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Magnetic-luminescent cerium-doped gadolinium aluminum garnet nanoparticles for simultaneous imaging and photodynamic therapy of cancer cells

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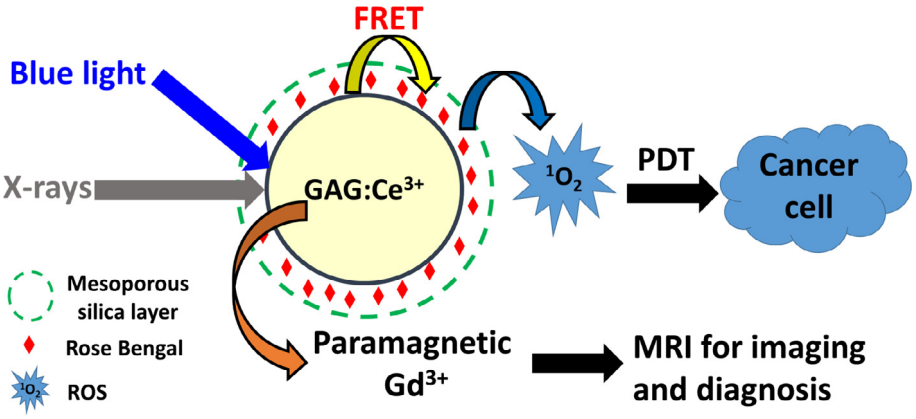
GRAPHICAL ABSTRACT



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ABSTRACT

Nanoparticle (NP) and photosensitizer (PS) conjugates capable of X-ray photodynamic therapy (X-PDT) are a research focus due to their potential applications in cancer treatment. Combined with X-PDT, appropriate imaging properties of the nanocomposite will make it suitable for theranostics of deep lying tumors. In this work, we describe the development of magnetic-luminescent $Gd_{2.98}Ce_{0.02}Al_5O_{12}$ nanoparticles (GAG) coated with mesoporous silica ($mSiO_2$) and loaded with rose bengal (RB) to yield a nanocomposite GAG@$mSiO_2$@RB capable of X-PDT. GAG nanoparticles were synthesized using the sol-gel method. The synthesized GAG nanoparticles showed a strong visible yellow emission with a quantum yield of ~32%. Moreover, the broad emission spectra of GAG nanoparticles centered at 585 nm showed a good overlap with the absorption of RB. Upon irradiation with X-rays (55 KV), the GAG@$mSiO_2$@RB nanocomposite produced significantly higher singlet oxygen compared with RB alone, as confirmed by the 1,2-diphenylisobenzofuran (DPBF) assay. The developed GAG@$mSiO_2$@RB nanocomposite significantly reduced the viability of human breast cancer (MDA-MB-231) cells upon irradiation with blue light

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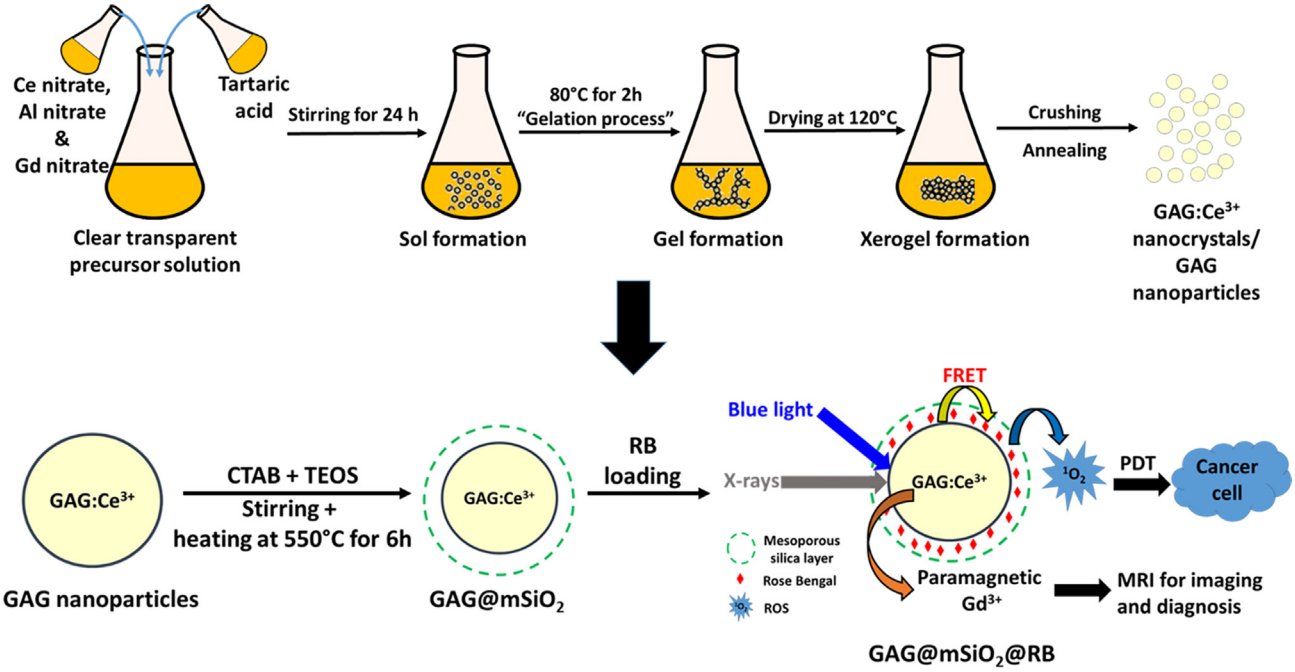
(λ = 470 nm). The calculated LC_{50} of GAG@mSiO_2@RB nanocomposites were 26.69, 11.2, and 6.56 μg/mL at a dose of ~0.16, 0.33 and 0.5 J/cm^2, respectively. Moreover, the nanocomposite showed paramagnetic properties with high magnetic mass susceptibility which are useful for high contrast T_1 weighted magnetic resonance imaging (MRI). Together with X-PDT, the paramagnetic properties of the proposed GAG@mSiO_2@RB nanocomposite system are promising for their future application in simultaneous detection and treatment of deep-lying tumors.

1. Introduction

Photodynamic therapy (PDT) has emerged as one of the most versatile minimal invasive modalities of cancer therapy [1]. In brief, a composite of inorganic or organic luminescent nanoparticles (donor) with a photosensitizer (PS) is developed in such a way that the emission wavelength of the nanoparticles falls within the absorption region of the PS molecule (spectral overlap). Due to the spectral overlap, the emitted energy is transferred from the donor to the PS, a phenomenon called Fluorescence Resonance Energy Transfer (FRET), which upon excitation emits reactive oxygen species (ROS). Various acceptor PS molecules such as porphyrin, zinc photocyanine, orginidium complex, verteporfin, and RB have been reported to produce ROS when excited with photons of proper wavelength [2–7]. As a donor rare-earth-doped nanoparticles are one of most popular choice due to their attractive optical and physicochemical properties such as strong photoluminescence (PL) emission, long luminescence decay lifetime, and non-photobleaching nature, tuning of emission and excitation wavelength, facile synthesis and surface functionalization strategies [8,9]. Due to the distinguished advantage of PDT in cancer theranostics, various rare-earth-doped core-shell nanocomposites have been proposed for PDT of cancer cells [10–14] (see Scheme 1).

The efficiency of PDT strongly depends upon the spectral overlap between the donor and acceptor PS molecule [15]. Therefore, a robust combination of donor and acceptor is necessary to obtain a highly efficient FRET system for PDT. However, high FRET efficiency between donor and acceptor could hinder their application in imaging and diagnostics due to two main reasons: (1) significant loss of luminescence output of the donor and (2) risk of harmful ROS generation upon photo-excitation of the donor-acceptor nanocomposite. Furthermore, poor penetration of light photons into the tissue is another factor that adversely disturbs the efficiency of PDT [16]. Lately, the development of nanocomposites with NIR excitation has significantly improved the efficacy of PDT [17–19]. However, NIR mediated PDT is effective for tumors seated only up to 1.5 cm beneath the skin [20]. Therefore, the development of novel multifunctional nanocomposites for the diagnosis and PDT of deep tumors is of great importance.

Conversely, X-rays due to their deep penetration power in tissues, have been utilized for PDT of deep-lying tumors [21]. For instance, Wang et al. reported the X-PDT of H1299 tumors with no side effects to normal tissues, using MC540 (photosensitizer) loaded mesoporous silica coated $SrAl_2O_4:Eu^{2+}$ nanoparticles [22]. At present, countable reports deal with the development of a nanocomposite system for X-PDT [23–26]. Most of these studies deal with X-PDT using porphyrin derivatives, which usually shows poor spectral overlap with the donor (rare-earth-doped nanoscintillator), thus resulting into reduced X-PDT efficacy [10]. Additionally, complicated surface modification process to conjugate the PS molecule to donor surface could lead to attenuation of luminescence output as well as the loss of available functional groups of



Scheme 1. Schematic representation of synthesis and construction of GAG@mSiO_2@RB nanocomposite for their potential application in imaging and deep PDT.