from the pristine silica particles. The pathobiological effect observed after 30 s of corona formation does not seem to alter significantly with longer incubation times.

The work of Tenzer and colleagues illustrates that a well-characterized protein corona can provide insights into the biocompatibility of a specific nanoparticle. There is, however, still much work to do. We have repeatedly seen that the material, size and surface modification of a nanoparticle will affect the composition of the biological material that will be adsorbed onto it, which suggests that all relevant nanomaterials need to be thoroughly characterized. Also, the question of the existence of a 'soft' corona (a protein layer that interacts with the hard protein corona and/or with the 'free' particle surface) is still disputed today and needs to be addressed. The presence of a soft corona could alter the interaction of the hard corona with the surrounding biological environment, affecting the nanoparticles' usefulness within nanomedicine and their toxicity. Similarly, how materials that are designed to have as little protein adsorption as possible, such as PEGgylated nanoparticles, interact with a biological surrounding also needs to be examined. ❐

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References
1. Gref, R. *et al. Colloids Surf. B* **18,** 301–313 (2000).
2. Cedervall, T. *et al. Proc. Natl Acad. Sci. USA* **104,** 2050–2055 (2007).
3. Lundqvist, M. *et al. Proc. Natl Acad. Sci. USA* **105,** 14265–14270 (2008).
4. Lundqvist, M. *et al. ACS Nano* **5,** 7503–7509 (2011).
5. Billsten, P., Freskgård, P.-O., Carlsson, U., Jonsson, B.-H. & Elwing, H. *FEBS Lett.* **402,** 67–72 (1997).
6. Tenzer, S. *et al. Nature Nanotech.* **8,** 772–781 (2013).

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NANOCRYSTALS

Shining a light on upconversion

By using lanthanide-doped upconversion nanoparticles, fibre-optic sensors can display sensitivities several orders of magnitude greater than those of existing fluorescent techniques.

Yuhai Zhang and Xiaogang Liu

Optical fibres can transmit energy in the form of light pulses over long distances due to total internal reflection, and have been key tools in the telecommunications and biomedical industries. Because of their fast response times, optical fibres are also used to sense molecules. However, their ability to sense molecules at low concentrations is limited due to noise. Significant levels of background noise can be produced in the fibres by impurities that absorb and immediately re-emit light, usually at longer wavelengths than that of the absorbed light[1]. Lanthanide-doped nanoparticles have previously been used to avoid this background noise[2]. These nanocrystals have long lifetimes and anti-Stokes luminescence, which is the re-emission of one photon with shorter wavelength on absorbing two or more photons of longer wavelengths, a process known as upconversion[3]. However, the use of such upconversion nanocrystals as luminescent bioprobes has so far been hampered by their weak emission peaks and low quantum efficiency[4]. Writing in *Nature Nanotechnology*, Dayong Jin and colleagues at Macquarie University, University of Adelaide, Peking University and Shanghai Jiao Tong University now report an approach that addresses the issue of low-emission signal strength in upconversion nanoparticles, and also present an intriguing assay platform for the rapid and highly sensitive detection of organic and biological species[5].

The key element of the approach is the high-power illumination of heavily thulium-doped upconversion nanoparticles with ytterbium sensitizers ($NaYF_4$:Yb/Tm). High doping levels of thulium ions, which act as luminescent centres or activators, are used to maximize the transfer of the excitation energy absorbed by the ytterbium sensitizers. However, high dopant concentrations have been found to result in quenching of the luminescence due to cross-relaxation[6]. To prevent this concentration quenching, previous works have used a relatively low concentration (typically less than 2 mol%) of activators. In these conditions, the efficiency of upconversion increases with increased excitation power, but quickly saturates for relatively low powers[7].

Jin and colleagues propose that an enhancement of upconversion emission can be achieved by applying high-power radiation fluxes onto upconversion nanocrystals with high thulium content[5]. They argue that interactions between heavily doped activators may lead to an increased saturation power. The researchers built a microstructured optical fibre with a suspended-core design (Fig. 1a), in which the laser excitation (wavelength of 980 nm) is confined in a micrometre-sized core, providing a power density as high as 2.5×10^6 W cm^{-2}. Unlike conventional core-cladding optical fibres, this suspended-core fibre provides three parallel hollow channels allowing for the capture of upconversion nanoparticles dispersed in solution. The nanoparticles near the fibre core are excited and their emission can be collected at the excitation end of the fibre. By examining the dependence of saturation power on thulium ion concentration, Jin and colleagues find that the integrated emission intensity increases with thulium concentration, with no signs of saturation up to 8 mol% for a pump power of 2.5×10^6 W cm^{-2}, leading to a 70-fold emission enhancement.

The mechanism behind the unsaturated activator emission for heavily doped nanocrystals in the presence of high pump power, and the corresponding observed enhancement in luminescence, is attributed to high doping levels. For high concentrations of thulium ions, their interionic distance decreases, boosting the probability of cross-relaxation between ions[8,9]. The observed emission enhancement may be due to the fact that cross-relaxation plays distinct roles in mediating the energy-transfer process with different pump powers. Thulium ions have four important energy states for optical transitions labelled $^3H_6$, $^3H_5$, $^3H_4$ and $^1G_4$ (Fig. 1b). Under low-power excitation, the cross-relaxation processes between $^1G_4$–$^3H_4$ and $^3H_6$–$^3H_5$ optical transitions are responsible for the concentration quenching of emission

from the $^1G_4$ state of the thulium ions. By comparison, a super-intense laser beam can assist in exciting the thulium ions, which are populated in the $^3H_4$ intermediate state through cross-relaxation, to higher-energy states. The combination of high-power excitation and cross-relaxation thus gives rise to enhanced upconversion emission of the nanoparticles.

The difference in upconversion intensity, induced by applying different power densities, is utilized by Jin and colleagues as a proof-of-concept demonstration for security printing. The researchers printed two different patterns on two layers using the nanoparticles doped with high and low activator concentrations, respectively. The pattern printed with the high activator concentration cannot be observed under weak illumination conditions and can only be visualized at a high power density. Furthermore, the combination of the high-power optical fibre and the heavily doped nanoparticles enables single-particle detection of these nanocrystals in solution within the hollow fibre. Two main factors contribute to the record high sensitivity: improved signal strength through the concentration enhancement effect, and background noise reduction.

A caveat of this work is that the lifetime data of $^1G_4$ versus thulium concentration were not included. Such information is essential for understanding the complex energy-transfer process in heavily doped nanoparticles. It would also be interesting to test nanoparticles doped with other activator ions, such as erbium and holmium. Nonetheless, Jin and colleagues present an important work that may be applied to rapid molecular sensing. Moreover, this fibre system may help in the development of new imaging methods, for example, real-time *in vivo* endoscopic imaging. ❐

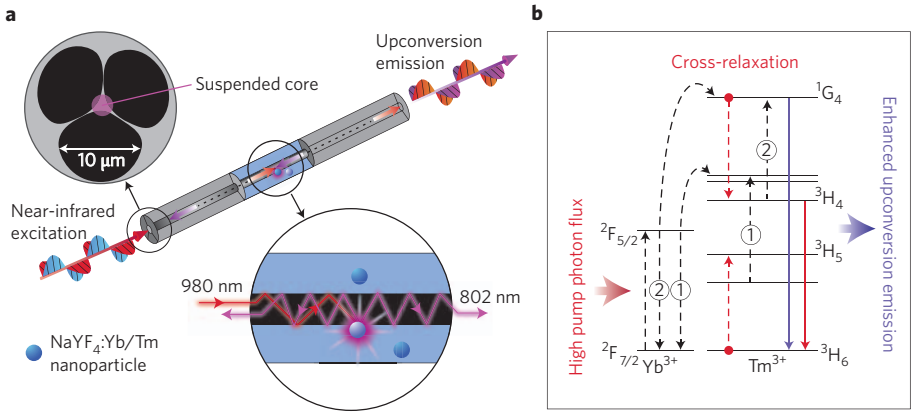

Figure 1 | An optical fibre coupled to upconversion nanoparticles. **a**, Schematic showing an optical sensor design that combines a suspended-core optical fibre with $NaYF_4$:Yb/Tm upconversion nanoparticles dispersed in the three hollow channels. A ray of light generated from a 980-nm diode laser is directed into the thin glass core of the fibre from one end and guided to the other end, which is immersed in a solution of upconversion nanoparticles. Note that only nanoparticles in close proximity to the glass core are excited by an evanescent wave. **b**, Simplified energy-transfer mechanism in $NaYF_4$:Yb/Tm nanoparticles under high-density excitation. Cross-relaxation (or self-quenching) between a pair of thulium ions (one in the excited state and the other in the ground state) dominates in nanoparticles with a high thulium dopant content, resulting in both thulium ions occupying two intermediate excited states. High pump power promotes optical transitions of the thulium ions from these intermediate states to higher-energy states by supplying high-density photons, leading to enhanced upconversion emission. The four main energy states for optical transitions in the thulium ion are $^3H_6$, $^3H_5$, $^3H_4$ and $^1G_4$. The transition states of an ytterbium ion that absorb energy from a 980-nm laser are $^2F_{5/2}$ and $^2F_{7/2}$. Steps 1 and 2 represent two subsequent energy-transfer processes from the ytterbium to thulium ions.

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References

1. Schartner, E. P., Ebendorff-Heidepriem, H., Warren-Smith, S. C., White, R. T. & Monro, T. M. *Sensors* **11,** 2961–2971 (2011).
2. Wang, F. *et al. Nature* **463,** 1061–1065 (2010).
3. Auzel, F. *Chem. Rev.* **104,** 139–174 (2004).
4. Boyer, J.-C. & van Veggel, F. C. J. M. *Nanoscale* **2,** 1417–1419 (2010).
5. Zhao, J. *et al. Nature Nanotech.* **8,** 729–734 (2013).
6. Yin, A., Zhang, Y., Sun, L. & Yan, C. *Nanoscale* **2,** 953–959 (2010).
7. Liu, H. *et al. Nanoscale* **5,** 4770–4775 (2013).
8. Su, Q. *et al. J. Am. Chem. Soc.* **134,** 20849–20857 (2012).
9. Zhou, B., Lin, H. & Pun, E.-Y. B. *Opt. Express* **18,** 18805–18810 (2010).

DNA COMPUTING

Molecules reach consensus

DNA molecules can be programmed to execute any dynamic process of chemical kinetics and can implement an algorithm for achieving consensus between multiple agents.

Ehud Shapiro and Tom Ran

The intersection of computer science and molecular biology is a fertile ground for new and exciting science. Two notable examples of this are molecular computing and molecular programming. Molecular computing is the use of molecules, and typically biological molecules, to create programmable autonomous computing devices[1–7]. Whereas molecular programming is the use of computer programming languages to describe, simulate, analyse and even engineer the behaviour of molecular systems, and typically systems made of biological molecules[8–12]. Writing in *Nature Nanotechnology*, Georg Seelig and colleagues[13] at the University of Washington, Microsoft Research in Cambridge, the California Institute of Technology and the University of California, San Francisco have now shown that the fields of molecular computing and molecular programming can join forces to create programmable chemical controllers