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Nanoscale upconversion for oxygen sensing

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ABSTRACT

Optical oxygen sensors have many promising qualities but rely on excitation by violet or blue wavelengths that suffer from high levels of scattering and absorption in biological tissues. Here we demonstrate an alternative method using 980 nm near-infrared light to initially stimulate ceramic upconverting nanoparticles (UCNPs) contained within a novel form, electrospun core-shell fibers. The emission of the UCNPs excites a molecular optical oxygen sensor, the subsequent phosphorescent emission being dynamically quenched by the presence of molecular oxygen. The potential for use of such an energy transfer within electrospun fibers widely used in biological applications is promising. However, current knowledge of such 'handshake' interactions is limited. Fiber-based carriers enabling such optical conversions provide unique opportunities for biosensing as they recapitulate the topography of the extracellular matrix. This creates a wide array of potential theranostic, fiber-based applications in disease diagnosis/imaging, drug delivery and monitoring of therapeutic response. Using a fiber-based vehicle, we observed gaseous oxygen sensing capabilities and a linear Stern-Volmer response allowing highly accurate calibration. Configurational aspects were also studied to determine how to maximize the efficiency of this 'handshake' interaction.

1. Introduction

In this paper we demonstrate that NIR stimulation of UCNPs contained within the shell of electrospun core-shell fibers can be used to produce blue (480 nm) light which in turn excites core-bound $Ru(dpp)_3Cl_2$ to produce a red (~625 nm) phosphorescence dynamically regulated by the amount of molecular oxygen present [1,2]. We refer to this overall process as a 'handshake' interaction between the UCNPs and the Ru complex to distinguish it from radiationless luminescence resonance energy transfer (LRET) [3].

Monitoring of local deep tissue oxygen concentrations in real-time could be achieved via this configuration, and such abilities are sought after in many biomedical applications. A potential specific application is the identification of hypoxic regions generated by cancerous tumors either in vivo or in vitro [4]. This ability would be especially relevant in detecting recurrence of glioma brain tumors. Gliomas often recur either at the original tumor site or within 2–3 cm [5–7]. However, gliomas must be at least 2.8 mm in diameter to be detectable by magnetic resonance imaging (MRI) [8]. Optical techniques of sensing local oxygen concentration could potentially be used to detect much smaller recurrences of gliomas because these tumors contain highly hypoxic regions [9]. Tumor oxygenation is a known indicator of metastatic potential [10], because hypoxia triggers mechanisms of tumor cell dispersion and apoptotic resistance [11–13]. As a result, traditional radiation and chemotherapy treatments are often ineffective in attacking cells found in such regions of low oxygen content [14,15]. In fact, both hyperbaric oxygen therapy and oxygen diffusion-enhancing compounds, such as trans sodium crocetinate (TSC), have been used to re-oxygenate hypoxic tumor tissue to render it more sensitive to radiation [16].

Due to their unique optical properties, upconverting nanoparticles (UCNPs) have enjoyed growing interest in such novel applications [17,18]. Via a multi-photon process, UCNPs can absorb near-infrared (NIR) light and emit visible light [19,20]. This anti-Stokes process makes them especially attractive for bioimaging applications due to the absence of 'blinking,' the lack of background auto-fluorescence, and the increased penetration depth characteristic of NIR light [17,21,22]. NIR can penetrate tissue more easily than visible light due to decreased levels of absorption and scattering. Rayleigh scattering decreases with increased wavelengths, while absorption is also low in the NIR region [23]. UCNPs are excited by 980 nm NIR light which falls within the

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600–1300 nm "optical window" for enhanced light transmission through biological tissue [22]. This window is bound by high pigment (i.e., hemoglobin) absorption at lower visible wavelengths and strong water absorption at higher wavelengths [22,24].

The optical properties of UCNPs may also make them useful for sensing applications. While a variety of luminescent probes can be used in sensors (i.e., for measuring local chemical concentrations), their reliance on visible wavelengths limits their applications in visually opaque biological environments or in tissues that are anatomically isolated and difficult to interrogate by non-invasive methodologies, such as the central nervous system. By using UCNPs in conjunction with luminescent probe molecules, the sensing of local chemical conditions can be extended to biological applications in which light energy must travel through a thick layer of tissue (including high-scattering tissue such as bone) to excite a chemical sensor.

One particularly useful application of UCNPs is the local excitation of co-localized oxygen-sensitive probes (i.e. organometallic complexes and metalloporphyrins), which exhibit a luminescence quenched in proportion to the amount of oxygen present. We have incorporated UCNPs ($LiYF_4$:Yb,Tm) with the oxygen-sensitive molecule tris(4,7-diphenyl-1,10-phenanthroline) ruthenium (II) dichloride ($Ru(dpp)_3Cl_2$) into electrospun core-shell fibers. Despite the longer lifetimes and, therefore, increased oxygen-sensitivity of such porphyrins as palladium (II) and platinum (II) tetrakis(pentafluorophenyl)porphyrin (PdTFPP and PtTFPP) [4,25], $Ru(dpp)_3Cl_2$ was chosen due to its broad absorption peak that overlaps efficiently with the upconverter emission at 480 nm [26–28]. The detailed electronic interactions between the UCNPs and the ruthenium complex are shown in Fig. 1. The $LiYF_4$:Yb,Tm contains sensitizer and activator ions, Yb^{3+} and Tm^{3+}, respectively. Yb^{3+} allows for 980 nm light to be absorbed (by its $^2F_{5/2} \leftarrow {}^2F_{7/2}$ transition), while Tm^{3+} allows for the emission of blue light (by its $^1G_4 \rightarrow {}^3H_6$ and $^1D_2 \rightarrow {}^3F_4$ transitions) [1]. The oxygen-sensitive $Ru(dpp)_3Cl_2$ then absorbs blue light radiatively emitted by the UCNPs to undergo a metal-to-ligand charge transfer in which a *d* orbital Ru electron is raised into a π^* ligand orbital. The subsequent decay results in a red (~625 nm) emission quenched by the presence of oxygen to dynamically regulate the ruthenium complex's phosphorescence [2].

To demonstrate this concept using a widely utilized biomaterial form, we incorporated UCNPs and an oxygen-sensitive complex into core-shell electrospun fibers with the goal of fabricating a nanoscaled carrier that could potentially be introduced in biological systems for long-term, minimally invasive, optical interrogation. In this method, multiple feed systems are utilized in the electrospinning process to create two separate flows each containing different polymer-based solutions. One solution becomes the core, the other the shell. A representative cross-section of a coaxial fiber is shown in Fig. 2. These core-shell electrospun polymeric fibers are an ideal matrix for several reasons. In general, electrospun fibers are useful for biological applications due to their biomimetic topography and their greatly enhanced surface-to-volume ratio [29]. We have shown that the small scale and increased surface area imparted by the fiber morphology greatly decreases the response time relative to these film counterparts in oxygen sensing applications [30]. Additionally, core-shell electrospinning allows polymers that could not normally be easily electrospun to be incorporated as a 'core.' [31] Core-shell polymers have also been used in drug release applications and are of growing interest in biological applications due to the ability to easily design and select a biocompatible 'shell' that shields cells from both the chemistry and the contents of the core [29]. The core-shell structure offers flexibility in the placement of the UCNPs and the oxygen-sensitive complex, and a choice must be made as to whether to collocate or separate these individual components based on their effects on sensor performance. Since the dimensionality of the system components are nanoscaled, diffusional equilibrium is obtained within microseconds whether the components are either collocated or separated into the core and shell.

Current combinations of UCNPs and optical sensing molecules are limited but some efforts have been carried out [32–37]. Achatz et al. studied the upconversion of NIR light by $NaYF_4$:Yb,Tm into wavelengths suitable for the excitation of an oxygen-sensitive iridium complex in an ethyl cellulose film [34]. Lv et al. and Liu et al. recently demonstrated this idea in a nanoparticle form, where luminescence resonance energy transfer occurs between an upconverting nanoparticle and oxygen-sensitive molecules contained within its shell [32,37]. However, many configurational aspects of the 'handshake' interaction have not been

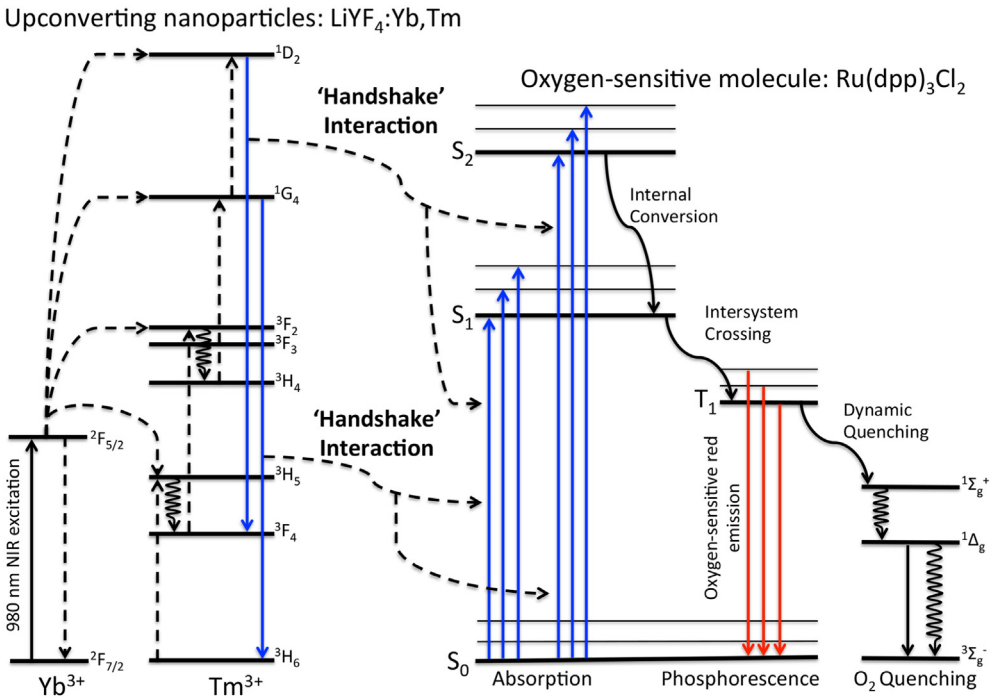

Fig. 1. Energy levels depicting the electronic 'handshake' between $LiYF_4$:Yb,Tm upconverting nanoparticles and $Ru(dpp)_3Cl_2$.