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Hybrid Ceramics-based Cancer Theranostics

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Abstract

Cancer is a major threat to human lives. Early detection and precisely targeted therapy/therapies for cancer is the most effective way to reduce the difficulties (e.g., side effects, low survival rate, etc.) in treating cancer. To enable effective cancer detection and treatment, ceramic biomaterials have been intensively and extensively investigated owing to their good biocompatibility, high bioactivity, suitable biodegradability and other distinctive properties that are required for medical devices in oncology. Through hybridization with other materials and loading of imaging agents and therapeutic agents, nanobioceramics can form multifunctional nanodevices to simultaneously provide diagnostic and therapeutic functions for cancer patients, and these nanodevices are known as hybrid ceramics-based cancer theranostics. In this review, the recent developments of hybrid ceramics-based cancer theranostics, which include the key aspects such as their preparation, biological evaluation and applications, are summarized and discussed. The challenges and future perspectives for the clinical translation of hybrid ceramics-based cancer theranostics are also discussed. It is believed that the potential of hybrid ceramic nanoparticles as cancer theranostics is high and that the future of these theranostics is bright despite the difficulties along the way for their clinical translation.

1. Introduction

1.1 Cancers and nanotechnology-enabled detection and treatment

Cancers are diseases characterized by the uncontrolled growth and spread of abnormal cells. If the cell growth and spread is out of control in human bodies, it can result in the catastrophic failure of human lives, i.e., death. Given that the causes of various cancers are not fully understood yet, cancers are regarded as one of the most serious public health problems in countries around the world. Cancer is the second most common cause for human death in the US, which is only exceeded by heart diseases. The American Cancer Society estimated that in 2020 there were about 1.8 million new cancer cases diagnosed and about 606,520 cancer deaths in the US (https://cancerstatisticscenter.cancer.org/#!/). Cancer death rates can be used to evaluate cancer progress against the disease because they are less effected by detection practices than cancer incidence and survival rates. Recent progresses in early cancer detection and treatment have led to the decline of overall age-adjusted cancer deaths, especially for the four most common cancer types: lung, colorectal, breast, and prostate. High mutation rate and easy metastasis of cancer cells are still major health concerns for humans. Cancer patients may not receive the most effective treatment because they are not aware of changes in their body and consequently miss the best opportunities to be diagnosed at an early stage of cancer. Moreover, the lack of diagnostic techniques with both high sensitivity and resolution is another major challenge for the early detection of cancer. In general, surgery, chemotherapy and radiotherapy are still major and standard treatments for cancer. Although it is a general practice to remove tumors and the rim of surrounding tissues as the first treatment of cancer, especially for the primary or original cancer, it is rather difficult to ablate tumor tissues completely through surgery particularly when lymph nodes are involved. The possibility of cancer recurrence remains high for patients with only surgical treatment. Therefore, chemotherapy and/or radiotherapy are frequently used as adjuvant approaches for cancer patients who undergo surgeries. Remains of microscopic bits of cancer can be killed through chemotherapy. Nevertheless, patients often suffer severe intolerable side effects caused by inherent off-target toxicity of chemotherapeutic drugs. Some side effects can last for a lifetime. Radiotherapy can kill cancer cells and shrink tumors through high doses of radiation. However, it can also bring damages to nearby healthy cells. Although immunotherapy can help the immune system fight against cancer, it often happens that the immune system acts against

healthy cells and tissues. Besides the aforementioned side effects, there is a more important problem associated with immunotherapy, which is the infection. Cancer patients are susceptible to infections due to their weakened immune systems. This problem can become worse after the immune system suffers more damage from cancer treatments via either surgery, chemotherapy or radiotherapy. The use of antibiotics may prevent infections; but it can also cause new problems such as occurrence of drug-resistant bacteria. Therefore, early detection and targeted cancer therapy are urgently needed for treating cancers.

Nanotechnologies, particularly new nanotechnologies (novel synthesis methods, micro- and nanofluidics, etc.), have advanced tremendously the development of new nanomaterials and nanodevices for applications in various areas concerning the well-being of humans. They have revolutionized our approaches to solve major health problems. Particularly, nanotechnologies can provide high accuracy and high flexibility to study and manipulate macrobiomolecules for the early detection and treatment of cancer. Cancer-related biomolecules may be effectively detected even when they only occur in small quantities in a small number of cells in the body. Meanwhile, new approaches are being developed to tackle cancer problems through new therapeutic agents and treatment that are enabled by nanotechnologies. Furthermore, the novel or unique characteristics of nanomaterials, including high surface area-to-volume ratio, unique properties (chemical, physical, electrical, etc.) and tunability of surface properties, make it possible to efficiently deliver diagnostic or therapeutic agents, to effectively detect cancer via diagnostic agents, and to successfully irradicate cancellous cells for cancer patients.

1.2 Cancer Theranostics

An emerging trend in the early detection and treatment of cancers through the use of nanotechnology or nanomaterials is the development of cancer theranostics, which integrates cancer diagnosis and therapy into a single entity. Theranostics function on the basis of nanoparticles for sensing, imaging and therapy using one nanosystem. Theranostics have shown various advantages such as improved diagnosis, tumor-specific drug delivery, and reduced lethal effects to surrounding normal tissues, which are beneficial for early diagnosis, accurate molecular imaging, and precise treatment at the right timing and with appropriate dose, realizing real-time monitoring of treatment efficacy [1]. Therefore, novel and effective theranostics can simplify multi-

step procedures for cancer patients and avoid delays in cancer detection and treatment, thereby providing much improved patient care for millions of people.

1.3 Attractiveness of ceramics for cancer theranostics

Traditionally, bioceramics, which include ceramics, glasses and glass-ceramics that are developed for biomedical applications, have been used for the repair of diseased or damaged parts of the human body, especially for hard tissues. For example, bioceramics can be used as bone fillers and as materials for scaffolds for bone tissue engineering. The wide application of ceramics in the biomedical field is due to their obvious attractiveness which includes the good biocompatibility, bioactivity, biodegradability, and sufficient mechanical properties. Moreover, nanotechnologies can further improve their properties, making them attractive for devices for cancer diagnosis and treatment. For example, nano-grained ceramics possess higher strength and toughness than their counterparts composed of micro-grains. The large surface area-to-volume ratio of nano-sized ceramics allows the ease surface functionalization using various facile approaches, making them excellent carriers for targeted drug or gene delivery. Moreover, some bioceramics have excellent biodegradability, which is considered as the ultimate and unique advantages for treating cancer [2]. Ideally, ceramics-based theranostics should be biodegradable and can be resorbed or excreted within a reasonable period after accomplishing their diagnostic and/or therapeutic functions. Nanoceramics have substantially high clinical translation potential.

Ceramics or metals can be used to construct vehicles to deliver some imaging agents for cancers, such as organic fluorophores (e.g., Cy3 [3], indocyanine green (ICG) [4]), metallic nanoparticles (e.g., gold/silver [5]), ceramic nanoparticles (e.g., iron oxide [6]), and quantum dots (QDs). A variety of imaging modalities based on ceramics may be realized by integrating the ceramics with the imaging contrast agents (Fig. 1). Meanwhile, ceramic nanomaterials can provide various therapeutic approaches when they are hybridized with therapeutic agents such as anti-cancer drugs or therapeutic genes (Fig. 1). However, nanoparticles with only one single function are not able to fulfill the missions under complex clinical environments. Therefore, multifunctional nanoparticles with the integration of different nanocomponents into one nanosystem should be created to realize diagnostic, therapeutic and possibly treatment-monitoring functions. Multifunctional nanoparticles therefore offer powerful tools to overcome the obstacles during patients' cancer treatment and reduce cancer mortality. With such rationale, ceramic cancer theranostics have been

developed to realize the incorporation of multiple payloads for providing multiple functions, including targeting, imaging and treatment in just one nanosystem.

In the open literature, there are already excellent review articles on the design, construction and application of ceramics for human tissue replacement or regeneration. However, despite increasing interest in developing ceramics cancer theranostics, there are rarely good reviews for recent research in this emerging field. Therefore, this article reviews the recent advances in ceramics-based theranostics for cancer detection and treatment, highlighting their combinational performance in both diagnosis and therapy.

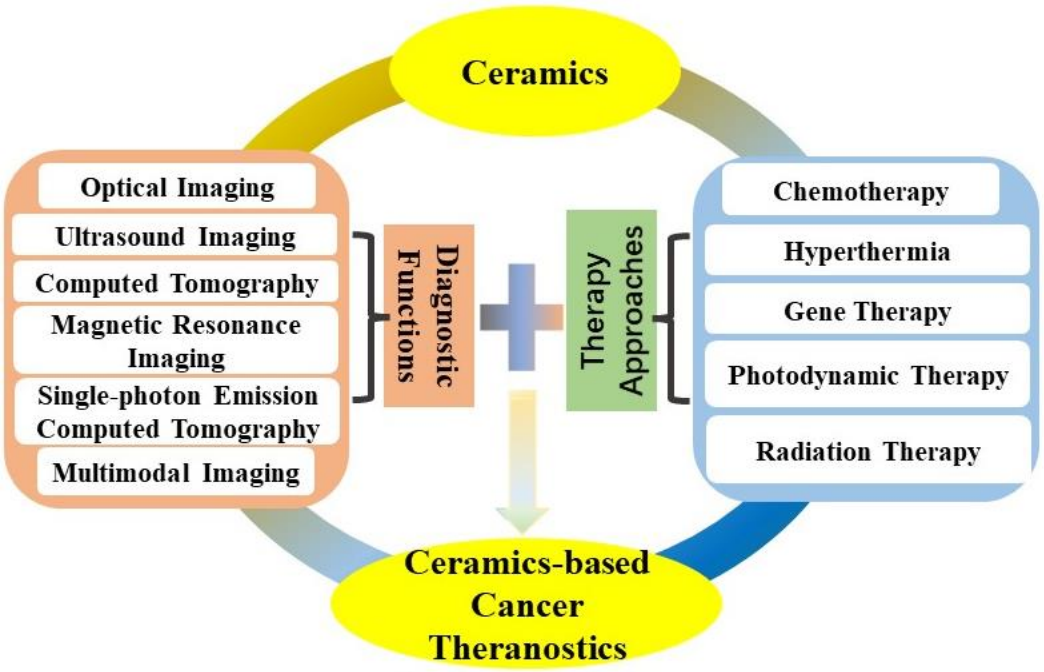

Fig. 1. Application of ceramics in cancer.

2. Ceramics for Cancer Detection or Treatment

2.1 An overview of bioceramics

Ceramics are generally defined as “inorganic, non-metallic materials”. Ceramics developed for biomedical applications are termed as bioceramics. In general, there are three categories of

bioceramics based on their interaction with human body tissues and their stability in the body, which are bioinert bioceramics (e.g., alumina and zirconia ceramics), bioactive [hydroxyapatite (HAp), Bioglass® and A-W glass-ceramics], and biodegradable or resorbable bioceramics [e.g., tricalcium phosphate (TCP)]. In addition, bioceramics, particularly the biodegradable ones, can be made into porous structures (the so-called "scaffolds") for regeneration hard tissues. Bioceramics are typically insulative to electricity and heat and non-biodegradable bioceramics are stable in corrosive environments when compared to metals and polymers. Bioceramics show high resistance to the plastic deformation and possess low ductility (they are hard and brittle). Nano-ceramic materials exhibit much higher hardness than conventionally processed counterparts. They also inherit the excellent heat and corrosion resistance, as well as electrical insulation properties. Therefore, bioceramics have distinctive advantages in biomedical applications, including but not limited to good biocompatibility, osteoconductivity, osteoinductivity (of only a few bioceramics), biodegradability, and hydrophilicity. Bioceramics are mainly applied for bone tissue replacement or regeneration, as well as in clinical dentistry. Ceramic nanobiomaterials may form different groups of materials, as illustrated in Fig. 2, for medical applications based on the types of main components that constitute the ceramics.

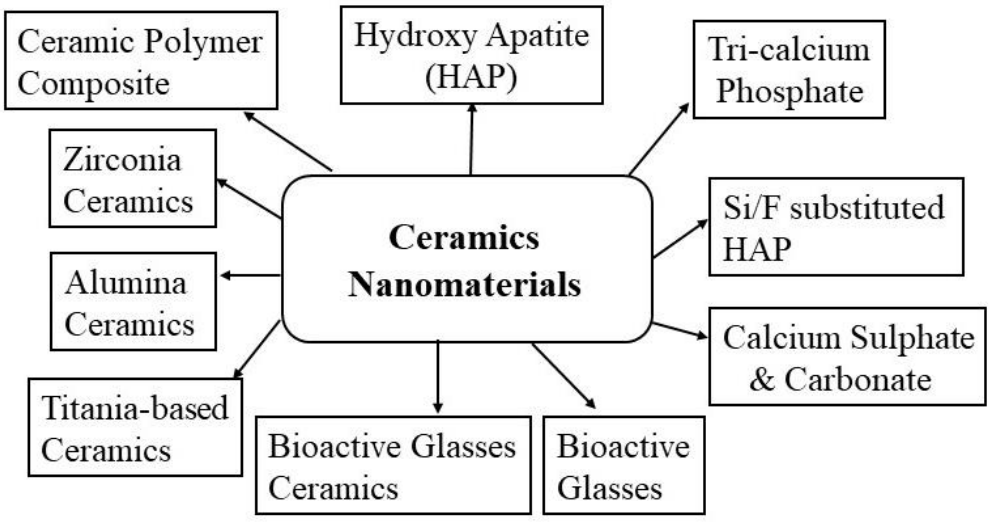

Fig. 2 Different groups of ceramic nanomaterials for medicine.

2.2 Calcium phosphates (CaPs)

Calcium phosphates (Ca-Ps, designated as CaPs in this article) are the major inorganic constituents of biological hard tissues such as bones and teeth and are therefore readily usable for biomedical applications owing to their inherent biocompatibility. CaP nanomaterials can avoid clearance by the human immune system and may serve as ideal carriers of therapeutic agents such as anticancer drugs or human genes. In fact, CaPs were first reported as non-viral carriers of plasma DNA to enable enhanced gene transfection in the 1970s [7]. CaP nanoceramics have abundant -OH groups and also Ca^{2+} cations on their surface. The Ca^{2+} cations can effectively absorb negatively charged molecules via electrostatic interactions. CaP nanomaterials can be readily functionalized with targeting ligands such as carboxylic group or phosphoric group to develop the targeting ability of the nanodevice. In general, as compared to other nanomaterial-based delivery systems, including polymers, liposome and dendrimers, CaP nanoceramics have several advantages: (1) simple preparation and easy functionalization, (2) suitable for hydrophilic or hydrophobic drugs, (3) good colloidal stability in the physiological environment, (4) providing stimuli-trigged drug release resulting from pH-dependent dissolution. Because of these advantages, CaP nanoceramics have been extensively investigated as delivery vehicles for encapsulating contrast agents or therapeutic agents for cancer diagnosis or treatment [8, 9].

There are various types of CaPs in terms of the Ca/P ratio, chemical composition and crystal structure [10]. Different CaPs exhibit different properties. The unique characteristics of CaPs can be tuned starting from aqueous solutions by controlling their synthesis/reaction conditions. In particular, nanostructured amorphous calcium phosphate (ACP), hydroxyapatite (HAp) and calcium-deficient hydroxyapatite (CDHAp) are frequently prepared for biomedical applications because they possess desired properties for the targeted applications and they are easy to be made from aqueous solution using a simple precipitation method.

As compared to conventional micro-sized particles, nanoparticles prepared by the chosen methods show drastic increases in surface area and active sites, leading to greater payload loading capability for drug or gene delivery applications. Considering their excellent biocompatibility and low immune response, ceramic phosphate nanoparticles (CPNPs) are considered ideal vehicles for nontoxic and efficient delivery of bioactive agents, as shown in recent reports [3, 11-13]. The

application of CPNPs for *in vivo* bioimaging can be realized by doping them with indocyanine green (ICG), which is a NIR contrast agent approved by the U.S. Food and Drug Administration (FDA) for use in deep-tissue imaging in humans. Spherical CPNPs doped with ICG were synthesized using co-precipitation of calcium chloride and disodium hydrogen phosphate via micro-emulsions (Fig. 3). The obtained results showed that the ICG-CPNPs provided improved fluorescence emission intensity, quantum efficiency, photostability in various solutions and most importantly, the ability of deep-tissue imaging in a mouse model [11]. The ICG-CPNPs therefore have great potential for early tumor detection and cancer imaging.

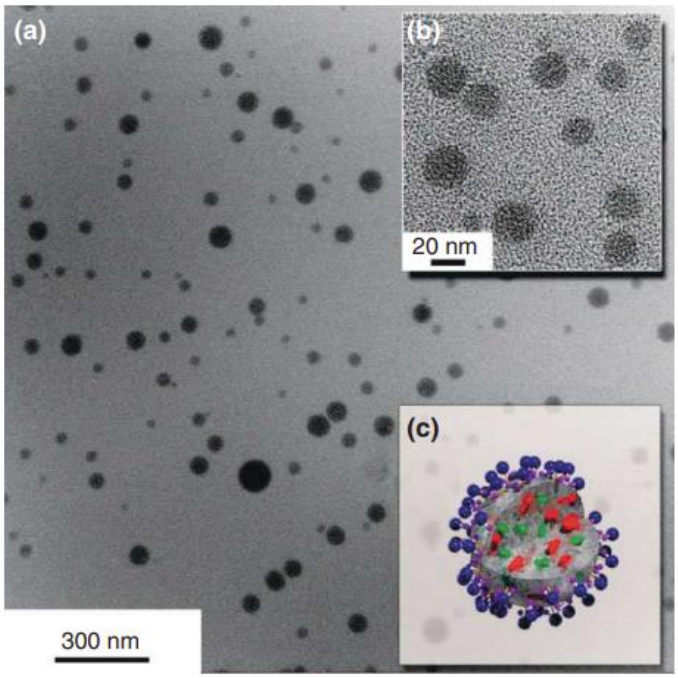

Fig. 3 Transmission electron micrographs of ICG doped CPNPs: (a) and inset (b) showing detailed view of the spherical particle morphology, and inset (c) depicting schematically the nanoparticle architecture (green: encapsulated dye; red: alternate encapsulant; blue: surface functionalization). Adapted with permission from Ref [11]

2.2.1. HAp

Hydroxyapatite (HAp) with the chemical formula of $Ca_{10}(PO_4)_6(OH)_2$ is a prominent member of the calcium phosphate family and is the most studied bioceramics so far. Since HAp is similar in chemical composition and crystal structure to the main inorganic component of bones, HAp intrinsically demonstrates excellent combination of biocompatibility and bioactivity (i.e., osteoconductivity with regard to bone tissue formation), making it particularly useful in interdisciplinary areas like chemistry, biology, and medicine. Meanwhile, as compared to other bioceramics based on calcium and phosphate, HAp shows superior osteoconductivity, promoting osseointegration for implants after their implantation in the body. However, HAp has poor mechanical properties including brittleness. Consequently, HAp is generally coated on metal implants (e.g., Ti implants) for medical applications or hybridized with polymers (sometimes also with other bioceramics or even metals) for making bioactive implants that will promote bone formation *in vivo*.

Besides of the use of non-porous or porous HAp structures for bone tissue replacement or regeneration, HAp nanoparticles can be used as carriers for delivering nucleic acid, proteins and anti-cancer drugs [14]. Interestingly, studies have found that HAp particles themselves could inhibit the proliferation of several types of cancer cells and demonstrate strong anti-cancer effect both in *vitro* and in *vivo* for liver cancer [15] , colon cancer, melanoma, breast cancer cell [16] and glioma cells. Fu et al. [17] suggested that HAp nanoparticle suspension had a greater inhibition effect on U2-OS cell proliferation than large-sized HAp suspension *in vitro* and that HAp nanoparticles had excellent inhibition effect for hepatocellular carcinoma Bel-7402 cells *in vitro*. Tang et al. [18] found that HAp nanoparticles expressed antitumor effect with low side-effect *in vivo* in a rabbit model. The inhibitory function shown by HAp nanoparticles can be attributed to their induction of apoptosis through the mitochondria-mediated pathway according to previous investigations [19]. HAp nanoparticles could induce the production of intracellular reactive oxygen species (ROS) and activate cell apoptosis related genes, which may be responsible for DNA damage and cell apoptosis. It was also speculated that the size of HAp nanoparticles and their cellular localization determined HAp nanoparticle-induced cytotoxicity. Meanwhile, Sobczak-Kupiec *et al.* [20] reported that the physicochemical properties and morphology of HAp particles also influenced their interaction with cancer cells. Synthetic HAp nanoparticle with chosen size, low crystallinity, high porosity and high surface area may be prepared by using appropriate synthesis method and controlling the synthesis/reaction parameters.

2.2.2. TCP

Like HAp, tricalcium phosphate (TCP, $Ca_3(PO_4)_2$) is another bone repair material. It becomes more attractive in recent decades owing to its biodegradability when bone tissue regeneration approaches are adopted. Commonly encountered TCP with a Ca/P ratio of 1.5 exists in the α-phase or β-phase. α-TCP has the crystal structure of a monoclinic space group and β-TCP shows the crystal structure of a rhombohedral space group. α-TCP can be formed at temperatures higher than 1125 °C; and β-TCP is generated at a temperature of 900-1100 °C. β-TCP is more stable than α-TCP in the biological environment and hence β-TCP is generally used in bone tissue repair. Compared to HAp, β-TCP has a higher solubility *in vitro* and *in vivo* and exhibits faster degradation after implantation. β-TCP can promote the proliferation of cells such as osteoblasts and bone marrow stromal cells. These advantages of β-TCP for bone tissue repair are due to the excellent biomineralization and cell adhesion properties. Consequently, β-TCP has gained more attention in recent years for bone repair (replacement or regeneration), particularly in the bone tissue engineering area.

TCP nanostructures have demonstrated good biocompatibility, excellent bioactivity, suitable degradability and high affinity to biomacromolecules. Like HAp nanoparticles, TCP nanoparticles exhibit high loading capacity, together with enhanced solubility, in drug delivery systems [21, 22]. TCP nanoparticles with porous microstructure should be able to deliver either diagnostic agent for cancer detection or anticancer drugs for chemotherapy. Furthermore, nanoporous TCP also shows inhibitory effect on several types of cancer cells and comparatively low effect on the proliferation of healthy cells [23, 24]. Therefore, nanoporous TCP has high potential in cancer treatment.

Considering the complex environment of cancer, nanoporous TCP is often hybridized with polymers, liposomes or other ceramics to realize multiple functions. Sarkar and Bose fabricated a bifunctional bone tissue engineering scaffold which could repair post-surgical bone defect and eradicate bone tumor cells in the surrounding tissues [25]. The anticancer drug curcumin was loaded into liposome and the drug-encapsulated liposome was deposited on porous TCP scaffolds. Results showed that the composite scaffolds could enhance the stability and anticancer efficacy of curcumin while showing excellent *in vitro* bone forming ability. Another study showed that

nanoporous TCP could be integrated with magnetic nanoparticles to perform magnetic resonance imaging and provide hyperthermia for cancer treatment [26].

2.3 Bioactive and biodegradable glasses

Bioactive glasses were firstly investigated and developed by Hench et al. in 1969. They represent a group of reactive materials that stimulate the formation and growth of new bone on implants made of these materials. Hench's Bioglass® and others' bioactive glasses are now widely studied/applied in the biomedical field. The first clinical application of Bioglass® was in the form of small solid pieces to replace the small bones in middle ear surgery. Subsequently, bioactive glasses have been used in dentistry and showed quantified improvement over HAp implants [27]. In recent years, bioactive glasses have been widely investigated in the tissue engineering field owing to their biodegradable properties when they are prepared through particular manufacturing routes. It is shown that their dissolution components can activate cells at the genetic level, providing better bone generation ability than CaPs bioceramics. In addition, 45S5 Bioglass® could bond to both hard tissue and soft tissue. In contrast, CaPs bioceramics can only bond to hard tissues.

Bioactive glasses are mainly composed of silica (SiO_2), calcium oxide (CaO), sodium oxide (Na_2O) and phosphorous pentoxide (P_2O_5). A wide range of bioactive glasses with attractive properties, such as biocompatibility and bioactivity, can be produced by varying proportions of the components (SiO_2, CaO, Na_2O and P_2O_5). Furthermore, some specific elements or oxides, such as Cu, Ba, metal ions, boron trioxide (B_2O_3) and iron oxide (Fe_2O_3 or Fe_3O_4), can be incorporated into the glasses to endow them with new properties and find new applications, as illustrated by Fig. 4. For example, magnetic bioactive glasses offer dual functions, i.e., formation of a bond with the body tissue by forming a biological active apatite layer at the implant-tissue interface and generation of heat under alternating magnetic field for hyperthermal treatment for cancer [28]. Various investigations have been performed to obtain bioactive glasses in different forms, such as bulk, powder, composite, and porous structure ("scaffolds"). Specific properties of bioactive glasses may be achieved when controlling their synthesis at the nanometer scale. For example, compared with non-porous bioactive glasses, mesoporous bioactive glasses (MBGs) have much more optimal surface area and pore volume, as evidenced by their greatly enhanced drug delivery capability, *in vitro* apatite mineralization and *in vitro* degradation. Therefore, MBGs have attracted

good attention and are explored for the possibility of acting as carriers for proteins, drugs and radionuclides for cancer treatment [29, 30]. By incorporating radionuclides, MBGs could provide a new approach for cancer therapy, delivering high levels of local radiation to kill cancer cells in organs such as liver through the achievement of a successful glass delivery system for radiation [31]. Furthermore, the incorporation of MBGs into silica, polymeric or liposome substrates can substantially expand their applications [32-34]. Overall, bioactive glasses and MBGs appear to have a bright future in the area of cancer treatment.

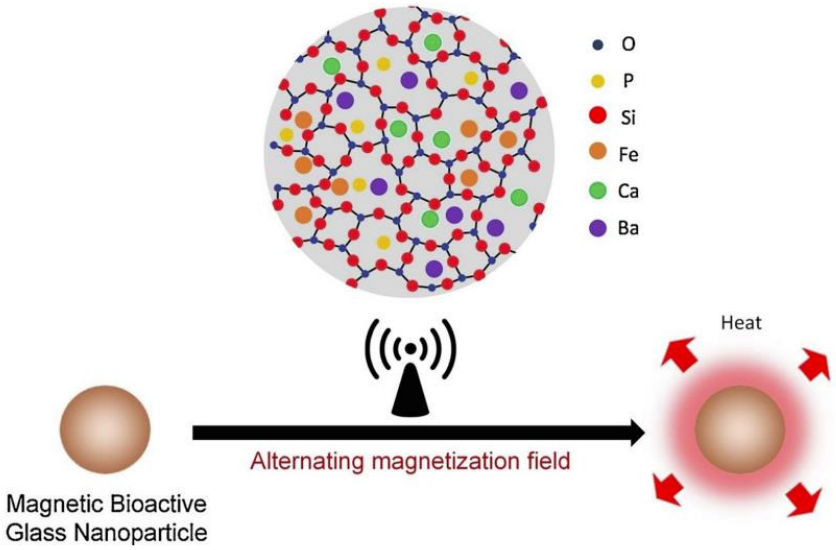

Fig. 4 Schematic illustration for magnetic bioactive glasses for providing hyperthermal therapy of cancer. Adapted with permission from Ref [29]

2.4 Silica

Silica and silica-based materials, which are proven biocompatible, have been frequently employed for biomedical applications. Nanoparticles made of silica are mainly solid or mesoporous nanoparticles. Different from solid silica nanoparticles, mesoporous silica nanoparticles can carry larger amounts of bio-agents (drug, protein, gene, etc.) owing to their porous structure in the particles. They are potentially efficient carriers of different therapeutic agents owing to their

enormous surface area, controllable pore size, good biocompatibility and thermal stability [35]. Quantum dots (QDs), fluorescence dye or magnetic nanoparticles have been embedded in the silica nanoparticles (solid or mesoporous) to serve as highly efficient imaging agents for fluorescence microscopy and magnetic resonance imaging (MRI). Anticancer drugs and therapeutic genes can also be delivered by mesoporous silica nanoparticles with different pore sizes and surface properties [36]. Functionalization of mesoporous silica nanoparticles with molecular, supermolecular and other polymer moieties improves their biocompatibility and also targeting function. Additionally, silica coating on the surface of other types of nanoparticles is often adopted to enhance colloidal chemical stability. Another advantage for using silica coating is that the particle surface is often terminated by a silanol group which can react with various coupling agents to covalently bind targeting ligands.

The combination of unique architecture, facile fabrication and controlled surface chemistry of solid and mesoporous silica nanoparticles should enable the development of new sophisticated multifunctional nanodevices to meet the challenges in different biomedical applications.

3. Hybrid Ceramics for Cancer Detection and Treatment

3.1 Ceramic-metal hybrids

Hybrid or composite materials containing ceramic and metal components often show enhanced mechanical properties owing to their reinforcing effect. Furthermore, these materials may also offer new properties. For example, since CaPs are prone to ionic substitutions, the fabricated CaP-metal hybrid materials may be developed into nanoparticles of different composition, structures, and solubility for targeted applications. Also, some new properties could be generated for cancer diagnosis and treatment [37], as shown in Table 1. For instance, lanthanide-doped HAp possesses luminescence properties, which is useful for biomedical imaging [38]. It was noted that the luminescence efficiency and color of the emitted light depended on the lanthanide element and the degree of crystallinity. CaPs doped with magnetic ions (such as Fe^{2+}/Fe^{3+}, Mn^{2+}, Gd^{3+}, etc.) can provide sensitive imaging ability for MRI and computed tomography (CT). Meanwhile, magnetic targeting, magnetic-induced treatment guidance, and magnetic hyperthermia may be simultaneously achieved through a single nanosystem to enable better treatment for cancer patients. In addition, radio-labelled CaPs with further radionuclides labeling may be utilized for nuclear

imaging such single photon emission computer tomography (SPECT) and positron emission tomography (PET). More importantly, ion-doping can modulate the internalization and also payload release for CaP-based nanoparticles [39].

Table 1 Examples of ion-doped CaP hybrid materials for cancer diagnosis and treatment

Doping ion	**Application**	**Ref.**
Fe^{2+}/Fe^{3+}	Magnetic targeting MRI Hyperthermia	6, 40, 41
Ag^{+}	Antimicrobial activity	42
Eu^{3+}, Gd^{3+}, Dy^{3+}, Yb^{3+}	MRI/CT/upconversion luminescence Hyperthermia therapy	38, 39, 43, 44
Mn^{2+}	MRI Chemodynamic therapy (CDT)	44
Cu^{2+}	Photothermal anti-tumor effect	45

Magnetic bioactive glasses are good candidates for thermoseeds for hyperthermia in cancer treatment. Compared to single-component magnetic nanoparticles, the magnetic phase in magnetic bioactive glasses is embedded within the bioactive glass matrix and hence the leaching of metal ions to surrounding tissue or environment could be effectively avoided or minimized. In addition, agglomeration may not cause big concern as particles are not in colloidal suspension. Furthermore, magnetic bioactive glasses can bond to bone so that they can stay at the targeted sites once they are implanted [46]. Hyperthermia effect can thus be repeatedly generated whenever needed at a later stage of cancer. These characteristics make magnetic bioactive glasses more attractive than other materials as thermoseeds, especially for treating bone cancer. Magnetic bioactive glass-ceramics were also found useful for cancer hyperthermia and at the same time for bone tissue regeneration[47].

Silica-based materials are frequently used as supporting substrates to either deposition or encapsulation of metallic materials for a variety of applications, including biomedical applications. Tremendous efforts have been made to develop various silica-metal hybrids as new theranostics that possess attractive properties (Fig. 5). Silica or mesoporous silica coating on noble metal nanoparticles can prevent or reduce the aggregation of these noble metal nanoparticles. Since the

surface of silica coating is rich in silanol groups, targeting ligands may be easily attached to the hybrid particles to realize the tumor targeting function. In addition, silica particles can be used as the supporting substrate for some nanoparticles such as iron oxide or gold nanoparticles for providing the sensing/imaging function. The silica-metal hybrids thus designed and fabricated can have both diagnostic and therapeutic capabilities. For the detailed discussions on this aspect, readers can refer to our recently published review article [48].

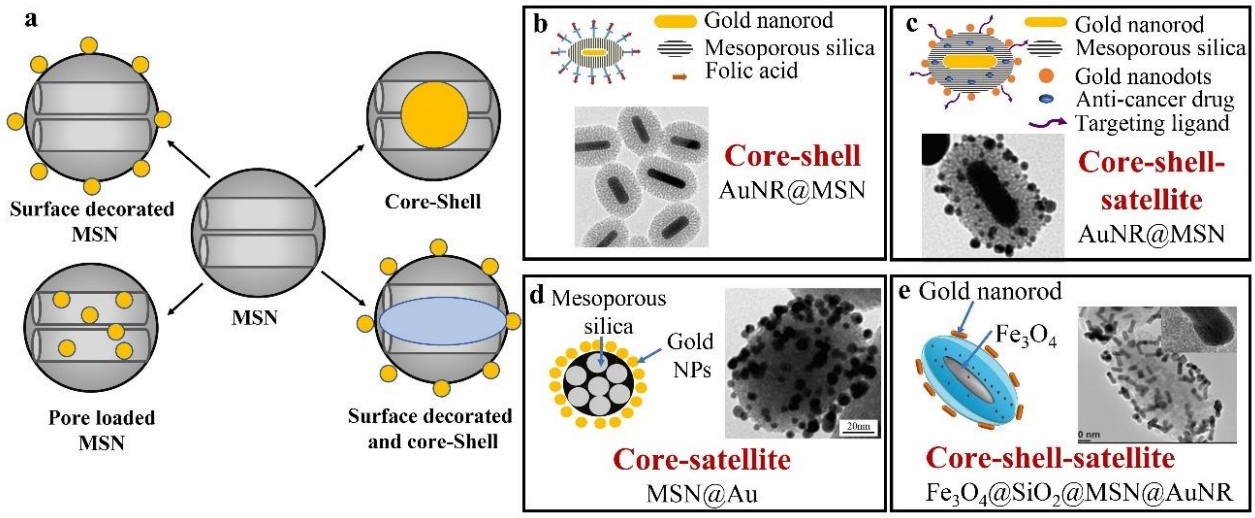

Fig. 5 Novel theranostics with the use of silica: (a) Schematic illustration of different ways to hybridize mesoporous silica with other components; (b) to (e) Examples of silica-metal hybrids designed and fabricated by different researchers: (b) Core-shell gold nanorod/mesoporous silica nanoparticles made by two-step and sol-gel methods, (c) Core-shell-satellite structured gold nanorod/mesoporous silica/gold nanodots theranostics for achieving combined chemo-phototherapy, (d) Core-satellite structured mesoporous silica/gold nanoparticle as surface enhanced Raman tag for cancer detection, (e) Multifunctional core/multishell/satellite structured Fe_3O_4/solid silica/mesoporous silica/gold nanorod nanoparticles. Adapted with permission from Ref [49]

3.2 Ceramic-polymer hybrids

Bioactivity and biodegradability are important characteristics of bioceramics that are required for non-porous biodegradable implants for replacing diseased or injured tissues (e.g., bone) or for porous biodegradable scaffolds for regenerating body tissues that are focuses of current research in the biomaterials and tissue engineering fields. They may be effectively achieved by combining bioactive ceramics with biodegradable polymers, creating desired composites/hybrids (non-porous, or porous) for the applications. Generally, it has been a challenge to deliver pharmaceutical agents to the interior of hard tissue for combating the disease/cancer because of the inherent biological barriers, less perfused and limited blood supply. Consequently, conventional administration routes for drugs are not very effective for treating bone cancer. Therefore, controlled drug delivery at local sites with long-term release profiles is needed. Ceramic-polymer composites/hybrids may be able to provide controlled long-term drug delivery at local disease sites while offering the benefit of regeneration of bone tissues at the bone defect sites. Biopolymers such as chitosan (CS) [50], sodium alginate (SA) [51] and PLGA (poly-lactide-co-glycolide) [52] are widely used materials in tissue engineering and possess excellent properties, including non-toxicity, biocompatibility and biodegradability, as well as commercial availability. Therefore, these polymers have been used with ceramics to realize controlled drug delivery. Liu and Webster [52] fabricated a nano-HA/PLGA composite which was capable of long-term drug release. A bone morphogenetic protein (BMP-7)-derived peptide (DIF-7c) was used as the model drug and was firstly loaded onto nano-HA via both covalent bond and physical absorption. The drug-loaded nano-HA was then dispersed in the PLGA matrix to form an implantable scaffold. The results showed that the nano-HA/PLGA composite achieved a greatly prolonged two-phase release profile. Also, the nano-HA/PLGA composite demonstrated *in vivo* bone regeneration ability, showing the promise for orthopedic application.

Porous ceramics have been made and assessed as delivery vehicles for antibiotics, anticancer drugs, proteins, and hormones by many researchers. The decrease in drug release speed caused by the formation of fibrous capsules on delivery vehicles may be compensated by the gradual degradation of the ceramic matrix. In contrast, a polymer coating on the ceramic matrix could improve surface properties and help to realize sustained drug release or pH-sensitive release of the drug, which could be controlled by the polymeric component containing weakly acidic or basic groups. For

example, phosphate-stabilized amorphous calcium carbonate (ACP) decomposes too fast in an acidic condition to achieve a long-term release of incorporated drug. Nie *et. al*. [53] fabricated monodispersed SA/ACP hybrid via ultrasonic treatment. The release rate of curcumin, which was used as a model anticancer drug in the study, from the hybrid became slower as the concentration of SA increased under the same pH value. The SA/ACP system was shown to provide good sustained-release profiles for long-term cancer treatment through controlling the ratio of SA to ACP in the hybrid.

3.3 Ceramic-ceramic hybrids

Mesoporous silica nanoparticles (MSNs) are one of the most frequently studied nanoparticles for drug delivery systems in light of their characteristics, including ease of functionalization, high surface area, and high pore volume for high drug loading. However, their poor degradability and long-term toxicity caused by their accumulation in some organs in the body remain a big concern and have limited their clinical application. CaPs may be used to deal with the shortcomings of MSNs owing to their bioactivity and biodegradability. The hybridization of CaPs with mesoporous silica could significantly increase their biodegradability with the release of Ca^{2+} ions from the CaP in an acid environment. Therefore, HAp-MSN hybrid materials were investigated and results showed that they could improve drug loading efficiency and also provide pH-stimulus controlled drug release, consequently generating better therapeutic outcomes.

Hao et al. [54] integrated HAp into MSNs to form hybrid nanoparticles which would degrade in the acidic environment owing to the dissolution of HAp in nanoparticles. As such, the drug loading efficiency was enhanced, together with required degradability and desired pH-responsive release profile. Song et al. [55] fabricated a core/shell hybrid drug carrier with a gold nanorod (AuNR) core and an $mSiO_2$/HAp shell for multi-responsive drug delivery (Fig. 6). AuNRs were coated by a silica shell trough the hydrolysis of silicate precursor with the *in situ* formation of HAp component through the reaction of calcium salt and phosphate. The incorporation of HAp modified the porous structure of original silica shell and resulted in higher drug loading capability and faster biodegradation of the hybrid nanoparticle. The AuNRs core could also generate heat under a near-infrared (NIR) light irradiation, which accelerated the dissolution of HAp. The drug release results using doxorubicin hydrochloride (DOX) as the model anticancer drug revealed that the fabricated

AuNR/mSiO$_2$/HAp nanoparticles had distinctive NIR- and pH-responsive drug release properties (Fig. 6), making the particles good candidates for use in controlled drug delivery.

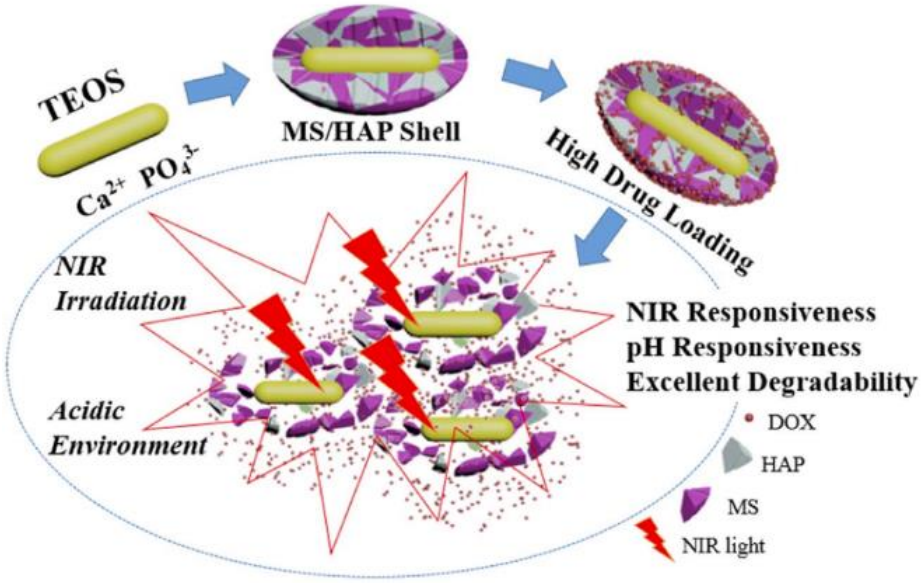

Fig. 6 Illustration for the fabrication and properties (i.e., high drug loading efficiency, excellent pH-sensitivity, NIR-sensitivity and biodegradability) of AuNR/mSiO$_2$/HAP nanoparticles. Adapted with permission from Ref [55]

Some targeting ligands could also be conjugated onto CaP-silica hybrids for tumor targeting. Kang et al. combined the advantages of MSNs and HAp with the fabrication of a spherical MSN/HAp hybrid (Fig. 7) [56]. They showed successful loading of DOX into the porous framework. Moreover, the surface of MSN/HAp hybrid was modified by grafting hyaluronan (HA) and oligosaccharides-cleaved HA (oHA) to enable the tumor targeting ability. The diameters of MSN/HAp hybrid nanoparticles were smaller than 100 nm, as shown in the TEM micrographs [Fig. 7(c) and 7(d)]. The DOX release profile and TEM images of hybrid nanoparticles were recorded under different pH values [Fig. 7(e)]. These results indicated that the MSNs/HAp nanoparticles had the potential to release DOX at tumor sites due to their weak acidic environment (pH 6.4-6.8) because of the

existence of HAp. The cytotoxicity of MSN/HAp nanoparticles tested on both healthy and cancer cells appeared to be almost negligible. HA or oHA coating on MSN/HAp nanoparticles showed distinct cytotoxicity on targeted cancer cells, and HA@MSN/HAp or oHA@MSN/HAp hybrid still preserved good tumor targeting ability.

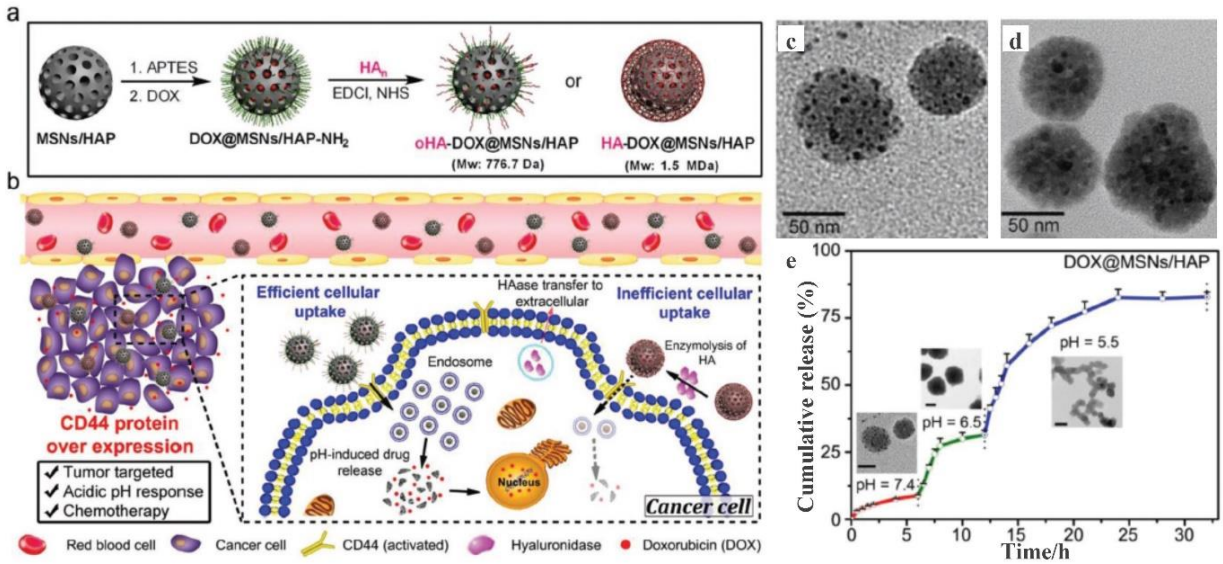

Fig. 7 (a) Schematic showing the preparation of oHA-DOX@MSN/HAp and HA-DOX@MSs/HAp nanoparticles, (b) Working principle of oHA-DOX@MSN/HAp and HA-DOX@MSN/HAp as nanodrugs for chemotherapy *in vivo*, (c) and (d) TEM images of oHA-DOX@MSN/HAp and HA-DOX@MSN/HAp, respectively, (e) Step release of DOX from DOX@MSN/HAp in phosphate buffered saline (PBS) at different pH values. (Inset TEM images were taken at 4, 10, and 24 h of incubation, respectively.) Adapted with permission from Ref [56]

The challenge of using mesoporous silica nanoparticles as “on-demand” drug carriers is to find the suitable gatekeeper to block the release of drugs from the open pore prior to reach the targeted release site and at the same time to ensure the controlled release of drugs at the release sites. A CaP coating on MSNs may be designed as a gatekeeper to accomplish precise targeting and controlled release. Previous research has shown that CaPs could be dissolved as nontoxic ions (calcium ions and phosphate ions) in acidic cellular environments such as endosomes (~pH5.0)

and lysosomes (~pH4.5) [57] and hence would not cause cytotoxicity issue. Rim et al [58] prepared mesoporous coating together with pH-controlled, absorbable CaP nanoshell as pore blockers. The hybrid nanoparticles provided triggered release of encapsulated drugs within intracellular endosomes. The surface of their mesoporous silica nanoparticles was decorated with urea (designated as Si-MP-UR) [Fig. 8(a)]; and then the anticancer drug DOX was encapsulated in the pores (designated as DOX-Si-MP-UR). Subsequently, a CaPs nanocoating formed on the surface of Si-MP-UR under urease-mediated surface mineralization as the pore-blocking agent [Fig. 8(c)]. *In vitro* results showed that the CaP pore-blocking nanocoating on DOX-Si-MP-UR was effective in holding DOX before endocytosis and that DOX release could be achieved within lysosomes by the dissolution of CaP nanocoating.

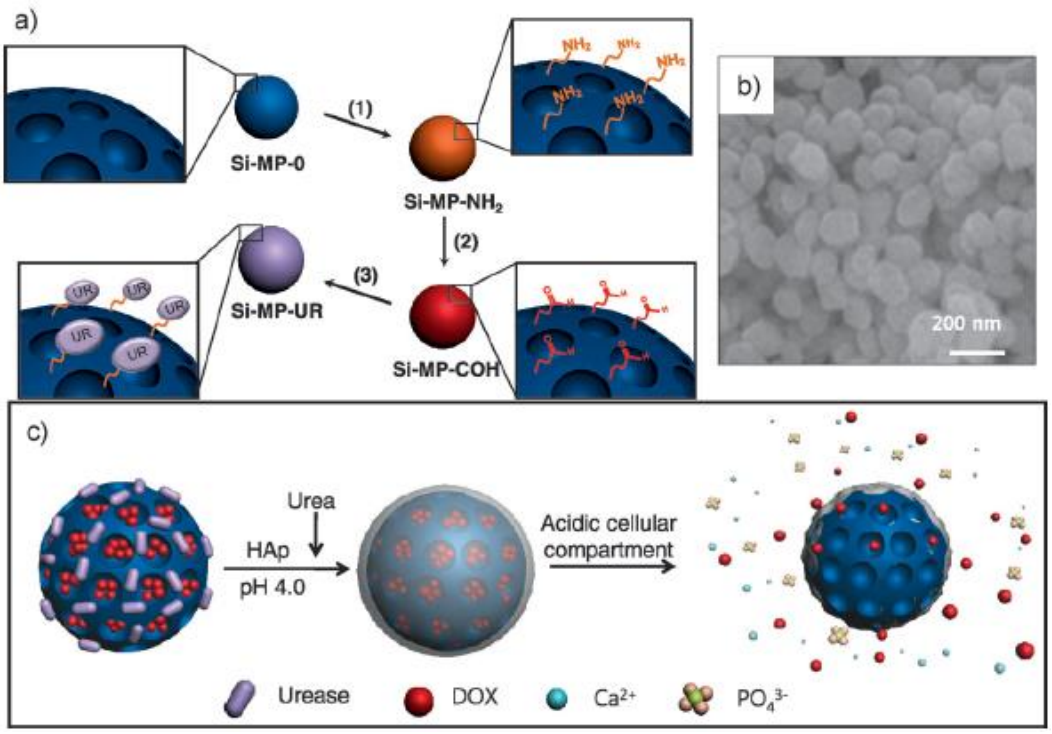

Fig. 8 (a) Synthesis route for Si-MP-UR: (1) APTES, (2) removal of cetyltrimethylammonium bromide, glutaraldehyde, (3) Jack bean urease (UR), (b) Field-emission SEM image of Si-MP-UR,

(c) Schematic of surface CaP mineralization of DOX-Si-MP-UR and triggered drug release under intracellular endo/lysosomal conditions. Adapted with permission from Ref [58]

Apart from CaP-silica hybrids, biphasic calcium phosphates consisting of TCP and HAp have also been investigated for tissue engineering and drug delivery. It is challenging to separate the components in biphasic or multiphasic calcium phosphates because the components are homogeneously and intimately mixed at the submicron level. Biodegradable porous nanocomposite scaffolds containing a β-TCP matrix and HAp nanofibers were fabricated and the scaffolds showed enhanced mechanical properties for possible load-bearing bone tissue engineering [59]. The biphasic CaP scaffolds had microporous structures that assisted cell growth and vascularization and were considered for bone regeneration after tumor removal. In addition, biphasic hybrids have been intensively studied for biosensing, bioimaging and drug delivery due to their attractive properties. Wiglusz et al. [60] fabricated HAp/β-TCP nanocomposites which were doped with Er^{3+}/Yb^{3+} ion-pairs. These composites were shown to have great potential for fluorescent imaging application.

4. Applications of Ceramics-based Hybrid Nanomaterials for Cancer Detection and Treatment

4.1 Development of Ceramics-based cancer theranostics

Applications of nanotechnology in oncology have been developed in several directions, including molecular sensing, diagnostic imaging, targeted therapy, and treatment-monitoring. Theranostics is a novel concept which entails the use of nanoparticles in a single nanosystem for both molecular sensing/imaging and therapy for cancer. Even though there are single-component nanoparticle systems, which is rare, that may be used as theranostics, such systems have major limitations and have not been vigorously pursued. Composite or hybrid nanoparticles are the systems that hold great promise for cancer detection and treatment. Currently, there are various types of theranostics based on different matrices. The applicability of theranostics is highlighted by liposomes which are intensively used in clinical trials due to their specific features. Several theranostics based on silica, silica-gold, cyclodextrin and iron oxide have also been used in clinical trials or pre-clinical work for cancer diagnosis and treatment [61]. Advanced theranostics have the ability to monitor

therapy response, providing opportunities to modify the ongoing cancer treatment and to develop new treatments in personalized medicine.

Different from other inorganic nanoparticles, such as gold, silver, or iron oxide nanoparticles, ceramic nanoparticles cannot be directly used as sensing or imaging agents for cancer detection due to their lack of unique optical or magnetic properties. The applicability of ceramic nanoparticles in sensing/imaging is highlighted by their function as carriers of some imaging moieties. The chosen ceramic nanoparticles are generally appraised for providing therapeutic functions for cancer treatment by way of delivering therapeutic agents (such as anticancer drugs and silencing genes) into the targeted sites, i.e., cancerous tumors. Recently, magnetic bioactive glasses have been proposed for providing both MRI-based imaging and hyperthermia-based cancer treatment, which opens new avenues for bioactive glasses for theranostics applications.

A thorough search for clinical trials in the US database (*clinicaltrials.gov*) has identified 34 clinical trials in which theranostics are being applied for cancer diagnosis and therapy, with only 6 cases of them being involved as bone graft or implants. Therefore, there is still a long way to go for ceramics-based theranostics to be used in clinics. Considering the desirable properties such as bioactivity, biodegradability and special functionality, ceramics-based hybrid nanomaterials should be investigated and assessed for future theranostics.

In the following sections, the fabrication, characterization and biological performance of some theranostics as typical examples are presented and discussed. These nanosystems are the highlights of ceramics-based theranostics with comparatively superior properties and functionalities.

4.2 Bioactive glasses and glass-ceramics for cancer therapy

Bioactive glasses have been successfully used in bone tissue replacement or regeneration. Even though bone is a complex tissue with the self-repair function, the regeneration capability of bone in large bone defect areas is often limited, which is generally the case after surgical removal of bone tumor. Therefore, multifunctional nanodevices with functions of both treating the possible remaining cancer cells after surgery and regenerating new bone are urgently needed. As a non-invasive cancer treatment, hyperthermal therapy has been considered as an alternative and competitive way to treat relatively large tumors in bone and other tissues. Bioactive glasses doped with thermoseeds are considered as excellent candidates to provide required thermal activity for

cancer hyperthermia and to offer bioactivity for bone regeneration. For example, Wang et al. [62] used the melting-quenching method to prepare bismuth-doped bioactive glasses, which consisted of SiO_2, Na_2O, CaO, P_2O_5 and Bi_2O_3. The biocompatibility, apatite formation and photothermal effect of the fabricated glasses were evaluated through *in vitro and in vivo* experiments. The *in vivo* experiments using nude mice showed that the bismuth-doped glasses could efficiently kill bone tumor cells under NIR irradiation. A laser of 808 nm wavelength was used to illuminate glass samples with different percentages of Bi_2O_3 in simulated body fluid (SBF) and the temperature change of the solution was monitored by an infrared sensor [Fig. 9(a)]. The temperature increase was larger for glass samples with higher percentages of Bi_2O_3 [Fig. 9(b)], indicating that glasses doped with Bi_2O_3 could be used to realize photothermal effect. Generally, the cell viability was greater than 80 % for the four types of cells tested (L929, MC3T3-E1, UMR106, and U2OS) after their culturing with different concentrations of Bi-doped glasses for 24 h [Fig. 9(c)], which suggested good biocompatibility of the doped glasses. The results of energy-dispersive X-ray spectroscopy (EDX) analysis [Fig. 9(d)] showed that P and Ca were the primary cation species in the surface deposit of glass samples after 3-day immersion in SBF. The traces of elements for the doped glass disappeared after 7-day immersion, indicating the apatite layer formation on glass. To assess the *in vivo* performance of bismuth-doped glasses, four parallel experiments were performed on nude mice, using "control", "S6P0B + laser", "S6P2B", and "S6P2B + laser" animal groups. (S6P2B was the bioactive glasses with the components of 41mol%SiO_2-6mol%P_2O_5-2mol% Bi_2O_3.) No bioactive glass or laser irradiation was applied to the "control" group. No laser irradiation was applied to the "S6P2B" group. After the rat osteosarcoma derived from UMR106 cells grew to the size of ~10 mm in mice, glass samples (S6P0B and S6P2B) were implanted into the tumor sites in mice [Fig. 9(e)]. The local temperature in the "S6P0B + laser" group increased by 6-7 °C while that of the "S6P2B + laser" group increased to ~55 °C quickly when the tumor sites were exposed to laser irradiation, suggesting strong photothermal effect of the doped glass as a result of the existence of Bi_2O_3. The *in vivo* results also showed that tumors in the "S6P2B + laser" group started to shrink on day 1 of laser treatment and vanished on day 3. All tumors were seen to be destroyed on day 15, demonstrating the capability of Bi-doped bioactive glass for treating bone tumor. The presence of Bi_2O_3 did not affect the bioactivity of the glass, and hence the doped glass could promote bone regeneration after bone tumor was destroyed.

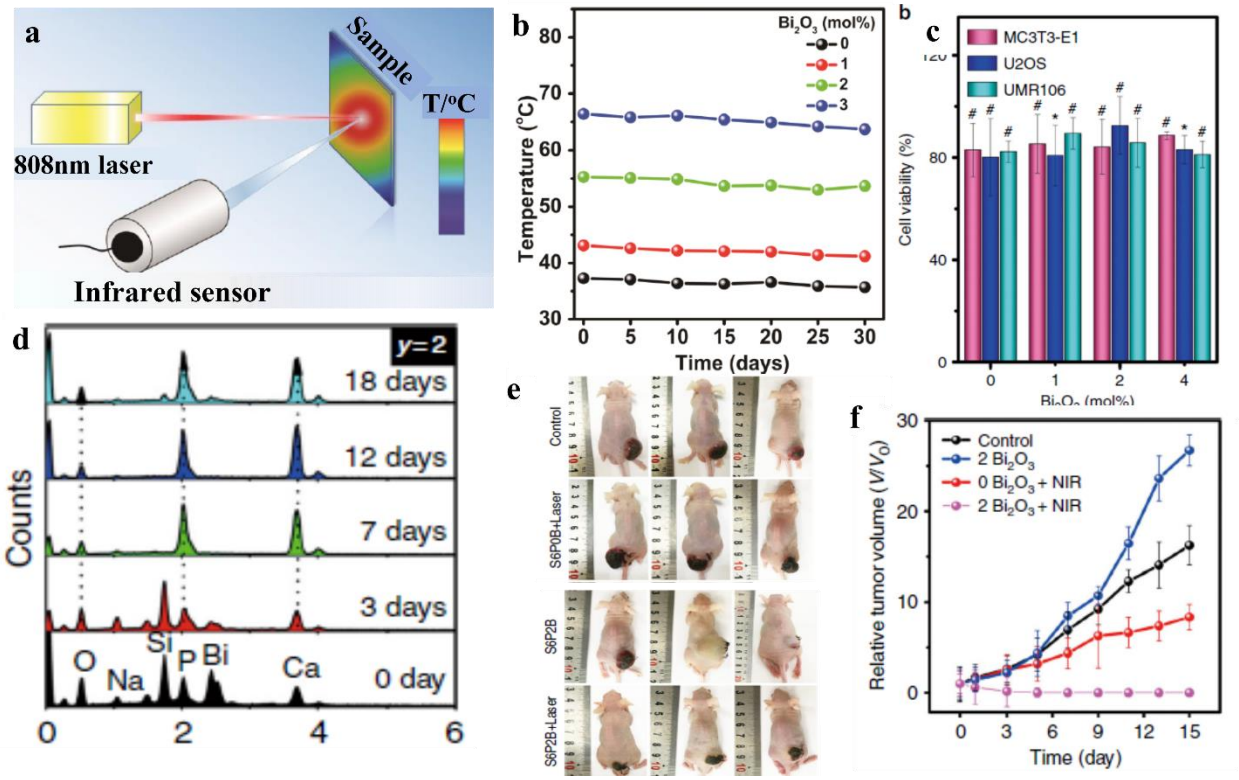

Fig. 9 (a) Experimental setup for quantifying the photothermal effect, (b) Photothermal effect of Bi-doped bioactive glasses with different percentages of Bi_2O_3 (The temperature was measured under laser irradiation for 10 min.), (c) Viability of normal cell MC3T3-E1, human osteosarcoma cell line U2OS and rat osteosarcoma cell line UMR106 after their culturing with Bi-doped bioactive glasses for 24h, (d) EDX analysis results showing the evolution of element distributions on surfaces of Bi-doped bioactive glasses (y is the percentage of Bi_2O_3 in glasses) after incubation in SBF for different days, (e) Mice in "control", "S6P0B + laser", "S6P2B" and "S6P2B + laser" groups at day 15 of laser irradiation treatment, (f) Changes of tumor size with times in the four animal groups. Adapted with permission from Ref [62]

Apart from photothermal therapy generated by optical input, magnetic fluid hyperthermia (MFH) or magnetic induction hyperthermia (MIH) can also cause thermal apoptosis through the use of alternating magnetic fields applied to magnetic bioceramics [63]. Ferrimagnetic/ferromagnetic/superparamagnetic materials, known as thermoseeds, can be injected into tumor sites, which produce heat once they are exposed to an alternating magnetic field. There

are two concerns for using magnetic nanoparticles for hyperthermia [64]. One is the possible leaching of metal ions from nanoparticles, which may be harmful to the body. The other is that the metal nanoparticles may agglomerate at tumor sites, greatly weakening their heating efficiencies [65]. These issues may be dealt with by using magnetic bioactive glass-ceramics (MBGCs) as bone implants and cancer cell killers, which was firstly proposed and developed by Kokubo and co-workers [66]. In addition to serving as thermoseeds in hyperthermia to kill tumor cells via inductive heating, MBGCs can also be used as an adjuvant treatment to carry out radiotherapy, chemotherapy, synergism with immunotherapy, etc. As compared to other magnetic-embedded carriers, MBGCs endow high biocompatibility and bioactivity which may cause less side effects on adjacent healthy tissues when they are injected into tumor sites. However, the addition of magnetic particles into MBGCs often causes decreases in bioactivity. Therefore, the challenge in designing new magnetic bioceramics for cancer treatment is about how to balance the optimal magnetic properties and bioactivity to ensure that the generated heat is high enough to kill tumor cells while not sacrificing the bioactivity.

Li et al. [67] synthesized CaO-SiO_2-P_2O_5-MgO-CaF_2-MnO_2-Fe_2O_3 MBGCs for achieving MIH for cancer. Through doping with MnO_2 and Fe_2O_3 to the bioactive glass matrix, the fabricated MBGCs demonstrate enhanced magnetic property which is desired for cancer hyperthermia. The bioactivity of MBGCs was substantiated by the formation of a non-continuous apatite layer on the MBGCs surface upon immersing in SBF for 14 days. Cells were shown to be well attached and proliferated on the MBGCs surface after 7-day cell culture. Recently, Miola et al. reviewed the development of magnetic glass-ceramics in terms of their composition and fabrication, as well as their application for hyperthermia in cancer treatment [47]. Another recent review by Danewalia and Singh summarized the application of MBGCs for MIH treatment of cancer and provided some insights into the correlations between their composition, bioactivity and outcome of heat treatment [68]. Although many research articles have appeared on MBGCs and resulting MIH treatment, there is still the lack of *in vivo* studies that can clarify the various effects of glasses and glass-ceramics on different cells. Moreover, clinical trials are barely in progress.

Well-ordered porous structures render ceramic matrices with a good capability for drug adsorption and release. Mesoporous bioactive glasses (MBGs) are a new type of bioactive glasses with well-ordered mesoporous channels, high surface area, and high bioactivity [69]. With the assistance of a

structure-directing block copolymer, highly ordered MBGs were synthesized through an evaporation-induced self-assembly (EISA) process [70]. The prepared MBGs showed improved *in vivo* bioactivity. MBGs are competitively advantageous over conventional bioactive glasses, as illustrated in Fig. 10. For instance, MBGs synthesized by EISA demonstrated a two-fold higher loading efficiency of the antibiotic gentamicin than bioactive glasses synthesized by the sol-gel method.

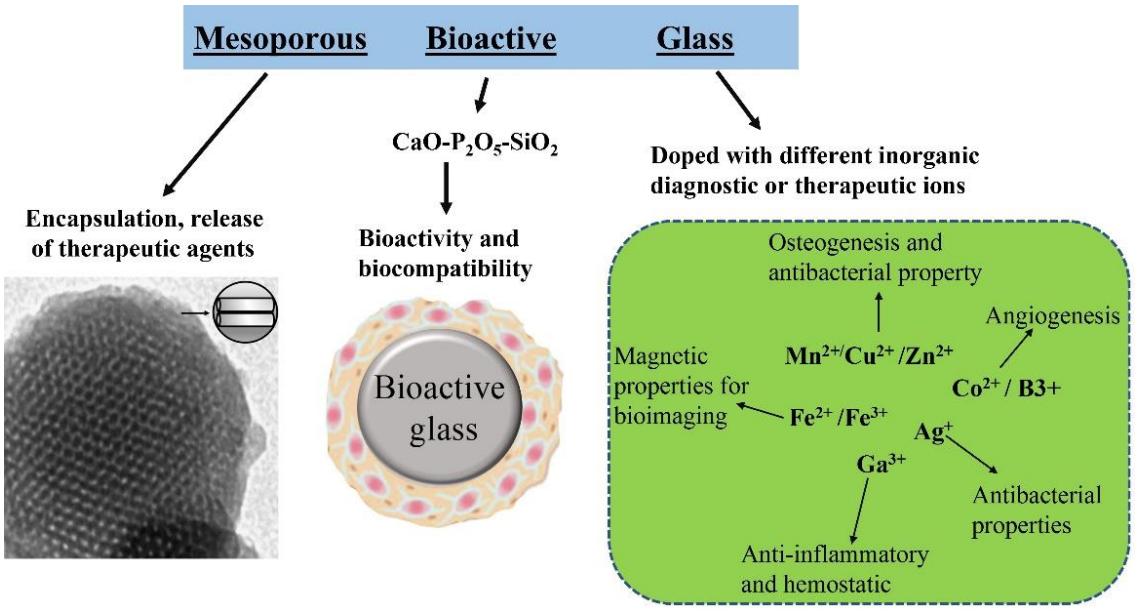

Fig. 10 Attractive characteristics of mesoporous bioactive glass as cancer theranostics.

More recently, MBGs were proposed to provide combined hyperthermia and photothermal therapy (PPT) for cancer treatment. The MBGs are already recognized as excellent platforms for anti-cancer drug loading and release owing to their porous structure with a highly controllable arrangement and diameters (2-50 nm). It is also possible to incorporate some specific elements such as (Fe) into the structure of MBGs to provide MBGs with magnetic properties so that PPT is also available for these glasses, and consequently the cancer treatment by these glasses can be enhanced. On the other hand, as angiogenesis is crucial for the proliferation and metastatic spread of cancer cells, developing novel MBGs with the ability to suppress new blood vessel formation,

which is regulated via releasing antiangiogenic ions or through delivering anti-angiogenic drugs/chemicals, is of great importance for finding/exploring new therapeutic approaches against cancer. The potential of glass-ceramics for cancer therapy has been reviewed recently by Miola et al.[47] Major efforts are needed to develop these materials/products into clinical applications, which is highly challenging.

4.3 Silica-based hybrid nanoceramics as cancer theranostics

MSNs are non-toxic and biocompatible according to *in vitro* and *in vivo* studies [70, 71], which have been approved for use by US Food and Drug Administration (FDA). As has been discussed in Section 2.4, MSNs have many unique properties, including large surface area, high pore volume, tailorable pore size and easy functionalization, which make them excellent candidates for biomedical applications. These excellent properties combined with their high cargo-carrying capacity put them into a highly advantageous position for being developed as novel and powerful theranostics. There are many excellent reviews on MSNs, covering their fabrication, characterization and biological performance [35, 72-74]. Therefore, to avoid repetition, this article only summarizes the recent developments (within the past five years) of MSN-based theranostics in terms of imaging techniques, types of carried cargos and stimuli for triggering the therapeutic effect (Table 2) and gives a few representative examples to provide a wide view about the possibility of their clinical transition in oncology. Many research efforts have focused on using mesoporous silica as carriers for either imaging contrast agents or therapeutic agents (Table 2), with these agents being loaded or encapsulated into their inner pores. Gatekeepers are used to block the pore entrances to avoid premature leakage of encapsulated agent. An ideal gatekeeper can be removed under specific internal or external stimuli to achieve controlled drug release at the targeted delivery sites. These stimuli include pH, redox potential, temperature, biomolecules, light, magnetic field, ultrasound, or a combination of these factors. Li et al. [75] fabricated a multifunctional drug delivery vehicle with an ordered mesoporous resin as a polymer core and Fe nanodots-doped silica as the biodegradable shell. The Fe-doped silica shell acted as a gatekeeper to block DOX leakage from mesoporous polymer cores and served as magnetic agents for magnetic targeting and MRI. Importantly, the Fe-doped silica shell could be degraded to release the loaded drug in the acidic tumor environment but had ultralow drug leakage during circulation in blood.

The cellular uptake and tissue biodistribution of theranostics are very important factors to determine the fate and efficacy of silica-based theranostics. Therefore, their surface modification via targeting ligands is necessary. Passive targeting caused by the enhanced permeability and retention (EPR) effect is widely applied for designing theranostics (Table 2). Meanwhile, active targeting enabled by targeting ligands, which include small molecules, proteins and peptides, is also highly pursued to reduce the side effects in cancer treatment. Magnetic mesoporous silica nanoplatforms can provide magnetic targeting which has been used by some researchers for effective isolation and detection of circulating tumor cells [76]. Samykutty et al., developed wormhole mesoporous silica nanoparticles as delivery vehicles by using chitosan as the gatekeeper and peptide for active targeting. The controlled release of imaging dye from MSNs triggered by pH could target orthotopically implanted ovarian tumors, thus generating high resolution images for spatiotemporal identification of submillimeter ovarian cancer [77].

Silica nanomaterials have shown more possibilities as cancer theranostics than other bioceramics because of their facile synthesis methods, versatility for functionalization, and integration with other materials. However, several challenges still remain prior to the clinical translation. For example, the potential toxicity or incompatibility with body tissue of silica-based theranostics is a concern. Fortunately, many types of silica-based theranostics in terms of their composition, morphology and surface properties are now available, which may help to address the concerns.

Table 2 Recent developments of MSN-based theranostics grouped according to their imaging technique involved, cargo carried and stimulus used to trigger the therapeutic effect

Material and Composition	*In vitro* or *in vivo* study	Imaging Modality	Stimulus		Cargo		Targeting		Therapeutic application	Ref
			Gate keeper	Stimulus	Imaging contrast agent	Therapeutic agent	Targeting ligand	Targeted tumor		
Mesoporous silica-coated bismuth sulfide nanoparticle (Bi_2S_3@MSN NP)	*In vivo*	CT		NIR	Bi_2S_3	DOX	RGD peptide	Osteosarcoma	Photothermal therapy-chemotherapy	[78]
Indocyanine green (ICG)-loaded zwitterion fluorescent carbon dot (CD)-encapsulating mesoporous silica nanoparticle (ICG-CD@MSN)	*In vitro*	FLI	Zwitterionic carbon dot-ICG hybrid	pH	Carbon dots	ICG	Passive targeting		Photothermal therapy	[79]
Fluorescent dye Cy7-labeled antimicrobial peptide PA-C1b loaded into MSN, folic acid-conjugated graphene oxide covered MSN (MSN@Cy7-PA-C1b@FA-GO)	*In vitro* and *in vivo*	FLI	GO	NIR	Cy7	PA-C1b	FA, antimicrobial peptide PA-C1b	Breast cancer cell	Photothermal therapy and anticancer therapy caused by antimicrobial peptide	[80]
5-Fluorouracil (5-FU) loaded hollow gold-silver nanoshell coated with mesoporous silica shell and lauric acid (LA) immobilized in the mesopores as gatekeeper	*In vitro*	Optical imaging	Phase change material lauric acid	NIR	Au-Ag nanoshell	5-FU	Passive targeting	Prostate cancer	Combined chemo-photothermal therapy	[81]
Gold nanorod/lauric acid-conjugated mesoporous silica core-shell nanoparticle followed by coating of tannic acid (TA) (AuNR@MSN-LA@TA)	*In vitro*	Optical imaging	Lauric acid and tannic acid as thermos-/pH-sensitive gatekeepers	pH and NIR	AuNR		Passive targeting		Combined chemo-photothermal therapy	[82]
Imaging dye and anticancer drug loaded wormhole silica nanoparticle with chitosan as capping agent	*In vivo*	Multispectral optoacoustic tomographic (MSOT) imaging	Chitosan	pH	IR780 imaging dye	Anticancer drug	Peptide	Ovarian cancer	Chemotherapy	[77]
Hollow mesoporous silica nanoparticle (HMSN) loaded with anti-cancer drug DOX, and surface functionalized with chitosan (CS) and copper sulfide (CuS) nanodot	*In vivo*	Thermal/photoacoustic dual-modality imaging	CuS nanodot	Glutathione	CuS nanodots	DOX	Passive targeting	Breast cancer	Combined chemo-photothermal therapy	[83]
Biodegradable mesoporous silica nanoparticle loaded multiple neoantigen and photosensitizer chlorin e6 (Ce6)	*In vitro*	Positron emission tomography (PET)			Photosensitizer chlorin e6	Photosensitizer chlorin e6 and multiple neoantigen	Passive targeting	Advanced cancer	Photodynamic therapy-enhanced immunotherapy	[84]
Hydrophobic mesoporous silica nanoparticle coated with an amphiphilic block copolymer (Pluronic F127)	*In vivo*	Ultrasound imaging		Ultrasound			Passive targeting		High-intensity focused ultrasound insonation induced cell ablation	[85]

(To be continued)

Table 3 (Continued.)

Anticancer drug DOX loaded superhydrophobic mesoporous silica nanoparticle (FMSN-DOX) with β-cyclodextrin as surface capping agent (FMSNS-DOX@β-CD)	*In vivo*	Ultrasound imaging		Ultrasound	Interfacial nanobubbles	DOX and interfacial nanobubbles	Passive targeting		Chemotherapy and anti-vascular disruption, and enhanced drug penetration effect	[86]
Perfluoropentane (PFP)-loaded, mesoporous silica shell and CuS nanoparticle core (CuS@mSiO_2-PFP-PEG, designated as CPPs)	*In vivo*	Photoacoustic /ultrasound imaging		NIR	Perfluoropentane, CuS		Passive targeting	Breast cancer	Photothermal therapy-primed cancer immunotherapy	[87]
Fe_3O_4/carbon dots-loaded MSN with encapsulation of paclitaxel and surface conjugation of folic-acid-conjugated cyclodextrin	*In vivo*	Long-wavelength FLI	Folic acid-conjugated β-CD	NIR	Carbon dots	PTX	Folic acid		Chemo-catalytic-photothermal therapy	[88]
Ultrasmall manganese oxide-capped mesoporous silica nanoparticle	*In vitro*	MRI		pH	Ultrasmall MnO	DOX	Passive targeting		pH-triggered chemotherapy	[89]
Suicide gene loaded rod-shaped magnetic mesoporous silica decorated with plasmid DNA	*In vivo*	MRI		Magnetic field	Fe_3O_4	Suicide gene	Magnetic targeting	Hepatocellular carcinoma	Magnetic hyperthermia induced gene therapy	[90]
Biodegradable magnetic silica sealed mesoporous polymer	*In vivo*	MRI	Fe-doped silica shell	pH	Ultrasmall γ-Fe_2O_3	DOX	Magnetic targeting		Chemotherapy	[75]
Gadolinium oxide (Gd_2O_3), DOX-loaded MSN capped with FA-conjugated polyelectrolytes	*In vitro*	MRI, FLI	pH responsive polyelectrolytes	pH	Gd_2O_3	DOX	Folic acid		pH-trigged chemotherapy	[91]
Magnetic gadolinium oxide–iron oxide core, mesoporous silica shell gated with boronic acid functionalized highly luminescent carbon quantum dot (BNSCQD)	*In vivo*	FLI and MRI	Luminescent carbon QDs	pH	Gd_2O_3-Fe_2O_3 carbon dots	5-FU	Passive targeting		pH-trigged chemotherapy	[92]
Cyclodextrin-grafted polyethylenimine (CP) functionalized mesoporous silica nanoparticle (MSNP) with encapsulation of DOX and siRNA	*In vivo*			pH		DOX and siRNA		Breast and ovarian cancers	Chemotherapy and gene therapy	[93]
Photosensitizer chlorin e6 (Ce6) and antitumor drug DOX loaded magnetic MSN with surface assembly of pH-responsive alginate/chitosan polyelectrolytes multilayer	*In vitro*	MRI and CT imaging	Alginate/chitosan polyelectrolyte	pH	Fe_3O_4-Au	DOX and photosensitizer Ce6	Passive and magnetic targeting		Combined photodynamic therapy and chemotherapy	[94]
Gd-doped DOX-loaded MSN conjugated with ICG-loaded thermosensitive liposome (DOX@GdMSNs-ICG-TSL)	*In vivo*	Fluorescence, photoacoustic, and MR imaging		NIR	Gd_2O_3, ICG	DOX and ICG	Folic acid		Chemo-photodynamic therapy	[95]
Core-shell gold nanorod/mesoporous silica nanoparticle with outer layer of metal organic framework (MOF) (GNR-MSN-MOF)	*In vivo*	MRI/CT/PA imaging	MOF	NIR	AuNR, MOF	DOX	Hyaluronic acid		Combined chemo-photothermal therapy	[96]

4.4 Calcium phosphate-based hybrids as cancer theranostics

Advanced theranostics can not only have tumor-targeting, medical imaging and cancer therapy functions but also provide the capability to trace the progress of drug release/delivery and monitor the efficacy and performance of cancer therapy. As discussed in Section 2.2, calcium phosphates may provide pH-controlled drug release profile. CaP-based hybrid ceramic theranostics formed by encapsulating both imaging contrast agents and anticancer drugs in the nanocarriers can enable imaging-assisted chemotherapy for cancer. Moreover, they can release drugs at the targeted site with desired dose(s), resulting in better therapeutic effect and less side-effects. Current CaP-based theranostics have been integrated with multiple payloads for achieving the expected functions, i.e., tumor targeting, imaging and therapy.

CaP-based hybrid nanoceramics can be designed to realize fluorescence imaging (FLI)-guided therapy and deliver anticancer drugs with fluorescence tracers. CaP nanocarriers equipped with fluorescence tracers can work as optical reporters, enabling real-time monitoring of drug delivery/release and evaluation of therapeutic effects of delivered drugs *in vivo*. Different fluorescence agents, including organic fluorescent dyes, quantum dots, fluorescent macromolecules, rare earth oxide and metals, are integrated into CaP nanocarriers [97]. For instance, Singh et al. reported a novel HAp-based nanocarrier with self-fluorescence imaging capacity [98]. The HAp nanorods were prepared through a hydrothermal process. The self-fluorescence HAp nanorods (fHAp) enabled imaging capability and exhibited great potential for theranostics applications due to the existence of $CO_2^{\bullet-}$ radical impurities. To increase the loading capacity, fHAp was enclosed with a mesoporous silica shell to form hybrid fHAp@mSi core-shell nanoparticles [99], with ~1% loading capacity for fHAp to the level of ~10% loading capacity for fHAp@mSi. The self-fluorescence property of the fHAp was derived from $CO_2^{\bullet-}$ radicals and was well preserved in the fHAp@mSi hybrid. fHAp@mSi hybrid showed low cellular toxicity and high intracellular uptake rate (80-90%). These results demonstrate that hybrid fHAp@mSi nanocarriers have great potential for effective loading of therapeutic molecules and for drug delivery within intracellular compartments, as well as the capability for *in situ* imaging.

Wang et al. fabricated Janus nanoparticles composed of folate acid-conjugated AuNPs (FA-Au) and poly(acrylic acid)-decorated mesoporous calcium phosphate (PAA-mCaP) [100]. The exposed

FA-Au part could achieve cancer cell-specific targeting and high contrast for CT imaging, while the PAA/mCaP part worked as carriers for DOX. Overall, FA-Au@PAA-mCaP nanoparticles demonstrated good biocompatibility and high stability. More importantly, they served as a multifunctional nanodevice for CT imaging and active-targeting chemotherapy.

CaPs could also be combined with Au nanoparticles for accomplishing multimodal imaging using one nanodevice and for providing multimodal imaging-assisted therapy [101]. Considering that Au nanoparticles can be used as a heat-generator under NIR-laser irradiation, hybrid CaP/Au nanocarriers can be used for dual-modality imaging-guided drug delivery, dual-responsive drug release, and chemo-photothermal therapy for cancer treatment. Li et al. fabricated gold nanorod@polyacrylic acid/calcium phosphate (AuNR@PAA/CaP) yolk-shell nanoparticles and used them to deliver DOX for cancer treatment [Fig. 11(a)] [5]. The AuNR@PAA/CaP nanoparticles showed the average length and width of about 100 and 65 nm, respectively [Fig. 11(b)]. The oval-shaped cavity inside the theranostics could be clearly seen under TEM, and such a hollow structure would provide more storage space for anticancer drug. AuNR@PAA/CaP nanoparticles showed pH and NIR dual-responsive drug delivery ability. The released DOX amount continuously increased due to the dissolution of the CaP shell at pH5.0. A burst-like drug release occurred when DOX-loaded AuNR@PAA/CaP nanoparticles were exposed to NIR irradiation, which was due to the heat generated by the AuNRs under NIR laser [Fig. 11(c)]. In addition, the AuNR@PAA/CaP nanoparticles produced enhanced CT signals and PA intensity with an increase in AuNR concentration [Fig. 11(d) and 11(e)]. Overall, AuNR@PAA/CaP yolk-shell nanoparticles were regarded as promising theranostics for simultaneous dual-mode CT/PA imaging and for providing chemo-photothermal therapy.

CaPs may also be integrated with magnetic nanoparticles or be dope with magnetic ions for providing MRI-guided therapy. There are already extensive reviews in this area in the open literature, and readers can refer to the corresponding review articles for detailed information [102 26, 41, 103-106].

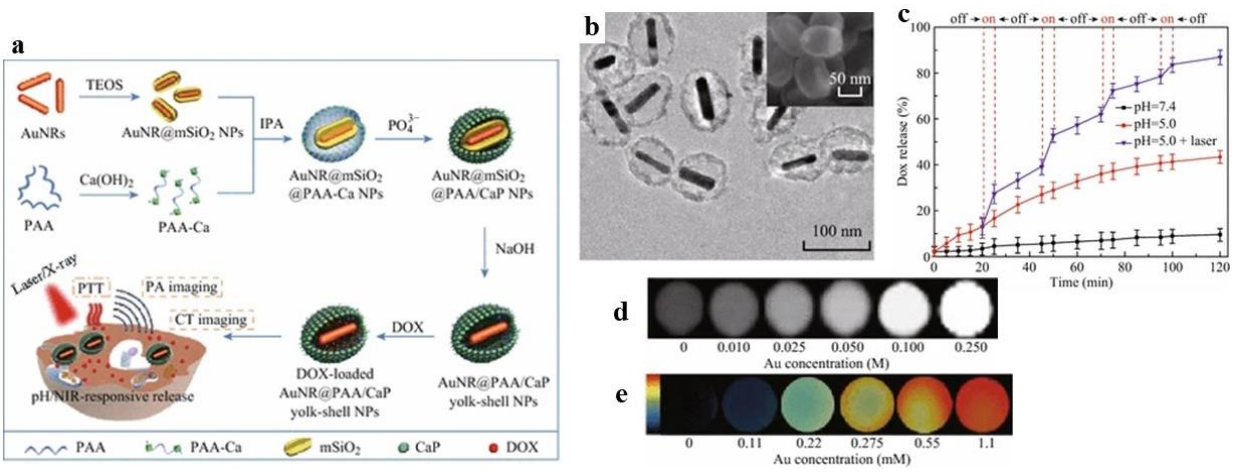

Fig. 11 (a) Schematic illustration of the synthesis process for AuNR@PAA/CaP yolk-shell nanoparticles as pH/NIR-responsive drug carriers and for achieving simultaneous dual-mode CT/PA imaging and providing chemo-photothermal therapy, (b) TEM image of AuNR@PAA/CaP yolk-shell nanoparticles with the inset showing their SEM image, (c) DOX release profiles for DOX-loaded AuNR@PAA/CaP yolk-shell nanoparticles in PBS at pH7.4, 5.0 and 5.0, respectively, with periodic NIR laser irradiation (808 nm, 1.0 Wcm^{-2}), (d) CT images of AuNR@PAA/CaP yolk-shell nanoparticles versus Au concentration, (e) PA images showing PA signal intensity increase with increasing Au concentration. Adapted with permission from Ref [5].

5. Challenges and Possible Developments for Hybrid Ceramics-based Cancer Theranostics

In this article, recent progresses in the fabrication, biological evaluation and application of hybrid ceramics-based cancer theranostics are reviewed. A good number of bioceramics with good biocompatibility, bioactivity, biodegradability and their own distinctive properties make them desirable candidates for theranostics for cancer diagnosis and therapy.

Considering the large presence of Ca^{2+} and PO_4^{3-} ions in human bodies and biodegradability of CaP nanoparticles, the great potential CaPs of working as theranostics through their combination with organic materials such polymers or liposomes to form hybridized nanomaterials is readily expected. CaP hybrids can combine the stability of the organic component under physiological conditions and the bioactivity of CaP to form advanced nanoplatforms for theranostics applications. Also, CaPs can be used as gatekeepers in drug delivery systems to avoid the premature leakage of

loaded cargos (drugs, proteins, genes, etc.) and provide pH-trigged release in the acidic tumor environment. Interestingly, bioactive glasses are hospitable for ionic substitutions which can modify their composition and structure to obtain new, desired properties. Magnetic bioactive glasses can be used for MRI-guided therapy. Mesoporous bioactive glasses can efficiently deliver imaging contrast agents and therapeutic agents and therefore can be used for new theranostics. Apart from these, silica-based theranostics have become the most widely studied nanosystems for oncology. In particular, mesoporous silica nanoparticles are considered to have the highest potential for oncological medicine. Great progresses and achievements have been made in the design and study of properties and biological performance of either single-component ceramic theranostics or hybrid ceramics theranostics. Even though there are substantial reports on biological studies performed *in vitro* and in animal models, very few investigations appear to have been conducted for the clinical trial of theranostics under development. The obstacles for their translation to clinical trial or commercialization include the following aspects.

Firstly, when clinical translation of ceramic theranostics is considered/planned (or even right at the beginning of the design and development of a new theranostic), both short-term and long-term toxicity should be thoroughly investigated. This is difficult for the research and researchers involved, particularly for new theranostics at the beginning of their development. The toxicity or biological incompatibility of ceramic theranostics could cause immunoreaction, inflammation, and/or related diseases when they interact with tissues, organs and the human body biological system itself. In general, the toxicity of theranostics is determined by many factors, including particles size, surface charge, solubility and surface chemistry. Therefore, physicochemical features of ceramic theranostics should be well studied upon the consideration of heterogeneity of cancer types and unwanted responses to the theranostics. Such investigations demand a large amount of work and are time-consuming but they are absolutely necessary. Most current reports present short-term biological test results, either *in vitro* or *in vivo*, but long-term biological studies are essential which are crucial for theranostics, existing or new, if they are scheduled/intended for clinical applications.

Apart from toxicity, the targeting ability of theranostics is another challenge. Either oral administration or intravenous injection of ceramic theranostics involves many biological barriers for the theranostics to reach their targeted sites in the body. These biological barriers often cause

them to preferentially accumulate in organs such as kidney, spleen and liver and consequently reduce their dosage at the targeted sites and cause concerns about their accumulation in these organs. The off-target problem and resultant insufficient dosage in the targeted tumor sites still exist and there are reported works in tackling these problems. Fortunately, there is already a body of knowledge, even though not as large as desired, on tumor-specific targeting ligands, targeting efficiency, and mechanisms to overcome the barriers, etc. With further research in biology, medicine and engineering, this body of knowledge will hopefully be enlarged significantly, and the targeting and associated problems can be dealt with efficiently and effectively.

Another issue is the applicability and effectiveness of some reported methods that employed to achieve the detection and treatment of cancer with the use of theranostics concerned. In laboratory studies and in *in vitro* conditions, these methods have appeared to work. However, considering that the human body is a very complex biological system and that the physiological conditions in the body are very different from the *in vitro* conditions used for the experiments, researchers should design proper (or, more proper) experiments in their studies when they investigate/evaluate theranostic functions of the nanoparticles that they have synthesized. Frankly speaking, a good percentage of the methods to cause detection and therapy of theranostics that are reported in published articles are not applicable or usable when the theranostics are at the targeted tissue site in the body. On this note, new methods can be developed for clinical use for achieving the detection and/or therapy function for the theranostics in the body.

Finally, it is still a challenge to formulate controllable and reproducible synthesis processes for theranostics. As hybrid ceramics-based theranostics integrate more than one type of materials in one nanodevice, it is a perquisite to precisely control the synthesis parameters to avoid batch-to-batch variations (and person-to-person and group-to-group variations if the published work/developed process is to be repeated by others, or, later to be commercialized). Meanwhile, multiple steps are very likely to be involved and harsh chemicals are often used in the fabrication of hybrid theranostics using the current synthesis routes for these theranostics. Natural or eco-friendly synthesis of theranostics can be an important R & D direction to make existing theranostics and develop new theranostics, thereby producing them reproducibly and efficiently and reducing the adverse impact to the environment.

Because of these challenges and also other issues, US FDA has not approved any ceramic theranostics for clinical trial yet. Nevertheless, the published research results have demonstrated the high potential of ceramics theranostics for effective and efficient cancer management. As can be seen, a solid foundation has been laid for the development of hybrid ceramics-based theranostics albeit there are many obstacles to overcome for their eventual clinical applications. It is very encouraging to see that over the past few years, more research groups around the world are directing their effects towards the development of novel theranostics. With these efforts and also new researchers to join in this area, the future looks bright for further development, solving the problems in science, engineering, and medicine.

Authorship contribution statement

Qingwen Guan and Min Wang: research and design of the review; Qingwen Guan and Binbin He: research and drafting of the manuscript; Jie Huang, Helen H. Lu and Min Wang: writing, reviewing and editing

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