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Sensed at the gut level

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Abstract

Naphthalocyanine nanoparticles offer intense photoacoustic signals for mapping the gastrointestinal tract.

Abdominal fluoroscopy and computed tomography are two X-ray based imaging techniques commonly used to diagnose and monitor bowel disease, which involves swelling, occlusion, perforation and bowel-wall thickening. Although computed tomography offers high-resolution and three-dimensional datasets, and fluoroscopy is an affordable real-time workhorse, these tools are limited by radiation dose, which can cause skin and hair damage, and a small but measurable increased risk in cancer. Furthermore, fluoroscopy suffers from spatial and temporal blurring and time lag during imaging. Moreover, both techniques are not suitable for molecular imaging of cell and protein targets and are used primarily for anatomic imaging. Endoscopic techniques, which use white light and targeted contrast agents, offer an alternative but are challenging for the long and winding small intestines; they are mostly used only to image the esophagus, stomach, rectum and colon. Writing in *Nature Nanotechnology*, Jonathan Lovell and colleagues at the State University of New York in Buffalo, Pohang University of Science and Technology, University of Wisconsin at Madison and McMaster University now describe a micelle-like nanoparticle for photoacoustic imaging of the gastrointestinal tract[1].

Photoacoustic imaging is a sub-type of traditional ultrasound imaging, and is a ‘light in, sound out’ technique, rather than ‘sound in, sound out’ as in ultrasound. Laser pulses delivered to tissues are absorbed and converted to heat. If the incident light pulse is sufficiently short (~5 ns), the heat is released via thermal expansion, which generates acoustic waves that are detected with an ultrasound transducer. Photoacoustic imaging combines the deep penetration, good spatial resolution and outstanding temporal resolution of ultrasound with the high contrast and spectral features of optical imaging[2,3]. However, achieving sufficient contrast between the target and the background can be difficult because melanin, haemoglobin, deoxyhaemoglobin and other biological molecules present in normal tissues also absorb light and produce photoacoustic signals. Therefore, contrast agents must be designed to absorb incident photons and to undergo thermal expansion efficiently.

To do this, Lovell and co-workers solubilized different hydrophobic dyes in Pluronic F127 surfactant and found that napthalocyanine formed the most stable nanoparticle. By controlling the critical micelle concentration — the concentration of the surfactant above which micelles form — the authors created a nanoparticle (called nanonaps) consisting of

nearly 500 naphthalocyanine molecules and eliminated all free Pluronic F127. Concentrating such a large number of dye molecules into the nanoscale regime brought about excellent near-infrared absorption with minimal scattering. Furthermore, freeze-dried nanonaps could be fully reconstituted at high concentration in minimal volumes of water. Importantly, the nanonaps are kinetically frozen due to the very high hydrophobicity of naphthalocyanine. This means that unlike traditional micelles, nanonaps do not exchange with their constituent materials in solution[4] (Fig. 1a).

The nanoparticles were administered through a feeding tube to a mouse model of human disease and imaged with photoacoustics as they passed through the intestines (Fig. 1b). The very high signal allowed the bowel to be imaged above the background photoacoustic signal from blood in the surrounding tissue. The signal was correlated to the rate of intestinal contraction, the time it takes for the nanonaps to pass through the intestines, and blockage of the bowel.

Gastrointestinal contrast agents must withstand the harsh pH environments of the stomach and intestines and should not be absorbed by the body. ‘Digestion’ of the contrast agent would increase background signal and complicate regulatory approval. The nanonaps remained kinetically frozen and passed through the entire tract and with complete recovery in the faeces. Histology showed that all the organs, including the intestines, remained healthy.

One of the limitations of photoacoustic imaging is that it is not a whole-body technique: images are produced only where the transducer is placed. To solve this challenge, Lovell and colleagues radiolabelled the nanonaps with ^{64}Cu for positron emission tomography. This serves as an initial whole-body but low-resolution technique to identify sections of the intestine that require further inspection. Photoacoustics and ultrasound could then be used on those regions for higher-resolution imaging.

Because photoacoustic imaging uses light, the technique is still limited by the poor depth of penetration through tissues. Although imaging through phantoms beyond 5 cm has been shown, the present work only studies the first 5 mm of tissue. Many groups are working to improve the depth of photoacoustics with novel contrast agents[5], alternatives to thermal expansion[6] or non-optical excitation pathways. Nevertheless, clinical deployment of photoacoustics will remain a challenge for the foreseeable future except for niche applications such as tomographic imaging of the breast, transrectal prostate imaging and transvaginal imaging of the ovary. Transabdominal photoacoustics is not for everyone — overweight or obese patients may be excluded due to limitations imposed by fat tissues. Furthermore, acoustic-based imaging is notoriously operator dependent and this may become especially crucial in photoacoustics where slight variations in light delivery (for example, angle of transducer) could significantly affect the photoacoustic signal.

Nonetheless, ultrasound is already common in abdominal imaging. Gastrointestinal applications include assessing bowel strictures associated with Crohn’s disease — expanding traditional ultrasound with nanonaps and photoacoustic imaging could increase the contrast and resolution to better identify early-stage occlusions or perforations. Lovell

and co-workers nicely illustrate anatomical land marking of the kidney and bladder with traditional ultrasound, and combining photoacoustics with other established ultrasound tools including Doppler measurements of vascularity and dynamic imaging of peristalsis offer exciting possibilities[7]. Beyond the bowel, nanonaps may find applications in perfusion imaging or as targeted tumour contrast agents.

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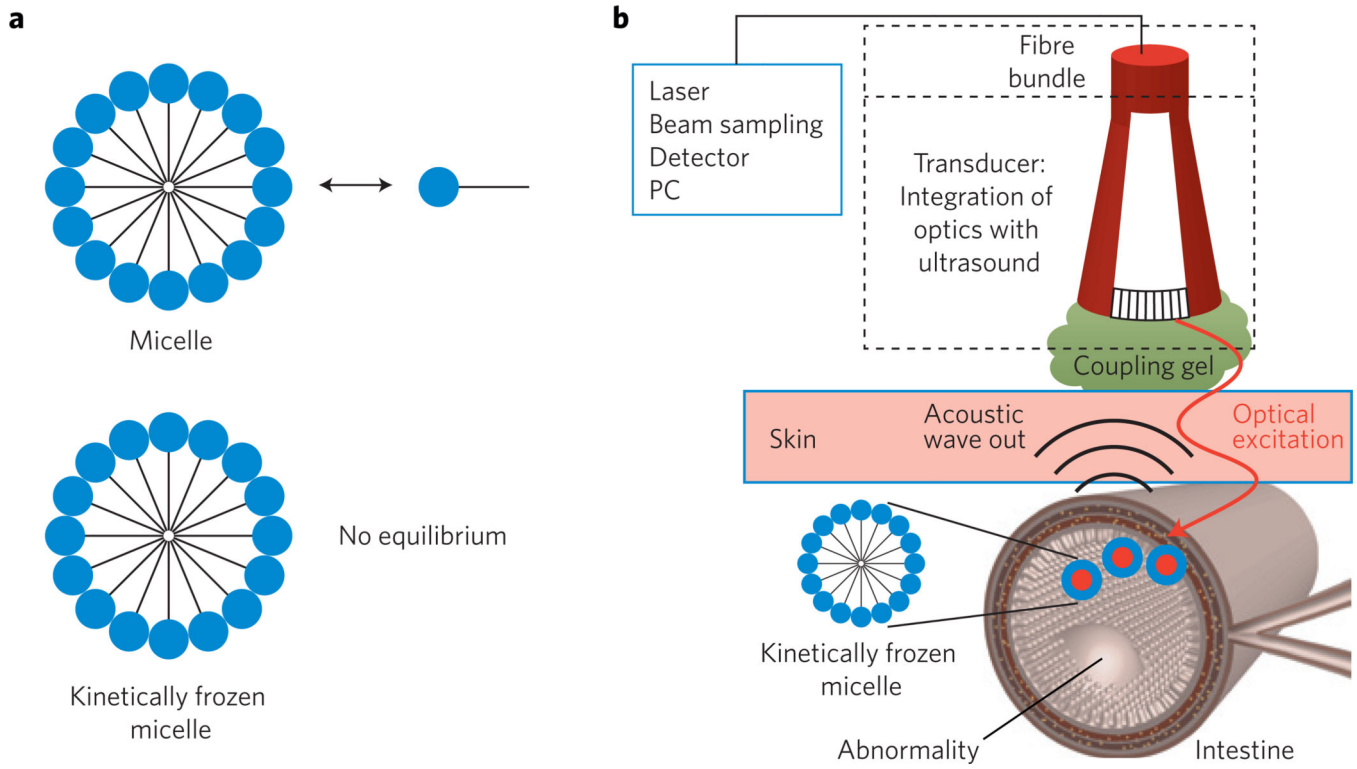

Figure 1.

Formation of micelles and photoacoustic imaging using nanonaps. **a**, Traditional micelles are colloids that are in equilibrium (double headed arrow) with their constituent materials in solution (top). Kinetically frozen micelles do not exchange with constituent monomers (bottom). **b**, Photoacoustic imaging employs a transducer to deliver optical excitation and collect acoustic energy. Nanonaps (blue) described by Lovell and co-workers[1] are delivered orally. They remain in the bowel to enhance contrast and define any abnormalities in the small intestines.