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## Review Article

# Recent Advances in Amino-Functionalized Mesoporous Silica Nanoparticles for Targeted Breast Cancer Therapy

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## ABSTRACT

Breast cancer, which represents a leading cause of cancer-related deaths around the world, poses challenges such as therapeutic resistance, poor specificity of treatments, and systemic toxicity. Amino-functionalized mesoporous silica nanoparticles (MSNs) represent innovative platforms for targeted therapy of breast cancer. With extremely high surface area, tuneable pore size, and versatile functionalization potential, MSNs are shown to efficiently encapsulate chemotherapeutics, genetic materials, and imaging agents. This functionalisation increases drug loading capabilities, stability, and stimuli-responsive release capabilities for precise delivery and minimisation of off-target effects. Key mechanisms explored include active targeting and passive targeting, controlled drug kinetics release, and combination therapies with photothermal, photodynamic, and chemotherapeutic approaches. Some discussion is also given about gene delivery applications and the ways by which MSNs can overcome multidrug resistance. In vitro and in vivo investigations highlight cellular uptake, therapeutic performance, pharmacokinetics, and the safety profile, which reflect biocompatibility and biodegradability. Challenges remain, such as the long-term toxicity, scaling up, and regulatory issues; however, hybrid nanoparticle development, personalized medicine, and AI-driven optimization are promising strategies. All these advances demonstrate the wide scope of amino-functionalized MSNs to transform treatments for breast cancer, through the provision of precise, multifunctional, and patient-tailored approaches to the advancement of precision oncology.

## INTRODUCTION

Breast cancer is the leading locally invasive cancer diagnosed in women and the second most common

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cause of death due to cancer diseases. From data from the WHO, in 2022, nearly 2.3 million new breast cancer cases were diagnosed globally, and over 670,000 deaths were caused by the disease. The disease constitutes a big proportion of cancer diagnoses, and the incidence is projected to rise every year by about 3%. The cases of breast cancer increase significantly due to population ageing, changing lifestyle patterns, and higher awareness and screening programs; it is highly prevalent among high-income countries. Lifetime risk of developing breast cancer also varies by region: approximately 1 in 12 women in the high-income countries, as compared to 1 in 27 in the lower-income regions, mainly because fewer women have early detection and treatment services, which would delay diagnoses and reduce survival chances. Despite advances in detection methods and therapeutic approaches, such as surgery, radiation therapy, chemotherapy, hormone therapy, and targeted biologics, difficult problems have remained in the management of breast cancer. An important problem is the issue of endocrine resistance in estrogen receptor (ER)-positive breast cancer. Although endocrine therapy with tamoxifen or aromatase inhibitors is efficacious up to some extent in 30-50% of patients, resistance develops in the later course. This eventually results in relapse and disease progression largely through the reactivation of other molecular pathways that provide a mechanism for escape from the inhibitory actions of the treatment..(1–8) Another challenging one is triple-negative breast cancer (TNBC) growing aggressively and lacking receptors for hormones like estrogen, progesterone, and HER2. This type of breast cancer constitutes about 10 to 20 percent of all reported cases and has a high possibility of recurrence within three years after treatment. As targeted therapies for TNBC are yet to arrive, patients have to resort to chemotherapy-based treatments, though these have proven effective,

they come with significant side effects and poor survival in the long term. For metastatic TNBC, the median survival has not yet improved beyond 12 months, reflecting an acute requirement for new therapies.(9–12) This complicates the management of the disease, because the nature of the physical and psychological impact of cancer treatments makes treatment management an inherent problem. For example, studies have shown that chemotherapy accelerates physical decline in older women, including the simplest activities of daily living, such as walking and climbing stairs. In a multicentre trial published in *Journal of Cancer Survivorship*, approximately 35% of patients had significant physical decline after chemotherapy compared with 8% for non-chemotherapy treatments. All these negative effects not only influence the quality of life but also limit the possibility of radical treatments in the vulnerable population.(13–15) These challenges demand new models for therapy. Such examples include the application of nanotechnology, better drug delivery systems, personalized medicine, and targeted therapies. Expanded access to early detection programs combined with extended support shall play a crucial role in relief from the prevailing burden of breast cancer globally, especially in low-resource facilities. As it increases in incidence and predominantly affects younger women, conquering therapeutic resistance, understanding ways of reducing treatment-related toxicities, and precision oncology will advance outcomes in patients with breast cancer worldwide.(16–19)

## 1.2 Nanotechnology in Oncology

Nanotechnology has revolutionized the frontier of oncology in terms of diagnosis, treatment, and monitoring of cancer across the barriers of manipulation material at the nanoscale. Nanoparticles have been prepared at sizes between



1 and 100 nanometres; they have been developed with enhanced drug delivery, optimized imaging, and introduced personalized therapeutic approaches. Traditional chemotherapy may result in side effects due to the improper targeting of tumours and unspecific distribution. Nanoparticles, including liposomes (such as Doxil®), and albumin-bound paclitaxel (Abraxane®), are clinically approved in order to improve the pharmacokinetics and diminish side effects. Functionalized nanoparticles or nanocarriers can be equipped with specific ligands, antibodies or peptides that can target particular cancer cell biomarkers, ensuring precise delivery of drugs to tumours while avoiding exposed healthy tissues.(20–24) Nanoparticles such as superparamagnetic iron oxide and gold nanoparticles have boosted imaging modalities during diagnostics which allow enhanced tumour contrast in MRI and CT scans, thus facilitating the early diagnosis and proper staging of cancers. Multi-functional platforms or theranostics refer to platforms which have therapeutic and diagnostic functionalities that enable real-time monitoring of the therapeutic response simultaneously with treatment delivery, or for example, by using gold nanoshells for combined photothermal therapy and imaging. Nanotechnology has been known to provide solutions in overcoming drug resistance by co-delivery of chemotherapeutic agents and resistance inhibitors from the same nanoparticle, thereby restoring their sensitivity against resistant cancer cells.(25–28) Novel photothermal and photodynamic therapies are now designed to exploit the activation of nanoparticles such as gold nanorods and carbon nanotubes to produce localized heating or reactive oxygen species to enhance the eradication of cancer cells. Stimuli-responsive drug delivery systems prepared to release drugs in response to pH, temperature, or enzymatic changes in the tumor microenvironment ensure accurate and controlled therapeutic action.

The delivery system of nanoparticles carrying siRNA, mRNA, or CRISPR/Cas9 allows the silencing of oncogenes or correction of genetic mutations to open up new avenues in the precision oncology for RNA and gene delivery systems.(29–31) Combination therapy involving nanoparticles allows for co-delivery of chemotherapy, immunotherapy, and radiotherapy agents while maximizing therapeutic efficacy but minimizing systemic toxicity. Nanovaccines that make use of nanoparticles in the presentation of antigens are revolutionizing cancer immunotherapy through the induction of robust tumor-specific immune responses. Radio-nanomedicine is the use of radiolabeled nanoparticles, a developing targeted radiation therapy modality that ensures localized delivery of radiotherapeutics to tumor tissues. These nanoparticles mimic the natural body pathways and aim to deliver agents in an effective way. Nanoparticles can also play their role by modulating the tumour microenvironment in ways such as normalization of abnormal vasculature or targeting stromal cells to improve the therapy penetration and efficacy. Biomarker discovery also occurs through nanotechnology: Biomarkers can help detect circulating tumour cells and extracellular vesicles for cancer early diagnosis and tracking metastasis.(31–36) Recent developments in the design, synthesis, and application of amino-functionalized MSNs for targeted breast cancer therapy have been included within the scope of this review. The nanocarriers have a high surface area, tenable pore size, and amino group functionalization, which allows for precise drug loading and controlled release with enhanced tumour targeting, and this avoids challenges like multidrug resistance and off-target toxicity.(37) The review will provide a comprehensive analysis of their mechanism of action, preclinical and clinical findings, and potential to integrate therapeutic and diagnostic functionalities in support of personalized



medicine. Placing an emphasis on leading-edge research and points of resistance, such as the boundaries of scale, long-term safety, or regulatory hurdles, this review attempts to bridge that gap between research and clinical translation. Lastly, it presents the future of amino-functionalized MSNs in changing the face of treating breast cancer and sets forth ways to enhance their development and implementation.

## **2. Mesoporous Silica Nanoparticles (MSNs): An Overview**

### **2.1 Structural characteristics and properties.**

Among new research studies, the structural uniqueness of amino-functionalized mesoporous silica nanoparticles is keeping many heads rolling because this material is very efficient in targeted drug delivery and cancer treatment. The characteristic feature includes a highly ordered mesoporous structure in a pore size range of 2 to 50 nm and typically shows exceptionally high surface area and pore volume. The architecture also accommodates wide range encapsulation of therapeutic agents. This therapeutic agent ranges through small molecules, nucleic acids, and proteins. The silica framework of MSNs is biocompatible and chemically stable and thus amenable to easy modification for the attachment of functional groups that may be tailored for use in nanoparticle design.(38,39) Introduction of the amine groups (-NH<sub>2</sub>) via amino-functionalization introduces new functionality onto the surface or pores of MSNs, thus enhancing their properties. The amine groups enhance the dispersibility of MSNs in physiological environments and permit electrostatic interactions with negatively charged biomolecules such as nucleic acids or cell membranes. Functionalization through amino groups also encourages covalent attachment of targeting ligands, antibodies, or other moieties for targeted delivery to achieve targeted

chemotherapy towards tumors. Furthermore, the surface amino groups provide extra locations for further chemical conjugation like with pH-sensitive linkers to allow the control drug release under acidic microenvironments found in tumour tissues.(39–42) The pore size tunability and high loading capacity combined with amino functionalization of MSNs impart unique structural properties that facilitate the controlled and sustained release of drugs while minimizing systemic toxicity and enhancing therapeutic efficacy. Their mesoporous framework can further protect encapsulated drugs from degradation before reaching their site of action. Importantly, the nanoscale size of MSNs can impart effective endocytosis for cellular uptake and, consequently, effective intracellular delivery. In its entirety, these structural features and properties make amino-functionalized MSNs a versatile platform for advanced therapeutics against cancer, offering precision targeting and efficient drug delivery solutions.(39,43)

### **2.2 Advantages of MSNs in drug delivery systems.**

#### **A. High Surface Area and Large Pore Volume**

MSNs show a very porous structure with a high surface area of typically 500-1000 m<sup>2</sup>/g and high pore volume. Such porosity enables the accommodation of large quantities of therapeutic agents, offering a very favorable basis for developing drug delivery systems with high drug loading capacities.

#### **B. Tuneable Pore Size**

The pore size of MSN can be tuned within the range between 2-50 nanometres, which ensures encapsulation of diverse drug molecules, ranging from small hydrophobic drugs to hydrophilic



compounds and even biomolecules such as proteins and nucleic acids.

### **C. Controlled and Sustained Drug Release**

The modification of MSNs with stimuli-responsive moieties, such as pH-sensitive or enzyme-degradable linkers, helps control the rate of drug release precisely, therefore avoiding drug burst release and providing prolonged therapeutic effects.

### **D. Biocompatibility and Chemical Stability**

The silica framework of MSNs offers a highly biocompatible and chemically stable structure, thereby conferring little toxicity and long shelf life. Moreover, *in vivo* silica degrades to nontoxic silicic acid, thus making it safe for biological applications.

### **E. Enhanced Targeting Capabilities**

MSNs are functionalized by targeting ligands such as antibodies, peptides, or folic acid to ensure targeted delivery to specific cells or tissues, such as cancer cells. This prevents off-target effects and maximizes therapeutic effectiveness.

### **F. Protection of Encapsulated Drugs**

For instance, MSNs protect drugs from premature degradation in the bloodstream to enhance drug stability and bioavailability up to the moment when the drugs reach the target site

### **G. Efficient Cellular Uptake**

The nanoscale size (50-200 nm) facilitates the uptake of MSNs by cells through endocytosis for efficient intracellular delivery of drugs. That is especially favorable in targeting cancer cells and intracellular pathogens.

### **H. Multifunctionality**

MSNs can be engineered for theranostics, which integrates both therapy and diagnosis. For example, it can be used to deliver drugs while being an imaging agent by incorporating materials like iron oxide or quantum dots.

### **I. Versatile Functionalization**

The surface of MSNs is highly modifiable, which involves the attachment of different functional groups such as pH-responsive polymers or hydrophilic coatings. This increases stability in physiological environments and tailors release profiles.

### **J. Overcoming Drug Resistance**

MSNs enable drugs to be co-delivered with MDR inhibitors, which effectively overcomes the resistance mechanisms in cancer cells and restores the therapy.

### **K. Low Immunogenicity**

MSNs have low immunogenicity generally, which minimizes the risk of adverse immune responses. Thus, MSNs are suitable for repeated administration in chronic diseases.

### **L. Scalable and Cost-Effective Synthesis**

Synthesis of MSNs is relatively simple, scalable, and cost-effective. Therefore, it is accessible for research as well as for commercially actualizing drug delivery applications.

### **M. Environment-Specific Drug Release**

MSNs can release drugs in response to particular environmental stimuli, such as the acidic tumour microenvironment, thus ensuring localized action and a decrease in systemic side effects.(43–53)



## 2.3 Functionalization potential of MSNs

MSNs possess excellent functionalization ability, making them versatile in drug delivery and therapeutic applications. Intrinsic properties of silica such as high surface area, large pore size tuneability, and availability of silanol groups allow for diverse chemical modification. The amino, thiol, carboxyl, or hydroxyl groups functionalized onto the surface enhance dispersibility, stability, and drug loading efficiency. For instance, amino-functionalized MSNs improve negative charged drug interaction, as well as pH-responsive polymers, enable drug release in an acidic tumour microenvironment.(38,39,39) Targeting ligands, such as folic acid, antibodies, or peptides, may be attached to the MSN surface to ensure selective delivery to diseased cells and minimize off-target effects. Functionalization even allows incorporation of multiple functionalities within a nanoscale entity, allowing for theranostic applications by combining therapy with diagnostics in the same nanoparticle. Coating the MSN surface with biocompatible polymers such as polyethylene glycol further stabilizes them and prolongs circulation times and minimizes immune clearance. In addition, functionalization allows for the formation of controlled drug delivery systems based on gatekeeping molecules such as cyclodextrins or dendrimers, enabling precision and sustained therapeutic delivery.(54–56) MSNs also can encapsulate biomolecules such as proteins, DNA, RNA, or enzymes towards advanced applications like gene therapy or biosensing. Hybrid systems combining MSNs with materials such as gold nanoparticles or magnetic nanoparticles make them even more useful for enhanced imaging and therapy or combination treatments. Functionalization also with biocompatible or natural biomolecules reduces immunogenicity and toxicity making MSNs safe for clinical applications. The ability to

tune surface chemistry of MSNs and introduce various functionalities makes them a potential candidate for being a promising platform for precision medicine, as it faces many problems of therapeutic and diagnostic challenges for modern healthcare.(57–60)

## 3. Amino-Functionalization of MSNs

### 3.1 Chemical methods for introducing amino groups

Amino function dramatically altered mesoporous silica nanoparticles and their utility in drug delivery, targeting, and other biomedical applications. The introduction of amine groups (-NH<sub>2</sub>) into MSNs allows for favorable electrostatic interactions and covalent conjugations with stimuli-responsive functionalities of the materials; hence, they are suitable for applications at various scales. Most of the techniques have made use of chemical methods in order to achieve the targets discussed above; every method has some merits and relies on specific outcomes.(56,61)

#### A. Silane Coupling Agents

Among all, the most common and frequently used method for amino-functionalization is the use of silane coupling agents, such as 3-aminopropyltriethoxysilane (APTES) or 3-aminopropyltrimethoxysilane (APTMS). They react through hydrolysis and condensation processes with the surface silanol (Si-OH) groups of MSNs to form stable Si-O-Si bonds that anchor amino groups onto the MSN surface. This method has advantages because it is simple and versatile and allows such a degree of control over the density of amino groups by adjusting such parameters as reaction time, temperature, and concentration of the silane reagent.(62)



## B. Post-Synthetic Grafting

The widely applied method is amino-functionalization directly performed on pre-synthesized MSNs. The silanol groups located on the surface of MSNs are reacted with amine-based silane reagents, for example, APTES, in an organic solvent, such as toluene or ethanol under reflux conditions. Post-synthetic grafting ensures that the amino groups are primarily localized on the surface of MSNs and the pores inside will remain free for drug loading. Such a method provides good flexibility as the extent of functionalization can be tailored by tuning various parameters of reaction, thus making the method suitable to applications requiring surface-specific modifications.(63)

## C. Co-Condensation Method

Co-condensation This procedure involves the simultaneous addition of a silica precursor, such as tetraethyl orthosilicate, TEOS, and an amino-functional precursor, for example, APTES during synthesis. Since the condensation occurs together, all these amino groups distribute uniformly in the MSN structure, including pore walls and surface. Co-condensation has an advantage in terms of stability because the amino groups are bonded into the whole silica framework, resulting in more stable functionalized MSNs than with post-synthetic grafting. Thus, optimization of the method is necessary to balance the pore structure and the density of functional groups because too high an amino precursor would disturb ordered mesoporous architecture.(64,65)

## D. Click Chemistry-Based Functionalization

Click chemistry is an extremely selective and efficient methodology for amino-functionalization. Here, azide-functionalized MSNs react with alkynes bearing amino groups

through copper-catalysed azide-alkyne cycloaddition (CuAAC) reactions. In general, click chemistry offers the ability to have precise control over the location and density of functional groups without altering the structure of the MSN. Orthogonal and biorthogonal conjugations in any application are particularly valuable utilizing this method.(66)

## E. Peptide and Polymer Grafting

MSNs can also be grafted with amino groups through the immobilization of polymers or peptides harboring abundant amine functionalities. For instance, polyethyleneimine is the polymer richest in primary, secondary, and tertiary amines. Indeed, PEI is most predominantly used for the coating of MSNs. The PEI layer not only provides high density of amino groups but also increases the biocompatibility, dispersibility, and stability of MSNs in physiological environments. Thus, it is possible to add bioactive functionalities besides amino groups with peptide grafting and has specific interactions with biological targets.(67)

## F. Layer-by-Layer Assembly

The process involves the layer-by-layer deposition of oppositely charged polyelectrolytes on the surface of MSN. Polymers with amino groups, such as poly-L-lysine or PEI, are selected as one of the layers. Layer-by-layer deposition of functional coatings using this technique provides excellent control over the thickness and density of the resulting coating, making generally an attractive technique for applications where tailored surface properties are required.(68)

## G. Enzyme-Mediated Functionalization

Enzyme-catalyzed reactions are very mild and highly specific for the introduction of amino groups onto MSNs. For example, transaminases



catalyze the transfer of amine groups to pre-immobilized selective substrates on the surface of MSN. While this approach has some advantages that are less often encountered in practice, the biocompatibility and environmentally friendly conditions of the reaction make it more favorable for sensitive applications like drug delivery and biosensing.(69)

### 3.2 Impact of amino functionalization on MSN properties

The factor which makes mesoporous silica nanoparticles versatile and effective for biomedical applications, especially in drug delivery systems and cancer therapy, is amino functionalization. The amino groups (-NH<sub>2</sub>) are valuable in developing favorable electrostatic interactions with negatively charged molecules like hydrophilic drugs, proteins, and nucleic acids. This ensures stable encapsulation and effective therapy. Moreover, amino groups improve the hydrophilicity of MSNs and increase their dispersion in aqueous and physiological media. Aggregation of nanoparticles is prevented, thus allowing uniform delivery of drugs.(39,70) Functionalized MSNs also present with stimuli-sensitive behavior because the protonation of amino groups in acidic environments triggers drug release in a controlled manner. This aspect is especially useful for targeting microenvironments within the tumor because such conditions are encountered, thereby allowing for a site-specific drug delivery and reducing systemic side effects. Amino groups on the MSN's surface also offer reactive sites that can be used for covalent bonding

with targeting ligands, polymers, and imaging agents. This thus enables the design of multifunctional MSNs where drug delivery can be integrated with therapy and diagnostics in one system.(61) Amino-functionalization also enhances the biocompatibility of MSNs as a result of further surface modification with biocompatible polymers, such as polyethylene glycol (PEG). These modifications reduce immunogenicity and prolong circulation times in vivo for safer clinical applications. The instability of MSNs under physiological conditions is significantly suppressed as a result of a reduction in the degradation of surface groups and inhibition of premature drug release so that therapeutic agents remain intact until reaching their target sites. The positive charge that amino groups confer on MSNs changes the zeta potential, thus allowing interaction with the negatively charged cell membrane and encouraging internalization. Thus, efficient intracellular delivery, especially in cancer cells or intracellular pathogens, is observed.(39,71) Amino-functionalized MSNs can also be compatible with biomolecules and may conjugate with enzymes, proteins, or nucleic acids for gene therapy or biosensing applications, among others. Functionalization also allows researchers to tailor their fabrication of MSNs according to specific therapeutic and diagnostic requirements since the density of amino groups during functionalization can be controlled. To cut it short, amino functionalization can prove to provide versatility, stability, and efficacy in MSNs, thereby making it a useful tool in modern nanomedicine and precision therapy.(72,73)

**Table 1: Summary of Polymers Used in Amino-Functionalized MSNs**

Polymer	Functional Properties	Role in Enhancing MSN Efficiency	Reference
<b>Polyethylenimine (PEI)</b>	Positively charged, high amine density, biocompatible	Enhances drug and gene loading efficiency through electrostatic interactions; improves cellular uptake.	(74)

<b>Chitosan</b>	Biodegradable, mucoadhesive, positively charged at acidic pH	Facilitates pH-responsive drug release and improves stability in physiological environments.	(75)
<b>Polyethylene glycol (PEG)</b>	Hydrophilic, biocompatible, reduces immunogenicity	Extends circulation time by providing a stealth coating; minimizes clearance by the immune system.	(76)
<b>Polydopamine (PDA)</b>	Biocompatible, strong adhesive properties	Provides a versatile platform for further functionalization and improves stability in biological fluids.	(77)
<b>Poly-L-lysine</b>	Cationic, biodegradable, amine-rich	Enhances nucleic acid binding for gene delivery; promotes efficient cellular uptake and transfection.	(78)
<b>Polyvinylpyrrolidone (PVP)</b>	Hydrophilic, stabilizes colloidal systems	Improves dispersibility and prevents nanoparticle aggregation in aqueous solutions.	(79,80)
<b>Polyacrylic acid (PAA)</b>	Negatively charged, pH-responsive	Enables dual-functional systems for controlled drug release and enhanced targeting in acidic environments.	(81)
<b>Zwitterionic Polymers</b>	Neutral net charge, antifouling properties	Reduces nonspecific protein adsorption; improves biocompatibility and circulation in vivo.	(82)

### 3.3 Advantages of amino-functionalized MSNs in biomedical applications

#### A. Enhanced Drug Loading Capacity

Such a framework has significant electrostatic interaction with negatively charged drugs, biomolecules, or therapeutic agents as well as the presence of amino groups (-NH<sub>2</sub>). This leads to enormous improvement for the drug loading capacity; therefore, amino-functionalized MSNs are among the best systems for carrying both hydrophilic and hydrophobic molecules.

#### B. Stimuli-Responsive Drug Release

Amino-functionalized MSNs can respond to specific environmental triggers, such as pH or

enzymatic activity. This is demonstrated through the controlled and targeted release of drugs in acidic tumour microenvironments supposed to minimize systemic side effects from the drug.

#### C. Improved Biocompatibility

The biocompatible polymers, such as polyethylene glycol (PEG), are attached to the amino groups for reduced immunogenicity and better compatibility with biological systems. This makes the compound safer for in vivo applications..

#### D. Targeted Drug Delivery

MSNs can have amino groups that serve as an active site for attaching targeting ligands, which may be antibodies, peptides, or even folic acid. These ligands allow nanoparticles to selectively bind to certain cells or tissues, such as cancer cells, thus providing therapeutic sensitivity.

### **E. Increased Stability in Physiological Environments**

This functionalized surface ensures that degradation of MSNs in biological environments is prevented, thus implying that the nanoparticles will stay intact with their structure as encapsulated drugs remain intact in circulation.

### **F. Facilitated Cellular Uptake**

The amino groups will have a positive charge that effectively interacts with the negatively charged cell membrane to induce endocytosis. This way, its internalization within cells is positively enhanced and, thereby, an effective tool for intracellular drug delivery.

### **G. Reduced Aggregation**

Dispersibility of amino-functionalized MSNs improved in an aqueous solution that prevents their aggregation. This ensures uniform distribution in the bloodstream or other biological fluids, enabling consistent therapeutic delivery.

### **H. Versatility in Functionalization**

The reactive amino groups of the MSN surface will provide a suitable place to attach imaging agents, therapeutic molecules, and other functional groups with which theranostic multifunctional nanoparticles can be designed.

### **I. Compatibility with Biomolecules**

Amino-functionalized MSNs have shown high compatibility with biomolecules such as enzymes, nucleic acids, and proteins. It makes them quite suitable for possible applications in gene therapy, enzyme delivery, or biosensing.

### **J. Overcoming Multidrug Resistance (MDR)**

These may be co-loaded with drugs and resistance inhibitors, so they might bypass or overcome the action of multidrug resistance mechanisms from cancer cells. This would increase the efficiency of chemotherapy drugs.

### **K. Integration of Imaging and Therapy**

Functionalized MSNs can encapsulate simultaneously therapeutic agents and imaging contrast material with other kinds, such as quantum dots or fluorescent dyes. This can be realized in real-time monitoring of drug delivery and therapeutic response, thus combining diagnostics and treatment through a single platform.

### **L. Scalability and Cost-Effectiveness**

Chemical methods of amino-functionalization are relatively simple and inexpensive, allowing for large-scale preparation of amino-functionalized MSNs for research and putative clinical applications.(55,61,80,83)

## **4. Mechanisms of Targeted Drug Delivery Using Amino-Functionalized MSNs**

### **4.1 Surface modification for active targeting**

Among these approaches, one of the most important surface modifications of amino-functionalized mesoporous silica nanoparticles for achieving active targeting in drug delivery systems is the functionalization of the nanoparticle surface



with specific ligands or molecules specifically interacting with overexpressed receptors on the surface of target cells, qualitatively in this case, cancer cells. This increases the specificity of the treatment and reduces off-target effects, where the safety and effectiveness of treatment improve.(38,84) The amino groups on the surface of MSNs can offer versatile reactive sites through which targeting ligands can be covalently attached. These targeting ligands include antibodies, peptides, aptamers, folic acid, and small molecules, all of which are capable of selectively recognising and binding cell-surface receptors which are often displayed on diseased tissues. For instance, folic acid is typically conjugated onto the surfaces of amino-functionalized MSNs to target folate receptors, which are characteristically overexpressed in different types of cancers. Similarly, peptides like RGD (arginine-glycine-aspartic acid) for the binding of integrin receptors in tumour cells and angiogenic endothelial cells allow targeted delivery to the vasculature of the tumours.(42,85) The third one is antibody-based targeting, whereby monoclonal antibodies are conjugated onto the surface of amino-functionalized MSNs. The antibodies bind to specific tumour antigens, such as HER2 in the case of breast cancer, which makes the therapeutic agent specifically delivered to the tumour site. Aptamers, for instance, may be attached onto amino groups and are very specific with a high affinity towards cancer biomarkers. These bifunctional ligands ensure that the drug-loaded nanoparticles will accumulate in diseased tissues only, making the therapeutic index higher.(86,87) Even higher accuracy in active targeting can be achieved through the use of dual or multi-targeting strategies. Attaching several ligands to the surface of MSN can target heterogeneous tumour environments or attain synergistic effects, such as the concurrent targeting of both the tumour cells and the tumour

vasculature. This flexibility underlines the flexibility of amino-functionalized MSNs in complex biological systems.(88,89)

#### 4.2 Passive targeting mechanisms

Passive targeting is drug delivery design that utilizes tissue-specific physiological and anatomical features, especially those of a tumor, to enable the accumulation of nanoparticles without the need for targeted ligands or active functionalization. This is supported by phenomena such as the EPR effect, vascular leakage, and poor lymphatic drainage, which are typical features of the microenvironment of both a tumor and inflamed tissues. One of the fundamental principles in the application of the passive targeting in cancer therapy is based on the EPR effect. Tumours possess leaky blood vessels with large fenestrations, usually 100–800 nm in size, which allows nanoparticles of suitable size (10–200 nm) to leak out and get retained in the tumour microenvironment. Poor lymphatic drainage in tumours also means there will be inefficient clearance of nanoparticles, thereby allowing for prolonged retention and increased drug delivery to the tumour site. This has significantly improved the therapeutic index of anticancer agents delivered through mesoporous silica nanoparticles (MSNs). One of the fundamental principles in the application of the passive targeting in cancer therapy is based on the EPR effect. Tumours possess leaky blood vessels with large fenestrations, usually 100–800 nm in size, which allows nanoparticles of suitable size (10–200 nm) to leak out and get retained in the tumour microenvironment. Poor lymphatic drainage in tumours also means there will be inefficient clearance of nanoparticles, thereby allowing for prolonged retention and increased drug delivery to the tumour site. This has significantly improved the therapeutic index of anticancer agents



delivered through mesoporous silica nanoparticles (MSNs). Passive targeting mechanisms make use of the unique characteristics of the tumor microenvironment. Acidity, hypoxia, and high interstitial pressure all create conditions that favor accumulation and retention of MSNs. For instance, pH-sensitive MSNs will release their drug payload in a precisely targeted manner in an acidic environment of a tumour while still relying on passive targeting pathways. Another important factor in passive targeting is prolonged circulation time. Functionally, stealth coatings, such as PEG, which inhibit immune clearance, increase the fraction of nanoparticles that get to the tumour site through increased exposure time to leaky vasculature. Such a mechanism is also efficient in inflamed tissues in which increased vascular permeability and local oedema mimic the conditions found at the tumour microenvironment, thus making such tissues ideal targets for passive drug delivery. While passive targeting has several benefits like less complex preparation and being cost-effective, it has some limitations. The EPR effect is less predictable and less efficient among the different types of tumors and among patients. In addition, off-target accumulation in organs like the liver, spleen, and kidneys may limit its usage on a larger scale. Despite these disadvantages, passive targeting remains a very useful strategy in nanomedicine, particularly when delivering anticancer medicines because it exploits physiological processes and is tolerated by various biological systems.(90–93)

### 4.3 Controlled drug release kinetics

Controlled release kinetics involves the well-controlled mechanism and release of a drug from a delivery system, which will provide sustained therapeutics while reducing side effects. Usually, this is achieved within MSNs through structural engineering and surface modification along with

introduction of stimulus-responsive mechanisms. The large surface area, tuneable pore size, and large pore volume that characterise MSNs facilitate the controlled release of drugs through diffusion from within the pores upon encapsulation. Smaller pore sizes decrease the release rates whereas higher pores allow fast diffusion into the target organ thus facilitating the flexibility to tailor the profiles of release. Mesoporous frameworks protect the encapsulated drugs from premature degradation, allowing them to survive circulation and be released in a controlled manner at the desired site. The next step further implements stimulus-sensitive mechanisms that enhance the controlled-release properties of the drugs in MSNs. pH-responsive MSNs are engineered to release the drug in the acidic condition of the tumors, and this is done through site-specific delivery. Enzyme-responsive MSNs exploit the overexpressed enzymes in diseased tissues to trigger the drug release. Advanced control over the kinetics of drug release can be achieved through the functionalization of the surface of the MSN with polymers, gatekeeper molecules, or responsive linkers. The polymer-based hydrophilic barriers are developed to delay the release; on the other hand, gatekeeper molecules like cyclodextrins block pores inside the MSN and respond accordingly to stimuli for release of drugs. Functional linkers can offer a good means of covalent attachment of drugs to the surface of MSN, ensuring a release only in the presence of specific triggers, such as redox conditions. Controlled release kinetics provide long therapeutic effects, reducing the frequency of dosing and minimizing the fluctuation of drug concentration. This is very useful in overcoming the systemic toxicity and, hence, improving compliance. The MSNs are suitable for combination therapies; different drugs with different release kinetics can be incorporated inside to get more synergy while loading



separately. The drug release kinetics can be well-controlled by the models available, such as zero-order, first-order, or Higuchi, establishing the rate and the mechanism of drug release. Controlling drug release kinetics in MSNs provides a versatile yet efficient platform for precise, sustained, and stimuli-responsive delivery and thus promotes advanced targeted therapies with improved clinical outcomes.(94,95)

## 5. Applications in Breast Cancer Therapy

### 5.1 Encapsulation and delivery of chemotherapeutic agents

Incorporation and delivery of chemotherapy agents in a mesoporous silica nanoparticles system have been recognized as a revolutionary concept in cancer therapy, which overcomes the limitations of traditional chemotherapy, including systemic toxicity and poor bioavailability, along with non-selectivity to tumor. MSNs also have unique structural and functional properties that make them very suitable for effective encapsulation, controlled release, and targeted delivery of anticancer drugs. MSNs have a high surface area and pore volume, combined with the possibility of tuning the pore size, which allows for efficient loading of chemotherapeutic agents, regardless of whether the drugs are hydrophilic or hydrophobic. This encapsulation in the porous structure of MSNs keeps the drugs away from premature degradation inside the bloodstream, hence enhancing their stability and integrity as they reach the target site. The capability also renders control over the pore size, thus providing optimal drug release rates and minimizing the burst release effect while maintaining therapeutic concentrations over time.

MSNs can be functionalized by attachment of various ligands, like antibodies, peptides, or folic acid, for targeted delivery to cancer cells.

Functionalization with folic acid allows for selective binding to folate receptors, which is overexpressed in the majority of tumors. Similarly, peptides, such as the RGD sequence (arginine-glycine-aspartic acid) peptide target integrin receptors of the vasculature of tumors for enhanced selective accumulation of drug-loaded MSNs within malignant tissues. This active targeting reduces off-target effects and systemic toxicity, common with traditional chemotherapy. Stimuli-responsive MSNs further amplify the delivery of chemotherapeutic agents. Specifically, drug payload released in the acidic tumour microenvironment by pH-sensitive MSNs, and drugs are released on interaction with enzymes overexpressed in the tumour site by enzyme-responsive MSNs. These mechanisms ensure site-specific drug release, thus increasing therapeutic efficacy and minimizing side effects. Combination therapies also present substantial merits with MSNs. More than one chemotherapeutic agent can be co-loaded into MSNs with various release profiles, and these drugs could be simultaneously or sequentially released to maximize synergistic effects. For instance, drugs that target multiple pathways in the cancer cells can be encapsulated further to enhance treatment outcomes. More importantly, MSNs are engineered to encapsulate chemotherapeutic agents and imaging contrast agents to facilitate real-time drug tracking for monitoring therapeutic responses upon drug delivery.(96–98)

### 5.2 Gene delivery applications

Mesoporous silica nanoparticles, or MSNs, have become a highly versatile and efficient drug delivery platform pushing to overcome key challenges in regard to stability, transfection efficiency, and target specificity. Gene therapy-the delivery of genetic material such as DNA, RNA, or gene-editing tools like CRISPR/Cas9-to cells



holds tremendous potential for the treatment of genetic disorders, cancers, and many other diseases. These structural properties of MSNs-high surface area, tuneable pore size, and biocompatibility-permit successful encapsulation and thus protection of nucleic acids. Encapsulation within MSNs protects genetic material from the devastating enzymatic degradation present in the bloodstream, leading to stability and improved delivery. Functionalization of the MSN surface with positively charged groups, like amino or polyethyleneimine groups, is achieved in order to favor electrostatic interactions with negatively charged nucleic acids. This aspect helps improve loading capacity and stability of formed complexes. Moreover, conjugation of targeting ligands, such as peptides, aptamers, or antibodies, onto MSNs facilitates selective delivery of genetic material to target cells or tissues. For example, the RGD (arginine-glycine-aspartic acid) peptides increase affinity to the receptors on tumor cells for the integrin, thus increasing therapeutic specificity while reducing off-target effects. MSNs can be engineered to depolymerize in response to specific stimuli, such as pH, redox conditions, or enzymatic activity, releasing their genetic payload. pH-sensitive MSNs activate within acidic environments, such as those found in tumors or endosomes, thereby ensuring intracellular delivery. Redox-responsive MSNs exploit glutathione concentrations found within the cytoplasm to liberate nucleic acids after endocytosis. Such stimulus-responsive mechanisms increase the specificity and efficiency of gene delivery. MSNs also facilitate cellular uptake via endocytosis. The payload delivery to the cytoplasm or nucleus can be achieved by applying pH-sensitive coatings or fusogenic peptides to enhance endosomal release and avoid lysosomal degradation. Besides DNA nucleic acid delivery, recent studies have explored the use of MSNs in applications with other gene-editing tools

like CRISPR/Cas9 complexes, whereby precise genome editing with minimal off-target effects can take place. This capability shall support MSNs as a promising tool in dealing with genetic disorders and cancers through targeted gene modification. Besides, MSNs allow for the co-delivery of genes with therapeutic agents. For example, MSNs can simultaneously deliver siRNA to silence oncogenes and chemotherapeutics to induce apoptosis, providing a synergistic therapeutic effect. In addition, with their excellent biocompatibility and low immunogenicity, MSNs also allow for in vivo safety, although further improvements can be achieved through surface modifications like PEGylation in order to extend the circulation time and reduce immune clearance.(96,98,99)

### **5.3 Photothermal and photodynamic therapy approaches**

Among the newly found non-invasive cancer treatments is photothermal therapy and photodynamic therapy. In them, light-activated mechanisms are involved that allow for selective damage to be executed on the tissues of the tumors. Mesoporous silica nanoparticles, or MSNs, have been shown to be a good platform for such therapies because they can encapsulate therapeutic agents, provide for the functionalization of surfaces, and offer exact targeting to the tumour, coupled with minimal damage to adjacent healthy tissues.

#### **A. Photothermal Therapy (PTT)**

Photothermal therapy is based on the transduction of light energy to local warmth, killing cancer cells. MSNs can be functionalized with photothermal agents; gold nanorods, graphene oxide, and carbon nanotubes are but a few examples. These agents could absorb NIR light with great efficiency and thus produced localized



hyperthermia upon irradiation, eventually causing permanent damage to tumor cells. This is achieved by acting as carriers for photothermal agents. This ensures that photothermal agents are accumulated in the tumour tissues either passively, via the EPR effect, or by active targeting. The high thermal conductivity and stability of MSNs prevent photothermal agent degradation and, therefore improve the efficiency of the treatment. The benefits of PTT are accurate spatial control in that it targets the light beam to the site where the tumor is. This reduces systemic toxicity and side effects. Additionally, MSNs can integrate PTT with drug delivery through co-encapsulation of chemotherapeutic agents, thus providing synergistic effects whereby hyperthermia could boost the permeability of cancer cell membranes to bring about enhanced uptakes of drugs.(100,101)

### **B. Photodynamic Therapy (PDT)**

Photodynamic therapy is a treatment that utilizes activated photosensitizer by wavelength of specific light to produce ROS that causes oxidative damage and tumor cell apoptosis. MSNs also act as efficient carriers for the photosensitizers such as porphyrins, phthalocyanines, or chlorin, which is protected from premature degradation and is selectively targeted to accumulate in the tumor tissue. High loadings of photosensitizers are possible with the porous structure of MSNs; meanwhile, surface functionalization can result in ligands targeting specific cancer cells for the nanoparticles to target. Once stimulated by light, ROS produced by the photosensitizers cause localized damage to the tumour while preserving healthy tissues. MSNs can even be designed to respond to specific stimuli such as pH or enzymes in the microenvironment of the tumour, thus ensuring that the release of the photosensitizer is strictly at the targeted site.(102,103)

### **C. Synergistic Applications of PTT and PDT**

A platform designed to integrate both PTT and PDT is thought to make use of a combination of mechanisms that might eventually maximize therapeutic efficacy. For instance, MSNs can encapsulate the photothermal agent simultaneously with the photosensitizer for generation of heat and ROS production upon light irradiation. In this regard, this approach may target cancerous cells through multiple pathways, reducing a good measure of resistance and increasing the chances of better outcomes. It also proves to be highly beneficial for the treatment of aggressive and drug-resistant tumors.(101)

### **5.4 Combination therapies and synergistic effects**

Combination therapy is the innovative concept of cancer treatment that seeks simultaneous or sequential application of multiple therapeutic strategies to achieve higher efficiency and overcome any limitations of single therapy. MSNs have been identified as an ideal platform for combination therapies since they can accommodate a wide range of therapeutic agents within their pores and release these agents in a controlled or stimuli-responsive fashion. MSNs could potentially offer synergistic effects, maximize therapeutic outcomes, and minimize systemic toxicity through the delivery of multiple agents with complementary mechanisms of action. For instance, MSNs may simultaneously deliver chemotherapeutic agents and genetic material such as siRNA or CRISPR/Cas9 complexes. In this manner, it is possible to silence oncogenes with siRNA while simultaneously causing apoptosis through chemotherapeutics so that the multiple pathways in cancer progression are targeted, reducing the opportunities for drug resistance.(49,104,105) Another application of MSNs as combination therapies is applied in drug



delivery systems in conjunction with phototherapy and chemotherapy. Among those, photothermal therapy is primarily based on the action of photothermal agents on the NIR light for interference of the tumour microenvironment, improving the uptake and efficacy of the co-delivered chemotherapeutic drugs. An example is also photodynamic therapy that produces ROS sensitizing cancer cells to chemotherapy and amplifies the therapeutic effect. Meanwhile, MSNs can also be targeted to the cancer cells and the TME. Agents targeted to the acidic or the enzyme-rich TME can normalize the tumor environment while chemotherapy agents target the cancer cells directly, hence creating a dual-action strategy aimed at breaking the tumor growth and metastasis cascade.(96,106) MSNs are also highly effective in the combination of immunotherapy and chemotherapy. For instance, MSNs can deliver checkpoint inhibitors, such as anti-PD-1 antibodies, to activate immune responses while simultaneously releasing chemotherapeutics to

reduce tumour burden. This synergistic effect enhances immune system activity and directly targets cancer cells. Further, MSNs allow for the sequential or controlled release of therapeutic agents to optimize their synergistic effects. For instance, the photothermal agents in PTT and chemotherapy first disrupt the tumour vasculature to improve drug delivery and uptake, after which the chemotherapeutic agents are released to achieve maximum efficacy.(107–109) Combination therapies involving MSNs have the benefits of increased therapeutic efficacy with reduced toxicity at lower doses of drugs and overcoming resistance by targeting multiple pathways. Application of functionalised MSNs ensures targeted delivery of combination therapies to the tumour sites while avoiding healthy tissues for improved treatment outcomes. Due to their structural and functional versatility, MSNs can open a wide avenue of opportunities for combination therapies, affording new hope for complex and drug-resistant cancers.(96,97)

**Table 2: Recent Studies on Amino-Functionalized MSNs in Breast Cancer Therapy**

Drug(s) Used	Mechanism of Action	Targeting Strategies	Therapeutic Outcomes	References
Doxorubicin	Induces DNA intercalation and apoptosis in cancer cells	Folic acid-functionalized MSNs targeting folate receptors	Enhanced drug uptake, reduced off-target toxicity, and significant tumour volume reduction.	(110)
Paclitaxel and siRNA	Inhibits microtubule dynamics and silences drug-resistance genes	Co-delivery via PEG-coated MSNs for passive targeting	Improved drug sensitivity and suppression of multidrug resistance in breast cancer cells.	(111)
Cisplatin and Curcumin	DNA crosslinking and ROS-induced apoptosis	pH-responsive MSNs targeting tumour microenvironment	Synergistic effects, increased apoptosis, and reduced systemic toxicity.	(97)
CRISPR/Cas9 and Doxorubicin	Gene editing of oncogenes and DNA intercalation	RGD peptide-functionalized MSNs targeting integrin receptors	Precise gene editing, enhanced apoptosis, and reduced tumour metastasis.	(112)

Gemcitabine and Photosensitizer	Inhibits DNA synthesis and ROS-mediated tumour destruction	Photodynamic therapy integrated with drug delivery	Enhanced tumour destruction, improved survival rates, and minimal damage to surrounding tissues.	(113)
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## 6. In Vitro and In Vivo Studies

### A. Cellular Uptake and Cytotoxicity Assessments

Cellular uptake and cytotoxicity testing play significant roles in determining the feasibility and safety of mesoporous silica nanoparticles (MSNs) as drug delivery nanosystems. The high surface area and modification on the surface of MSNs make them prone to endocytosis inside cells. Factors affecting the cellular uptake include particle size, surface charge, and functionalization of MSNs. For example, positively charged MSNs, which are most often functionalized with amino groups, have greatly enhanced uptake because of the electrostatic attraction between those species and the negatively charged cell membrane. Cellular internalization is most commonly assessed by fluorescence or confocal microscopy observations of nanoparticle uptake and intracellular localization. Cytotoxicity studies are performed to confirm that MSNs with their encapsulated drugs could kill target cells effectively-in the case of cancer cells-with no damage inflicted on normal cells. Assays, such as MTT or CCK-8, are used to determine the cell viability and proliferation. The developed MSNs potentially have therapeutic applications, accompanied by a good safety profile.(114)

### B. Animal Model Studies and Therapeutic Efficacy

Animal model studies would be of the highest desirability for evaluating the in vivo therapeutic

efficacy of MSNs in drug delivery. These would involve studies on the ability of MSNs to target diseased tissues or systems, deliver their pharmaceutical cargo, and induce desired effects in physiological settings. In the majority of cases, the commonly used models are mouse models of xenograft or orthotopic tumor models. For example, functionalized MSNs have been engineered for active targeting, causing preferential accumulation at the tumour site, thereby minimizing systemic toxicity. Therapeutic effectiveness is measured by reporting on aspects such as the reduction in size of the tumor and/or progression rate and survival. Besides effectiveness, animal studies assess the safety profile of MSNs based on the evaluation of effects on major organs and general health. This study's results provide important preclinical data concerning the translational potential of MSN-based drug delivery systems.(115)

### C. Pharmacokinetics and Biodistribution Profiles

Pharmacokinetics and biodistribution profiles are important to understand the in vivo behavior of MSNs especially their ADME: absorption, distribution, metabolism and excretion. Pharmacokinetics studies focus on the circulation time, the elimination of MSNs considering especially size, surface modifications and presence of stealth coatings like polyethylene glycol (PEG). MSNs with longer circulation times allow them to accumulate preferentially at the target sites, such as tumors, due to the EPR effect. Biodistribution studies monitor the localization of MSNs in vivo

by imaging techniques, such as fluorescence imaging, MRI, or positron emission tomography. It is evident from these studies that there is preferential accumulation of MSNs at the target site and reduced clearance from other non-target tissues, like the liver and spleen. Pharmacokinetics and biodistribution analyses play a significant role in the optimization of MSN design to achieve maximum therapeutic efficacy and minimum off-target effects, which makes them suitable for their clinical translation.(116)

## 7. Safety and Toxicity Considerations

### A. Biocompatibility and Biodegradability of Amino-Functionalized MSNs

Biocompatibility and biodegradability are the keys for the effective utilization of amino-functionalized mesoporous silica nanoparticles as nanocarriers in drug delivery and therapeutic systems. The silica framework of MSNs is biocompatible per se, but functionalization with an amino group further enhances this property by allowing further surface modifications, including attachment of biocompatible polymers like PEG, that limits nonspecific interactions and minimizes cytotoxic effects. MSNs hydrolyze in vivo to silicic acid, a nontoxic degradation product that is excreted non-toxically through the kidneys. The hydrolysis rate can be controlled by the preparation conditions and adjusted for compatibility with numerous therapeutic time scales. In vivo biodegradation research demonstrates that amino-functionalized MSNs degrade efficiently so that the long-term accumulation in the body with potential toxicity issues is ruled out. Biocompatibility and biodegradability indicate this family of NPs as good candidates for clinical applications.(117)

### B. Potential Immunogenic Responses

Despite these advantages, the potential immunogenicity of amino-functionalized MSNs must be carefully taken into consideration. The functionalized nanoparticles may interact with the immune cells and evoke inflammatory or immune responses. The surface charge and hydrophilicity of MSNs would affect the recognition of the MPS, leading to opsonization and clearance. Amino-functionalized MSNs are positively charged; therefore, they will possibly have higher interactions with immune cells, and this interaction will possibly result in cytokine release and complement activation. To further mitigate such risks, the surface coatings of PEG or zwitterionic polymers are often used to enhance stealth properties and reduce immune recognition. In vitro and in vivo preclinical studies are important to evaluate the immunogenicity of MSNs, so their safety for systemic administration and repeat dosing in the clinical setting is ensured.(118)

### C. Long-Term Toxicity Studies and Clinical Implications

Long-term toxicity studies are required to evaluate the safety profile of amino-functionalized MSNs, especially for chronic or repeated-use applications. Although MSNs are generally biocompatible, their retention in organs such as the liver, spleen, and lungs over a long period may be toxic. Some of the experimental studies comprise histopathological examination of the main organs, monitoring the serum biomarkers for toxicity, and clearance of MSNs over an extended time. For instance, an amino group or biocompatible coating can mitigate some of these toxicities, though rigorous evaluation must be done to exclude delayed adverse effects. Clinical implications involve patient safety features through well-defined dose limits, optimized degradation rates, and comprehensive toxicity data. Long-term study



outcomes drive the translation of these amino-functionalized MSNs from preclinical research to clinical trials with assurance in their employment as effective and safe drug delivery systems.(119)

## 8. Challenges and Future Perspectives

### A. Current Limitations in Clinical Translation

Despite the high promise of amino-functionalized MSNs in drug delivery and therapy, several challenges still cloud their clinical translation. Lack of information or a history of long-term safety and toxicity profiles is one of them. These structures are mostly biocompatible and biodegradable; however, their behavior concerning potential accumulation and potential long-term effects in organs like liver, spleen, and lungs could be a dilemma. Variability in the EPR effect among different types of tumours and patient populations also decreases predictability for passive targeting mechanisms. Manufacturing challenges, such as scalability, batch-to-batch consistency, and regulatory compliance, represent an important set of barriers to clinical implementation. Added to these is the relatively high cost of functionalization, especially for targeted delivery systems involving ligands or stimuli-responsive coatings.

### B. Strategies to Overcome Existing Challenges

Several approaches are under development to overcome these limitations. For example, regarding long-term toxicity, degradation of MSNs is optimized through modification of the chemical composition for improved rapid clearance and thus not contributing to accumulation in significant organs. Coating with biocompatible materials, such as PEG, minimizes immune recognition and enhances the circulation time, thus improving targeting efficiency. There is development in the production methods.

Development includes mechanization and scalable synthesis techniques towards making the process repeatable and economical. Regulatory issues can also be overcome through the development of standardized protocols on the characterization of MSNs, including their size, charge, surface modification, as well as their degradation profiles. Regarding the selectivity of the EPR effect, scientists are actively targeting the delivery by for example functionalizing MSNs with ligands that target specific tumour biomarkers ensuring consistent delivery. A transition from the laboratory to the clinic of MSNs is accomplished through collaborative efforts among researchers in academia, the industry, and regulatory agencies.

### C. Future Research Directions and Potential Innovations

Emerging technologies and innovative approaches would have to be used to explore future research in this amino-functionalized MSN field, such that current limitations are addressed. For instance, hybrid nanoparticle development is a promising direction where MSNs would be combined with lipids or polymers, for example, or metallic nanoparticles, to develop better multifunctional and targeted nanoparticles. The development of stimuli-responsive systems is also explored, such as light, temperature, and specific enzymes activated systems, which can enhance the precision of drug delivery. Another significant area of focus is personalized medicine, where MSNs can be designed specifically for patient-specific therapeutic agents, including gene therapies and immune modulators. Artificial intelligence and machine learning can be applied towards designing, optimizing, and accelerating nanoparticle-based delivery systems for more effective disease treatments. The horizon of the impact of MSNs may also be expanded beyond cancer therapy to infectious diseases, regenerative



medicine, or vaccine delivery. With these innovations coupled with rigorous preclinical and clinical studies, these are able to bypass current impediments and establish amino-functionalized MSNs as the cornerstone of advanced nanomedicine.(52,97,117)

## 9. CONCLUSION

Amino-functionalized mesoporous silica nanoparticles (MSNs) are a landmark in the targeted therapy of breast cancer, as they can rectify foremost problems that conventional treatments face: they can retain high structural features combined with functionalization capabilities to be able to provide efficient encapsulation, controlled release, and precise delivery of therapeutic agents. It enhances the drug's efficacy and reduces systemic toxicity as well as off-target effects. Other areas, like photothermal therapy and photodynamic therapy, gene delivery, can further help to illustrate their possible uses in combination therapies which provide synergistic effects to amplify therapeutic outcomes. Long-term toxicity, scalability and regulatory compliance are concerns and hurdles that are still outstanding for the development of nanomaterials. Nanoparticle engineering, biocompatible coatings, hybrid systems appear more promising and progress toward clinical translation. For example, the introduction of AI in nanoparticles optimization and the opening up of MSNs to non-oncological applications has revealed their vast potentials beyond oncology. And while research is unfolding, amino-functionalized MSNs will be that pillar of sophisticated nanomedicine where innovative research is merged with clinical application, bringing an improvement to the patient results in breast cancer treatment and providing a stride toward precision medicine.

### Author's contribution

All authors have equal contribution.

### Conflict of interest

Authors declare no conflict of interest.

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