Gene therapy and small molecule treatment of chronic pain without addiction

Unmet Need

Chronic pain is an escalating issue worldwide – in the U.S., an estimated one of five adults are affected. Chronic pain is difficult to treat, often requiring powerful opioids to provide relief. These oftentimes have moderate analgesic benefit and cause long-term unwanted effects including habituation, escalating drug use and outright addiction. Over 75,000 Americans died from opioid overdoses in the year ending April 2021, up from over 56,000 the year before. The compelling need to develop new safe and effective analgesic treatments, devoid of opioid liabilities, is rooted in the synergistic crises of chronic refractory pain epidemic plus opioid epidemic, both ongoing and with ongoing synergy. Thus, there exists an urgent need for new ways of treating chronic pain that do not have side effects such as addiction and sedation.

Technology

Duke inventors and colleagues have developed new therapeutic approaches to chronic pain management that are effective and long-lasting, yet not addictive or sedative. The team elucidated an epigenetic mechanism that upregulates the expression of the *KCC2* gene. The KCC2 transporter pumps chloride ions out of neurons. Enhancement of *KCC2* gene expression normalizes the inhibitory effects of GABA, and repairs this function in the pain gate of the spinal cord where the primary defect in chronic pain is lack of expression of *KCC2*. The team demonstrated safe and effective treatment of chronic pain due to nerve injury and metastatic bone cancer in preclinical mouse models with two approaches: one by repurposing the cancer drug candidate kenpaullone, the other by delivering a

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Meet the Inventors

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Publication(s)

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External Link(s)

• From the lab of Dr. Wolfgang Liedtke, M.D., Ph.D.
• New life for a cancer drug that reprograms pain pathways to treat chronic pain (Press release, EurekAlert!)

delta-catenin transgene to the spinal cord through viral vector gene therapy. Both approaches were effective at enhancing gene expression of *KCC2* in key pain relay nerve cells in the dorsal spinal cord, thus rendering GABA transmission more effective. Enhancing *KCC2* expression was also effective against itch in a contact dermatitis preclinical model.

Other Applications

The *KCC2* gene has been linked to other neurological pathologies, including spinal cord and brain injury, epilepsy, Rett syndrome, Huntington's disease, autism spectrum disorders, schizophrenia, and beyond. Enhancing *KCC2* expression could be beneficial for diseases with impaired function of GABA caused by elevated neuronal chloride.

Advantages

- No observed side effects such as addiction, sedation, motor impairment
- Onset of action is delayed by a few days, indicative of gene regulation renormalization, then pain relief has prolonged duration over weeks
- Novel targeted pathway and mechanism of action elucidated as involving delta-catenin and KAISO transcription factors
- Multiple therapeutic approaches demonstrated
- *KCC2* gene expressed only in neurons, providing a promising target for gene therapy