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Gene Therapy for Pain: A Perspective

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We recently reported results of the first clinical trial of gene transfer as a treatment for pain (Fink et al. 2011). Ten subjects with moderate to severe intractable pain from cancer received NP2, a replication defective herpes simplex virus (HSV)-based vector engineered to express human preproenkephalin, injected intradermally into the dermatome(s) corresponding to the radicular distribution of pain. There was no placebo control in this relatively small phase I trial, but in addition to achieving the primary safety outcome, there was an apparent dose-dependent analgesic effect. Subjects receiving a low dose of NP2 reported no substantive effect, while subjects in the middle and high dose cohorts reported clinically meaningful pain relief as measured by patient reported numeric rating scale (NRS) and Short Form McGill Pain Questionnaire (SF-MPQ) for four weeks following injection of NP2. Based upon these results, we have initiated a Phase II, double-blind, randomized, placebo-controlled, clinical trial [ClinicalTrials.gov identifier NCT01291901].

Replication defective HSV vectors injected into the skin are carried by retrograde axonal transport to dorsal root ganglia (DRG), where the vector establishes a persistent state within the nucleus of those cells as a circular episomal element. Transgene products produced from the otherwise quiescent vector genome are carried by anterograde axonal transport to axon terminals in the spinal cord. The approach of using HSV-mediated gene transfer to treat pain is based on the premise that targeted delivery and expression of genes coding for anti-nociceptive products to DRG neurons can be used to produce analgesic effects by selectively interfering with nociceptive input at the anatomic level corresponding to the regional distribution of the pain. Among the potential viral-based gene transfer vectors, HSV is particularly well-suited for this purpose since the parental wild-type virus from which the replication defective gene transfer vectors are constructed naturally targets DRG neurons from skin infection to establish a life-long persistent (latent) state.

The NP2 vector administered to subjects contained the gene for human preproenkephalin. Neurons transduced with this vector release enkephalin peptides, the endogenous agonists for the delta opioid receptor. The human clinical trial was preceded by preclinical studies that examined the effect of HSV vectors expressing preproenkephalin in rodent models of inflammatory pain, neuropathic pain and pain caused by cancer in bone (Goss et al. 2001; Goss et al. 2002; Hao et al. 2003). Similar analgesic effects of preproenkephalin-expressing replication defective HSV-based vectors have been reported by other investigators in several different models of pain (Wilson et al. 1999; Braz et al. 2001; Meunier et al. 2005; Yeomans et al. 2006). We chose to proceed with a clinical trial in patients with intractable pain resulting from terminal cancer because, despite the evidence of safety from preclinical biodistribution and toxicology studies, this was the first clinical trial using HSV to deliver transgenes to patients.

Disclosures: David Fink is co-inventor on patents that are held by the University of Pittsburgh and for which he may receive royalties. He received grant funding from Diamyd for the conduct of the human trial, but has no other financial relationships with Diamyd. Darren Wolfe is an employee of Diamyd and a co-inventor on patents held by the University of Pittsburgh.

The strategy of employing targeted gene delivery to the DRG to treat pain is not limited to preproenkephalin. We have constructed a synthetic gene cassette that produces endomorphin peptides, the endogenous agonists for the mu opioid receptor. The endomorphin-expressing replication-defective HSV vector provides significant analgesic effects in models of inflammatory pain (Hao et al. 2009), and through actions on the mu opioid receptor is likely to have anti-inflammatory effects as well. Transduction of DRG with an HSV vector expressing glutamic acid decarboxylase (GAD) resulted in constitutive release of gamma amino butyric acid from afferent terminals in the dorsal horn and reduced pain-related behaviors in animal models of neuropathic pain resulting from nerve injury or from diabetes (Hao et al. 2005; Chattopadhyay et al. 2011). In addition to inhibitory neurotransmitters, HSV vectors expressing anti-inflammatory proteins interleukin-4, interleukin-10 and the tumor necrosis factor soluble receptor have demonstrated reproducible analgesic effects; HSV-delivered RNA interference can be used to knock down expression of genes in the DRG that are involved in maintaining chronic pain.

HSV is not the only vector that can be used to modify pain-related behaviors. In animal studies, gene transfer achieved by intrathecal injection of non-viral plasmid-based gene transfer vectors, as well as adenovirus, adeno-associated virus (AAV)-, and retroviral-based gene transfer systems have been shown to provide analgesic effects in a wide range of models of pain (Cope and Lariviere 2006), presumably by producing continuous release of peptides with analgesic effects from transduced meningeal cells. Transduction of neurons in the DRG has been demonstrated in animal models following direct injection of an AAV-based vector into DRG (Xu et al. 2003), and by intrathecal inoculation of an AAV type 8 vector (Storek et al. 2008), but none of these alternates have yet reached human clinical trials.

NP2 exemplifies a generalizable HSV vector mediated gene transfer platform that can be employed to deliver genes to DRG neurons by intradermal inoculation, an approach that has been termed the nerve targeting drug delivery system (NTDDS). An NTDDS vector expressing GAD is currently progressing through preclinical evaluation and cGMP manufacturing in prelude to a clinical trial in patients with painful diabetic neuropathy. We have used the same approach to direct the local release of neuroprotective proteins from transduced DRG to protect against the progression of nerve damage (Mata et al. 2006), and an NTDDS-neurotrophic factor vector is being developed for potentially the first human trial in patients at risk for the development of chemotherapy induced peripheral neuropathy.

Chronic pain is a difficult clinical problem, and the history of drug discovery in this field over the past several decades has not been encouraging (Burgess and Williams 2010; Kissin 2010). Advances in the basic understanding of acute and chronic pain have greatly expanded the range of potential targets for analgesic therapy. But just as with well-established analgesic drugs, like opiates, whose use is often limited by the widespread distribution of receptors that result in side effects from systemic administration, even newly discovered targets that may initially appear to be expressed exclusively in nociceptive pathways (Premkumar and Sikand 2008) are often found to be widely distributed. Gene transfer, if it proves successful in placebo-controlled studies, is not an approach that is likely to be useful for all forms of chronic pain. For example, gene transfer to DRG would not be applicable to diffuse pain syndromes such as that seen in fibromyalgia, and is unlikely to be useful in central pain syndromes such as occur after thalamic stroke. Nonetheless, the results of the phase 1 clinical trial mark an important step in the development of this novel platform for the treatment of pain, one that we hope will ultimately add to the therapeutic choices available to physicians who treat patients with chronic pain.

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