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Review

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# Construction of smart inorganic nanoparticle-based ultrasound contrast agents and their biomedical applications

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**Abstract** Ultrasound (US) imaging in combination with US contrast agents (UCAs) is a powerful tool in the modern biomedical field because of its high spatial resolution, easy access to patients and minimum invasiveness. The microbubble-based UCAs have been widely used in clinical diagnosis; however, they are only limited to the blood pool imaging and not applicable to the tissue-penetrated imaging due to their large particle size and structural instability. Inorganic nanoparticles (NPs), such as silica, gold and $Fe_xO_y$, featured with both satisfactory echogenic properties and structural stability have the potential to be used as a new generation of UCAs. In this review, we present the most recent progresses in the tailored construction of inorganic UCAs and their biomedical applications in the US imaging-involved fields. Firstly, the typical inorganic NPs with different structures including solid, hollow and multiple-layer forms will be comprehensively introduced in terms of their structure design, physicochemical property, US imaging mechanism and diverse applications; secondly, the recent progress in exploring the gas-generating inorganic NP system for US imaging purpose will be reviewed, and these intelligent UCAs are multifunctional for simultaneous US imaging and disease therapy; thirdly, several nanocomposite platforms newly constructed by combining inorganic UCAs with other functional components will be presented and discussed. These multifunctional NPs are capable of further enhancing the imaging resolution by providing more comprehensive anatomical information simultaneously. Last but not the least, the design criteria for developing promising UCAs to satisfy both clinical demands and optimized US imaging capability will be discussed and summarized in this review.

**Keywords** Inorganic nanoparticle · Ultrasound imaging · Theranostic · Contrast agent

## 1 Introduction

Ultrasound (US) imaging has been widely used around the world for clinical diagnosis, owing to several remarkable advantages including low cost, flexibility and non-radiative effect. However, the image resolution of US is generally inferior to the magnetic resonance imaging (MRI) and X-ray computed tomography (CT). To solve this problem, the US imaging contrast agents (UCAs) are widely introduced in the clinical examination [1, 2]. The UCA is acoustically active to externally applied US energy, resulting in the amplification of echo signals to offer enhanced imaging quality based on echogenicity difference between itself and surrounding tissues.

The microbubbles generated by agitated saline was the first generation of UCA, which was successfully used in 1968 by injection into the ascending aorta and cardiac chambers for echocardiographic imaging, producing strong echoes in the heart by the acoustic mismatch between air microbubbles and the surrounding blood stream [3]. In recent years, with the development of material science and industrial production, the second generation of the United States Food and Drug Administration (FDA)-approved UCAs, such as

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Sonovue®, Optison® and Definity®, has been successfully invented and clinically used [4]. Most of these UCAs consist of gas phase microbubbles using either liposome or protein as carriers. However, due to the relatively large particle diameter (generally in micrometer scale), they display short circulation time in human body owing to the rapid clearance by reticuloendothelial system (RES). Taking the Optison® as an example, the clinical results demonstrated that 96 % of perfluoropropane gas was eliminated within lungs within 10 min and a large scale of albumin shell was cleared during the liver circulation. Another issue with these UCAs is the short imaging time duration under continuous wave pressure because of the structure instability [5]. Although some nanometer-sized microbubbles have been or are now under development by introducing fluorocarbon liquid into the core of a core–shell structure, unfortunately, their stability in enhanced tumor imaging is still far from ideal. These organic UCAs are usually restricted to the diagnosis of a limited number of tissues/organs, such as vascular compartment [4, 6]. Thus, much efforts have been focused on the construction of more advanced UCAs satisfying the following requirements: (1) stable structure in circulation and US exposure; (2) small enough particle size for effective tumor accumulation and (3) high imaging quality [7].

Nanostructured inorganic materials, such as silica, magnetic NPs, quantum dots, have received great attentions in the field of biomedical application owing to their unique size-dependent physical properties [8–13]. Besides, the NPs could be readily conjugated with a large amount of molecules with the diverse functionalities in tumor-selective recognition, dispersity improvement, molecular imaging probe, etc. [14–16]. Meanwhile, the rational design of hybrid echogenic NPs with specific inorganic material can help to realize the multiple-modal imaging and therapy on one platform. Moreover, the inorganic composition has superior advantages such as excellent chemical stability compared to organic NPs, ensuring the longtime circulation in body and higher accumulation into tumor tissue. More attractively, recent studies demonstrated that inorganic NPs exhibited both satisfactory echogenic properties and structural stability in enhanced US imaging, which are expected to be used in different medical fields including cancer diagnosis, imaging-guided surgical treatment and stem cells labeling [17, 18]. Combining above factors, it is assured that the exploration of high-efficient inorganic UCAs, which are recognized here as third generation of UCAs, will bring great benefits to the biomedical researches and clinical practice. In this review, we focus on the very recent progresses made in these third-generation inorganic NP-based UCAs, including the designed construction, imaging mechanism and their extensive applications in US imaging-involved multimodal imaging.

## 2 Solid inorganic NPs as UCAs

The inorganic NPs with rigid structure could offer a better US imaging resolution compared to the soft ones, owing to the larger difference in acoustic impedance between solid phase and soft tissues [19]. Shklyar et al. [19] confirmed the acoustic properties of several metal oxides, such as $Al_2O_3$, $Fe_xO_y$ and $ZrO_2$, could satisfy the requirement for medical imaging of organs and tissues. They emphasized that the aggregations formed by nanometer-scaled metal oxides in aqueous media could critically contribute to the overall ultrasonic image brightness, though the individual particle with nanometer scale (around 50 nm) seems acoustically inactive in theory. Moreover, the experiment results evidenced that there was a direct correlation between the acoustic signal intensity and the degree of aggregation [20]. Inspired by this "aggregation" induced intensified imaging mechanism, introducing large NP aggregates into the cells has been becoming one of the efficient strategies to realize the real-time cell tracking by US imaging [21].

Among various nanomaterials for the construction of inorganic UCAs, the silica NPs received the greatest interest since they exhibit low cytotoxicity, low hemolytic activity and relatively higher biodegradability [22, 23]. For example, the silica has been approved to be safe by FDA [24–26]. Besides, Lu et al. [22] confirmed that silica NPs are biocompatible at high dosage of 100 mg/kg of mouse and could preferentially accumulate in tumor by the enhanced permeability and retention (EPR) effect. Thus, the silica NPs are feasible for the systemic administration through the bloodstream for cancer diagnosis and of great potential for the future clinical translation for US imaging. Chiriaco et al. [27] reported the feasibility of pure silica nanospheres for the enhanced US imaging at conventional diagnostic frequencies in a range from 7.5 to 10 MHz. They studied the size effect of silica NPs on the US imaging backscatter. It was demonstrated that the particles smaller than 50 nm can be hardly detected at a relatively low-volume concentration; however, the pronounced peak of US backscattering could be detected when particle size was around 330 nm at relatively higher frequencies (3.5 and 4.5 MHz). They also confirmed that the coating of silica NPs with nanodots (such as $Fe_3O_4$ and FePt) could be efficient for dual-mode MRI/US imaging; however, the US backscattering intensity slightly decreased compared to pure silica due to the roughness increment in structure nature which is a key factor affecting the US backscattering pattern.

The combined technique of US imaging and solid inorganic NPs is a powerful tool for labeling the stem cells. This real-time cell-tracking platform ensures the long-term monitoring of cells and thus favors the therapeutic efficacy enhancement in the cellular implantation surgery. Jokerst et al. [28] described a triple-modal stem cell imaging via