Precision gene therapy for treating severe pain

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Chronic pain is a major socioeconomic problem. It affects more than 25% of adults in the US, costs over $500 billion annually, and drives the opioid epidemic. Human genetic evidence based on the voltage-gated sodium channel NaV1.7 and independent confirmation in mouse models together demonstrate that reducing the firing of first-order nociceptors (pain-sensing neurons) is sufficient to abrogate pain. Estimates from rodent studies using inhibitory optogenetic constructs suggest that silencing as few as 15% of nociceptors would be sufficient to yield a marked reduction in pain. However, efforts focusing on NaV channels have faced substantial challenges in translational development.

We propose an AAV-based gene therapy strategy to overexpress potassium channels in nociceptors and block pain. Potassium channels hyperpolarize the neuronal membrane potential and thereby decrease firing. Human genetic evidence supports this strategy as potassium channel gain-of-function haplotypes are protective in several pain conditions.

Our gene therapy strategy will allow us to address critical limitations in current pain treatment: although most severe pain complaints are focal, almost all existing therapies are systemic and therefore associated with side effects and limited efficacy. Such concerns are particularly important in elderly patients and those with medical comorbidities, who have a greater risk of side effects from systemic medications. Our AAV-based approach enables focal injection to spatially target potassium channel overexpression in order to treat pain aggressively while minimizing side effects. To further precisely target our gene therapy to nociceptors specifically, we identified human short promoter segments that facilitate nociceptor-specific payload expression but are small enough to fit together with the potassium channel in a standard AAV vector.

Thus, our dual spatial and cell-type precision strategy offers a highly targeted approach supported by human genetic evidence to treat severe focal pain conditions while minimizing adverse effects.