Title:	Nontoxic In Vivo Clearable Nanoparticle Clusters for Theranostic Applications
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Abstract:	Disintegrable inorganic nanoclusters (GIONs) with gold seed (GS) coating of an iron oxide core with a primary nanoparticle size less than 6 nm were prepared for theranostic applications. The GIONs possessed a broad near-infrared (NIR) absorbance at ∼750 nm because of plasmon coupling between closely positioned GSs on the iron oxide nanoclusters (ION) surface, in addition to the ∼513 nm peak corresponding to the isolated GS. The NIR laser-triggered photothermal response of GIONs was found to be concentration-dependent with a temperature rise of ∼8.5 and ∼4.5 °C from physiological temperature for 0.5 and 0.25 mg/mL, respectively. The nanoclusters were nonhemolytic and showed compatibility with human umbilical vein endothelial cells up to a concentration of 0.7 mg/mL under physiological conditions. The nanoclusters completely disintegrated at a lysosomal pH of 5.2 within 1 month. With an acute increase of over 400% intracellular reactive oxygen species soon after γ-irradiation and assistance from Fenton reaction-mediated supplemental oxidative stress, GION treatment in conjunction with radiation killed ∼50% of PLC/PRF/5 hepatoma cells. Confocal microscopy images of these cells showed significant cytoskeletal and nuclear damage from radiosensitization with GIONs. The cell viability further decreased to ∼10% when they were sequentially exposed to the NIR laser followed by γ-irradiation. The magnetic and optical properties of the nanoclusters enabled GIONs to possess a T2 relaxivity of ∼223 mM–1 s–1and a concentration-dependent strong photoacoustic signal toward magnetic resonance and optical imaging. GIONs did not incur any organ damage or evoke an acute inflammatory response in healthy C57BL/6 mice. Elemental analysis of various organs indicated differential clearance of gold and iron via both renal and hepatobiliary routes.
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