Gene therapy may be powerful new treatment for major depression

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In a report published in the Oct. 20 issue of *Science Translational Medicine*, researchers at NewYork-Presbyterian Hospital/Weill Cornell Medical Center say animal and human data suggest gene therapy to the brain may be able to treat patients with major depression who do not respond to traditional drug treatment.

The researchers hope to rapidly translate their findings into a human clinical trial using the same kind of gene therapy modality the investigators have pioneered to treat Parkinson's disease. A 45-patient randomized blinded phase II multicenter clinical trial using the gene therapy to treat Parkinson's has recently ended and results are being readied for publication.

"Given our findings, we potentially have a novel therapy to target what we now believe is one root cause of human depression," says the study's senior investigator, Dr. Michael Kaplitt, associate professor and vice chairman for research of neurological surgery at Weill Cornell Medical College and a neurosurgeon at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

"Current therapies for depression treat symptoms but not underlying causes, and while that works for many patients, those with advanced depression, or depression that does not respond to medication, could hopefully benefit from our new approach," adds Dr. Kaplitt.

The *Science Translational Medicine* study demonstrates that a brain

protein known as p11 in a single, small brain area, the nucleus accumbens, is critical to the feelings of reward and pleasure that are often missing in depression. This brain region had primarily been studied in addiction research, but the inability to find satisfaction with positive life experiences is one of the major sources of disability in depression.

While investigators believe that depression is a complex disorder that likely involves a number of brain areas and neural circuits, they say their findings suggest that restoring p11 may significantly alter the course of depression in humans.

"Applying molecular neurobiology and gene therapy to depression could dramatically alter the approach to psychiatric diseases," Dr. Kaplitt says. "Our results provide further evidence that the underlying causes of psychiatric disorders are due to molecular changes in key brain circuits, so that they are much more similar to common neurological disorders -- such as Parkinson's disease -- that might be helped by restoring molecular function."

The study pulls together human and animal data contributed by a team of researchers at NewYork-Presbyterian/Weill Cornell, as well as by investigators at Rockefeller University, Karolinska Institute in Sweden, the University of Texas Southwestern Medical Center and Neurologix in Fort Lee, N.J.

The idea for the new research began in conversations between Dr. Kaplitt, a pioneer of brain gene therapy, and Dr. Paul Greengard, of Rockefeller University, a neuroscientist who won a Nobel Prize in 2000 for his work in neurotransmission between brain neurons. In 2006, Dr. Greengard and his Rockefeller colleagues discovered that the p11 gene appears to play a key role in depression. They found p11 protein is needed to bring receptors that bind to the neurotransmitter serotonin to the surface of nerve cells. In the brain, serotonin regulates mood,

appetite and sleep, among other functions, and most antidepressants seek to regulate serotonin.

"In the absence of p11, a neuron can produce all the serotonin receptors it needs, but they will not be transported to the cell surface and therefore won't stick out and latch on to the neurotransmitter," says Dr. Kaplitt.

So the researchers decided to disable function of the p11 gene in mice using a virus which would produce an siRNA -- small pieces of double-stranded RNA -- that blocked the gene's expression. Once they showed this could be done, they chose to selectively target p11 expression in the nucleus accumbens brain area because human functional MRI studies at Weill Cornell had shown this area to be particularly affected in depressed patients.

"Focusing exclusively on this area is fairly novel because it had been thought to be mostly involved in behaviors that are tied to addiction," Dr. Kaplitt says.

The mice without p11 all exhibited depression-like behaviors. That prompted Dr. Kaplitt and his team to adapt the gene therapy vehicle they had successfully tested in Parkinson's disease patients in a phase I clinical trial reported in the Lancet in 2007. The therapy uses an inert "smart" virus as a Trojan horse to enter brain cells and deposit a genetic payload into the genome of neurons. These new genes then produce their protein.

To treat Parkinson's disease Dr. Kaplitt used the virus to deliver glutamic acid decarboxylase (GAD), the enzyme that synthesizes the neurotransmitter GABA. In the current study, he inserted the p11 gene into the virus and delivered them to the nucleus accumbens of the p11-free mice. The treatment effectively reversed depression-like behaviors in the mice.

This study also reports that autopsy studies of patients with severe depression revealed significantly reduced levels of the p11 protein in their nucleus accumbens, compared with individuals without depression.

"Together, these studies provide strong evidence that maintaining adequate levels of this particular protein, p11, in this pleasure-reward area of the brain may be central to preventing or treating depression," Dr. Kaplitt says.

The researchers say that not only could the gene therapy used here restore p11, but future research may identify a small molecule to restore p11.

Provided by New York- Presbyterian Hospital

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