Nav-i-gating antibodies for pain

By Lauren Martz, Staff Writer

Nav1.7 entered the limelight in the last decade as a pain target that could provide wide-ranging analgesia, but it has been difficult to target selectively over other voltage-gated sodium channels. Now, a team at the **Duke University Medical Center** has found a unique epitope on Nav1.7 and used it to create a highly selective antibody that blocks the channel by locking it in a closed state.¹

In mice, the antibody reduced pain and inflammation and suppressed acute and chronic itch. The Duke researchers are in discussions with companies to create a humanized form of the antibody.

Nav1.7 (SCN9A) emerged as a pain target in 2006 when a **University of Cambridge** team found loss-of-function mutations in the channel in patients with a rare congenital inability to feel pain.² Because the mutations caused no other overt pathology, drug developers jumped on the possibility that channel inhibitors could provide analgesia without causing major side effects.

At least six companies have Nav1.7-targeted compounds in clinical or preclinical development for pain (see Table 1, “Nav1.7 small molecule inhibitors and antibodies”).

However, the biggest challenge has been to find Nav1.7-selective compounds—which is particularly important because of the many processes triggered by other channel family members.

“There are nine subtypes of voltage-gated sodium channels in humans. They are very similar in sequence, but many sodium channel subtypes are responsible for very important but distinct roles in physiological processes,” said Seok-Yong Lee, an assistant professor of biochemistry at Duke.

For example, he said, Nav1.4 (SCN4A) and Nav1.5 (SCN5A) are responsible for muscle and cardiac action potentials, respectively. “Therefore, to reduce serious side effects, it is critical to make a subtype-specific inhibitor for sodium channels. But because of their sequence conservation, it has not been very easy,” said Lee.

In 2011, researchers at the **University of Washington** published the first crystal structure of a voltage-gated sodium channel, thus paving the way for structure-based drug design to target these channels.³

Now, Lee, Ru-Rong Ji and colleagues at Duke have used that structure to home in on the voltage sensor paddle region of Nav1.7—a domain that allosterically controls channel gating and differs between channel subtypes.

Ji is a professor in the Department of Anesthesiology and Neurobiology at Duke.

The team started by developing an active mAb to an epitope in the paddle region that responds to changes in membrane potential. It also created a control antibody against a different epitope that is not involved in channel gating in the same region.

In a cell line expressing human Nav1.7, the active antibody decreased sodium currents compared with the control and stabilized the closed state of the channel. The antibody had about 400-fold selectivity over subtype Nav1.6 (PN4; SCN8A) and no detectable activity against the six other channel subtypes tested.

Next, the researchers showed that the antibody suppressed formalin-induced pain and inflammation in mice after i.v., intrathecal or intraplantar administration. They noted that the i.v. and intrathecal analgesic doses were lower than morphine doses reported by others for the same model.

In a mouse model of neuropathic pain caused by chronic constriction injury, the antibody suppressed pain for several hours and did not lose its potency after repeated injections. That suggested the antibody does not cause tolerance, a problem commonly found with opioid analgesics.

Because Nav1.7 is involved in synaptic transmission of pain in nociceptive neurons in the dorsal root ganglion, and the pruriceptive neurons that mediate itch are a subset of nociceptive neurons, the team tested whether the sodium channel is also involved in the transmission of itch.

The researchers found that the Nav1.7 antibody suppressed the itch response in mouse models of acute pruritus and chronic models representing dry skin and allergic contact dermatitis.

In spinal cord sections from the pain and itch models, the antibody inhibited spontaneous excitatory postsynaptic currents in nociceptive neurons triggered by both pain and itch stimuli. These findings suggest that blocking Nav1.7 suppresses pain and itch by preventing synaptic transmission in the spinal cord.

Data were published in *Cell*.

Selective advantage

Glenn King, a professor in the Division of Chemistry and Structural Biology at **The University of Queensland's** Institute of Molecular Bioscience, told *SciBX*, “I think this is the most important paper on Nav1.7 since the original observation reported in *Nature* in 2006.”

He said that it shows for the first time that pharmacological blockade of Nav1.7 provides relief for most types of pain, Nav1.7 is critically involved in transmission of pruriceptive receptors and it is possible to design a highly selective mAb against the target.

According to several experts who spoke with *SciBX*, the selectivity of the Nav1.7 antibody provides it with a significant advantage over competitor compounds.

Peter Ulrichs, senior scientist at **arGEN-X B.V.**, said, “Recent

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**—Seok-Yong Lee,
Duke University Medical Center**

Table 1. Nav1.7 small molecule inhibitors and antibodies. Specifically blocking the Nav1.7 (SCN9A) voltage-gated sodium channel subtype suppresses pain. At least six companies have small molecule inhibitors or antibodies against Nav1.7 in clinical and preclinical testing to treat pain. Source: *BCIQ: BioCentury Online Intelligence*

Company	Product	Description	Phase of development
Convergence Pharmaceuticals Ltd.	CNV1014802	Small molecule, state-dependent Nav1.7 inhibitor	Phase II
Dainippon Sumitomo Pharma Co. Ltd. (Tokyo:4506)	DSP-2230	Small molecule inhibitor of Nav1.7 and Nav1.8 (PN3; SCN10A)	Phase I
Pfizer Inc. (NYSE:PFE)	PF-05089771	Small molecule Nav1.7 inhibitor	Phase I
SiteOne Therapeutics Inc.	ST-200	Small molecule Nav1.7 inhibitor	Discovery
arGEN-X B.V.	Nav1.7 antibodies	Antibodies against Nav1.7	Discovery
Numab AG	ND004	Antibody against Nav1.7	Discovery

published reports have described human Nav1.7-selective small molecules and venom-derived peptides, but none have the selectivity of the human Nav1.7 antibody described in the article.”

According to George Miljanich, CEO of SiteOne Therapeutics Inc., the difficulty of developing selective small molecules is partly caused by their hydrophobicity. John Mulcahy, director of R&D at SiteOne, added that Nav1.7-selective small molecules so far have generally shown

poor pharmacokinetics, which has held up their development.

SiteOne is developing small molecule Nav1.7 blockers based on marine guanidinium toxins that are natural inhibitors of the channel.

“We know already from our interactions with big pharma that Nav1.7 is a highly attractive and compelling target in pain and that antibodies are being taken seriously as a potential new treatment modality,” said Ulrichs.

However, Miljanich said that although antibodies against the channel might reach the market first, they will most likely be used to guide the design of small molecules that will eventually supplant them. He noted that small molecules replacing biologics is the course of drug development that has been unfolding in the autoimmune disease market.

Itching for more

Lee said that the next step will be for the Duke team to create a humanized version of the Nav1.7 antibody that retains the specificity of the mouse antibody and optimize its pharmacokinetic properties.

However, the humanization process itself can be tricky, said Ulrichs. “It would be hoped that its humanization and further engineering would not have any adverse effects on its functional properties,” he said.

Frank Zufall told *SciBX* that even if specific channel targeting is achieved with a humanized antibody, there could be side effects associated with targeting the channel itself. “Nav1.7 is important in anosmia. The people with loss-of-function mutations in Nav1.7 can’t smell. It is interesting that the same channel hits the three sensory systems—pain, itch and smell—and the goal now may be to target these systems independently,” he said.

Zufall is a professor of physiology at the **Saarland University Medical Center** and an expert in molecular medicine of sensory systems including olfaction.

However, he added that losing some sense of smell may be a tolerable risk for pain patients. “As long as you know that loss of olfaction is a side effect and the treatment effectively gets rid of pain, most patients may be OK with this side effect. Most patients will do anything to get rid of pain.”

The antibody’s ability to suppress itch could add to the commercial interest in Nav1.7 as a therapeutic target.

“Current antihistamines are insufficient to treat chronic itch. The Nav1.7 antibody can treat both histamine-dependent and -independent itch as well as chronic itch,” said Lee. The authors added that the antibody might benefit patients with skin diseases such as dermatitis.

Miljanich told *SciBX* that this is an opportunity for companies developing therapeutics targeting Nav1.7.

“The major contribution from this work is the implication that Nav1.7 is involved in the transmission of itch,” he said. “Although I have not done market research, I expect that there is a significant unmet need for itch and specifically severe chronic itch.”

He added, “We may add itch as a target indication at SiteOne because itch trials could be faster and easier than pain trials. Itch may be an easier clinical endpoint to measure.”

Lee told *SciBX* that **Duke University** has filed a patent application covering the work. The IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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