Vaccine triggers immune response, prevents Alzheimer's

May 19 2008

A vaccine created by University of Rochester Medical Center scientists prevents the development of Alzheimer's disease-like pathology in mice without causing inflammation or significant side effects.

Vaccinated mice generated an immune response to the protein known as amyloid-beta peptide, which accumulates in what are called "amyloid plaques" in brains of people with Alzheimer's. The vaccinated mice demonstrated normal learning skills and functioning memory in spite of being genetically designed to develop an aggressive form of the disease.

The Rochester scientists reported the findings in an article in the May issue of Molecular Therapy, the journal of *The American Society of Gene Therapy*.

"Our study demonstrates that we can create a potent but safe version of a vaccine that utilizes the strategy of immune response shaping to prevent Alzheimer's-related pathologies and memory deficits," said William Bowers, associate professor of neurology and of microbiology and immunology at the Medical Center and lead author of the article. "The vaccinated mice not only performed better, we found no evidence of signature amyloid plaque in their brains."

Alzheimer's is a progressive neurodegenerative disease associated with dementia and a decline in performance of normal activities. Hallmarks of the disease include the accumulation of amyloid plaques in the brains of patients and the loss of normal functioning tau, a protein that

stabilizes the transport networks in neurons. Abnormal tau function eventually leads to another classic hallmark of Alzheimer's, neurofibrillary tangle in nerve cells. After several decades of exposure to these insults, neurons ultimately succumb and die, leading to progressively damaged learning and memory centers in the brain.

The mice that received the vaccines were genetically engineered to express large amounts of amyloid beta protein. They also harbored a mutation that causes the tau-related tangle pathology. Prior to the start of the vaccine study, the mice were trained to navigate a maze using spatial clues. They were then tested periodically during the 10-month study on the amount of time and distance traveled to an escape pod and the number of errors made along the way.

"What we found exciting was that by targeting one pathology of Alzheimer's — amyloid beta — we were able to also prevent the transition of tau from its normal form to a form found in the disease state," Bowers said.

The goal of the vaccine is to prompt the immune system to recognize amyloid beta protein and remove it. To create the vaccine, Bowers and the research group use a herpes virus that is stripped of the viral genes that can cause disease or harm. They then load the virus container with the genetic code for amyloid beta and interleukin-4, a protein that stimulates immune responses involving type 2 T helper cells, which are lymphocytes that play an important role in the immune system.

The research group tested several versions of a vaccine. Mice were given three injections of empty virus alone, a vaccine carrying only the amyloid beta genetic code, or a vaccine encoding both amyloid beta and interlueikin-4, which was found to be the most effective.

"We have learned a great deal from this ongoing project," Bowers said.

“Importantly, it has demonstrated the combined strengths of the gene delivery platform and the immune shaping concept for the creation of customized vaccines for Alzheimer’s disease, as well as a number of other diseases. We are currently working on strategies we believe can make the vaccine even safer.”

Bowers expects the vaccine eventually to be tested in people, but due to the number of studies required to satisfy regulatory requirements, it could be three or more years before human trials testing this type of Alzheimer’s vaccine occur.

Source: University of Rochester Medical Center