Liposomes loaded with anesthetic payload provide method for repeatable, adjustable local pain management

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A pair of preclinical studies published in the *Proceedings of the National Academy of Sciences* and *Nano Letters* reveal two methods for using a laser to trigger on-demand release of a local anesthetic to provide repeatable, long-lasting pain management, either directly at the site of an injury or by blocking pain signals transmitted from an injury.

Both studies, conducted by researchers in the Laboratory for Biomaterials and Drug Delivery (LBDD) at Boston Children's Hospital and at the Massachusetts Institute of Technology (MIT), point to ways of addressing a long-standing and hotly-debated issue in pain medicine: how to provide patients with durable, localized and personalized control of surgical, traumatic or chronic pain.

"Current approaches to postoperative pain rely on systemic analgesics, especially narcotics, which come with side effects and risks of tolerance, addition and diversion," said Daniel Kohane, MD, PhD, director of the LBDD and a physician in the Division of Anesthesiology, Perioperative and Pain Medicine at Boston Children's and senior author on both studies. "While there is extensive literature on targeted drug delivery, the technologies developed to date are either on or off; they cannot be adjusted or repeatedly triggered to provide a desired, durable level of analgesia. Our goal was to engineer an approach to pain control that once administered could be triggered as needed."

Both technologies rely on lipid microspheres carrying tetrodotoxin, a potent local anesthetic, and a laser producing a focused beam of near-infrared (NIR) light, which is able to penetrate tissues without causing direct injury. In the technology reported in PNAS, the microspheres also contained a photosensitizing agent that, when exposed to laser light, produces molecules of reactive oxygen. The microspheres in the Nano Letters report were instead embedded with gold nanorods that heat up when targeted with the laser.

In both cases, the microspheres' surface becomes permeable when exposed to the laser, allowing the drug to escape. Once the laser is turned off, the microspheres reseal, retaining the rest of their drug payload for later triggering.

In the *PNAS* study, lead author Alina Rwei, a graduate student in the LBDD and the MIT Department of Materials Science and Engineering, successfully blocked hindpaw pain in rats by injecting the photosensitizer-containing microspheres near the sciatic nerve (which transmits pain signals from the lower limbs to the brain) and testing the animals' reactions when stepping on a heat source. Rwei's team found they could tune the level and duration of pain blockade by changing how frequently and for how long they exposed the injected microspheres to the laser beam, as well as the intensity of the beam. For instance, by repeatedly triggering the microspheres, they found they could block pain signals for approximately 24 hours. In addition, they found that the microspheres could be triggered for up to two days after injection.

"The photosensitivity of this system is fairly high, so you only need a relatively low light dose to trigger anesthetic release," Rwei explained. "This allows you to go deeper into tissue without harming the tissue with the laser itself."

In the *Nano Letters* study, lead author Changyou Zhan, PhD, a fellow in

the LBDD, injected gold nanorod-modified microspheres containing both tetrodotoxin and dexmedetomidine (which prolongs the effects of tetrodotoxin) directly into the footpads of rats and testing the animals' reaction to mechanically-induced pain. As with Rwei's experiment, Zhan and his colleagues found they could trigger pain control by repeatedly exposing the rats' nanosphere-injected paws to the NIR laser for up to 5 days.

"By loading two drugs into the same system and phototriggering the release of both simultaneously, we're able to prolong the duration of and increase the intensity of local anesthesia," Zhan noted.

In neither study did the investigators find any signs of tissue damage caused by the laser, the microspheres or tetrodotoxin itself.

Kohane noted that while both technologies need to be refined and optimized, both represent significant steps to addressing an unmet medical need for patient-adjustable local pain relief. In his vision, patients who have undergone surgery or who suffer chronic pain would receive an injection of anesthetic-loaded microspheres at the site of pain and be sent home with a laser device. Upon experiencing discomfort, the patient would use the laser to trigger anesthetic release until she achieves a desired level of pain relief.

"If we can translate these technologies to patients, it could change dramatically the way we approach postoperative pain care by providing pain relief that doesn't involve narcotic agents and which doesn't have to fade away within a few hours," Kohane said. "And in my mind, pain is the low-hanging fruit. There are many clinical situations and applications where repeated, modulated, on-demand drug release would be desirable."

"This work may represent a major advance in the management of pain,"

said Robert Langer, ScD, co-senior author on the *PNAS* study and the David H. Koch Institute Professor at MIT. "It is also a striking demonstration of the capabilities that remotely triggerable drug delivery systems can have."

More information: Alina Y. Rwei, et al. Repeatable and adjustable on-demand sciatic nerve block with phototriggerable liposomes, *PNAS* 2015 ; published ahead of print December 7, 2015, DOI: 10.1073/pnas.1518791112

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