Alzheimer's Cognitive Decline Slowed In Gene Therapy Patients

April 24, 2005

Sue Pondrom

PET scans and cognitive tests have suggested that Alzheimer's disease patients with genetically modified tissue inserted directly into their brains show a reduction in the rate of cognitive decline and increased metabolic activity in the brain, according to a study published in the April 24, 2005 online issue of the journal *Nature Medicine* by researchers at the UCSD School of Medicine.

PET scans demonstrated an increase in the brain's use of glucose, an indication of increased brain activity, while mental-status tests showed a slowing of the patients' rate of cognitive decline was reduced by 36 to 51 percent. In addition, researchers examined the brain tissue of a study participant who had died and found robust growth of extensions from the dying cholinergic cells near the site of growth factor gene delivery. Cholinergic neuron loss is a cardinal feature of Alzheimer's disease, a progressive brain disorder affecting memory, learning, attention and other cognitive processes.

"If validated in further clinical trials, this would represent a substantially more effective therapy than current treatments for Alzheimer's disease," said Dr. Mark Tuszynski, UCSD professor of neurosciences, neurologist with the VA San Diego Healthcare System, and the study's principal investigator. "This would also represent the first therapy for a human neurological disease that acts by preventing cell death."

In this first-ever gene therapy for Alzheimer's disease, UCSD physician-scientists took skin cells from eight patients diagnosed with early Alzheimer's disease. The tissue was modified in the lab to express nerve growth factor (NGF), a naturally occurring protein that prevents cell death and stimulates cell function. In surgeries that took place in 2001 and 2002 at UCSD's John M. and Sally B. Thornton Hospital, the genetically modified tissue was implanted deep within the brains of the eight patients who had volunteered for the study.

The human clinical trial was undertaken following extensive studies in primates conducted by Tuszynski and colleagues, which showed that grafting NGF-producing tissue into the brains of aged monkeys restored atrophied brain cells to near-normal size and quantity, and also restored axons connecting the brain cells, essential for communication between cells. The recent human studies were a Phase I clinical trial, designed to test safety and toxicity. The procedure was initially performed while patients were awake but lightly sedated, and two patients moved as the cells were being injected, resulting in bleeding in the brain. One of these patients died five week later. As a result of the bleeds, the protocol was redesigned to perform the procedure under general anesthesia and all subsequent procedures were performed without complication.

Cognitive outcomes were assessed in the six patients who completed the NGF delivery procedure safely. The Mini Mental Status Examination (MMSE), which evaluates cognitive function, was administered at screening, the time of treatment and at several intervals after treatment. Over an average post-treatment follow-up period of 22 months, the rate of decline on the MMSE among NGF-treated patients was reduced by as much as 51 percent. An additional test, called the Alzheimer's Disease Assessment Scale-Cognitive Subcomponent, or ADAS-Cog, also showed improvements in rates of decline followed the MMSE findings.

Post-operative PET scans in four subjects showed significant increases in the brain's absorption of a radioisotope called 18-fluorodeoxyglucose, an indicator of increased metabolic activity in the brain. The

researchers noted that the increase was observed in most cortical regions that receive cholinergic input from forebrain nerve cells called the nucleus basalis, and in the cerebellum, a structure associated with cortical plasticity.

In addition to Tuszynski, authors of the paper in *Nature Medicine*, were Dr. Leon Thal, UCSD chair of neurosciences, director of the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC), and a neurologist with the VA San Diego Healthcare System; Mary Margaret Pay., R.N., David P. Salmon, Armin Blesch, Dr. Gilbert Ho, Dr. Gang Tong, Dr. Lawrence Hansen, and James Conner, of the UCSD Department of Neurosciences; Dr. Hoi Sang U, UCSD Department of Surgery; Lee Vahlsing, UCSD Department of Neurosciences and VA San Diego Healthcare System; Dr. Roy Bakay, Rush University Department of Surgery; Dr. Piyush Patel, UCSD Department of Anesthesiology; Dr. Steven G. Potkin, and Christine Gall, UC Irvine Department of Neurology; James Fallon, UC Irvine Department of Neurobiology; Elliott J. Mufson, and Jeffrey H. Kordower, Rush University Department of Neurosciences.

The study was supported by the Institute for the Study of Aging and the Shiley Family Foundation.

Based on the positive findings of this Phase I trial, a new Phase I/II study using direct NGF gene delivery to the brain, thereby eliminating the need for grafting cells, is currently underway at Rush University Medical Center in Chicago, sponsored by the San Diego biotechnology company Ceregene, Inc. The Chicago trial is under the direction of Dr. David Bennett, director of the Rush University Alzheimer's Disease Center, and Dr. Zoe Arvanitakis, a Rush neurologist.

Media Contact: Sue Pondrom (619) 543-6163