Volume 1 | Number 1 | Jan 2013 | Pages 1–100

Nanoscale

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A paradigm shift in the excitation wavelength of upconversion nanoparticles

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The past two decades witnessed the emergence of upconversion nanoparticles (UCNs) as promising luminophores finding multifarious uses from biological studies to solar cells. Progress in its practical use, however, has been hampered by requirements to be excited within a narrow absorption band around 980 nm. Since the main constituent of biological tissue – water - absorbs strongly in this region (Fig. 1a), significant reduction in penetration depth is anticipated as the 980 nm light gets attenuated travelling through tissues, besides also risking tissue damage from overheating effect (Fig. 1b). Just recently, remarkable efforts to engineer the excitation of UCNs to a more suitable wavelength for biological applications were reported[1-6].

UCNs exhibit a unique phenomenon of absorbing low-energy photons and emitting higher-energy light. By co-doping sensitizer and activator ions in matrices such as $NaYF_4$ and $NaGdF_4$, low-energy near-infrared (NIR) photons absorbed by sensitizer ions can be successively transferred to nearby activator ions[7,8] that get further excited to emit photons of higher energy[9,10]. Various activator ions, typically erbium (Er^{3+}), thulium (Tm^{3+}) and holmium (Ho^{3+}) have been used but ytterbium (Yb^{3+}) remained the choice sensitizer ion for classical UCNs. The narrow maximum absorption of Yb^{3+} at 978 nm, however, restricts the excitation wavelength that could excite UCNs. Commendable effort to excite UCNs with another absorption peak of Yb^{3+} at 915 nm has been made[11], albeit at a compromised excitation efficiency. The weaker luminescence emitted is however insufficient for effective photoactivation. It is thus imperative to shift the excitation of UCNs to shorter NIR wavelengths where water absorbs minimally, without sacrificing its excitation efficiency.
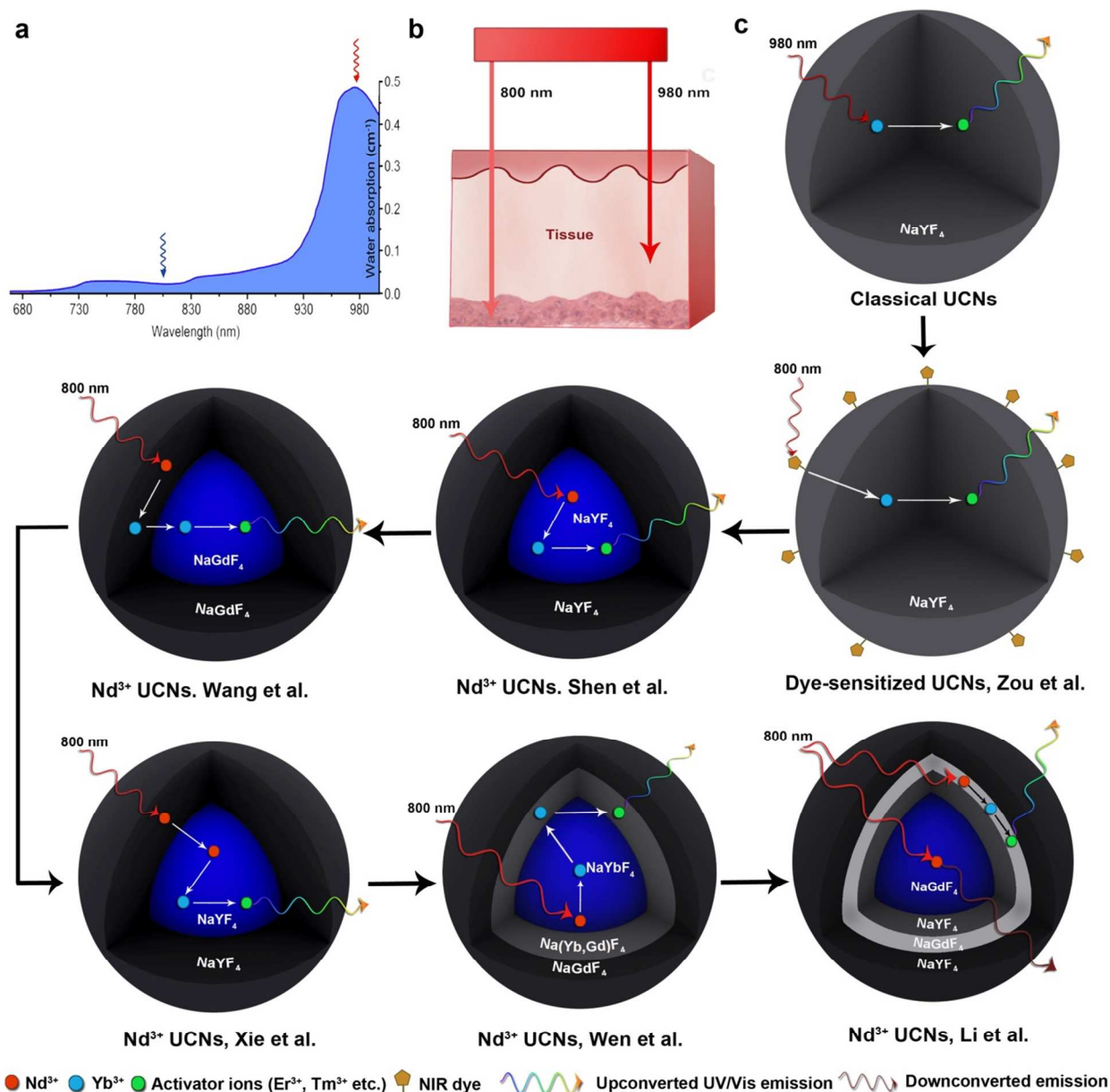
Figure 1 | Shifting the excitation wavelength of UCNs to a more appropriate range for biological applications. **a,** Absorption of water in the NIR region. **b,** Schematic comparison of 800 nm versus 980 nm light penetration depth in tissue. **c,** Chronological evolution of shifting the excitation wavelength of UCNs from classical 980 nm to 800 nm.

In 2012, Zou *et al.* opened the door to tune the excitation wavelength of UCNs. Reporting in *Nature Photonics*[1], they introduced a novel concept of harvesting light over a broad region in the shorter NIR wavelengths (740 to 850 nm) by NIR dye-sensitized UCNs. The surface-bound NIR dye serves as an antenna absorbing light in the specified spectrum for Förster Resonance Energy

Transfer (FRET) to UCNs core to produce an upconverted light (Fig. 1c). The NIR dye-sensitizer can be flexibly changed to other organic dyes, thus allowing broadband tuning of UCNs excitation over the desired spectrum. It is foreseeable, though, that the dye could leach out from the nanoparticles over time in biological environments. Furthermore, unlike UCNs, organic dyes succumb to photobleaching, thus making these dye-sensitized UCNs unsuitable for long-term imaging/activation applications.

Just a year later, five groups separately tackled this problem by replacing the organic dye with neodymium (Nd^{3+})[2-5] (Fig. 1c). Nd^{3+} were doped into a typical sensitizer/activator UCN system to serve as a primary sensitizer, taking over the role of Yb^{3+} as the main NIR absorber while Yb^{3+} now serves as a bridging sensitizer to facilitate energy transfer from Nd^{3+} to the activator ions. Nd^{3+} would kick-start the energy transfer cascade by absorbing NIR photons for transfer to nearby Yb^{3+} that in turn initiate a typical upconversion process with the activator ions. As Nd^{3+} displays an absorption maximum around 800 nm, its doping is expected to extend the excitation of UCNs from the 978 nm band characteristic of Yb^{3+} to the 800 nm of Nd^{3+}, altogether alleviating the short penetration depth and overheating effect associated with the former.

A notable challenge in previous effort to find a replacement for the organic dye sensitizer is the difficulty in choosing the right element that can efficiently execute the transfer of excitation energy to Yb^{3+}. Shen *et al.*[2] was the first to introduce the concept of replacing organic dye with Nd^{3+} as sensitizers. They proved that doping Nd^{3+} with Yb^{3+} and activator ions Er^{3+}/Tm^{3+} in the UCN core allows successful energy transfer from $Nd^{3+} \rightarrow Yb^{3+} \rightarrow Er^{3+}/Tm^{3+}$. Packing all the lanthanide ions in the same matrix, however, limits the amount of Nd^{3+} that can be doped since deleterious energy transfer from activator ions to Nd^{3+} via cross-relaxations can occur. Such a design thus affords only up to 1% Nd^{3+} doping, leading to poor NIR absorption and consequently weak upconverted emission. An attempt to separate Nd^{3+} and activator ions was made by Wang and colleagues[3] who adopted a core-shell strategy comprising of $NaGdF_4$:Yb,Er(Tm,Ho) core and $NaGdF_4$:Nd,Yb shell. By confining Nd^{3+} to the shell and thus spatially separating it from activator ions in the core, an elevated Nd^{3+} doping of 10% was achieved. Xie *et al.*[4] further improved this to 20 % Nd^{3+} doping by utilizing an optimized active-shell approach. In their core-shell architecture made up of $NaYF_4$:Nd,Yb,Er(Tm,Ho) core and $NaYF_4$:Nd shell, Nd^{3+} was doped in both the core (1-2 %) and shell (20 %), while co-doping of Yb^{3+} with Nd^{3+} in the shell

was disallowed to reduce surface quenching of Yb^{3+}. Shortly later, a novel design by Wen and peers[5] outperformed all previously reported doping of Nd^{3+} into UCNs. With a rich core-shell-shell architecture of $NaYbF_4$:Nd core, $Na(Yb,Gd)F_4$:Er(Tm,Ho) inner shell and $NaGdF_4$ outer shell, a phenomenal 50 % Nd^{3+} doping in the core was achieved. Doping Nd^{3+} in the core instead of the shell is indeed strategic since it does not render surface defect on the UCN. Hence, this enables a high Nd^{3+} doping in the core besides maintaining spatial separation from activator ions in the inner shell. Yb^{3+} doped in the core and inner shell is necessary to efficiently bridge energy transfer from excited Nd^{3+} in the core to activator ions in the inner shell. The outer $NaGdF_4$ shell elegantly serves as a protective shield against surface quenching and also a means to tune the upconversion emission through optional doping of activator ions. Indeed, this incremental progress in Nd^{3+} doping of UCNs for improved upconversion fluorescence has paved the way in shifting its excitation wavelength from classical 980 nm to 800 nm. Aside from this, Li *et al.*[6] recently reported a four-layer core-shell-shell-shell strategy to dope Nd^{3+} into UCNs that enabled a unique dual-mode up- and down-converting luminescence to be emitted under a single 800 nm excitation. Apparently, Nd^{3+} also provides a means to have down-conversion luminescence under the same 800 nm excitation and it is undisputed that such NIR-to-NIR down-conversion having both excitation and emission wavelengths within the optical transmission window where light is minimally absorbed by biomolecules[12], is unmatched when used for *in vivo* imaging[13-15] as it allows deep access to the biological specimen being investigated besides producing a high contrast. The down-conversion luminescence of Nd^{3+} was achieved by doping it at an optimum concentration of 5 % into the core comprising of a $NaGdF_4$ matrix while up-conversion luminescence was concurrently achieved in the second shell that has the same $NaGdF_4$ matrix but was packed with Nd^{3+}, Yb^{3+} and activator ions Er^{3+}. The intervening and outermost shell comprised of inactive $NaYF_4$ matrix layers that serve as protective shields against unwanted energy transfer between the down- and up-converting processes (first shell) as well as to minimize surface defects and external deactivators (outermost shell). A better design, however, is warranted as packing all the lanthanide ions in the second shell limits the doping of Nd^{3+} to only 0.5 %, beyond which the up-conversion emission was observed to quench due to the aforementioned deleterious energy transfer from activator ions to Nd^{3+} via cross-relaxations. Collectively, these Nd^{3+}-sensitized UCNs fluoresce well with no photobleaching under 800 nm excitation[2], comparable to that of classical UCNs under 980 nm excitation[4]. Importantly, they

exhibit superior penetrability through water[2] and pork skin[5,6], and a lowered heating effect in solutions[2,5] and *in vivo*[3,6] with 800 nm than 980 nm excitation.

Undeniably, Nd^{3+}-sensitized UCNs holds potential of being the next generation of luminophore, resolving the long-standing problem of a 980 nm excitation requirement. Shifting the excitation of UCNs to shorter wavelength in the therapeutic window where water absorbs minimally is a major game changer foreseen to be routinely adopted in all future upconversion systems. It remains to be seen how far this new luminophore advances the imaging, diagnostic and therapeutic capabilities of current upconversion technology.

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