2. LITERATURE SURVEY

2.1. Cancer

Human body is made up of millions of cells which grow, divide and die in conventional manner. Sometimes the system goes wrong and uncontrolled number of cells grow, which leads to cancer. Cancer, the uncontrolled growth of cells, combines these cells and leads to the formation of extra mass tissue known as tumor.[1] With 8.8 million deaths reported in 2015, cancer is found to be the second leading cause of death globally. Globally, nearly 1 in 6 deaths is due to cancer and approximately 70% of deaths from cancer occur in low- and middle-income countries.[2] Cancer metastasis is defined as the formation of new tumors (secondary and tertiary tumor nests) in tissues and organs away from the primary site of tumor origin and these metastases account for a vast majority of morbidity and mortality of cancer patients and is associated with about 90% of all cancer-associated deaths.[3]

2.2. Breast Cancer

Breast cancer, the most commonly occurring cancer in women, comprises almost one third of all malignancies in females.[4] Figure 2.1 represents the most commonly diagnosed cancer among female in 2012 and it can be clearly seen that females are suffering from breast cancer throughout the world including India. Breast cancer is the leading cause of cancer-related death among females worldwide. In 2012, an estimated 1.7 million cases and 521,900 deaths occurred.[5] Mortality rates are highest in the very young (less than age 35) and in the very old (greater than age 75).[6] It comes into sight that the very young have more aggressive disease, and the very old may not be treated aggressively or may have co-morbid disease that increases breast cancer fatality.[7]

Women from less developed regions (883 000 cases) have slightly more number of cases compared to more developed (794 000) regions.[8] In India, about 1,44,937 new cases of breast cancer were diagnosed and the number of women dying of breast cancer was 70,218. So, in India, for every 2 women newly diagnosed with breast cancer, one lady is dying because of breast cancer.[9]

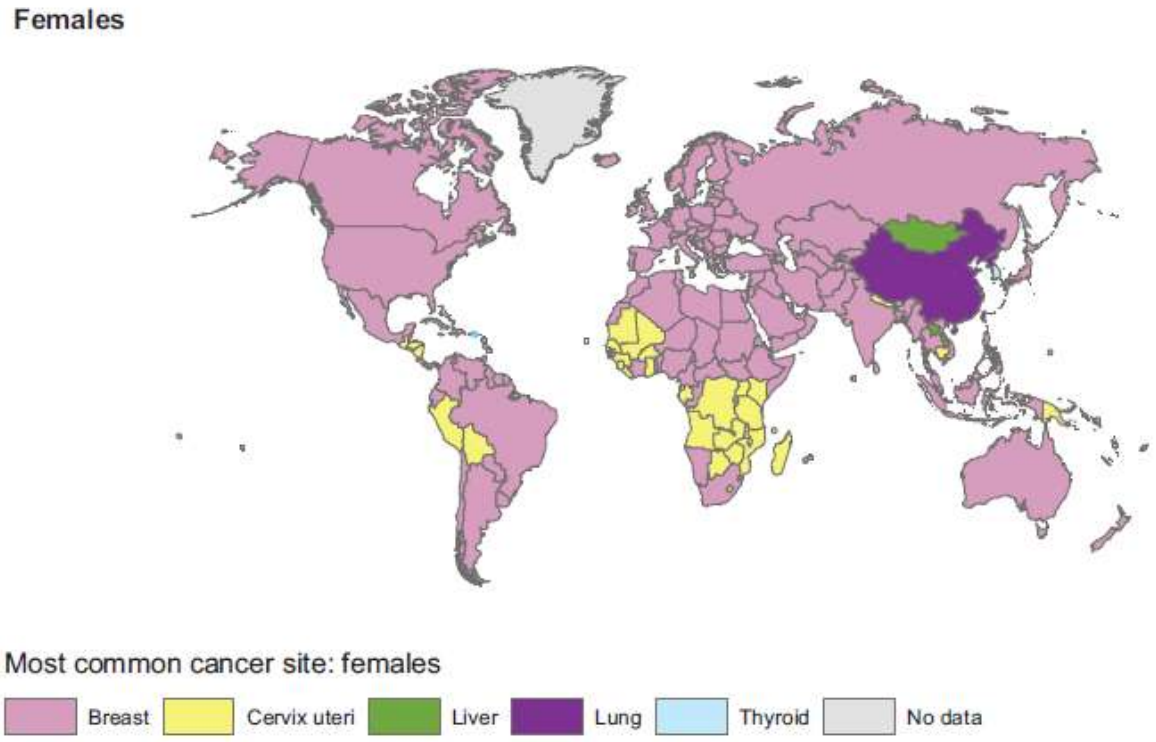

Figure 2.1: Most commonly diagnosed cancers, 2012. (Compiled from GLOBOCAN 2012.)

2.2.1 Current treatment approaches

Though great strides have been made in the treatment of cancer over the past years, it continues to be a major health concern and, therefore, extensive efforts have been made to search for new therapeutic approaches.[10] The conventional therapeutic approaches for cancer are surgery, chemotherapy, and irradiation; chemotherapy being an important component of treatment for cancer patients.[11]

The use of cytotoxic chemotherapy in both advanced and early stage breast cancer has made significant progress in the last few years with several landmark studies identifying clear survival benefits for newer therapies. Despite improvements with better understanding of the use of adjuvant therapies for early stage breast cancer, the treatment of metastatic disease remains a major challenge. The use of anthracyclines and taxanes in the adjuvant setting has led to an increasing number of women presenting with metastatic disease having already been exposed to these agents adding to the complexities of their management. Despite being incurable, metastatic breast cancer (MBC) often remains chemo-sensitive such that symptom control and prolongation

of survival can be achieved. However, response duration remains disappointingly short and long-term survival remains uncommon.[12]

2.2.1.1 Adjuvant Therapy:

Early breast cancer is limited to the breast alone or, in the case of women with node-positive disease, the breast and loco regional lymph nodes, and all detected disease can be removed surgically. The delay in the initiation of chemotherapy post surgery is no longer an issue due to improved surgical techniques. Chemotherapy is routinely commenced within six weeks of surgery if indicated. However, micrometastatic disease may remain either locally or at distant sites that, if left untreated, could over the coming years develop into a life-threatening clinical recurrence.[12]

Over the past few years, thousands of women have been enrolled into various clinical trials addressing questions over the role of chemotherapy versus no chemotherapy, role of polychemotherapy versus single agents, role of anthracyclines versus no anthracyclines, role of doses and schedules, and more recently adding taxanes and other novel compounds in chemotherapy arms. The most commonly used standard adjuvant chemotherapy regimens are listed in Table 2.1.

Table 2.1: Standard Adjuvant Chemotherapy Regimens.[4]

Standard Regimens	Components
AC (w or w/o T)	Adriamycin, cyclophosphamide, Taxol
CMF	Cyclophosphamide, methotrexate, fluorouracil (5-FU)
CEF	Cyclophosphamide, epirubicin, fluorouracil (5-FU)
CAF	Cyclophosphamide, adriamycin, fluorouracil (5-FU)

Polychemotherapy using an anthracycline-containing regimen has been the cornerstone of treatment for women without pre-existing heart disease who require adjuvant chemotherapy for breast cancer.[13,14]

2.2.1.2 Chemotherapy for Metastatic Breast Cancer (MBC):

Although generally incurable, MBC remains chemosensitive such that symptom palliation and prolongation of survival can be achieved. However, response duration remains disappointingly short- and long-term survival remains uncommon, such that ongoing research is required.[12]

Anthracyclines possess significant activity in chemo-naive patients or those who received them in the adjuvant setting more than 12 months ago. Response rates of 30-40% have been documented in patients with MBC.[15,16] Despite their significant role in the adjuvant setting, the use of anthracyclines in patients with MBC may be limited by significant toxicity. For patients exposed to anthracyclines in the adjuvant setting or who have failed in the metastatic setting, taxane based treatment is currently the standard of care.[17] Capecitabine has demonstrated single agent activity in MBC, with a response rate in excess of 20% and median survival greater than 1 year even in patients with disease refractory to both anthracycline and taxane, and with a favourable toxicity profile and oral bioavailability.[18]

Trastuzumab, in combination with chemotherapy has demonstrated a survival benefit over chemotherapy alone in patients with Her-2/neu expressing breast cancer. Trastuzumab in combination with either doxorubicin and cyclophosphamide or with paclitaxel achieved significantly greater time to progression, response rates, and 2-year survival compared to chemotherapy alone.[19]

2.2.1.3 Doxorubicin:

Doxorubicin hydrochloride (Dox)/Adriamycin HCl ((7S,9S)-7-[(2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7H-tetracene-5,12- dione; hydrochloride) is the prototype agent of anthracycline antibiotic, isolated from Streptomyces peucetius var caesius. It contains an amino sugar and an anthracycline ring.[20] It is among the most useful cytotoxic anticancer drugs as it is the most active agent against solid tumours, particularly breast cancer.[21] Dox has multiple mechanisms of action, including DNA intercalation and prevention of transcription, inhibition of topoisomerase II, and induction of cytotoxicity by the formation of oxygen free radicals. It is known to be rapidly and extensively distributed to various organs such as the heart, liver, kidney, and spleen.[22]

Though Dox is a highly efficient antitumor drug, its organotoxic potential (cardio-, hepato-, and nephrotoxicity) limits its clinical use. Dox is mainly metabolised in the liver, with doxorubicinol,

doxorubicinone, and 7-deoxydoxorubicinone as its major metabolites. Various mechanisms of Dox-induced toxicity have been proposed, including the inhibition of nucleic acid and protein synthesis, the generation of free radicals and the induction of apoptosis, but the exact metabolic causal mechanism of toxicity has not yet been fully elucidated.[22]

Li et al. used the plasma metabolomics technology to identify the toxic metabolites and metabolic pathways related to Dox-induced toxicity, providing information for the mechanism of system toxicity induced by Dox. Male Wistar rats were treated with Dox at a dose of 15 $mg.kg^{-1}$. Clinical chemistry analysis and histopathological examination showed that Dox caused liver, kidney, and heart injury in rats. The metabolomics result showed that fifteen metabolites were changed due to drug administration.[22]

Nylen et al. observed 50 patients with progressive metastatic breast carcinoma who were treated with weekly bolus injections of doxorubicin (15-20 mg). They concluded that weekly Dox with low doses is a moderately effective treatment in stage IV breast carcinoma. It is devoid of severe toxicity which makes it useful even in old and debilitated patients.[23]

2.2.1.4 Limitations of Chemotherapy:

Despite the significant advances in cancer detection, prevention, surgical oncology, chemotherapy and radiation therapy, there is still no common cure for cancer.[24,25] Chemotherapy is an effective treatment against cancer but undesirable chemotherapy reactions and the development of resistance to drugs which results in multi-drug resistance (MDR) are the major obstacles in cancer chemotherapy.[26]

- **Lack of selectivity & undesirable side effects:**

  Conventional chemotherapy relies on the premise that rapidly proliferating tumor cells are more likely to be destroyed by cytotoxic agents than normal cells. In reality, however, these cytotoxic agents have little or no specificity, which leads to systemic toxicity causing undesirable side effects.[25,27]

  "We have met the enemy, and he is us," a quote from the comic strip "Pogo" by Walt Kelly, summarizes the primary difficulty of treating tumors using chemotherapeutics, namely, that cancerous and normal cells are remarkably similar. Although cancer cells harbor mutated genes and resultant mutated proteins that affect cell division and/or contribute to oncogenesis, the tumor and normal cells share the same DNA and major metabolic pathways. Thus, traditional chemotherapeutic compounds that attack DNA

replication or cell division in a cancer cell can also attack a normal dividing cell, resulting in serious side effects such as neutropenia, anemia, hair loss, damage to liver, kidney, bone marrow and gastrointestinal toxicity.[28]

- **Multi drug resistance (MDR):**

  Apart from toxicity, chemotherapeutic drug resistance in cancer therapy further limits the usefulness of anticancer agent. Although the mechanism of drug resistance is not clearly understood, however the cancer drug resistance is mainly due to pump and non-pump resistances. Pump resistance is due to ATP binding cassette (ABC) transporters including over-expression of P-glycoprotein (P-gp), a multidrug resistance protein that alter anti-tumor drug transport mechanisms, multidrug resistance-associated protein such as mutated Topoisomerase II which decrease drug activation and accelerate drug degradation where drug gets inactivated by conjugating with increased glutathione and ABC sub-family G member 2 (ABCG2), which expel drugs from cancer cells. In addition, non-pump resistance is mainly caused by overexpression of antiapoptotic proteins (B-cell lymphoma 2 [BCL-2]) that prevent apoptosis in cancer cells.[29,30]

2.3. Nanotechnology in Cancer Therapy

The intrinsic limits of conventional cancer therapies prompted the development and application of various nanotechnologies for more effective and safer cancer treatment[31] as nanotechnology has the potential to revolutionize cancer diagnosis and therapy[32]. The increasing interest in applying nanotechnology to cancer treatment is attributable to its outstandingly appealing features for drug delivery, diagnosis and imaging, synthetic vaccine development and miniature medical devices, as well as the therapeutic nature of some nanomaterials themselves.[33-36] Distinctive features of nanotechnology in oncological applications are as follow:

- Improvement of the drug therapeutic index by increasing efficacy and/or reducing toxicities
- Targeted delivery of drugs in a tissue-, cell- or organelle-specific manner
- Enhancement of the pharmaceutical properties (for example, stability, solubility, circulating half-life and tumour accumulation) of therapeutic molecules
- Enabling of sustained or stimulus-triggered drug release
- Facilitation of the delivery of biomacromolecular drugs (for example, DNA, small interfering RNA (siRNA), mRNA and protein) to intracellular sites of action

- Co-delivery of multiple drugs to improve therapeutic efficacy and overcome drug resistance, by providing more precise control of the spatiotemporal exposure of each drug and the delivery of appropriate drug ratio to the target of interest
- Transcytosis of drugs across tight epithelial and endothelial barriers (for example, gastrointestinal tract and the blood–brain barrier)
- More sensitive cancer diagnosis and imaging
- Visualization of sites of drug delivery by combining therapeutic agents with imaging modalities, and/or real-time feedback on the in vivo efficacy of a therapeutic agent
- Provision of new approaches for the development of synthetic vaccines
- Miniaturized medical devices for cancer diagnosis, drug screening and delivery
- Inherent therapeutic properties of some nanomaterials (for example, gold nanoshells and nanorods, and iron oxide nanoparticles) upon stimulation

Nanotherapies that incorporate some of these features (for example, improved circulation and reduced toxicity) are already in use today, and others show great promise in clinical development, with definitive results expected in the near future. Several therapeutic nanoparticle (NP) platforms, such as liposomes, albumin NPs and polymeric micelles, have been approved for cancer treatment, and many other nanotechnology-enabled therapeutic modalities are under clinical investigation, including chemotherapy, hyperthermia, radiation therapy, gene or RNA interference (RNAi) therapy and immunotherapy.[31]

Table 2.2 represents the list of nanoparticles either approved for human use or entered in clinical trials for improved treatment of cancer.

Table 2.2: Examples of clinical-stage nanomedicines for cancer therapy.

Therapy modality	Generic name and/or proprietary name	Nanotechnology platform	Active pharmaceutical ingredients	Cancer type	Status	Refs
Chemothera	Liposomal	Pegylated	Doxorubicin	HIV-related	Approv	36

py: non-targeted delivery	doxorubicin (Doxil)	liposomes		Kaposi sarcoma, ovarian cancer, and multiple myeloma	ed by FDA	
	Liposomal daunorubicin (DaunoXome)	Liposomes	Daunorubicin	HIV-related Kaposi sarcoma	Approved by FDA	36
	Liposomal vincristine (Marqibo)	Liposomes	Vincristine sulfate	Acute lymphoblastic leukaemia	Approved by FDA	36
	Liposomal irinotecan (Onivyde or MM-398)	Pegylated liposomes	Irinotecan	Post-gemcitabine metastatic pancreatic cancer	Approved by FDA	37
	Liposomal doxorubicin (Myocet)	Liposomes	Doxorubicin	Metastatic breast cancer	Approved in Europe and Canada	36
	Mifamurtide (Mepact)	Liposomes	Muramyl tripeptide phosphatidyl-ethanolamine	Nonmetastatic, resectable osteosarcoma	Approved in Europe	36
	Nab-paclitaxel (Abraxane)	Albumin NP	Paclitaxel	Breast, lung and pancreatic cancer	Approved by FDA	36
	SMANCS	Polymer	Neocarzinost	Liver and	Approv	36

		conjugate	atin	renal cancer	ed in Japan	
	Polymeric micelle paclitaxel (Genexol-PM)	Polymeric micelles	Paclitaxel	Breast cancer and NSCLC	Approved in Korea	36
	Liposomal cisplatin (Lipoplatin)	Pegylated liposomes	Cisplatin	NSCLC	Phase III	38
	NK-105	Polymeric micelles	Paclitaxel	Metastatic or recurrent breast cancer	Phase III	39
	Liposomal paclitaxel (EndoTAG-1)	Liposomes	Paclitaxel	Pancreatic cancer, liver metastases and HER2 negative and triple-negative breast cancer	Phase II	40-42
	Nab-rapamycin (ABI-009)	Albumin NP	Rapamycin	Advanced malignant PEComa and advanced cancer with mTOR mutations	Phase II	43,44
	CRLX 101	Polymeric NP	Camptothecin	NSCLC, metastatic renal cell carcinoma	Phase II	45,46

				and recurrent ovarian, tubal or peritoneal cancer		
Chemotherapy: targeted delivery	MM-302	HER2 targeting liposomes	Doxorubicin	HER2-positive breast cancer	Phase II/III	47
	BIND-014	PSMA-targeting polymeric NP	Docetaxel	NSCLC and mCRPC	Phase II	48-50
	MBP-426	TfR targeting liposomes	Oxaliplatin	Gastric, oesophageal and gastro-oesophageal adenocarcinoma	Phase I/II	51
	Anti EGFR immunoliposomes loaded with doxorubicin	EGFR targeting liposomes	Doxorubicin	Solid tumours	Phase I	52
Chemotherapy: stimuli-responsive delivery	ThermoDox	Liposomes	Doxorubicin	Hepatocellular carcinoma	Phase III	53
Chemotherapy: combinatorial delivery	Liposomal cytarabine–daunorubicin (CPX-351 or Vyxeos)	Liposomes	Cytarabine and daunorubicin (5:1)	High-risk acute myeloid leukaemia	Phase III	54

	CPX-1	Liposomes	Irinotecan and floxuridine (1:1)	Advanced colorectal cancer	Phase II	55
Hyperthermia	NanoTherm	Iron oxide NP	NA	Glioblastoma	Approved in Europe	36
	AuroLase	Silica core with a gold nanoshell	NA	Head and neck cancer, and primary and metastatic lung tumours	Pilot study	56,57
Radiotherapy	NBTXR3	Hafnium oxide NP	NA	Adult soft tissue sarcoma	Phase II/III	58
Gene or RNAi therapy	SGT53	TfR targeting liposomes	Plasmid encoding normal human wild-type p53 DNA	Recurrent glioblastoma and metastatic pancreatic cancer	Phase II	59,60
	PNT2258	Liposomes	DNA oligonucleotide against BCL-2	Relapsed or refractory non-Hodgkin lymphoma and diffuse large B-cell lymphoma	Phase II	61,62
	SNS01-T	Polyethylenimine NP	siRNA against	Relapsed or refractory B	Phase I/II	63

			eIF5A and plasmid expressing eIF5A K50R	cell malignancies		
	Atu027	Liposomes	siRNA against protein kinase N3	Advanced or metastatic pancreatic cancer	Phase I/II	64
	TKM-080301	Lipid NP	siRNA against PLK1	Neuroendocrine tumours, adrenocortical carcinoma and advanced hepatocellular carcinoma	Phase I/II	65
	DCR MYC	Lipid NP	Dicer-substrate siRNA against MYC	Hepatocellular carcinoma	Phase I/II	66
	MRX34	Liposomes	miR 34 mimic	Primary liver cancer, solid tumours and haematological malignancies	Phase I	67
	CALAA-01	TfR targeting polymeric NP	siRNA against ribonucleotide reductase M2	Solid tumours	Phase I	68

	ALN-VSP02	Lipid NP	siRNAs against KSP and VEGFA	Solid tumours	Phase I	69
	siRNA EPHA2 DOPC	Liposomes	siRNA against EPHA2	Advanced cancers	Phase I	70
	pbi shRNA STMN1 LP	Lipid NP	shRNA against stathmin 1	Advanced and/or metastatic cancer	Phase I	71
Immunotherapy	Tecemotide	Liposomes	MUC1 antigen	NSCLC	Phase III	72
	dHER2 + AS15	Liposomes	Recombinant HER2 (dHER2) antigen and AS15 adjuvant	Metastatic breast cancer	Phase I/II	73
	DPX-0907	Liposomes	Multi-tumour associated antigens	HLA-A2-positive advanced stage ovarian, breast and prostate cancer	Phase I	74
	Lipovaxin-MM	Liposomes	Melanoma antigens	Malignant melanoma	Phase I	75
	JVRS 100	Lipid NP	Plasmid DNA	Relapsed or refractory leukaemia	Phase I	76

	CYT 6091	Colloidal gold NP	TNF	Advanced solid tumours	Phase I	77

EGFR, epidermal growth factor receptor; eIF5A, eukaryotic initiation factor 5A; EPHA2, ephrin type A receptor 2; FDA, US Food and Drug Administration; HLA A2, human leukocyte antigen A2; KSP, kinesin spindle protein (also known as KIF11); mCRPC, metastatic castration resistant prostate cancer; miR, microRNA; mTOR, mammalian target of rapamycin; MUC1, membrane bound mucin 1; NA, not applicable; nab, nanoparticle albumin bound; NP, nanoparticle; NSCLC, non small cell lung cancer; PEComa, perivascular epithelioid cell tumours; PEG, poly(ethylene glycol); PLK1, polo like kinase 1; PSMA, prostate specific membrane antigen; RNAi, RNA interference; shRNA, short hairpin RNA; siRNA, small interfering RNA; SMANCS, poly(styrene *co* maleic acid) conjugated neocarzinostatin; TfR, transferrin receptor; TNF, tumour necrosis factor; VEGFA, vascular endothelial growth factor A.

Nanotechnology has made considerable contributions to the field of oncology over the past several decades. Liposomes (for example, liposomal doxorubicin (LD); Doxil and Myocet) were the first class of therapeutic NPs which received clinical approval for cancer treatment.[78] The recent phase III results of liposomal cytarabine–daunorubicin (Vyxeos; also known as CPX-351) was compared with the standard of care regimen of cytarabine and daunorubicin in patients with high-risk acute myeloid leukaemia and it showed improved overall survival.[79] NP albumin-bound paclitaxel (nab-paclitaxel; Abraxane) was the second class of nanomedicines to be commercialized. The nab platform enables formulation of hydrophobic drugs while largely mitigating the need to use toxic excipients. The result may be a better-tolerated drug that can be used at higher doses and administered more quickly, thus enabling a higher drug C_{max} and plasma area under the curve (AUC). The every-3-week dosing schedule of nab-paclitaxel is superior to paclitaxel in terms of response rate and time to progression for patients with breast cancer.[80] Polymeric micelles (for example, Genexol-PM[81] and NK105)[82] and polymeric NPs (for example, CRLX101[83], BIND-014[84] and AZD-2811 Accurin[85]) represent two newer classes of cancer nanotherapeutic agents.

Inorganic nanomaterials (for example, gold nanoshell[86], iron oxide NP[87] and hafnium oxide NP[88]) are also being investigated for use in cancer patients, with the iron oxide NP-based NanoTherm[87] already marketed in Europe for glioblastoma.

By integrating diagnostic and therapeutic functions into a single NP formulation, theranostic nanomedicine offers a promising strategy to monitor the PK and accumulation of therapeutics and the progression of disease, giving important insights into heterogeneities both within tumours and between patients for potential personalized treatment.[89] By co-delivering multiple active pharmaceutical ingredients (APIs), NPs have also facilitated synergistic cancer therapy and avoided some mechanisms of drug resistance, as evidenced by the large number of in vivo studies (Table 2.3).

Table 2.3: In vivo studies of nanoparticle-mediated combination therapies for cancer treatment in mouse tumour models.

Nanotechnology platform	Active pharmaceutical ingredients	Therapeutic mechanism	Tumour model	Refs
Organic NPs				
Liposomes or lipid-based NPs	Irinotecan and cisplatin	Combination of chemotherapies	SCLC	90
	Combretastatin and doxorubicin	Combining anti-angiogenesis and chemotherapy	Melanoma	91
	Doxorubicin and antisense oligonucleotides	Combination of chemotherapy and antisense therapy (targeting MRP1 and BCL 2)	NSCLC	92
	Vorinostat and siRNA	Combination of chemotherapy and RNAi therapy (targeting MCL1)	Cervical cancer	93
	Docetaxel and DNA	Combination of chemotherapy and gene therapy using survivin suppressor	Hepatocellular carcinoma	94

	siRNAs	RNAi therapies against MDM2, MYC and VEGFA	NSCLC	95
	Oligonucleotide G3139 and D-$(KLAKLAK)_2$ peptide	Combining antisense therapy (targeting BCL-2) and peptide-enhancing apoptosis	Melanoma	96
Polymeric micelles or NPs	Doxorubicin and paclitaxel	Combination of chemotherapies	NSCLC	97
	Doxorubicin and disulfiram	Combination of chemotherapy and anti-drug resistance	Drug-resistant breast cancer	98
	Paclitaxel and siRNAs	Combination of chemotherapy and RNAi therapy (targeting SNAIL and TWIST)	Breast cancer	99
	Camptothecin and DNA	Combination of chemotherapy and gene therapy using TRAIL encoded plasmid	Colon cancer	100
	Paclitaxel and DNA	Combination of chemotherapy and gene therapy using IL-12-encoded plasmid	Breast cancer	101
	siRNAs	RNAi therapies against VEGFA and BCL 2	Prostate cancer	102
	Antisense oligonucleotides	Antisense therapies against miRNAs miR 10b and miR 21	Triple-negative breast cancer	103
Lipid–polymer hybrid NPs	Combretastatin and doxorubicin	Combining anti-angiogenesis and	Melanoma and Lewis lung	104

		chemotherapy	carcinoma	
	Cisplatin and siRNAs	Combination of chemotherapy and RNAi therapy (targeting REV1 and REV3L)	Prostate and breast cancer	105
	Doxorubicin and siRNA	Combination of chemotherapy and RNAi therapy against MRP1	Triple-negative breast cancer	106
	Doxorubicin and TRAIL	Combination of chemotherapy and cytokine-induced apoptosis	Breast cancer	107
	TGFβ inhibitor SB505124 and IL-2	Enhancing tumour immunotherapy	Melanoma	108
	siRNAs and miRNA	Combination of RNAi therapy (targeting MYC, MDM2 and VEGFA) and miR 34a induced apoptosis	Lung metastasis	109
	Cisplatin and pyrolipid	Combination of chemotherapy and photodynamic therapy	Head and neck cancer	110
	Paclitaxel and yittrium-90	Combination of chemotherapy and radiotherapy	Ovarian intraperitoneal metastasis	111
Dendrimers	Doxorubicin and DNA	Combination of chemotherapy and gene therapy using TRAIL encoded plasmid	Liver cancer	112
	Doxorubicin and CpG	Combination of chemotherapy and	Prostate cancer	113

	oligonucleotides	immunotherapy		
Inorganic NPs				
Iron oxide NP	Doxorubicin and curcumin	Combination of chemotherapies	Glioma	114
Graphene	Doxorubicin and TRAIL	Combination of chemotherapy and cytokine-induced apoptosis	NSCLC	115
Carbon nanotube	siRNA	Combination of hyperthermia and RNAi therapy	Prostate cancer	116
Gold nanorod	Doxorubicin	Combination of hyperthermia and chemotherapy	Cervical cancer	117
MoS_2 nanosheet	Doxorubicin	Combination of hyperthermia and chemotherapy	Breast cancer	118

IL, interleukin; MCL1, myeloid cell leukaemia 1; MoS_2, molybdenum sulfide; miRNA, microRNA; MRP1, multi drug resistance associated protein 1 (also known as ABCC1); NPs, nanoparticles; NSCLC, non small cell lung cancer; RNAi, RNA interference; SCLC, small cell lung cancer; siRNA, small interfering RNA; TGFβ, transforming growth factor-β; TRAIL, tumour necrosis factor (TNF) related apoptosis inducing ligand; VEGFA, vascular endothelial growth factor A.

Most therapeutic NPs for solid tumour treatment are administered systemically; they accumulate in the tumour through the enhanced permeability and retention (EPR) effect[119,120], which is generally thought to be the product of leaky tumour vasculature and poor lymphatic drainage. However, this interpretation of EPR is somewhat oversimplified, as multiple biological steps in the systemic delivery of NPs can influence the effect, such as NP–protein interaction, blood circulation, extravasation into and interaction with the perivascular tumour microenvironment (TME), tumour tissue penetration and tumour cell internalization. In turn, NP properties (for example, size, geometry, surface features, elasticity, stiffness, porosity, composition and

targeting ligand) can influence these biological processes, thus determining the EPR effect and therapeutic outcomes (Figure 2.2).[31]

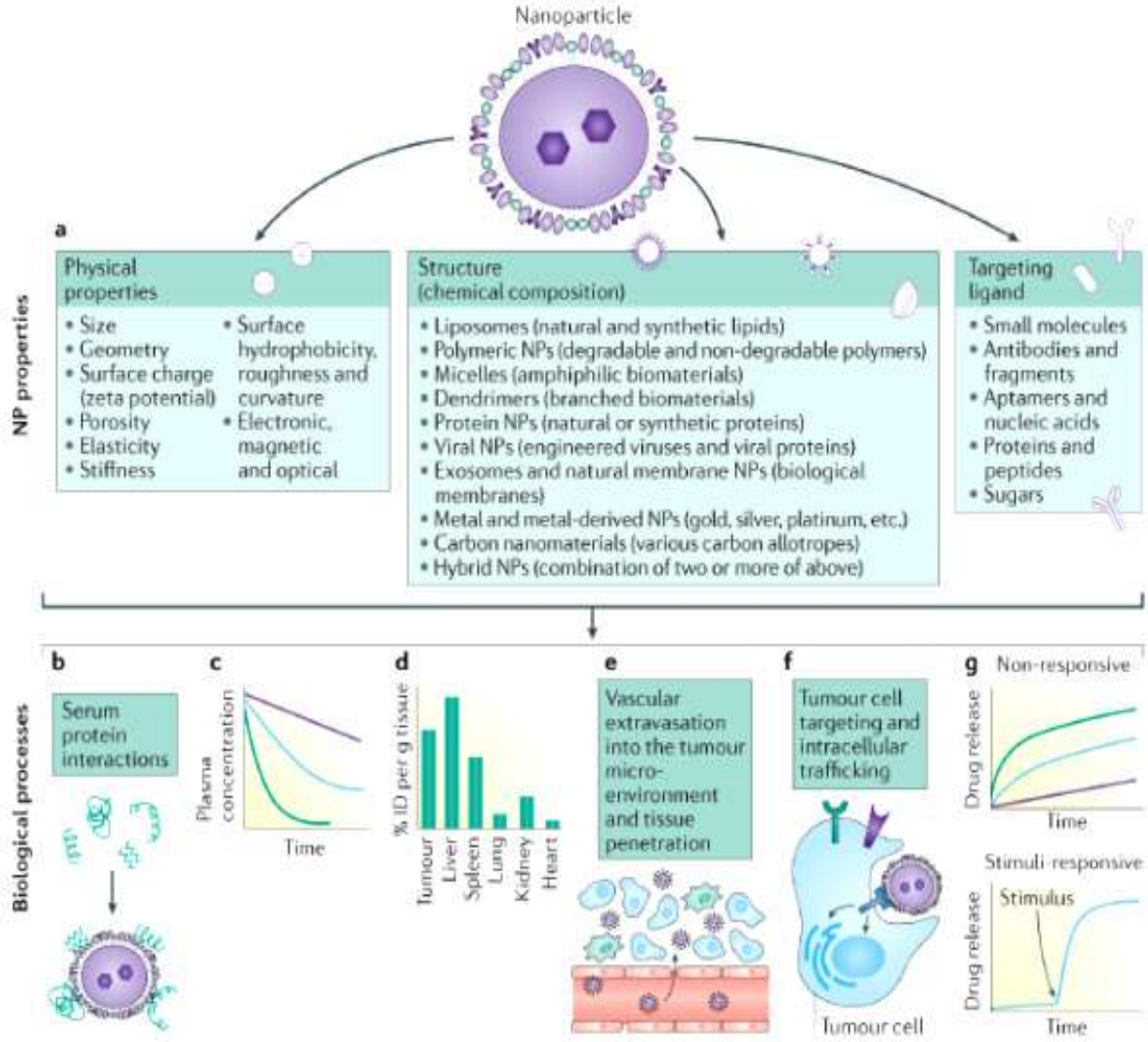

Figure 2.2: The impact of nanoparticle properties on systemic delivery to tumours.

2.4. Inorganic nanoparticles:

Although a detailed classification of NPs for biomedical applications has not yet been definitely developed, the majority of NPs can be divided into organic (NPs that are composed of organic materials) and inorganic (which have physicochemical properties that can be attributed to their inorganic components, such as metals or semiconductor materials). Historically, organic NPs,

such as dendrimers, polymeric nanoparticles, solid lipid nanoparticles, polymeric micelles and liposomes have attracted attention for potential applications in medicine.[121]

In contrast to organic NPs, inorganic NPs were developed at the end of the last century and their biomedical applications are relatively recent. Almost all inorganic NPs share a typical core/shell structure. The core can contain metals (iron oxide, gold and quantum dots [QDs]) or organic fluorescent dyes encapsulated in silica. The shell is usually made of metals or organic polymers that protect the core from chemical interactions with the external environment and/or serves as a substrate for conjugation with biomolecules, such as antibodies, proteins and oligonucleotides.[121] Research endeavors of inorganic nanomaterials were initially focused on physics, optics, and engineering, but have for quite some time now included also biological and medical applications. Often, the same nanomaterials can serve as biochemical sensors, contrast agents in cellular or tissue imaging, drug delivery vehicles, or even as therapeutics.[122] The major benefits associated with these systems are low toxicity and promise for controlled drug/gene delivery providing a true alternative to viral vectors and cationic carriers. Inorganic nanoparticles are generally versatile materials, including wide availability, rich functionality, good biocompatibility, and potential for controlled release and targeted delivery of the carried drugs/genes. Oftentimes, however, the inorganic materials as such are not suitable for biomedical use. Therefore, hybrid nanomaterials and nanocomposites are warranted. Fine metal and other inorganic particles with nanometer-scale dimensions are of great interest due to their favorable functional properties. Biocompatibility and biosafety are crucial parameters for the development of inorganic nanomaterials towards therapeutical applications.[123]

Table 2.4 lists some of the major properties, benefits and drawbacks, and applications towards targeted drug delivery of inorganic nanoparticles and nanocomposites.

Table 2.4: Inorganic nanoparticles and nanocomposite materials for controlled and targeted drug delivery and imaging purposes.[124-128]

Nanoparticle/ nanocomposite materials	Properties	Benefits	Drawbacks	Therapeutic goals
Mesoporous silicon/silica	Well-defined silanol groups on surface; suitable for chemical treatments and pore- and/or surface functionalization	Versatility, biocompatibility, low cytotoxicity; ease of functionalization	Dark color of porous silicon; surface chemistry dependent biosafety profiles	Dissolution enhancement; drug and gene delivery and targeting
Gold (Au)	Strong plasmon absorption and photothermal conversion of Au nanoparticles has been utilized in cancer therapy through selective localized photothermal heating of cancer cells	Easily tailored to a desired size range (1–200 nm); the surface can be modified for various functionalities, typically via thiols; good biocompatibility	Biosafety issues of Au	Targeted cellular delivery after conjugation; imaging applications; conjugated gene delivery vector with other nanomaterials
Silver (Ag)	Ag nanoparticles are promising materials for targeted anticancer	Act as a radiosensitizing agent, increase oxidative stress and cause apoptosis	Biosafety issues of Ag	Nanosilver based; biosensors; anti cancer therapy

	therapy			
Super-paramagnetic iron oxide	Magnetite(Fe_3O_4) and maghemite (Fe_2O_3) have been studied and used for targeted drug delivery using strong magnetic fields	Precisely targeted delivery at a specific site; versatile manufacture and shape as nanowires, nanospheres, nanotubes and magnetic thin films	Need for a strong external magnetic field	Drug delivery and targeting; bioimaging; hyperthermal treatment of tumors
Quantum dots (QDs)	QDs are inorganic nanocrystals (2–10 nm) that possess unique luminescent properties; semiconductor core over-coated by a shell to improve optical properties, and a cap-improving aqueous solubility	Often used as fluorescent labels with better brightness and resistance against photobleaching, with multicolor fluorescence emission	Derivatization and ligands needed for hydrophilicity	Potential intravascular probes for both diagnostics (imaging) and therapeutics (drug delivery); tumor targeting and imaging
Gadolinium oxide	Shape of the nanocrystals readily controlled by tailoring reaction parameters such as temperature	Highly uniform Gd_2O_3 nanoplates self-assemble into nanofi bril-like liquid-crystalline superlattices with long-range	Size and shape dependency of biological interactions; monodispersity requirement for the reliable	Multimodal bioimaging probes

	and time	orientational and positional order; strong paramagnetic response for a potential magnetic resonance imaging contrast agent	biological interaction measurements	
Layered double Hydroxide (LDH)	Natural or synthetic anionic exchanging clays MII MIII (OH) Am·H_2O (MII = Mg, Zn, Ca, Co, Fe, Ni, Cu…; MIII = Al, Fe, Cr, Ga…; Am = Cl, CO_2, NO…); e.g., hydrotalcite $Mg_6Al_2(OH)_{16}CO_3{\cdot}4H_2O$	Tailored nanomaterials (30 100 nm) with a high zeta potential (+45mV); hydrophilicity, biodegradability biocompatibility and relatively low toxicity; release controlled by pH adjustment		Drug delivery and targeting; effective non-viral gene delivery agents
Carbon nanotubes (CNTs)	Hydrophobic CNTs can be modified water-soluble nanotubes; peptide-conjugated CNTs can move across cell membranes and even reach the nucleus of the	Good biocompatibility, low cytotoxicity, unique physicochemical properties	Needle-like shape of the CNTs, possible asbestos like effects; low drug delivery capacity inside the CNTs	Drug delivery and targeting

	cell			
Graphene	Nano-graphene oxide materials aresingle-layer graphene oxide sheets of a few nanometers in lateral width	Electronics, membranes, and nanocomposites applications; large specific surface area; nanohybrids and nanocomposites	Graphene aggregates easily in biological fluids; chemical functionalizat on needed to improve solubility and compatibility in biological environments	Drug delivery and targeting; live cell imaging
Dendrimers	Globular nanostructures specifically engineered to carry molecules encapsulated in the interior void spaces or attached to the surface structures	Size, shape, and reactivity are determined by generation (shells), chemical composition of the core, interior branching, and surface functionalities; truly customizable nanomaterials Multicomposite systems with expertise requested in manufacturing	Multicomposit e systems with expertise requested in manufacturing	Drug or gene carriers; contrast agents and sensors for different metal ions

Nanoscale inorganic metal analogs are attracting huge interests for important biomedical applications owing to their unique magnetic, optical, thermal, catalytic and electrical properties. Properties and applications of metal nanoparticles depend on their size, shape and chemical composition. The size of metal nanoparticles plays an important role in their interaction with membrane proteins, enzymes and/or other component of cells. Apart from size, in vivo biodistribution, biological activities and toxicity of metal nanoparticles depends on nanomaterial composition. Several studies based on different metal nanoparticles have provided valuable insights about the role of nanoparticle's composition on their biological activity.[129] Almost all the anti-cancer drugs have severe systemic toxic effects because of their lack of specificity and thereby increasing their side effects and multiple drug resistance. Metal nanoparticles are novel antitumor agents having absolute specificity towards the cancer cells.[130] The physicochemical properties of nanoparticles contribute for its potential anticancer activity, which may either be related to its intrinsic or extrinsic features. The internal or intrinsic antitumor effects includes its antioxidant activity, which decreases the rate of tumor progression.[131] Researchers are showing great interest towards the use of metal nanoparticles against tumor formation, development and progression due to their intrinsic antitumor effects. The extrinsic features include the application of external stimuli, such as hyperthermia where metal nanoparticles, acting as co-adjuvants are stimulated by external radiations like IR or X-Rays to produce free radicals to kill cancer cells and also increasing the cytotoxic effect of ionizing radiations.[132] Metal nanoparticles which are commonly used for drug delivery are cerium oxide, copper oxide, zinc oxide, iron oxide, gold, silver nanoparticles etc.[129]

2.5. Role of Copper Oxide nanoparticles (CuO NP) in Cancer Therapy:

CuO NPs are synthesized by γ-radiolysis, laser irradiation, reverse micelles, thiol-induced reduction and green synthesis. They may be synthesized by aqueous precipitation method while copper (II) acetate [$Cu(CH_3COO)_2.H_2O$] as a precursor and sodium hydroxide (NaOH) as a reducing agent are used.[133] The copper oxide nanoparticles are synthesized from different plant extracts like *Ficus religioss and Acalypha indica*. This is called as green synthesis of Nanoparticles which is found to be reliable, simple, non-toxic and environment friendly method. These nanoparticles have shown cytotoxic effect by causing apoptosis and increase in the generation of ROS in human lung cancer cells.[134] Spherical shaped CuO NPs have been synthesized through green synthesis using plants by Nagajyothia et al.[135,136] as well as by

chemical reduction process by Pramanik P. et al. The size from green synthesis varied from 5-100nm depending on plant species and from chemical reduction, the size was found to be around 30nm. These CuO NPs were very effective on cervical as well as breast cancer cells (HeLa, MCF-7). The mode of action was found to be due to ROS mediated DNA damage which causes stress inside the cells leading to autophagy (a survival strategy of cell to fight against cellular stress) and finally causing apoptosis upon inhibiting autophagy. Copper oxide nanoparticles were used in-vitro to treat melanoma and metastasis lung tumors of mouse by using B16-F10 cells. The authors observed the targeting of CuO NPs to the mitochondria of HeLa cells and release of Cytochrome C followed by activation of Caspase-3 and Caspase-9.CuO NPs were further targeted to cancer cells by conjugating folic acid in order to address their selectivity. The results demonstrated rapid clearance of CuO NPs from the organs without any toxicity.[137]

2.6. Role of Zinc Oxide (ZnO) in cancer therapy:

ZnO nanoparticles, with their unique properties such as biocompatibility, high selectivity, enhanced cytotoxicity and easy synthesis, may be a promising anticancer agent. Zinc, as one of the major trace elements of the human body and co-factor of more than 300 mammalian enzymes, plays an important role in maintaining crucial cellular processes including oxidative stress, DNA replication, DNA repair, cell cycle progression and apoptosis. Thus, it is evident that an alteration in zinc levels in cancer cells can cause a deleterious effect.[138] Zinc Oxide nanoparticles (ZnO NPs) behave like genotoxic drugs because they form micronucleus into the cells. Arooj and co-workers conducted an extensive experimental investigation to determine the oxidative potential of zinc oxide (ZnO) and its nanocomposites in human fibroblast malignant melanoma (Ht144) cells. Experimental results suggested that incorporation of Silver into ZnO NPs significantly improves their photo-oxidation capabilities.[139] The zinc oxide nanoparticles in combination with current chemotherapeutics like paclitaxel and cisplatin[140] or daunorubicin[141] in breast cancer cell line shows reduced toxicity and increased efficacy. It is evident from the results that differently-sized ZnO NPs greatly facilitate the accumulation of daunorubicin in the leukaemia cancer cells and therefore act as efficient carrier for drug delivery.[141] ZnO NPs showed dose dependent response. Varying doses of ZnO NPs change the level of ROS production and finally apoptosis rate in melanoma cancer.[142] The effect of dose variation on cell viability, rate of apoptosis and mRNA level of apoptosis genes was observed against HepG2

(liver cancer) and MCF-7 (breast cancer) cancer cells. The cell viability measured by MTT assay demonstrated less than 10% viability at very low concentration i.e. 25µg/ml of ZnO NPs in HepG2 cells and showed dose dependent decrease response. The increase in concentration of ZnO NPs will increase the rate of apoptosis.[143] To check the level of mRNA of apoptosis markers (P53, Bax-2, bcl-2 and Caspase-3), quantitative real time PCR was used. The mRNA level of the tumor suppression gene p53 was found to be 1.9 folds higher, the antiapoptotic gene bcl-2 was found to be decreased by 2.5 fold whereas the pro-apoptotic gene Bax was found to be decreased by 2.7 fold as compared to untreated cells. The mRNA expression level of caspase-3 was found to be 1.8 folds higher in treated cells as compared to untreated cells. Apoptosis is controlled by mRNA expression level. According to quantitative real time PCR study, ZnO NPs unregulated the mRNA levels of p53 and Bax and down regulated the mRNA levels of bcl-2. This promoted the caspase activation by increase in permeability of mitochondrial membrane followed by release of soluble protein to cytosol from inter-membrane space.[143] Under different acidic and basic conditions, there may have different charges on the surface of the ZnO NPs as per their electrostatic property. They can be conjugated with various therapeutic agents. They are also used as photodynamic agent and produce large amount of ROS thereby causing apoptotic cell death.[144] After the treatment with metalloprotein in cell viability was found to be decreased proving to have anticancer activity in metalloproteins. ZnO NPs carrying asparaginase, anticancer agent have high specificity, effectiveness and stability.[145]

2.7. Mesoporous Silica Nanoparticles (MSNs)

Mesoporous materials have known a great development since their discovery in the early 1990s by Kuroda et al. and by the Mobil Oil Company. The unique characteristics of periodic mesoporous materials with very large specific surface areas usually above 1000 m^2 g^{-1}, well-defined mesopores of controlled size (2 nm ≤ size ≤ 20 nm) and morphology are obtained owing to the use of assemblies of amphiphilic organic molecules as pore-forming agents and structure-directing agents, which ensure the formation of ordered hybrid organic–inorganic mesophases as precursors of the inorganic porous structures.[146] Due to their very interesting surface properties, mesoporous materials have found a great utility in different domains such as catalysis, separation, adsorption, sensor technology, gas storage, nanocasting, chromatography, and medicine.[147]

Since 2001, when Vallet-Regí et al.[148] introduced for the first time MCM-41 as a drug delivery system, much effort has been devoted to the design of versatile MSNs for treating diverse pathologies, with special emphasis in cancer treatment (Figure 2.3).[149] Their high drug loading capability, the possibility to attain localized and even combined therapy make them promising alternatives to develop advanced nanotherapeutics.[150]

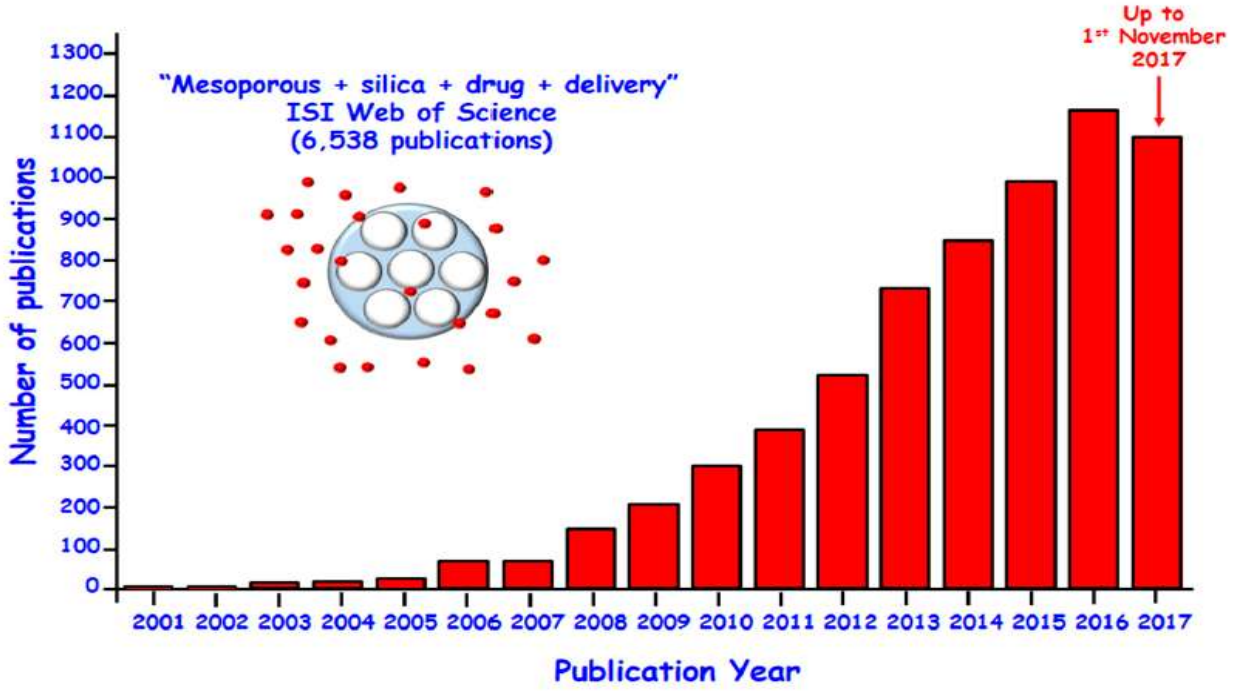

Figure 2.3: Number of publications per year indexed in the ISI Web of Science on the topic of "mesoporous" and "silica" and "drug" and "delivery" up to 1st November 2017.

Compared to other metal oxides such as titania and iron oxide, silica is considered to have better biocompatibility and can be safely taken up by living cells through endocytosis.[151] The abundant presence of silanol groups in silica can have an affinity to phospholipids, which can be actively taken up by the cells. Additionally, its active surface property allows developing MSN with various surface properties through surface functionalization with different molecules, which consequently allows targeted delivery of different types of therapeutic agents. Due to its strong Si–O bond,[152] silica nanoparticles are more stable to external stimuli such as mechanical stress and degradation compared to liposomes and dendrimers, eliminating the need for any additional stabilization such as covalent linkers used in other delivery systems.[153]

2.7.1 Synthesis of MSNs:

The synthesis of ordered mesoporous silica usually consists of several steps. Two different mechanisms are found to be involved for the formation of MSNs:

- True liquid-crystal templating (TLCT) in which the concentration of the surfactant is so high that under the prevailing conditions (temperature, pH) a lyotropic liquid-crystalline phase is formed without requiring the presence of the precursor inorganic framework materials (normally tetraethyl- (TEOS) or tetramethylorthosilica (TMOS)).[154]
- On the other hand, it is also possible that this phase forms even at lower concentrations of surfactant molecules, for example, when there is cooperative self-assembly of the structure directing agent (SDA) and the already added inorganic species, in which case a liquid-crystal phase with hexagonal, cubic, or laminar arrangement can develop (Figure 2.4).[155]

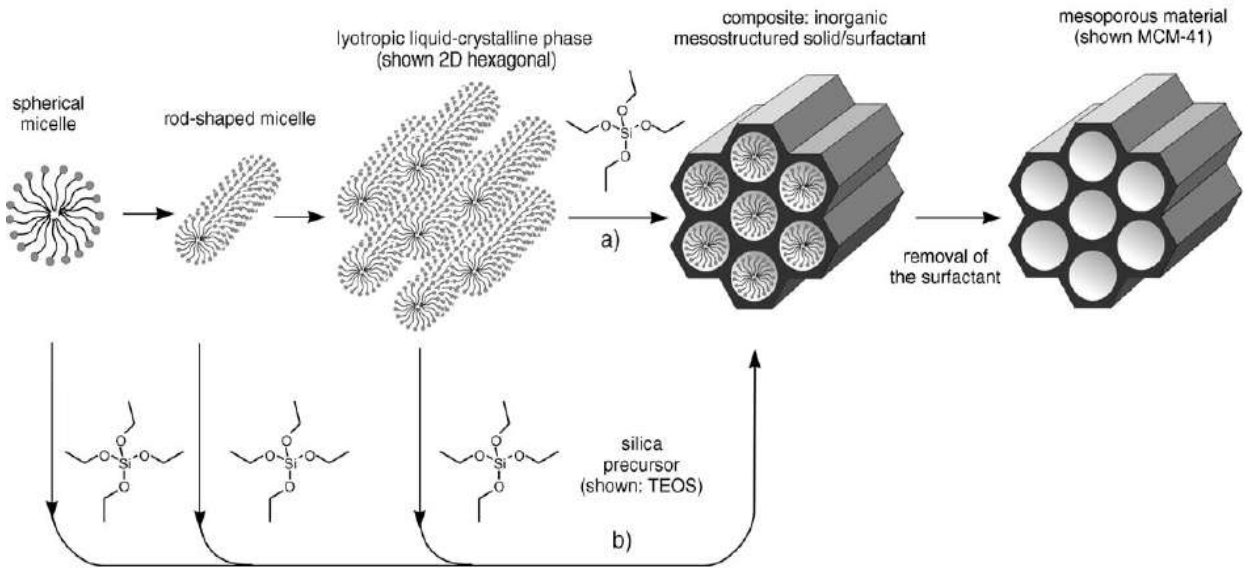

Figure 2.4: Formation of mesoporous materials by structure-directing agents: a) true liquid-crystal template mechanism, b) cooperative liquid crystal template mechanism.

In the meantime, the original approach has been extended by a number of variations, for example, by the use of triblock copolymer template under acidic conditions by which means the so-called Santa Barbara amorphous (SBA) silica phases may be synthesized.[156] Table 2.5

represents different types of mesoporous silica nanoparticles synthesized till date using different surfactants.

Table 2.5: Different types of mesoporous silica, type of used surfactant, crystallographic structure.

Label	Origin / name	Surfactant	Structure	Ref.
MCM-41	Mobil composition of matter	Alkyltrimethyl ammonium salt CnH2n+1N+(CH3)3X$^-$ (with n = 12, 14, 16 or 18 and X = Cl or Br)	P6mm, hexagonal	146
MCM-48	Mobil composition of matter	Alkyltrimethyl ammonium CnH2n+1N+(CH3)3X$^-$ (with n = 12, 14, 16 or 18 and X = Cl or Br)	Ia3d, cubic	146
FSM-16	Folder sheet mesoporous	Alkyltrimethyl ammonium CnH2n+1N+(CH3)3X$^-$ (with n = 12, 14, 16 or 18 and X = Cl or Br)	P6mm, hexagonal	157
HMS	Hexagonal mesoporous silica	Uncharged amine surfactant CnH2n+1NH2	Wormhole framework structure	158
SBA-15	Santa Barbara amorphous	P123	P6mm, hexagonal	159
SBA-16	Santa Barbara amorphous	F127	Im3m, cubic	160
KIT-6	Korea Advanced Institute of Science and Technology	P123	Ia3d, cubic	161
FDU-1	FuDan University	Poly(ethylene oxide)–poly(butylene oxide)–poly(ethylene oxide) triblock copolymer B50-6600	Fm3m, cubic	

		(EO39BO47EO39, Dow Chemicals)		
COK-12	Centrum voor Oppervlaktechemie & Katalyse	P123	P6mm, hexagonal	162

A fundamental condition for the synthesis of MSNs is an attractive interaction between the template and the silica precursor to ensure inclusion of the structure director without phase separation taking place.[156] Thus, the synthesis of MSNs involves mainly two reactants: Structure directing agents (template/surfactant) and silica source.

- **Structure directing agent:**

Utilization of surfactant self-assemblies to direct the silica mineralization process is the most commonly studied route towards the synthesis of highly ordered mesoporous silica.[146] The general idea of using amphiphilic molecules as templates is based on the fact that such systems can simultaneously form a hybrid surfactant/silica interface and self-assemble into robust and regular superstructures. Surfactants which are commonly used in the synthesis of OMS are frequently classified according to the nature of the interactions between their polar group and the hydrolyzed silica precursors. Cationic surfactants are efficient directing agents owing to the strong ionic interactions between their cationic head-group and the negatively charged silica precursors under basic conditions (synthetic route S^+I^- where S^+ = surfactant cations and I^- = inorganic precursor anions).[147]

Utilization of neutral alkylamines was also demonstrated under neutral pH conditions.[158] In this case, the synthesis mechanism relies on the formation of H-bonds between primary amines and neutral inorganic species (synthetic route S^0I^0, where S^0 = nonionic surfactants and I^0 = neutral silica species). Stabilization of the hybrid interface is also possible via the formation of H-bonds between the silicic acid and the ether oxygens of a PEO chain of nonionic surfactants (synthetic route S0I0 or $S^0H^+X^-I^+$ under strong acidic conditions, where X^- = inorganic counter ions such as Cl^-, Br^-, I^-, SO_4^{2-} or NO_3^-).[163] The higher molecular weight and the wide variability in size and composition of this family of surfactants (that includes the commercial oligomeric acid alkyl–

PEO, alkyl–phenol–PEO, sorbitan ester and PEO-based block copolymers) considerably extend the range of accessible pore size as well as the diversity of mesopore structures attainable.[159]

A last synthetic route consists in using surfactants with an anionic polar head under basic conditions. The charge matching effect is ensured by the addition of cationic amino groups of organoalkoxysilanes to the reaction mixture (synthetic route $S^-N^+–I^-$, where S^- = anionic surfactants, I^- = silicate species and N^+ = cationic amino groups).[164]

The choice of alkylated quaternary ammonium salts to synthesize the first ordered mesoporous silica was motivated by their similarities with the ammonium salts commonly used as molecular templates in the synthesis of zeolites. The first ordered mesoporous alumino-silicates synthesized by Mobil scientists in 1992 were achieved in basic solution by using the cationic surfactant CTAB§ through the (S^+I^-) synthetic pathway. The synthesis was achieved under hydrothermal conditions with temperatures ranging from 100℃ to 150℃.[146] Well ordered mesoporous silica were then produced with the same quaternary ammonium-base cationic surfactants under acidic conditions (the $S^+X^-I^+$ synthetic route where S^+ = cationic surfactants, I^- = silicate species and X^- = inorganic counterions such as Cl^-, Br^-, I^-, SO_4^{2-} or NO_3^-). This acidic route presents the advantage of shorter synthesis time and lower surfactant concentrations. Furthermore, synthesis under acidic conditions could be achieved at room temperature.[165]

The utilization of neutral primary amines for the synthesis of hexagonal mesoporous silica in 1995 was the first example of a neutral synthesis route S^0I^0.[158] Advantageously, syntheses by using neutral alkylamines are performed under mild pH conditions, avoiding the addition of a high amount of mineral base (NaOH) or acid (HCl). Furthermore, this route makes possible the easy and efficient removal of the template.

PEO-based nonionic surfactants such as polymeric (Pluronic P123 and F127 respectively) and Tween surfactants (ethoxylated derivatives of fatty esters of sorbitan) enabled the synthesis of highly ordered silica phases in relatively dilute aqueous solution. A highly acidic pH is yet required to generate the long range organic–inorganic coulombic interactions at the start of the cooperative assembly process.[147]

➢ **Silica source:**

Development of sustainable strategies for the synthesis of ordered mesoporous silica implies the careful choice of silica precursor. Table 2.6 represents the comparision of different silica sources with their advantages and disadvantages.

Table 2.6: Comparison of the different silica sources available for the synthesis of silica-based mesoporous materials.

Origin	Type	Advantages	Drawbacks	Ref
Synthetic	Silicon alkoxides (TEOS, TMOS)	Homogeneous silicate oligomers composition in solution Suitable for syntheses of highly organized mesostructures at any pH	Energy-intensive and expensive synthesis procedures Synthesized from toxic precursors Require the use of catalysts Soluble in organic solvents only Release of alcohols during the hydrolysis/condensation process	158, 166
	Soluble silicates (sodium silicate solution, colloidal silica, fumed silica)	Cheap Simple synthesis procedure Soluble in water	Silicate solutions composed of a variety of silicate oligomers with different degrees of polymerization Inorganic polycondensation difficult to control under neutral and acidic pH	165, 166

Natural	Natural clays, diatomaceous earth, natural zeolites, other natural silica-containing minerals, gramineae plants (rice husk)	Abundant, Cheap Non-toxic Possibility of forming mesoporous materials without the addition of organic surfactants: by taking advantage of metal cation impurities (K+) or residual natural organic molecules (lignin)	The same drawbacks as soluble silicates Strong acids and high temperatures are used for purification	167, 168
Recycling	Industrial wastes (coal ash, rice husk ash), electronic wastes (packaging resin), domestic wastes (glassware), regeneration of porous silica materials (hard templates used for nanocasting)	Abundant, Cheap and non-toxic Additional functionality (acidity) conferred by the residual metal ions included within the silica matrix An answer to the problem of waste disposal	Slightly lower surface area and pore volume than with synthetic precursors	169-171

Development of ordered mesoporous silica materials is tightly related to the development of the sol–gel process. Historically, sol–gel technology to form silica originates from the hydrolysis of tetraalkoxysilanes ($Si(OR)_4$) in the presence of either acid or basic catalysts. Mesoporous silica materials are typically synthesized by using tetraethoxysilane ($Si(OCH_2CH_3)_4$), TEOS and TMOS ($Si(OCH_3)_4$). Because of its lower price and lower toxicity, TEOS is much more often

used than TMOS. Indeed, methanol vapors released as a by-product of TMOS hydrolysis are known to be toxic to eyes and can cause blindness. Successful use of TEOS in the synthesis of organized mesoporous silica[158,166] is due to the possibility of tailoring the silicate oligomers present in solution by regulating the experimental conditions of hydrolysis and condensation. Structures and different degrees of polymerization of the polysilicic acids can indeed affect their ability to interact with the organic templates through electrostatic interaction or hydrogen bond formation. Major drawbacks of silicon alkoxides are their toxicity and high cost that limit their development from the laboratory to the industrial scale.

In the case of more sustainable production of silica mesostructures, soluble silicates have recently attracted much attention owing to their low price and low toxicity compared to silicon alkoxides. Soluble silicates are purely inorganic amorphous glasses and are mainly used in the form of aqueous alkaline sodium silicate solution (Na_2SiO_3, also known as water glass or liquid glass), fumed silica and colloidal silica.[172] Soluble silicates have been successfully used in chemical grouting and other geotechnical applications. They are also used as detergents and flocculating agents.[173] Sodium silicate solutions, colloidal silica and fumed silica are the most commonly used inorganic silica sources for the preparation of organized mesoporous silica. The low cost of these inorganic precursors is due to their methods of production that involve the direct transformation of natural quartz deposits. Regarding the large variety of the silica mesostructures generated, differences between silicon alkoxides and soluble silicate precursors are not so obvious.

A natural silica source is defined as a non-toxic silica-containing mineral that is extracted from natural deposits and that can be straightaway used as a reagent in the synthesis of mesoporous silica. Synthesis procedures starting from natural silica sources involved a first step of pretreatment under acidic or basic conditions and at mild temperatures in order to extract silicate species fromthe material. But in contrast to synthetic silica sources (TEOS, water glass, colloidal silica, fumed silica, etc.), both chemical composition and structure of the natural silica source are very close to that of the corresponding raw material. The exploitation of these silica sources does not imply any energyintensive and non-ecological silicon extraction or chemical transformation steps and therefore they can be considered as readily available chemical sources.[147]

Recycled industrial and agricultural by-products that contain silica were recently considered as abundant silica resources. In addition to converting toxic wastes into high value silica-based

materials, recycling processes afford solutions to solve the problem of waste disposal and to guarantee the long-term availability of natural silicon resources.[147]

2.7.2 Functionalization of MSNs:

Two different pathways are available to functionalize the synthesized mesoporous silica nanoparticles:

1) The subsequent modification of the pore surface of a purely inorganic silica material ("grafting"),
2) The simultaneous condensation of corresponding silica and organosilica precursors ("cocondensation")

- **Postsynthetic functionalization of silicas ("Grafting")**

Grafting refers to the subsequent modification of the inner surfaces of mesostructured silica phases with organic groups. This process is carried out primarily by reaction of organosilanes of the type $(R'O)_3SiR$, or less frequently chlorosilanes $ClSiR_3$ or silazanes $HN(SiR_3)_3$, with the free silanol groups of the pore surfaces (Figure 2.5).[156] In principle, functionalization with a variety of organic groups can be realized in this way by variation of the organic residue R.

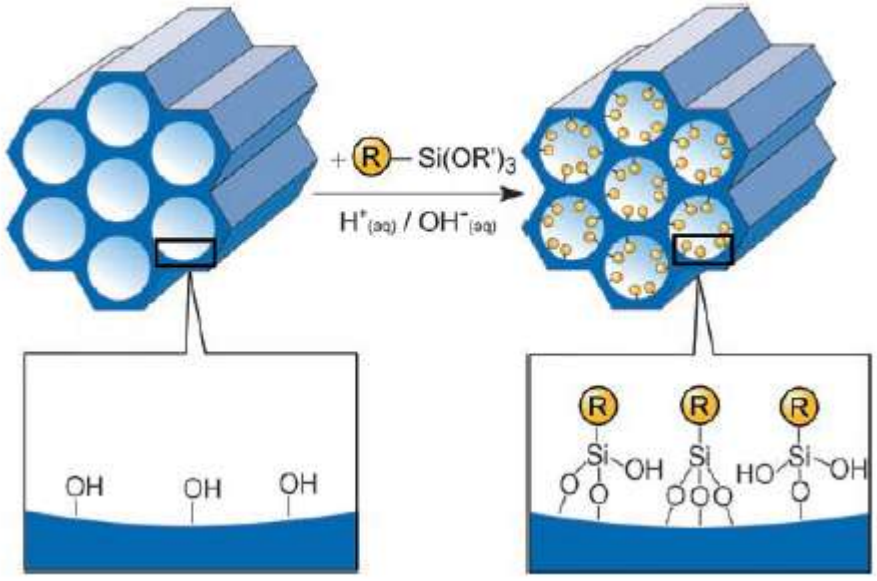

Figure 2.5: Grafting (postsynthetic functionalization) for organic modification of mesoporous silica with terminal organosilanes of the type (R'O)3SiR. R=organic functional group.

This method of modification has the advantage that, under the synthetic conditions used, the mesostructure of the starting silica phase is usually retained, whereas the lining of the walls is accompanied by a reduction in the porosity of the hybrid material (albeit depending upon the size of the organic residue and the degree of occupation). If the organosilanes react preferentially at the pore openings during the initial stages of the synthetic process, the diffusion of further molecules into the center of the pores can be impaired, which can in turn lead to a nonhomogeneous distribution of the organic groups within the pores and a lower degree of occupation. In extreme cases (e.g., with very bulky grafting species), this can lead to complete closure of the pores (pore blocking).[156]

- **Co-Condensation (Direct Synthesis)**

An alternative method to synthesize organically functionalized mesoporous silica phases is the co-condensation method (one-pot synthesis). It is possible to prepare mesostructured silica phases by the co-condensation of tetraalkoxysilanes [$(RO)_4Si$ (TEOS or TMOS)] with terminal trialkoxyorganosilanes of the type $(R'O)_3SiR$ in the presence of structure-directing agents leading to materials with organic residues anchored covalently to the pore walls (Figure 2.6). By using structure-directing agents known from the synthesis of pure mesoporous silica phases (e.g., MCM or SBA silica phases), organically modified silicas can be prepared in such a way that the organic functionalities project into the pores.[156]

Since the organic functionalities are direct components of the silica matrix, pore blocking is not a problem in the cocondensation method. Furthermore, the organic units are generally more homogeneously distributed than in materials synthesized with the grafting process. However, the cocondensation method also has a number of disadvantages: in general, the degree of mesoscopic order of the products decreases with increasing concentration of $(R'O)_3SiR$ in the reaction mixture, which ultimately leads to totally disordered products. Consequently, the content of organic functionalities in the modified silica phases does not normally exceed 40 mol%. Furthermore, the proportion of terminal organic groups that are incorporated into the pore-wall network is generally lower than would correspond to the starting concentration of the reaction mixture.

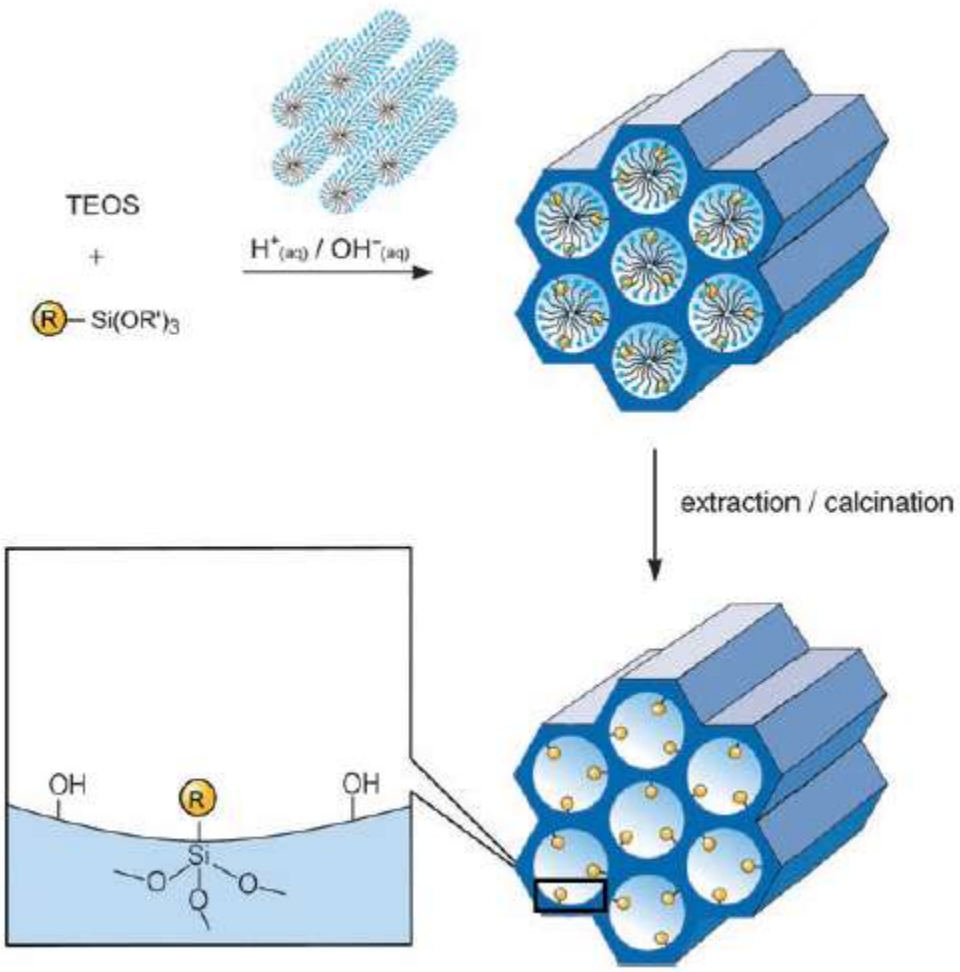

Figure 2.6: Co-condensation method (direct synthesis) for the organic modification of mesoporous silica. R=organic functional group.

2.7.3 MSNs based drug delivery systems (DDS) for cancer therapy:

With the versatile and tunable structures, MSNs have been proven to be capable of loading a variety of guest molecules including pharmaceutical drugs, therapeutic peptides and proteins and genes. MSNs have been used as drug delivery systems of kinds of chemotherapeutic drugs of different hydrophobic/hydrophilic properties, molecule weights, and biomedical effects such as doxorubicin, camptothecin, cisplatin, paclitaxel, docetaxel, methotrexate etc.[174]

➢ **Active targeting of cancer cells by MSNs based DDS:**

Active targeting as a complementary strategy to EPR effect has opened up a new area for traditional chemotherapy to enhance the efficiency of anti-cancer, which known as ligand-mediated targeting involving functionalization of the MSNs surface with active targeting ligands. The active targeting ligands, such as small molecules, peptides, antibodies, proteins, saccharides and aptamers, have specific affinity to the over-expressed receptors on the tumor cells. Typically, there are three paths (targeting to tumor vessels, tumor cells, nuclear) to achieve effective enrichment of drugs in tumor tissues.[175] The most relevant results derived from the conjugation of active targeting ligands to MSNs-based nanosystems to promote specific recognition and cellular uptake by cancer cells are summarized in Table 2.7.

Table 2.7: Active targeting ligands conjugated to mesoporous silica nanoparticles-based nanosystems that permit their specific recognition.

Site	Targeting ligand	Targets/ mechanism	Model	Model drug	Ref.
Tumor cell membrane	Hyaluronic acid (HA)	CD44 receptor	MDA-MB-231	rhodamine B	176
	Hyaluronic acid (HA)	CD44 receptor	HCT-116	Doxorubicin	177
	Folic acid (FA)	folate receptor	A549, HeLa	Doxorubicin	178
	Anti EpCAMDNA aptamer (AP)	EpCAM	SW620	Doxorubicin	179
	YY146 (an anti-CD146 antibody)	CD 146	U87MG	Doxorubicin	180
	antibody /single-chain variable fragment (Ab-/scFv)	Specific receptor affinity	OVCAR-5	bevacizumab	181

	K4YRGD peptide	αvβ3 receptor	HepG2	Doxorubicin	182
	Lactose	ASGPR	HepG2	Docetaxel	183
	AS1411 aptamer	Nucleolin	HeLa	Docetaxel	184
	N3GPLGRGRGDK-Ad	αvβ3 integrins	SCC-7	Doxorubicin	185
	PEI-cRGD	αvβ3 integrins	blood−brain barrier model	Doxorubicin	186
	cRGDfK	αvβ3 integrins	MDA-MB-231 triple-negative breast cancer	arsenic trioxide (ATO)	187
	CRGDKGPDC	α2β3 receptor	HeLa	Combretastatin A4 , Doxorubicin	188
	CRGDyK	αvβ3 integrins	U87MG	Sunitinib (SUN)	189
	HB5 aptamer	HER2	SK-BR-3	Doxorubicin	190
	Anti-TRC105	CD105	HUVE-Cs	Doxorubicin	191
Nucluei	TAT peptide	Nuclear membrane receptors	MCF-7/ADR	Doxorubicin	192
	MONs–PTAT	Nuclear membrane receptors	HeLa	DNA	193

	$MSN^{SA}TAT\&^{DMA}K_{11}$	stepwise-acid-active	HeLa	Doxorubicin	194
	dexamethasone (DEX)	glucocorticoid receptor (GR)	HeLa	Doxorubicin	195
Multistage target Tumor and nuclei	FA and dexamethasone (DEX)	folate receptor and glucocorticoid receptor (GR)	HeLa	Doxorubicin	195
tumor cells and vessels	tLyp-1 peptide	neuropilin (NRP)	MDA-MB-231, HUVECs	Doxorubicin	196

Different from normal tissues, many proteins show specific over-expression on the surface of tumor-associated endothelial cells due to the abnormal overgrowth of intratumoral vasculature, which can be utilized as targets for targeted drug delivery and cancer treatment. According to the literature, targeting to the endothelial cells of the tumor vessels and subsequently killing them can lead to the necrosis of tumors because tumor vasculatures are the transport channel of nutrition which guarantees the fast proliferation of tumor cells[197], which has become a promising alternative in treating solid tumors. In 2013, Chen *et al.*[191] reported the first example of *in vivo* tumor vascular targeted drug delivery system based on MSNs. In this nanosystem, TRC105 antibody targeting to CD105 receptor was conjugated onto MSNs surface. In the 4T1 tumor tissue, the receptors (CD105) only overexpressed in the tumor vasculature but did not express on 4T1 tumor cell. Various tumor vascular targeting ligands, such as vascular endothelial growth factor (VEGF) specific for VEGF receptors (VEGFRs), arginine-glycine-aspartic acid (RGD) peptides targeting to α v β 3 integrin receptor, HB5 aptamer which was specific for human epithelial growth factor receptor 2 (HER2), anti-VCAM-1 monoclonal antibody specific for vascular cell adhesion molecule-1 (VCAM-1) receptors, have been connected to the surface of MSNs to develop vascular targeted drug delivery systems with enhanced therapeutic efficiency.

Very recently, Li *et al.*[188] reported a novel vascular-targeting co-delivery DDS based on targeting molecules (iRGD peptide) modified MSNs. In this system, antiangiogenic agent (combretastatin A4) and chemotherapeutic drug (DOX) were payloaded, leading to significantly improved anti-cancer efficacy even at a very low DOX dose (1.5mg/kg). Furthermore, the disruption of vascular structure caused by combretastatin A4 which was released quickly at tumor vasculatures had a synergetic effect with DOX which released slowly in the subsequent delivery of DOX into tumors.

After reaching tumor tissues, drug loaded nanocarriers are often expected to target to tumor cells through specific interaction between ligand and receptor, leading to the enhanced cellular uptake and drug delivery efficiency and the enhanced therapeutic efficacy. Ligand mediated targeting to tumor cells need meet the following requirements: (I) A threefold overexpression of the targeted receptor on the cancer cell compared with normal cells is generally considered to be sufficient to warrant further investigation, although greater upregulation is preferred[198]. (II) The density of active targeting ligands on the surface of nanoparticles should be carefully manipulated and optimized in order to obtain maximized targeting and therapy efficiency. Because the ligand/ nanoparticle ratio strongly affects the cell recognition specificity, so greater selectivity and targeting efficiency can be obtained with higher density of active targeting ligands[199]. But excessively high density of active targeting ligands may increase the steric hindrance effect and lead to poor cellular uptake efficiency. (III) Preventing targeting ligands coated by the plasma protein is also a noteworthy issue because the targeting ligands can be shielded by opsonization, which can result in loss of their targeting ability in a complex in vivo environment. (IV) The targeted receptor on the cancer cell can induce endocytosis. Various tumor cell targeting ligands such as antibodies (anti-CD146 antibody, antibody fragment (Ab-/scFv)), proteins (transferrin (Tf)), peptides (K4YRGD peptide), saccharides (hyaluronic acid (HA), lactobionic acid (LA), Lactose, small molecules（folic acid (FA), aptamers (anti-EpCAMDNA aptamer, AS1411 aptamer), have been conjugated onto MSNs surface to receive tumor cell targeted property. Quan *et al.*[183] designed a hepatoma targeting DDS based on lactose conjugated MSNs (Lac-MSNs) with anticancer drug DTX loaded. The DTX-Lac-MSNs showed specific targeting to ASGPR-positive SMMC7721 and HepG2 cells, and the cellular uptake of Lac-MSNs was an energy-consuming process and predominated by clathrin-mediated endocytosis. Thanks to active

targeting, significantly enhanced inhibition of the growth of HepG2 and SMMC7721 cells *in vitro* was obtained.

The nucleus is important space for the storage, replication and transcription of genetic material and plays an important role in cell metabolism, growth and differentiation. Therapeutic genes must enter the cell nucleus and correct dysfunctional and/or missing genes. Some anti-cancer drugs, such as cisplatin and DOX, must enter into the cell nucleus to induce apoptosis. Therefore, the nuclei of cancer cells has become an ultimate target point and nuclear-targeted treatment systems are hoped to be more efficiently and directly deliver therapeutic drugs to kill tumor cells. There are a lot of nuclear pore complexes distributing on the nuclear membrane, the pore with a diameter value of 20-70 nm. The diameter of the pore is related to the cell type and cell cycle, especially, the nuclear pore diameter of tumor cells is bigger than normal cells.[200] Lin et al[195] reported a cancer-cell-specific nuclear targeted delivery system based on both FA and dexamethasone (DEX) targeting ligand modified MSNs. In which, the nuclear targeting ligand dexamethasone is a potent glucocorticoid with the capability of enlarging nuclear pore up to 60 nm during the translocation process, it can promote transport from cytoplasm to nucleus via specifically binding to the nuclear receptor, glucocorticoid receptor (GR) expressed in almost style cell. FA acting as tumor cell targeting ligand can enhance cancer cellular uptake. The results demonstrated that the constructed FA-MSN-DEX showed higher anticancer efficacy of DOX on Hela cells via enhanced cellular uptake and active nucleus accumulation with the calculated IC50 of 0.78 μg mL^{-1} at 48 h.

- **Stimuli responsive MSNs:**

The value of having the most selective targeting system is of course lost if the cargo is released from the carrier before it reaches the target site. For chemotherapy applications it is desirable that no release of cargo should occur in the extracellular environment, while a fast release of the cargo should occur once the carrier particle has reached its point of action. The release of cargo from mesoporous silica is often diffusion-controlled and typically associated with a pronounced initial burst. Therefore, there is a strong current interest in the development of means to prevent a fast initial release of the cargo, which in the optimal case would be sensitive to the local environment of the carrier particles in a way that release of the cargo is only triggered inside the cells or within specific cellular compartments after internalization.

Stimuli-responsive MSNs only release the cargos in the targeted cancer sites upon triggering by intratumoral stimuli (pH, redox, enzyme, temperature) or exogenous stimuli (magnetic field, ultrasound, light) with nearly no premature drug release. Stimuli-responsive MSNs have been regarded as promising approach to improve the therapeutic effect of anticancer agent and simultaneously reduce the undesirable side effects to normal cells.[175]

- **Internal stimuli-sensitive MSNs**

Various kinds of tumor tissues share similar microenvironment distinct from normal ones, such as leaky vasculatures, acidic and hypoxic environments, high redox potential, increased level of cancer-associated enzymes and higher local temperature. Based on these, stimuli-sensitive delivery system can be designed to response to the tumor.[175]

- **pH responsive MSNs:**

Among the various stimuli-sensitive DDSs, pH-responsive CDDSs have been widely researched since the human body exhibits variations in pH. The pH value approximately 7.4 in extracellular of normal tissues and blood, while between 6.0 and 7.0 in tumor microenvironment, which is mainly caused by high level of CO_2 and high glycolysis rate. The pH value will decrease further inside cancer cell such as endosomes (pH=5.5-6.0) and lysosomes (pH=4.5-5.0). The pH-responsive nanosystems based on MSNs are shown in Table 2.8.

Table 2.8: The pH-responsive nanosystems based on MSNs.[202-210]

Type	Material	pH-responsive mechanism
Acid cleavable linker/ bond	gold NP-acetal linker- MS	acetal linker
	lanthanide doped NP-acetal bond-MS	acetal bond
	Fe3O4 NP- boronate ester bond-MSNs	boronate ester bond
	Poly(Nsuccinimidyl acrylate)-acetal linker-MS	acetal linker
	MSN-hydrazone-Dox	hydrazine
	Dox@PAA-ACL-MSN	ACL
	Au NPs-DNA-MSNs	DNA

Polymer gatekeepers	Dox-MSN s-Gelatin	Gelatin
	Dox-MSNs-chitosan	Chitosan
	Dox@MSNs-PVP-PEG	PVP
	DOX@MSNs-PLGA	PLGA
	PAH /PSS MSNs	PAH/PSS polyelectrolyte multilayers
	Alginate/Chitosan-NH2-MSNs	Alginate/Chitosan Multilayers
	Chitosan /dialdehyde starch-MSNs	chitosan/dialdehyde starch polyelectrolyte multilayers charge-reversal
	PAH-cit/APTES-MSNs	polymer PAH-cit
	Cur@PAMAM- MSNs	PAMAM
	PDEAEMA- MSNs	PDEAEMA
	Dox@PAA-MSNs	PAA
	Dox@PPEMA/PEG-MSNs	PPEMA
	i-motif DNA-MSNs	i-motif DNA
Supramolecular - nanovalves	β- cyclodextrin caps- aromatic amines stalks-MSNS	Aromatic amines stalks
	α-cyclodextrin- *p*-anisidino stalks - MCM-41	*p*-anisidino stalks
	cucurbit(6)uril-trisammonium stalks MSNS	Trisammonium stalks
Acid decomposable gatekeepers	ZnO@MSN	ZnO
	Dox-Si-MP-CaP	pH-Tunable Calcium Phosphate
	LDHs-MSNs	LDHs

PAA, Polyacrylic acid; ACL, acid cleavable linker; PVP, polyvinylpyrrolidone; PEG, poly(ethylene glycol); PLGA, poly(lactic-co-glycolic acid); PAH, poly(allylamine

hydrochloride); PSS, poly(styrene sulfonate); PAMAM, (polyamidoamine); PDEAEMA, Poly(2-(diethylamino)ethyl-methacrylate); PPEMA,poly(2-(pentamethyleneimino)ethyl-methacrylate); CaP, calcium phosphate; LDH, layered double hydroxides.

The pH-sensitive linkers, such as acetal bond, hydrazine bond, hydrazone bond and ester bond can be cleaved under acidic condition, thus providing opportunities for designing pH-responsive DDS applied in cancer treatment.[211] Liu et al[212] reported a new pH-responsive nanocarrier by capping gold nanoparticles onto the surface of mesoporous silica through acid-labile acetal linkers. $[Ru(bipy)_3]Cl_2$ dye was loaded as a model drug to investigate the pH-responsive release behavior, and the dye-loaded MSN was dispersed in water at different pH values to test the release profiles. At pH 7.0, no free dye was observed as the intact acetal linker and gold nanoparticles blocked the nanopores to inhibit cargo release. However, the solution at pH 4.0 induced a quick release of dye molecules and almost 100% dye molecules were totally released in 13 hours. On decreasing the pH to 2.0, an even faster molecular transport was observed with 90% release within 30 minutes and reached equilibrium in 2 hours. Similarly, a pH-responsive nanocarrier was designed by Chen et al[213] via capping graphene quantum dot (GQD) onto the nanopores of mesoporous silica through an acid-cleavable acetal bond. The amount of drug leaked from GQD@MSN remained negligible (nearly 3.5%) after 24 hours of incubation, indicating that GQD caps can efficiently block the nanopores. However, ~48% and 86% of the drug molecule were released when the pH value decreased to 5.0 and 4.0, respectively. The accelerated DOX release was ascribed to the cleavage of the acetal bond under the acidic conditions and the continuous separation of GQDs from MSN. Besides that, hydrazine bond is another widely studied acid-labile linker.

Polyelectrolyte is a commonly used blocking material in pH-responsive drug delivery. Feng et al[214] constructed an MSN-based pH-responsive DDS with polyelectrolyte multilayers. Polyallylamine hydrochloride and polystyrene sulfonate were coated onto the surface of MSN via a layer-by-layer technique, and doxorubicin hydrochloride (DOX) was loaded into the nanopores of the as-prepared polyelectrolyte multilayer (PEM)-MSN. Results showed that there was a tendency of layer thickness–dependent drug release, and MSN with 20 layers exhibited the highest DOX release rate. Moreover, MSN at acidic condition (pH 5.2) showed a significant higher drug release rate than those at neutral condition (pH 7.4).

Many studies have reported efficient pH-responsive delivery systems using other polyelectrolytes as gatekeepers, such as poly-4-vinyl pyridine, poly [2-(diethylamino)ethyl methacrylate], polyacrylic acid, poly(methyl acrylic acid), and poly-l-glutamic acid. Thus, the tumor tissues with weak acidity make pH-responsive release systems suitable for controlled release of anti-cancer drugs.[211]

In addition, the application of supramolecule was also reported as a gatekeeper to develop pH-responsive DDS for controlled cargo release such as pseudorotaxanes, rotaxanes, and analogues. Li et al[215] have developed several pH-responsive mesoporous silica DDS utilizing the pH-dependent pseudorotaxanes and rotaxanes. In 2009, they constructed a β-cyclodextrin (β-CD) and N-methylbenzimidazole-based pH-responsive MSN DDS. N-methylbenzimidazole was immobilized onto the MSN surface to serve as stalks and β-CD was introduced to encircle the stalks and form a polypseudorotaxane complex. The nanovalves remain closed at pH 7 with no cargo leakage; however, by decreasing the pH to 5, a rapid release of the guest molecules was detected.

- **Redox responsive MSNs:**

The development of redox-responsive vehicles for targeted intracellular drug/gene delivery is a very efficient cancer therapeutic strategy. The basic principle of redox-responsive DDS is based on the significant differences in redox concentrations between tumors and normal tissues. It is well documented that concentration of reducing agents such as glutathione (GSH) existing in tumor cells is approximately three times higher than that in normal cells.[216] As a redox-sensitive group, the disulfide bond (S–S) could be easily cleaved in the presence of GSH, which makes it an attracting receptor site in the design of redox-responsive DDS. Many inorganic nanoparticles have been used as nanovalves to seal the drug molecule into the channels of MSN through covalently functionalizing MSN with disulfide containing linkers, such as CdS, Fe_3O_4, gold and ZnO.

Table 2.9: Redox-responsive nanosystems based on MSNs.[217-220]

Type	Material	Mechanism
Redox responsive	CdS, Au, Fe_3O_4	Inorganic NPs-disulfide

		bonds-MSNs
	poly(propylenimine) dendrimers, PEG, heparin, peptides, polyethylenimine(PEI), cyclodextrin, PDS, cytochrome c, PEG-PCL	Organic molecules disulfide bonds-MSNs
	mPEG@6-MP@CMS HA@6-MP@CMS	Thiolated drug-disulfide bonds-MSNs
	MSN@MnO_2	Glutathione degradable gatekeepers

Zhang et al[221] reported redox-responsive nano-gated MSN by grafting β-CD or adamantane onto the nanopores of MSN through disulfide. After the drug-loaded nanoparticles internalized and then escaped from the endosome to diffuse into the cytoplasm of cancer cells, the high concentration of GSH in the cytoplasm leads to the removal of the β-CD/adamantane caps by cleaving the pre-installed disulfide bonds, further promoting the release of drugs from the nanocarriers.

Liu et al[222] reported a redox-responsive DDS by using cross-linked poly *N*-acryloxysuccinimide as a gatekeeper. Poly *N*-acryloxysuccinimide was anchored to the outlet of silica mesopore through reversible addition-fragmentation chain transfer polymerization. The loaded molecules were released from the hybrid materials by the cleavage of the disulfide linker of the polymeric network with the addition of disulfide reducing agents DTT.

- **Enzyme responsive MSNs:**

The upregulated expression profile of specific enzymes in pathological conditions such as cancer makes it an interesting stimulus to achieve enzyme-mediated drug release. Recently, the developments of enzyme-triggered DDS based on functionalized MSN have attracted much attention. As one of the important physiological changes in the tumor microenvironment, matrix metalloproteinases (MMPs), especially MMP2 and MMP9, are overexpressed in almost all the types of cancer cells and associated with tumor invasiveness, metastasis, and angiogenesis, whereas they are minimally expressed in healthy tissues.[211]

Table 2.10: Enzyme-responsive nanosystems based on MSNs.[223-225]

Type	Material	Mechanism
Enzyme responsive	MSN-GFLGR7-RGDS/α-CD	protease-sensitive crosslinker
	DNA68 HA69 gelation, cellulose, galacto-oligosaccharides	enzyme degradable polymer

Recently, specific protease-sensitive peptide sequences have been designed as linkers that allow the controlled release of chemotherapeutics from MSN. Rijt et al[226] developed avidin-capped MSN functionalized with linkers that could be specifically cleaved by MMP9, thereby allowing controlled release of chemotherapeutics from MSN in high MMP9-expressing lung tumor cells. The avidin-capped MSN demonstrated an efficient protease sequence-specific release of the incorporated chemotherapeutic cisplatin and a rapid tumor cell apoptosis.

Liu et al[227] reported phenyl boronic acid–conjugated human serum albumin (PBA-HSA)-capped MSN for MMPs-responsive drug delivery. PBA-HSA was grafted onto the surfaces of MSN as a sealing agent via an intermediate linker of a functional MMP2 cleavable peptide. When the MSN-based DDS reaches the tumor site, the overexpressed MMP2 in the tumor microenvironment breaks down the intermediate linker and releases the drugs to induce cell apoptosis in vitro and inhibit tumor growth in vivo.

- **Temperature responsive MSNs:**

Thermo-responsive drug delivery is one the most investigated stimuli-responsive strategies and has been widely explored in tumor therapy. Thermo-responsive MSN DDSs are usually composed of MSN and surface-coated thermo-responsive materials. The drug release was closely dependent on the variation of the surrounding temperature to control the switch of the nanovalves. Poly *N*-isopropyl acrylamide (PNIPAM) has been well known as a thermo-responsive polymer.

Table 2.11: Thermo-responsive nanosystems based on MSNs.[228-230]

Type	Material	Mechanism
Thermo responsive	poly(ethyleneoxideb-N-vinylcaprolactam), Zwitterionic sulfobetaine copolymers, paraffins supramolecules, rotaxane, copolymer-lipid bilayers	Thermo sensitive polymers
	DNA, peptide sequences	Thermo sensitive bio-molecules

Singh et al[231] developed a temperature-sensitive MSN for triggered drug release by a relatively simple technique. The anionic surface of MSNPs was functionalized with bifunctional N-(3-aminopropyl) methacrylamide hydrochloride, and the acrylamide group was subsequently covalently cross-linked to NIPAM and poly(ethylene glycol) diacrylate by radical copolymerization at room temperature. DOX was used as a model drug molecule and the polymer-coated MSN showed a high drug-loading capability (~50% of total DOX added). At temperatures (37°C) greater than the lower critical solution temperature (LCST, 31°C), approximately 50% DOX was released within the first 2 hours, which is relatively higher than those maintained at room temperature. Other researchers also investigated the PNIPAM-based thermo-responsive DDS using MSN as the drug container.

- **External stimuli sensitive MSNs:**

Unlike endogenous stimuli, exogenous stimuli are carried out via an external physical treatment. Although this approach seems unappealing, exogenous stimuli-responsive DDSs might be more encouraging and favorable due to the heterogeneous physiological conditions of human population. Various externally applied stimuli include: magnetic fields, ultrasounds, and light.[211]

- **Magnetic responsive MSNs:**

Magnetic-responsive DDS relies on the delivery of magnetic and drug-loaded nanoparticles to the tumor site under the influence of external magnetic field. The external magnetic field can not only drive the magnetic nanoparticles to the desired location precisely, but also can act as an exogenous stimulus to induce the controlled drug release. Superparamagnetic iron oxide nanoparticle is one of the most widely employed magnetic particles.

Table 2.12: Magnetic-responsive nanosystems based on MSNs.[232-235]

Type	Material	Mechanism
Magnetic responsive	Poly(N-isopropylacrylamide/N hydroxymethylacrylamide), poly(ethyleneimine)-b-poly(N isopropylacrylamide), lipid bilayer, pseudorotaxanes	Heat produced by AFM + thermo-sensitive gatekeeper
	mNPs+DNA+MSNs Azo-PEG@ Fe_3O_4@SiO_2	Heat produced by AFM + thermally unstable chemical linkers
	SPION@MSN-DA	Heat produced by AFM + thermally reversible cycloreversion reaction

Chen et al[236] constructed a novel nanocarrier (MSN@Fe_3O_4) using a facile technology by capping amine-modified MSN with 2,3-dimercaptosuccinic acid–functionalized Fe_3O_4 nanoparticles through chemical amidation. In the absence of magnetic field, a negligible amount of the drug was released from the MSN@Fe_3O_4. However, some nanocaps can be removed by breaking the chemical bonds when subjected to an external controllable magnetic field, which subsequently leads to a fast drug release. Also, the results showed that the release profiles were dependent on the strength and time duration. Moreover, MSN@Fe_3O_4 nanocarriers could perform well as T_2-weighted magnetic resonance contrast enhancement agents for molecular imaging.

- **Ultrasound responsive MSNs:**

Ultrasound is one of the most promising exogenous stimuli for drug delivery with the advantages of noninvasiveness, ability of deep tissue penetration, and controllable frequency. Moreover, ultrasonic irradiation could enhance drug release rate from both biodegradable and non-biodegradable polymer matrices.

Table 2.13: Ultrasound (US)-responsive nanosystems based on MSNs.[237]

Type	Material	Mechanism
Ultrasound responsive	MSNC@Au-PFH-PEG	Ultrasound sensitive material+cavitation
	p(MEO2MA)-co THPMA	Ultrasound- cleavable moieties
	Fc-CONH-MS	Ultrasound sensitive of ferrocene derivative

Wang and coworkers[238] synthesized Au NPs-capped, perfluorohexane(PFH)-encapsulated and PEGylated mesoporous silica nanocapsules-based enhancement agents (MAPP). Hydrophobic pyrene as model drug was loaded into MAPP (pyr-MAPP) to verify the effect of US on inducing drug release behavior of MAPP. Before US irradiation, nearly no pyrene was released, By contrast, under/after ultrasound irradiation, a plenty of smaller-sized phase-changed PFH micro bubbles in MAPP solution were generated, subsequently further swelled and merged into larger microbubbles which could enhance the release of pyrene. This indicated that the nanosized inorganic MAPP possessed excellent US sensitivity, and the loaded drug release could be trigger controlled and enhanced via external US.

- **Light responsive MSNs:**

Due to their non-invasiveness property and the possibility of remote spatiotemporal control, a variety of light-responsive systems have been developed in recent years to achieve on-demand drug release in response to light irradiation at a specific wavelength (in the ultraviolet [UV], visible, or near-infrared regions). The mechanism relies on the photo-sensitiveness-induced conformational transition of the nano-carriers.[211]

Azobenzene (AB) is a type of light-sensitive molecule. When irradiated with UV light at a wavelength of 351 nm, AB is able to isomerize from the more-stable trans to a less-stable *cis* configuration. Different studies have demonstrated that there was a high binding affinity between

β-CD and trans-AB derivatives and a low binding affinity between β-CD and cis-AB derivatives in aqueous solutions. According to this principle, a lot of AB-liable light-responsive DDSs were designed.

Table 2.14: Light-responsive nanosystems based on MSNs.[239-242]

Type	Material	Mechanism
UV-Vis light responsive	β-CD and/ or Py-β-CD- azobenzene stalks-MSNs α-CD-azobenzene stalks-MSNs	The isomerized of azobenzene group from cis to trans
	thymine derivatives-MSNs o-nitrobenzyl ester moiety -MSNs poly(N-isopropylacrylamide-co-2-nitrobenzylacrylate)-MSNs	Photoresponsive polymers gatekeeper
	7-amino-coumarin derivative (CD)-MSNs, S-coordinated Ru(bpy)2(PPh3)-moieties-MSNs, TUNA-MSNs	Photoresponsive linkers
NIR light responsive	DNA-Au@MSNs DNA-$Cu_{1.8}S$@mSiO_2 1-tetradecanol-GNR@MSNs sulfonatocalix[4]arene-AuNR@MSN	NIR-absorbing materials+ thermal-responsive materials

	Au-nanocage@$mSiO_2$@ PNIPAM CuS@$mSiO_2$-PEG SWNT@MS-PEG UCNP@$mSiO_2$-Ru	

Mal et al[243] described an UV light-induced reversible drug-release system for the first time. 7-[(3-Trihydroxysilyl) ropoxy]coumarin was attached to the silanol groups of cholestane-loaded MSN that acted as "hinged double doors" to block the drug molecules in the nanopores. When the system was irradiated at the UV light wavelength greater than 310 nm, coumarin underwent a photodimerization reaction and cyclobutane dimer rings were formed that spanned the pores to hinder drug diffusion. Whereas when the system was irradiated with UV light of wavelength of ~250 nm, cyclobutane rings were photocleaved, yielding new coumarin monomers to release the entrapped drug molecules.

Chang et al[244] have reported an NIR light-responsive oligonucleotide-gated ensembles for intracellular drug delivery. The system is composed of gold nanorods–encapsulated MSN and surface-decorated DNA double strands as gatekeepers. When this device was irradiated with NIR laser (808 nm, 1.5 W/cm^2), the generated heat enables denaturing of the duplex oligonucleotides of the DNA strands opening the pores and allowing the drugs to diffuse out of the carrier.

- **Multi stimuli responsive MSNs:**

Compared to single stimuli-responsive drug delivery systems, dual or multi-responsive DDSs are sensitive to two or more stimuli, either in a synergistic fashion or in an independent style, which has gained considerable attention in the current decades for its capability of further improving the delivery. Table 2.15 represent the different multi stimuli responsive approached developed using mesoporous silica as a carrier.

Table 2.15: Multi stimuli responsive nanosystems based on MSNs.[245-248]

Mechanism	Material	Release condition	Biological model	Model drug
pH/cellulase	Cellulose	pH 4.0/ cellulose	HepG2	DOX
Redox/enzyme	HA	GSH/ hyaluronidases	HCT-116	DOX
pH/redox/UV	PDEAEMA/disulfide bond/o-nitrobenzyl ester	pH 5.0/ DTT/UV	HeLa	DOX
NIR/PH/thermo	Au25(SR)18/P(NIPAm-MAA)	980nm(NIR)/ tumor sites	A549, HeLa, SKOV3	DOX
pH/redox	poly(allylamine hydrochloride) citraconic anhydride/galactose-modified trimethyl chitosan-cysteine	pH5.0/ Cytoplasmic glutathione	QGY-7703	DOX/ siRNA
Esterase/pH	poly(β-amino ester)	liver esterase/pH <5.0	MDA-MB-231	DOX
Enzyme/Redox or thermo/Redox	AND logic gates(DNA) AND logic gate (PAA/PCL)	DNase I/DTT or 50°C/DTT pH5.5@esterase	A549 SK-N-BE(2), HeLa,	Calcein DOX

pH/enzyme			MRC-5	
pH/redox	Disulfide bonds/ benzoic-imine bond	Glutathione/ pH5.0	U87MG	DOX
Magnetic/NIR	Fe3O4@poly-L-lysine@Au@ dsDNA	MagneticTarget/ 808nm NIR	HeLa,nude mice	DOX
Ultrasound/pH/ Magnetic	Crown-Ether/SPION	Ultrasound/pH/ Magnetic	L929	DOX

Zhao et al colleagues[249] capped mesoporous silica with hyaluronic acid (HA) through cleavable disulfide (SS) bonds, and the loaded DOX release occurred either in a redox responsive way by addition of glutathione (GSH) or in an enzyme responsive way by introducing of hyaluronidases (HAase). In this system, HA acted as both gatekeeper and targeting ligand owing to the specific affinity with CD44 receptors with a high level of expression on various tumor cells such as human HCT-116 cells. The MSN-SS-HA/DOX had the high drug loading efficiency up to 12.5% and *in vitro* drug release study showed that the release of DOX was triggered by GSH and HAase. Without GSH and HAase, DOX released from MSN-SS-HA/DOX was obviously inhibited with less than 20% for a period of 48 h, Nevertheless, in the presence of HAase, GSH, GSH and HAase, the cumulative amount of released DOX was significantly increased to 30%, 50% and 60% within 48 h, respectively. In addition, fluorescence-activated cell sorting (FACS) and confocal laser scanning microscopy (CLSM) showed a higher cellular uptake via CD44 receptor-mediated endocytosis with increasing 3.0-times and 2.7-times for 100 and 200 μgmL-1 MSN-SS-HA in HCT-116 cells compared with that in CD44 receptor-negative NIH-3T3 cells.

Very recently, Zhang *et al.*[250] reported a reduction, pH and light triple responsive nanocarriers (HMSNs-PDEAEMA) based on hollow mesoporous silica nanoparticles (HMSNs) coated by poly (2-(diethylamino)-ethyl methacrylate) (PDEAEMA). pH-sensitive PDEAEMA polymer capped on the surface of HMSNs through linkages including reduction cleavable disulfide bond and light-cleavable o-nitrobenzyl ester. DOX was easily loaded into the nanocarriers with high drug loading efficiency, and the rapidly released of DOX was triggered by the stimuli of acid

environment, reducing agent or UV light irradiation. In addition, the results of flow cytometry analysis, CLSM and cytotoxicity indicated that the DOX loaded HSNs-PDEAEMA was efficiently uptaked by HeLa cells, showing (i) smart control on drug delivery and release, (ii) the enhanced DOX release into the cytoplasm under external UV light irradiation, and (iii) higher cytotoxicity against HeLa cells.

2.7.4 Multi functional MSNs for theranostic applications:

Theranostic nanomedicines combine the therapeutic and diagnostic agents on a single platform to simultaneously monitor and treat the disease. Besides the therapeutic agent, the theranostic nanoparticles should contain contrast agents or molecular probes to characterize biological processes at the cellular and subcellular levels for diagnostic purposes, using optical imaging, computed tomography (CT), radionuclide imaging, and magnetic resonance imaging. Among other theranostic nanomedicines, MSNs have attracted an increased interest for theranostic purposes, mainly due to their ability to carry different cargoes simultaneously and their intrinsic optical and photochemical properties.[251]

An et al. developed a nanoplatform combining chemo-photothermal synergistic therapy and photoacoustic/ computed tomography imaging, and tested it on HeLa tumorbearing nude mice.[252] These multifunctional nanoprobes (GMS/DOX@SLB-FA) were based on gold nanostar core and DOX-loaded mesoporous silica shell (GMS), coated with thermosensitively supported lipid bilayer containing a mixture of PEG-phospholipid, dipalmitoyl phosphatidylcholine, and distearoyl phosphatidylcholine, and functionalized with FA (SLBFA). A precise control on the DOX release from the MSNs channels was achieved by using NIR laser to heat the gold core on the thermosensitive support lipid bilayer, providing a synergistic effect of the localized photothermal ablation and. Female Balb/c mice were subcutaneously injected with 106 HeLa cells, and once the resulting tumor had reached ≈0.1 cm3 in volume, the mice were treated with different nanoprobes (probe concentration 1.4 mg mL−1 , DOX concentration 200 μg mL−1 , in 100 μL PBS). After intratumoral injection of PBS, free DOX, GMS@SLB-FA, and GMS/ DOX@SLB-FA, the mice were exposed to 808 nm laser for 10 min. Consequently, the temperature at the tumor site only increased 9 °C after injection with PBS and DOX, which was not sufficient to kill tumor cells, resulting ≈1.3 and ≈0.5 cm3 tumor volumes, respectively, on day 22. However, the temperature at the tumor site increased by 34 °C, reaching 65 °C after

combined treatment using laser with GMS@SLB-FA or GMS/ DOX@SLB-FA. Consequently, the tumor cells were efficiently killed and a lower tumor growth compared to the controls was observed with GMS@SLB-FA resulting in ≈0.4 cm3 and GMS/ DOX@SLB-FA in ≈0.1 cm3 tumor volumes on day 22. These results indicated that the combination of photothermal ablation and chemotherapy could significantly improve the efficacy of tumor therapy.

Yang et al.[253] prepared magnetic MSNs (M-MSNs), with the core consisting of Fe_3O_4-Au NP and photosensitizer Ce6 and DOX adsorbed onto their surface. Next, polyelectrolyte multilayers (PEM) composed of biocompatible alginate/chitosan were assembled on the M-MSNs to fabricate a pH-responsive drug delivery system and adsorb P-gp shRNA (M-MSN(DOX/Ce6)/PEM/P-gp shRNA nanocomposite) to overcome the multidrug resistance. The in vivo therapeutic efficacy of final M-MSN(DOX/Ce6)/PEM/P-gp shRNA nanocomposites (average diameter 280 nm) was compared with the respective controls using EMT-6 tumor-bearing Balb/c female mice, with initial tumor size of 0.8–1.6 cm^3. The group treated with M-MSN(DOX/Ce6)/PEM/P-gp shRNA nanocomposite with laser irradiation accomplished a significant tumor ablation as a result of the combined chemotherapy, PDT, and gene therapy of cancer in vivo. Moreover, the measured body weight of mice during the treatment showed no significant changes, suggesting that the treatment with the nanocomposite was not severely toxic within the 18 d of treatment. Therefore, the developed multifunctional nanocomposites were able to be used as an efficient nanoprobe for magnetic resonance and X-ray CT imaging of both in vitro and in vivo xenografted tumor models.

2.7.5 Biodegradation and clearance of MSNs:

MSN biodegradation and clearance are strongly interdependent processes. MSNs dissolve fairly rapidly under physiological conditions when the concentration levels are kept below the saturation level of silica, as demonstrated in several in sink studies.[254] The rate of silica dissolution is dependent on parameters such as the particle size, functionalization and the degree of silica condensation, which in turn is highly dependent on the heat-treatment history of the silica particles. For circulating particles, the liquid (aqueous) volume is typically large with respect to the silica concentration and, therefore, it can be expected that the particles dissolve under in vivo conditions. Dissolved silica is known to be adsorbed by the body[255] or excreted in urine in the form of silicic acid or oligomeric silica species. Here, forces exerted by blood

pressure would be expected to assist in disintegration of partially dissolved particles, which can be expected to have a lower mechanical stability as compared with the original particles. Interestingly, it has been observed that, depending on the particle size, the particles can dissolve from inside out leaving the initial particle size virtually intact under static conditions. This has also been corroborated by recent in vivo data, where partially degraded MSNs with particle dimensions close to that of the injected particles were found in urine[256-258], suggesting the same degradation mechanisms may also be operative in vivo. However, the renal cut-off limit is approximately 5 nm, which is why the exact excretion process remains unclear in this case. Landry and coworkers investigated rat urine after intraperitoneal injection of tetraethylene glycol functionalized Gd-containing mesoporous microparticles and found particle-shaped objects most likely originating from the microparticles, and concluded that particulates could also be partially excreted renally.[256] This observation was also corroborated by MRIs of the lower abdominal cavity of the Wistar rats used, demonstrating enhanced contrast in the bladder at time points 2–25 h postinjection. As the animals did not exhibit any signs of Gd3+ toxicity up to 1 week postinjection, the signal was not likely to be caused by free Gd3+. Huang et al. found the same phenomenon for their studied MSN rods, when they were able to image (by TEM combined with energy dispersive x-ray spectroscopy) MSNs in both urine and fecal samples at 24 h postadministration (iv.) confirming by energy dispersive x-ray spectroscopy that they consisted of silica elements.[257] Also, Lu et al. were able to TEM-image intact MSNs in urine samples.[258] In the iv. biodistribution study by He et al.[259], they found distinctly less degradation products in the urine at shorter time points (30 min) for PEGylated MSNs than for nonPEGylated MSNs; and the degradation products also increased with increasing particle size. They concluded that this observation was because MSNs of larger particle sizes were more easily captured by the liver and spleen in 30 min, which led to their faster biodegradation and thus larger excreted quantities of their degradation products, whereas the PEGylation would hinder the capture by these RES organs and consequently slow down the biodegradation. The biodegradation and elimination mechanisms based on this argumentation, however, remain unclear. Also, the urine analysis relied on absolute fluorescence (FITC) values, which suggests the results should be interpreted as indicative. However, when combined with ICP analyses, Lu et al.[260] were able to correlate the fluorescence observed in a smear of urine at 4 h postinjection (iv.) to that of the amount of Si in the urine, for which the highest amount was detected 24 h postinjection. By contrast, the excreted

amount of Si in feces increased with time and peaked at the last time point (4 days), at which nearly all Si injected was excreted. It is important to note that no background level was recorded. The authors pointed out that the silica content in the feces was very small compared with that of urine. On this topic, Lo and coworkers[261] studied the effect of the surface charge on the two proposed elimination routes of MSNs and found that MSNs with high positive charge exhibited rapid hepatobiliary excretion. They found correlations between fluorescence and ICP analyses, but in this case both the negatively and positively charged MSNs (size 50–100 nm) entered hepatobiliary transport within 24 h of injection, with no detectable renal excretion. In this case, the background Si levels (dietary sources) were determined, which otherwise often seems to be overlooked in ICP analyses of urine and organs, and thus they could pinpoint the peak exertion to occur 2 days postinjection. However, based on organs harvested and ICP-analyzed 3 days postinjection, it was suggested that a possible onset of MSN biodegradation to orthosilicic acid with potential renal excretion could be operative. For the differently charged particles studied, they concluded that while both were sequestered by the liver; the one with the higher charge could have been more opsonized by serum proteins and thus more amenable to hepatobiliary excretion into the GI tract.[261] Thus, surface charge tuning could not only constitute a complement for targeting but also a means for regulation of the rate of excretion.

2.7.6 Safety and toxicity of MSNs:

The number of studies regarding safety and toxicity of MSNs has increased rapidly during the last years. In a recently published study MSNs showed significantly less cytotoxicity and apoptotic cell death and lower expression of proinflammatory cytokines than colloidal silica nanoparticles in vitro, and MSNs neither induced contact hypersensitivity nor acted as immunogenic sensitizer in vivo, which was shown with local lymph node assay.[262] Depending on the type of MSNs studied to date, quite different conclusions have been drawn. On a very general level, surface functionalized MSNs seem to reduce the observed harmful effects as compared with pristine mesoporous silica.[263] Porosity, particle size, and postsynthetic treatment (calcination/solvent extraction) may be other significant contributors. The porosity effect is mainly connected to the increase or decrease in available surface area and postsynthetic treatment giving rise to different degrees of condensation and consequently biodegradation rate, possible residual template surfactants, as well as surface density of silanol groups. The latter has

been especially brought forward in terms of hemocompatibility[264-265], whereby the silanol groups have been found to interact specifically with surface phospholipids on the red blood cell membranes. This effect was moreover enhanced by either a higher density of surface silanols on nonporous silica surfaces as compared with corresponding porous surfaces, giving rise to a higher accessible surfaces, giving rise to a higher accessible external surface area[265], ultimately leading to hemolysis. Blocking the access to the silanol groups by functionalization with organic groups, however, diminished the observed hemolysis. Remarkably enough, primary amine groups were also very (and almost equally as PEG) effective in preventing hemolysis in a dose-dependent manner [265], even though the common conception is that positively charged groups would enhance the interaction with the negatively charged cell membrane. The favorable effect of surface functionalization on biocompatibility also seems to be reflected in some of the existing biocompatibility studies, whereby the disadvantageous observations especially in vivo have pronouncedly been recorded for nonfunctionalized silicas.[266] Whereas 240 mg/kg nonmodified MSNs resulted in immediate death when injected iv. into mice, the lethal dose (LD50) value for mesoporous hollow silica nanoparticles was found to be greater than 1000 mg/kg. These discrepancies have also been observed for the same type of materials when either solvent-extracted or calcined, whereby the extracted materials were found to inhibit cellular respiration [267], whereas the calcined counterparts were later shown to be reasonably biocompatible in terms of interference on bioenergetics when incubated at high concentrations (200µg/ml) with murine tissues.[268] One main contributing factor was also thought to be the surface density of silanol groups, as well as differences in accessible surface area between the studied materials possessing different pore sizes (~3 and ~7 nm, respectively). Similar findings have also been appointed for nonmesoporous silicas (as well as references therein).[268] A disadvantage for the calcined MSNs could be the consequently lower hydrophilicity, arising from the lower density of silanols, potentially leading to poorer dispersability under physiological conditions. Once dispersable MSNs have been successfully produced, however, surface functionalization can facilitate the dispersability of the nanoparticulatate carriers in the physiological environment. Another concern that has to be solved, originated from metabolic changes caused by MSNs, resulting in melanoma promotion. It was suggested that the effect induced by MSNs was due to the decrease of endogenous reactive oxygen species in cells and upregulation of antiapoptotic molecules. These results show that tumor growth can be regulated by nanocarriers themselves in a reactive

oxygen species-dependent manner, and this important finding highlights the need for more tests aiming at a clearer understanding of metabolic deviations in MSN-targeted cells.[269]

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