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Photoechogenic Inflatable Nanohybrids for Upconversion-Mediated Sonotheranostics

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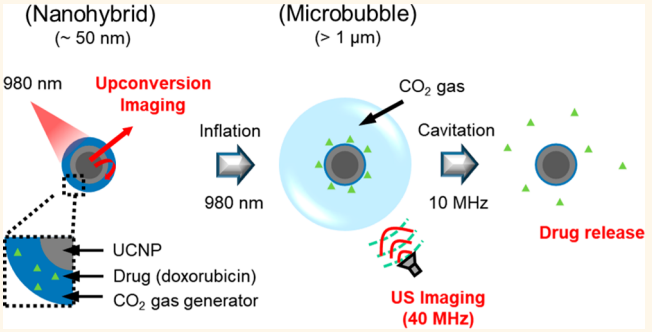
ABSTRACT: **Hybrid nanostructures are promising for ultrasound-triggered drug delivery and treatment, called sonotheranostics. Structures based on plasmonic nanoparticles for photothermal-induced microbubble inflation for ultrasound imaging exist. However, they have limited therapeutic applications because of short microbubble lifetimes and limited contrast. Photochemistry-based sonotheranostics is an attractive alternative, but building near-infrared (NIR)-responsive echogenic nanostructures for deep tissue applications is challenging because photolysis requires high-energy (UV−visible) photons. Here, we report a photochemistry-based echogenic nanoparticle for *in situ* NIR-controlled ultrasound imaging and ultrasound-mediated drug delivery. Our nanoparticle has an upconversion nanoparticle core and an organic shell carrying gas generator molecules and drugs. The core converts low-energy NIR photons into ultraviolet emission for photolysis of the gas generator. Carbon dioxide gases generated in the tumor-penetrated nanoparticle inflate into microbubbles for sonotheranostics. Using different NIR laser power allows dual-modal upconversion luminescence planar imaging and cross-sectional ultrasonography. Low-frequency (10 MHz) ultrasound stimulated microbubble collapse, releasing drugs deep inside the tumor through cavitation-induced transport. We believe that the photoechogenic inflatable hierarchical nanostructure approach introduced here can have broad applications for image-guided multimodal theranostics.**



KEYWORDS: *ultrasound, upconversion, near-infrared, microbubble, nanohybrid*

Highly echogenic gas-filled microbubbles (>1 μm) are staple ultrasound (US) contrast agents in the clinic.[1,2] When exposed to US energy, these microbubbles reflect echo signals for contrast-enhanced imaging. More recently, these microbubbles have been loaded with drugs and repurposed as sonotherapeutics,[3,4] where high-energy ultrasound is used to collapse the microbubbles for drug release. However, these preformed microbubbles are too large to cross biological barriers, resulting in poor targeting, low therapeutic efficacy, and undesired side effects. Ideally, echogenic particles are small enough to penetrate tissues but large enough to generate strong echo signals.

Hybrid nanostructures are attractive solutions because they are small and multifunctionality and cascade reactions that trigger the generation of echo signals can be systematically and hierarchically built into a single nanoparticle by combining organic and inorganic materials. These nanostructures, which respond to stimuli across different length scales and display multiscale properties, have been developed as sonotherapeutics *via* triggered drug delivery.[5,6] Biological barriers are of less concern with many of these nanoparticles because they respond to stimuli and form microbubbles *in situ* only after deep tissue delivery. In most cases, the nanoparticles have been fabricated to operate in response to endogenous stimuli such as temperature, pH, reactive chemical species, and other metabolites.[7−17] The problem is they produce weak echogenic contrast and/or premature drug leakage because the endogenous signals that trigger microbubble inflation are also present in normal tissues.[18]

Other echogenic hybrid nanostructures that respond to light (photoechogenic), including those responsive in the tissue-transparent near-infrared (NIR) window (700−1000 nm) for

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