Gene therapy for chronic pain gets first test in people

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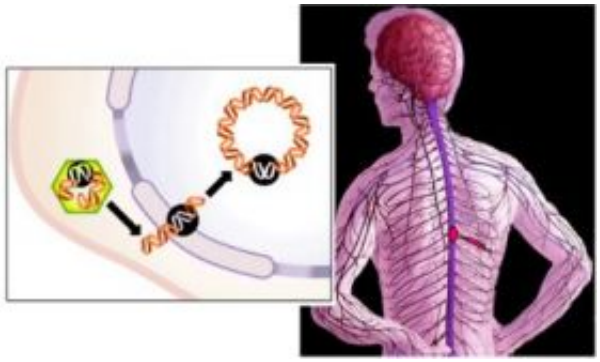

The gene transfer vector (left) is injected into the skin in the area of pain (red line, right). From the skin, the vector is carried into sensory nerves and releases the inhibitory neurotransmitter locally in the spinal cord (red oval). Image: University of Michigan

This week, University of Michigan scientists will begin a phase 1 clinical trial for the treatment of cancer-related pain, using a novel gene transfer vector injected into the skin to deliver a pain-relieving gene to the nervous system.

A gene transfer vector is an agent used to carry genes into cells. In this groundbreaking clinical trial, the investigators will use a vector created from herpes simplex virus (HSV) – the virus that causes cold sores – to deliver the gene for enkephalin, one of the body's own natural pain relievers.

"In pre-clinical studies, we have found that HSV-mediated transfer of enkephalin can reduce chronic pain," says David Fink, M.D., Robert Brear Professor and chair of the department of neurology at the U-M Medical School. Fink developed the vector with collaborators and will direct the study.

"After almost two decades of development and more than eight years of studies in animal models of pain, we have reached the point where we are ready to find out whether this approach will be effective in treating patients," Fink says. The investigators are recruiting 12 patients with intractable pain from cancer to examine whether the vector can be used safely to deliver its cargo to sensory nerves.

The trial represents two firsts, says Fink: It is the first human trial of gene therapy for pain, and the first study to test a nonreplicating HSV-based vector to deliver a therapeutic gene to humans. Fink says the technique may hold promise for treating other types of chronic pain, including pain from nerve damage that occurs in many people with diabetes.

The HSV vector, genetically altered so it cannot reproduce, has a distinct advantage, Fink says: "Because HSV naturally travels to nerve cells from the skin, the HSV-based vector can be injected in the skin to target pain pathways in the nervous system."

Gene therapy for pain

Chronic pain is an important clinical problem that, despite a wide array of therapeutic options, cannot be effectively treated in a substantial number of patients. Fink notes that one key problem in treating pain is that the targets of conventional pain-relieving medications tend to be widely distributed in the nervous system, so that "off target" side effects of the drugs often preclude the use of those drugs at fully effective

doses.

"This provides the rationale for using gene transfer to treat pain," Fink says. "We use the vector to deliver and express a chemical that breaks down very quickly in the body. The targeted delivery allows us to selectively interrupt the transmission of pain-related signals and thus reduce the perception of pain."

Enkephalin is one member of the family of opioid peptides that are naturally produced in the body. Opioid peptides exert their pain-relieving effects by acting at the same receptor through which morphine and related opiate drugs achieve their pain-relieving effects. In this trial the enkephalin peptide, produced as a result of the gene transfer, will be released selectively in the spinal cord at a site involved in transmitting pain from the affected body part to the brain.

"We hope that this selective targeting will result in pain-relieving effects that cannot be achieved by systemic administration of opiate drugs, " Fink says. "This trial is the first step in bringing the therapy into clinical use. A treatment is at least several years off."

Preclinical studies led to human trial

The phase I clinical trial represents the culmination of studies performed by investigators working in the U-M laboratory co-directed by Fink and his wife, Marina Mata, M.D., also a professor of neurology at U-M, along with colleagues at the University of Pittsburgh led by Joseph Glorioso, Ph.D. In published studies, the researchers have demonstrated that HSV-mediated gene transfer is effective in rats with pain resulting from inflammation, nerve damage or spinal cord injury, and in mice with pain caused by cancer. The extensive preclinical data in animal models were reviewed by the Recombinant DNA Advisory Committee at the National Institutes of Health. The Food and Drug Administration

approved an investigational new drug application for the therapy in February.

Source: University of Michigan