (the DUMP cascade for short).

The authors synthesized 80-nm ovalbumin loaded-MSNs with different pore sizes (7.8 nm, 10.3 nm, and 12.9 nm), varying the con-centration of TEOS. From the analysis performed, pore size did not affect the first three step of DUMP cascade. On the contrary, the presentation of peptide–MHC I complexes to CD8$^+$ T cells resulted affected by vesicle sizes. Particles with larger pores induced stronger immune responses and tumor suppression effects compared to the smaller pore MSNs because of a better antigen cross-presentation ability, the last step in the DUMP cascade. MSNs with 30 nm extra-large pores (XL-MSN) have also been synthesized by Kim et al. [204] to improve the encapsulation of large therapeutic biomolecule, IL-4 an anti-inflammatory cytokine used in immune cell modulation. XL-MSNs showed significantly higher IL-4 loadings compared to conventional small pore MSNs. Phagocytic myeloid cells, such as neutrophils, monocytes, macrophages, and den-dritic cells, were the major cell population that took up XL-MSNs *in vivo*. The author observed that IL-4-loaded MSNs triggered M2 macrophage polarization both *in vitro* and *in vivo*, suggesting their potential for de-livery of cytokines for immune modulation in clinical therapies.

Besides, the influence of surface functional groups on MSN adjuvant efficacy has been investigated [205]. Specifically, the authors investi-gated the effect of MSN surface modification with –OH, –NH$_2$ and –C$_{18}$ groups on *in vitro* and *in vivo* immune system activation. Studies per-formed have shown that hydrophobic -C$_{18}$ groups modified MSNs elicit significantly stronger humoral and cell-mediated immunity than that of –OH or –NH$_2$ groups. The results suggest once again how an engineered approach to the nanostructure has profound impact on the immune response, so representing a valid tool for the design of effective nano-material based vaccines. Morphology of nanostructure resulted also able to affect cancer immune-adjuvant efficiency. Yu and collaborators [206] reported the synthesis of dendritic mesoporous organosilica hollow spheres with controllable number of shells and investigated the effect of the shells on immune response. The double-shelled structure and organic–inorganic hybrid framework improved the adjuvant immunity in cancer immunotherapy compared to their counterparts either with a pure silica composition or a single-walled architecture, suggesting that have an important role in the design of a vaccine delivery systems to achieve an excellent tumor inhibition. Extremely promising for cancer vaccine design are MSNs engineered by Chen et al. [207] for enhanced chemo-photodynamic immunotherapy. In this work, the activity of Chlorin e6 (Ce6) and PTX loaded MSNs coated with a layer responsive to MMP2 high levels was improved by the external grafting of an anti-PD-L1 antibody (aPDL1). This antibody, indeed, was able to avoid the PD-1/PD-L1 interaction between receptors overexpressed in tumor cell and its binding on the surface of T cells reducing immune response evasion. The outer layer, made up of cross-linked gelatin, avoids drug leakage during systemic circulation and enhances the accumulation in tumor site where is degraded by MMP2 in the tumor microenvironment leading to the exposition of PDDL1 and, thus, the suppression of immune systems evasion. At the same time, the activation of the photosensitizer Ce6 via irradiation induced an intensive immune response through the production of cytotoxic reactive oxygen species (ROS) and pro-inflammatory cytokines that facilitate the presentation of tumor-associated antigens (TAA) to cytotoxic T lymphocytes (CTLs). The activity of immune system was further combined with PTX anticancer activity, and this synergic therapy resulted in a potent *in vivo* reduction of tumor growth and metastasis to distant sites. Zhao et al. [208], instead, proposed the combination of cancer chemotherapy and anti-programmed cell death protein 1 antibody (aPD1) immunotherapy for melanoma treatment. Specifically, antibodies were associated with biomimetic nanocarriers based on MSNs camouflaged with cancer cell membrane (CCM) and loaded with dacarbazine (DTIC). These biomimetic devices offered several advantages in cancer targeted therapy such as prolonged blood circulation evading opsonization and reticuloendothelial system clearance, effective immune escape, homologous targeting ability and be the source of tumor-associated antigens. A good targeting capability of the designed nanocarriers toward melanoma cancer cells and anticancer killing activity were, in fact, confirmed by *in vivo* studies as a result of the synergic action of the chemotherapeutic drug DTIC, the activation of tumor-specific T cells and regulation of the immuno-suppressive tumor microenvironment. In summary, MSNs provide an optimal solution for maximizing therapeutic efficacy and reducing side toxic effects of immunotherapeutic agents and represent a revolutionary method for cancer treatment.

3.2. Diagnostic

Accurate and early diagnosis is one of the critical factors influencing the prognosis of tumor disease. Traditional imagine techniques such as optical imaging (OI), X-ray computed tomography (CT), positron emis-sion tomography/single photon emission computed tomography (PET/ SPECT), magnetic resonance (MR), have many limitations in detecting cancer in early progression stages since imaging contrast agents are commonly small molecules with fast metabolism and a non-specific distribution [209]. A large variety of imaging agents including fluores-cent organic dyes, contrast agents, radioisotopes, and luminescent inor-ganic nanoparticles may be loaded or conjugated to MSN surface to design advanced bioimaging tools Fig. 10 [210]. The delivery of imaging agents in mesoporous nanostructures, indeed, led to the development of more powerful contrast agents, as smart nanomaterials exhibit enhanced permeability and retention effects in tissues and, if opportunely engi-neering, may detect specific cancer cell at an early stage. In fact, the conjugation of specific biomarker on MSN for diagnostics is a strategy widely used to differentiate between benign and malignant disease. For instance, this approach was performed by Guo et al. [211] that have developed PSA-targeted manganese oxide-–MSNs for multimodal imag-ing of prostate cancer *in vitro* and *in vivo*. Prostate-specific membrane
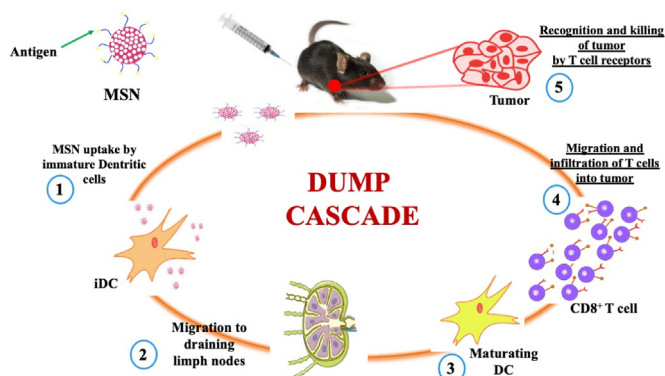
Fig. 9. Schematic representation of MSN-mediated modulation of immune response to improve the effectiveness of cancer immunotherapy. Engineered MSNs are recognized by immature dendritic cells (DC) and migrate to the lymph nodes, where transition to mature DC occurs leading to cytotoxic T cells.
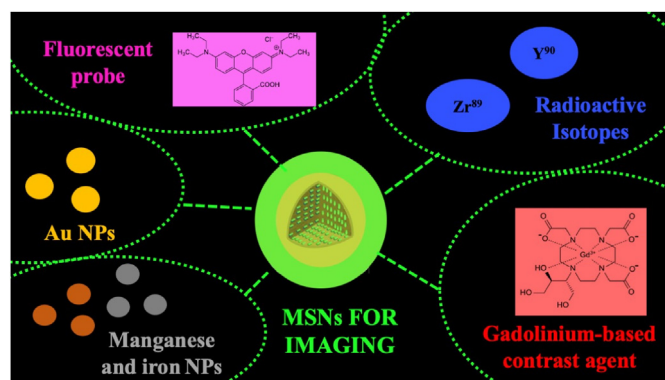
Fig. 10. Conceptual graphical overview of various types of MSNs loaded with several imaging agents used in diagnostics and theranostic applications reported in this review.

antigen (PSA) is a biomarker of prostate cancer and, therefore, its conjugation on MSN surface enhanced the *in vitro* and *in vivo* accumulation in tumor but not in noncancerous cells, as demonstrated by optical and MR images.

Trivalent gadolinium (Gd^{3+}) is a common contrast agent used in MRI due to the highly paramagnetic nature (f^7) of the Gd^{3+} ion and its long electronic spin relaxation time. In last years, the functionalization of gold nanoparticles (AuNPs) with Gd^{3+} has been applied to improve the performance of contrast agents in terms of relaxivity. In this sense, Li and co-workers [212] designed AuNPs co-doped with Gd_2O_3 mesoporous silica nanocomposite (Au/Gd@MCM-41) as a novel targeted nanoprobe to human nasopharyngeal carcinoma (NPC) cell lines (CNE-2) using fluorescence lifetime imaging (FLIM). A significant fluorescence difference between CNE-2 cells and NP69 normal cells was observed thanks to the enhanced optical sensitivity of nanoprobe related to the interaction between AuNPs and Gd^{3+}, suggesting its application as ideal diagnostic probe for early nasopharyngeal carcinoma detection.

Another strategy to improve MR imaging *in vivo* is the use of external stimuli such as near infrared (NIR) laser to remodel internal tumor structure and improve tumor vasculature and tissue permeability, enhancing nanoparticles accumulation in tumor site. Wang and collaborators [213] in 2021 developed new tools for precise cancer diagnosis through the development of NIR powered nanomotors based on Gd (III) doped MSNs functionalized with Au on the half-sphere (JMS). NIR irradiation formed a self-thermophoretic force that promoted the active motion of JMS nanomotors inside solid tumors to enhance the *in vivo* intratumoral penetration and, thus, MR imaging capability *in vitro*.

New MSNs for intracellular imaging and sensing of nuclei were developed by surface deposition of a luminescent anionic cluster complex $[\{Re_6S_8\}(OH)_6]^{4-}$ on MSN surface [214]. Specifically, the authors designed both pH sensitive and pH-insensitive luminescent nanodevices varying the deposition mode of luminescent probe. For the pH-insensitive tools, the cluster $\{Re_6S_8\}(OH)_6]^{4-}$ was deposited on MSNs decorated with amino groups via electrostatic attraction and the resulting nanoparticles exhibited a bright luminescence invariable in pH range from 4.0 to 12.0. Instead, a luminescence sensitive to pH-changes within 4.0–6.0 was obtained by the self-assembly of polyethyleneimine (PEI) chains at the negative MSN surface. The sensitivity derived from the pH-triggered conformational changes of PEI chains from coil-to-linear resulting in clusters release from the MSNs. Moreover, the use of PEI resulted able to enhance MSN stability to aggregation in comparison with MSN decorated with amino groups, due to the formation of the highly hydrated PEI-based exterior layer. It has also been found that PEI improved cell internalization of anionic cluster units and results in efficient staining of the cell nuclei in the confocal images indicating a uniform intracellular distribution.

In addition to fluorescent dye and contrast agent, the use of positron-

emitting radioisotope has been recently emerged as an advantageous imaging modality for its non-invasive nature and high sensitivity. For instance, Zirconium-89 (^{89}Zr) is a radio-isotope with a relatively low positron energy, suitable for PET imaging but characterized by a limited stability of its chelator labelling. Cai and collaborators [215] proposed to use MSN as stable chelator of ^{89}Zr thanks to the large availability of deprotonated silanol groups on nanoparticle surface able to act as hard Lewis bases for the free ^{89}Zr. ^{89}Zr labeling yield resulted to be directly dependent on the concentration and temperature used. Serum stability studies demonstrated that ^{89}Zr-MSN exhibited high *in vivo* stability with very little bone uptake over 3 weeks. The detachment rate of ^{89}Zr from MSN meso-channels was further found to be > 20-fold slower than that of ^{89}Zr from amorphous dense silica nanoparticles used as a control, highlighting the vital role of meso-channels in stabilizing ^{89}Zr inside MSNs.

A further candidate used in PET imaging is Fluorine-18 (^{18}F) that have several favorable physiological and nuclear properties, but its application is limited by its short half-life. To overcome this drawback, Kim and co-workers [216] proposed the radiolabeling of nanostructure silica material via an *in vivo* strain-promoted alkyne azide cycloaddition (SPAAC) covalent labeling reaction between aza-dibenzocyclooctyne-tethered PEGylated mesoporous silica nanoparticles (DBCO-MSNs) and ^{18}F inside the macrophage cells. The developed macrophage cell-tracking protocol increased radioisotope half-life time, providing a persistently strong tumor imaging until 8 days after treatment. Recently, Dong and co-workers [217] developed multifunctional enzymatic MSNs able to detect cancer via GSH sensing and FA targeting using dendritic mesoporous silica nanoparticle (DMSN) and MnO_2 nanocomposites. The proposed devices had high sensitivity and "switch-on" signal response by fluorescence, UV–vis absorbance, and color brightness triple mode due to the integration of fluorescence resonance energy transfer and ultrasensitive oxidase mimic activity of the MnO 2 shell, suggesting their potential role for targeted cancer cell recognition.

3.3. Brain targeting

Blood brain barrier (BBB) makes brain tumor nearly inaccessible to systemic therapies. Several different attempts to engineer MSNs in order to possess the ability to cross the BBB have been recently reported. Various ligands have been shown to possess high binding affinities to specific BBB receptors and, when conjugated to nanoparticles, confer them an obvious brain tumor targeting properties. Liu et al. [218] proposed the modification of MSN surface with a tumor-targeting/penetrating peptide RGD for simultaneous delivery of chemotherapeutic agents (Dox) and immune checkpoint inhibitor (1-methyltryptophan, 1 MT) across the BBB. A significant increased accumulation of RGD modified nanoparticles was detected in glioma tumor cells compared to non-modified nanoparticles and these results confirmed that iRGD modified nanoparticles could recruit drug to the orthotopic brain tumors with minimal systemic side effects. These tools, also, elicited a robust antitumor immune response against glioblastoma and, compared with single chemotherapy, the synergistic chemo-/-immunotherapy via Dox@MSN–SS–iRGD&1 MT extended mouse survival with a 50% durable cure rate. These results demonstrated that engineered MSNs effectively inhibited tumor proliferation, thanks not only to Dox cytotoxic effect but also to the significant activation of immune response, representing a potential clinical method for glioma treatment. Turan et al. [219], instead, engineered MSNs to be selectively addressed to the altered glioblastoma endothelium by targeting fibronectin, an overexpressed perivascular biomarker in GBMs with insignificant expression on healthy brain endothelium. In addition, researchers combined vascular targeting with low-power radiofrequency (RF) sensibility to enhance the effective delivery of drug across the BBB, developing MSNs with an iron oxide core and external functionalized with the fibronectin-targeting peptide CREKA. This peptide allowed to direct nanoparticles to brain tumor endothelium and, then, the exposure to

low-power RF induced a rapid drug release from the Fe@MSN nanoparticles, enhancing a widespread distribution of drug molecules across the blood-brain tumor interface, with remarkable anticancer outcomes and tumor shrinkage.

A further strategy widely employed to improve brain drug delivery across BBB is mesenchymal stem cells (MSCs)-mediated transcytosis that exploits the tumor tropic properties of MSCs as platform for targeted drug delivery to tumor. A significant limit of MSCs is the impossibility of engineering them to have multifunction properties for simultaneous therapy and imaging. To overcome this drawback, Chen et al. [220] prosed to combine tumor targeted delivery of MSCs and multimodal imaging of MSNs. Specifically, the authors developed MSNs coated with HA (HA-MSNs) and labelled with FITC, NIR dye ZW800, Gd^{3+}, and ^{64}Cu as imaging agents for optical, MR, and PET imaging. *In vivo* multimodal imaging showed that NP-labelled MSCs induced a 5.2 ± 1.3-fold higher tumor accumulation than the free NPs, demonstrating the feasibility of glioma tumor tropism delivery of this multifunctional MSC-platform.

3.4. Theranostic

In recent years, a great interest has been addressed to design nanodevices that combine diagnosis and therapy approaches. These systems, namely nanotheranostics, are able to specifically target a pathological tissue and to release the drug in a controlled and time-dependent manner in combination with assisted imaging to monitor therapy effectiveness in real time.

For the first time, Ferreira and al [221] in 2021 radiolabeled silica nanoparticles with an isotopic pair $^{90/86}Y$ to obtain a theranostic tool. Researchers specifically used as starting materials sub-15 nm porous silica nanoparticles with prolonged blood circulation and enhanced tumor uptake properties. For the radiolabeling process, ultrasmall porous silica nanoparticles (UPSN) were first conjugated with DOTA chelator and then with $^{90/86}Y$. *In vivo* PET imaging highlighted a prolonged blood circulation and fast tumor accumulation of ^{86}Y-labelled nanoparticles reaching around 12% ID/g in the tumor, and a tumor regression of about 30% was recorded in mice treated with ^{90}Y-UPSN after 1 day from administration, even though complete tumor eradication was not achieved. On the contrary, in the group treated with free ^{90}Y-DOPA or non-treated an exponential tumor growth was observed. Moreover, 100% of animals injected with radiolabeled UPSNs were still alive at the end of the study in comparison to 20% for those injected with ^{90}Y-DOTA and 0% for the other group, suggesting the potential role in future of this devices as cancer theranostic agent. Rafenia and co-workers [222] designed a nanotheranostic system for pH- dependent fluorescence imaging and targeting curcumin delivery based on both MSN and chitosan nanoparticles. Specifically, curcumin was first encapsulated into chitosan-triphosphate nanoparticles and then the resulted nanoparticle was loaded into MSN and then functionalized with MUC1 aptamer. These devices were able to act as "on/off" biosensors thank to the ability of aptamer double strands to separate under the low pH condition when the aptamer specifically binds to the MUC-1 receptor, leading to the drug release and the recovery of the fluorescence ("On" state).

The strategy proposed by Jänicke et al. [223] was based, instead, on the coupling of fluorochromes N-methyl isatoic anhydride (M) or lissamine rhodamine B sulfonyl chloride (L) on emodin (EO) loaded MSN surfaces. Cytotoxic studies demonstrated that the non-fluorescent MSNs and the fluorescent materials (MSN~M, MSN~L) alone were not toxic to HT-29 colon human tumor cells, while a significant toxic effect was recorded for those loaded with EO. Fluorescence microphotography showed that silica nanomaterial uptake by the tumor cells occurred within 2 h and the release of EO occurred within 48 h of treatment. Furthermore, cell death mechanism was investigated by Western blot analysis that displayed a stronger expression of phosphorylated ERK and LC3A/B proteins, suggesting that autophagy is the main mechanism involved in cell death.

Chen et al. [224] fabricated a new multifunctional drug delivery system based on MSNs capped by gadolinium-based bovine serum albumin complex (BSA-Gd) and HA via reductive-cleavable disulfide bond. In this nanodevice (MSN-ss-GHA), BSA-Gd component worked as both smart gatekeeper and contrast agent for MR imaging, while HA acted as the targeted molecule to improve the specific affinity of MSN-ss-GHA toward cancer cells. The MSN-ss-GHA exhibited excellent biocompatibility and distinctly enhanced cell uptake by 4T1 cells. More importantly, the Dox@MSN-ss-GHA demonstrated efficient Dox delivery into 4T1 cells and showed enhanced cytotoxicity as compared to that of nontargeted nanocarrier, with negligible toxicity of MSN-ss-GHA and improved antitumor suppression of Dox@MSN-ss-GHA. This multifunctional MSN-based theranostic agent holds potential for efficient redox-responsive targeting drug delivery and MR imaging.

A new theranostic tool was proposed by Fredius and collaborators [225] based on the loading in MSNs of a new synthetic drug, CurNQ, derived from curcumin (Cur) and naphthoquinone (NQ). This new compound was insoluble at pH 7.4, while at acid pH, such as that of tumor microenvironment, it became soluble and fluorescent. Moreover, CurNQ exhibited cytotoxic effect on two ovarian cancer lines. The loading of this compound into MSNs, thus, allowed obtaining a fluorescent nanoparticle that had also targeting and therapeutic properties. The shift in solubility was also observed when CurNQ was loaded into MSNs as the release of CurNQ from the MSN was pH dependent. The new device also showed a high intensity fluorescence, confirming its application in molecular imaging. Moreover, MSN-CurNQ induced cytotoxicity culminating in a reduction below 50% cell viability in OVCAR-5, CACO-2, CHLA, and MCF-7 cancer cell lines compared to a healthly fibroblast cell lines, demonstrating also its chemotherapeutic potential.

In 2020, Huang and co-workers [226] designed a theranostic tool to improve tumor radiosensitivity of quercetin in cancer treatment that is limited by its poor water solubility and poor tumor tissue targeting ability. Researchers, in fact, proposed drug-loaded MSNs capped with tumor cell membrane in order to improve tumor tissue targeting and *in vivo* biodistribution. Results of the *in vitro* and *in vivo* experiments demonstrated that the developed MSNs had excellent tumor targeting ability and, when combined with radiotherapy, promoted tumor cell apoptosis and effectively inhibited tumor growth. In the same year, Saha et al. [227] successfully proposed a novel multifunctional theranostic MSN to improve the human colorectal carcinoma cells (HCT-116) treatment in clinical practice. Authors combined several functional properties: a) active targeting by surface conjugation of FA; b) contrast imaging properties by surface conjugation of acid-labile magnetite Fe_3O_4 nanoparticles; c) pH-triggered drug release; d) activation of multiple signaling pathways due to quercetin. A marked tumor suppression and notable contrasting MRI behavior of the developed device suggested the successful theranostic perspective of the nanoplatform in cancer management.

An advanced nanoplatform for osteosarcoma therapy that combined in the same system bone targeted chemo-chemodynamic treatment and dual-modality CT/MR imaging, was developed by Sha and collaborators [228]. To this purpose, gold nanoparticles (AuNPs) were coated with MSNs and then doped with manganese (Mn^{2+}) for its ability to increase the ROS levels via Fenton reactions and the production of OH radicals, able to induce cell apoptosis. Moreover, nanoparticles were functionalized with a hydroxyapatite target, alendronate (Ald), and loaded with Dox. This surface modification resulted able to improve cellular internalization of nanoparticles in 143 B cells as emerged in confocal laser scanning microscope image. After internalization, tumor microenvironment triggered the degradation of Mn–O bonds in the nanoparticle structure and the Mn^{2+} release lead to the Fenton-like reaction and, consequently, to the overproduction of highly cytotoxic ·OH radicals. Free radicals, combined with Dox release, effectively killed tumor cells *in vitro* and suppressed bone tumor growth *in vivo* through chemo-chemodynamic combination therapy. Significantly was also the

MR contrast effect of Au nanoparticles that allowed to monitor Fenton-like Mn^{2+} release and the chemodynamic therapy process *in vivo*, suggesting the wide potentiality of these devices as nano-theranostic tool for osteorsacoma therapy.

3.5. Gene therapy

Gene therapy could offer potential opportunities in medical healthcare but the short half-life, fast enzymatic degradation and low cellular uptake of such nucleic acid-based drugs represent critical obstacles in therapeutic use. The delivery of gene drug in mesoporous silica nanostructures has been advanced as a potential solution for clinical translation of these systems.

siRNA stability involved in drug resistance inhibition has been improved by Elahian and co-workers [229] loading them in MSNs capped with chitosan as a protective layer. Gel assay analyses demonstrated that chitosan coating protects siRNA adsorbed on the external MSN surface from enzymatic cleavage. In addition, targeting moieties such as TAT and FA anchored to chitosan via PEG-spacers improved cellular uptake by approximately two-fold in folate receptor-rich HeLa-RDB than EPG85.257-RDB cells. Moreover, developed nanoparticles demonstrated a greater silencing ability of P-gp in HeLa-RDB cells and, consequently, an enhanced anticancer activity of daunorubicin due to P-gp knockdown.

In another work, nuclei acid (e.g., DNA, mRNA) and genome editors (e.g., RNP, RNP + ssODN) were successfully encapsulated in multifunctional and GSH-responsive MSNs to develop an innovative tool for genetic disease treatment [230]. Specifically, imidazole moiety and PEG were incorporated in nanostructure to improve endosomal escape, *in vivo* stability and circulation time. Instead, conjugation with targeting ligands such as all-*trans*-retinoic acid (ATRA) and *N*-acetylgalactosamine (Gal-NAc) was carried out to localize nanocarrier accumulation in retinal epithelium (RPE) and liver, respectively. *In vivo* studies showed a successful delivery of nucleic acid and RNP in the RPE and liver with good biocompatibility, and a higher DNA and mRNA transfection efficiency, indicating the applicability of these systems in a variety of gene therapy and genome editing application.

Chen et al. [231] in 2020 designed a smart device for gene delivery combining the advantages of magnetic mesoporous nanoparticles (M-MSNs), air-containing microbubbles (MBs) and ultrasound sensitivity to improve gene transfection. Authors proposed the loading of a plasmid DNA in M-MSN and, then, the resulting devices was loaded in MBs. In fact, MBs resulted able to protect the gene-loaded M-MSNs from reticuloendothelial system uptake and confer an ultrasound sensitivity. Ultrasound induced MBs degradation and, thus, release of M-MSNs, but also enhanced M-MSNs accumulation to tumor tissue by opening blood- −tumor barrier and increasing permeability. Furthermore, the magnetic properties of the developed tools allowed not only to localize in a selective manner the MSNs at the tumor site but also confer them an ideal MR imaging effect, that combined with US imaging make them a dual-mode imaging tools for cancer therapy.

3.6. Critical discussion

The development of MSN-based nanoplatforms for cancer therapy, thanks to the high potential of nanotechnology applied to nanomedicine, introduces the never before imagined opportunity to face the same problem according to several strategies, each of which can include different approaches.

This is a deeply unusual condition that has never before characterized the process of selecting a technological solution to a well-defined problem. In other fields, in fact, a brief investigation is able to reveal a limited number of appropriate and adoptable solutions and provide elements, whose relevance can be easily evaluated without complex procedures such as animal testing, for comparing smoothly the related advantages and disadvantages of each solution.

In the scenario presented here, the number of potential solutions is high and, despite the appearances, this is a dramatic situation as there is no possibility of achieving the necessary technical awareness to make a decision on the strategy/approach to be adopted due to the untreatable amount of information and factors that should be considered.

The *in vivo* performance of the new nanomedicine solution, in fact, despite the promising *in vitro* results [232], cannot be predicted and even where some predictions might be attempted, a new *in vivo* test has to be planned for confirmation. Furthermore, additional *in vivo* tests, aimed at optimizing administration protocols that provide relevant information for improving the therapeutic efficacy, should usually be considered.

With these premises, we can observe how the most important strategies for the development of MSNs-based nanoplatforms for cancer therapy such as drug targeting, immunotherapy, nanodynamic therapy, nanotheranostic and gene therapy represent a series of real and promising opportunities but all of them have some limitations, and more *in vivo* safety and efficacy data are needed to evaluate nanomedicine solutions for the clinical transactions.

Target therapy-designed nanodevices introduce a precise control in drug delivery able to improve therapeutic efficacy while reducing toxicity. MSN-based nanodevices for drug targeting, although using already approved drugs, should show a further improvement on the advantage in toxicity until now obtained and presented in open literature if compared with traditional therapy. Immunotherapy is directly focused on amplifying anticancer immune responses, in combination with nanomedicine, particularly usig MSNs, represents a promise for a huge improvement in patients' quality of life and survival percentage.

The use of MSNs, in fact, for the development of cancer vaccines has been promisingly approached encapsulating biomolecules to favor their protection and to enhance the immune response, as adjuvants to boost immunostimulation, in subcutaneous or intramuscular injections or in lymph nodes targeting. Nevertheless, more efforts are required to understand their interactions with the immune system [233].

MSN-based nanodynamic therapies show superior properties such as non-invasiveness, selectivity, great specificity and low toxicity towards healthy tissue. However, it is necessary to improve the sensitivity to stimuli of MSN-based nanosensitizers, and obtain greater safety and higher energy transfer efficiency to achieve cascade free radicals/ROS production [30].

The purpose of nanotheranostic is to diagnose and treat the diseases at their earliest stage, mostly curable or at least treatable. Notably, nanotheranostics also provide the control of hybrid nanocarriers transport inside the body by means of external physical forces and or energy. Modifiable surface and bulk chemistry, biocompatibility and biosafety and correlated potential for imaging and drug delivery in living systems are key aspects in MSNs-based nanotheranostic platforms [234]. The most interesting results of nanotheranostics are achieved only for *in vitro* studies while more challenges need to be addressed for *in vivo* applications at pre-clinical and clinical level, limiting clinical translation [235, 236].

Naked genetic material molecules are unable to successfully target specific tissue before being degraded by lysosomes in the endocytic pathway [237]. In addition, viral vectors suffer from crucial limitation such as immunogenicity, insertional mutagenesis, poor selectivity, and poor efficiency of delivery. The use of nanotechnology, in particular mesoporous silica nanocarriers, can successfully improve gene therapy development, overcoming these critical barriers. In fact, the nanosystems could selectively deliver genes with controlled release kinetics, reduce undesired side-effects, improving the transfection efficiency of the treatment [238].

Despite the potential of gene cancer therapy, the boost in technological innovation is greatly outpacing the safety. A crucial limitation is related to the few numbers of therapeutic genes that can currently be used in clinical trials [239].

In our opinion, MSNs represent a unique opportunity in cancer therapy and more in general in bionanotechnology thanks to the high level of the engineering allowed in developing platforms for interfacing

with complex and heterogeneous biological systems.

The high number of partial successes presented in the last decade suggests the reshaping of the objectives in terms of feasibility and sustainability including, in addition to the eradication of primary tumor and metastases, also the reduced incidence of Multi-Drug Resistence (MDR) through the careful design of multi-strategy treatments involving different nanomedicine solutions [240,241].

4. Conclusions and future outlook

In this review, we have described recent advances in the design and development of mesoporous silica nanoparticles as therapeutic nanocarriers. Nanostructured mesoporous materials possess worthful properties that make them ideal tools for a large variety of therapeutic applications. Ordered structure, chemical and thermal stability, great surface areas and high degree of tuneability are some of the many advantages of MSNs that could be exploited to obtain safer and personalized nanomedicines. Very interesting is the high surface reactivity that allow to modify the inner and outer surface with a wide versatility. They can be, indeed, designed in such a way that they also exhibit simultaneously combinations of various targeting strategies. As reviewed, the number of papers reported regarding MSN-based nanomedicine is enormous and their quality is surprisingly high if we look at the potential added values from the different engineering strategies shown. A large availability of preclinical data has successful proved the efficacy and better *in vivo* pharmacokinetic outcomes of multifunctional MSNs. However, there are different issues to be addressed for enhancing translation of MSN-based nanomedicines from preclinical to clinical studies.

First, as previously reported, size, shape, porosity, and surface chemistry significantly affect tissue distribution, cellular uptake and release kinetics. Anyway, few studies have been focused to understand the biological effects of these biomaterials, pathways and mechanisms by which they reach the target site, *in vivo* fate and their clearance. Consequently, a systematic study on MSN *in vivo* fate and how different physicochemical parameters affect this process should be undertaken. Moreover, it will be necessary to evaluate the safety from chronic exposure, establish long-term toxicological profiles from different routes of administration, investigate reliable scale-up methods and synthesize reproducible MSNs. Despite the efficacy demonstrated by *in vivo* studies, MSNs are not actually evaluated into any clinical trial. This could be due to the different physiology of animals and humans and a lack of understanding of the differences specifically how these differences affect the behavior and functionality of nanomedicines in the body.

These types of particles have proved to be outstanding platforms for multiple application such as cancer targeted therapy, gene therapy, immunotherapy and theranostics. The rational design of MSNs is a very prolific and competitive field of research and could have a remarkable potential in clinical practice. The MSN *in vivo* behavior and clinical efficacy could be optimized by tailoring MSN properties, improving the synthesis and the design of strategies oriented to clinical application, in order to facilitate the translation of these tools from laboratory research to clinical practice and, eventually, to the market. Factors such as biological safety, process scale-up, inter-batch reproducibility and architecture complexity need immediate consideration and discussion to enable a realistic knowledge of the difficulties and obstacles in the clinical translation process.

With regard to biological safety, recent findings suggest that MSN do not accumulate, which accomplishes FDA regulations for getting a device into clinical use [233]. Besides, respect to the other issues, we hardly worked on the engineering process of our smart chemotherapy and, after having previously verified the high inter-batch reproducibility and the feasibility of the scaling-up process, we successfully developed an advanced MSN-based nanosystem. The simple and suitable synthetic procedure [see reference 194], due to its reproducibility, allows to employ a starting mesoporous silica resulting from five different preparations mixed before the characterization.

In our opinion, to avoid accumulation, attention should be paid to the complexity of the MSN nanoarchitecture to plan degradation in the different biological environments of MSNs and all fragments eventually produced during modification procedures. To this regard, as above-suggested, the options of a multi-strategy treatment carried out using a mix of simple-architecture nanodevices jointly administered, could be considered. Finally, the stability of the suspensions which determines drug concentration should be carefully monitored to ensure the correct dose of drug is administered.

We truly believe that MSNs represent a great and innovative tool for drug delivery and their near future could be very bright in the treatment of various diseases and other applications. This perspective is supported from the observation that in the "materials engineering era" a plethora of different exceptionally imaginative and, at the same time, strictly valid and functional nanomedicine devices have arisen around the world in a relatively short time as demonstrated in this review. In these processes drug molecules are usually only one of the elements employed in the engineering process and they are mostly approved or generic molecules whose efficacy and toxicity are well-known due to the previously passed approval paths. The feasibility of a nanomedicine-era without the costs of the approval of a new chemical entity, as it could seem possible, can takes place in the imagination of our future.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Elisabetta Mazzotta reports financial support was provided by University of Milan-Bicocca. Luigi Pasqua, Antonella Leggio reports a relationship with NanoSiliCal Devices that includes: board membership. Luigi Pasqua, Antonella Leggio has patent #EP 3288955 B1 issued to NanoSiliCal Devices. Nothing to declare.

Data availability

No data was used for the research described in the article.

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