manipulations can be conducted at any desired time during an experiment.

This novel approach to hydrogel design should be particularly appealing for fields such as developmental biology, stem-cell biology or tumour-cell biology, in which the role of the microenvironment in controlling cell function is particularly important and is still relatively poorly understood. With these novel ECM models at hand, researchers could, for example, study how stem cells renew themselves or specialize in response to local changes in the availability of signalling cues or in their spatial organization, providing knowledge that will be crucial to help move stem-cell biology closer to the clinic. Thus, the benefits of this technology in basic biological studies are already clearly apparent, but it would not be surprising if in the not-too-distant future tissue-mimetic 'constructs', fabricated with the help of light-controlled three-dimensional gel patterning, could be successfully used for pharmaceutical high-throughput screening. ❐

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TUMOUR TARGETING

Nanoantennas heat up

Advances in the functionality of multifunctional nanoparticles push their potential for the remote detection and treatment of cancer nearer to real-life patient care.

Weian Zhao and Jeffrey M. Karp

The growth of biomaterial-based therapeutics, and particularly the new generation of nanoscaled materials that allow an unprecedented capability to detect and treat cancer and other immune diseases, were highlighted at this year's 35th Annual Northeast Bioengineering Conference (NEBEC) held in Boston on 3–5 April 2009. The Boston academic community has a strong history of biomedical research and has had a central role in pushing the boundaries in the field of biomaterials and in the training of biomedical engineers[1,2]. This strong academic contingent, coupled with dozens of companies that are dedicated to the development of clinically useful biomaterial products, made the conference an excellent venue at which to find the most innovative and exciting research in biomedical sciences and technologies.

The conference featured cutting-edge developments in the field of biomaterials and tissue engineering, nanotechnology-based therapeutics and diagnostics, wearable technologies, bio-microelectromechanical systems (BioMEMs) for global health, and advanced biomedical imaging technologies. Of particular interest is the new generation of nanomaterials, specifically nanoparticles, which have been armed with superior physical and surface properties enabling long-term stability and a long circulation half-life under physiological conditions, ultrasensitive detection platforms for identifying unique cell types, and bioactivity to control biological processes such as the promotion of a specific immune response. These multifunctional nanoparticles represent a new paradigm for providing better diagnostic and therapeutic tools for treating diseases such as cancer. (Fig. 1)

Nanoscaled materials have significant potential utility in medical applications for therapeutics, diagnostics and prophylaxis. Tunable plasmonic nanoparticles — those made from gold and silver — are particularly attractive because of the unique interaction between their surface electrons and light, a phenomenon called surface plasmon resonance, which provides these particles with the superior capability of absorbing and scattering light at distinct wavelengths depending on their size, shape and surface properties. This enables their detection *in vivo* for a variety of applications including cell tracking, *in vivo* imaging for mapping of diseased tissue, biosensing and for photothermal therapy, in which absorbed light is converted to local heat. Despite the rapid progression of the field during the past decade, however, clinical translation of such particles has been limited as a result of toxic and unstable coatings. Furthermore, in a potentially ideal situation, these particles should possess both detection and remotely controlled therapeutic capabilities. Sangeeta N. Bhatia, Geoffrey von Maltzahn and colleagues (Massachusetts Institute of Technology) reported during the conference that these multifunctional nanoparticles, which they called nanoantennas, are well on their way to becoming useful in patient therapy[3,4].

Nanoantennas are gold nanorods 13-nm wide and 47-nm long, selected for their strong absorbance of near-infrared light with minimal non-specific interaction with tissue. The MIT group conjugated a non-toxic polymer to the surface of the nanorods to enhance the circulating time and improve biocompatibility[3]. The modified particles were found to be highly stable under physiological conditions with an *in vivo* circulation half-time of 17 hours, one of the longest achieved so far[3]. To enable the ultrasensitive detection of nanoantennas by Raman spectroscopy, near-infrared-absorbing Raman active molecules were immobilized simultaneously with the non-toxic polymer ligands[4].

The long circulating time allowed intravenously infused particles in a mouse to accumulate within a tumour, in contrast with non-specific sites. Given that gold is also an X-ray contrast agent because of its high density, imaging was initially conducted with X-ray computed tomography to monitor the spatial and temporal distribution of the particles[3]. For ultrasensitive detection, Raman dyes attached to the particles were tracked *in vivo* by Raman spectroscopy with the use of a surface-enhanced Raman

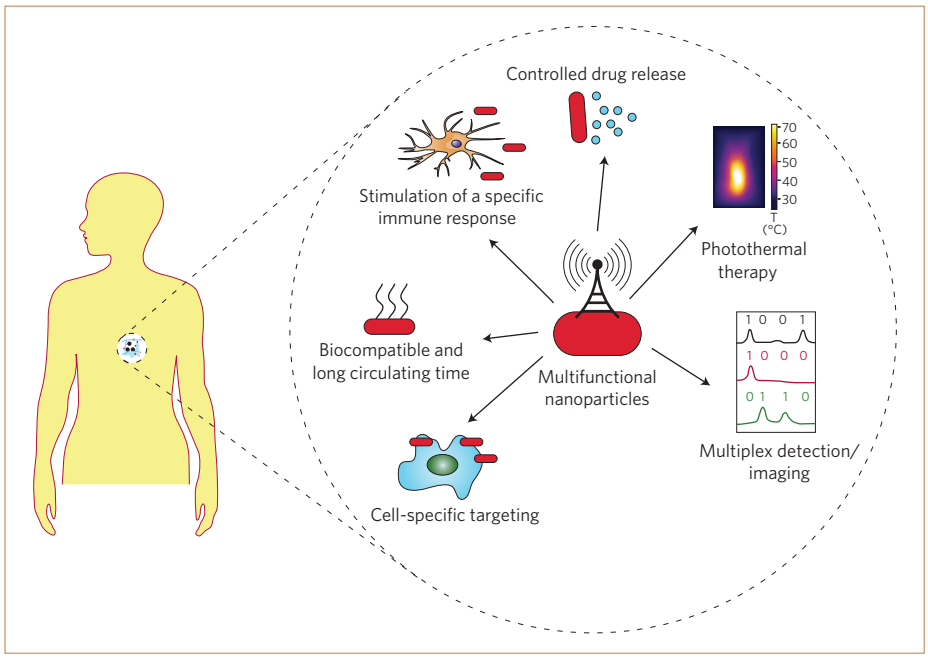

Figure 1 | Biocompatible and long-circulating multifunctional nanoparticles could allow multiplex ultrasensitive detection for imaging. They could also allow highly selective and precise cancer-cell termination by means of both photothermal therapy and delivered chemotherapeutic drugs, and the promotion of a specific biological response such as activation of the immune system.

scattering technique that enhanced the Raman scattering of dyes on the surface of gold up to 10^{14}-fold, making it possible to detect attomolar (10^{-18} M) concentrations of particles within tumour tissue. After carefully screening a variety of Raman dyes, the MIT group identified those that could be uniquely distinguished from one another. This enabled the encoding of multiple Raman dye fingerprints onto different particles, which could be used for quantitative multiplexing assays[4].

Nanoantennas can also be remotely heated with high selectivity through the conversion of absorbed near-infrared energy into local heat of up to 70 °C for tumour ablation. Moreover, by computational heat-transport modelling, the MIT group can now better predict the photothermal heating effects. Ultimately the parameters — beam intensity, shape, cross-section and duration — were optimized to ablate the complete tumour selectively[3].

Additionally, nanoantennas possess integrated diagnostic and therapeutic functions to target tumours through a remote control process. Another exciting report from the conference involved programming nanoparticles to autonomously stimulate a specific biological response *in vivo*, which could be used to trick the immune system, for example. Anna Bershteyn and Darrell Irvine (Massachusetts Institute of Technology) reported a 'synthetic pathogen' system in which biodegradable poly(lactide-co-glycolide) nanoparticles are coated with toxic lipid molecules that are often present on viral pathogens. This fake pathogen particle can then trigger an immune response *in vivo* and could potentially be used in new vaccines for establishing protective immune responses.

Multifunctional nanoparticles represent the new generation of diagnostic and therapeutic biomaterials that could change the standard of care for patients in unprecedented ways. Engineered nanoparticles can be used for quantitative multiplex diagnostics and to kill tumours in a highly selective and precise manner (theoretically with single-cell precision). The further integration of targeting biomolecules and chemotherapeutic drugs will improve their targeting efficiency and specificity[5,6]. It is also possible to release chemotherapeutic drugs from these nanoparticles in a smart thermoresponsive system in which controlled drug release can be guided by remote laser irradiation[7]. A combined orchestrated approach with ultrasensitive image-based tracking, drug release and photothermal ablation may provide a more effective tool for cancer treatment, especially for small tumours or individual cancer cells. ❐

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