CEDARS-SINAI MEDICAL CENTER. NEWS

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RESEARCHERS AT CEDARS-SINAI REPORT THAT TWO SPECIFIC PROTEINS DELIVERED VIA A GENETICALLY ENGINEERED VIRUS PREVENTED THE PROGRESSIVE LOSS OF NERVE CELLS THAT CAUSE PARKINSON'S DISEASE IN LABORATORY RATS

LOS ANGELES (September 8, 2004) – In recent years, scientists have made important strides in developing drugs that help patients manage the symptoms of Parkinson's Disease – a chronic, progressive movement disorder affecting as many as one million Americans. But despite their effectiveness, the drugs don't stop Parkinson's disease from progressing, causing patients' symptoms to eventually grow worse in spite of medication.

Now, researchers at Cedars-Sinai Medical Center have found that two specific proteins – "Sonic Hedgehog" and "Gli-1" – delivered via a genetically engineered virus into the brains of laboratory rats, prevented the progressive degeneration of nerve cells in the brain that cause Parkinson's disease. The study, published in the September issue of the journal, *Molecular Therapy*, may lead to a new way to treat patients with advanced Parkinson's Disease.

"Our results establish, for the first time, that viral transfer of Sonic hedgehog and Gli-1 - two proteins that are involved in early brain development, but are no longer present in the adult brain – may provide a new strategy to prevent progressive degeneration of the nerve cells in the brain that cause Parkinson's disease," said Pedro Lowenstein, M.D., Ph.D., Director of the Gene Therapeutics Research Institute at Cedars-Sinai Medical Center, and a Professor of Medicine and Pharmacology at UCLA.

Parkinson's disease occurs when the nerve cells in the part of the brain known as the "substantia nigra" that produce a chemical called dopamine begin to malfunction and progressively die. Dopamine acts as a chemical messenger to send signals to a part of the brain called the *basal ganglia* that controls movement and coordination. But as more of these cells die, less and less dopamine is produced, causing Parkinson's disease.

To treat the symptoms of Parkinson's disease, doctors rely on various types of drugs that work by helping to replenish dopamine. A drug called L-DOPA (levodopa), for example, is absorbed in the brain and changed into dopamine. Other drugs, work differently by either prolonging the effect of levodopa-formed dopamine or by actually mimicking dopamine. But regardless of how they work, patients often have to take more than one drug to either enhance the drug's effects or to reduce the side effects that many of the drugs cause. As more cells die during the progression of the disease, these drugs lose their effectiveness.

"Because these drugs don't stop the disease from progressing, we used a genetically engineered viral vector to deliver very specific molecules to see whether they would prevent the nerve cells in the brain from dying in adult rats with Parkinson's," commented Maria Castro, Ph.D., Co-Director of the Gene Therapeutic Research Institute at Cedars-Sinai and a senior author of the study. "Ultimately, because we found that two of these

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molecules prevented cell death, we aim to translate this type of gene therapy into a clinical trial to determine whether it will stop the progression of the disease. Importantly, *Sonic Hedgehog* and *Gli1*, display novel mechanisms of action compared to other drugs utilized so far."

Genetically engineered viruses are used to transport genes and/or proteins into cells and have been used in gene therapy research for the last ten years. Just like a viral infection, they work by tricking cells into accepting them as part of their own genetic coding. The trick has been to alter the virus so that it delivers the desired genetic material, while removing any characteristics that make the virus dangerous.

To make viruses safe and effective, scientists remove the genetic coding that causes infection and engineer them so that they stop reproducing. The adenoviral vector used in this study, for example, has been genetically manipulated to selectively express proteins that can protect the neurons that are damaged during the course of Parkinson's disease.

"Currently, we are constructing other versions of this virus that could eventually be used in clinical trials in humans that are safe even when the body mounts an immune response, and that could be switched 'on' and 'off' at will," said Dr. Castro. "In other words, these new viral vectors would effectively resist any attack by the immune system and have built-in switches that allow the doctor to regulate the delivery of the neuroprotective proteins as needed."

In the laboratory study, the investigators used an adenoviral vector to test the effectiveness of three proteins: Sonic Hedgehog (Shh), a signaling molecule that plays a key role in the development of the brain but is no longer present in the adult brain; Gli-1, a protein that turns genes on and off within the same signaling pathway; and Nurr1, a protein receptor that is needed to produce *substantia nigra* neurons in the brain.

To determine whether any of the three proteins would prevent nerve cells in the brain from dying, the investigators injected Shh, Gli-1 and Nurr1 into the brains of laboratory rats with Parkinson's disease. The investigators found that nerve cells in the rats treated with Shh and Gli1, were protected, while no effect was seen in those treated with Nurr1.

"Given that these proteins are only present in the developing brain, our study demonstrates that we were able to use a genetically engineered virus to deliver them into the adult brains of laboratory rats with Parkinson's disease and that they significantly protected nerve cells from dying," said Dr. Lowenstein.

Cedars-Sinai Medical Center is one of the largest non-profit academic medical centers in the Western United States. For the fifth straight two-year period, Cedars-Sinai has been named Southern California's gold standard in health care in an independent survey. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthrough in biomedical research and superlative medical education. The Medical Center ranks among the top 10 non-university hospitals in the nation for its research activities.

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