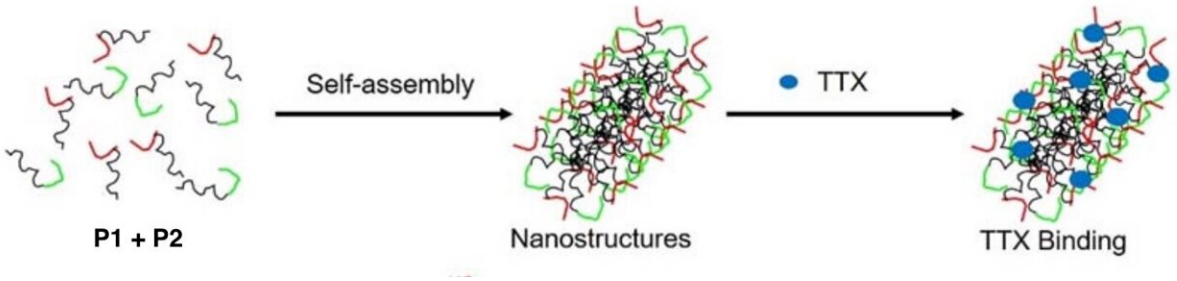
Mimicking nature to provide long-lasting local anesthesia

September 13 2021



This schematic shows the peptides P1 and P2 with hydrophobic modifications that enable them to self-assemble into nanostructures that bind to tetrodotoxin (TTX). Credit: Tianjiao Ji, PhD, Kohane lab in Nature Biomedical Engineering, Sept. 13, 2021.

Site 1 sodium channel blockers such as tetrodotoxin and saxitoxin are small-molecule drugs with powerful local anesthetic properties. They provide pain relief without toxic effects on local nerves and muscles, and are an attractive alternative to opioids. But injected by themselves, they can easily float away, causing severe systemic toxicity.

Encapsulating these drugs in safe delivery systems has been a challenge: Because they are extremely water soluble, they tend to exit into the surrounding water in the body.

"The toxicity becomes dose-limiting, and you can't get a long-lasting nerve block," says Daniel Kohane, MD, Ph.D., director of the Laboratory for Biomaterials and Drug Delivery at Boston Children's Hospital and vice chair for research in the Department of Anesthesiology, Critical Care and Pain Medicine.

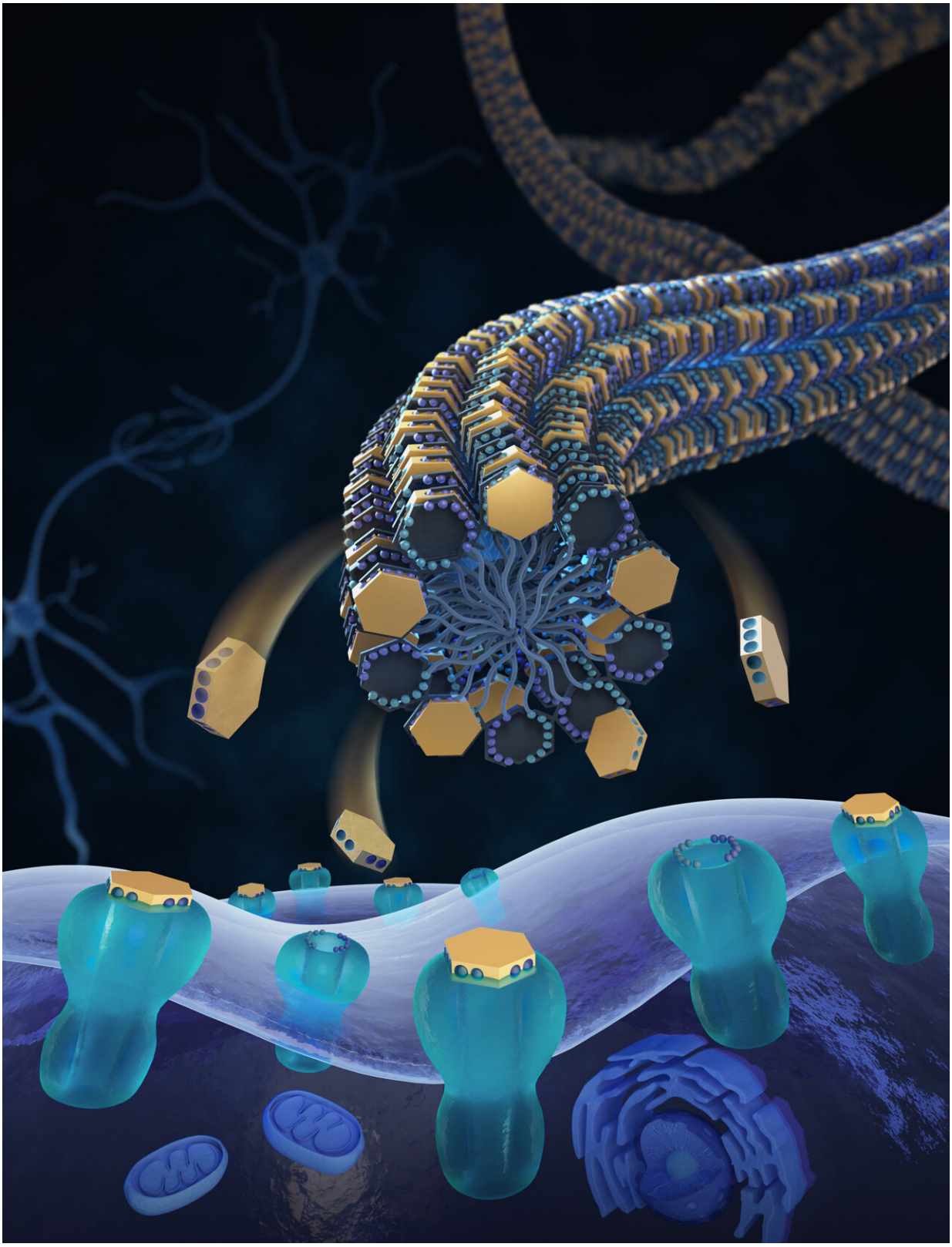
Tianjiao Ji, Ph.D., a former postdoc in Kohane's lab, had an idea for a biomimetic system that would release local anesthetics slowly, prolonging their effect. As described in the September issue of *Nature Biomedical Engineering,* the system mimics the body's own receptors for the anesthetic. The mimics grab onto the drug and the system, once in place, slowly releases the anesthetic, providing prolonged nerve blockade with minimal toxicity.

The Kohane lab has created many slow-release systems, including ones to deliver tetrodotoxin, but this one is the first to hijack nature's design. Although tetrodotoxin and saxitoxin were the test anesthetics, the approach could potentially be applied to other drug delivery systems.

Taking cues from nature

To create the slow-release system, Ji, with co-first author Yang Li, Ph.D., and other lab members, began with a mixture of two peptide sequences, P1 and P2. Both peptides are part of the actual sodium ion channel; when tetrodotoxin is delivered to the nerve, it binds simultaneously to both peptides.

The team then modified P1 and P2 with long chains of hydrophobic (water-repelling) molecules. This caused the resulting molecules to assemble themselves into nanostructures with the two peptides positioned together, mimicking the way they're positioned on the sodium channel. The peptide pairs take up the anesthetic, just as they would on the sodium channel itself.



The bio-inspired nanofibers carry two peptides (shown as arrays of blue and violet dots) that are modified from peptides on tetrodotoxins' natural binding site on voltage-gated sodium channels. These adapted peptides bind to tetrodotoxin (shown as gold hexagons) and release it when the nanofibers are injected near the nerve, providing prolonged local anesthesia. Credit: Fantastic Color/Nature Biomedical Engineering

"When you add the hydrophobic chains, the peptides form a long fiber with thousands of P1s and P2s waving around," Kohane explains. "Each set of peptides binds one tetrodotoxin molecule. Think of the peptides like hands—if you're trying to catch tetrodotoxin, you need two hands to come together to hold it."

When this structure is injected near the target nerve, the tetrodotoxin slowly releases itself by diffusion and other processes, and binds to P1 and P2 on the nerve itself.

Putting the design to work

The team then put the tetrodotoxin-bearing nanostructures to the test, injecting them near the sciatic nerves of live rats. The anesthetic stayed in place longer than free tetrodotoxin, with no toxic tissue reaction, and neurobehavioral tests in the animals showed that the nerve block lasted for as long as 16 hours.

"By hijacking nature's design, we created a synthetic receptor for anesthetic drugs that acts as a delivery and release system," says Ji.

The team has patented their approach. "In theory, it could be applied to different drugs and other receptor–drug interactions," Kohane says.

More information: Delivery of local anaesthetics by a self-assembled supramolecular system mimicking their interactions with a sodium channel, *Nature Biomedical Engineering* (2021). DOI: 10.1038/s41551-021-00793-y , www.nature.com/articles/s41551-021-00793-y

Provided by Children's Hospital Boston