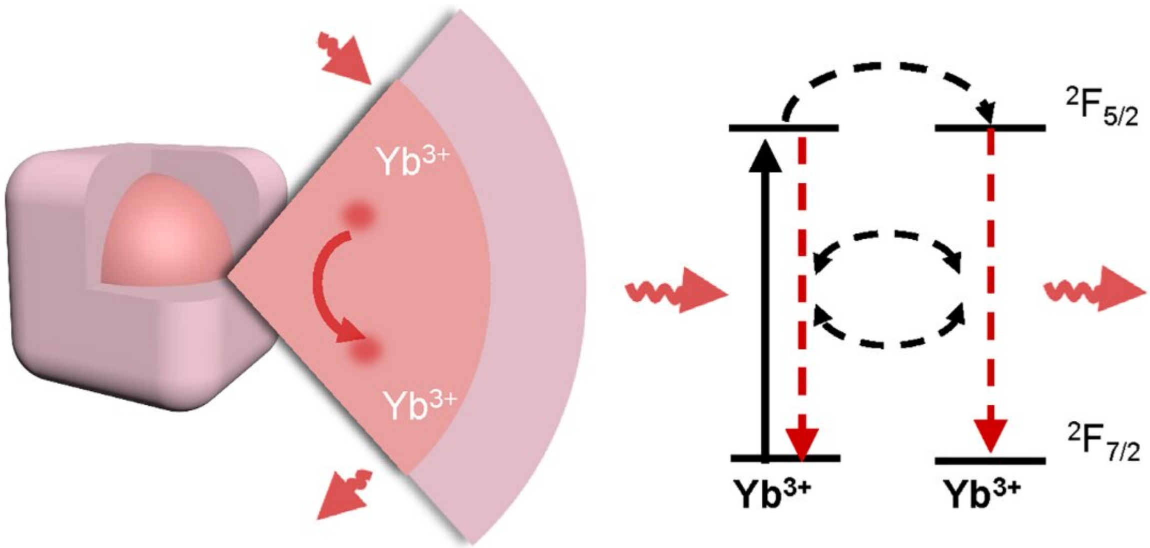
Thinking outside the box: 'Seeing' clearer and deeper into live organs

May 20 2019



New material design and photonics technology permit over 5,000 pure ytterbium emitters to be condensed within a 10 nm crystal matrix without quenching, effectively overcoming the issue of 'concentration quenching'. Credit: University of Technology Sydney

Scientists using a unique approach have developed a new biomedical imaging contrast agent. They say the breakthrough overcomes a major challenge to "seeing" deeper into live tissue, and opens the way for significant improvements in optical imaging technology.

The development, a result of international collaboration between Fudan

University in China and the University of Technology Sydney (UTS), has the potential to take bio-imaging resolution beyond what is currently possible with CT and PET imaging technology. The research is published in *Nature Photonics*.

Professor Dayong Jin, a senior author on the study and Director of the UTS Institute for Biomedical Materials & Devices (IBMD), said "this outcome is a great example that shows how we transform advances in photonics and material sciences into revolutionary biotechnologies at IBMD".

Optical contrast agents are used primarily to improve the visualisation and differentiation in tissue and blood vessels in both clinical and research settings.

To optimize the brightness of a contrast agent, and to efficiently illuminate single cells and biomolecules, the challenge lies in overcoming a limitation in physics, called "concentration quenching". This is caused by the cross relaxation of energy between emitters when they are too close to each other, so that having too many emitters leads to a quenching of the overall brightness.

"The new approach in this research was to unlock the concentration quenching effect by using the pure rare earth element ytterbium that only has a single excited state to avoid inter-system cross relaxation", explained by Professor Jin, "so that a network of over 5,000 pure ytterbium emitters can be tightly condensed within a space of 10 nm in diameter, a thousand times smaller than a cell".

At this emitter density all possible atomic doping sites are occupied by ytterbium within the crystal lattice structure, and once properly passivated (made unreactive), by a thin layer of biocompatible calcium fluoride, the material is free of concentration quenching.

"This enables the efficiency of photonics conversion to approach the theoretical limit of 100%. This not only benchmarks a new record in photonics and material sciences, but also opens up a lot of potential applications", Professor Jin said.

Lead author on the paper, Mr Yuyang Gu, a Ph.D. student at Fudan University, said "using this new contrast agent in a mouse model allowed us to see through whole mice".

The fundamental physics of the fluorescent probes used in optical imaging means there is only a narrowly defined near infrared (NIR) "window" [optical transparency window] beyond which visible light cannot penetrate tissue. To design a contrast agent that both absorbs and emits in the NIR without losing the energy is difficult.

"Although ytterbium has a 'pure energy' level that helps protect photons absorbed in the NIR band before being emitted, with negligible loss of energy, the simple excited state only permits emissions in the very similar band of NIR, which makes it impractical to use the conventional colour filters to discriminate the emissions from the highly scattering environment of laser excitation", Professor Jin said.

"The research needed 'new physics'. We really had to think outside the box."

Instead of spectrally "filtering" the signal emissions, the researchers further employed a time-resolved technique that paused the excitation light, and took advantage of the "photon storage" property of ytterbium emitters, slowing down the emission of light, long enough to allow a clearer separation between the excitation and emission of light in the time domain. Professor Jin likens this phenomena to the scenario when, after powering off a TV, the long-lived fluorescence of a "ghost" image is seen as an afterglow in the darkness.

For the past five years, Professor Jin and his team have developed a library of Super Dots, ?-Dots, Hyper Dots and Thermal Dots as multiphoton luminescent probes for sensing and imaging applications.

"This outcome is another quantum leap, bringing us a new set of research capacities towards the development of more efficient and functional nanoscale sensors and biomolecular probes" Professor Jin added.

Fudan University Chief Investigator, Professor Fuyou Li said "This is a 'new' luminescent process with high efficiency. We hope to find more suitable applications based on the fine tuning of the decay process of such kind of probes."

The combined use of high density of ytterbium emitters and time-resolved approach meant it was possible to maximise the number of emitters, the light conversion efficiency and the overall brightness of the contrast agent, and thereby significantly improving detection sensitivity, resolution and depth.

Professor Jin said that it was another example of how breakthroughs in physics can lead to the development of new and improved medical technologies citing the evolution, and revolution, in diagnostic methods such as X-rays, CT and PET imaging.

More information: High-sensitivity imaging of time-domain nearinfrared light transducer, *Nature Photonics* (2019). DOI: 10.1038/s41566-019-0437-z ,
www.nature.com/articles/s41566-019-0437-z

Provided by University of Technology, Sydney