CHAPTER 1: INTRODUCTION

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1.1 Cancer:

Cancer is one of the deadliest diseases affecting mankind. It causes a huge burden on society in all countries, those which are developed, developing and under developed alike. Enumerable new cases of cancer are being reported annually worldwide with most of them still remaining incurable. Amongst all these, the major prevalent cancers contributing to vast number of deaths are those of lung, gastric, breast and prostate (1, 2). So far, no sure shot treatment is available for cancer and complete cure still remains a distant dream (3). Even in patients getting cured by heavy doses of chemotherapy and radiation therapy, relapses are frequently observed. Hence, it becomes imperative to find a cure for this menace.

1.2 Epidemiology:

One of the most complex human genetic disease and a result of uncontrolled proliferation of the damaged cells due to underlying regulation errors, cancer figures amongst the leading causes of mortality globally. There are many factors which affect cancer. However, two major reasons behind transition of normal cells to cancer cells are inactivation of tumor suppression genes like p53 and activation of oncogenes (4). The genetic mutations can be caused de novo, induced by external environment due to carcinogen exposure, inherited, virus induced or might be due to age related genetic instability. Amongst all types of cancer the incidence of prostate cancer increasing is faster and surpassed even the number of cases reported for brain cancer and it is the most common cancer in grouping by occurrence (5)

As per the National cancer registry of ICMR more than 1300 everyday deaths are reported due to cancer. There was an approximate increase in cancer deaths by 6% between 2012 and 2014 itself (6) with highest cancer related mortality reported in northeast parts of India. Breast cancer and lung cancer are leading causes of death in women and men respectively.

In united states itself 29,430 patients suffering from prostate cancer died and about 1,64,690 new cases are reported as per the latest statistics (7). In 2019, 17,62,450 new cases of cancer are estimated and 6,06,880 cancer deaths are projected (8).It is also reported that prostate cancer has an occurrence rate 1 amongst every 5 new diagnosis. With such a high occurrence rate and being the second leading cause of cancer related deaths in men (9), it becomes imperative to find a sure shot cure for the same.

The risk factors for cancer also include immunosuppressive state, genetic and environmental factors. Other known risk factors for human malignancy are tobacco, alcohol, high animal fat intake, ionizing and UV radiations, occupational exposure to aromatic amines arsenic, asbestos, hydrocarbons, wood dusts etc. and certain immunosuppressants and steroid medications. Men from black Afro-Caribbean ethnicity or family history of this particular disease are at high risk of developing prostate cancer in future (10). Though, prostate cancer mortality was reduced and stabilized during 2013-2016 due to advances in treatment and earlier stage of diagnosis. A familial tendency exists for prostate cancer (11) and another major contributor is cadmium exposure (12). Smoking and drinking alcohol have been found of not being guilty in causing cancer of prostate(12, 13). Infection of prostate (prostatitis) and vasectomy though not confirmed is also thought to be causative agents for this disease. The risk factors and causes associated with cancer are shown in figure 1.1.

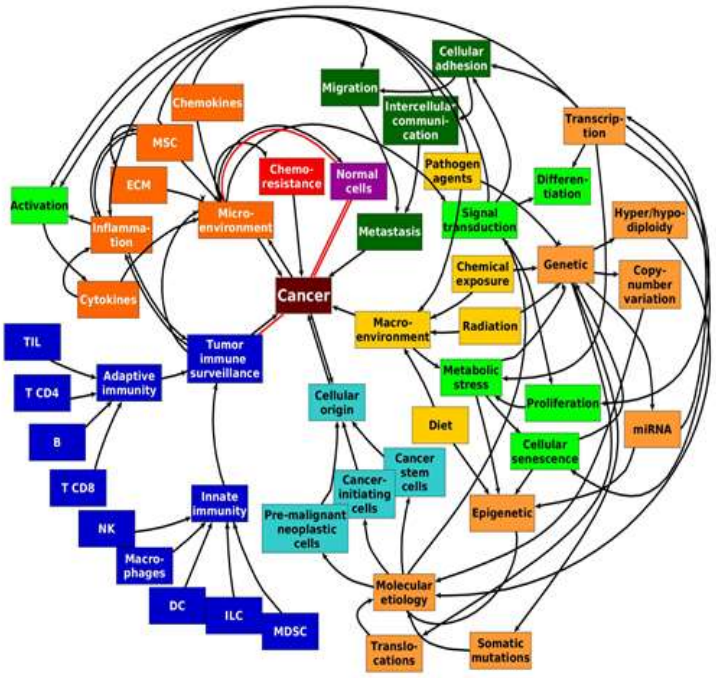

Figure 1.1. Epidemiology for cancer: risk factors and causes for cancer development

1.3 Pathogenesis of prostate cancer

Most of the cases of prostate cancer are identified as adenocarcinomas or glandular cancers and begins with the normal secretory cells of prostate gland which get mutated to cancer cells. Peripheral zone is the region where adenocarcinoma is very common. Small group of cancer cells get confined to prostate glands initially and this is known as prostatic intraepithelial neoplasia (PIN) or carcinoma in *situ*. As time progresses these cells spread and multiply causing tumors and metastasis into major organs like bones, lymph nodes, bladder and rectum. Absence of zinc via silencing of transporter protein ZIP1 leads to zinc deficiency, which is responsible for fails to give anti-proliferative effect and cause apoptosis (14). In early carcinogenesis there is loss of cancer suppressor genes localized into 8p, 10q, 13q and 16q chromosomes. Tumor suppressor genes like PTEN gene and KAI1 also play an active role. P53 mutations occur at a later stage in prostate cancer. The androgen receptor aids in survival of prostate cancer cells and PSMA hydrolyses glutamated folates, increasing the use of available folates. Thus, folic

acid ligand can be useful in treating prostate cancer by targeted therapy (15). The pathogenesis for prostate cancer is shown in figure 1.2.

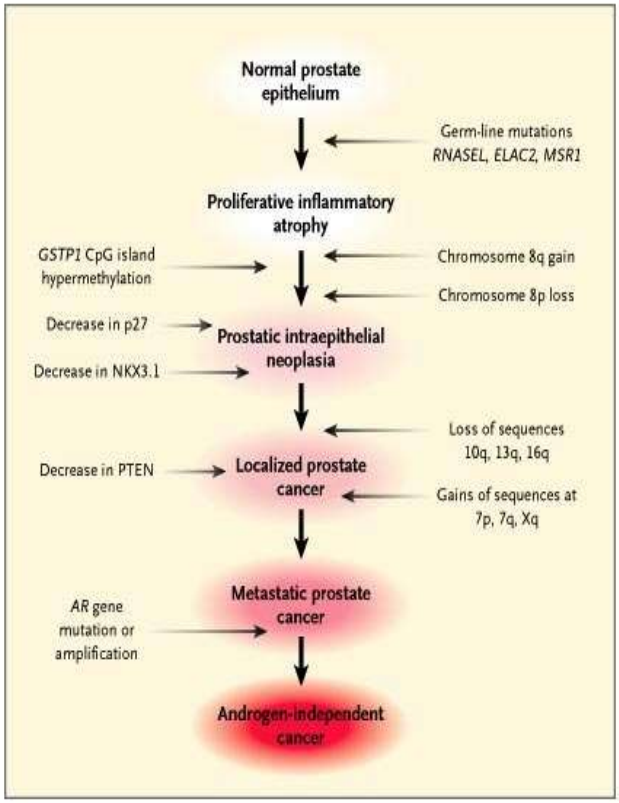

Figure 1.2. Pathogenesis of prostate cancer

1.4 Symptoms associated with the disease

The ambiguity is that the early symptoms do not exist. And in patients with the local disease the symptoms are quite similar to BPH (Benign prostatic hypertrophy) (16). Local symptoms include urinary dysfunction, erectile dysfunction, perineal pressure, hematuria, hematospermia etc. Whereas symptoms in advanced cases include sudden weight loss, weakness, anemia, paraneoplastic syndromes like venous thromboembolism etc.

1.5 Diagnosis and management of prostate cancer

The diagnosis of prostate cancer is done by various ways. Advancement in technology and diagnostic instruments has aided in fast and early diagnosis of prostate cancer. Clinical diagnosis involves digital rectal examination (DRE) detecting hard fixed tumor or loss of

median grove. Transrectal ultrasound, CT scan and MRI are the most advanced means of diagnostics available for confirming lump in prostate. Even metastasis spread to bones can be effectively detected with MRI. Prostate MRI has a much better soft tissue resolution and hence it is much preferred over poor soft tissue resolution ultrasound (17). PSA (Prostate Specific Antigen) marker is also used in laboratory examinations but it can be misleading and finally Biopsy –TURP (Transurethral resection of the prostate) is another effective way of diagnosis. During tissue examination Gleason score of any cancers found are calculated. It is indicative of folate hydrolase activity. Higher is this protein expressed, higher is the score, higher is the dedifferentiated tissue(18). Small scale carcinoma is rarest and cannot be diagnosed using PSA tumor marker (19). BCL-2 expression and prostate cancer progression are also said to be related (20). Certain drugs like Bicalutamide, Etoposide, Enzalutamide, Docetaxel, Prednisone etc. are used in treatment of prostate cancer along with surgery or radiation therapy in severe cases. Risk assessment is given in table 1.1.

	LOW RISK	MODERATE RISK	HIGH RISK	Locally advanced
Primary tumor, cT	cT1/2a	cT2b	cT2c/3	Clinical stage T3b or T4
PSA value (ng/mL)	≤10	>10≤20	>20	Any
Gleason score	≤6	7	≥8	Any
Further diagnostics	None	Bone scinillography optional	MRI or CT of pelvis, Bone scintigraphy, other symptom-oriented diagnostics	-

Table1.1. Risk assessment as per NCCN guidelines (21).

1.6 Current challenges in prostate cancer diagnosis and treatment

Overall risks associated with prostate cancer can be classified into three broad categories (10). The foremost being assessment of risk of an individual of developing or susceptibility to prostate cancer during his entire lifetime. The likeliness and pre-preparedness can be very useful in this regard to provide a complete cure. The second challenge is differential diagnosis

and prognosis of aggressive vs non-aggressive cancer. The third and most challenging is developing new advanced treatments for complete cure of disease.

Another issue is associated with diagnosis of prostate cancer, the PSA test does indicate that there is some problem with the prostate but it is not sufficient in identifying whether cancer is present or not.

- One of the challenges is overdiagnosis which leads to over-treatment. Over-treatment ultimately leads to unnecessary side effects associated with radiation and chemotherapy. Major side effects of androgen therapy include erectile dysfunction, hot flashes, anemia, osteoporosis and those associated with brachytherapy are distressing urinary symptoms, diarrhoea and rectal bleeding (22).
- Early detection of prostate cancer is possible but early discrimination is not and hence there is always an uncertainty associated whether a particular cancer in individual will become aggressive or not (23).
- Castrate resistant prostate cancer (CRPC) is the type of cancer which keeps growing even when amount of testosterone in body is very low. They do not require normal levels of testosterone to grow even in the early stages and hence the treatment becomes very challenging.
- A relatively newer term oligometastatic disease in patients suffering from prostate cancer(24). It basically includes 1-5 lesions. Patients with low metastasis show high response to treatment and it is a challenge to completely cure those suffering high metastasis.
- The most important challenges faced in treatment is targeted treatment of cancer so as to provide an effective cure and most importantly minimize the side effects of drugs on healthy organs.

It is well established that oral drug delivery has better patient compliance than injectables. But the major hindrance is low solubility and permeability issues associated with some of the major anticancer drugs which belong to BCS- class II and IV. This in turn limits their bioavailability and efficacy. High first pass metabolism could also affect the bioavailability of drug. A vast amount of research is already being carried out which focuses on improving these aspects of drug by design effective drug delivery systems apart from the traditional forms available. The physicochemical properties can be altered for concerned moieties and their effect on release and permeability can be studied. Further, nano drug delivery forms in injectables are also effective in achieving a targeted treatment of cancer along with minimized side effects. Thus, nanotechnology plays a major role in preparing effective drug delivery systems for targeted treatment of various cancers.

1.7 Recent scenario

Several advances and treatment options are available for prostate cancer treatment apart from watchful waiting and surgery(radical retropubic prostatectomy) (25). Some of them and most recent are worth mentioning here (26).

External beam radiation therapy- also known as intensity modulated radiation therapy and radiations are given externally. Mostly an outpatient procedure 5 times per week for 6-8 weeks. The disadvantage is lacking the corrective ability of prostate movement during treatment and hence damage to healthy regions occurs.

1. Brachytherapy- Herein, small radioactive seeds are implanted within the prostate gland. As time proceeds the seeds give off radiation to the surrounding prostate area killing the lethal cancer cells. It's a one-day treatment and requires hospital care post treatment.
2. Proton therapy- uses a focussed proton ray to destroy the prostate cancer cells. The beam of protons is delivered using a particle accelerator. The charged particles damage the DNA

of cells and ultimately cause death of harmful cells thereby interfering their ability to proliferate. Duration of treatment is 5 days a week for around 8 weeks.

3. Stereotactic body radiation therapy- Utilizes cyberknife® technology to deliver the targeted radio beams to prostate. It compensates the prostate movement and hence minimizes damage to the surrounding healthy tissue. It is an outpatient treatment and takes one-two week.
4. Focal therapy- useful in patients with low risk cancer and aims at eradicating all foci of cancer(27). Focal laser ablation works via thermal destruction of tissue by a laser (28). Some other are high intensity focussed ultrasound and cryosurgery(29). It ensures minimum harm to adjacent structures necessary for preservation of urinary, sexual and bowel function. However, it is necessary to include appropriate endpoints and timely monitoring. It can be highly useful in improving quality of life and life expectancy in affected patients.

The ultimate therapy options depend on the stage of the disease (30). The primary objective involves relief from cancer related symptoms followed by chemotherapy-based treatment. It is indicated in hormone refractory prostate cancer. About 50% of affected people have shown decrease in PSA level of about 50 % with chemotherapy treatment.

Overall, the main side effects are damage to healthy vital organs hampering their functioning. This occurs due to drug going off-site or high doses. The answer lies in targeted therapy for prostate cancer such that the healthy tissues remain unaffected by drug exclusively reaching the cancer cells. Lots of nanodrug delivery-based systems have been researched upon for this purpose. Nanoparticles, with the capacity to store large payloads within their cores and "targeting" molecules on their surfaces, would seem ideally suited to the task (31). Contemporary research attempts to tackle this fundamental challenge by utilizing nanoparticles as carriers for anticancer drugs. Risk stratification is given in figure 1.3.

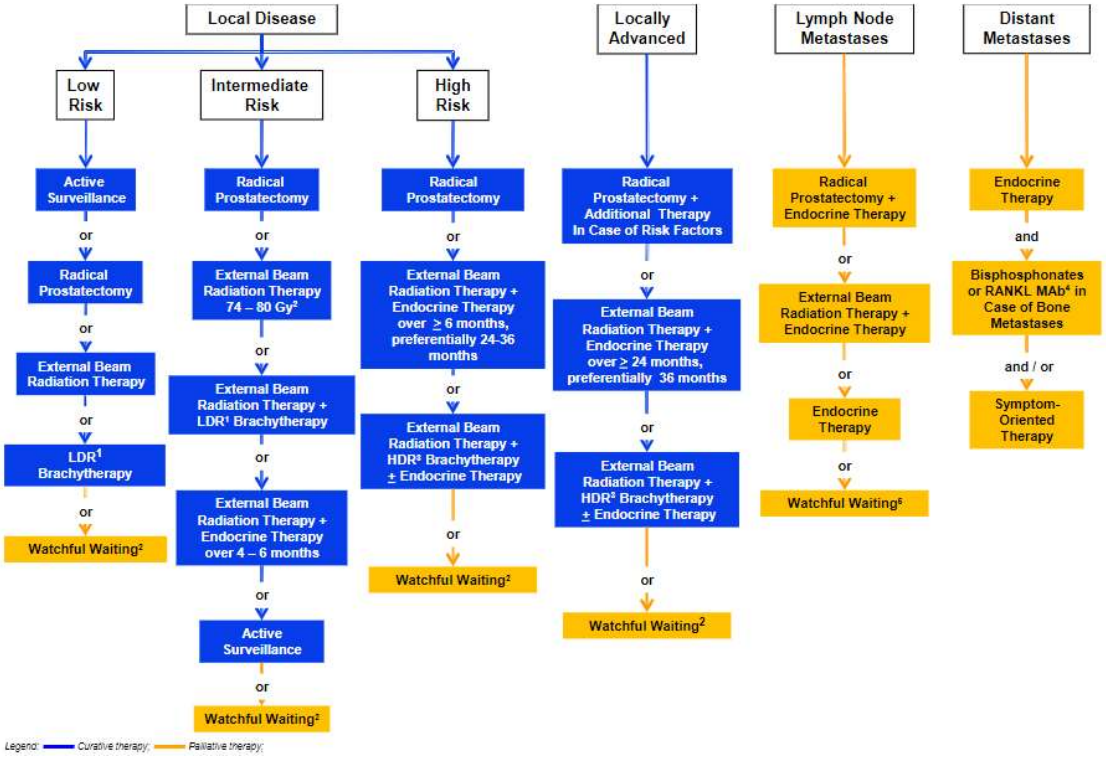

Figure 1.3. Risk stratification and further diagnostics of localized cancer (LDR-low dose range, HDR- High dose rate, RANKL Mab – antibodies directed against RANK ligand in asymptomatic patients) (32)

1.8 Anticancer drugs

Anticancer drugs or anti-neoplastic agents are the drugs useful in effective treatment of malignant or cancerous diseases via different mechanisms. The major classes of these anti-cancer agents include alkylating agents, antimetabolites, natural products, hormones. They are used in chemotherapy alone or in combination with surgery or radiation therapy. Further, there are major challenges associated with anticancer drugs which needs to be addressed.

i. The foremost include challenges related to their properties and formulation. The major hindrance here is solubility and permeability. Since majority of anticancer NCEs belong to BCS class II and IV, this hampers their efficacy due to poor bioavailability attributed to limited solubility or permeability or both.

ii. The second major challenge associated with anticancer drugs is related to their efficacy and side effects. Their lack of tumour targeted approach leads to causing harm to healthy organs and tissues. Thus, apart from treatment other dangerous side effects like decrease in blood cells, increased risk of infections, hampered functioning of major organs and excessive bleeding due to decreased platelets occur. The potency of anticancer drugs apart from killing tumours; leads to causing more harm than cure.

The answer to both the major challenges described above lies in formulation part. If novel drug delivery systems are designed in such a way that they can enhance the solubility and permeability of the anticancer drugs. This will in turn lead to enhanced efficacy due to increased bioavailability attributed to nano drug delivery formulation. Overall, it can be said that targeted anticancer agents are more beneficial than conventional chemotherapeutics (33).

Further, nanodrug delivery agents can also be surface modified or suitable ligand attached targeting particular receptors overexpressed in cancer cells. The differences in normal and cancer cells environment can be effectively exploited and appropriate groups attached to achieve the goal of targeted therapy either active or passive. This leads to the anticancer drugs exclusively reaching the targeted cancer cells and sparing healthy cells and can be a strong candidates for sure shot treatment of cancer. The details of nanodrug delivery systems and mesoporous silica nanoparticles in particular are mentioned further.

1.9 Nanotechnology

Nanotechnology is the branch of science dealing with engineering materials and systems on a molecular scale. Its application to therapeutic field and nanomedicine, has enabled the development of various nanoparticle drug-delivery vehicles. Nanoparticles (NP) are solid colloidal particles ranging in size from 1 to 200 nm and used as drug carriers. These have the ability to deliver therapeutics to cancer affected sites (34, 35). Conventional chemotherapeutics disseminate throughout the body; hence they affect both cancer cells as well as normal cells.

Nanoparticles, possess enhanced permeability and retention (EPR) effect, therefore favourably accumulate in tumours. This divergent bio distribution allows nanoparticle-based chemotherapeutics to achieve enhanced intra-tumoral drug concentration and lower concentrations in normal tissue than their conventional small- molecule counterparts. It can also lead to higher therapeutic efficacy and lower toxicity for nanoparticle therapeutics (36).

Various nanocarriers include Polymeric nanoparticles, dendrimers, polymeric micelle, liposome, inorganic (iron, silica, quantum dot core), biological nanoparticles, hybrid nanoparticles amongst many others. Over last couple of decades many nano drug delivery systems have been developed using organic as well as inorganic materials. Numerous nanodevices have been reported like carbon nanotubes, quantum dots, and polymeric micelles, etc., in the field of nanotechnology. Nanocarriers can encapsulate a variety of therapeutic agents and small molecules, which leads to increase in solubility and controlled release to maintain drug concentration within therapeutic window. One such promising nanocarriers are mesoporous silica nanoparticles.

1.10 Mesoporous silica nanoparticles

Over the last two decades, a large number of nanoparticle delivery systems have been developed for cancer therapy, including organic and inorganic materials. Among inorganic materials, the functionalization of Mesoporous Silica Nanoparticles (MSNPs) with molecular, supramolecular or polymer moieties, gives them great versatility while performing drug delivery tasks, which makes the delivery process highly targeted and controllable. Mesoporous silica nanoparticles are biodegradable and mostly eliminated through renal clearance. The unique mesoporous structure of silica facilitates effective loading of drugs and their subsequent release of the target site. Other features such as tunable pore size, and uniform pore size leading to uniform release, zero premature release and good biocompatibility and biodegradability are an added feather to the cap.

Due to strong Si-O bond, silica-based mesoporous nanoparticles are also more stable to external response such as degradation and mechanical stress Hence, potential drugs which were earlier ignored because of poor pharmacokinetics, can be re-evaluated (37). The surface of the nanocarriers can be modified to increase blood circulation half-life and enhanced biodistribution, while attachment of targeting ligand to the surface of nanocarrier can lead to increase in their cellular uptake (38). Among a variety of nano drug-delivery systems, mesoporous silica materials have several attractive features for use in the delivery of water-insoluble drugs (39). These particles have porous interiors and large surface areas which can be used as reservoirs for storing hydrophobic anticancer drugs. Textural properties of MSNs provide the possibility to load high percentage of drugs within MSNs carriers. The pore size is tunable can be tailored to selectively store different molecules of interest, (40, 41) while the size and shape of the particles can be altered to maximize cellular uptake. Unlike polymer-based nanoparticles, these sturdy inorganic materials can withstand many organic solvents (42). Silica-based materials have been successfully used as drug-delivery agents (43, 44), gene transfection reagents (44), cell markers (45), and carriers of molecules (46). Thus, the need of MSNs is justified. Moreover, silica is an endogenous substance, especially abundant in bone, cartilage and other supporting tissue. It is 'generally recognized as safe' by the US FDA.

1.11 History associated with MSNs

Amorphous silica was proposed as a drug delivery carrier as early as 1983 (47). Amongst these, ordered mesoporous silica materials (OMMs) have been recognized as one promising class due to the controllable structural and morphological features on the nanometer and micrometer scale. Though the idea of employment of mesoporous materials in field of drug delivery and pharmacological activity was conceived in the year 1998-1999 (48). Balkus and colleagues published the first instance of MSNs having drug loading and release ability (49). The combination of DAM-1(Dallas amorphous material-1) combined with the modified Stober

process paved the way for development of MSNs as drug delivery platforms (50). MSNs were synthesized independently by researchers in Japan (51) and later produced at Mobil corporation laboratories, thus named Mobil crystalline materials or MCM-41(52, 53). Through further research a better and strict control of their porosity and other characteristics could be achieved. Later on, several mesoporous carriers having different characteristics were synthesized as summarized below (Figure 1.4, Table1.2).

Sr No.	MSN Family	MSN Type	Pore symmetry	Pore size (nm)	Pore volume (cm^3/g)
1	M41S	MCM-41	2-D hexagonal	1.5-8	>1.0
		MCM-48	3-D cubic	2-5	>1.0
		MCM-50	Lamellar	2-5	>1.0
2	SBA	SBA-11	3-D cubic	2.1-3.6	0.68
		SBA-12	3-D hexagonal	3.1	0.83
		SBA-15	2-D hexagonal	6-0	1.17
		SBA-16	Cubic	5-15	0.91
3	KIT	KIT-5	Cubic	9.3	0.45
4	COK	COK-12	Hexagonal	5.8	0.45
5	Disordered MSU-X Aluminum oxide mesoporous	Michigan State University-X	Large pore 2-D hexagonal	2.5-5 (avg 3.8)	--
		MSU-H	Large pore 2-D hexagonal	7.1	0.91
6	Disordered TUD-1	Technische Universiteit Delft -1	3-D foam like	0.55	0.45

Table 1.2. MCM- Mobil crystalline materials, SBA- Santa Barbara Amorphous, KIT-Korea advanced institute of science and technology, COK- center for research chemistry and catalysis (54-63)

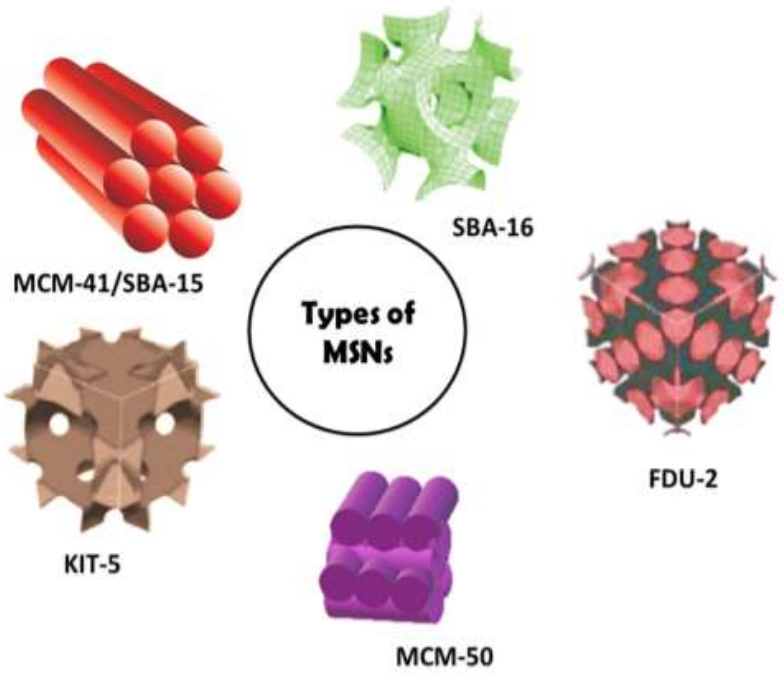

Figure 1.4. Representation of different MSN types (60)

1.12 Synthesis of Mesoporous silica Nanoparticles

The present synthesis methods for MSNs are based on use of a surfactant template which is employed as a structure directing agent. There are four major methods widely used for MSN synthesis (64).

1.12.1 Sol-gel synthesis

Sol gel method is advantageous in providing controlled surface decoration of MSNs. It is two stage process. The foremost step is formation of particles in the glue body suspension solution. This is followed by formation of a 3D (dimensional) network of polymer chain gel. General synthesis templates are block co-polymer template, surfactant template, floating template etc. The perks of this method are high purity final product and low temperature environment (65).

1.12.2 Hydrothermal synthesis

This is based on use of surfactant as a template with acid/alkali as a catalyst. Followed by inorganic substance (silica source) addition to obtain a hydrogel for ultimate transfer to an

autoclave unit. High temperature and pressure both are critical for this reaction and later precursor is separated with removal of organic matter (66). The superiority of this method lies in the fact that precursor is completely dissolved and improved hydrothermal stability of the material. The disadvantages are complex process and long reaction times.

1.12.3 Microwave synthesis

Microwaves are a type of electromagnetic waves. Here heating is both from inside and outside in an electromagnetic field. Thus, it is an energy efficient process and involves rapid heating. The synthesis time is hugely reduced to less than 6 h as well in this relatively simple operation. A good crystallinity is also obtained (67).

1.12.4 Template synthesis

Template based synthesis method is basically of two types: soft template method and hard template method. Non-covalent bond between surface active agent and inorganic reaction is a soft template technique and gives NPs of size between 10-1000nm. A hard template consists of filling the object pores. It gives a relatively narrow and small size range NPs (68).

1.13 Characterization of MSNs

Monitoring of synthesis and post synthetic evaluation or characterization plays a pivotal role in determining its loading capacity and further course of action. The characterization of MSNs is performed both before as well as after drug loading. The MSNs are characterized for various properties like surface area and porosity, zeta potential and size, internal structure and intactness of skeleton by TEM and XRD respectively. The characteristic peaks of MSN carriers are identified in the small angle XRD spectra. Drug loading conformation is obtained by the wide angle XRD determination. FT-IR and DSC are used in preliminary analysis at initial stages. Zeta potential is useful in surface charge determination and plays a major role in case of surface functionalization of MSNs as grafting of different groups induces different positive or negative, increased or decreased potential based on the nature decorated surface moiety.

1.14 Drug loading

Drug loading into MSNs is highly influenced by adsorptive properties of MSNs(60). Possessing large pore volumes and surface area makes MSNs much more capable of high loading capacity as compared to other nanoparticles. Drug loading can be carried out both pre and post grafting. Different methods employed for loading of drugs into MSNs are rotavapor, soaking, centrifugation and immersion method. The initial step common to all these methods include dissolving the drug in a suitable solvent followed by addition of carrier in a suitable drug: carrier ratio. Rotavapor method includes evaporation of solvent under reduced pressure. Soaking involves use of vacuum filtration with Buchner funnel attached to a water aspirator. Immersion method includes attaining equilibrium in a closed container by reaction mixture on a magnetic stirrer followed by vacuum filtration. Centrifugation involves separation by rotation at a high speed. However, Rotavapor has been found to be a more reliable method giving a higher loading percentage of drug(69).

1.15 Surface functionalization of MSNs

The functionalization of Mesoporous Silica Nanoparticles (MSNPs) with molecular, supramolecular or polymer moieties, gives them great versatility while performing drug delivery tasks, which aids in attaining a highly targeted and controllable drug delivery (70). Enhanced surface-drug interactions are most useful in achieving a controlled drug release by surface modification with chemical bonds using ionic and bonds/ester groups (71). Further, there are numerous silanol groups on the surfaces of mesoporous channels, which facilitate the surface decoration to allow for a better control over the drug diffusion kinetics (72). Surface modification and attachment of various moieties on MSNPs as per requirement of drug release is depicted in figure 1.5. The surface functionalization is generally needed to load proper type of drug molecules (hydrophobic/hydrophilic or positive/negative charged), specific actions can also have a natural quality or characteristics by the functionalization through chemical links

with other materials such as stimuli-responsive, luminescent or capping materials, leading to smart, and multifunctional properties (73). In addition to the attractive structural features of OMMs, the flexible and straightforward surface functionalization means allow for control of OMM surface charge, optimization of drug–carrier interactions, as well as enhanced OMM dispersion stability. The platform can easily be further functionalized, for instance, by attachment of fluorophores for imaging and ligands for cell-specific targeting. Active surface enables functionalization to changed surface properties and link therapeutic molecules. The biggest challenge in cancer treatment is not able to achieve targeted or selective delivery of drug molecule. Various targeting moieties like folate (74), aptamers, antibodies (75) and others can be attached on surface functionalized MSNs. They are used as widely in the field of diagnosis, target drug delivery, bio-sensing, cellular uptake, etc., in the bio-medical field. They are also suitable for multi drug delivery.

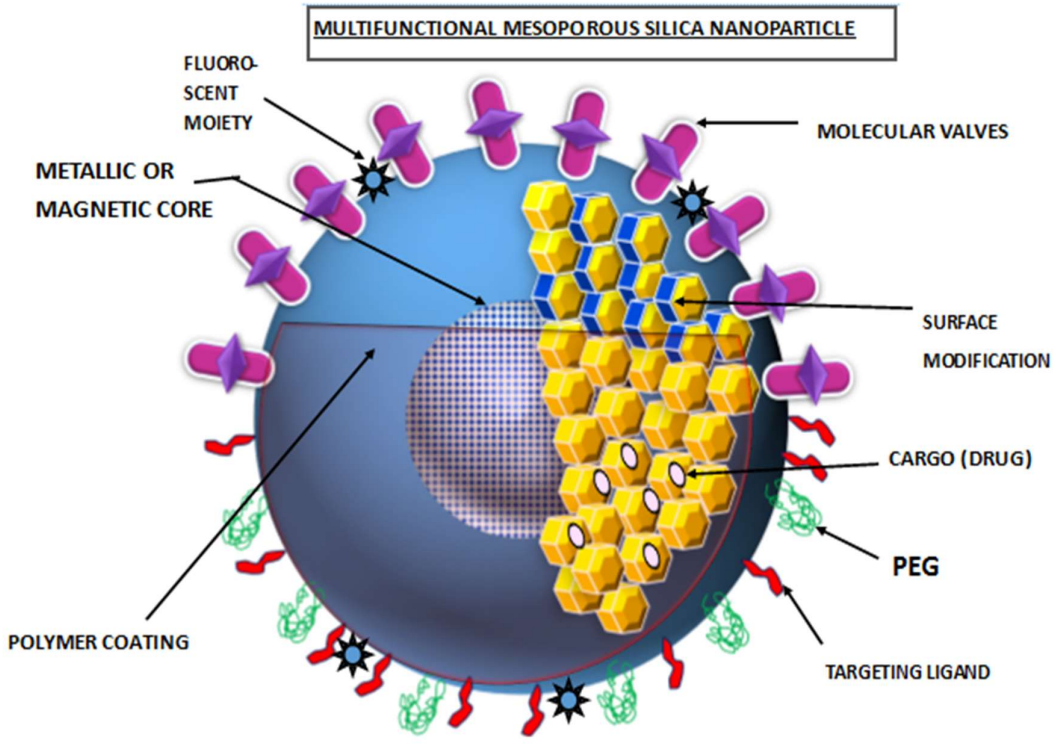

Figure 1.5. Surface modification and attachment of various moieties on MSNPs

On a very general level, surface functionalized MSNs seem to reduce the harmful effects associated with pristine mesoporous silica (76). Blocking the access to the silanol groups by functionalization with organic groups also diminishes the observed hemolysis. Remarkably enough, groups like primary amine groups and PEG have been proven to be quite effective in preventing hemolysis in a dose-dependent manner (77). As nanocarriers, mesoporous silica nanoparticles with unique mesoporous structure have been explored as effective drug delivery systems for a variety of therapeutic agents to fight against various kinds of diseases including diabetes (78) inflammation (79) and cancer (80).

Present drug delivery systems, however, do not have the ability to guide themselves to a target. So, the active targeting is required to guide the drug/drug carriers to a target site. Hence, the current research is focused on developing a mesoporous silica nanoparticle for targeting cancer cells to obtain maximum effective treatment for cancer and spare the healthy cells and organs from unwanted side effects. Some recent mesoporous formulations along with the surface modification done and their use in cancer is summarized in Table 1.3.

Sr No	MSN	Modification	Stimuli/ligand	Application	Reference
1	FNP-VIN@FAMSN	Fullerenol capped FA@MSN	FA receptor targeted	Targeted Breast cancer treatment	(81)
2	DOX-loaded MSNs@PDA-PEP	Polydopamine and peptide coating	pH based	Bladder cancer therapy	(82)
3	DOX loaded Hollow MSNs	Transferrin via disulphide bond conjugation	Redox stimuli based (Glutathione concentration)	Targeted cancer therapy	(83)
4	DOX loaded MSNs	PAA-lectin concanavalin	pH responsive	Targeted bone cancer treatment	(84)
5	Curcumin loaded MSN@Graphene nanohybrid	Aspartic acid fucntionalized PEGylated MSNs	pH responsive	Breast cancer targeted treatment	(85)

6	MSNs-anti-miR-155@PDA-Apt	Polymerized Dopamine and AS1411 aptamer	micro-RNA 155 overexpression	Colorectal cancer therapy	(86)
7	CS-MCM-48	Chitosan modification	pH responsive	Breast tumour	(87)

Table 1.3. Recent surface modified MSNs and their applications [2016-2018]

1.16 Efficiency of surface functionalization

As described in section 1.15 surface functionalization does leads to a major enhancement in efficacy of MSNs. Commonly, the need of surface functionalization arises to enhance the physical properties; in turn giving a better drug delivery, increased drug adsorption and sustained release of drug onto the target for a longer period(88). Ease of chemical modification is attributed to the presence of silanol groups. Certain drugs like Ibuprofen have been shown to have higher adsorption capacity on surface functionalized MSNs as compared to bare carriers attributed to strong hydrogen bonding(89) even though with decreased surface area and volume. Surface decoration also enhances the release properties. The release can in turn be altered and controlled as desired by using a suitable organic moiety for adorning the mesoporous surface. Modification with longer alkyl chains decreases the degradation rate aiding in simplicity of controlling the release rate. The modification of silica surface can also decrease the wettability of pore surface by aqueous solutions. Furthermore, the major advantage still remains the high success rate of attaining a stimuli based release. A bulky moiety on the surface further increases the circulation time. Lastly, an important aspect of surface functionalization remains its role in reducing the toxicity of MSNs, like PEGylation has been reported to have caused reduction in toxicity of MSNs on lungs(90). A reduced toxicity can be further obtained with surface functionalization with proteins, biosafe polymers etc.

1.17 Targeted drug delivery using MSN

1.17.1 MSNs in cancer treatment:

Targeting therapy for cancer is indeed a paradigm shift in the therapeutic arena. A lot of the research thrust today focuses on formulating strategies which are highly effective in targeting and at the same time reduce off-target side effects. MSNs are thought to possess high potential in cancer treatment due to their flexibility in size and capacity to carry large amount of cargo. They also have potential to provide affordable, effective and safe health care option. Most of the anticancer moieties are hydrophobic and this limits their use, their water solubility can be improved by encapsulating into mesoporous Nano shells and additionally they can be decorated with desired agents depending upon targeting requirement (39). There are a couple of types of targeting strategies active targeting and passive targeting which is employed for tumor targeting.

1.17.2 Passive targeting in cancer

Passive drug delivery is based on the EPR (Enhanced permeation and retention effect). It is a pathophysiological characteristics of diseased tissues which aid in enhanced drug accumulation in pathological sites (36). Leaky vasculature in blood vessel epithelial layers and inefficient drainage system are characteristics of a tumor tissue ideal for passive targeting. Nanoparticles with 10-100 nm in size are found to stay for a longer period of time in circulation (91). For this purpose, MSNs are adorned with various coating materials and groups like polyethylene glycol (PEG) coated MSNs. Moieties like PEG and other polymers add bulk to the nanoparticle and gives an anti-phagocytic property to it. This prolongs the circulation time as they skip the RES (Reticular endothelial system). Here the logic applied is that nanoparticle is made hydrophilic as water molecules get attached to the oxygen of PEG through hydrogen bonding (92).

1.17.3 Active targeting

Active targeting in simple words means identification of receptors overexpressed or specific to cancer cells and attaching these receptor specific targeting moieties on the surface of nanoparticles to target these receptors. It is notable that since folate receptors are overexpressed in almost all types of major cancers. Folate targeting using folic acid as a ligand is an important strategy for active targeting of cancer cells. There has been active role of folic acid decorated MSNs in aiding receptor mediated endocytosis for enhanced cellular uptake (93). So far this has proved to be an important strategy in case of FR positive cancer cells. Certain cells also show overexpression of CD44 receptors. For this purpose, Hyaluronic acid has been used as a ligand. Likewise, various ligands are used as guiding and targeting moieties for selected receptors overexpressed in various cancers.

1.18 Biocompatibility and biodegradation of MSNs

Seeing the increasingly positive outcome of MSNs applicability in cancer theranostics, it becomes imperative to look into the safety and biocompatibility aspect of the same. To transfer MSN treatment for clinical use, it is of high priority to determine their safety and effectiveness in humans. Toxicity can depend upon various properties of MSNs like charge, size, shape and surface properties (94). The working of MSNs inside human body is highly dependent on its size. It is believed that EPR (Enhanced permeation and retention) effect plays a role in passive targeting of tumors. Notably, when circulating in the body, they are prone to clearance by the mononuclear phagocytic system (MPS). NPs with greater than 100 nm diameter are removed by kupffer cells in liver (95). Those less than 5 nm in size are capable of crossing the glomerular filtration system and can be excreted through urine. While the NPs with 30-200 nm hydrodynamic diameter are optimized to be accumulated in the tumor tissue. This is designed for passive targeting based on the EPR effect. The internalization is known to occur by endocytosis mechanism.

Biocompatibility issues can result with MSNs interfering with biological processes occurring in the body. At cellular level the potential toxicities can occur due to the interaction of MSNs with biological systems by various mechanisms, like mitochondrial dysfunction, glutathione depletion, membrane peroxidation and DNA damage (96). It is also observed that as functionalization proceeds further, the toxicity is decreased as compared to bare silica which is one of the logic behind surface functionalization of MSNs. In many cases aminated MSNs have proved to exhibit more hemocompatibility than pristine silica. In depth study is necessary to know the effect various MSNs have on different vital organs like lung, kidney, liver, heart and brain. Even though large-scale animal and *in vitro* studies have been conducted, still a lot remains to be done to study similar effects in humans. The biocompatibility of MSNs is ultimately depended on their translocation (97). Effect of size, shape, surface functionalization and structure definitely play a major role in determining their biocompatibility. As the size of NPs increases their excretion from urine also increases.

The size dependent cytotoxic effect is present and smaller MSNs are more toxic as compared to larger ones (98). Thus, that bigger nanoparticles have been known to exhibit less cytotoxicity. A concentration and size dependent hemocompatibility of nanoparticles conducted found that smaller nanoparticles have greater hemolytic effect as compared to bigger MSNs (99). The administered MSNs have to first of all cross the cellular barrier and hence particle morphology play an important role in biocompatibility. MSNs having these much higher aspect ratios were significantly active in disrupting the cytoskeleton and inducing prominent cytotoxicity. Spherical MSNs were internalized faster as compared to rod shaped counterparts. This might be due to their lower tendency to aggregate. It is also known that type of cells also plays a major role in uptake apart from the shape itself (96, 100).

Surface modification of MSNs may prove the advantages in the form of enhanced cellular uptake, reduction in undesirable interactions with internal organelles and enhanced endosomal

escape Thus, this is also an important factor determining the extent of endocytosis by MSNs. Ligand affinity and surface charge could also play a role. For an instance, a positively charged amine functionalized MSNs tend to hold on to negatively charged cell membranes rather than entering cytoplasm (93).It is also necessary to determine the maximum tolerated dose (MTD) and to determine whether the amount lower than that of MTD is effective for anticancer purposes (100).

The degradation pattern of MSNs plays a major role in upgrading them to human clinical trials. A knowledge of interaction among physical and chemical properties and biodegradation behavior have a significant impact during synthesis of MSN based targeted drug delivery system. Moreover, *in vitro* degradation study of hollow MSNs in human umbilical vein endothelial cells (101) proved that degradation took place in cytoplasm initially and later in lysosomes. It is also testified that MSNs are converted into non-toxic silicic acid moieties and excreted from body majorly through the kidneys (102). Further, it has already been proven that the silica particles mainly converts into bioavailable form, *i.e.* monomeric Ortho silicic acid form which is essential for bone and connective tissue hemostasis (103, 104).

1.19 Recent advances and other applications of MSNs

MSNs are widely used in drug delivery for aforementioned reasons and lately also employed as “theranostic” or “theragnostic” agents. The term Theranostic synonymous to theragnostic describes platforms which serve dual role of diagnostic and therapeutic (105, 106). Thus, MSNs in this role can help to keep a regular check on circulation as well as bio distribution of drug delivery carriers. This could lead to the emergence of a new era in cancer targeting. Multifucntional MSNs are also useful in passive targeting owing to their nanosize and real time non-invasive monitoring will be helpful in getting precious feedback on state of disease (107). An important fact in this regard is that nanomaterials already employed for diagnostic purpose can be upgraded to incorporate therapeutic agent as both of these require more accumulation

in the diseased area. MSNs bearing photosensitizing agents are employed as for PDT (Photodynamic therapy).

Drug delivery applications of MSNs are summarized in Table 1.4. The other arena of MSN applications includes Quantum confined nanowire host in Electronics or energy, Environmental applications in form of heavy metal and contaminants removal, enzyme encapsulation for biocatalysts, Phospholipid extraction from biological matrices and separation of chemicals.

Sr No	MSN	Drug	Category	BCS-class	Purpose	Reference
1	Spherical MSNs	Telmisartan	Anti-hypertensive	II	Dissolution rate enhancement and drug loading capacity improvement	(108)
2	MCM-41	Vorinostat	Anti-cancer	IV	Enhancement of solubility and permeability	(109)
3	NFM-1, AMS-6 and STA-11	Atazanavir	Anti-HIV	II	Bioavailability enhancement	(110)
4	SBA-15	Carbamazepine	Anti-convulsant	II	Bioavailability enhancement	(111)
5	Hyaluronic acid modified MSN	Doxorubicin	Anticancer	III	Targeted delivery to CD44 expressing cancer cells	(112)
6	Fluorescent MSNs	Paclitaxel	Anticancer	IV	Targeted treatment of pancreatic cancer	(113)

Table 1.4. Drug delivery applications of MSNs for wide range of drugs.

1.20 Challenges of MSN application in cancer therapy and Present scenario:

Though vast research has been done proving safety of MSNs *in vitro* in various cell lines, However, its efficacy and safety *in vivo* in human clinical trials still remains to be tested and proved. MSNs face considerable and essential hurdles starting from scale up of MSN synthesis

to required dosage and ultimately acceptable pharmacokinetic and pharmacodynamic profiles (114).

- Synthesis of large amounts with consistent quality and uniform characteristics like shape, size and properties.
- Suitable concentration of drugs which can be incorporated. It may not be necessary that all drugs could be accommodated at an advantageous dose than conventional formulations.
- Maximum tolerated dose for MSNs need to be determined in humans so that minimal safe concentration can be established.
- Establishing the biocompatibility and efficacy of modified MSNs as surface moieties acting as gatekeepers or targeting ligands might change their safety aspects. This needs to be evaluated for each suitable modification.
- Immune response, systemic toxicity and associated side effects need to be critically evaluated.
- Failure of MSN to carry drug or cargo safely to the targeted site could lead to burst release and ultimately systemic toxicity. So as to prevent this kind of incident more fool proof formulation needs to be synthesized.

Recently, Cornell dots (C-dots form of MSNs) have been approved by the united states food and drug administration (USFDA) for stage 1 clinical trial in the year 2014 and are 20 times more fluorescent than normal dyes (115, 116). C-dots are a type of inorganic silica nanoparticles designed for fluorescence imaging applications. They are to be utilized for lymph node mapping in cancer and they include cyclic RGD peptides as a targeting moiety, a polymer layer and NIR fluorescent dye labelled internal silica core (117). As such silica is recognized as generally regarded as safe (GRAS) by the USFDA. A first trial in human in 5 patients indicated a favorable pharmacokinetic and safety as a tumor targeting agent, creating opportunities for further trials in future (118). Hybrid nanomaterials based on a conjunction of

iron oxide nanoparticles (IOPs) with MSNs have also proved to be successful. The IOPs have been useful for magnetic drug targeting and shown success in reducing side effects and accumulation of cancer drug at the target tumor site. Many *in vivo* and few clinical trials have proved their efficacy (119, 120). Some of the recent marketed products of silica fit for human use include zeodent 113 sillica toothpaste, Lancome™ microlift cosmetic product and chocolate slim milk shake.

1.21 References

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