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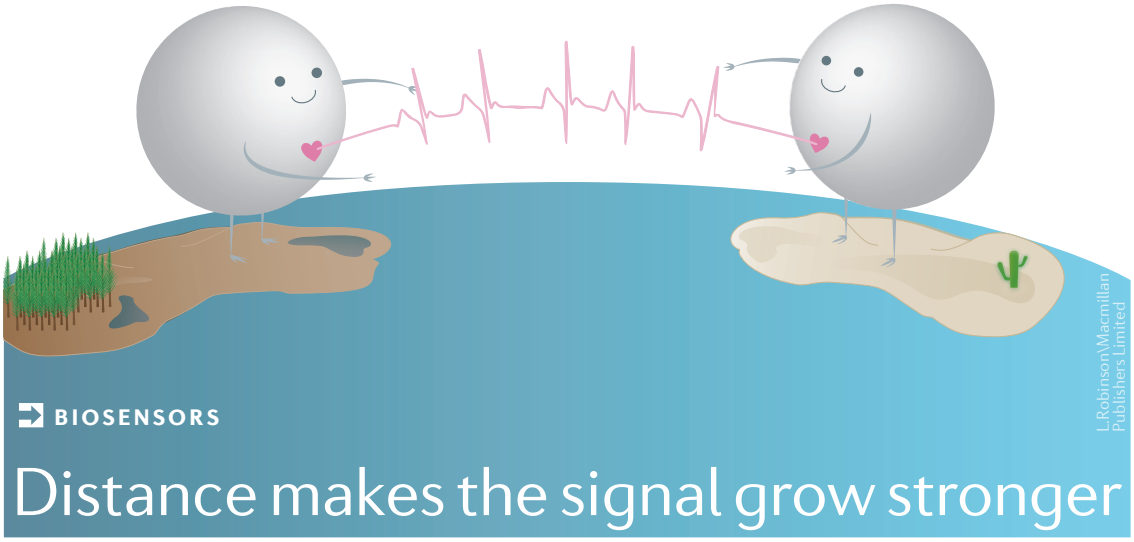

BIOSENSORS

Distance makes the signal grow stronger

A new MRI-based 'nanoruler' allows the *in vivo* sensing of a range of biological targets, including pH changes and the presence of cancer biomarkers. As Jinwoo Cheon and co-workers report in *Nature Materials*, this nanosensor overcomes the limitations of conventional, optics-based biosensors.

The sensing platform is a modular assembly comprising an MRI 'enhancer' and 'quencher' that are separated by a linker. Electron spin fluctuations in the paramagnetic enhancer nanoparticle accelerate the relaxation of excited water protons and thus increase the T_1 MRI signal. By contrast, the superparamagnetic quencher nanoparticle slows the spin fluctuations in the enhancer, thereby suppressing the T_1 signal when the two particles are closer than a critical distance. Accordingly, modulation of the distance between the two particles changes the signal intensity and forms the basis of the sensor.

> We introduce the concept of a nanoruler-based, two-component magnetic material that functions as a versatile 'on/off' MRI sensing platform

The researchers had previously developed dual-mode MRI contrast agents incorporating both paramagnetic and superparamagnetic materials in a core–shell design. Now, by connecting the different nanomaterials through responsive linkers, they are able to follow biological processes that cause cleavage or unfolding of the linker (which increases the signal) and processes that bind initially unbound particles (which quenches the signal). "Our previous studies focused on the correlation of T_1 and T_2 MR imaging modes to construct high-contrast MRI probes. In this work, we introduce the concept of a nanoruler-based, two-component magnetic material that functions as a versatile 'on/off' MRI sensing platform," explains Cheon.

Putting this concept into practice, Cheon's team used a peptide linker that is cleaved by a cancer biomarker. The concentration-dependent increase in the T_1 signal allowed visualization and quantitative analysis of the biomarker *in vivo* in a mouse model. In the opposite scenario, they were able to follow DNA hybridization and copper-catalysed click reactions that linked the quencher and enhancer, leading to a decrease in the signal. Then, using a linker that undergoes reversible folding and unfolding at different pH values, they developed a pH sensor using the nanoruler concept.

Owing to the generality of its sensing principle, extension of this probe to a vast range of other biological processes that induce linker cleavage, binding or folding is possible. Moreover, the authors demonstrated that the probe operates for various combinations of superparamagnetic and paramagnetic particles. This modular nature is advantageous for optimizing particles for selective targeting and for avoiding an immune response and rapid clearance. Another advantage of using MRI-based sensors for *in vivo* imaging is that they are not limited by the penetration depth, unlike conventional, light-based sensors.

Moving forward, the researchers seek to improve their sensing platform with increased functionality. "The next step will be developing smarter nanoparticle probes that can simultaneously record and interpret multiple biological targets to allow a better understanding of biological processes and accurate diagnosis," explains Cheon. In more general terms, they plan to tackle several challenges facing nanoparticle imaging probes. "For example, we are trying to design nanoparticles to be more sensitively responsive to stimuli and generate amplified signals for sensing," says Cheon. "Our research efforts are also underway to have effective delivery of nanoprobes to the *in vivo* targets."

Adam Brotchie

ORIGINAL ARTICLE Choi, J.-s. *et al.* Distance-dependent magnetic resonance tuning as a versatile MRI sensing platform for biological targets. *Nat. Mater.* http://dx.doi.org/10.1038/nmat4846 (2017)