Nature Reviews Materials | Published online 16 Aug 2017; doi:10.1038/natrevmats.2017.58

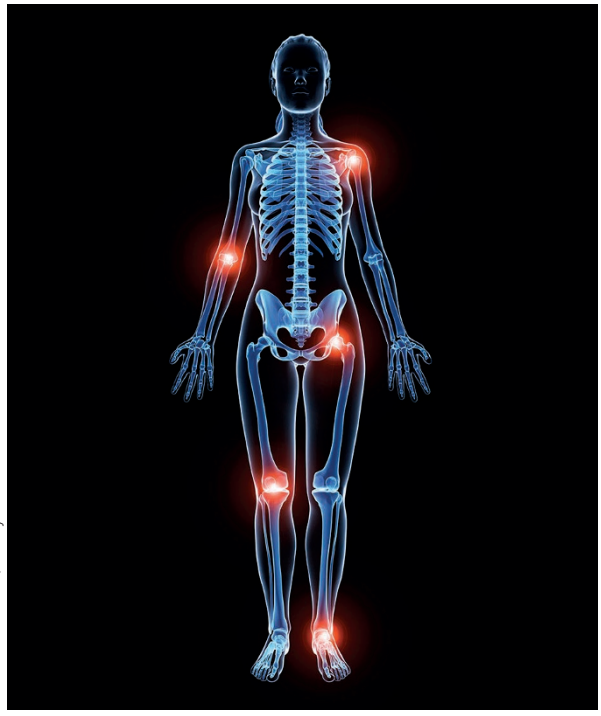
DRUG DELIVERY

Ultrasound soothes the pain

> The duration and degree of nerve block could be adjusted *in vivo* simply by modifying the duration and intensity of applied ultrasound

Ultrasound can trigger the release of a potent local anaesthetic, demonstrating potential for on-demand pain management and for avoiding the use of opioids in the management of acute pain, as Daniel Kohane and colleagues report in *Nature Biomedical Engineering*.

Acute pain is often treated with opioids, which have severe side effects, or local anaesthetics, the dose of which cannot be adjusted after administration. To overcome such limitations, the researchers combined two research areas: sustained drug delivery systems and externally triggered drug delivery systems. "We hypothesized that marrying these two lines of investigation would create systems that could be triggered by the patient or a health care worker to provide local anaesthesia whenever desired, and that the intensity of pain relief could be adjusted to meet the patient's needs," explains Kohane. More specifically, they took a potent nerve blocking agent (site 1 sodium channel blocker) and developed an ultrasound-responsive delivery system that allowed controllable and sustained release.



Sebastian Kaulitzki / Alamy Stock Photo

Externally triggered drug delivery systems have been explored for a variety of therapeutic purposes. In the context of pain management, Kohane's team previously used near-infrared light as a trigger; however, a potential drawback of light is its limited penetration depth in tissue. By contrast, ultrasound can penetrate tissue with relatively low attenuation. Although ultrasound is more commonly associated with diagnostic and sports medicine, in so-called sonodynamic therapy, ultrasound is used together with a 'sonosensitizer' to generate reactive oxygen species that can, for example, be used to induce cancer cell death in a process analogous to the more conventional photodynamic therapy. It is thought that the effects of acoustic cavitation — the formation of free radicals (sonochemistry) and/or the emission of light (sonoluminescence) from the violent collapse of microbubbles — are responsible for the generation of reactive oxygen species.

Instead of directly using reactive oxygen species as the therapeutic agent, Kohane's team harnessed them to induce drug release by co-encapsulating the drug and a sonosensitizer in liposomes comprising unsaturated lipids. The idea is that reactive oxygen species peroxidate the lipids, disrupting the membrane and causing the release of the drug. *In vitro*, they observed repeatable payload release, reactive oxygen species generation and peroxidation upon sonication. Similar release behaviour under light in the presence of the sonosensitizer (also a photosensitizer) confirmed the role of reactive oxygen species in the release mechanism. Moreover, in the absence of the sonosensitizer, drug release was rapid and could not be controlled by ultrasound; the presence of the sonosensitizer not only provided triggered release, but also improved the elastic modulus of the liposome membrane to reduce passive release.

The researchers then injected the liposomal drug depots at the sciatic nerve in a rat model, visualized the liposomes and tested the neurobehavioral response. "We found that the duration and degree of nerve block could be adjusted *in vivo* simply by modifying the duration and intensity of applied ultrasound," says Alina Rwei, a graduate student and first author of the paper. "In addition, diagnostic ultrasound could be used to visualize the particles. These findings suggest that patients may be able to adjust the degrees of pain relief at will, precisely and non-invasively." To further optimize the performance, they co-delivered the drug with an adjuvant, which provided up to 36 hours of anaesthesia.

Not surprisingly, the team will now work towards translating these results clinically. "We would like to test this formulation in larger animals as it will give us a better sense of the parameters that need to be adjusted to suit clinical needs. The ingredients of the formulation are, to the best of our knowledge, all approved for use in humans by the FDA, which may facilitate translation," says Kohane. "One potentially interesting area of clinical research would be to determine whether systems like these could mitigate or even obviate opioid use."

Adam Brotchie

ORIGINAL ARTICLE Rwei, A. Y. *et al.* Ultrasound triggered local anesthesia. *Nat. Biomed. Eng.* http://dx.doi.org/10.1038/s41551-017-0117-6 (2017)

© 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.