Multiplexed In Vivo Epigenome Engineering for Therapeutic Targeting of Chronic Pain

Principal Investigator: MALI, PRASHANT
Institution Receiving Award: CALIFORNIA, UNIVERSITY OF, SAN DIEGO
Program: PRMRP
Proposal Number: PR210085
Award Number: W81XWH-22-1-0401
Funding Mechanism: Investigator-Initiated Research Award
Partnering Awards:
Award Amount: $2,528,000.00

PUBLIC ABSTRACT

In the U.S. and worldwide, pain is a leading cause of disability and diminished quality of life and normal functioning. It impacts more people than diabetes, heart disease, and cancer together. Patients have come to routinely expect pharmacological management, with the prevalent aggressive approach for managing pain states being based on opiates. While the utility of opiates has made them a mainstay of pain management, resulting in a massive increase in opioid prescriptions over the last decade and an attendant epidemic of opioid use leading to abuse, and overdose deaths. Notably, the national opioid crisis affects every demographic, but in particular Veterans, who according to estimates are twice as likely to die from an opioid overdose than civilians. Veterans are more susceptible to opioid addiction as they are more likely to suffer from chronic pain, and mental health problems like post-traumatic stress disorder (PTSD), which make them even more likely to inappropriately use drugs in an attempt to self-medicate.

There are at least four key reasons supporting the need for new and alternative pain therapeutics: (1) limited efficacy of opiates in many pain states; (2) abuse potential of the molecule representing the positive reinforcing properties of analgesics that characterize the classic opiates secondary to their robust reward phenotype; (3) progressive loss of response with continued exposure (e.g., tolerance) characterized by a gradual increase in dose to achieve a given state of anti-nociception; and (4) observation that paradoxically the use of opiate analgesics (as in trauma and surgery) may lead to an enhancement of post-wounding pain states by activating a number of signaling cascades leading to an enhanced pain state.

Pain arising from somatic or nerve injury/pathologies typically initiates by activation of populations of primary afferent neurons, which terminate in the spinal dorsal horn. The cell body of a primary afferent lies in its dorsal root ganglion (DRG). Genome-wide association studies (GWAS), gene arrays, and proteomics analyses have identified a large number of relevant targets that are associated with function of these nociceptive afferents carrying the information generated by tissue and nerve injury. For instance, hereditary loss-of-function mutation in NaV1.7 leads to insensitivity to pain without other neurodevelopmental alterations. However, the high sequence similarity between NaV subtypes has frustrated efforts to develop selective inhibitors. In recent preliminary work, we investigated targeted epigenetic repression of NaV1.7 via epigenome engineering approaches based on CRISPR as a potential treatment for chronic pain. Towards this end, by the lumbar intrathecal route we delivered adeno-associated viruses (AAVs) and confirmed the ability to ameliorate paclitaxel-induced neuropathic pain.

This presents a novel non-addictive pain prevention and amelioration approach for enabling long-lasting analgesia.

The human genome encodes genes whose modulation can potentially confer protection to painful stimuli. For example, several point mutations in the sodium channel Nav1.7 are associated with rare monogenic conditions of hypersensitivity and insensitivity to pain. While an excellent target, the creation of blockers for this site has not led yet to a druggable entity. Inspired by this, we propose here to programmably regulate genes that, alone or in combination, will directly dampen encoding of the pain stimuli. Our therapeutic approach directly regulates the changes in spinal function generated by pain input, reducing the likelihood of pain chronification and circumventing the use of opioids, thereby avoiding their attendant adverse effects. Our approach thus presents a completely new paradigm in pain management.

Building on this preliminary data, we propose here to develop safe and efficacious in vivo epigenome engineering-based approaches for enabling durable pain management. Specifically, we aim to achieve the following three objectives via this proposal: Aim 1: We will expand our CRISPR and Zinc finger based approaches to target the NaV1.7 and NaV1.8 channel proteins, singly and in combination, as both of these are involved in key steps of the pain sensation cascade.; Aim 2: We will engineer small molecule inducible AAV-CRISPR/ZF-mediated repression of the NaV1.7 and NaV1.8 channel proteins to enable on-demand turning on or off of the sensing of pain. Aim 3: We will rigorously assess the therapeutic profile and efficacy of the inducible AAV-CRISPR/ZF systems targeting Nav1.7 and Nav1.8 in multiple murine pain models.

Highly and directly relevant to the PRMRP topic area: “non-opioid therapy for pain management,” our novel approach for targeting chronic pain, both durably (for months at an end via a single dose treatment), inducibly (i.e., turned on or off on demand), and efficaciously (with high target specificity and no risk of addiction), will enable a new paradigm for treating our population, both as preemptive administration in anticipation of a pain stimulus (pre-operatively) or during an established chronic pain state.