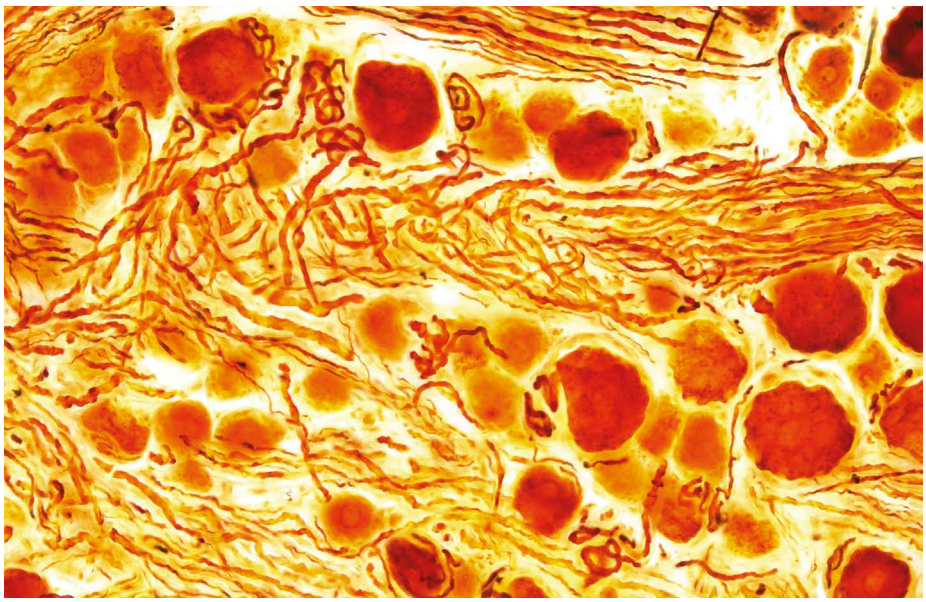

JOSE CALVO/SPL

Pain signals are transmitted to the brain through neurons similar to these in the spinal cord.

CRISPR-BASED GENE THERAPY DAMPENS PAIN IN MICE

The approach could lead to an opioid-free way of treating chronic pain.

By Ariana Remmel

A gene-silencing technique based on CRISPR can relieve pain in mice, according to a study[1]. Although the therapy is still a long way from being used in humans, scientists say it is a promising approach for squelching chronic pain that lasts for months or years. Chronic pain is typically treated with opioids such as morphine, which can lead to addiction.

"It's a real challenge that the best drugs we have to treat pain give us another disease," says Margarita Calvo, a pain physician at the Pontifical Catholic University of Chile in Santiago, who wasn't involved in the research. That's why the new technique is exciting, she says.

Scientists are already evaluating CRISPR therapies that edit a person's genome as treatments for blood diseases and some forms of hereditary blindness. The new version of CRISPR doesn't edit genes directly — it stops them from being expressed — and so shouldn't cause permanent changes, although it's unclear how long its effects last for.

Some studies estimate that a large proportion of the population in Europe and the United States — as high as 50% — experiences chronic pain[2,3]. This pain can become debilitating over time by limiting a person's activity and affecting their mental health. Despite the condition's prevalence, few options exist for providing long-term relief without side effects.

This plight inspired bioengineer Ana Moreno and colleagues at the University of California, San Diego, to seek an alternative.

Pain registers with the brain when a stimulus — such as touching a scalding hot pan — triggers neurons to send an electrical signal through the nerves in the spinal cord and upwards to the brain. This happens when pore-like openings along the neuron — called ion channels — open and close to allow ions to pass through, which transmits a current along the nerve. With chronic pain, parts of this pathway can become hyperactive.

> **"It's a real challenge that the best drugs we have to treat pain give us another disease."**

Although there are many types of ion channel, studies have suggested that a sodium channel called $Na_v1.7$ could play a central part in chronic pain. When people have mutations in the gene coding for this channel, they either experience extreme, constant pain, or can't feel any pain at all.

So Moreno and her team thought that they might be able to stop pain signals travelling to the brain by preventing neurons from producing $Na_v1.7$. Chemists have been trying to block $Na_v1.7$ with small-molecule drugs and antibodies, but have struggled because these therapies also interact with structurally similar sodium channels in the body, causing side effects including numbness and poor coordination. But with CRISPR, which targets genes with precision, the researchers thought they might be able to hit $Na_v1.7$ directly, without any off-target effects.

Harnessing CRISPR's precision

The team started with a modified version of the Cas9 protein that's normally part of the CRISPR gene-editing system. It could target, but not cut, the DNA sequence encoding $Na_v1.7$. The researchers attached to the modified Cas9 a second, 'repressor' protein that stops the $Na_v1.7$ gene from being expressed. The researchers packaged this system in a small, inactive virus called an adeno-associated virus that could shuttle it into cells.

They gave mice a spinal injection of the gene-silencing therapy, then tried to induce chronic pain by injecting the animals with chemotherapy drugs or inflammatory agents. These mice were more tolerant of painful stimuli. And mice that were already suffering from chronic pain benefited from the therapy, the team showed. For instance, mice that received doses of chemotherapy became highly sensitive to pain, but lost that sensitivity after a single injection of the gene therapy. The results were published in *Science Translational Medicine* on 10 March[1].

The pain relief seemed to last, in some cases, for as long as 44 weeks after the injection. "That's quite remarkable," says Sulayman Dib-Hajj, a neuroscientist at Yale University in New Haven, Connecticut.

Importantly, says Calvo, the treatment seems to have knocked down expression of $Na_v1.7$ without shutting down other sodium channels — the mice didn't lose any sensations apart from pain.

Despite their excitement, scientists caution that these results are still preliminary, and need to be translated to humans. "It gives us hope" for treating chronic pain in humans, says Dib-Hajj, "but more work needs to be done."

Moreno is now chief executive of Navega Therapeutics in San Diego, which plans to continue developing the treatment with the hope of one day trialling it in humans.

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2. Breivik, H., Collett, B., Ventafridda, V., Cohen, R. & Gallacher, D. *et al. Eur. J. Pain* **10**, 287 (2006).
3. Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A. & Dworkin, R. H. *J. Pain* **11**, 1230–1239 (2010).