Recent Advances in Porous Nanoparticles for Drug Delivery in Antitumoral Applications: Inorganic Nanoparticles and Nanoscale Metal-Organic Frameworks.

ABSTRACT

Introduction

Nanotechnology has provided new tools for addressing unmet clinical situations, especially in the oncology field. The development of smart nanocarriers able to deliver chemotherapeutic agents specifically to the diseased cells and to release them in a controlled way has offered a paramount advantage over conventional therapy.

Areas covered

Among the different types of nanoparticles which can be employed with this purpose, inorganic porous materials have received great attention in the last decade due to their unique properties such as high loading capacity, chemical and physical robustness, low toxicity and easy and cheap production in the laboratory. This review discuss the recent advances performed in the application of porous inorganic and metal-organic materials for antitumoral therapy, paying special attention to the application of mesoporous silica, porous silicon and metal-organic nanoparticles.

Expert Opinion

The use of porous inorganic nanoparticles as drug carriers for cancer therapy provide promising opportunities for improving the life expectancy of the patients affected by this terrible disease. However, much work is needed in order to overcome their drawbacks, which are aggravated by their hard nature, exploiting the advantages which provide the highly ordered pore network of these materials.

1. INTRODUCTION

In the recent years the scientific community has devoted huge efforts in the search of novel treatments against unmet clinical situations such as inoperable cancers, degenerative pathologies or resistant infections, among others. The application of nanotechnology to medicine, the so called nanomedicine, has become into a key discipline for the discovery of novel therapies against these terrible diseases. This discipline comprises the use of nanometric systems as drug delivery carriers, medical imaging or sensors for clinical diagnostics, [1] [2-3] being the first application the most exploited counting with around 76% of the research papers in nanotechnology in 2014.[4] The utilization of nanoparticles as drug carriers provides several advantages such as improved pharmacokinetic profile, possibility to employ lipophilic drugs, higher circulation time in comparison with the administration of the free drugs and lower toxicity as a consequence of the lower dosages employed in the nanovehicles.[2][5] In 1986, the Japanese researchers Maeda and Matsumura reported that macromolecules bigger than 40 KDa injected in the blood stream had tendency to be preferently accumulated within tumoral tissues. They called to this phenomenon *enhanced permeation and retention* (EPR effect).[3][6] This preliminary finding paved the way of the utilization of nanoparticles as drug delivery systems for antitumoral applications.[4][7] The reason of the accumulation of nanoparticles and big macromolecules into tumoral areas lies on the characteristic blood vessel architecture of tumoral tissues. Tumoral cells show a fast growing rate which requires high amounts of nutrients and oxygen. When the size of a tumoral mass exceeds 1 mm^3 the diffusion of the nutrients is not enough to support the accelerated metabolism of the tumoral cells and they begin to suffer starvation. Thus, they force to the surrounding healthy cells to produce proangiogenic factors which induce the creation of novel blood vessels.

However, these novel vessels are not properly built, but they present pores and fenestrations with diameters up to a few hundred of nanometers.[5] [8] When the nanocarriers reach the tumoral tissue, they are able to pass through these fenestrations whereas they cannot pass through blood vessel epithelium present in healthy tissues. Additionally, the rapid growing rate of the tumoral cells usually compresses the lymphatic vessels compromising their normal function, which causes an inefficient drainage in the zone. The lack of a drainage system induces a higher retention of the nanoparticles extravasated in the tumoral mass.[9] These two characteristics, higher permeability of the tumoral blood vessels (enhanced permeation) and lack of efficient lymphatic systems (enhanced retention) explain the preferential accumulation of the nanocarriers within the tumoral lesion. Almost 30 years later, a countless number of drug delivery nanosystems have been reported for oncological applications and even some of them have reached the market.[6][10] These nanocarriers can be formed by organic materials resulting soft systems such as liposomes, polymersomes and micelles, among others,[11-12] or can exhibit an inorganic nature originating tougher systems such as metallic or ceramic nanoparticles.[7][13-15] However, the use of pure inorganic materials in nanomedicine is strongly limited and it usually requires the creation of hybrid materials which conjugate the advantages of both type of systems.[8][16] Among the different materials that have been employed to build these hybrid nanocarriers, those systems which present ordered porosity constitute excellent materials for drug delivery applications due to their unique characteristics such as high loading capacity, chemical and physical robustness, low toxicity and easy and cheap production in the laboratory. In this review, the recent advances carried out in the application of porous inorganic and metal-organic materials in drug delivery will be presented paying special attention to the application of mesoporous silica, porous

silicon and metal-organic nanoparticles in antitumoral applications. For the synthesis of these materials, the reader could be referred to some excellent reviews.[9,10] Additionally, detailed descriptions of the different functionalization strategies for the decoration of nanomaterials with different (bio)moieties can be found elsewhere.[11]

2. MESOPOROUS SILICA NANOPARTICLES

Mesoporous silica nanoparticles (MSNs), specially presenting the MCM-41 structure, is a very promising material for drug delivery applications thanks to their specific properties. These nanoparticles can be easily obtained in the laboratory showing a wide range of morphologies, particle size and pore diameters.[12][22] [23-24] MSNs presents high loading capacity (600-1000 $m^2 \cdot g^{-1}$), high pore volume (0.6-1 $mL \cdot g^{-1}$) and pore size between 2-5 nm. This last property allows the loading of species with very different nature, from small molecules to macromolecules such as proteins or DNA which can reach sizes of around a few dozens of nanometers. Additionally, the external and/or internal surface of these particles can be decorated with different functional groups such as amino, thiol or carboxylic groups, among others, using the correspondently functionalized alcoxysilanes through direct addition in one pot (co-condensation) or after the particle formation (post-synthesis). When a nanocarrier is employed for oncological applications, it is particularly important to avoid the premature release of the housed drugs due to the highly toxic nature which usually present these therapeutic agents. In the case of MSNs, it is possible to avoid the unwanted drug departure employing two different strategies. The first of them consist in the attachment of different moieties (gatekeepers) on the pore outlets through covalent bonds which can be broken by an externally applied stimulus (light, magnetic fields, ultrasounds or temperature) or by an internal stimulus characteristics of the treated pathology (acid or basic environments, change in redox conditions, presence of enzymes, etc.)[13] [25-26]

The second strategy for controlling the drug release consists in the coating of MSN surface with polymeric or lipidic shells which hampers the diffusion of the drugs trapped within the silica network.[14] [27-28] These polymeric or lipid coatings are engineered to allow the drug release due to conformational changes in the polymeric layer once are exposed to certain stimuli (**Figure 1**). In this section, the recent advances in the development of these stimuli-responsive materials carried out in the latest years will be briefly described. Due to the huge number of stimuli-responsive MSNs which have been reported, these devices will be separately described according with the stimulus employed for triggering the release. A more exhaustive description of this field has been reviewed elsewhere.[15][29-30]

[Please, insert Figure 1 here]

2.1. Light

Light irradiation as triggering stimulus provides a precise control of the drug release location, being possible to apply the light beam in sub-millimetric regions. Contrariwise, its main liability is poor penetration in living tissues. Only light with wavelength located in the near infrared (NIR) window (650-1350 nm) is able to penetrate a few dozens of millimeters into a tissue. UV and, in lesser extension, visible light, are strongly absorbed by living tissues and their use are limited to exposed or transparent regions. After the pioneering work of Fujiwara *et al.* who described the attachment of coumarin molecules on the pore entrances as UV-cleavable gatekeepers,[16][31] many different responsive MSNs which are triggered by UV light have been described.[17][32-34] Despite the poor penetration of UV light, the application of these devices could be possible for the treatment of exposed lesions such as skin, esophagus or colon tumors, or the light can be delivered to the target zone using

a optic fiber. Lu *et al.* have reported the use of polymeric coatings on the surface of hollow MSN which can be degraded by the irradiation with green light (540 nm).[18] [35] Additionally, folic acid was conjugated to the polymer branches in order to provide selectivity against tumoral cells which overexpress folate receptors showing excellent antitumoral response only under light irradiation. A modified azobenzene molecule able to suffer photoisomerization with red light (625 nm), which is more penetrating in living tissues, has been recently reported as light-sensitive gatekeeper.[19] [36] The group of Thomas Bein has widely studied the attachment of photosensitizers (as protoporphyrin IX) on MSN surface in order to induce endosomal escape of these carriers when they are exposed to radiation at 405 nm.[20] [37-38] Nearly all the nanocarriers that are internalized by mammalian cells are uptaked via endocytosis.[39] Therefore, to achieve rapid escape from the endosomes is of paramount importance for intracellular drug delivery in order to avoid the degradation of the transported molecules within late endosomes or lysosomes. Gold nanorods have been encapsulated within MSNs for inducing temperature increases in the surroundings after NIR exposition due to plasmonic photothermal conversion. Thus, Yang *et al.* employed calix[4]arenes which binds by supramolecular interactions quaternary ammonia groups placed on MSN that contains gold nanorods.[21] [40] NIR irradiation produces hyperthermia in the region which reduces the binding affinity of the calix[4]arenes by the ammonia stalks causing the dissociation of these gatekeepers and the subsequent drug departure. Drug-loaded MSNs have been anchored on the surface of single-walled carbon nanotubes (SWNT) in order to combine the high loading capacity of MSN with the ability to transform NIR into thermal energy of SWNT.[22] [41] This hybrid device is able to be accumulated into tumoral lesions in a mice model and once there, to release its payload under NIR exposition acting as the same time as contrast agent for

photoacoustic imaging. Other approaches which exploit NIR-to-visible upconversion phenomena[23] [42] and even X-rays[24] [43] have been recently reported providing more strategies to the use of light as triggering stimulus.

2.2. Temperature, magnetic field and ultrasounds

There are different pathological conditions which are associated with a temperature increase. A general approach to achieve temperature-responsive behavior consist to cover the external surface of MSN with thermosensitive polymers, mainly based in poly(*N*-isopropylacrylamide) (PNIPAM).[44] This polymer suffers a conformational change from linear to globular state when the temperature exceeds 32 ^{o}C. A polymeric shell placed on the external surface of MSNs act as a diffusion barrier which avoids premature release of the housed drugs when the temperature is kept below this value. However, if the temperature is higher, the polymer shell suffers a collapse and the retained drugs are able to escape from the silica matrix. This transition temperature is not useful for *in vivo* applications but it can be tuned to higher values between 40-45 ^{o}C adding hydrophilic monomers such as acrylamide, acrylic acid or *N*-hydroxymethylacrylamide to the polymer composition.[45] Significant temperature increases can be achieved under alternative magnetic fields exposition of MSNs containing superparamagnetic iron oxide nanoparticles (SPIONs) trapped inside. Zink *et al.* have reported that the temperature of the particle surroundings can be increased almost 20 ºC after a short time magnetic field exposition, depending of the size of the SPIONs trapped within the silica matrix.[25] [46] Thus, different engineered polymer coatings have been employed in combination with magnetic MSNs in order to control the release of both drugs trapped inside the pore network[26] [47-48] and also higher macromolecules trapped within the polymer branches.[27] [49] Moreover, magnetic MSN have been coated lipid bilayers which are spontaneously disrupted at high

temperatures.[28] [50] Finally, DNA or peptide motifs[52] have also been used as temperature responsive gatekeepers. [29] [51]

Recently, Paris *et al.* have described the use of ultrasounds as triggering stimulus for drug release.[30] [53] In this case, MSN surface was coated with a thermosensitive polymer which contains 2-tetrahydropyranyl methacrylate (THPMA) as monomer sensitive to ultrasounds. This polymer is collapsed at physiological temperature (37 ºC) sealing the pore entrances which avoids the drug leakage. Under ultrasound irradiation, the acetal group of THPMA is broken enhancing the hydrophillicity of the polymer shell which places the transition temperature above this temperature and therefore, produces the pore opening.

2.3. pH

A nanoparticle which is travelling through the body will experience significant pH variations, from neutral pH in the blood stream to mild acidic conditions (pH 5.5-6) in tumoral, inflamed and infected tissues.[54] Additionally, the pH inside the cells is generally more acidic that the pH present in the intracellular media, especially in endosomes and lysosomes.[55] Therefore, it is possible to exploit this fact in order to design nanocarriers able to release their payloads when they reach these intracellular organelles. One well established strategy to synthesize pH-sensitive MSN consist to coat the MSN external surface with polymers which present neutral charge at physiological pH whereas they become positively charged at mild-acidic conditions.[31] [56-58] The dense polymer layer hampers the drug release at neutral pH but if pH drops to certain values, the repulsion forces exerted between charged chains distort the polymer layer allowing the drug departure. Other approach is the use of pore blockers which are attached on the pore outlets through sensitive bonds which are

broken at mild-acidic conditions. Cai *et al.* have recently reported the development of hollow MSNs which exhibit a cascade process triggered by pH.[32] [59] The particle surface is functionalized with beta-cyclodextrins (β-CDs) through boronate bonds. β-CDs bind to adamantane groups attached to PEG chains through imine bonds producing the pore closure. When the particle reaches the tumoral area (pH = 6.8), the imine bonds are broken causing the PEG detachment which enhance the particle internalization by the tumoral cells. Then, as a consequence of the more acidic environment within endosomes (pH = 4.5-6.5) boronate bonds suffer cleavage triggering the drug release. β-CDs bound to MSN surface by boronate bonds have been employed for the fabrication of MSNs responsive not only to pH variations but also to the presence of fructose exploiting the affinitive of vincinal diols present in sugar moieties with the boronate group.[33] [60] Lu *et al.* have described the use of small lanthanide nanoparticles as pore blockers which are bound to the pore outlets through acid-sensitive acetal bonds.[34] [61] This device is able to release cytotoxic compounds loaded inside the pore network, acting at the same time as magnetic resonance imaging (MRI) contrast agent thanks to the presence of the rare-earth oxides. In^{3+} complexes have also been used as pH-sensitive pore blockers and fluorescent probe.[62] Zink *et al.* have recently described a MSN device able to release antibiotics in a pH-triggered manner in order to destroy bacteria (*F. tularensis*) which infects human cells.[35] [63] The pore closure/opening mechanism is based on supramolecular interactions between anilinoalkane attached on MSN surface and different cyclodextrins. Villegas et al. have recently published the decoration of the external surface of MSN with pH sensitive polymeric nanocapsules which contains collagenase trapped within their structure.[36] [64] Thus, when the nanocarrier reaches the tumoral area, the acidic environment present in the tissue causes the disintegration of the polymeric capsule releasing

collagenase which starts the degradation of the tumoral extracellular matrix. Therefore, an enhanced penetration of the nanocarrier is achieved which is of paramount importance in order to achieve a homogeneous distribution of the nanomedicine along the diseased tissue (**Figure 2**).

[Please, insert Figure 2 here]

2.4. Redox

The intracellular media is enriched in reductive species as glutathione (GSH) in comparison with the extracellular environment.[65] One approach to exploit this imbalance for triggering drug release consist to attach polymers or pore blockers on the particle surface using dithiol bonds (S-S) which are broken by the presence of GSH.[37] [66-67] Additionally, the polymer itself can be formed using redox-sensitive monomers or crosslinkers.[38] [68-69] Shi *et al.* have synthesized hollow MSNs with large pores (24 nm of diameter, average) decorated with poly (β-amino esters) through dithiol bonds in order to deliver, in a redox responsive manner, siRNA and doxorubicin, simultaneously.[39] [70] Peptide chains containing the RGD sequence as targeting agent have been grafted on MSN surface through S-S bonds.[71] These moieties act as pore blockers and targeting agents at the same time. Kim *et al.* have described the use of a specific Fmoc-functionalized peptide chains which contain a S-S bond as redox-sensitive pore blocker.[40] [72] These peptides adopt a specific turn-like conformation when are attached on the pore entrance avoiding the drug release. The addition of GSH produces a conformational change to a random structure allowing that the retained drug can leak out from the particle. Finally, in a very recent work, De Cola *et al.* have reported a very interesting approach which consist in the preparation of MSNs which contains breakable S-S- bonds within the silica framework in such a way that they are

able to undergo accelerated degradation when are exposed to the reductive intracellular media.[41] [73]

2.5. Macro- and small-molecules

There are different pathologies in which certain enzymes or molecules are produced most abundantly than in healthy state. In the case of oncology, tumoral cells of solid tumors usually overexpress proteolytic enzymes as metalloproteinases (MMP) or cathepsins in order to degrade the extracellular matrix and colonize other tissues.[74] Cai *et al.* have conjugated bovine serum albumin (BSA) to the external MSN surface using a peptide linker which contains a sequence sensitive to MMP-13.[75] Thus, the presence of BSA kept the drug trapped within the pore network but when the proteolytic enzyme is present, the linker is broken allowing the drug release. Avidin has been anchored on MSN surface by a biotynilated peptide chain which contains a sequence sensitive to MMP-9.[42] [76] This device has been capable to deliver two therapeutic agents (cisplatin and proteasome inhibitor bortezomib) specifically to tumoral cells in *ex vivo* 3D lung tissue cultures without affecting the healthy cells also present in the tumoral mass. α-Cyclodextrins (α-CD) was used as pore blockers attaching them to MSNs using a peptide linker sequence (GFLG) sensitive to cathepsin B.[77] Martinez-Mañez *et al.* have reported the development of anticoagulant loaded MSN capped with a peptide (LVPRGS) sensitive to thrombin, which can be useful for the treatment of pathologies associated with disorders in the coagulation cascade.[78] This work extends the potential application of enzyme-sensitive MSN beyond oncological applications. Zhu *et al.* have recently described a very interesting MSN device able to release its payload in the presence of micro-RNA (miR-21) which is overexpressed by several tumoral cells.[43] [79] This system is composed by MSN which contains quantum dots housed within the silica matrix in order to allow its traceability by fluorescence

microscopy. The external surface is decorated with specific DNA strands which bind, by complementarity, hybrid DNA strands which contain the anti-miR-21 sequence and the AS1411 aptamer, this last in charge of the recognition of the tumoral cells. This hybrid structure acts as reversible pore blocker and targeting agent at the same time and it can be uncapped by the exposition to miR-21. Additionally, the presence or the higher concentration of small molecules or ions in pathological tissues can be exploited for triggering drug release. Zink *et al.* have described the use of cyclodextrins attached by boronic bonds as sugar sensitive MSN.[80] Au nanoparticles, as removable caps, have been anchored to the pore outlets using Cu^{2+} complexes as binding ion.[44] [81] These cooper complexes are broken at low pH values (< 5) and also in the presence of higher concentration of ATP (> 4mM). Finally, Paik *et al.* have describe the use of Au nanoparticles covered with a mutant protein enriched in cystein (α-synuclein) as capping agent sensible to Ca^{2+}.[82]

3. POROUS SILICON NANOPARTICLES

Porous silicon nanoparticles (PSiNP) are composed by crystalline silicon crossed by multitude of pores with diameters comprised between 5-20 nm. Similarly to MSNs mentioned in the previous section, PSiNP present interesting properties for drug delivery applications such as high loading capacity (external surface of 200-500 $m2 \cdot g^{-1}$ and pore volume of 0.5-2 $cm^3 \cdot g^{-1}$) excellent biocompatibility, biodegradability and non-immunogenic nature. Additionally, it exists a wide number of strategies for surface functionalization with different (bio)-moieties which provide targeting or stealth capacities in living hosts.[83] Unlike MSNs which are synthesized using bottom-up approaches, PSiNP are generally produced by top-bottom strategies such as etching (chemical, laser-induced, metal-assisted, chemical vapor, etc.) and milling.[45] [84] The PSiNP surface can be chemically modified previous or after the nanoparticle formation

by different techniques as oxidation, carbonization and hydrosilylation. as have been described elsewhere.[84] PSiNP are generally loaded by capillarity once the particles are immersed into a concentrated solution of the compound to be trapped. Positively charged molecules are more retained in this material than neutral or negative molecules due to the intrinsic negative charge of PSiNP. Additionally, as in the previously described material, the drugs or cargo molecules can be covalently attached in the pore walls. The attached drugs are released to the surrounding media once the material is degraded or due to the rupture of the covalent bonds which binds the drug on the pore walls. Other option to retain molecules within the pore network consists in the oxidation of PSiNP after the loading procedure. Thus, the pore openings are closed retaining the drugs trapped as a consequence of the volume expansion caused by the oxygen incorporation.[46] [85] Finally, when PSiNP are administered into a living organism is degraded to silicic acid, which is a harmless compound.[86-87] PSiNP which contains large pores are rapidly degraded (8 hours) in PBS at pH = 7.2. However, this time is higher in the case of PSiNP with small pores (<10 nm) or it can be extended by external functionalization with different groups or polymers as PEG.[88] In this section, some representative advances carried out with PSiNP will be briefly described in order to provide a panoramic picture of the power of this material for drug delivery applications.

Antitumoral drugs have been loaded within the pore matrix of PSiNP producing nanocarriers able to destroy tumoral cells. Xia *et al.* have reported the fabrication of PSiNP functionalized with styrene groups in order to retain high amounts of doxorubicin (660 $\mu g \cdot mg^{-1}$) by π-π stacking between the aromatic rings of styrene and doxorubicin (Dox), respectively. The same research group has employed bovine serum albumin grafted on the particle surface in order to increase the colloidal stability of the system and also for loading Dox by electrostatic interactions.[47] [89] This systems was

able to release the retained Dox at mild-acidic pH. RNA interference encapsulated within small liposomes (30-40 nm) has been trapped within PSiNP in order to silence oncoproteins which play key role in tumoral progression.[48] [90] The administration of one single injection of this system in a murine model of ovarian cancer was capable not only to reduce the tumor burden but also to hamper angiogenesis and tumoral cell proliferation without observing toxicity in the host. Voelker *et al.* have reported the use of PSi nanodiscs decorated with antibodies as targeted antitumoral nanocarriers.[49] [91] In this work, MLR2 anti-p75 antibodies were grafted on the particle surface enhancing its selectivity for neuroblastoma cells (SH-SY5Y) which overexpress p75NTR neurotrophin receptors. These targeted nanodiscs were loaded with camptothecin showing high cytotoxicity and selectivity against the tumoral cells. Ferrari *et al.* has employed an engineered thioaptamer able to recognize E-selectin for achieving selective homing of PSi microparticles to bone marrow.[50] [92] The employed thioaptamer specifically binds to E-selectin, which is usually expressed by the bone marrow endothelium, whereas it shows little affinity by other selectin family members. The surface of PSiNP can be decorated not only with targeting molecules but also with imaging agents giving place to theranostics devices, i.e. nanocarriers able to deliver therapeutic compounds and to provide information by imaging techniques about their biodistribution or therapeutic efficacy in real time. In a recent paper, a theranostics PSiNP has been synthesized placing iRGD as targeting agent and ^{111}In-DOTA and Alexa-Fluor 488 as single photon emission computed tomography (SPEC) and fluorescent agent, respectively.[51] [93] This device combines the enhanced selectivity against metastatic prostate cancer provided by iRGD, a dual-modality imaging capacity and a controlled antitumoral drug release. Polymeric coatings can be placed on the particle surface in order to control the release kinetic of the housed drugs. Chitosan has

been employed with this purpose on the surface of oligonucleotide-loaded PSiNP.[52] [94] The positive charge of this polymer promotes its adhesion by electrostatic interactions on the negatively charged particle surface. Additionally, the resulting particle presents a positive surface which facilitates the interaction with cell membranes and therefore, the particle uptake. In the case of naked particles, the retained oligonucleotides are rapidly released (80% of the cargo is released in the first 4 hours) whereas it requires more than 35 hours when the particles are coated. PSiNP can be loaded with two or more species, even with molecules which present very different nature, in order to combine several therapeutic effects or to beat the acquired drug resistance of tumoral cells (**Figure 3**).

[Please, insert Figure 3 here]

Thus, indomethacin, a hydrophobic anti-inflammatory drug and hydrophilic peptides as PYY3-36, a 36 aminoacids peptide that inhibit the appetite were effectively loaded within PSiNP showing acceleration in their release profile and higher drug permeation in tissue models as a consequence of their mutual influence.[53] [95] In other recent work, methotrexate, a folic acid analog which is used as antitumoral drug was chemically grafted on amino-functionalized PSiNP walls and sorafenib, an anti-angiogenic hydrophobic drug, was loaded within the pore network.[54] [96] This material shown fast release of the hydrophobic drug thanks to the highly porous nature of the carrier and prolonged release of methotrexate, due to the necessity to break the covalent bond that maintains this molecule attached to the surface. This particular release kinetic could be exploited for achieving a rapid angiogenesis inhibition followed by tumoral cell death. Weitz *et al.* have reported an assembled nanocarrier composed by PSiNP embedded within giant liposomes. This device is able to deliver different species such as hydrophilic and hydrophobic drugs, DNA nanostructures and gold

nanorods and iron oxide nanoparticles.[55] [97] The presence of the metallic cores provides responsive capacities under photothermal and magnetic exposition because the heat generated by the application of these stimuli distorts the lipid bilayer. The combined release of different cytotoxic drugs in combination with the release of certain DNA nanostructures engineered to enhance the action of the antitumoral drugs have demonstrated the capacity to destroy multi-drug resistance breast cancer cells which are resilient to the administration of these cytotoxic drugs alone.

These types of particles are uptaked by tumoral cells through endocytosis in a similar way that MSNs and the vast majority of nanocarriers. Thus, endosomal escape is of paramount importance in order to reach the cytosol avoiding the aggressive environment usually present in the late endosomes or lysosomes. This fact is even more dramatic in the case of the transportation of labile molecules as proteins, DNA, RNA, etc. Santos *et al.* have reported the use of a zwitterionic polymer coating composed by polyethylene imine (PEI) and poly(methyl vinyl ether-co-maleic acid) (PMVE-MA) which provides several interesting advantages such as increased colloidal stability caused by electrostatic repulsion between the particles, endosomal escape as a consequence of the proton sponge effect originated by the presence of tertiary amines in PEI and finally, a sustained drug release behavior due to the polymer coat.[56] [98]

Finally, similarly to the case of MSN although much less exploited, different stimuli-responsive gatekeepers can be anchored on the pore outlets in order to control drug departure. Thus, cyclodextrins have been anchored on the pore entrances using supramolecular interactions which can be broken at mild acidic conditions.[57] [99]

4. METAL-ORGANIC FRAMEWORKS (MOFs)

Coordination polymers (CPs) have emerged as a novel family of nanostructured materials for encapsulation and drug release applications over the last years.[100-101] Advantages, if properly addressed, are multifold: (i) nanoscale CPs show intrinsic benefits associated with its hybrid nature, i.e. the combination of metal ions and organic ligands; (ii) they exhibit a high synthetic flexibility as long as metal-ligand bonds exhibit directional interactions that can be used to systematically control and tune their dimensionality; (iii) CPs have magnetic, electronic, optical, and catalytic properties associated with the limitless choice of metallic elements they can contain and (iv) different metal elements have ubiquitous functions in natural biological systems. Therefore, although CPs in crystalline forms are known for many years, their miniaturization to the nanometer scale has represented a novel opportunity to develop a unique class of highly tailorable functional materials that combine the rich diversity of CPs with the advantages of nanomaterials.

Two different approaches, schematically represented in Figure 4, have already been followed for the encapsulation and controlled release of antitumoral drugs:[106] I) amorphous coordination polymer nanoparticles, refereed from now on as nanoscale coordination polymers (NCPs)[107] and II) nanoscale crystalline and porous coordination polymer structures, referred from now on as NMOFs.

[Please, insert Figure 4 here]

Although nanoscale NCPs do not exhibit an open-framework structure, they have already shown great potential for encapsulation of different drugs with yields up to 20%[114] and improved IC50 values with respect to the corresponding free drug[115]. In these system, encapsulation takes place through a physical entrapment of the drug

within the amorphous polymeric internal structure of the nanoparticles, However, much better encapsulation yields and modified release profiles can be obtained by incorporating the drugs as constitutive units of the coordination network in the form of active ligands or with connecting metal ions such as Pt(IV) complexes.[118]

On the contrary, NMOFs exhibit tunable pores with an exceptionally high surface area and high loading capacities.[120,] Their geometries, size, and functionalities can be systematically varied to yield architecturally robust porous structures with a typical porosity up to 50% of the crystal volume. Accordingly surface areas can range from 1000 to 10,000 m^2/g, much higher than those of other traditional porous materials such as zeolites and carbons.–Therefore, encapsulation usually takes place within the pores though some authors such as Monti *et al.* have demonstrated that drug encapsulation can also be mediated through the reactivity of the drug with the metal ions of the framework.[124] For this, MIL-100(Fe) nanostructures of ~200 nm diameter were loaded with DOX and the binding constants determined via absorption and fluorescence titrations. Spectroscopic data indicated that DOX binding occurs via the formation of highly stable coordination bonds between one or both deprotonated hydroxyl groups of the aglycone moiety and coordinatively unsaturated Fe(III) centers. Alternatively, other area of interest within the field is the functionalization of the NMOFs to improve their colloidal stability and biocompatibility. In this direction, Bein *et al.* have demonstrated that MOF@lipid systems can effectively store dye molecules inside their porous scaffold while the addition of a protective lipid bilayer: I) prevents their premature release, II) increases the colloidal stability of the nanoparticles and III) favors a high uptake of lipid coated nanoparticles by cancer cells (see Figure 5).[125]

[Please, insert Figure 5 here]

Finally, as far as the loading of active drugs within MOFs is concerned, the group of Ferey is considered one of the pioneering groups. Back in 2006, they already demonstrated that MIL-101 (Cr) can adsorb 138 wt % ibuprofen and MIL-53 can adsorb 22 wt % ibuprofen. The release of ibuprofen from the MILs was evaluated using simulated body fluid at 37 °C. It was found that the MIL-101 (Cr) released ibuprofen slowly in several stages, reaching completion after 6 days.[126] The MIL-53 materials showed an even slower release, reaching completion after 21 days.[127] Lin *et al.* have also been pioneers to show the potential application of NMOFs in magnetic resonance imaging and anticancer drug delivery applications.[128]

As previously described, NMOFs have already been demonstrated to be excellent carriers for drug delivery applications. Among the different therapeutic areas of interest, recent advances in the development of NMOFs for drug delivery have been specifically focalized in antitumoral applications, which are summarized next.

As far as the encapsulation of antitumoral drugs is concerned, Li *et al.* reported back in 2009 the synthesis of the MIL-101 NMOF and its loading with an organic fluorophore and an anticancer drug via covalent modifications of the as-synthesized nanoparticles.[129] Afterwards, Horcajada, Greft *et al.*[130] encapsulated antitumoural and retroviral drugs such as busulfan, azidothymidine triphosphate, doxorubicin or cidofovir within non-toxic porous iron(III)-based metal–organic frameworks with high loadings. Beyond the encapsulation process, these authors also demonstrated the potential association of therapeutics and diagnostics. Since then, the number of examples describing the potential use of NMOFs with antitumoral applications has considerably increased, as summarized next. **4.1. Single reports of small drugs**

Wong *et al.* have reported the loading of a dinuclear gold(I) pyrrolidinedithiocarbamato complex within a Zn^{2+}-based metal–organic framework (Zn-MOF) with in vitro cytotoxic activities towards A2780cis cisplatin-resistant ovarian cancer cells. Interestingly, drug-release testing was done using a set of transwell assay-based experiments instead of the conventional dialysis approach.[131] Zr-based UiO-66 cubical nanostructures with average diameters of 70 nm were also reported by Shi *et al.* to load Alendronate (AL), a bisphosphate anticancer drug. Cytotoxicity assays in HepG2 and MCF-7 cells showed that the these nanostructures enhance cell killing by comparison with free AL.[132] Alternatively, Wang *et al.* developed Zn^{2+} or Cu^{2+} NMOFs, using the cytotoxic ligand, 3,5-bis(pyridine-3-ylmethylamino)benzoic acid, which exhibited cytotoxicity effects in three human cancer cells (NCI-H446, MCF-7 and HeLa).[133]

An enjoyable example of the advantages of drug encapsulation was given by Gref *at el.*.[134] As schematically shown in Figure 6, these authors encapsulated the highly hydrophilic prodrug phosphated gemcitabin (Gem-MP), known for its instability and inability to bypass cell membranes, within MIL-100 NMOFs. Interestingly, the storage stability of the loaded NMOFs was strongly dependent on the media; indeed, while the NMOF turns out to be stable in water at least for three days, significant release was found in media containing phosphates since it induces particle degradation. Moreover, the drug-loaded NMOFs were effective against pancreatic PANC-1 cells in contrast to free drug and empty NMOFs, which apparently did not show any cytotoxic effect.

Finally, multifunctional systems combining anticancer activity and imaging capacities have also been a target of interest. With this aim Sahu *et al.* have incorporated Fe_3O_4 nanoparticles, used as an MRI contrast agents, into nanostructures smaller than 100 nm of the porous isoreticular IRMOF-3.[135] Such nanostructures were subsequently

conjugated with folic acid (to achieve targeted drug delivery towards cancer cells) and the fluorescent rhodamine B isothiocyanate (RITC) (for biological imaging), and loaded with the hydrophobic anticancer drug paclitaxel. *In vitro* biological toxicity studies revealed that the resulting nanoparticles targeted and killed the cancer cells in a highly effective manner.

[Please, insert Figure 6 here]

4.2. Encapsulation and controlled release of most common drugs

Camptothecin (CPT) and Doxorubicin (DOX). In a recent work crystals of the well-known ZIF-8 were loaded with DOX and used as efficient drug delivery carriers with efficacies on breast cancer cell lines remarkably higher than those found for free DOX.[136] Yamauchi *et al.* used the same family of ZIF-8 NMOFs to encapsulate 0.049 g DOX/g ZIF-8; in this case, cytotoxicity studies against three different human cancer cells (NCI-H292, HT29 and HL-60) resulted in a moderate activity by comparison with free DOX.[137] Moderate cytotoxicity versus leukemia cell line U937 was also found for Gd-based nanostructures of ~140 nm obtained upon mechanical downsize from bulk MOFs via ball milling and encapsulating up to 12 wt % of DOX .[138] In a further work, NMOFs of the MIL-101 loading doxo were developed by a one-pot synthesis and its premature drug release controlled upon surface modification with a pH responsive benzoic imine bond and a redox active disulfide system. Accordingly, *in vitro* and *in vivo* results demonstrated how this system exhibited effective cancer cell inhibition while having reduced side effects.[139]

Methotrexate (MTX). Gd-BDC nanorods coated with MTX, PNIPAM-co-PNAOSco-PFMA-MTX, and further linked with a targeting ligand GRGDS-NH_2 were shown to

exhibit enhanced cytotoxicity in sarcoma cells FITZ-HAS as compared to nontargeted NMOFs. Moreover, and thanks to the presence of the gadolinium ions, the nanoorods have simultaneous MRI activity.[140] MTX has also been used as a bridging ligand in NMOFs combined with Zn^{2+} or Gd^{3+} metal ions, resulting in astonishing high drug loadings (up to 79 wt %). The spherical nanostructures, with diameter ranging from 40 to 100 nm, were stabilized with a lipid bilayer and targeted with anisamide. Efficient cellular uptake was confirmed by confocal microscopy studies though cytotoxicity studies revealed a behavior comparable to that of free drug.[141] Qian *et al.* also encapsulated MTX with high yields into inner pores and channels of the porphyrin-based MOF PCN-221 by diffusion and controlled its posterior release under physiological environment without "burst effect".[142] While the empty MOF framework exhibited low cytotoxic effects on the PC12 cells, the controlled pH release of the corresponding loaded nanoparticles revealed its activity in oral drug delivery.

5-Fluorouracil (5-Fu). This is without any doubt one of the antitumoral drugs most widely loaded within NMOFs, as confirmed by the numerous examples so far reported. For instance, very recently Yang *et al.* have described microporous UiO-66-NH_2 particles loading the drug and [2]pseudorotaxanes as gates of the nanocarriers linked via host–guest complexation to regulate the drug-controlled release.[143]

More emphasis has been given to Zn-based NMOFs. Wang *et al.* used zinc and the hexadentate ligand 5,5′,5″-(1,3,5-triazine-2,4,6-triyl)tris(azanediyl)triisophthalate (TATAT) to prepare a chiral nanoporous MOF with high porosity. Afterwards, the antitumoral drug 5-Fu was loaded with high yield (about 50% of the transported drug versus the carrier material) and shown to be slowly released with a complete delivery time of about one week.[144] Other authors have reported a Zn_3(L) MOF that can accommodate up to 0.36 mg of 5-Fu per mg MOF combined with lanthanide (III)

cations for luminescence applications.[145] Loading of 5-Fu in into the well-known ZIF-8 NMOFs have also been reported on different examples. For instance, Wang *et al.* reported control over the loading of 5-Fu into ZIF-8 NMOFs with a amount up to ~40 wt % and the posterior release under a pH sensitive environment.[146] Lan *et al.* also demonstrated that ZIF-8 MOFs could load 5-Fu with high loading amounts (31 wt %) and 5-Fu could diffuse out of the framework without burst.[147] Wang *et al.* showed that ZIF-8 NMOFs with a diameter of 100−200 nm by TEM could carry both 5-Fu and green fluorescent C-dots for pH-responsive drug release and fluorescence imaging.[148] Other authors developed three polyoxometalates (POMs) and loaded the POMs into ZIF-8 NMOFs with an average size of 50−200 nm.[149] The authors demonstrated that the incorporation of POMs into the frameworks led to more efficient loadings of 5-Fu and slow release of 5-Fu from the particles. Zhang *et al.* have very recently studied the biocompatibility and biodistribution of fluorouracil loaded ZIF-8 nanoparticles (ZIF-NPs). A surprising high concentration was found in lung though the drug levels drop dramatically with time, revealing the fast degradation and elimination of these nanosystems. Accordingly, at the given doses, ZIF-NPs exhibit reasonably biosafety in animal tests as evidenced by their acceptable system and blood biocompatibilities, and minimal impacts on the liver and renal functions, immune cells, inflammatory factors, etc. However, ZIF-NPs with fluorouracil loading (5Fu@ZIF-NPs) significantly improve the therapeutic outcome of lung metastasis tumor in a nude mice model.[150]

Finally some examples of copper-based MOFs have been reported. For example, Ng *et al.* reported MOFs with a formula of [Cu(L)(4,4′-bipy)(H_2O)], where H_2L stands for diphenylmethane-4,4′-dicarboxylic acid, loaded with amounts of 5-Fu up to 28 wt %.[151] Nascimento and co-workers reported the synthesis of a Cu-BTC MOF incorporating the 5-Fu drug with yields of ~45 wt %.[152] The cytotoxicity of drug

loaded MOFs was evaluated in different cell lines (NCI-H292, MCF-7, HT29 and HL60) showing enhanced cytotoxicity mainly in MCF-7 and HL60 cells. In a further example, Zhou *et al.* synthesized a Cu-based MOF with conjugated PEG5K on the surface via click chemistry resulting in PEGylated MOF nanoparticles of ~50 nm that allow for the controlled loading and release of the drug.[153]

Platinum and Ruthenium. NMOFs based on the assembly of Zn^{2+} metal ions and a functionalized pyrazol-based organic spacer have been recently reported by Barea *et al.*[154] These system were shown to exhibit excellent colloidal stabilities under different relevant intravenous and oral-simulated physiological conditions, fact that the authors attributed to the formation of a protein corona on their surface. Furthermore, two antitumor drugs (mitroxantrone and [Ru(p-cymene)Cl_2(pta)] (RAPTA-C) where pta =1,3,5-triaza-7-phospaadamantane) were encapsulated with a loading capacity that directly depends on the surface area of the solids and its functionalization.

Multifunctionality has also been explored by Morris *et al.* upon combined loading of platinum and ruthenium drugs with NO. For instance, incorporation of cisplatin and a Pt(IV) cisplatin prodrug into two zirconium-based UiO66 and UiO66-NH_2 MOFs following two different approaches has been reported.[155] In the first route, the Pt(IV) cisplatin prodrug was incorporated into UiO66-NH_2 through an amide coupling reaction with the NH_2 groups whereas in the second route, cisplatin was encapsulated into the large cavities of both MOFs. The cytotoxicity of the formulations was assessed on the A549 lung cancer cell line showing that the cisplatin loaded MOF turns out to be more efficient because its higher loading capacity. The same authors also investigated the multifunctionality of these systems by incorporation of the antithrombotic NO into the drug-loaded MOFs; surprisingly, the amount of NO released from these formulations is much greater than that from the pure MOFs. Morris and co-workers further loaded not

only platinum but also the chemotherapeutic agent, [Ru(p-cymene)Cl_2(pta)] (RAPTA-C), along with NO into the same MOF by direct interaction with the Ni open metal sites and physically entrapment, respectively. The loading efficiency of NO and RAPTA-C was not affected by the presence of each other. However, the presence of RAPTA-C in the MOFs significantly retarded the desorption of NO under a humid flowing gas. MIL-88(Fe) MOFs were also exploited as the delivery vehicle for NO by Morris and co-workers. A significant amount of NO was adsorbed at room temperature by the nontoxic, biodegradable, and flexible MIL-88(Fe) MOFs at a high loading amount of 1−2.5 mmol/g. NO was released from MOFs over a long period of time (>16 h), suggesting these MOFs can adsorb NO with high efficiency and release NO in a controlled manner.[156]

Multifunctionality has also been reported with other systems beyond NO. For example, Lin and co-workers reported the first use of NMOFs for the combined delivery of cisplatin and pooled siRNA.[157] For this, cisplatin and a pool of siRNAs targeting multidrug resistant genes were loaded into UiO hexagonal plate like NMOFs with ∼100 nm diameter and ∼30 nm thickness with high loading amounts. Interestingly, these systems efficiently delivered both siRNA and cisplatin to four cisplatin-resistant human ovarian cancer cells (ES-2, OVCAR-3, SKOV-3 and A2780/CDDP) decreasing the cisplatin IC50 values by an order of magnitude as compared to free cisplatin. This efficacy increase was attributed to the activation of the drug resistant gene from the ovarian cancer cells to cisplatin mediated by siRNA/UiO-Cis NMOFs.

5. CONCLUSIONS

Even though porous materials are still from becoming a real and widely approved solution for drug delivery into the market, these materials have already shown their versatility and efficiency in many crucial areas of relevance, from high yield encapsulation to targeted cytotoxicity. Comparatively, most of the work has been done on mesoporous silica nanoparticles by comparison with the two other approximations having some prototypes in clinical trials.

First reports on the use of PSiNP and NMOFs for antitumoral applications were described less than a decade ago but since then the number of citations and papers being reported in the area is increasing exponentially. Much of the work so far devoted is focussed on fundamental concepts of increasing loading encapsulation yields, surface functionalization and the interaction of drug with different carriers. Though, work in the near future should be concentrated more on their colloidal stability, permeability and drug release responses in real biological environments.

6. EXPERT OPINION

I) *General Comments*: Porous nanoparticles constitute one of the most promising materials for clinical use in the treatment of cancer. Advantages are multifold: I) they exhibit a *great loading capacity* clearly higher than the capacity showed by other organic systems as polymersomes, micelles, liposomes, or definitely over non-porous inorganic materials, II) trapped drugs can be *released in a controlled manner* both placing stimuli-responsive gatekeepers on their external surface as well as modifying the inner pore walls in order to release the cargo under certain conditions and III) the solid nature of the carrier provides *high protection* to the trapped species against the aggression of external agents. Most of the successful examples so far reported with

hybrid porous materials for drug delivery in antitumoral applications are based on mesoporous silica nanoparticles and porous silicon in lesser extent. On the contrary, though successful examples have already been reported, much work is needed for NMOFs. Efforts in this direction are already being undertaken through the introduction of a large number of different functional groups within the pores of MOFs. This yields multivariate frameworks in which the varying arrangement of functionalities gives rise to materials that offer a synergistic combination of properties. Another area to be studied with more detail in NMOFs is their biodistribution and accumulation, including cellular transit, degradation, excretion, physiological barrier penetration, and chronic toxicity. *In vivo* studies of the pharmacokinetics and efficiency of drug-containing NMOFs should be the next major steps to evaluate their real performance in medicine. Nevertheless, and in spite being at relative early stages of development, we do believe that the precise chemical control that is possible to attain over the assembly of NMOFs will definitely propel this field further into new realms of synthetic chemistry in which far more sophisticated materials may be accessed. For example, materials can be envisaged as having (i) compartments linked together to operate separately, yet function synergistically; (ii) dexterity to carry out parallel operations; (iii) ability to count, sort, and code information; and (iv)capability of dynamics with high fidelity.

II) Size and shape: Another area of relevance is that of the final dimensions of the nanostructures. Indeed, the collapse of lymphatic vessels within a tumor facilitates the retention of extravasated nanoparticles in the tumoral area, nevertheless, this also causes the apparition of interstitial fluid pressure which strongly hampers their diffusion within the zone.[163] Therefore, the action of these nanomedicines are only concentrated in the periphery of the tumors which drastically reduces their therapeutic efficacy.[164] As a general rule to overcome this limitation is smaller sizes of nanocarrier achieve deeper

penetrations.[165] However, higher sizes involves a better discrimination between healthy and tumoral tissues. Therefore, it is necessary to optimize the size carrier for each type of tumor. MSNs can be easily prepared with a wide range a shapes, sizes and external functionalization.[22] The influence of these parameters in cell uptake process have been widely studied showing that the aspect ratio and surface charge play an important role in cell internalization and this process is highly cell dependent.[166-167] Additionally, in the case of intravenous administration (that is the usual case for antitumoral therapy) it is necessary to take into account the influence of these parameters in the interaction of the nanocarriers with the blood cells.[168] However, in most cases these parameters have been evaluated using simplistic *in vitro* models and much work is required in order to know their significance in animal models. NMOFs with good dimensions between tens of nanometers and a few hundred nanometers have been reported though with some irregular shapes in some cases, plate-like structures or not perfectly round-shaped nanoparticles. Therefore detailed studies about the effect of the shape would be required. Other limitation of nanocarrier diffusion is caused by the high collagen density present in tumoral tissues. In order to improve the diffusion, proteolytic enzymes have been administered a few days before nanoparticle administration,[169] or even these enzymes have been anchored on the particle surface.[170,64] In the case of porous nanoparticles, their lack of flexibility may difficult even more the penetration in living tissues and the barriers mentioned above play an even more important role. Thus, it is compulsory to take into account these barriers in order to design a suitable nanocarrier for future developments.

III) Surface functionalization: Another area of relevance lies at the *surface functionalization* of the nanoparticles and their effect on their improved stabilities and cell internalization. Indeed, one of the main advantages of nanoparticles as drug carriers

for oncological applications is their passive accumulation within tumoral lesions by EPR effect. Once there, the presence of targeting agents attached on the particle surface enhances their uptake in these diseased cells, without affecting the healthy ones, also present in the tissue. This allows the selective destruction of malignant cells in the presence of healthy ones. However, despite the good outcomes observed in *in vitro* experiments, only a few targeted nanodevices has demonstrated a good performance in animal models.[171] There are several reasons which contribute to this failure. One of them is that when a nanocarrier comes into contact with blood, it is immediately covered by a protein layer called *protein corona*.[172] This corona masks the targeting agents being the real readable part of the nanocarrier. Thus, the fate of the nanocarrier is not ruled by the presence of the targeting agents on the surface but it depends of the proteins bound on particle surface. Additionally, the presence of the protein corona usually accelerates the particle clearance by the mononuclear phagocytic system (MPS). These limitations can be alleviated grafting the targeting agents employing hydrophilic or zwitterionic polymers as spacers.[173-174] These polymers avoid protein adsorption enhancing the circulating time and they also present more effectively the targeting agents to tumoral cell receptors. Other issue which limits the *in vivo* nanocarrier performance is the high complexity and heterogeneity of the tumoral mass which not only present several types of tumoral cells but it also contains a huge number of non-tumoral cells as mesenchymal, immune, supportive cells, etc. which, in many cases, play an important role in tumor progression.[175] In many cases, the efficacy of targeted nanodevices is tested employing simplified *in vitro* models which contain only the tumoral cell. It is true that *in vitro* models provides valuable information about the recognition process between the targeting agent and the specific tumoral cell receptor but, before to reach *in vivo* evaluation, it should be necessary to evaluate this capacity

employing more realistic models such as 3D tissue models or tumor spheroids which contains a representative mixture of tumoral and non-tumoral cells, as well as cells from the immune systems. Finally, other drawback associated to the use of targeted nanomedicines is the *binding site barrier*, which is caused by the strong affinity between the targeting moiety and its receptor.[176] This fact provokes that the nanomedicines are firmly bound to the first cell line near tumoral blood vessels exacerbating even more the poor penetration problem mentioned above. One way to reduce this effect is to employ stimuli-responsive targeting agents which travel through the body in a hidden conformation, whereas they can be activated by certain stimulus present in the tumoral area or externally applied.[177] Great success has been achieved on the surface functionalization of silica nanoparticles. A high number of synthetic strategies for the decoration of the external surface of MSN and PSiNP have been described. Even, it is possible to functionalize differently the external surface and inner pore walls.[178] However, in many cases it is necessary to achieve a precise control of the orientation of the grafted biomolecule, as in the case of antibodies or other recognition moieties. In this point, it would be very useful to employ the wide arsenal of synthetic alternatives which provides the bioorthogonal chemistry.[179] Once more, surface functionalization is less common for NMOFs most of the times limited to the reactivity of some metal ions lying at the surface of the nanostructures or mainly to some polymeric or lipidic coatings.

Another limitation, not only for porous nanoparticles but common to several nanocarriers, lies at the fact the passive accumulation by EPR effect is not always guaranteed because it is not universal. It not only depends of the tumor type but it exhibits great heterogeneity within one tumoral lesion. Moreover, EPR is also a dynamic phenomenon which undergoes variations during the treatment. Thus, tumors

which exhibit a significant EPR effect at the beginning of the treatment could show scarce passive accumulation after some cycles of treatment. Therefore, it is necessary to monitorize the vascular architecture of the tumoral lesion before recommending a treatment based on nanomedicines. It is possible to enhance the EPR effect through the previous administration of drugs as angiotensin I-converting enzyme (ACE) inhibitors or NO releasing agents.[7]

It is important to keep in mind that the design of a nanocarrier able to overcome all of these barriers would lack of sense because it could require to build really complex systems which would be difficultly approved by regulatory agencies.[180] The administration of diverse type of nanocarriers, each of them responsible for different tasks, could be simpler and more efficient than the design of one single carrier able to perform all of them. There are a few examples of cooperative work between nanoparticles in which, for example one of them facilitate the extravasation of the second one in the tumoral area,[181] but more efforts are needed in this point. As have been pointed out above, there are many parameters which affect to the efficacy of these types of nanocarriers and more knowledge is needed in order to find solutions for them. For the design of the next generation of novel porous inorganic nanocarriers we have to bear in mind the well-known quote in engineering world "*embrace complexity, design versatility and deliver simplicity*".

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FIGURES

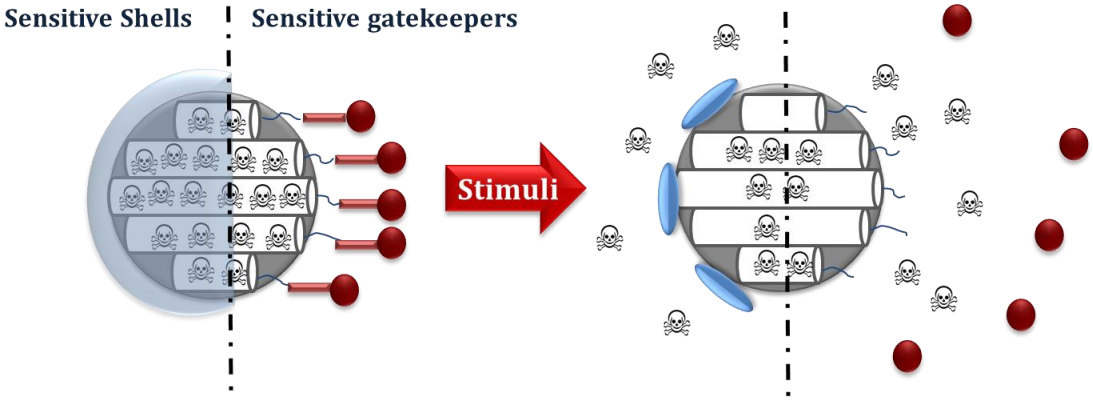

Figure 1. *Strategies for controlled release in MSNs*

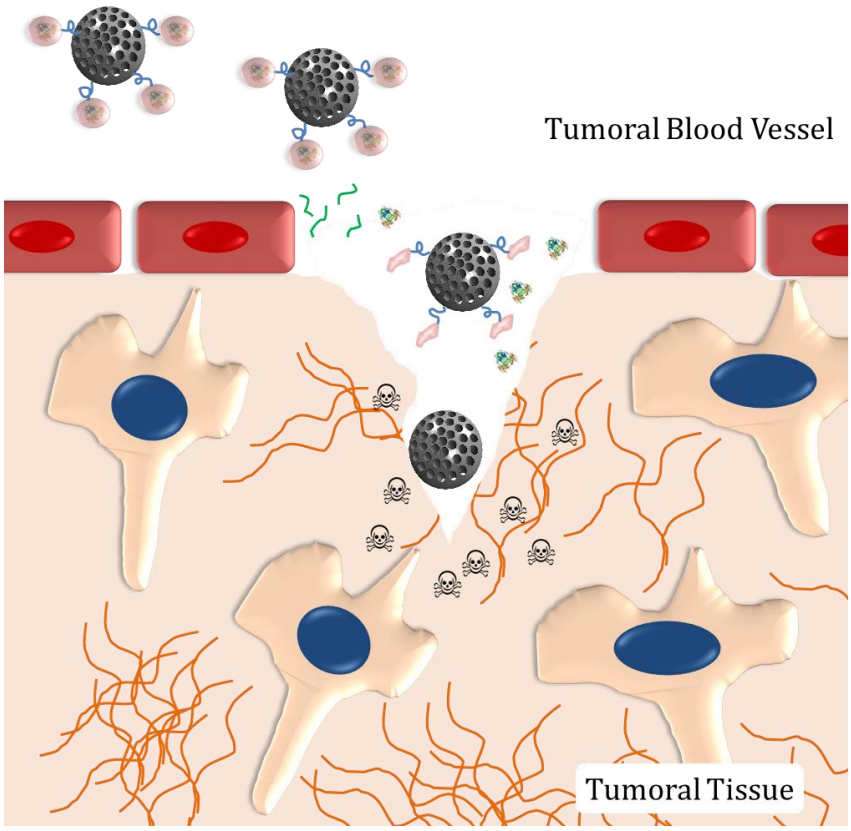

Figure 2. *pH-sensitive collagenase nanocapsules grafted on MSNs for improved penetration in tumoral tissues*

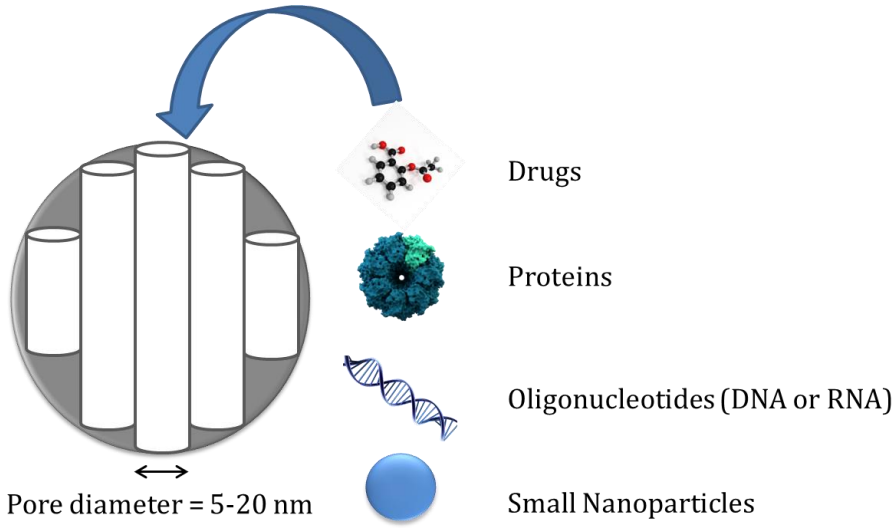

Figure 3. *Multidrug delivery capacity in PSiNP*

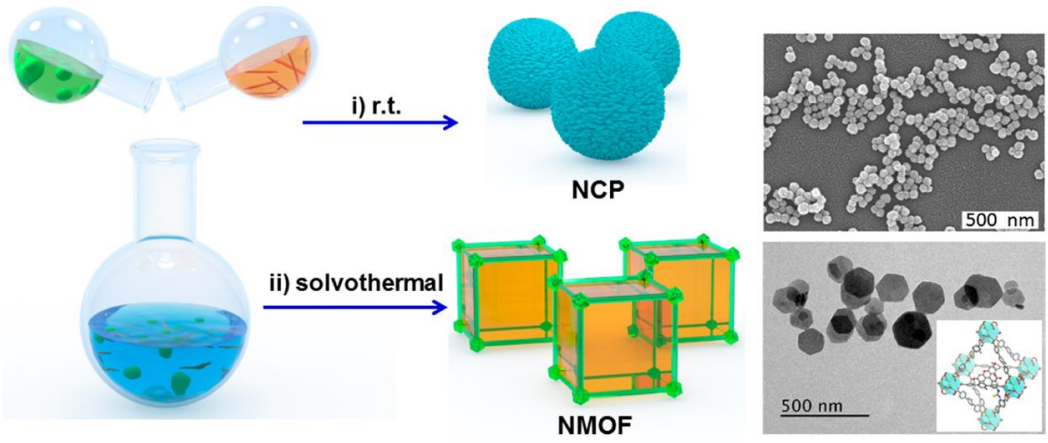

Figure 4. Schematic representation of the two different approaches followed with coordination polymers for their use as drug carriers. Extracted from Reference 106.

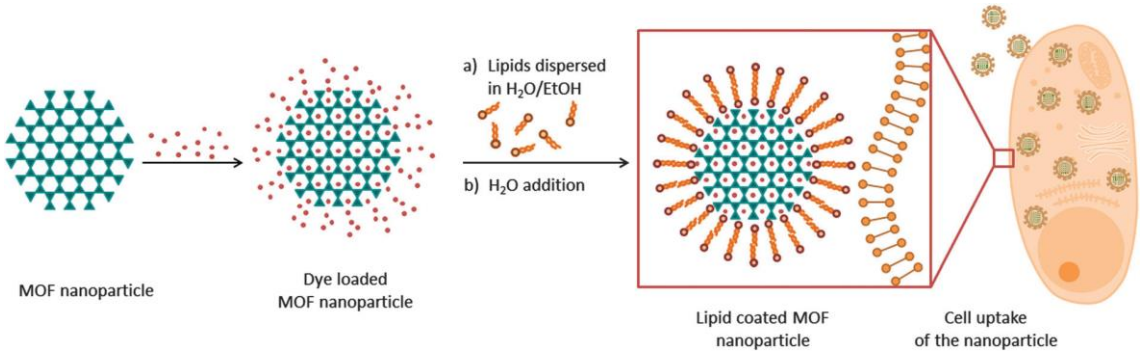

Figure 5. Schematic description of the synthesis of lipid bilayer-coated MOF nanoparticles loaded with dye molecules and their uptake in cancer cells. Extracted from Reference 125.

Figure 6. Schematic representation of the ‘‘green’’ (solvent-free) procedures involved in: (1) the synthesis of MIL-100 nanoMOFs and (2) the encapsulation of Gem-MP.. Extracted from Reference 134.