

***Judy Fund Awards for
Alzheimer's Disease Research***

**Overview of
Recent Studies**

Support from the Judy Fund has enabled six teams of researchers to pursue the answers to important scientific questions about the causes of Alzheimer's disease, ways to prevent or detect the disease, and the best approaches for providing medical care for patients already affected by the disease or related disorders. These research studies have spanned the spectrum of scientific approaches for addressing these issues, and studies have provided important clues about the causes of Alzheimer's disease and ways to treat it. In addition, support from the Judy Fund has been the catalyst for several research teams to attract other research grants, which has allowed them to expand their studies to address unanswered scientific and medical questions about Alzheimer's disease.

Research teams led by Edward H. Koo, M.D. and George Perry, Ph.D. are studying some of the basic mechanisms in the brain that are thought to lead to the development of Alzheimer pathology. Dr. Koo's team is studying how a key protein in Alzheimer pathology affects the activity of genes in the brain. This protein, amyloid precursor protein (APP), normally resides in the cell membrane but is cut into fragments in some situations. One of the fragments of APP is beta-amyloid, which accumulates in the spaces outside of nerve cells and forms amyloid plaques, a characteristic feature of Alzheimer pathology. The other fragment of APP, known as the APP intracellular domain (AICD) remains inside the nerve cell, and many researchers have suspected that AICD may activate certain genes. Dr. Koo's team is working to identify which genes are activated by AICD. They have identified segments of genetic material that bind to AICD, and they are now working to characterize the most important of those genes and their functions.

Dr. Perry's team is studying another important aspect to nerve cell function in persons affected by Alzheimer's disease, the function of mitochondria inside of the cells. Mitochondria are crucial structures inside of cells that produce energy for other cellular functions. Researchers have known for some time that mitochondria in the brain cells of persons with Alzheimer's disease behave abnormally, producing large amounts of free radicals, which cause oxidative damage to the cell possibly leading to cell death. Researchers have also suspected that the abnormal behavior of mitochondria may be caused by APP, so Dr. Perry's team is studying the function of mitochondria in brain tissue from persons who died of Alzheimer's disease. They have found that the location of mitochondria within the nerve cell is different in persons with Alzheimer's disease as compared to cells from normal healthy

individuals. The researchers also found high levels of oxidative stress in the brain cells of people with Alzheimer's, but they found that certain antioxidant treatments can reduce these levels. As they continue their studies, Dr. Perry and colleagues plan to examine the mechanisms that cause abnormal behavior of mitochondria in the brain cells of people affected by Alzheimer's.

Two other research teams supported by the Judy Fund are studying ways to prevent Alzheimer's disease or to detect it at its earliest stages, thereby optimizing the chances that it can be treated or slowed. Bruce T. Lamb, Ph.D. and colleagues are studying how genetics and lifestyle interact to influence the risk of Alzheimer's disease. The researchers are studying the accumulation of beta-amyloid and amyloid plaque formation in 4 different strains of mice with differing genetic characteristics. They feed the mice diets with differing amounts of fat and cholesterol to examine how a high-fat or high-cholesterol diet influences the development of Alzheimer-like pathology in the brain. Dr. Lamb's team has found one strain of mice that is especially susceptible to plaque formation when fed a high-fat/high-cholesterol. They are now working to identify the genetic characteristics that cause this susceptibility. These studies could help to identify genetic factors that influence the development of Alzheimer pathology in humans, possibly leading to treatments that prevent development of disease or slow its progression.

The research team led by Ramon Diaz-Arrastia, M.D., Ph.D. is studying another risk factor for Alzheimer's disease, homocysteine levels in the blood. Homocysteine is a chemical in the body related to one of the amino acids, the building blocks of proteins. Homocysteine levels in the blood are influenced by levels of vitamin B12 and folic acid. Previous research has found evidence that persons with Alzheimer's disease often have low levels of these nutrients, and hence high levels of homocysteine. Dr. Diaz-Arrastia and colleagues sought to measure blood homocysteine levels in persons who participated in a study of mild cognitive impairment (MCI), a condition that sometimes progresses to Alzheimer's disease. In one large study of such individuals, the researchers found that treatment with vitamin B12 modestly reduced the rate of cognitive decline in persons with MCI. Dr. Diaz-Arrastia's team plans to continue these studies, and to begin studying genetic factors influencing how homocysteine levels affect the rate of cognitive decline.

The final two research teams that have benefited from support of the Judy Fund are studying ways to improve the diagnosis of Alzheimer's disease and the medical care provided to affected individuals. William Jagust, M.D. and colleagues have initiated a study of brain imaging in an effort to identify features of early Alzheimer's disease that can be used for early detection and diagnosis. They are using magnetic resonance imaging (MRI) and positron emission tomography (PET) to examine the development of amyloid plaques in the brain, as well as changes in brain volume in healthy older individuals. The researchers plan to follow these individuals over time

and assess how changes in brain features correlate with changes in cognitive function measured using cognitive function tests. The ultimate goal of this research is to identify changes in brain images that predict later declines in brain function, leading the way for early diagnosis and treatment of MCI or Alzheimer's disease.

Philip Sloane, M.D., M.P.H. and colleagues have utilized their Pioneer award, supported by the Judy Fund, to spearhead a number of innovative efforts to improve the medical care of people with Alzheimer's in assisted living facilities. Dr. Sloane's team began by studying ways to take advantage of the skills offered by volunteer retired physicians. They discovered several practical barriers to this approach, but have now combined their efforts with a large-scale project with similar goals in the North Carolina region. Dr. Sloane's team has also conducted several pilot studies of innovative ways to reduce pain among older individuals recovering from hip fracture, reduce medication errors in assisted living facilities, and to compare different models of health care at facilities in 7 states. These pilot studies have allowed the researchers to successfully apply for several other research grants to expand their research efforts toward improving medical care and quality of life for people with Alzheimer's disease and related conditions in assisted living facilities.

Overall, support from the Judy Fund has been crucial for the advancement of research along several fronts related to the causes of prevention and detection of Alzheimer's disease, as well as ways to improve medical care for persons with the disease and related conditions. It is expected that important results from these research efforts will continue to arise in coming years. Furthermore, support provided by the Judy Fund has allowed researchers to obtain key results that allowed them to obtain additional funding for continued research.