DANIEL STOLLE

DRUGS

# A different path

*Fresh strategies and targets for chronic pain could deliver much-needed replacements for opioid-based painkillers.*

**BY ANTHONY KING**

Pain is one of the main reasons why people consult a doctor. Often, especially in North America, they walk away with an opioid prescription. But opioids are increasingly viewed as unsuited to managing chronic pain. "Opioids are unbelievably effective for short-term pain relief, such as after operations, but for long-term pain they are less effective and come with a very considerable burden of side effects," says Peter McNaughton, a pharmacologist at King's College London. Their use can lead to dependency, addiction and even death.

Chronic pain can be inflammatory, such as that associated with osteoarthritis, or neuropathic, which includes pain caused by direct injury to nerves. An example of an excruciating neuropathic pain is that which accompanies diabetic neuropathy, a condition in which blood-sugar anomalies damage tiny blood vessels at the extremities that supply the body's smallest nerve fibres. The quality of life of those affected nosedives: often they cannot sleep, concentrate or walk because of the pain.

Opioids offer only limited assistance. A meta-analysis published in 2018 concluded that opioids provided small improvements for people dealing with chronic pain caused by conditions other than cancer[1]. "The data is pretty overwhelming that the level of pain relief from chronic non-cancer pain is very low indeed," says Clifford Woolf, a neurobiologist at Boston Children's Hospital in Massachusetts.

A few new options for treating pain have arrived in the past 30 years, says Jianguo Cheng, a medical neuroscientist at Cleveland Clinic in Ohio. However, most have been borrowed from epilepsy or neurology, and they often do a poor job or come with intolerable side effects. "Almost half of existing analgesics were developed for other purposes, and that reflects how poorly we have done," says Woolf. For example, doctors can treat people in pain with anti-seizure medications called gabapentinoids, which include pregabalin or gabapentin, but these can cause drowsiness and dizziness and are only partially effective. "Gabapentinoids are the first-line therapy, yet the mantra is that they are 30% effective in 30% of patients," says Allan Basbaum, a neuroscientist at the University of California, San Francisco. He and other pain researchers cite the 'number needed to treat' as a measure of how good an analgesic is. This is the average number of people who must be treated to achieve 50% pain relief in one person. A drug that is effective in everyone would receive a score of 1. Most drugs for chronic pain have a score of around 7. Some have a score of more than 10. "These drugs are appallingly ineffective," says McNaughton. "There is a crying need for better analgesics."

Although pharmaceutical companies recognize this need, many have shied away from pain research, after pouring tens to hundreds of billions of US dollars into developing new painkillers without success. The subjective nature of pain chilled their ardour further. "Large pharma largely abandoned neuroscience," says Woolf, especially in areas in which treatment outcomes are subjective, including pain, anxiety and depression. Part of the blame lies with the placebo effect, in which pain relief from interventions that hold no therapeutic value fogs the efficacy data of potential analgesics that might have fewer side effects.

But now, the opioid crisis is transforming pain research. The US National Institutes of Health (NIH) is injecting US$850 million into the HEAL (Helping to End Addiction Long-term) Initiative, with Congress having decided in 2018 to allocate $500 million per year to the opioid crisis and pain research. "Pain is now one of the top priorities of the NIH, which it has never been before," says Woolf. There's a surge of optimism among pain scientists, with fresh avenues of research opening up. These include treatments comprising antibodies, toxins, channel blockers, stem cells and even spruced-up opioids with fewer side effects. The pharmaceutical industry also recognizes the need and opportunity for new painkillers.

## CHANNELLING ORIGINAL DRUGS

Another important target for pain drugs is a

molecule called nerve growth factor (NGF), which promotes the growth and differentiation of neurons. NGF does this by binding to tyrosine kinase receptor A, which triggers a cascade of effects that include boosting the number of pain receptors and sensitizing nerves. Injecting NGF into rodents and people causes their pain neurons to become sensitized. And NGF levels have been shown to spike in laboratory animals that are experiencing inflammation or peripheral nerve injury[2]. Clinical trials suggest that a single injection of an anti-NGF monoclonal antibody (tanezumab) could mop up enough NGF to take away osteoarthritic pain for months[3].

"There is also evidence that NGF is effective against chronic back pain, as well as mixed evidence that it works to relieve pain from diabetic neuropathy," says Steven P. Cohen, a pain clinician at Johns Hopkins Medicine in Baltimore, Maryland. The anti-NGF antibody strategy stalled when some participants with osteoarthritis experienced joint disintegration, which forced the US Food and Drug Administration (FDA) to pause trials in 2010. The trials were restarted in 2015, accompanied by advice that patients should not mix the therapy with non-steroidal anti-inflammatory drugs. In April, pharmaceutical companies Eli Lilly of Indianapolis, Indiana, and Pfizer in New York City announced positive phase III results from a trial of tanezumab in more than 3,000 people with osteoarthritis. Some side effects in joints were still observed. Given the trial's efficacy data, however, Basbaum predicts that anti-NGF antibodies could be approved in the next two years. "Back pain and osteoarthritis pain are probably predominant in opioid use for non-cancer chronic pain, so coming up with a non-opioid treatment is potentially transformational," Basbaum says. The results of a positive phase III tanezumab trial in people with chronic lower-back pain were also announced this year.

Another strategy for unearthing painkillers involves studying people who are impervious to pain. In 2002, researchers heard about a boy from Pakistan who did not feel pain. He was presumed to have a mutation in a channel protein that controls the entry of sodium ions into neurons. Known as $Na_V1.7$, this voltage-gated sodium channel plays a part in getting neurons ready to fire. A study of families from Pakistan who do not experience pain showed that the family members have a mutation in the gene that encodes a subunit of $Na_V1.7$ (ref. 4), which suggests that the channel is crucial for pain amplification in neurons.

Excited researchers at drug companies soon set about finding $Na_V1.7$ blockers to stop pain, but despite their enthusiasm, efforts floundered. In fact, a number of pharmaceutical companies have dropped Nav 1.7 blockers after clinical trials. The problem is that such drugs seem not to work, says McNaughton. But pain researchers remain convinced that sodium channels hold the key to a new form of pain relief. Two other channels found in pain neurons, $Na_V1.8$ and $Na_V1.9$, are attracting researchers' attention, and some suggest that a multipronged approach might bring more success. "The results of going after a single ion channel have been disappointing," says Woolf. "The excitability of neurons is determined by many different ion channels and maybe targeting just one may not be enough by itself."

A discovery in 2011 opened up yet another anti-pain angle. McNaughton showed that a subtype of voltage-gated ion channel was responsible for increasing the excitability of nerve fibres[5]. HCN ion channels are widespread in the central nervous system. Best known is HCN4, which controls heart rate. Deleting another HCN ion channel, HCN2, in mice stopped inflammatory pain and neuropathic pain, but acute pain was preserved. This feature would be crucial to retain when treating pain so that people do not to injure themselves. McNaughton discovered a selective blocker of HCN2 that would not interfere with other HCN channels, including the one involved in regulating heartbeat. Importantly, the drug is excluded from the central nervous system, and therefore does not trigger adverse neurological side effects. In March, King's College London, London-based biomedical research charity Wellcome and Merck of Kenilworth, New Jersey, signed an agreement to develop this therapy for neuropathic pain, including pain associated with diabetic neuropathy.

BASTIAN RAST

**A toxin from the Togo starburst tarantula is helping researchers to understand pain pathways.**

## STEM-CELL SOLUTIONS

Feeling pain was once thought of as being similar to the brain receiving an old-fashioned wired telephone call from a site of injury. Now, pain is viewed as a vast, molecularly complex network. The perception of pain differs between people, and pain can change a person's biology. It reconfigures neural circuits, especially by strengthening connections in nociceptors, the neurons that detect injuries, send signals to the spinal cord and process pain in the brain. This sensitization can turn the pain dial up to maximum volume. "The pain circuit becomes stronger through synaptic reinforcement in chronic pain. It's like learning," says Greg Neely, a geneticist at the University of Sydney in Australia.

One approach to treating chronic pain could be to refit the cellular brakes in pain circuits. Transplanting neurons that produce the inhibitory neurotransmitter GABA (γ-aminobutyric acid) into a mouse with a condition similar to epilepsy was reported to rebuild a pain-inhibiting circuit, reducing seizures[6]. Basbaum has transplanted GABA-producing neurons from mouse embryos to successfully treat a mouse model of neuropathic pain[7]. "The idea of putting these cells into patients with neuropathic pain is viable," says Basbaum, who is particularly interested in trigeminal neuralgia, an extreme form of pain that affects the face. He is also a scientific adviser to Neurona Therapeutics, which aims to treat epilepsy, and then pain, using stem-cell therapy. Basbaum suggests that human embryonic stem cells modified to secrete GABA could be deployed to treat people with chronic pain in the next five years.

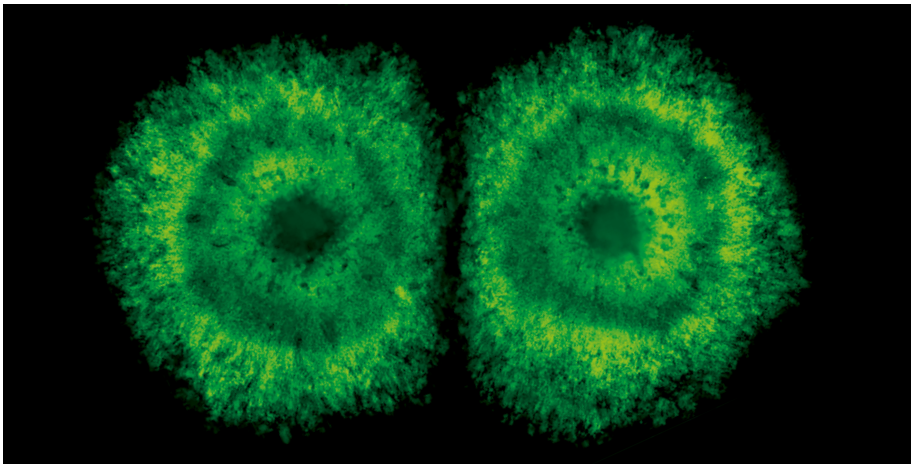
Basbaum has spurred on others to take this road. Neely launched a project three years ago that aims to transform human pluripotent stem cells into GABA-producing neurons and then inject them into the mouse spinal cord to treat pain. In September 2018, he received funding to develop this approach for use in people. Next year, Neely hopes to be ready to treat up to four individuals who experience extreme, so far untreatable, pain. Pain researchers are usually cautious about touting preclinical results. As soon as Neely's clinical project was announced, e-mails started to ping in from people begging to be part of the trials.

## TOXIN HOPE

Glenn King, a biochemist at the University of Queensland in St Lucia, Australia, hunts small invertebrates for their venoms, and then screens those substances for short proteins, or peptides, that target pain receptors. "Venoms are a great place to look for selective modulators of voltage-gated sodium channels," says King. Because these neurotoxins are evolutionarily honed to cause discomfort, they boast a better selectivity for the target channel than do small-molecule drugs. King is interested in understanding the pathways that they tap into, in the hope that they might reveal a potential off-switch for pain.

A toxin that he discovered in the Togo starburst tarantula (*Heteroscodra maculata*) revealed a role for $Na_V1.1$ in causing pain[8], which opened up another sodium channel of interest to pain researchers. King has also found a peptide in the venom of a purple tarantula (*Pamphobeteus nigricolor*) that blocks $Na_V1.7$ and, when combined with the inhibition of another ion channel, treated chronic pain in a mouse model of irritable bowel syndrome[9]. "Our $Na_V1.7$ inhibitor works for visceral pain, but not other types of pain," says King. Some parts of the body might be more sensitive to $Na_V1.7$ blockers than others, because neurons that innervate one organ might have different populations of ion channels than neurons in another. Drugs might therefore have to be designed to target specific sites of pain.

Bazbek Davletov, a cell biologist at the



CORY NICHOLAS, PHD; NEURONA THERAPEUTICS

**Neuron precursor cells derived from human pluripotent stem cells.**

University of Sheffield, UK, is also interested in toxins for pain relief. Such molecules have specific targets, whereas many pain drugs cause side effects by straying towards unintended receptors. Davletov and his collaborator Stephen Hunt, a neurobiologist at University College London, have been experimenting with delivering botulinum toxin — more commonly known as botox — to peripheral nerves to mute pain. Often used as a cosmetic wrinkle flattener, the molecule acts as a muscle relaxant: it triggers muscle paralysis by entering nerves that control muscles, damaging a protein and thereby blocking the release of neurotransmitters. The nerve goes silent for months, until the protein is replaced.

To adapt the toxin to block pain neurons, Davletov refitted the toxin's receptor binding site with an opioid so that it could bind to pain nerves rather than those associated with muscles. "The beauty of the botulinum toxin is that it doesn't spread around the body. When you inject it, it quickly binds to nerves," says Davletov. Injecting nanograms of the engineered toxin into a mouse with neuropathic pain proved effective in relieveing pain[10]. Davletov hopes to move the treatment into clinical trials in the next two years.

## BETTER OPIOIDS

Conventional opioids alleviate pain by activating μ-opioid receptors to engage protein pathways inside the cell, such as G proteins and β-arrestins. The quest for a biased agonist to engage some pathways, and not others, was kicked off by researchers in the United States who reported[11] that deleting β-arrestin-2 in mice boosted pain relief from morphine, with reduced respiratory depression. There is renewed interest in whether selectively avoiding β-arrestins would reduce side effects of opioids, such constipation and cessation of breathing, as well as lessening addiction. Oliceridine, a biased agonist created by pharmaceutical firm Trevena in Chesterbrook, Pennsylvania, has completed phase III trials. However, the FDA requested further safety data on the agonist at the end of 2018. Trevena plans to resubmit the drug for approval in early 2020.

Another approach, being pursued by Nektar Therapeutics in San Francisco, California, deploys a μ-opioid-receptor agonist that was designed to limit its transit across the blood–brain barrier. This prevents the spike in dopamine in the brain that opioids usually trigger, thereby reducing associated feelings of euphoria and sedation. A phase III clinical trial is under way. Other companies aim to hit the κ- or δ-opioid receptors, which regulate pain seemingly without addiction and dependence liabilities. Cara Therapeutics, a biotechnology company in Stamford, Connecticut, is conducting phase III trials of a molecule that targets κ-opioid receptors, which has also been designed to minimize its entry into the brain.

*"Almost half of existing analgesics were developed for other purposes."*

Some researchers are reconfiguring existing opioids. BU08028, a molecule based on buprenorphine that is showing promise, targets the μ-opioid receptor as well as another type of receptor: the nociceptin opioid peptide (NOP) receptor. Stephen Husbands, a medicinal chemist at the University of Bath, UK, has treated pain in macaques (*Macaca mulatta*) using BU08028. The animals showed no signs of respiratory depression, addiction or physical dependence[12]. "It is a partial agonist at both NOP and μ-opioid receptors, so that should mean it avoids side effects from either," says Husbands. Partial agonists induce changes at receptors, but not to the same degree as do full agonists. A follow-up study with a related compound also delivered morphine-like pain relief and was not addictive in monkeys[13]. "We now have seen strong analgesia from two compounds from different chemical series, with minimal side effects," says Husbands. "This gives us confidence that what we are seeing is a real effect."

## FEDERAL STIMULUS

As the population ages and more people develop osteoarthritis and diabetes, the effects of chronic pain are increasing. Yet pain research has been neglected. Health foundations tend to fund research on specific diseases rather than on pain science. "When someone dies, people give money to the disease that killed the person, not pain research," says Basbaum, "even though the person may have died in terrible pain." Given the societal cost of pain, many researchers feel that public funding for pain research has also been neglected.

A remarkable turnaround is under way — particularly in the United States. Owing to the opioid crisis, a massive injection of federal funding is buoying optimism that new therapies for chronic pain can be delivered. The HEAL Initiative, in particular, should not only stimulate fundamental pain science and drug screening, but also lead to clinical trials, drug optimization and epidemiological studies. Industry is also re-energizing its interest. The FDA is looking for ways to shorten the regulatory path for painkillers.

Progress is being aided by advances in technology, including more efficient *in silico* screening of molecules that target pain receptors, as well as the ability to generate human stem cells to test pain strategies in human tissue. There's renewed focus on improving animal models of pain. Woolf's lab is relying on artificial-intelligence algorithms to pick up subtle behavioural signs that reflect pain or anxiety in rodents, rather than relying on simpler tests such as an animal withdrawing from a pain stimulus. These approaches "more closely align with a patient's experience of pain, rather than artificial reflex measures", says Woolf.

There's optimism in the pain community, and determination. Opioid overdoses have been "a true societal catastrophe", says Woolf. "Having worked in pain for most of my career, I feel I have a moral obligation to pay society back for the huge mistake my profession — the medical profession — made in using opioids for managing non-cancer chronic pain." ■

**Anthony King** *is a science journalist in Dublin.*


1. Busse, J. W. *et al. J. Am. Med. Assoc.* **320**, 2448–2460 (2018).
2. Chang, D. S., Hsu, E., Hottinger, D. G. & Cohen, S. P. *J. Pain Res.* **9**, 373–383 (2016).
3. Lane, N. E. *et al. N. Engl. J. Med.* **363**, 1521–1531 (2010)
4. Cox, J. J. *et al. Nature* **444**, 894–898 (2006).
5. Emery, E. C., Young, G. T., Berrocoso, E. M., Chen, L. & McNaughton, P. A. *Science* **333**, 1462–1466 (2011).
6. Baraban, S. C. *et al. Proc. Natl Acad. Sci. USA* **106**, 15472–15477 (2009).
7. Bráz, J. M. *et al. Neuron* **74**, 663–675 (2012).
8. Osteen, J. D. *et al. Nature* **534**, 494–499 (2016).
9. Deuis, J. R. *et al. Sci. Rep.* **7**, 40883 (2017).
10. Maiarù, M. *et al. Sci. Transl. Med.* **18**, eaar7384 (2018).
11. Raehal, K. M., Walker, J. K. & Bohn, L. M. *J. Pharmacol. Exp. Ther.* **314**, 1195–1201 (2005).
12. Ding, H. *et al. Proc. Natl Acad. Sci. USA* **113**, E5511–E5518 (2016).
13. Kiguchi, N. *et al. Br. J. Anaesth.* **122**, e146–e156 (2019).