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Interim Progress Report **Mitochondrial Abnormalities in Alzheimer's Disease**

2007 Zenith Fellows Award—\$250,000 over two years
Sponsored by the Zenith Fellows and The Judy Fund

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Location of Research Case Western Reserve University

Background Mitochondria are cellular structures that use oxygen and nutrients to produce energy for a cell. In Alzheimer's disease, however, abnormalities often occur in the mitochondria of nerve cells. Such abnormalities can result in the excessive production of free-radicals, or toxic oxygen molecules that damage the neurons. Free-radical damage, also called oxidative stress, often leads to nerve cell death in Alzheimer's.

George Perry, Ph.D., and colleagues have been studying the relationship between abnormal mitochondria and Alzheimer's disease. Preliminary research with autopsied brain tissue has suggested a correlation between altered mitochondrial function and brain levels of amyloid precursor protein (APP). APP is the parent molecule of beta-amyloid, a key suspect in Alzheimer's. When APP accumulates in the brain, it may block the ability of mitochondria to move around the neurons' axons, or "arms." Such reduced movement may help induce the mitochondrial abnormalities that, in turn, lead to excessive release of free-radicals.

Goal of Study—Specific Aims For this grant, Dr. Perry's team conducted a more extensive study of abnormal mitochondria using autopsied brain tissue. The researchers hope to learn more about how APP and other proteins may cause mitochondrial dysfunction. Results from the study could lead to new therapeutic avenues for the treatment of Alzheimer's disease.

Research Outcomes and Significance

During the first year of their grant, Dr. Perry and colleagues analyzed the distribution of mitochondria in autopsied cells from people with Alzheimer's disease and from healthy people. The researchers administered the cells with cytochrome oxidase subunit 1 (COX-1), an enzyme that binds to mitochondria and makes them easier to detect through microscope and imaging techniques. Results showed that the mitochondria in normal nerve cells appeared in both the soma (main body) of the cell and in the cell's axons. In the Alzheimer cells, however, the mitochondria appeared almost exclusively in the soma. This finding confirms the hypothesis that Alzheimer's disease may restrict the ability of mitochondria to move around the axons.

In another experiment with their Alzheimer cells, the researchers treated the cells with both COX-1 and a compound called lipoic acid, which also binds to mitochondria. Results found that the lipoic acid bound to the mitochondria and also collected in cell structures that are involved in a kind of programmed cell death called autophagocytosis. Such findings suggest that mitochondria and abnormal autophagocytosis may be closely linked in Alzheimer's disease.

Dr. Perry and colleagues also tested the autopsied cells to find indicators of oxidative stress. They observed that the Alzheimer cells contained several key compounds linked to oxidative stress. Moreover, the team also found that lipoic acid and n-acetyl-l-cysteine (NAC)—two substances that have antioxidant properties—reduced the levels of oxidative stress compounds in the cells. This result suggests a novel treatment for oxidative stress in Alzheimer's disease.

Future work

For their study's second year, the researchers hope to learn more about the biological mechanisms underlying how mitochondria become harmfully redistributed in Alzheimer cells. They will also continue their analyses of the connections between mitochondria and autophagocytosis and between mitochondria and oxidative stress.

Publication

Moreira PI, Harris PLR, Zhu X, Santos MS, Oliveira CR, Smith MA, Perry G. Lipoic acid and *N*-acetyl cysteine decrease mitochondrial-related oxidative stress in Alzheimer disease patient fibroblasts. *Journal of Alzheimer's Disease* 2007; 12: 195-206.

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 and the Judy Fund. Alzheimer's Association grant ZEN-07-59500 year-one progress report.