Scientific Abstract

Up to 80% of patients with cancer ultimately suffer from chronic pain [1], the most common cause of which is metastasis to bone. The pathogenic mechanism underlying bone cancer pain is not completely understood, but tumor metastasis stimulates osteoclast activity resulting in bone resorption and the release of soluble factors that may sensitize primary nociceptive afferents [2]. Nerve root compression or muscle spasm may also occur. Treatment directed at reducing tumor size or attenuating the inflammatory response may reduce pain [3], but ultimately many patients require treatment with narcotic analgesics. These opioid agonists acting at both spinal and supraspinal sites [4,5] are effective in relieving pain in 70-90% of patients but have relatively low potency in cancer pain [6]. Adverse effects resulting from CNS (e.g. sedation) or systemic (e.g. constipation, urinary retention) stimulation of opioid receptors limit the effective dose that may be given. Intrathecal delivery using mechanical pumps may reduce systemic adverse effects, but is not without complications [7,8].

Targeted delivery and expression of endogenous opioid peptides in the nervous system by gene transfer is a strategy to exploit the use of these natural peptides as effective analgesic agents. In this regard, the unique targeting properties of herpes simplex virus (HSV)-based vectors that allow for efficient uptake by dorsal root ganglia (DRG) neurons from peripheral inoculation [9,10] provide a means for directed expression and release in the spinal cord. We have demonstrated that a non-replicating HSV vector expressing human proenkephalin transduces DRG after subcutaneous inoculation to reduce pain-related behavior in models of inflammatory pain [11], neuropathic pain, and pain caused by cancer.

In this Phase-I dose escalation clinical trial, NUREL-P1, a replication defective HSV-1 vector containing the coding sequence for human proenkephalin (PE) under the control of the human cytomegalovirus immediate early promoter (HCMV IEp) will be administered by subcutaneous inoculation to transduce the dorsal root ganglia of patients with intractable pain from cancer unresponsive to maximal therapy. The <u>primary goal</u> of this study is to determine the safety of subcutaneous inoculation of the NUREL-P1 in human patients with intractable pain, and to establish the parameters of vector persistence and transgene expression in these patients. The <u>secondary goals</u> of this study are to determine whether NUREL-P1 has pain-relieving properties (analgesia) measured by a reduction in pain, a decrease in the requirement for concurrent opioid therapy, and improvement in other measures of activity and sleep. Ultimately, we hope to develop a new therapy to offer patients when conventional therapies are ineffective or the patient's pain therapies are complicated by significant and dose-limiting side-effects.

18 patients with intractable localized pain from cancer metastatic to vertebral bodies will be studied. The study will follow a standard Phase I escalation scheme. Three subjects will be treated at each dose level (1/2 log increments). If the highest dose prescribed by protocol is reached, three additional subjects will be treated at same dose for a total of six subjects. Patients will be treated with 10^7, $3x10^7$, 10^8, $3x10^8$, 10^9, and 3×10^9 PFU of NUREL-P1. This study will determine the maximal tolerated dose (MTD) of the vector, and the nature of possible dose-limiting toxicity (DLT). The amount and of pain, and the dose of analgesic medication will be recorded to determine the possible clinical response to the treatment.