Cancer Nanotechnology

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Mesoporous silica nanotechnology: promising advances in augmenting cancer theranostics

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Abstract

Owing to unique facets, such as large surface area, tunable synthesis parameters, and ease of functionalization, mesoporous silica nanoparticles (MSNs) have transpired as a worthwhile platform for cancer theranostics over the last decade. The full potential of MSNs in cancer theranostics, however, is yet to be realized. While MSNs can be employed for targeted drug delivery and imaging, their effectiveness can frequently be hindered by factors, such as biological barriers, complex tumor microenvironment, target non-specificity and ineffectiveness of individual functionalized moieties. The primary purpose of this review is to highlight technological advances such as tumor-specific, stimuli-responsive "smart" MSNs and multimodal MSN-based hybrid nano-platforms that have the potential to overcome these limitations and improve MSN effectiveness in cancer theranostics. This article offers an extensive overview of MSN technology in cancer theranostics, outlining key directions for future research as well as the challenges that are involved in this aspect. We aim to underline the vitality of MSN technology and the relevance of current research and advancements in this field to potentially enhance clinical outcomes through the provision of more precise and focused theranostic approaches.

Keywords: Mesoporous silica nanoparticles, Cancer theranostics, Stimuli-responsive

Introduction

Cancer is an alarming public health crisis that affects millions of people worldwide, estimated at 19.3 million newly diagnosed cases per year and 10 million fatalities per year (Chhikara and Parang 2023). It is a heterogeneous disease characterized by uncontrolled and abnormal cell growth, invasion, and metastasis (Pedraza-Fariña 2006). Treating cancer is challenging as cancer cells can evolve to evade the normal mechanisms of cell death, proliferate, and differentiate at astonishing rates, migrate to other organs, and easily acquire resistance to conventional therapies (Zhou et al. 2009). Conventional cancer therapies, such as surgery, chemotherapy, and radiotherapy, have been widely used to treat different types of cancers (Tannock 1998). Surgery is limited by the ability to define the true extent of disease pre- and intra-operatively and the ability to resect all

of the disease safely without damaging structure or function of the involved or adjacent organ(s) (Constine et al. 2019). Radiation therapy is constrained by the tolerance of adjacent normal tissues to the targeted tumor, the ability to accurately define the extent of disease, and the sensitivity of the tumor to ionizing radiation (Emami 2013; Nambiar et al. 2011). Chemotherapy is also restricted by lack of specificity, cytotoxicity, transient half-life, limited solubility in physiological conditions, occurrence of multi-drug resistance, and occurrence of stem-like cells (Cheng et al. 2021). Moreover, these conventional therapies pose a risk of tumor recurrence as they often fail to eradicate the entire tumor mass and may also cause damage to nearby healthy tissues and organs during treatment (Abbas et al. 2018; Aly 2012). Therefore, there is an urgent need for more effective and safer cancer therapies that can target the tumor cells selectively and precisely.

Over the last few decades, the emerging field of nanotechnology has offered new prospects for effective cancer diagnosis and therapy (Cuenca et al. 2006). Nanoparticles are nanoscale-dimensional materials (~ 1–100 nm), which endow them with unique physical, chemical, optical, and biological properties (Uddin et al. 2016). Among various types of nanoparticles, mesoporous silica nanoparticles (MSNs) have engrossed considerable attention for cancer applications due to their advantages, such as large surface area, tunability of pore size and shape, substantial loading capacity, easy surface modification, low toxicity, and biodegradability (Gisbert-Garzarán et al. 2020; Huang et al. 2020). Over the years, MSNs have carved out their niche as carriers for a plethora of anticancer agents, such as small molecules, macromolecules, genes, proteins, and radionuclides (Ahmed et al. 2022; Alyassin et al. 2020; Mamaeva et al. 2013; Zhou et al. 2018). MSNs can also be used for cancer imaging purposes by incorporating contrast agents or fluorescent probes into their pores or on their surface (Cha and Kim 2019). MSNs possess the ability to amplify the sensitivity and specificity of imaging techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), optical and photoacoustic imaging (Lee et al. 2022; Ni et al. 2019; Pellico et al. 2019). This allows researchers to gather information on the location, size, shape, and metabolic activity of the tumor cells and tissues.

However, using MSNs for imaging or therapy alone may not be sufficient to achieve the optimal outcomes for cancer patients. Imaging alone cannot provide therapeutic effects, while therapy alone cannot monitor the drug delivery, release, and efficacy (Fernandez-Fernandez et al. 2011; Sajja et al. 2009). Moreover, using separate nanoparticles for imaging and therapy may increase the complexity of the system and the risk of adversative outcomes (Arora et al. 2012; Krug and Wick 2011). Therefore, there is a need for integrating the duality of imaging and therapeutic operations into a single nanoparticle system. This concept is known as theranostics, which combines the terms therapeutics and diagnostics (Kelkar and Reineke 2011).

Theranostics is a promising approach that aims to provide personalized and precision medicine for cancer patients. Theranostic nanoparticles can simultaneously or sequentially perform diagnosis and treatment of cancer in a single platform (Sumer and Gao 2008). Theranostic nanoparticles can enable real-time monitoring of the drug dispersal process and the resultant therapeutic response (Jo et al. 2016) while enhancing the effectiveness of oncological treatments via facilitation of dose adjustment, treatment optimization, and early detection of treatment failure (Mura and Couvreur 2012).

MSNs are promising in this regard as they can be designed to incorporate different imaging and therapeutic agents into their pores or on their surface. MSNs can also be functionalized with various stimuli-responsive moieties or targeting ligands to achieve controlled drug release or enhanced tumor accumulation (Thi et al. 2019; Moodley and Singh 2021). MSNs can also be combined with other nanomaterials to create hybrid or core–shell structures that can provide synergistic effects or multimodal functions (Fernandes et al. 2023).

This review paper aims to highlight the prominent advances in cancer theranostics using mesoporous silica nanotechnology. We also discuss the different strategies for designing "smart" MSNs for precision oncology, that can respond to various internal or external stimuli and deliver multiple anticancer agents in a coordinated manner. This review also summarizes the challenges and opportunities for translating MSN-based theranostics into clinical practice.

Synthesis of MSNs

The synthesis of MSNs is augmented by a fascinating interplay of materials science and chemistry. Synthesis procedures of MSNs encompass different methodologies that enable the controlled fabrication of these nanoparticles, each technique bearing its distinct facet on the final structure and functionality (Wu and Lin 2013). Some of the most commonly used synthesis techniques include the sol–gel method, evaporation-induced self-assembly (EISA), and hard and soft templating techniques. These methodologies are steered through the manipulation of precursors, solvents, and templating agents. While the sol–gel method harnesses the power of controlled hydrolysis and condensation reactions (Vazquez et al. 2017), EISA exploits the equilibrium between solvent evaporation and molecular self-organization (Kimura 2016) (Fig. 1). Complementing these approaches, the methods of hard and soft templating

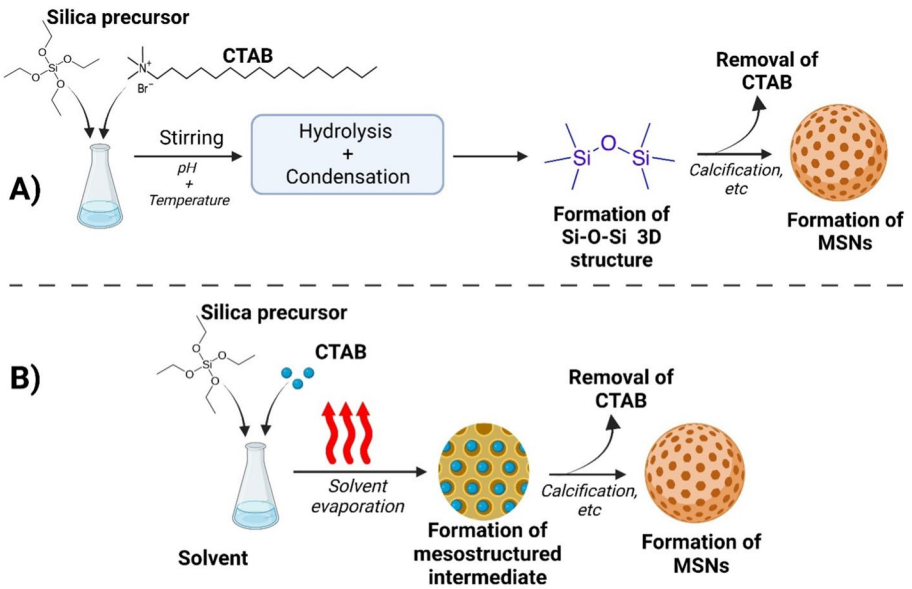

Fig. 1 MSN synthesis via **a** sol–gel method and **b** Evaporationinduced self-assembly

offers a templated guidance to mold the nanoscale architecture of the MSNs (Malgras et al. 2019) (Fig. 2).

Synthesis of MSNs by sol–gel synthesis

The sol–gel method, a modified variant of the Stober synthesis process, is a versatile and arguably the most favored method for the synthesis of MSNs (Vazquez et al. 2017). This method involves the use of a silica precursor, namely, tetraethyl orthosilicate (TEOS) or tetramethyl orthosilicate (TMOS), and a pore-generating template, such as cetyltrimethylammonium bromide (CTAB), to create a sol–gel reaction that produces MSNs (Frickenstein et al. 2021) (Fig. 1). To facilitate the loading and adsorption of the drug or protein moieties, organosilane coupling agents such as (3-aminopropyl) triethoxysilane (APTES) are also added during synthesis (Wang et al. 2016). The sol–gel synthesis process entails two steps, namely, hydrolysis and condensation (Vazquez et al. 2017). A change in alkaline or acidic pH, facilitated by the addition of a catalyst, can be used to stimulate the course of hydrolysis which results in the formation of colloidal elements and silanol groups. The condensation step occurs progressively at a neutral pH which results in the establishment of a 3D structural network due to Si–O–Si (siloxane) cross-linking (Bharti et al. 2015). As template molecules such as CTAB display toxicity when used in vivo, it is vital to remove as much CTAB as possible after synthesis of the core MSN nanoconstruct (Carvalho et al. 2022). Methods such as ethanol washing, dialysis, and calcination are used for removal of surfactant CTAB molecules (Frickenstein et al. 2021; Urata et al. 2009). As the CTAB is removed, it leaves behind a porous, intricate network of silica characterized by the synchronous polymerization of silica particles over the MSN surface.

The sol–gel process offers several advantages, including high homogeneity and purity of the final product, as well as the ability to control the porosity and morphology of the MSNs by varying the synthesis parameters (Azadani et al. 2021). For example, the

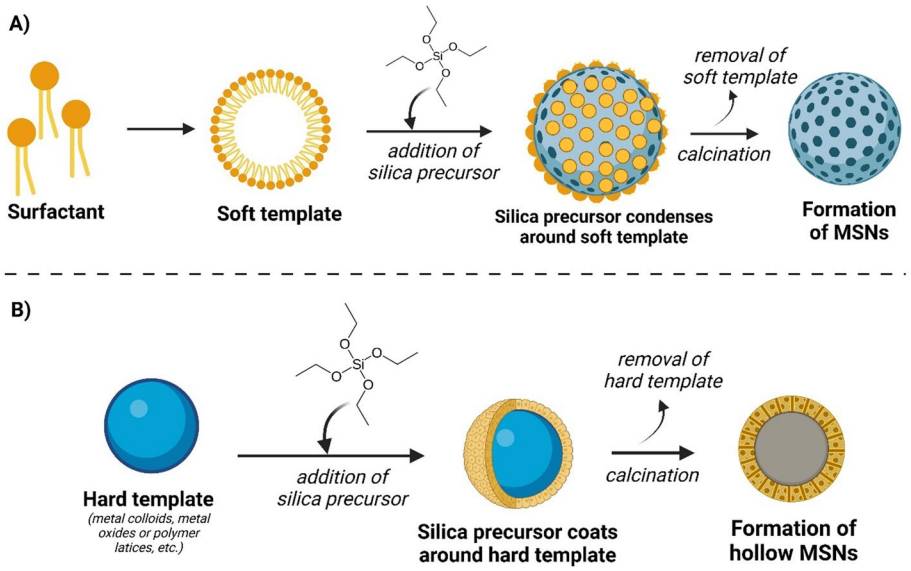

Fig. 2 MSN synthesis via **a** Soft template and **b** Hard template method

specific surface area and porosity of the MSNs can be affected by the addition of CTAB and the amount of water used in the reaction (Ganguly et al. 2010).

Synthesis of MSNs by evaporation induced self-assembly (EISA)

In this process, as the name suggests, evaporation induces a change in concentration of all the reactants present in mixture; consequently, generating a liquid–crystal template that mirrors silica surfactant molecules (Kimura 2016) (Fig. 1). This method of MSN synthesis involves dissolving a silica precursor, such as TEOS (tetraethyl orthosilicate), CTAB, in a solvent such as water or ethanol and introducing amphiphilic molecules (Narayan et al. 2018). These amphiphilic molecules serve as structure-directing agents and self-assemble at the solvent–air interface as the solvent evaporates (Yang et al. 2003). This concoction is then added to an aerosol generator to generate monodispersed droplets. Then, solvent evaporation occurs during the drying phase. This facilitates formation of micelles and concurrently forms MSNs (Kim et al. 2013). The self-assembly of micelles at the solvent–air interface helps create ordered pores within the silica structure (Gauthey 2014). By controlling the reaction conditions, such as the choice of solvent, concentrations, temperature, and template, it is possible to tailor the properties of the resulting MSNs for specific applications.

Soft and hard templating methods

Soft template synthesis is a technique for creating hollow MSNs with a large pore volume and high surface area, making them ideal for drug delivery (Lin et al. 2009). This method uses surfactants and soft materials such as microemulsions or micelles as templates to guide the formation of the MSNs (Wu and Lin 2013). Amphiphilic molecules with both hydrophilic and hydrophobic domains self-assemble into vesicular-type structures, which act as soft templates for the silica precursor to condense around (Parshad et al. 2020). After the silica has formed, the template can be removed by washing or calcinations (Frickenstein et al. 2021) (Fig. 2). While the soft templating process is simple and produces MSNs under mild conditions, it has some limitations. One challenge is the difficulty of completely removing the template while preserving the good dispersibility of the nanoparticles. In addition, the silica coating can be susceptible to deformation during the coating procedure (Jadhav et al. 2020).

Hard template synthesis is a technique for creating MSNs with a uniform size and structure (Li and Zhao 2013). This method uses rigid materials such as silica colloids, polymer lattices, or metal oxides as templates to guide the formation of the MSNs (Savic et al. 2018). The template is coated with a silica precursor, and after the silica has formed, the template is removed, leaving behind a mesoporous silica structure (Fig. 2).

Both soft and hard templating approaches have their advantages and disadvantages. Soft templating is generally easier and more versatile, as it can be used to create a wide range of nanostructures. However, it may be problematic to maintain control over the physiological parameters of the resulting MSNs. Hard templating offers more control over the MSN dimensions but is generally more complex and time-consuming (Kankala et al. 2022).

Physicochemical properties of MSNs

The term 'mesoporous' describes the porous nature of the silica nanomaterial. The 'honeycomb' such as structure of mesoporous silica nanoparticles permits it to be loaded with effective concentrations of drug molecules and further assists to carry these therapeutic molecules to their designated target locations, which consequently decreases any chance of unwanted early release of drug molecules in the body (Karimi et al. 2016). MSNs possess numerous physicochemical attributes that are advantageous over other nanoparticles which help cement their recognition as ideal drug delivery systems. The surface area and volume of pores of MSNs are fairly high; this allows them to accommodate high loads of drug molecules. This high volume of pores not only helps interactions between the drug and matrix but also encourages drug–drug interactions (Vallet-Regí et al. 2018). The MSN particle size can be tuned during synthesis at anywhere between 50 and 300 nm. This tunability of its particle size permits easy cellular uptake via clathrin and caveolin dependent uptake, phagocytosis, pinocytosis, and endocytosis while significantly lessening cellular cytotoxicity (Fig. 3) (Gan et al. 2012). MSNs have extremely stable Si–O bondings in their structure. This highly stable and firm assembly makes them resilient to high temperatures, variations in pH, environmentally induced mechanical stress, and degradation by hydrolysis reactions (Vallet-Regí et al. 2018). Tunable size of MSN pores (between 2 and 6 nm) permits precise drug payload for efficient activity (Yazdi et al. 2015). The superficial surface of the MSN particle and the cylinder-shaped pores offer two functional surfaces; this facilitates both external and internal functionalization of the MSN with different molecules to boost their efficiency in theranostic applications (Slowing et al. 2008).

Adding to the efficacy of these properties is the fact that every physicochemical aspect of the MSNs—ranging from particle size, shape, and porosity is tunable:

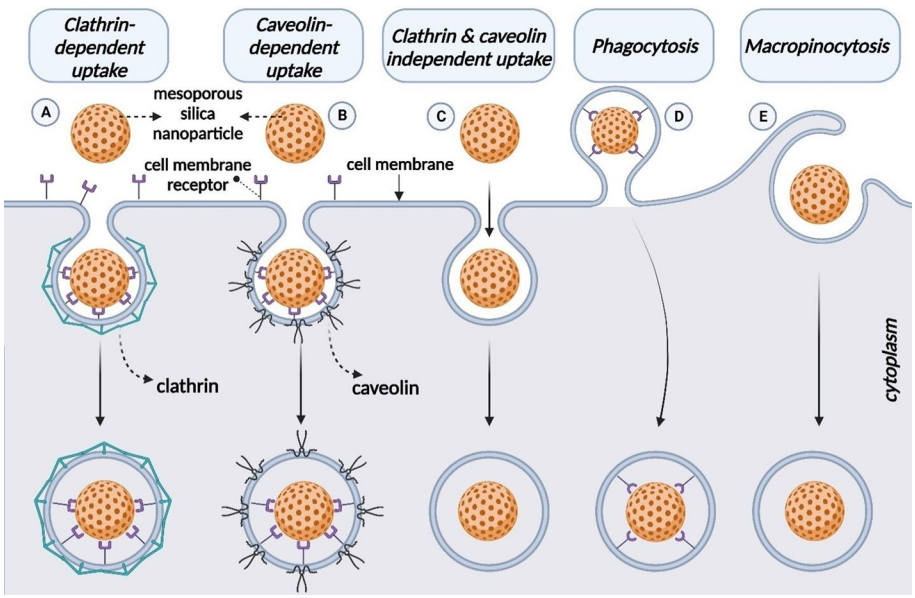

Fig. 3 Different methods of cellular uptake of MSNs—**a** Clathrin-dependent uptake, **b** Caveolin-dependent uptake, **c** Endocytosis, **d** Phagocytosis, **e** Macropinocytosis

i. Controlling particle size: Different organ systems and drug routes have specific uptake constraints, so MSNs must be created with an appropriate size to avoid being filtered out by the kidney, liver, or spleen. Additions such as inorganic salts and bases, alcohols and amines can be used to effectually regulate the size of the MSNs by quickening the hydrolysis and condensation steps of nanoparticle synthesis; subsequently, causing a reduction in the size of the nanoparticles (Kolimi et al. 2023). Previous experiments have demonstrated that compounds such as triethanolamine (TEA) when used along with bases such as sodium hydroxide (NaOH) and ammonium hydroxide (NH_4OH) led to the development of discrete nanoparticles and that increasing the ratio of TEA augmented the size of the resultant nanoparticles (Möller et al. 2007). TEA creates alkaline reaction conditions in the synthesis medium to help synthesize small size nanoparticles (~ 20 nm) by avoiding aggregation of silica monomers due to rapid hydrolysis(Kankala et al. 2022). Addition of surface polymers has also been investigated for regulating the size of MSNs. Studies involving the use of polyethylene glycol (PEG) confirmed that particle size was governed by the timing of addition of PEG–silane to TMOS—immediate addition of PEG–silane to TMOS resulted in 5 nm sized particles, whereas addition of PEG–silane with a substantial delay of about 50 min–1 h resulted in nanoparticles sized more than 13 nm (Ma et al. 2013). Increasing the amount of silica precursor has also been found to instigate secondary condensation reactions which resulted in formation of different sizes of nanoparticles rather than monodisperse ones (Kim et al. 2007; Zainal et al. 2013). Temperature also dictates the size of the nanoparticles as increasing the temperature results in larger size nanoparticles; which may be attributed to the intensification of reaction rates (Zainal et al. 2013). The pH of the synthesis medium also governs the particle size to a certain degree. The pH generally affects the rates of hydrolysis and condensation of the silica precursor and it has been found that a higher initial pH of the medium results in the formation of larger size MSNs (Alvarado Meza et al. 2023).

ii. Pore size control: The type of co-solvents added to the synthesis mixture regulates the pore nature, shape, and porosity of the MSN. Pores in the shape of the conventional honeycomb are formed when the co-solvent used is a strong base-like NaOH, whereas wormhole-like pores are created when co-solvents such as TEA are used (Frickenstein et al. 2021). The nature of these pores is a strong determinant of the release dynamics of the encapsulated therapeutic cargo. The concentration of the surfactant is also a critical parameter for defining the pore size as surfactants with larger chain lengths create larger pore sizes, while surfactants with shorter chain lengths create smaller pore sizes (Egger et al. 2015; Yano and Fukushima 2004). Experiments to observe pore size distinctions due to the effect of counter-ions on the templating compound have also been investigated. In one such study, it was observed that using large tosylate ions like cetyltrimethylammonium tosylate (CTATos) as counter-ions induced the growth of the pore radius and also transformed the morphology of the pores to a star-like shape from the preliminary wormlike one (Möller and Bein 2017). Temperature can also affect the pore size as it can influence the hydrolysis and condensation rates of the silica precursor. A higher temperature would accelerate these reaction rates and cause a rapid aggre-

gation and growth od silica particles resulting in a larger pore size of the MSNs. Contrastingly, a lower reaction temperature would significantly slow down the reaction rates, thus facilitating more time for the self-assembly of silica particles; consequently resulting in MSNs with a smaller pore size (Pal et al. 2020).

iii. Controlling the shape: The shape of the nanoparticle is a key aspect in defining the physiological performance of the nanoparticles as parameters such as intracellular uptake, distribution within the body, etc. are reliant on the shape. MSNs occur mostly in 3 shapes—spherical, short rod-shaped and long rod-shaped (Selvarajan et al. 2020). The in vivo effect of the nanoparticle's shape was conducted previously in a study, where it was found that in distinction to spherical and short rod-shaped nanoparticles; the long rod-shaped nanoparticles had more retention time in the body and less prospects of being excluded by the renal system. Similarly, due to their highly specific surface area, short rod-shaped nanoparticles exhibit a quicker biodegradability in the body as compared to spherical and long rod-shaped MSNs (Zhao et al. 2017). Rod shaped MSNs show faster uptake by specific cell lines (such as HeLa) and this type of uptake is also accredited to surface morphology as it has been observed that MSNs with rough external surfaces tend to be taken up faster by the cells of interest (Frickenstein et al. 2021). Therefore, designing an MSN's shape ideally suited to a particle target or cell line significantly refines the efficacy of the therapeutic outcome. Amending the concentration of parameters such as water, catalyst bases and surfactant allows construction of nanoparticles with different shapes. It was observed in previous studies that manipulating the concentrations of surfactant CTAB, silica precursor and the base catalyst can be used to attain different shapes of MSNs, such as spheres, rods, etc. (Cai et al. 2001).

By carefully titrating the synthesis temperature, the use of a template(Han et al. 2013), and varying the concentrations of TEOS, base catalyst (say, sodium or ammonium hydroxide), surfactant (say, CTAB) (Cai et al. 2001), co-surfactants (say, sodium dodecylbenzenesulfonate) (Hao et al. 2014), co-solvents (say, heptane) (Huang et al. 2010; Pang et al. 2005), co-polymers (say, Pluronic) (Cui et al. 2006), and water; the shape, size, porosity, internal morphology, and shell architecture can be tuned. In turn, the possible shapes achievable are limitless; the more common non-spherical ones include rods (Huang et al. 2010; Pang et al. 2005) of all aspect ratios, ellipsoids (Hao et al. 2014), films, platelets (Björk et al. 2013), sheets, and cubes (Narayan et al. 2018). Often changes in cellular uptake and cell function that accompany these transformations in shape and structure are exploited for enhanced biological activity (Huang et al. 2010).

Functionalization of MSNs

The functionalization of MSNs serves as a vital determinant for the effective and controlled distribution of pharmaceuticals. Functionalization of MSNs is the most crucial aspect of cancer theranostics, because it facilitates the presentation of functional components into the inner space or surface of MSNs as imaging or gate keeping moieties for the engineering of "smart" nanomedicine (Chen et al. 2020). A multi-functionalized MSN conjugate can be used to effectively accomplish a combination of both targeting and biomolecule delivery mechanisms (Fig. 4). For example, an MSN can be

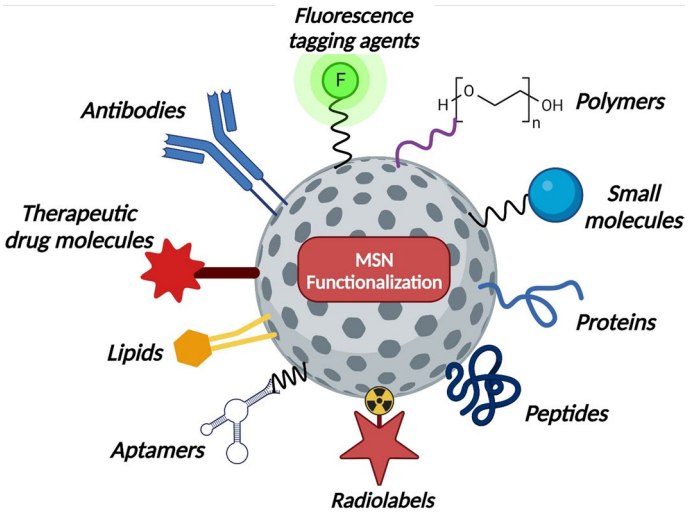

Fig. 4 Examples of different moieties that can be functionalized onto MSNs for effective cancer theranostics

functionalized with various combinations—PEG for increasing the stability of the nanoconstruct, a fluorescence tagging agent, protein- or antibody ligands for targeting, a therapeutic drug molecule, a functional group for the surface and groups for altering the surface charge (Nam et al. 2018).

It is also recognized that surface functionalization of the MSN is extremely crucial to enhance its efficiency in vivo while reducing toxicity. Deprived of any functionalization, an uncoated MSN particle possesses a negative charge due to the presence of silanol groups. This negative charge has undesirable consequences, such as hemolysis, initiation of unsolicited immune signals, impedance of lymphocyte activity, and increased in vivo protein opsonization (Frickenstein et al. 2021). A surface modification can be done to substitute the negative charge with a neutral one to overcome these detrimental effects. For example, strategies, such as coating the MSNs with cationic liposomes, can be able to induce a net neutral charge over the surface while consequently diminishing the toxic effects of the MSNs (Pavan et al. 2019). Similarly, naturally occurring molecules such as chitosan and hyaluronic acid can be used as surface modifying agents for biomedical applications, such as healing, reconstruction of skin tissues and even in cancer treatment while significantly reducing in vivo toxicity (Salis et al. 2016).

Applications of MSNs in cancer theranostics

Over recent years, along with cancer therapies, MSNs have been employed for therapies against various other diseases as well (Table 1). Theranostics is a fast-emerging field that combines therapy and diagnostics. Cancer theranostics holds promise in detecting the disease early, obtaining precise cellular images, administering treatment accurately at the appropriate time and dosage, and monitoring the effectiveness of the treatment in real time (Chen and Wong 2014). In this context, MSNs have emerged as a versatile and compelling choice due to their exceptional tunability, biocompatibility, and multifunctional capabilities (Karimi et al. 2016). As discussed previously, the process of functionalization adds a whole new dimension to their potential by giving these tiny particles a

Table 1 Examples of MSNs employed for the treatment of cancer and other diseases

Therapy for	MSN Formulation	Outcome of study	References
Breast cancer	MSNs functionalized with carbon dots, coated with chitosan and targeted by an anti-MUC1 aptamer	Nanoparticles demonstrated potent and selective anticancer activity, and potential for targeted cancer therapy and fluorescence imaging	Kajani et al. (2023)
Antibacterial	MSNs loaded with curcumin	Permissible hemolytic and antibacterial activity against various bacterial strains	Krishnan et al. (2023)
Antibacterial	MSNs loaded with levofloxacin	Development of a levofloxacin-based nanoplatform holding promise for applications against resistant bacterial infections	Haroon et al. (2022)
Amyotrophic Lateral Sclerosis (ALS)	MSNs loaded with therapeutic cocktail of Leptin and Pioglitazone	Treatment TDP-43A315T mice (an ALS animal model) with a drug cocktail (leptin/pioglitazone) delivered via MSNs slowed disease progression and improved motor performance	Díaz-García et al. (2022)
Alzheimer's disease	Curcumin-loaded MSNs dispersed in thermoresponsive hydrogel	High permeation of curcumin through the porcine nasal mucosa. In a streptozotocin-induced Alzheimer's model in mice, they also reversed the cognitive deficit,	Ribeiro et al. (2022)
Myocardial infarction (MI)	MSN-conjugated CD11b antibody, loaded with Notoginsenoside R1 (NGR1)	demonstrated that NGR1 can protect cardiomyocytes from oxidative stress and apoptosis, promote angiogenesis and M2 macrophage polarization, and modulate inflammatory responses and chemokines in MI mice. They also revealed that NGR1 can activate AKT, MAPK and Hippo signaling pathways in vitro and in vivo, and that these pathways are involved in the cardioprotective mechanisms of NGR1	Li et al. (2022)
Melanoma (skin cancer)	MSNs were functionalized with a histidine-tagged targeting peptide (B3int), and loaded with an anticancer drug (cisplatin (CP)) and a lysosomal destabilization mediator (chloroquine (CQ)). Cu^{2+} was used to seal the pores of the MSNs via chelation	nanoparticles release the loaded drugs (cisplatin and chloroquine) in response to the acidic pH of the lysosomes/endosomes, where the Cu2 + ions dissociate from the peptide and act as a catalyst for generating ROS that damage tumor cells. Exhibition of potent anticancer activity in vitro and in vivo, with significant reduction of tumor volume	Zhang et al. (2022c)

Table 1 (continued)

Therapy for	MSN Formulation	Outcome of study	References
Bladder cancer	miR-34a/siPD-L1 was loaded on MSNs modified with poly (lactic–co-glycolic acid), polyethylene glycol and c(RGDfK) peptide	nanoparticles could deliver miR-34a and siPD-L1 to T24 cells while protecting from serum degradation, and modulate the expression of PD-L1, a key immune checkpoint molecule, to improve the anti-tumor response	Shahidi et al. (2022)
Pancreatic ductal adenocarcinoma	MSNs loaded with an sonic hedgehog pathway inhibitor, cyclopamine (CyP), and chemotherapeutic drugs Gemcitabine and Cisplatin	Inhibition of sonic hedgehog pathway, stromal modulation facilitation increased uptake and accumulation of nanoparticles at tumor site in mice	Tarannum et al. (2022)
Hepatitis C	Velpatasvir (VLP) loaded MSNs	nanosystem demonstrated improved solubility and dissolution, absorption, and blood concentration of VLP, as well as its accumulation in the liver, the target site for hepatitis C virus infection, in comparison with pure VLP, both in vitro and in vivo	Mehmood et al. (2020)

toolbox of capabilities that can be used for a range of biomedical applications. This has allowed researchers to develop highly efficient theranostic platforms for cancer treatment by functionalizing therapeutic molecules as well as image-enhancing agents onto MSNs.

A recent example outlined the synthesis of MSNs that combine the properties of magnetite nanoparticles, mesoporous silica, chitosan, and Abemaciclib, a medication for the treatment of advanced or metastatic breast cancers (El-Shahawy et al. 2022). At its core, this nanoplatform leveraged the distinctive properties of the MSNs to act as carriers for Abemaciclib, which is a discerning inhibitor of cyclin-dependent kinases 4 and 6. The MSNs demonstrated diagnostic prowess by incorporating magnetite and silica elements. These elements conferred magnetic resonance imaging (MRI) capabilities to the nanocomposites, thus enabling non-invasive visualization of their distribution in vivo. The chitosan added another degree of biocompatibility and stability to the overall nanoformulation. The integration of all these functionalities within a single nanoparticle system is a prime example of theranostics. MSNs can also be conjugated with other nanoparticles as well to enhance the theranostic efficacy of the overall nanoformulation. In this context, a study investigated the theranostic efficacy of mesoporous silica-coated SPIONs (superparamagnetic iron oxide nanoparticles) loaded with curcumin and silymarin, offering a multifaceted strategy for breast cancer theranostics (Sadegha et al. 2022). The mesoporous silica shell, enveloping the SPION core, provides a versatile platform for drug encapsulation and controlled release. Meanwhile, the SPION core imparts magnetic properties, enabling non-invasive imaging through MRI. Overall, the results indicated great efficiency of the nanoparticles in demonstrating both therapeutic and diagnostic prowess in the treatment of breast cancer. Apart from drugs, MSNs

exhibit versatility in transporting a spectrum of therapeutic molecules, thus amplifying treatment efficacy by overcoming conventional drawbacks, such as occurrence of drug resistance, etc. (Bharti et al. 2015). This versatility can be underscored by a recent study that explores the potential of MSNs to co-deliver drugs and siRNA within a polyethylenimine framework, encapsulated by fluorescent core–shell silica nanoparticles (Zhang et al. 2022b). In, this study, Zhang et al. used the nanopores of silica to load the chemotherapeutic drug doxorubicin and electrostatic interaction augmented the assembly of the nanostructure with cross-linked polyethylenimine. This facilitated the potential to bind with siRNA that harnessed a negative charge. On the therapeutic front, the nanoparticles were engineered to carry both drug molecules and siRNA. This co-delivery strategy was designed to enhance the potency of therapeutic intervention, since this approach holds potential to modulate cellular processes at various levels, leading to synergistic therapeutic effects that may not be achievable by individual interventions alone. Moreover, the nanoparticles featured a fluorescent core–shell silica component, endowing them with diagnostic properties. The fluorescent core–shell design allows real-time visualization of the nanoparticles' distribution and cellular uptake, offering insights into the efficacy and specificity of the co-delivery system.

In addition, MSNs can be functionalized with target specific ligands, stimuli-sensitive gate keeping molecules for an 'on-demand' response and even radionuclides to divulge a diverse spectrum of capabilities that go beyond conventional approaches of MSN-based cancer-theranostics (Baeza and Vallet-Regí 2020; Thi et al. 2019). These advances highlight the stimuli-sensitive tunability of MSNs which activate their theranostic potential in response to specific cues, and non-conventional functionalization capabilities which ultimately enhance precision and efficacy of cancer theranostics.

Light-based theranostics

Light has widely been used as a stimulus for MSNs in various ways, such as controlled drug release, photodynamic therapy and photothermal therapy (Moodley and Singh 2021). These MSNs can be used to release drugs and simultaneously get activated by light to generate heat upon irradiation to kill cancer cells (Wang et al. 2020) (Fig. 5). Recent advances in making MSNs which are more stimuli-sensitive and can activate theranostic capabilities; make them promising candidates for personalized medicine.

Previous studies have demonstrated MSNs to be quite capable in light-responsive cancer theranostics. A prime example can be observed from a study by Lv et al. (2015), wherein the researchers devised an innovative approach to enhance antitumor efficacy by amalgamating photodynamic therapy (PDT), photothermal therapy (PTT), and chemotherapy. This was achieved by fabricating unique multifunctional mesoporous capsules, utilizing GdOF:Ln (Gadolinium oxyfluoride and Lanthanide ions) as an up-conversion luminescence core, and a layer of mesoporous silica as the outer shell. These capsules enabled a synergistic therapeutic strategy where the amplified red emission originating from co-doped Yb/Er/Mn in GdOF proficiently transferred energy to the PDT agent–zinc (II) phthalocyanine (ZnPc), consequently producing singlet oxygen. Moreover, external carbon dots induced controlled thermal effects under laser irradiation, preventing ZnPc leakage and enhancing doxorubicin (DOX) release, thereby improving chemotherapy. The developed system established

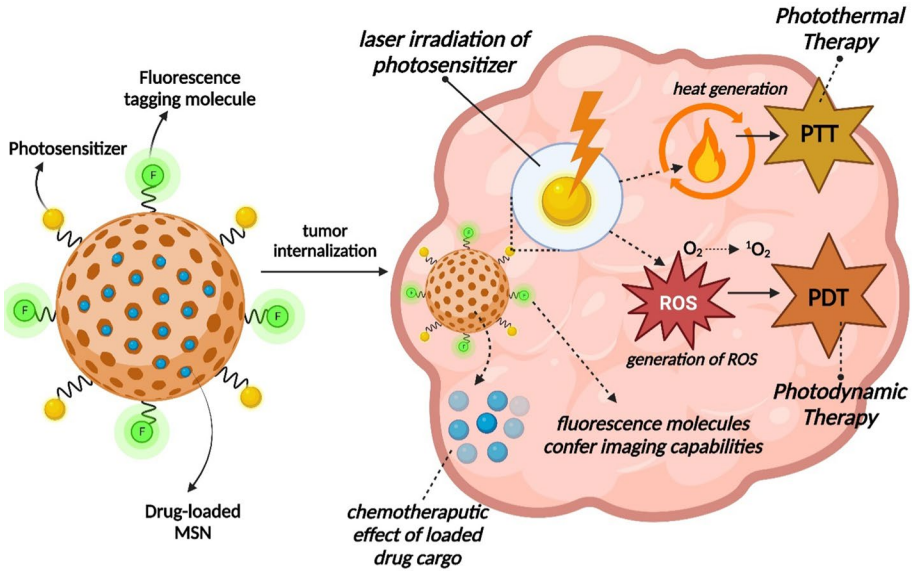

Fig. 5 Graphical representation of a drug-loaded theranostic MSN platform designed to have light-based triggers for therapeutic responses

substantial efficacy in inhibiting tumor growth, as observed in both in vitro and in vivo studies. Rare earth ion doping was reported to provide multimodal imaging capabilities encompassing up-conversion luminescence, MRI, and computed tomography (CT), thereby facilitating precise imaging-guided theranostic interventions (Lv et al. 2015).

Over the past decade, rare-earth compounds have played a vital role in biological applications attributing to unique optical assets, such as strong photoluminescence emissions, long luminescence decay lifetimes, and high sensitivity, making them ideal for use as biosensors and molecular probes. Their low cytotoxicity also makes them safe for use in biological systems (Bazhukova et al. 2021). A recent breakthrough study ingeniously combined the prowess of these compounds within a theranostic nanocomposite, comprised of MSNs with magnetite (Fe_3O_4) and gadolinium oxide (Gd_2O_3) components (Oliveira and de Sousa 2023). The doping of MSNs with rare-earth compounds allowed for exhibition of both ferrimagnetism and photoluminescence as a theranostic strategy for cancer therapy. The nanostructure demonstrated high efficiency as a theranostics due to enhanced imaging as well as the ability to cause magneto-hyperthermia to treat cancer cells. The synergistic combination of rare-earth compounds with MSNs exemplifies the ingenuity of contemporary theranostic strategies, underscoring the significance of precise nanostructure design. However, as the field advances, new strategies are continually integrated to address unique challenges.

Synthesis of hybrid nanomaterials confers unique attributes of both materials in a single nanostructure (Sailor and Park 2012), enabling not only the transport of therapeutic payloads but also the elucidation of tumor behavior through advanced imaging modalities (Johnson et al. 2021). Based on this concept, a recent study reported the precise layering of a mesoporous silica layer over an MXene surface for the

theranostic treatment of hepatocellular carcinoma (HCC) (Li et al. 2018b). The surface mesoporous silica layering on MXene unified numerous distinctive features for enhancing the biomedical operations of MXenes by promoting distinct mesopores for drug delivery, improved hydrophilicity, dispersity, and plentiful surface alterations for target-specific engineering. The nanocomposite demonstrated an impressive ability to specifically target HCC tumor sites, utilizing the RGD peptide for active targeting. Moreover, the integration of mesopores within the MXene enabled synergistic cancer treatment effects. The mesopores facilitated the chemotherapy, ensuring effective drug delivery, while the inherent photothermal properties of titanium carbide (Ti_3C_2) doping and MXene contributed to photothermal hyperthermia—a treatment modality that utilizes light stimulus to induce localized heating and destroy cancer cells. This combination of therapeutic strategies resulted in complete tumor eradication, effectively mitigating the chances of recurrence. Combination theranostics in cancer research has witnessed pivotal strides (Sharmiladevi et al. 2021). Studies have showcased the potential of drug-loaded MSNs to concurrently house chemotherapeutic agents and photosensitizers, offering a potent alliance for light-based cancer theranostics. Studies demonstrating combination theranostics via chemotherapy and PDT have been recorded, where drug-loaded MSNs containing cisplatin prodrug (Zhang et al. 2016) and doxorubicin (Sun et al. 2018) have been conjugated with Chlorin e6 (Ce6) photosensitizer for enhanced efficiency in cancer theranostics.

The unique ability of functionalized fullerenes to produce singlet oxygen ($^1O_2$) in water under visible light irradiation proposes its potential application to determine cytotoxic effects in various cancer cells, degrade organic pollutants and inactivate viruses (Lee et al. 2009; Otake et al. 2010). Fullerene derivatives are shown to be potent agents for oxidative water treatment and disinfection under visible light. However, the techniques of recovery and subsequent reuse of fullerene derivatives from aqueous solutions necessitate further improvement. In a study involving development of an effective visible light sensitizer with magnetic separation function, functionalized mesoporous silica was used to encapsulate Fe_3O_4 nanoparticles, as a magnetic host for immobilization of photoactive aminofullerene. The potential of the aminofullerene–magnetite composite as a visible light photocatalyst is based on: (1) high efficiency of visible light sensitized $^1O_2$ generation, (2) consecutive cycles of photosensitized singlet oxygenation and magnetic separation without significant loss of photochemical activity, and (3) rapid degradation of emerging organic pollutants and inactivation of MS-2 bacteriophage. The productivity comparison of SiO_2-gel and fumed SiO_2 (as alternative host materials for magnetite and fullerene) for $^1O_2$ production and viral inactivation suggested that ordered pore structure is critical to the surface loading of fullerene sensitizer on a magnetic host (Choi et al. 2014).

Ultrasound-based theranostics

Ultrasound has become a popular choice for stimulating cancer nanoparticle therapy due to its numerous benefits over light-based methods. It can penetrate deeper into tissues, allowing for effective treatment of hard-to-reach tumors, and offers greater precision and control for targeted therapy with minimal damage to healthy tissues (Tharkar et al. 2019). Ultrasound is also non-ionizing, non-phototoxic, and can trigger various

therapeutic responses, making it a versatile and effective stimulus in cancer nanoparticle therapy (Bailey et al. 2003; Davies et al. 2011). Addition of ultrasound is a great way to enhance efficiency of cancer theranostics (Fig. 6).

An example of such a theranostic approach is a biocompatible mesoporous organosilica-based structure loaded with an organic sonosensitizer, such as protoporphyrin (PpIX), and chelated with paramagnetic transitional metal manganese (Mn) ions, forming MnPpIX (Huang et al. 2017). After accumulating effectively within tumor tissues via the enhanced permeability and retention (EPR) effect, a significantly heightened MRI contrast was provided by the paramagnetic aspect of the chelated MnPpIX—facilitating precise imaging and localization of the nanoparticles within the tumor tissue. Upon external ultrasound stimulus, the encapsulated MnPpIX within the nanoparticle generated toxic singlet oxygen; a highly reactive molecule thus inducing cancer cell death via sonodynamic therapy (SDT).This integration of sonosensitizers and paramagnetic agents underscores the transformative potential of ultrasound-responsive theranostics, offering a glimpse into the rapidly evolving field. However, as the therapeutic landscape advances, further novel refinements are imperative to fully realize the clinical promise of ultrasound-based interventions.

In a very recent study, a sophisticated approach to cancer theranostics was made by the development of an anoplatform activated by ultrasound for synergistic SDT and nitric oxide (NO) treatment (Wang et al. 2023a). This remarkable fusion not only capitalizes on the inherent power of sound waves but also leverages the therapeutic potential of NO, resulting in an integrated strategy that surpasses individual modalities. By harnessing the non-invasive nature and deep tissue penetration capabilities of ultrasound-triggered SDT along with NO, this approach effectively addressed the limitations of SDT in solid tumors caused by intrinsic hypoxia (Um et al. 2021). The nanoplatform developed by Wang et al., termed MH-SNO@RB, ingeniously integrated a sonosensitizer

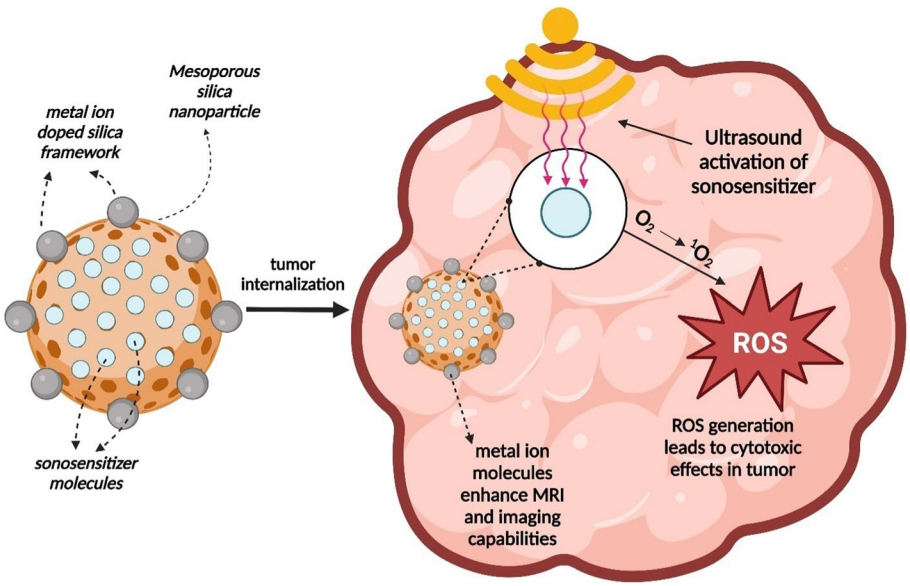

Fig. 6 Graphical representation of sonosensitizer-incorporated theranostic MSN platform based on ultrasound as a trigger for cancer therapy

(Rose Bengal, RB) and an NO donor (SNO) within manganese-doped onto the hollow MSNs (MH). The MH-SNO@RB nanoplatform took advantage of the tumor microenvironment, which is characterized by acidity and reducing conditions (Trédan et al. 2007). This environment accelerated the manganese (Mn) ion release from the MH, transforming the nanoplatform into a contrast agent for MRI. Upon ultrasound stimulation, the nanoplatform released RB and SNO, augmenting reactive oxygen species (ROS) generation. These two entities, simultaneously triggered by ultrasound, interacted to produce highly reactive peroxynitrite (ONOO–) ions which amplified the therapeutic impact by inducing a potent cytotoxic effect within the tumor. The nanoplatform also exhibited good hemocompatibility and histocompatibility, further validating its potential as a safe and efficient tool for oncological theranostics. The ingenious combination of sonodynamic and nitric oxide therapies within an ultrasound-responsive nanoplatform exemplifies the significant strides underpinning contemporary cancer theranostics.

The evolving nature of scientific inquiry continually demands fresh perspectives and innovative adaptations. A subsequent example unveils a novel avenue by introducing biodegradable gas-stabilizing nanoparticles, a novel addition that aims to revolutionize ultrasound-based theranostic interventions. Herein, biodegradable gas-stabilizing nanoparticles (GSNs) were synthesized for enhanced cancer theranostics using focused ultrasound (Sabuncu et al. 2023). This novel approach hails as a paradigm shift in enhancing theranostics via focused ultrasound. These GSNs were created by coating different protein solutions onto hydrophobically modified MSNs. These hydrophobic GSNs were reported to possess the unique ability of surface stabilization of small gas pockets, making them effective contrast and cavitation moieties for ultrasound-based theranostics. The biodegradable GSNs rapidly degraded in simulated body fluid (SBF) and in vivo over several weeks, making them suitable for clinical translation. The biodegradable GSNs facilitated tumor ablation at lower ultrasound intensities, minimizing the side effects associated with high-intensity ultrasound treatments. This demonstrated the potential of GSNs to enhance the efficacy of ultrasound-based therapies while ensuring patient safety. Tumors treated with these GSNs and ultrasound also exhibited specific enrichment of circulating tumor DNA, presenting enhanced liquid biopsies to comprehend tumor heterogeneity and therapeutic response, thus opening new avenues for outlook and research into advanced cancer diagnosis and monitoring.

pH-responsive theranostics

pH-responsive MSNs have cemented their status as promising platforms for cancer theranostics, owing to their capability to modulate their physicochemical properties in response to the dynamic pH gradients characteristic of tumor microenvironments (Yang et al. 2014). This offers a tailored approach for controlled drug delivery, diagnostic imaging, and therapeutic interventions by capitalizing on the pH-sensitive release of encapsulated payloads (He et al. 2011a). The integration of pH-responsive MSNs holds great promise in optimizing cancer theranostics, facilitating a multi-faceted approach that addresses the challenges of selective targeting and effective treatment while minimizing off-target effects (Lee et al. 2011) (Fig. 7).

To test the pH-responsive dynamics of MSNs, a novel theranostic nanostructure was devised, MSN–CurNQ, which was composed of MSNs encumbered with

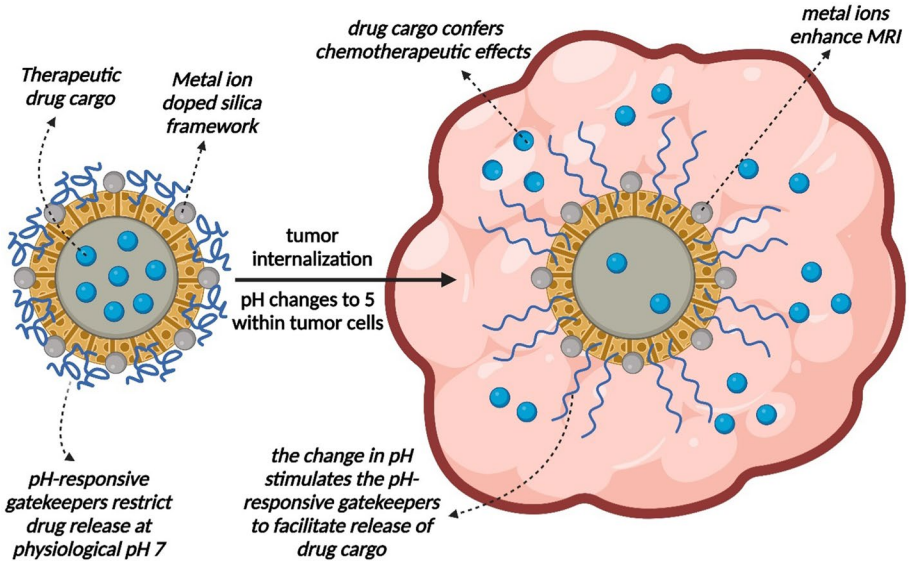

Fig. 7 Graphical representation of drug-loaded theranostic MSN platform designed to have pH-sensitivity as a trigger for drug release to elicit a chemotherapeutic effect

a curcumin–naphthoquinone conjugate (CurNQ) (Freidus et al. 2021). A principal outcome of this study was that the MSN–CurNQ nanoparticles exhibited pH-responsivity. After 96 h, 31.5% of CurNQ was released from the MSNs at pH 7.4, in contrast to a 57% release at pH 6.8. This pH-responsivity is important, because it allows for targeted drug delivery to the acidic tumor microenvironment. In addition, the MSN–CurNQ nanoparticles also exhibited inherent luminescence, accompanied by a substantial ratio of background to target signal indicating its potential for use in molecular imaging. On the chemotherapeutic front, the nanoparticles exhibited a preferential toxicity towards cancer cells, significantly diminishing viability in multiple cancer cell lines while having a negligible impact on a healthy fibroblast cell lines. The transposition of this pH-responsive behavior offers a unique glimpse into the precision with which nanotechnology can be harnessed to navigate the intricate landscape of cancer therapy and diagnosis. The development of pH-responsive theranostic platforms, exemplified by the synergy between MSN–CurNQ, underscores the precision engineering that fuels the evolution of cancer theranostics. However, the dynamic nature of biological environments necessitates a broader outlook.

Advanced theranostic strategies that underscore the importance of co-engineering have also been investigated in a bid to unlock new horizons in pH-responsive interventions. In a recent study, researchers developed an innovative pH-responsive theranostic nanoplatform that incorporates ferrite and ceria conjugated MSNs (Fe/Ce-MSNs) (Dou et al. 2022). These nanoparticles exhibited enhanced scavenging of reactive oxygen species (ROS), owing to increased superoxide dismutase mimetic activity from elevated Ce^{3+} content and sustained catalase mimetic action facilitated by the inclusion of ferrite ions. The biodegradation of Fe/Ce-MSN nanoparticles was accelerated within the mildly acidic pH microenvironment of inflammation, leading to the release of Fe/Ce ions that enhanced T2-weighted MRI at the site of

inflammation. Fe/Ce-MSNs, when PEGylated, were observed to efficiently alleviate inflammation, oxidative stress, and apoptosis in macrophages by scavenging intracellular ROS. The authors also reported substantial anti-inflammatory effects, demonstrated by their ability to inhibit the expression of pro-inflammatory cytokines induced by lipopolysaccharide (LPS), and to facilitate the polarization of macrophages from a pro-inflammatory M1 state to an anti-inflammatory M2 state.

A recent milestone in pH-responsive theranostics emerges from the fusion of magnetic MSNs (SPION–MSNs) with a pH-triggered gold gatekeeper (Al-Mosawi et al. 2023). The SPION–MSNs were designed to incorporate a pH-responsive gold gatekeeper, restricting the release of a thymidylate synthase inhibitor—5-fluorouracil (5-FU) under physiological conditions. Notably, 5-FU release from the nanoparticles exhibited a pH-dependent pattern, featuring a preliminary quick release within 6 h, trailed by a sustained release over 96 h at pH 5.4. Cumulative release at neutral pH was minimal, indicating the pH-responsive nature of the drug release. Furthermore, using aptamer-based targeting, the nanoparticles exhibited enhanced cytotoxicity and anti-cancer activity against EpCAM-positive HT-29 cells, validating the effectiveness of the targeting ligand. These findings highlight the possibilities to develop 'smart' MSNs for controlled and on-demand dynamics of cancer theranostics. The strategic integration of magnetic attributes and pH-responsive mechanisms encapsulated within SPION–MSNs exemplifies the dynamic synergy of various facets of functionalization to maximize the efficacy of cancer theranostics. The prowess of hybrid systems yet again bring together different elements to achieve advanced pH-responsive functionality with potential implications for theranostic applications.

In a recent study, a pH-sensitive hybrid system based on Eu^{3+}/Gd^{3+} (europium and gadolinium, respectively) co-doped hydroxyapatite and MSNs was developed for potential theranostic applications (Rodrigues Dos Apostolos et al. 2023). The synthesis process successfully incorporated europium and gadolinium ions into the MSN matrix, and the polymerization with pH-sensitive polymer P(MAA) proved effective in mediating a pH-sensitive response. The photoluminescence results exhibited the luminescent potential of europium-doped systems. Moreover, the co-doping of nanoparticles with gadolinium led to enhanced luminescence, attributed to energy transfer from Gd^{3+} to Eu^{3+}. The authors reported promising outcomes for diagnostic imaging applications using photoluminescence and vibrational sample magnetometry (VSM) to detect magnetic moment, thus confirming the presence of rare earth elements and demonstrating luminescent and magnetic properties of the synthesized materials. The system's capability for pH-responsive drug release was established by investigating the release dynamics of doxorubicin. Controlled drug release from nanoparticles was detected at pH 5 and no significant release at pH 7, which is relevant for drug delivery systems targeting cancer treatment. These findings collectively highlight the potential of pH-sensitive hybrid MSNs for effective cancer theranostics, where the pH-responsiveness of the system offers controlled drug release within tumor microenvironments, while the luminescent and magnetic properties enable accurate imaging and tracking.

Tumor-specific biological marker responsiveness

The recognition of specific biological markers holds profound significance in the realm of cancer theranostics using MSNs (Zhu et al. 2017). These biomarkers are distinct biomolecules expressed on cancer cells, provide a key avenue for tailoring MSN-based therapies (George et al. 2019). By leveraging the inherent ability of MSNs to selectively bind to these markers using functionalized ligands, a targeted approach emerges, enabling precise drug delivery and accurate imaging (Turan et al. 2019) (Fig. 8).

Early research showcasing the theranostic prowess of MSNs in this aspect could be witnessed from a study targeting matrix metalloprotease (MMP), wherein the authors developed a smart MSN nanoplatform coated with stimuli-responsive polymers which released the encapsulated drug cargo upon interaction with MMP (Singh et al. 2011). Another study, later introduced a novel MMP-responsive theranostic nanoplatform, built upon MSNs designed for synergistic tumor imaging and targeted drug delivery (Hu et al. 2016). MMP-2 is an enzyme that degrades extracellular matrix proteins, allowing cancer cells to migrate and form metastases by breaking down the extracellular matrix (ECM) (Kleiner and Stetler-Stevenson 1999). In the work by Hu et al., MSNs served as efficient hydrophobic drug carriers, while surface-bound matrix metalloprotease-2 (MMP-2) triggered the activation of fluorescence imaging peptides, thus acting as both diagnostic probes and enzymatically responsive nanovalves regulating pore access. Functionalization with cRGD peptides enhanced tumor targeting through receptor-mediated endocytosis. Without the presence of MMP-2, the proximity between fluorescent dye TAMRA and quencher Dabcyl resulted in fluorescence suppression. Nonetheless, when exposed to a tumor microenvironment rich in MMP-2, the MMP-2 sensitive peptide substrate underwent hydrolysis, which resulted in the restoration of fluorescence and the release of the drug, facilitating both imaging and therapeutic efficacy. This intelligent design capitalizing on biomarker recognition and enzyme-responsive stimuli,

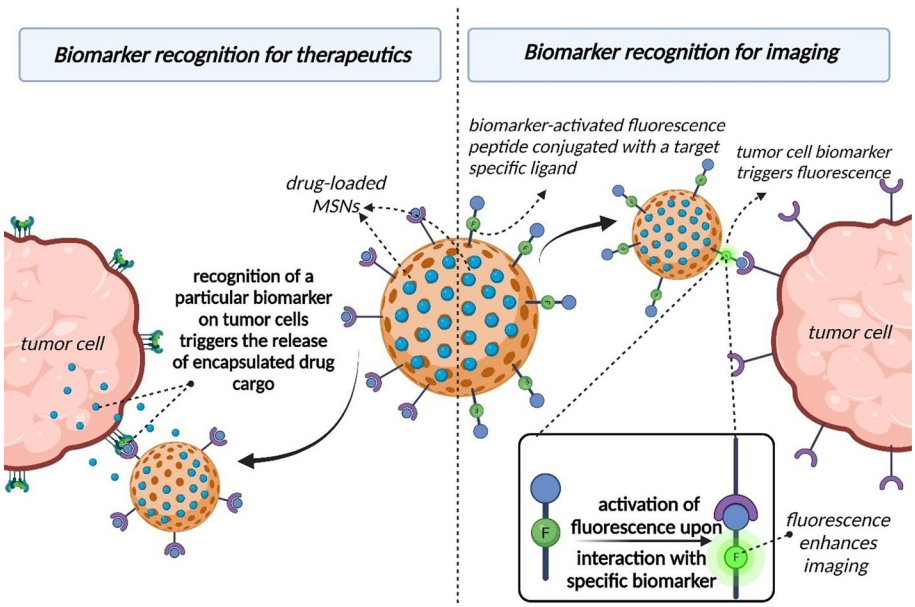

Fig. 8 Strategies to develop drug-loaded MSN platforms with specific biomarker recognition to trigger responses for therapeutic activity or enhancing imaging capabilities

offered a promising avenue for advanced MSN-based theranostic applications in cancer treatment.

Advancing the frontier of biomarker recognition-responsive theranostics, a novel magnetic drug delivery system emerged as a hallmark in the field. A sophisticated system involving magnetic drug delivery with an "OFF–ON" state via precise molecular recognition and conformational fluctuations was developed for explicit theranostics (Liu et al. 2020). The system, named IONP@MSN/DOX–DNA, integrated the merits of controlled drug release, tumor targeting, and magnetic guidance. The mesoporous structure of MSNs was gated using a DNA hairpin structure selective to miRNA-21, thus preventing premature drug leakage during circulation. miRNA-21 is a short non-coding RNA moiety for regulating gene expression and has been established to contribute to the oncological onset, progression, and metastasis (Mitchell et al. 2008). Its amplified expression in tumor tissues than healthy tissues makes it a great tumor biomarker for targeted interventions (Ulivi and Zoli 2014). Upon encountering the tumor microenvironment with over-expressed with miRNA-21, the DNA hairpin structure underwent conformational changes triggered by the presence of miRNA-21, releasing the encapsulated drug DOX. This intelligent "OFF–ON" switch mechanism allowed for tumor-specific drug delivery, abating side effects, and consequently boosting therapeutic effectiveness. The magnetic targeting facet of the nano-system enabled MRI-mediated precise localization of the tumor sites through concurrent whole-body diagnosis. Combined with its tumor cell stimulated therapeutic action, the nanoparticle synergistically improved the bioavailability of the medication at the tumor site, resulting in a potent antitumor effect in HepG-2 tumor-bearing mice and enhanced imaging capabilities for real-time diagnosis. Implications of these research studies lie in the engineering of further versatile and targeted drug carriers that address issues of drug leakage, specificity, and therapeutic effectiveness. The strategic integration of magnetic guidance and molecular responsiveness serves as a testament to the evolving synergy between nanotechnology and biomolecular interactions. By harnessing the specificity of markers, such as miRNA and MMP-2, this approach opens avenues for tailored treatments based on molecular recognition and biomarker activation.

Carbon-dot-assisted theranostics

Carbon dots, a new and emerging class of fluorescent materials, have recently gained attention for their potential in cancer theranostics, mostly for imaging due to their exceptional optical and chemical properties, such as high photostability, tunable fluorescence, and low toxicity (Desmond et al. 2021). Certain carbon dots may also exhibit the capability to eradicate cancer cells and impede the progression and invasion of malignant tumors (Wang et al. 2023b). Importantly, carbon dots are extremely small in size (< 10 nm), enhancing rapid renal clearance in vivo (Truskewycz et al. 2022). However, when incorporated into nanoparticles, they can enhance the efficacy of cancer theranostics (Ornelas-Hernández et al. 2022) (Fig. 9).

Among early research in the evolving landscape of cancer theranostics, carbon dots have been incorporated into MSNs to provide a multifunctional platform for cancer theranostics (Kang et al. 2017).A pioneering advancement in this realm was presented by Kang et al., by designing carbon dots housed in mesoporous hollow organo-silica

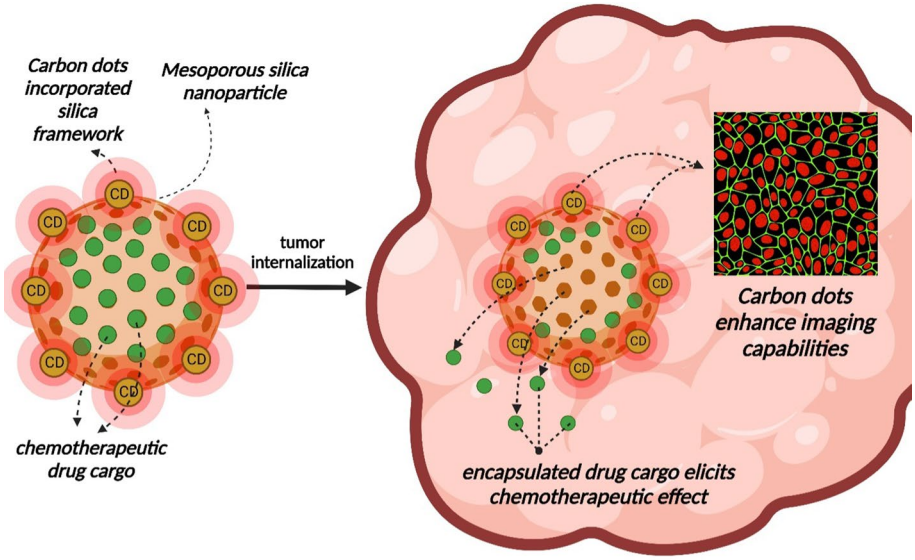

Fig. 9 Graphical representation of a drug-loaded theranostic MSN incorporated with carbon dots to enhance imaging capabilities

nanoparticles (C-hMOS), establishing a powerful nanocarrier platform for simultaneous anticancer drug delivery and optical imaging. An ingenious hollow architecture was achieved through the nanorod core template removal while concurrently imparting fluorescent properties to the organo-silica network through controlled heat treatment. The hollow and mesoporous characteristics of MSNs facilitated the efficient encapsulation of doxorubicin (DOX), a potent anticancer drug, for controlled release over a span of 12 days. This strategy enabled highly effective internalization of DOX-loaded C-hMOS by cancer cells, inducing cellular apoptosis. Moreover, the C-hMOS exhibited exceptional potential for multi-color visualization in vitro and notably in vivo studies established strong and stable optical signals upon intra-tumoral injection of C-hMOS in murine models, showcasing both promising optical imaging capabilities and excellent biocompatibility. The simultaneous harnessing of carbon dots and mesoporous silica technology in C-hMOS was a paradigm-shifting study underscoring the rationale for exploiting these nanoparticles as a versatile platform, bridging the gap between drug delivery and non-invasive imaging techniques in cancer treatment.

In a recent research article, an innovative approach was presented, bordering at the intersection of MSNs, multi-nuclear gold/carbon quantum dots, and pH-responsive drug-loaded nanosystems, thereby forging a 'smart' theranostic frontier (Akbarian et al. 2022). With MSNs as the versatile scaffold, a multifunctional assembly was meticulously designed for pH-responsive delivery of the anti-cancer drug doxorubicin. Three distinct variants of MSNs were synthesized, each serving a unique purpose. The conventional MSNs, functionalized with propylamine groups, acted as the controlled-size base. Accompanying this was the advent of two fluorescence-type mesoporous silica variations, doped with gold/carbon quantum dot nanoparticles. This strategic doping engendered a transfer of the distinct optical properties of gold/

carbon quantum dots onto the mesoporous matrix, resulting in a remarkable fluorescence effect. The UV–Vis spectroscopy quantified the Schiff-base linkage conjugated doxorubicin, and subsequent release profiles confirmed the pH-responsive nature, further validated across physiological pH ranges. The nanoparticles exhibited effective drug release and consequential cytotoxicity against MCF-7 cancer cells. By amalgamating MSNs, multi-nuclear gold/carbon quantum dots particles, and pH-triggered nanoconstructs, this work unveiled a promising avenue in the pursuit of smart cancer treatment modalities.

To enhance the therapeutic efficacy of MSNs while minimizing off-target effects, functionalization of ligands for a targeted approach has been a prime choice for therapeutic interventions. To highlight this, a recent publication demonstrated the theranostic capabilities of monodisperse and spherical MSNs with hydrothermally synthesized anticancer carbon dots, all achieved through a sustainable and eco-friendly approach (Kajani et al. 2023). Further enhancement of the nanostructure achieved by functionalizing MSNs–CDs with chitosan and coupling them with an anti-MUC1 aptamer using glutaraldehyde as a cross-linker for tumor-specific targeting. The nanoparticles exhibited impressive anticancer efficacy against MCF-7 and MDA-MB-231 tumor cells, with a noteworthy cell mortality of up to 71.8%, after a mere 48-h exposure while being comparatively less toxic to human cell lines. Moreover, the prowess of the developed nanoplatform extended to fluorescence imaging, demonstrated through compelling results in imaging MCF-7 cancer cells upon exposure to MSNs–CDs. The synergistic combination of carbon dot incorporated MSNs along with targeted aptamers are thus a promising strategy for precision oncology.

As we have discussed works regarding pH-responsive MSNs as well as target-specific MSNs, it is noteworthy that a synergistic combination of both these parameters in a single nanosystem can lead to the development of an enhanced theranostic intervention, thus offering the 'best of both worlds'. This innovative and intricate landscape has been traversed in a recent study by Shirani et al. (2023). The study involved a "smart" amine–mesoporous silica (MSN–NH_2)-based nanoparticle loaded with therapeutic Gemcitabine (GEM), coupling potent fluorescence emission and imaging capabilities to achieve targeted payload delivery to HeLa and K562 tumor cells. A transformative step was introduced through the electrostatic coating of hydroxyl and carboxylic acid carbon dots onto MSNs to generate biocompatible carbon dot capped MSNs. Covalent grafting off olic acid onto the carboxyl groups of the nano-construct resulted in the formation of a site-specific nanocarrier, since folate receptors are over-expressed on HeLa and K562 cell lines (Li et al. 2014; Soleymani et al. 2021). The nanoparticles exhibited amplified cytotoxicity in HeLa and K562 cell lines and fluorescence microscopy and flow cytometry assays deciphered its targeting prowess and cellular uptake competence towards HeLa cancer cells. Molecular docking further elucidated GEM's molecular interactions with human deoxycytidine kinase (dCK). The research's implications are profound, offering a novel perspective on the evolution and current state of tailored theranostic strategies, thus elevating the prospects of efficacious cancer treatment.

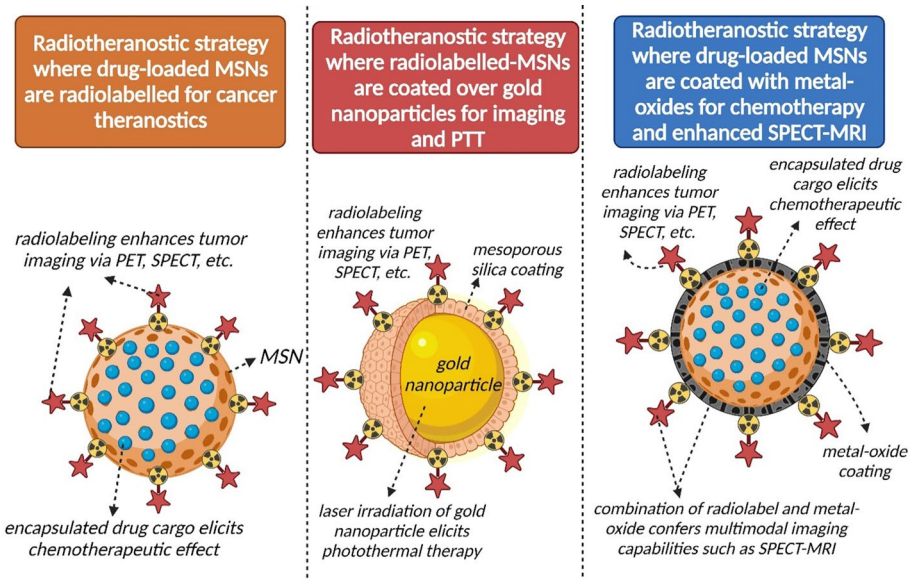

Fig. 10 Different strategies that can be incorporated to develop radiolabeled mesoporous silica nanoplatforms for effective radiotheranostics for cancer

Radiotheranostics

Radiotheranostics involves radio-based techniques, such as positron emission tomography (Wood et al. 2007), single photon emission computed tomography (Brandon et al. 2011), MRI (Hesketh and Brindle 2018), and X-rays (Kauffman et al. 2023), for the diagnosis and treatment of cancer (Fig. 10).

By incorporating radioactive elements into nanoparticles, they can be detected using various techniques, with positron emission tomography (PET) being one of the most commonly used (Welch et al. 2009). PET works by detection of gamma-rays produced when positrons discharged by radioactive elements combine with electrons in the surrounding tissue, allowing for 3D imaging of the tissue (Ott 2010). A theranostic nanoparticle incorporating this approach was achieved by coating MSNs over gold nanorods (Xu et al. 2018). ^{89}Zr labelling conferred PET and photoacoustic susceptibility, while PEGylation facilitated efficient loading of Doxorubicin in the nanostructure. Capitalizing on these features, the nanoparticles adeptly orchestrated PET and photoacoustic imaging-guided chemo-photothermal cancer treatment, with ^{89}Zr-labeling facilitating PET imaging to affirm passive tumor targeting in 4T1 murine breast cancer-bearing mice, courtesy of the EPR effect.

Single-photon emission computed tomography or SPECT, is a type of nuclear imaging test that uses radioactive substances or radiotracers to 3D images of in vivo conditions (Israel et al. 2019). Significant advantages of SPECT over PET are that SPECT radiotracers are able to stay in vivo for longer durations, are widely available and more affordable (Davis et al. 2020; Petersson et al. 2007). In the rapidly evolving landscape of medical imaging and therapy, the integration of diverse imaging modalities has garnered significant attention, recognizing the limitations of single imaging techniques. Addressing this need, the convergence of single photon emission computed tomography–magnetic resonance imaging (SPECT–MRI) has sparked the

demand for multifunctional dual-probe agents capable of harnessing the high sensitivity of SPECT and the precise spatial resolution of MRI (Bouziotis and Fiorini 2014; Hutton et al. 2018). Over the last few years, nanoparticles have emerged as attractive candidates to manifest this multimodal possibility for therapeutic interventions (Lamb and Holland 2018). One such study showcased this pioneering leap by conjugating technetium-99 (^{99m}Tc), a commonly employed radiolabel, onto manganese oxide-based MSNs (MnOx–MSNs) to engineer a dual-modal imaging agent that seamlessly fuses the strengths of SPECT and MRI (Gao et al. 2016). This synergistic approach capitalized on the inherent pH-responsive property of MnOx–MSNs, which yielded a remarkable radiolabelling yield of 99.1% ± 0.6% and endowed the nanoparticles with a high relaxivity value ($r1 = 6.60\ mM^{-1}\ s^{-1}$) for T1-weighted MRI. The in vivo assessment on tumor-bearing mice validated the robust performance of this SPECT–MRI dual-modal imaging system, furnishing semi-quantitative insights into tumor detection. By leveraging the MSN capabilities, the nanostructure also extended its capabilities in demonstrating its efficiency in delivering Doxorubicin.

Radio- and Photodynamic treatments have long been pivotal strategies, yet their efficacy has been impeded by limited penetration of light and insufficient accumulation of radiation in soft tissues, often accompanied by acute toxicity caused by radiation (Mallidi et al. 2016; Roeder 2020). To surmount these challenges and advance cancer management, the imperative arises for a versatile nanoplatform capable of synergistic radio- and photodynamic therapy, complemented by diagnostic tools that facilitate early diagnosis. Concurrently, the integration of cancer therapy with untargeted analysis of metabolomics holds promise for enhancing clinical relevance by enabling early disease detection and prognosis (Zhang et al. 2014, 2013). In this pioneering context, a recent study focused on enhancing the scintillation of mesoporous silica coated cerium fluoride (CeF_3) nanoparticles through strategic co-doping with terbium (Tb^{3+}) and gadolinium (Gd^{3+}) ions (Ahmad et al. 2019). The mesoporous silica coating allowed the nanoparticles to be loaded with Rose Bengal to establish a multifunctional theranostic platform poised for computed tomography (CT) and MRI-directed X-ray-induced combined radiotherapy and photodynamic therapy (RT + XPDT). The experimental findings unveiled compelling tumor deterioration outcomes with the synergetic RT + XPDT approach, demonstrating superiority over singular radiotherapy. The integration of global untargeted metabolomics provided mechanistic insights into this efficacy, elucidating how the treatment leads to the selective deprivation of non-essential amino acids pivotal for synthesis of protein and DNA, as well as energy-mediating pathways crucial for up-regulating tumor growth (Choi and Coloff 2019). This study also underscored that tumor and serum metabolite shifts are robust biomarkers that mirror disease progression and regression, affording a powerful tool for early disease assessment and prognosis (Havas et al. 2017). Radiotheranostics based on the intersections of radiotherapy and X-ray sensitivity for enhanced cancer treatment and diagnostics is an emerging theranostic intervention in the current research landscape and is widely being investigated in combination with MSNs for effective theranostic breakthroughs (Koosha et al. 2021; Winter et al. 2020; Wu et al. 2022).

Multimodal synergistic approaches

A synergistic approach for cancer therapy refers to the combination of different methods, such as PDT, photothermal therapy, chemotherapy, radiotherapy, etc. (Fan et al. 2017; Yang et al. 2020). Having a combination of multimodal therapeutic facets would significantly enhance the therapeutic outcome as well as mitigate discrepancies of traditional approaches, such as development of drug resistance or chances of tumor recurrence (Kemp et al. 2016). Advances in this context have led to the development of ingeniously engineered nanoparticles, capable of multimodal synergistic therapies for effective cancer theranostics. In a recent study, a magnetic MSN platform for combined magnetothermal therapy and chemotherapy was developed (Zhao et al. 2022a). The MSNs with Fe_3O_4 cores and mesoporous silica shells was designed to carry doxorubicin and achieve magnetothermal heating under an alternating magnetic field (AMF). The conjugation of folic acid ensured target-specific drug delivery to folate receptor-over-expressing cancer cells, whereas the addition of disulfide-linked chitosan conferred the pH- and redox responsive behavior of doxorubicin release from the nanoparticle. The authors reported the redox/pH/AMF-responsive release of doxorubicin from the MSNs exhibited superior cytotoxicity towards HeLa cells in combination with AMF, demonstrating the effective synergy between chemotherapy and magnetothermal therapy. This study highlights the potential for multimodal synergistic therapies with implications for the betterment of precision oncology in the future.

Image-guided combination therapy can help to overcome the challenges of low bioavailability and severe side effects associated with traditional cancer chemotherapy, leading to more effective and targeted treatment (Fernandez-Fernandez et al. 2011). To exemplify this approach, Shi et al., recently developed a dual-responsive MSN platform to achieve MRI-guided synergistic chemo-photothermal therapy (PTT) and chemodynamic therapy (CDT). This nanostructure combined the benefits of polydopamine (PDA), manganese oxide (MnO_2), hyaluronic acid (HA), and drug-loaded hollow MSNs to create an intelligent core–shell platform. The nanoparticle exhibited both intrinsic and externally triggered responses, where the tumor microenvironment (pH/GSH) initiated gatekeeper degradation, releasing anti-tumor drugs, and near-infrared light exposure accelerated degradation, facilitating PTT. The MnO_2 component facilitated chemodynamic therapy, enhancing treatment efficiency while also enabling MRI-based tumor localization through Mn^{2+} release. In vitro and in vivo experiments exhibited effective targeting, biocompatibility, and successful MRI-guided combined therapy, leading to remarkable tumor eradication within a short timeframe (Shi et al. 2023).The use of MRI-guided therapies has been recorded in radiation-based theranostics as well. In a first of its kind study, Kuthala et al., addressed the formidable challenge of treating glioblastoma multiforme (GBM), an aggressive brain tumor, through a groundbreaking approach combining theranostics and Boron Neutron Capture Therapy (BCNT) guided by MRI. The authors used mesoporous silica to develop a biocompatible coating for a novel boron nanoparticle, enriched with ^{10}B, surface-modified with RGD-K peptide to target GBM, and equipped with fluorescence and MRI capabilities. This multimodal nanoplatform enabled precise imaging for tumor diagnosis and efficiently delivered high boron concentrations to tumor cells while sparing normal brain tissue. The integrated MRI-guided

BNCT effectively suppressed brain tumors and extended mouse survival (Kuthala et al. 2017).

Cancer immunotherapy is another promising avenue which enables harnessing the power of the immune system to fight cancer, offering a promising approach to treat cancer (Bastien et al. 2019). However, it has some drawbacks when it comes to theranostics. Cancer immunotherapy can be limited by immune-related adverse events and the evasion of the immune system by cancer cells (Cappelli et al. 2017). To address these challenges, researchers are exploring the incorporation of nanomedicine as a promising tool to improve treatment outcomes (Irvine and Dane 2020; Lakshmanan et al. 2021; Shi and Lammers 2019).The efficacy of cancer immunotherapy can also be significantly maximized by incorporating a synergistic approach. One such study presented an innovative approach with the blend of PDT and PTT with immunotherapy to mitigate the post-treatment risks, such as tumor recurrence and metastasis (Zhou et al. 2020). The nanoparticle developed by Zhou et al., was a multi-functional platform for tumor theranostics with sequentially coated Cu_9S_5 nanocrystals with mesoporous silica and MnO_2 shells, and then adsorbing the immunoadjuvant CpG. This platform enabled the combination of phototherapy and immunotherapy for enhanced cancer theranostics. Through the synergistic action of Cu_9S_5 nanocrystals, mesoporous silica and MnO_2 shells, the nanoparticles efficiently generated heat and ROS upon laser irradiation. Both in vitro and in vivo outcomes underscored substantial tumor regression achieved through this innovative platform. This approach induced cell death while promoting dendritic cell activation and cytokine secretion, leading to an enhanced immune response. The nanoparticle's ability to promote CpG uptake resulted in an increase in the penetration of cytotoxic T-lymphocytes into the tumor tissue. This in-turn stimulated the production of interferon gamma (IFN-γ) and significantly enhanced immune response, thus presenting a promising approach for advancing cancer theranostics. This concept demands a paradigm shifting insight, which holds great potential for future therapies. This synergistic and multimodal approach for immunotherapy is widely being investigated today in a quest for new scientific breakthroughs (Yang et al. 2023).

Improving pharmacokinetics and biocompatibility of MSNs

MSNs have established prodigious potential in imaging, drug delivery and biomedical applications. However, to establish the MSN formulation as an effective theranostic system, it is critical to evaluate its in vivo performance, bio-distribution, and biocompatibility (Zhang et al. 2022a). This would enable researchers to improve the efficiency of therapeutic molecules and introduce new deliver strategies which overcome inefficacies of conventional drugs.

Controlling the lixiviation rate is a vital parameter. The degradation of the MSN in the body is accredited to parameters, such as the morphology of the MSN, surface area, chemical configuration, the molecules it has been functionalized with, the drug load it possesses and the environment it is subjected to inside the body. Various strategies can be applied to control the in vivo behavior of the MSN (Vallet-Regí et al. 2018). Owning to its larger surface area designing a spherical MSN allows quicker disintegration of the nanoparticle compared to a rod-shaped MSN (Hao et al. 2012). Similarly, a large surface area would mean a greater area of interaction with the physiological environment.

Thus, a larger surface area permits a faster rate of lixiviation of the silica framework (Huang et al. 2014). Altering chemical composition also affects MSN behavior. The rate of dissolution can be amplified by addition of cations, such as Ca^{2+} (Li et al. 2007) and Fe^{3+} (Mitchell et al. 2012). This is utilized as a doping strategy, as they hamper the silica framework. Doping MSNs with these cations, allows for a faster rate of dissolution and release of the encapsulated therapeutic cargo, thus improving the therapeutic efficiency of the nanoformulation. Alternatively, surface modification or functionalization augments a decisive role in determining the degradation behavior of the MSNs. Addition of PEG (PEGylation) has been proved to significantly slow down the rate of dissolution and causes a rather non-conventional mode of dissolution, i.e., the MSN disintegrates from inside first (Cauda et al. 2010). This strategy to boost therapeutic efficiency is attributed to the fact that the slowed down dissolution rate would render for a more sustained and slower release of the drugs or other therapeutic cargo. The drug load possessed by the MSN also determines the rate of disintegration. A study regarding the dissolution of the silica framework was investigated previously in a doxorubicin loaded MSN. Being kept at 37 °C in a phosphate buffered saline (PBS) solution; it was observed that the acidification due to PBS caused an extremely high rate of degradation (Choi and Kim 2017). In another study; comprising of FBS, MSNs were tested in the incidence of proteins and the outcome exhibited a decline in the MSN stability (Hao et al. 2012).

Biocompatibility of a nanocarrier is one of the most important criteria as MSNs (if) exhibiting cytotoxicity or unwanted accumulation in the body, cannot be employed for efficient therapeutics. As mentioned previously, different adjustments and modifications can be done to MSNs to make them more biocompatible and enhance their biodistribution. Utility of PEG as a surface modification can enhance the colloidal stability of the MSN, help it escape exclusion by spleen or liver and boost the circulation period of the MSN in vivo (He et al. 2011b). Addition of different surface moieties and lowering the overall charge of the surface can also significantly reduce the cytotoxicity of the MSN (Nabeshi et al. 2011). A previous study also demonstrated that MSNs coated with lipid bi-layer appeared to have a good compatibility with blood as even at higher concentrations, these functionalized MSN possessed the ability to interact with RBCs without causing any damage to them (Roggers et al. 2014). MSNs have been shown to have acceptable biocompatibility in various biomedical applications (Tao et al. 2020). A mouse model study performed by Liu et al., demonstrated good biocompatibility of MSNs even at higher doses. The LD_{50} was found to be more than 1000 mg/kg and even after multiple administrations, no mortality in mice was observed at 2 weeks and at lower doses no toxicity was observed in organs, such as spleen, liver, kidney, or lungs (Liu et al. 2011). However, biocompatibility of MSNs depends on various factors, such as their size, shape, surface chemistry, and dose; thus, design parameters of the MSNs must be carefully considered to make a nanoformulation suitable for theranostic applications (Tao et al. 2020).

Toxicity, limitations, and other challenges

MSNs exhibit cytotoxicity in cells due to two main reasons—(i) presence of silanol groups, which due to electrostatic interactions can cause lysis of membranes, and (ii) cell death caused by silica reactive oxygen species (Croissant et al. 2018). MSN cytotoxicity

can be attributed to various mechanisms, such as depletion of glutathione, peroxidation of membrane, damage to DNA and dysregulation of mitochondrial function. Studies have shown than administration of MSNs in a single large dose is more cytotoxic than when administered in multiple smaller doses (Petushkov et al. 2010). As mentioned previously, MSNs hold a large amount of negative charge on their surface. This negative charge influences consequences such as hemolysis, initiation of unsolicited immune signals, impedes lymphocyte activity and increases in vivo protein opsonization (Frickenstein et al. 2021). This process of opsonization which significantly affects the biological performance of MSN is attributed to the formation of a "protein-corona". Another challenge is the strong affinity of MSNs to blood proteins, which can affect their performance as drug delivery systems (Küçüktürkmen and Rosenholm 2021).Plasma contains hundreds of proteins which tend to agglomerate on the surface of the nanoparticle as and when it encounters our blood. Interactions such as binding to target cells, internalization into cells, etc. are affected due to presence of a protein-corona. Formation of protein-corona also affects aspects such as dispersity of nanoparticle, alterations in the surface charge, increase in size of the nanoparticle and also the solubility of the nanoparticle in the physiological environment; all of which can affect the efficient performance of the MSN (Florek et al. 2017). Attributes of the nanoparticle such as its surface functionalization, overall size and the amount of time it is exposed to the plasma all determine the extent of protein-corona formation (Tenzer et al. 2013). If not functionalized properly, MSNs tend to have improper biodegradability and retention time. Recent research suggests that larger MSNs might be more detrimental than smaller ones. Larger MSNs may accumulate and may cause more adverse effects in the organs and tissues, since they have lower clearance rates and longer retention periods in the body (Niroumand et al. 2023). The structure and function of biological components including proteins, lipids, and DNA may change as a result of stronger interactions of larger MSNs' with them (Tan et al. 2023). Greater oxidative stress, inflammation, and apoptosis in the cells triggered by larger MSNs can result in tissue damage and dysfunction as well (Niroumand et al. 2023; Tan et al. 2023). In such cases, the MSNs do not disintegrate properly and tend to keep accumulating inside the body; thus, causing undesirable toxicity.

The morphology of MSNs refers to their shape and structure, which can affect their performance and safety in various applications. Different shapes of MSNs, such as rods, spheres, cubes, etc., may influence their toxicity and efficacy. The shape of MSNs affects their cellular uptake, biodistribution, and clearance rates, because different shapes have different surface areas, aspect ratios, and orientations, which influence how they interact with the cell membrane and the biological barriers. For example, rod-shaped MSNs have higher uptake and longer retention than spherical MSNs (Niroumand et al. 2023). MSNs with different structures, such as core–shell, hollow, or yolk-shell, also have different aspects, which may affect their functionality and biocompatibility. The structure of MSNs affects their stability, loading capacity, and release kinetics, because different structures have different pore volumes, surface modifications, and stimuli-responsiveness, which determine how they store and release the cargo molecules (Niroumand et al. 2023). For example, core–shell MSNs have higher stability and lower leakage than hollow MSNs (Stephen et al. 2022; Tiburcius et al. 2022). MSNs with different surface roughness or porosity may also alter their bioactivity. The surface roughness or porosity of MSNs

affects their interactions with biological components, because different surface features have different adsorption, aggregation, and biodegradation behaviors, which influence how they affect the structure and function of the biological components (Pal et al. 2020). For example, rough MSNs have higher adsorption and aggregation than smooth MSNs (Lin et al. 2019).

MSNs of a medium pore size demonstrated enhanced capabilities in inhibiting cell growth in vitro, inducing tumor cell apoptosis, and slowing down tumor growth in vivo, compared to MSNs with either smaller or larger pore sizes (Alberti et al. 2023; Hong et al. 2020). On the contrary, MSNs with small pore sizes (< 10 nm) can offer high stability and controlled release, but they may also limit the loading capacity and diffusion rate of the guest molecules, which can affect their penetration kinetics and bioactivity (Hong et al. 2020). This is because small pore sizes reduce the available space and surface area for the guest molecules to enter and exit the MSNs, and also increase the interaction strength between the MSNs and the guest molecules, which can slow down the release process. In a previous study, MSNs with varying pore sizes—small (2.3 nm), medium (5.4 nm) and large (8.2 nm) were assessed to determine their effects on in vivo performance of MSNs (Li et al. 2018a). The overall experiment established that MSNs with a medium pore size are more efficacious as compared to smaller and larger pore sizes. Medium pore size MSNs exhibited a more rapid and complete release of DOX, higher cellular uptake, and nucleic accumulation of DOX. MSNs of a medium pore size demonstrated enhanced capabilities in inhibiting cell growth in vitro, inducing tumor cell apoptosis, and tumor growth retardation in vivo, compared to MSNs with either smaller or larger pore sizes.

Therefore, it is crucial to engineer MSNs with a suitable size, surface alterations and functionalization, to make them more biocompatible and reduce their toxic side effects.

These complications associated with silica pose significant challenges for regulatory approval and clinical transition of silica-based nanomaterials. The regulatory approval procedure for silica-based medications or treatments is a stringent and rigorous process that considers a variety of aspects, such as toxicity, effectiveness, and safety (Bangarurajan 2021). The assessment of MSN safety and toxicity is the initial stage in this approach. After the MSNs' safety has been verified, the next stage is to demonstrate their effectiveness in vivo (Jain and Thareja 2019). Preclinical investigations in animal models are followed by three to four stages of clinical trials in humans (Jang et al. 2016). Many nanoparticle-based therapeutic candidates may fail later stages of clinical studies. Currently, very few examples of nanomaterials incorporating the use of silica have been granted regulatory approval for clinical trials. AGuIX® nanoparticles are a promising radiotheranostic drug against cancer incorporating gadolinium-chelated polysiloxane-based nanoparticles (Lux et al. 2019). AGuIX® has currently been approved for clinical trials for various types of cancers. Back in 2011, the Food and Drug Administration (FDA) had granted approval for the initiation of phase-I human clinical trials for silica-based diagnostic nanoparticles, known as Cornell dots or C dots (Benezra et al. 2011). As of 2021, C dots have begun their third human clinical trial. As of now, there are no specific MSN-based drugs approved by the FDA for progressing towards clinical trials, but given the rapidly advancing progress of research in this field, the possibility of this happening in the near future is not too distant.

Addressing current challenges and future scope

In the preceding sections, we have discussed various research advancements and strategies that address overcoming therapeutic limitations. The development of multifunctional and/or hybrid nanoparticles do seem to significantly enhance the capabilities of the nanoformulations in terms of augmenting cancer theranostics. Designing the nanoformulations to be "smart", i.e., responsive to a particular stimulus such as light, pH, ultrasound, etc. aids in increasing the specificity of the nanoconstruct while minimizing loss of therapeutic cargo. Limitations in theranostic efficiency continue to emerge with context to biocompatibility, target specificity, biological barriers, etc. Based on the points covered in this review, one would suggest developing nanoformulations with a proper size, morphology, pore dimensions and surface functionalization to overcome these limitations. However, as with any rapidly evolving field, new challenges necessitate further research and innovative solutions.

Controlled Radical Polymerization (CRP) techniques are a game-changer in terms of functionalization. CRP techniques confer precise control over the polymerization process (Parkatzidis et al. 2020). Meaning that the size, composition, and architecture of the polymer chains can be accurately manipulated. This high level of control results in polymers with uniform chain lengths and well-defined structures, which is crucial for the functionalization of MSNs (Zhou et al. 2022). In the context of MSNs, CRP techniques can be used to graft polymers, resulting in well-defined and effective functional groups on the surface of the nanoparticles. The polymer chains serve as functional groups that can interact with other molecules, enhancing the performance and effectiveness of the functionalized MSNs by improving biocompatibility, stability, and target specificity as well as mitigate ineffectiveness of functionalized moieties (Nebhani et al. 2020). Atom Transfer Radical Polymerization (ATRP) (Lorandi et al. 2022), Reversible addition–fragmentation chain transfer (RAFT) polymerization (Zhao et al. 2022b), and Nitroxide Mediated Polymerization (NMP) (Wagner et al. 2023) are some of the most common CRP techniques that can be used for this purpose.

One of the challenges in nanomedicine is to overcome the biological barriers that hinder their performance and effective delivery of therapeutic agents to the target tissues or cells. Some of these barriers are:

i. Immune clearance: MSNs can be recognized and eliminated by the immune system, especially if they are not functionalized or coated with biocompatible materials leading to inflammation, toxicity and reduced efficacy of the drugs loaded on the MSNs (Huang et al. 2020; Palmieri and Caracciolo 2022).
ii. Blood–brain barrier (BBB): It is a complex structure that safeguards the brain from harmful substances in the blood, controlling the transport of molecules and cells (Hajal et al. 2021). However, it poses hinderance for MSNs to permeate and reach the brain tissue due to its low permeability attributed to the size or morphology of the nanoparticles. It is a major barrier in terms of delivery of MSNs to the brain tissue for treatment of cancers, such as glioblastoma (Song et al. 2023).
iii. Endosomal entrapment: MSNs can be internalized by cells via endocytosis (Fig. 1), but they may not be able to escape from the endosomes due to their size and charge. This can result in premature release of the drugs or accumulation of the

MSNs in the endosomes, causing oxidative stress and cell damage (Gisbert-Garzarán et al. 2020).

iv. Lack of selective internalization and accumulation in tumor tissues: MSNs may not be able to reach the tumor sites due to several factors, such as blood circulation, tissue barriers, tumor heterogeneity, etc., thus hindering their therapeutic potential (Izci et al. 2021). Reduced efficiency and specificity may also be attributed to MSNs not being able to target specific cancer cells due to their non-specific interactions with cell surface receptors or molecules (Marques et al. 2020).

As discussed over the course of this review, engineering the nanoformulation with a suitable size and morphology can help with the crossing/penetrating biological barriers as well as efficient cellular uptake. Surface functionalization or modifications such as addition of polymers, proteins, peptides, or antibodies can help in improving target specificity and biocompatibility of the nanoformulation. A polymer focused study assessed the transport, uptake and cytotoxicity of promising drug nanocarriers in in vitro models of the BBB. They found that coating with poly(ethylene glycol)–poly(ethylene imine) (PEG–PEI) copolymers clearly facilitated the uptake of rod-shaped MSNs across the BBB without causing significant damage (Baghirov et al. 2016).Compared with the non-functionalized MSNs which induced the severe injury impact on neuron cells, thiol modified MSNs have showed significantly lower damage, suggesting the possibility to mediate the neurotoxicity by modifying the surface chemistry of this kind of the nanomaterial for biomedical applications (Zhou et al. 2016).

However, apart from these strategies, we can draw upon some rather newer methods to improve the design of MSNs, Current advances in the field on nanotechnology facilitate novel and fascinating approaches that one can incorporate while designing MSN-based nanoplatforms to significantly improve overall performance.

"Transformable" nanoparticles, that can alter their shape to cross biological barriers for biomedical applications have recently gained an investigative attention. These nanoparticles can be designed to respond to stimuli from their surrounding environment which can facilitate the nanoparticles to change their morphology. By being able to effectively modify their size and shape, they can enhance their drug delivery efficiency, tumor penetration, and biocompatibility. A gelatin/laponite/doxorubicin (GLD) nanoplatform, which consists of crosslinked gelatin-coated laponite nanoparticles loaded with doxorubicin, is a recent example of such nanoparticle systems (Li et al. 2023). According to this new study by Li et al., when the GLD encounters the matrix metallopeptidase-2 (MMP-2), an enzyme that degrades gelatin, the nanoparticles shrink down to 40 nm and release doxorubicin into the tumor cells. This transformation to a smaller size enables nanoparticles to easily pass through the blood–brain barrier and deliver a potent dose of anticancer medication to the tumor spot.

As discussed, MSNs can be effectively fused with different materials to create an efficacious hybrid-nanoplatform. For example, fusion with magnetite nanoparticles can assist with imaging, such as MRI. In this context, it has also been investigated that addition of magnetite nanoparticles can help improve its targeting abilities as well. In a recent study, magnetite nanoparticles have been subjected to dual magnetic fields (alternating and external) to test their efficacy against the BBB (Gupta et al. 2022).The results of this

study suggest that apart from the ability to induce magnetic hyperthermia, the use of magnetic fields can also enhance the delivery of magnetite nanoparticles across the BBB in a rodent model. The results demonstrate that exposure to the alternating magnetic field open up the tight junctions of the BBB, allowing the MNPs to cross into the brain. The findings validate that the combined approach of using both external and alternating magnetic fields leads to a higher concentration of magnetite nanoparticles in the brain, as compared to the application of an external magnetic field alone.

Biomimetics, i.e., the imitation of natural biological designs or processes, is a fascinating and swiftly evolving field in nanomedicine (Zhao et al. 2023). It offers innovative solutions to overcome several limitations associated with traditional cancer therapies, such as target specificity, biocompatibility as well as tackling biological barriers (Johnson et al. 2022). Biomimetics usually involves coating the nanoparticle with the cell membrane of a biological entity, such as red/white blood cells, cancer cells, etc. Biomimetic nanomedicine, by emulating biological systems, can boost the precision and targeting of therapeutic agents, with nanoparticles engineered to simulate cell surface properties, facilitating specific binding to cancer cells and direct drug delivery to tumors (Soprano et al. 2022). Biomimetics enhances the biocompatibility of nanoparticles by duplicating the traits of natural biological materials, allowing these nanoparticles to safely interact with biological tissues and cells, thereby minimizing the potential for adverse reactions (Gareev et al. 2022). Another significant advantage is potential immune evasion, as biomimetic nanoparticles, by mimicking the body's cells, can circumvent immune detection and clearance, thereby prolonging their circulation and enhancing therapeutic effectiveness (Zhu et al. 2023). Incorporation of mesoporous silica in this context is also being widely investigated as a viable augmentation for cancer theranostics. A recent example, involves a novel biomimetic nanosystem has demonstrated the ability to induce ferroptosis and immunogenic cell death in gastric cancer (Guo et al. 2023). This nanoplatform developed by Guo et al., is comprised of MSNs doped with manganese (Mn^{2+}) ions, loaded with a cisplatin prodrug and coated with a cancer cell membrane. Owing to its biomimetic surface, the nanoparticle demonstrated enhanced homologous tumor targeting as well as immune evasion. The nanoplatform showed great biocompatibility, enhanced T1 signal under MRI and was effectively able to induce ferroptosis-mediated immunogenic cell death (ICD) by depleting intracellular glutathione (GSH), releasing Mn^{2+} ions, and transforming cisplatin from Pt(IV) to Pt(II). This process damages nuclear DNA, increases lipid peroxidation (LPO) content, and recruits cytotoxic T lymphocytes, thereby facilitating anti-tumor immunotherapy. This study demonstrates the potential of biomimetics in cancer theranostics using cancer cell membrane as a versatile platform for delivering multiple therapeutic agents and inducing synergistic effects.

The use of a "nano-regulators", i.e., nanoscale compounds that have the ability to specifically modify the biological processes of cells, tissues, or the immune system, is another promising strategy. A recent example in this context, is a nano-regulator developed by Huang et al., which is a metal–organic framework (MOF) that can target and deliver chemotherapeutic drugs to bone metastatic prostate cancer cells while suppressing the immune system and thereby minimizing the side effects of immunotherapy. The researchers developed a nano-regulator based on phytic acid (PA) and iron (Fe^{3+}) to form a MOF, which can encapsulate mitoxantrone (MTO), a chemotherapy drug (Huang

et al. 2023). The nano-regulator could selectively kill the cancer cells by inducing their death through immunogenic cell death (ICD) while sparing the normal cells by preventing the tumor microenvironment from producing TGF-β, a cytokine that suppresses the immune response. The results also showed that the nano-regulator improved the blood circulation and tumor accumulation of MTO, and enhanced its anti-tumor effect when combined with αCTLA-4, an antibody that blocks another checkpoint inhibitor called PD-1. This example suggests that nano-regulators could be used as an alternative or complementary strategy for bone metastatic prostate cancer treatment, especially for patients who are resistant or intolerant to conventional therapies as well as in counteracting immune system complications. Nano-regulators could be applied to other types of cancers that have bone metastasis, such as breast cancer, lung cancer, and multiple myeloma.

The use of nanomotors are also a highly cutting-edge approach in terms of novel approaches in this field. This technique involves the design of nanoplatforms that under the trigger of a stimulus such as an enzyme or light can autonomously self-propel towards cancer cells to deliver a chemotherapeutic cargo. The use of nanomotors incorporated with MSNs have been investigated in the recent years with promising examples such as MSNs containing platinum nanodendrite facilitating propulsion due to catalytic decomposition of low concentrations of hydrogen peroxide (Díez et al. 2021) and also MSN systems self-propelled by decomposition of chemicals due to NIR trigger to deliver cargo to cancer cells (Chen et al. 2022). The use of nanomotors would significantly help in achieving more target-specific deliveries with higher speed and precision. Similarly, with a growing focus on autonomous nanosystems, it is very likely that the field of robotics would make an appropriate accomplice in enhancing the performance of MSNs. Nanorobots can significantly help in applications, such as sensing and diagnosis of tumors, mitigate the needs for invasive surgeries and aid nanoparticles in accessing hard-to-reach tumor locations (Kong et al. 2023). Research involving nanorobots still seems to be in early stages, limited by a lack of perspective on interactions with biological interfaces and associated complications, such as biocompatibility of newer nanomaterials or tumor heterogeneity. However, with advancing research, the development of more capable and sophisticated nanorobots would likely provide a significant boost to performing medical tasks in terms of augmenting cancer theranostics.

Artificial Intelligence (AI) can also revolutionize the design of MSNs for cancer theranostics by enabling precise control over their properties. Based on vast available data sets, patterns in in vitro and in vivo data, AI algorithms can analyze to predict optimal nanoparticle characteristics, such as size, shape, and porosity, which are crucial for biocompatibility, biological performance, drug loading and release (Serov and Vinogradov 2022). Furthermore, AI can facilitate enhancing the efficacy of cancer therapeutics while minimizing side effects by predicting the biological performance of nanoparticle formulation (Lin et al. 2022; Singh et al. 2020). This fusion of nanotechnology and AI holds immense potential for advancing personalized cancer treatment strategies.

Although holding a significant promise for therapies, MSNs have lacked in clinical translations. Apart from reasons of failure, such as toxicity, MSNs are also hindered by the lack of regulatory agencies and guidelines to ensure safety and efficacy. There is lack of regulatory guidelines and agencies that can address issues related to MSNs in terms

of biocompatibility, pharmacokinetics, toxicity and systemic clearance. The current regulatory approaches for nanomedicines are insufficient and inconsistent which may be attributed to a lack of science-informed regulatory guidance (Youden et al. 2022). Lack of clinical translation is also owed to ethical challenges, lack of planning to determine suitable formulations and candidates eventually leading to failure in early stages of trials. This calls for the development of an overseeing governance, planning committees and agencies to regulate ethical oversight (Mishra and Sharma 2021). The commercial application of nanomedicines faces key obstacles, such as ensuring reproducibility of formulation, accurate description, and stringent biological assessment. There is a pressing need for comprehensive research and strict protocols to guarantee the safe and effective creation and usage of nanomedicines (Thapa and Kim 2022). Teams from various disciplines such as academia, industry and government agencies must work together to advance nanomedicine by integrating material science, characterizing new technology platforms, and creating disease models that closely mimic clinical conditions. This collaborative effort, along with the adaptation of current regulatory standards to be more science-based, can undoubtedly produce the necessary data such as design, synthesis, testing, registration, and monitoring for the approval of nanomedicines into the clinical stages (Đorđević et al. 2021).

Conclusion

In the ever-evolving landscape of cancer theranostics, the problem of achieving precise, targeted treatment while minimizing adverse effects remains paramount. The constant evolution of cancer to overcome conventional treatment strategies has invoked a pressing need for innovative and effective theranostic approaches. This review has elucidated the tremendous promise that MSNs hold in addressing this challenge owing to their promising facets, such as distinct physicochemical assets, tunability, ease of functionalization, and biocompatibility.

This review has comprehensively discussed numerous applications of mesoporous silica nanotechnology in cancer theranostics, spanning recent developments and strategies to design hybrid, "smart" modalities such as light-based, ultrasound-based, pH-responsive, biomarker-recognition-based, carbon-dots-based, and radiolabeled nanoplatforms for effective cancer theranostics. This versatility of MSNs offers a transformative platform for tailoring cancer theranostic interventions to usher a new era of precision medicine. Moreover, the potential for multimodal synergistic theranostics harnesses the strengths of these different approaches to enhance treatment efficacy while minimizing side effects.

The rationale for further research in this domain is resounding. First, the untapped potential of MSNs in combination with emerging technologies demands exploration. There are innumerable combinations of MSNs with biomolecules and other moieties yet to be investigated in a theranostic context; the future possibilities and implications are endless. Continued investigation into the fine-tuning of MSN properties and their interactions with biological systems will surely lead to groundbreaking advancements. Second, understanding the long-term effects and potential toxicity concerns associated with MSN-based theranostics is vital for clinical translation. Addressing these aspects

comprehensively is essential for harnessing the full potential of MSNs for effective cancer theranostics.

This review offers a comprehensive survey of the present understanding in this domain, highlighting the promising advances over the last few years and the need for further research to fully realize the potential of MSNs in cancer theranostics. MSNs represent a groundbreaking avenue in the realm of cancer theranostics and continued research in this field has the potential to significantly improve cancer diagnosis and treatment, ultimately benefiting patients worldwide.

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