BIOLOGICAL LABELS

Here comes the spaser

Plasmonic nanolasers embedded in living cells and animal tissues are shown to emit strongly, making them promising potential biocompatible probes.

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Cancer tumours are known for their ability to proliferate or metastasize. This happens through cancer cells spreading through the blood circulation to distant organs by the so-called circulating tumour cells (CTCs). Detection of these CTCs remains a challenge due to their very low concentrations (one cell within millions of normal blood cells) and their plasticity, which enables their shape and expression to change from those of typical marker proteins[1]. Thus, it is of primary importance to be able to find and differentiate them from normal blood cells. For this purpose, one highlights the cancer cells by marking them with labels that are usually fluorescent objects: dye molecules or tiny semiconductor nanospheres called quantum dots. Writing in *Nature Communications*, Vladimir Zharov and colleagues[2] propose the use of spasers as alternative biological labels.

The spaser (surface plasmon amplification by stimulated emission of radiation) is the plasmonic counterpart of the laser, with photons (quanta of the electromagnetic field) replaced by surface plasmons (quanta of electromechanical oscillations); it was proposed in 2003 (ref. 3) and developed further later[4–8]. In a spaser, the cavity (resonator) of a laser is replaced by a metal nanoparticle (the spaser core), which supports surface plasmons whose fields are tightly localized in the vicinity of this core. Excitation of the spaser with an external laser pump generates electron–hole pairs in the spaser shell and stimulated near-field emission of coherent plasmons into the metal nanoparticle core (Fig. 1a,b). To date, spasers of many configuration and sizes have been reported to emit in a wide spectral range, from ultraviolet, across all visible, and into mid-infrared.

The main requirement for biological labels, in order for them to be clearly distinguishable from light scattering produced by the living tissues[9], is bright emission of a characteristic colour under optical illumination. For *in vivo* use, these labels should be biocompatible and non-toxic for humans. Some of the labels can also be used for therapy — particularly for photodynamic[10] or thermal therapy[11], where cancer cells are killed by the photo-production of chemically active singlet oxygen or heat, respectively.

The fundamental advantage of the spaser over the conventional laser in micro- and nanoscopic applications is that it is a near-field quantum generator, and its size can be much smaller than the wavelength — on the order of sizes of biological molecules and viruses. Moreover, in contrast to common fluorescent labels its emission does not saturate: it is a stimulated emission and its intensity linearly depends on the pump power as long as the spaser is not physically damaged. Consequently, the brightness of the spaser and the energy released inside the targeted cell are orders of magnitude greater than with conventional labels (Fig. 1c). Interestingly, transient vapour nanobubbles around the spaser can play the role of a dynamic

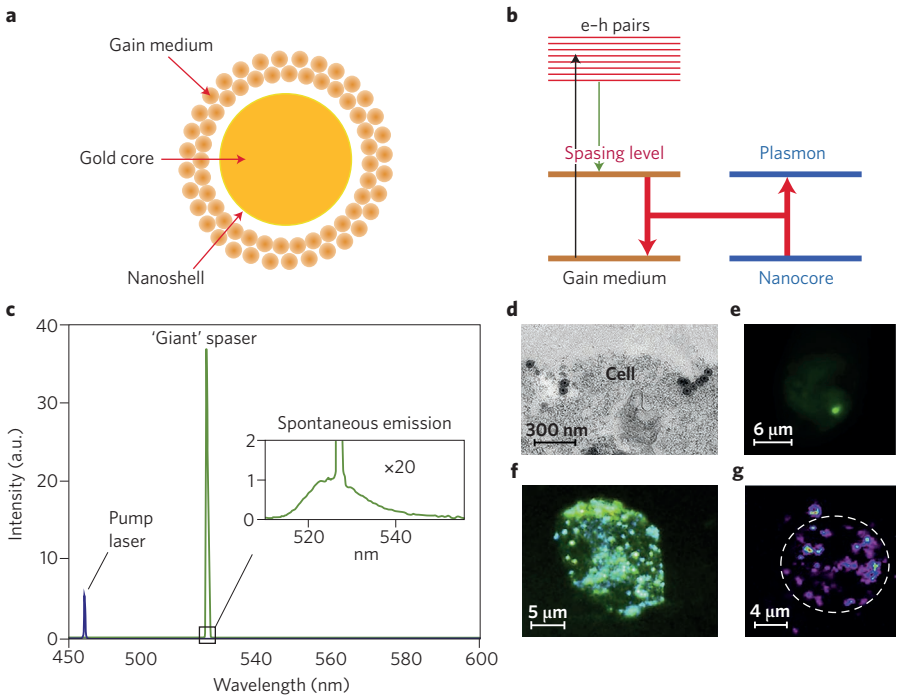

Figure 1 | Principles of spaser and its theranostic applications. **a**, Schematic of the spaser geometry where the metal nanocore is surrounded by a thin insulating shell and the gain nanoshell containing a fluorescent dye uranine. The colour bar provides a scale for local optical field amplitude. **b**, Schematic of the spaser functioning principles. The pumping radiation excites electron–hole pairs that relax in energy down to the spasing level. The energy is transferred in the near-field to surface plasmons by stimulated emission of plasmons without photon radiation. **c**, Spectrum of the spaser emission inside the cells where a giant narrow spaser line dominates over the spontaneous emission (pump laser is attenuated by a filter). **d**, Electron micrograph where the spaser nanoshells (the grey circles of the gain medium surrounding a dark point-like core) are seen inside a living cancer cell. **e**, Emission of a single spaser inside a cancer cell is shown in real colours. **f**, The same as **e** but for multiple spasers taken up by the cell. **g**, Photothermal image of a living cell showing multiple spasers inside. Adapted from ref. 15, Macmillan Publishers Ltd (**a**,**b**); reproduced from ref. 2, Macmillan Publishers Ltd (**d**–**g**).

optical resonator with positive feedback, thereby amplifying the spaser light and creating intense emission that is important for cancer diagnosis at cellular levels in deep tissue. Zharov's team has already studied the properties of laser-induced vapour nanobubbles around overheated plasmonic gold particles, and has reported clusters for photomechanical killing of single tumour cells without harming neighbouring normal cells.

The spasers are chemically conjugated with folate and incubated with tumour cells that they could selectively target (Fig. 1d). The radiation of the spaser is so bright that even a single spaser is clearly seen inside the cell (Fig. 1e). Multiple spasers produce images within a cell with unprecedented brightness (Fig. 1f). They are also excellent agents for photothermal and photoacoustic imaging because they are also equally efficient, unsaturable nanogenerators of heat inside the cells (Fig. 1g), which are greatly advantageous over conventional imaging and theranostics agents[12–14]. Moreover, ultra-sharp photoacoustic resonances and red–blue resonance splitting[5] can improve identification of targeted cancer cells in complex absorption backgrounds.

The enormous and unsaturable optical absorption by the spasers and the corresponding efficient generation of heat, nanobubbles[5] and shock waves inside the cell allows one to effectively use them for theranostics — just a few laser pulses are sufficient to reliably kill tumour cells using photomechanical effects within the irradiated volume without damaging the healthy cells. Indeed, laser-induced nanobubbles around the heated spaser during fast expansion and collapse provide the high kinetic energy and localized pressure that can damage vital structures of tumour cells that are resistant to conventional techniques. One can envision that it will become possible to detect and eliminate single CTCs as they pass through a blood vessel: a very intense and highly monochromatic (narrow spectral band) radiation of the spasers might enable a physician to continuously monitor the passage of the CTCs through surface blood vessels. As soon as CTCs are detected in the blood circulation via their spaser radiation, a high-power laser pulse is sent to kill them, one tumour cell at a time. Nevertheless, clinical trials need to be initiated in the future to demonstrate the feasibility and safety of this innovative approach. In particular, the impact of killing trafficking CTCs on established clinical outcome parameters, such as progression-free or overall survival, must be assessed. It can be envisaged that cancer patients with inoperable tumours (for example, from lung cancer) but no signs of already established gross metastases might profit from stopping further blood-born dissemination of tumour cells. Besides cancer, the spasers are also applicable to other medical fields, such as tracing sub-populations of specific immune cells in immune disorders or after organ transplantation. ❐

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