UT SOUTHWESTERN MEDICAL CENTER NEWS

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DNA gene vaccine protects against harmful protein of Alzheimer's disease

DALLAS – March 29, 2006 – Doses of DNA-gene-coated gold particles protect mice against a protein implicated in Alzheimer's disease, researchers at UT Southwestern Medical Center have found.

By pressure-injecting the gene responsible for producing the specific protein – called amyloid-beta 42 – the researchers caused the mice to make antibodies and greatly reduce the protein's build-up in the brain. Accumulation of amyloid-beta 42 in humans is a hallmark of Alzheimer's disease.

"The whole point of the study is to determine whether the antibody is therapeutically effective as a means to inhibit the formation of amyloid-beta storage in the brain, and it is," said Dr. Roger Rosenberg, the study's senior author and director of the Alzheimer's Disease Center at UT Southwestern.

The gene injection avoids a serious side-effect that caused the cancellation of a previous multi-center human trial with amyloid-beta 42, researchers said. UT Southwestern did not participate in that trial. In that earlier study, people received injections of the protein itself and some developed dangerous brain inflammation.

The new study is available online and appears in an upcoming issue of the *Journal of the Neurological Sciences*.

The researchers used mutant mice with two defective human genes associated with Alzheimer's, genes that produce amyloid-beta 42. "By seven months, the mice are storing abundant amounts of amyloid-beta 42," said Dr. Rosenberg.

While the mice were young, the scientists coated microscopically small gold particles with human amyloid-beta 42 genes attached to other genes that program cells to make the protein. The particles were then injected with a gene gun into the skin cells of the mice's ears using a blast of helium.

After receiving 11 injections over several months, the mice showed a high level of antibodies to amyloid-beta 42, and a 60 percent to 77.5 percent reduction of plaques in their brains.

As controls, the researchers also either injected mutant mice with the gene for a related but harmless protein, amyloid-beta 16, or with a gene vaccine that lacked any amyloid genes. These

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treatments did not cause antibody production, and the mice showed the large amounts of amyloid-beta 42 brain plaques normally seen in animals with these mutations.

The gene injection showed superior results compared to a previous human study in which amyloid-beta 42 protein itself was injected into muscle, Dr. Rosenberg said. That study was halted when a small percentage of participants developed inflammation of the brain and spinal cord.

Injecting the gene, in contrast, caused no brain inflammation in the mice.

Dr. Rosenberg said the difference was partly because in the human trial, the protein was injected along with a substance called an adjuvant, which increased the immune response to abnormal excessive levels, causing the dangerous brain inflammation. In addition, the immune response in humans may have involved antibodies called Th1, which were probably partly responsible for the inflammation. The gene injection in the mouse study produced Th2 antibodies, which have a low probability of causing brain inflammation. Furthermore, no adjuvant was needed for antibody production.

The gene immunization is now undergoing further animal studies, with the ultimate goal being a clinical trial in humans. The researchers also plan to see if it can reverse the size of established plaques in the brains of mice.

Other UT Southwestern researchers involved in the study were Drs. Bao-Xi Qu, assistant professor of neurology, Philip Boyer, assistant professor of pathology, and Linda Hynan, associate professor of clinical sciences and psychiatry. Dr. Stephen Johnston, formerly with UT Southwestern and now at Arizona State University, also participated.

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