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IN THE LAB

The Quest for Better Pain Relief

The unusual inspiration behind promising new pain drugs

By JEANNE WHALEN

Scientists searching for better painkillers are taking inspiration from an unusual population: people who feel no pain at all.

Research has shown that rare mutations in a gene called SCN9A can give people complete immunity to pain. Now, pharmaceutical companies are aiming to develop drugs to mimic that genetic mutation.

Robert A. Lisak

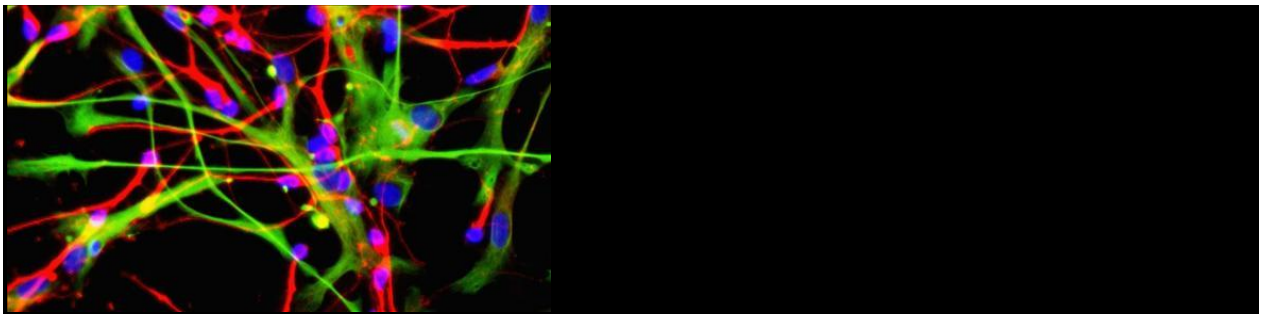
Yale University neurologist and pain-disorder specialist Stephen Waxman, with red tie, meets with fellow research scientists, left to right, Joel Black, Shannon Shields and Sulayman Dib-Hajj.

Scientists have struggled to find better treatments for chronic pain, which affects about 1 in 5 people. Anti-inflammatory drugs such as ibuprofen and naproxen sometimes don't work very well, while more powerful opiates such as morphine, codeine or oxycodone can be dangerously addictive. People suffering from neuropathic pain tied to nerve damage, meanwhile, often get little relief from current painkillers.

Now Pfizer Inc. and a handful of smaller companies such as Canada's Xenon Pharmaceuticals Inc. and the U.K.'s Convergence Pharmaceuticals Ltd. are working on new methods tied to the SCN9A gene. Instead of muting pain by reducing inflammation, as ibuprofen and similar drugs do, or by switching on the body's own analgesic properties, as opiates do, the new experimental drugs seek to block the ability of nerve cells to send pain signals.

Nerve cells send these signals with the help of a certain type of protein, called a sodium channel, that forms a pore in the cell's membrane. Inherited mutations in the SCN9A gene block the functioning of these sodium channels, called Nav1.7 sodium channels.

The experimental drugs also seek to block them—or at least to blunt their ability to transmit pain.



A rare genetic mutation makes some people resistant to pain, and drug makers are pursuing therapies that mimic that effect. Jeanne Whalen reports. Photo: Getty Images.

Because pain serves a useful biological function—it keeps us from burning ourselves, or breaking bones—complete congenital insensitivity to pain is actually a big problem. Children born with the rare pain-free syndrome need to be taught to abstain from the kind of dangerous behavior that a quick twinge of discomfort tells the rest of us to avoid.

Scientists linked the pain-free condition to SCN9A mutations in 2006, after studying several families in northern Pakistan afflicted with the syndrome, including a 10-year-old boy who worked as a street performer, entertaining crowds by walking on hot coals and forcing knives through his arms.

"Even as babies they had shown no evidence of pain appreciation," the researchers wrote of the families in a paper in the journal Nature. "None knew what pain felt like, although the older individuals realized what actions should elicit pain."

All subjects had injuries to their lips or tongues, caused by biting themselves as young children, and many had suffered frequent bruises, cuts or fractures.

Because the individuals were otherwise healthy, the researchers concluded that drugs that mimic their genetic mutation, by blocking Nav1.7 function, "have the potential to produce new and potentially safer analgesia."

Inspired by this sort of research, Pfizer and a biotech company it later acquired developed a drug that blocks Nav1.7 sodium channels, and decided that the best initial test of it was in patients with erythromelalgia—another rare genetic disease that is the mirror opposite of the pain-free syndrome.

The Pain Patrol

Several firms are developing experimental painkillers that block the functioning of Nav1.7 sodium channels in nerve cells:

- Pfizer Inc. (New York, N.Y.) Currently testing its drug in erythromelalgia, a severe type of pain caused by rare genetic mutations. Results expected by year-end.
- Xenon Pharmaceuticals (Burnaby, British Columbia) and Teva Pharmaceutical Industries Ltd. (Jerusalem) Testedadrug in erythromelalgia, reporting significant pain reduction, and in post-dental-surgery pain, reporting 'encouraging' results.
- Convergence Pharmaceuticals Ltd. (Cambridge, U.K.) Testing a drug in patients with trigeminal neuralgia, which causes stabbing bursts of pain in the face. Results expected by year-end.

Sources: *Pfizer Inc., Xenon Pharmaceuticals, Teva Pharmaceutical Industries Ltd., Convergence Pharmaceuticals*

People with erythromelalgia, also known as Man on Fire Syndrome, experience extreme sensitivity to pain. In these patients, a different type of mutation to the SCN9A gene causes Nav1.7 sodium channels to go haywire, resulting in hyperactive pain signaling.

"These people experience searing, scalding, burning pain in response to mild warmth. They describe it as feeling as if hot lava had been poured into their bodies," says Stephen Waxman, a neurologist and expert on rare pain disorders at Yale University and the Veterans Affairs Connecticut Healthcare System who has collaborated with Pfizer. Erythromelalgia often strikes the hands and feet, so sufferers spend a lot of time soaking their limbs in cold water, Dr. Waxman says. Most wear sandals, even in winter, because it keeps them cool.

Erythromelalgia is so rare that Pfizer has located just a handful of families in the U.S. to participate in the trial, says Ruth McKernan, chief scientific officer at a Pfizer unit in Cambridge, U.K., that focuses on pain.

To test the efficacy of the drug, the clinicians first trigger a pain attack in the patients by putting a warm blanket around their legs, she says. After the pain sets in, patients are given either the drug or a placebo and their pain levels are assessed. The blanket test is repeated several times over a 24-hour period. Pfizer hopes to have results of the trial by year-end.

Erythromelalgia is one, rare type of neuropathic pain, which results from nerve damage or dysfunction that is most often caused by injuries, infections or metabolic disorders such as diabetes.

Neuropathic pain affects about 8% of the population, and less than half of patients get satisfactory pain relief from current treatments, says David Bennett, a neurologist and pain expert at Oxford University in the U.K. Aside from anti-inflammatory drugs and opiates, drugs originally developed to treat epilepsy and depression also are used for neuropathic pain, with mixed success.

If the results of Pfizer's erythromelalgia study are successful, the company hopes to test the drug in other types of neuropathic pain, and possibly in pain associated with inflammation, Dr. McKernan says.

British Columbia-based Xenon Pharmaceuticals, working with partner Teva Pharmaceutical Industries Ltd. of Israel, also has tested a Nav1.7-blocking drug against a placebo pill in erythromelalgia. In the journal Pain last year, the companies reported that the drug "significantly reduced the amount of pain" in the four patients in the study. A second study of the drug's efficacy against post-dental-surgery pain also showed "encouraging" results, the partners say, though they haven't yet published the results in a medical journal.

While the efficacy of Nav1.7-blocking drugs is still far from clear, one possible benefit is their potential to be non-addictive, says Simon Tate, chief scientific officer of Convergence Pharmaceuticals, which is developing its own drug that blocks Nav1.7 sodium channels. Other types of drugs on the market today for epilepsy and other diseases block several sodium channels, including Nav1.7, and show "no evidence of addiction," he says.