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Cleveland, Ohio

Final Report

Gene-Environment Interactions in Alzheimer's Disease Mouse Models

*2005 Zenith Fellows Award—\$250,000 over two years
Sponsored by the Zenith Fellows and The Judy Fund*

Period Covered by This Report

April 1, 2006 through March 31, 2008

Location of Research

The Cleveland Clinic Foundation

Background

Most experts agree that sporadic, non-familial forms of Alzheimer's disease are caused by combination of risk factors, including genetics, environment, diet and socioeconomic demographics. Deciphering which factors have the biggest impact could help scientists devise preventions and treatments for this disease. However, teasing out the roles of these various factors in human populations is exceedingly difficult.

Bruce Lamb and colleagues planned to examine the potential role of genetic and environmental factors in Alzheimer pathology by examining the effect of diet and therapeutics in mice. The researchers planned to examine how diet and dietary intervention impact disease progression in four different strains of mice with known genetic backgrounds.

Goal of Study— Specific Aims

The researchers focused on cholesterol metabolism since elevated levels of the lipid have been linked to Alzheimer's disease. They reared the mice on either high-fat, or high-cholesterol diets and also treated some of the animals with cholesterol-lowering drugs. As the animals aged, the researchers tested their fat and cholesterol profiles and also tested for key markers of Alzheimer pathology, including deposits of beta-amyloid, the small protein that makes up senile plaques.

Research Outcomes and Significance

The researchers found that in one strain of mice, called B6-R1.40, a high-fat/high-cholesterol diet led to increased accumulation of beta-amyloid in the brain. These animals showed no changes in beta-amyloid production, however, suggesting that the accumulation of the peptide might be due to

reduced clearance from the brain. In B6-R1.40 mice, the researchers also did not find any alterations in the level of apolipoprotein E (ApoE), a major cholesterol carrier that has been implicated in beta-amyloid pathology.

These findings suggest that this particular strain of mice is genetically predisposed to beta-amyloid accumulation under high-fat/high-cholesterol conditions. Identifying the genetic sequences that bestow that susceptibility could help the researchers pinpoint genetic variants that increase risk for Alzheimer's in humans. The researchers have identified some factors that may contribute to disease susceptibility in these mice, including other proteins that interact with cholesterol, and enzymes or cutting proteins that degrade beta-amyloid. These factors may also influence Alzheimer pathology in humans.

Future Work

The researchers have also conducted widespread study to identify which genes are activated or repressed in the B6-R1.40 when fed high-fat/high-cholesterol diets. This study turned up 225 genes that are either turned on or off under these dietary conditions. They plan to study these genes individually to test if they may represent risk factors of Alzheimer-like pathology in mice and Alzheimer's in humans.

Publication

Ryman D, Lamb BT. Genetic and environmental modifiers of Alzheimer's phenotypes in the mouse. *Current Alzheimer Research*. 2006; 3: 465-473.

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Ryman D, Gao Y, Lamb BT. Genetic loci modulating amyloid-beta levels in a mouse model of Alzheimer's disease. *Neurobiology of Aging*. 2008; 29; 1190-1198.

Budget

With every peer-reviewed research grant awarded by the Alzheimer's Association, all indirect costs are capped at 10 percent (rent for laboratory/

office space is expected to be covered by indirect costs paid to the institution). The Association expects and enforces that 90 percent of the grant goes directly to funding the research itself. No more than 10 percent of the grant can be directed to administrative costs.

Approved by William H. Thies, Ph.D., vice president of Medical and Scientific Relations, as a confidential communication to the Zenith Fellows. Alzheimer's Association grant ZEN-05-14712 research progress report.