

Media Contact: Simi Singer  
E-mail: [Simi.Singer@cshs.org](mailto:Simi.Singer@cshs.org)  
Telephone: (310) 423-4768

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## **RESEARCHERS AT CEDARS-SINAI MEDICAL CENTER DEMONSTRATE A NEW WAY TO SWITCH THERAPEUTIC GENES “ON” AND “OFF”**

### **Novel Signaling System May Eventually Help Make Gene Therapies More Effective**

Los Angeles (December 22, 2005) – A gene therapy research team at Cedars-Sinai Medical Center has developed a new method of signaling therapeutic genes to turn “off” or “on,” a mechanism that could enable scientists to fine-tune genetic- and stem cell-based therapies so that they are safer, more controllable and more effective.

Although other similar signaling systems have been developed, the Cedars-Sinai research is the first to give physicians the flexibility to arbitrarily turn the gene expression on or off even in the presence of an immune response to adenovirus, as would be present in most patients undergoing clinical trials. This has been a major obstacle in bringing the testing of genetic therapies to humans in a clinical setting.

As reported in a study published in the January issue of the *Journal of Virology*, the development of a new delivery system that can more effectively regulate therapeutic gene expression has important implications for efforts to advance gene and stem cell therapy strategies that may ultimately be used to treat life-threatening neurodegenerative diseases in the clinical setting. The study, which involved laboratory rats, focused on the area of the brain that has already been the target for research into genetic therapies for Parkinson’s disease.

“Since some diseases treated with gene therapy will require constant therapeutic expression while others may have periods of remission and therefore only require treatment during ‘active’ disease states, a system that can more closely monitor the ‘how much’ and ‘when’ the therapeutic gene is produced is a critically important tool in the development of gene therapy treatments that could help people suffering from Parkinson’s and other diseases,” said Maria Castro, Ph.D., co-director of the Board of Governors’ Gene Therapeutic Research Institute at Cedars-Sinai and lead author of the study.

“Until now, researchers working to develop successful gene therapy for diseases such as Parkinson’s have hit roadblocks such as toxic side-effects from over-expression of the therapeutic gene, and adverse events caused by immune system reactions to the viral delivery systems currently used to deliver the therapeutic genes,” said Pedro Lowenstein, M.D., Ph.D., co-director of the Institute and co-author of the study. “Now, we’ve engineered a genetic switch in a novel gene transfer vector that will overcome those barriers and set the stage to allow the next phase of research to occur.”

Gene therapy is an experimental treatment that uses genetically engineered viruses (vectors) to transfer therapeutic genes and/or proteins into cells. As in a viral infection, the viruses work by tricking cells into accepting them as part of their own genetic machinery. To make them safe, scientists remove the viral genes that cause infection and engineer them so that they stop reproducing after they have delivered the therapeutic gene.

In this study, researchers created a genetic switch system that is turned on in the presence of the antibiotic tetracycline. Therefore, if this method is tested eventually in humans, patients would need to be given this antibiotic before they begin gene therapy treatment. The switch system also produces a protein called silencer, which completely shuts down gene expression in the “off” state, thereby preventing leakage of the therapeutic gene when it is no longer needed. According to Castro, this novel vector system is much less likely to create an undesirable immune response in the host and would still be functional in the presence of an infection to wild type adenovirus (a non-engineered virus that causes conjunctivitis and upper respiratory tract infections) as is present in a high percentage of patients undergoing clinical trials. These are the main hurdles that needed to be overcome before gene therapy can be considered a safe and efficacious clinical strategy.

According to Drs. Castro and Lowenstein, the next step in the development of this new signaling system is to activate the newly developed genetic switch to actively express compounds that are known to be effective at reversing the symptoms and rescuing the damaged neurons in Parkinson’s disease patients. Researchers hope to begin a Phase 1 clinical trial in humans in the near future.

The Board of Governors Gene Therapeutic Research Institute at Cedars-Sinai Medical Center is a world-renowned translational research program. Established in 2000, the Institute is engaged in state-of-the-art technologies to develop genetic and stem cell-based therapies for the treatment of life-threatening disorders such as cancers, chronic neurodegenerative diseases and autoimmune disorders. It includes more than 30 scientists and physicians devoted to bringing these new therapeutic approaches to the clinical arena. Additional information is available at [www.cedars-sinai.edu/gtri](http://www.cedars-sinai.edu/gtri).

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