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Human pain neuroscience and the next generation of pain therapeutics

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https://doi.org/10.1016/j.neuron.2025.04.005

The recent approval of suzetrigine for acute pain treatment highlights both the success of targeting peripheral sensory neurons for pain management and the potential of developing new pain therapies primarily in human-based systems. To realize this transformative potential, further research into somatosensation and pain neuroimmunology in human systems is essential.

The U.S. Federal Drug Administration approval of suzetrigine (Vertex Pharmaceuticals) for moderate to severe acute pain is a turning point for the pain field. Suzetrigine is a specific and potent inhibitor of the voltage-gated sodium channel Nav1.8.[1] This channel is preferentially expressed in peripheral sensory neurons specialized to detect noxious stimuli,[2] called nociceptors, whose cell bodies reside in the dorsal root ganglion (DRG) and trigeminal ganglion (TG) of mammalian species, including humans. The selective expression of Nav1.8 in human nociceptors, in comparison with that of other neurons in the central or autonomic nervous system, is a key factor in the safety and specificity of this therapeutic target[1] and supports more expansive targeting of nociceptor-specific proteins for treating acute, and potentially some chronic, pain disorders. Indeed, additional inhibitors that target Nav1.8 and Nav1.7, another voltage-gated ion channel highly expressed in human nociceptors, are already under development. The approval of suzetrigine is likely to be the first in a series of new drugs that target nociceptors for acute and chronic pain. However, in order to fully realize this potential, a more detailed understanding of human nociceptor-specific gene expression patterns will be required.

Suzetrigine's path to the clinic was different from that of most other drugs that have gone through clinical trials for pain in the past two decades. This target was selected based on human genetics: some individuals harboring genetic mutations of Nav1.8 gene (SCN10A) have a rare condition called congenital insensitivity to pain.[3] Suzetrigine was developed by using a screening funnel that focused on human recombinant Nav1.8 channels with human DRG neurons recovered from organ donors to assess functional efficacy. This drug does not inhibit Nav1.8 outside of human and non-human primate species,[1] so no preclinical efficacy screening was done in rodent models, which have long been the mainstay of target identification and validation in the pain field. This human-focused effort has now led to the approval of the first new acute pain drug acting on a novel target in many decades and should reduce overall opioid consumption for acute post-surgical and post-traumatic pain. This new option for acute pain treatment represents an important step in the direction of reducing the opioid epidemic in America.

Although suzetrigine is an exciting new advance for acute pain treatment, its role in neuropathic and chronic pain conditions remains to be seen. Two chronic pain clinical trials of suzetrigine have been disclosed: a phase 2 trial in diabetic neuropathic pain and a phase 2 trial in lumbar radiculopathy, a low-back pain condition characterized by pain radiating down one or both legs. The disclosed but unpublished data suggest that suzetrigine was statistically more effective than placebo in the diabetic neuropathic pain trial but not in the radiculopathy trial. Results from these and other ongoing trials will further clarify the role of Nav1.8 inhibitors for chronic pain. In any case, it is clear that improved understanding of mechanisms to inhibit human nociceptors can lead to effective and novel treatment options for multiple types of pain.

In parallel, the rise in opioid-related deaths has prompted an urgent need for the development of safe, non-addictive analgesics. Tasked to address this crisis,

the NIH Helping End Addiction Long-term (HEAL) Initiative established an innovative new program in 2022 focused on human pain biology: the PRECISION Human Pain Network. PRECISION presently comprises four research centers and a data coordinating center that aim to apply cutting-edge technologies to molecularly profile human nociceptors and other pain-related cells and networks in both physiological and chronic pain states. Using both healthy tissues and those obtained from individuals with chronic pain, the PRECISION program hopes to provide additional mechanistic insight into vexing pain conditions that have not seen the development of effective new treatment strategies and accelerate the development of new, non-opioid pain therapeutics. Importantly, all data generated by PRECISION will be freely available to the public through its web portal (http://precisionpainnetwork.com; https://sparc.science/about/consortia/precision), which already includes several published datasets,[4–6] protocols,[7] and a harmonized atlas of DRG and TG neurons across species.[8]

A primary goal of these centers is to develop comprehensive datasets describing the genes, proteins, cell types, and functions of tissues in the human body that transmit normal, and potentially pathological, sensory information related to pain. Although single-cell and spatial multi-omic profiling of human pain-related tissues—including DRG, TG, peripheral nerves, and spinal cord—is the primary endpoint for many of these studies, scientists are also applying physiological techniques like patch-clamp electrophysiology, microneurography, and cellular signaling to match physiology to gene expression patterns. There is also an effort to profile tissues that are innervated by somatosensory neurons in painful disease states such as the lumbar discs of low-back patients or painful peripheral neuromas. By carefully phenotyping patients, the PRECISION Human Pain Network plans to identify molecular and cellular correlates with human pain conditions that can be targeted therapeutically to alleviate pain.

Three exciting areas of science and medicine now intersect, giving us an incredible opportunity to fundamentally change how chronic pain will be treated. First, the scientific work behind the approval of suzetrigine validates that human nociceptors can be specifically targeted for pain relief. Second, the increasing availability of de-identified human nervous-system tissues such as DRG, TG, and peripheral nerves from donors who have consented to research (e.g., from organ procurement organizations, autopsies, and surgeries) creates new opportunities for human neuroscience insights into pain mechanisms. In many cases, human cells can be maintained *in vitro* and studied at both the molecular and physiological levels. Third, the amazing advances in high-throughput multi-omics technologies now enable studies into human diseases with a level of detail that was unimaginable even a few years ago. Through integrated multi-omic and multi-modality characterization of the peripheral and central nervous system across multiple tissues and different pain conditions, the PRECISION Human Pain Network is well positioned to identify the genes, proteins, cells, and networks underlying a range of chronic pain and headache conditions. With this and other emerging efforts in the pain field, we anticipate identifying a range of new therapeutic strategies for safely and effectively offering the development of non-opioid analgesics in the near future.

CONSORTIA

The members of the NIH PRECISION Human Pain Network are Abby Pei-ting Chiu, Allison M. Barry, Amy Anderson, Asta Arendt-Tranholm, Andi Wangzhou, Ayesha Ahmad, Cathryn Payne, Christoph Paul Hofstetter, Claudio Tatsui, Diana Tavares Ferreira, Felipe Espinosa, Gregory O. Dussor, Ishwarya Sankaranarayanan, Jeffrey Jarvik, Joseph B. Lesnak, Juan Pablo Cata, Judith A. Turner, Karen Segar, Katelyn Sadler, Katherin Althea Gabriel, Khadijah Mazhar, Marisol Mancilla-Moreno, Megan L. Uhelski, Michael D. Burton, Michele Curatolo, Muhammad Saad Yousuf, Nguyen Tran, Olivia Catherine Davis, Patrick M. Dougherty, Robert Yates North, Stephanie Shiers, Theodore J. Price, Úrzula Franco-Enzástiga, William Renthal, Evangelia Semizoglou, Shamsuddin A. Bhuiyan, Parth Bhatia, Dustin Griesemer, Erika K. Williams, Jiaxiang Wang, Lily S. He, Hannah MacMillan, Clifford Woolf, Barbara Gomez, Aakansksha Jain, Selwyn Jayaker, Brian Wainger, Sanghun Lee, Xianjun Dong, Himanshu Chintalapudi, Anthony Cicalo, Jeffrey Moffitt, Hao Zhang, James R. Stone, Iris A. Lopez, Kyle Eberlin, Floris V. Raasveld, Kevin Spiegler, Wenqin Luo, Huasheng Yu, Eric A. Kaiser, Caitlin E. Cronin, Ebenezer Simpson, Hao Wu, Julie Leu, Dongming Liang, Ying Li, Mingyao Li, Hanying Yan, Patrik Ernfors, Dmitry Usoskin, Hakan Olausson, Saad Nagi, Katarina Laurell, Maria Bograkou, Otmane Bouchatta, Ewa Jarocka, Johan Nikesjo, Robert W. Gereau IV, Bryan A. Copits, Rakesh Kumar, Grace E. Moore, Deblina Nandi, Lite Yang, Juliet Mwirigi, John S. Del Rosario, Jun-Nan Li, Prashant Gupta, Adam Dourson, Maria Payne, Alexander Chamessian, Gary F. Marklin, John A. Lemen, Elvisa Mehinovic, Zitian Tang, Jenna Ulibarri, Emma Casey, Zefan Li, Brian Yu, Sheng Chih Jin, Kevin Boyer, Ibrahim Olabayode Saliu, Bijesh George, George Murray, Huma Naz, Guoyan Zhao, Valeria Cavalli, Pauline Meriau, Sarah F. Rosen, Isabelle Gordon, Jeffrey Milbrandt, Aaron DiAntonio, Aldrin K.Y. Yim, Amy Strickland, Liya Yuan, Joseph A. Bloom, Jyl Boline, Sam Kessler, Joost Wagenaar, Maryann Martone, and Sue Tappan.

ACKNOWLEDGMENTS

We would like to acknowledge the NIH HEAL Initiative for their support, through U19NS130607 (B.C., R.W.G., G.Z.), U19NS130608 (T.J.P., M.C., P.D.), U19NS135528 (H.O., W.L.), U24NS135547 (M.M.), and U19NS130617 (W.R., C.J.W.).

DECLARATION OF INTERESTS

M.C. is the chief medical officer and holds equity in 4E Therapeutics and has received research grants from NIH and Merck. R.W.G. is cofounder and holds equity in NeuroLux and has served as an advisor to Sparian Biosciences, Grunenthal, Agrithera, Neurop, and Cygnal Therapeutics. R.W.G. is a member of the NIH HEAL Initiative Multidisciplinary Working Group. W.L. has received research grants from Eli Lilly and NIH, and her spouse is an Eli Lily employee and holds equity. T.J.P. is a cofounder of and holds equity in 4E Therapeutics, NuvoNuro, PARMedics, and Nerveli. T.J.P. has received research grants from AbbVie, Eli Lilly, Grünenthal, Evommune, Hoba Therapeutics, and NIH. W.R. has received research grants from Pfizer and NIH and has consulted for Grünenthal and Eli Lilly. C.J.W. is a founder of Nocion Therapeutics, Quralis, and BlackBox Bio; an SAB member of Lundbeck Pharma, Tafalgie Therapeutics, and Axonis; on *Neuron*'s advisory board; and has received grants from NIH.

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