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RESEARCH UPDATE

New Efforts Promise Accelerated Progress

The ALS Association (ALSA) has funded the following investigator-initiated research projects aimed toward finding a successful treatment for ALS. Proposed research includes a possible way to diagnose ALS by early imaging of changes in the brain and an epidemiological investigation into the aftereffects of herbicide spraying during the Vietnam War, a controversial issue for veterans who are documented to be at higher risk for ALS.

Proposed funding is for six starter grants and five multiyear projects. Researchers from around the world have secured funding, including investigators from Japan, Israel, France, Uruguay, and Australia as well as Canada and the United States.

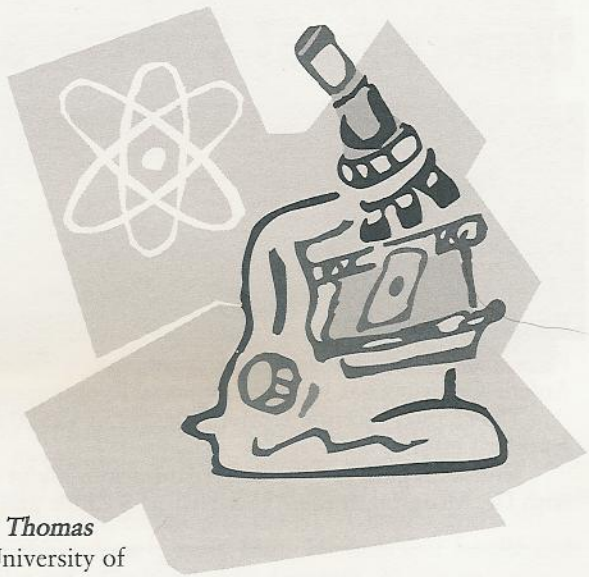
The total commitment for all awards arising from the autumn 2005 round of Investigator Initiated Grants is $1,155,857. Single year grants are funded at a total of $239,246, and multiyear grants total $590,000.

History of Herbicide Exposure and ALS Risk

Stellman at Columbia University in New York will compare the exposure to herbicides of 74 veterans of the Vietnam War who have ALS with that of unaffected veterans as controls. The case-control comparison will be enabled by an ongoing study of risks for cancer and other chronic diseases in a large sample of veterans. The study will be aided by a geographic database that provides maps of herbicide spraying and troop location during the war. This study should provide direct information about possible risks for ALS that have been proposed but never confirmed.

Approaches to Targeting Mutant SOD1

Urushitani and Julien at Laval University in Quebec have discovered that helper molecules called chromogranins are binding to mutant SOD1. These are proteins that play a role in secreting other proteins from cells. When mutant SOD1 is secreted in cell culture, the investigators find an inflammatory response by microglia cells as motor neurons die. A one year starter grant has yielded published findings on this new insight into the disease process in ALS. Julien and his group will now have SOD1 mutant mice produce more than the usual amount of chromogranins in the spinal motor neurons, or have no chromogranin production at all, to see if either of these mice will show worsening of disease.



Thomas at University of Texas Southwest Medical Center in Dallas has generated a model system in a dish to measure abnormalities in the folding of SOD1. Using this model he will screen for proteins that are associated with this abnormal folding, which may yield important targets for developing small molecule drugs and eventually a therapy for ALS.

Cassina and Sotelo Silveira at the Universidad de la República in Montevideo, Uruguay, have preliminary evidence that the cellular power plants called mitochondria form clusters with mutant SOD1 along the axons of motor neurons in SOD1 mutant rats. The clusters progressively accumulate after birth, suggesting SOD1 is trapping the mitochondria as it clumps together. The investigators intend to explore the mitochondria defects in motor neurons and their supportive neighbor cells, the astrocytes, in order to seek possible therapeutic targets.

A bond between two sulfur atoms in the paired SOD1 molecule may be the weak link in the chain of molecular events that produces ALS. ***Atkin*** at the University of Melbourne in Australia plans to see if protection can be offered by an enzyme called protein disulfide isomerase, which acts to prevent aggregation of single SOD1 molecules.

Stem Cells and Targeting Gene Therapies

Studer and Tabar at the Sloan Kettering Institute for Cancer Research in New York will develop a human embryonic stem cell line which permanently marks motor neurons with a fluorescent label. This will be an important resource for the ALS community to generate large pools of human motor neurons for transplant and drug screening studies.

continued on page 9

Research Update

continued from page 8

Drachman and Lu at Johns Hopkins School of Medicine in Baltimore will improve on a molecular means to help deliver gene therapies for ALS. They will be working with a molecule that should act as a Trojan horse to get a therapeutic gene to specifically enter motor neurons.

Imaging Technique to Aid ALS Patients

The ability to aid patients with ALS would benefit greatly from knowing early which patients are at greater risk for rapid decline in their motor and cognitive capacities. ***Henry and Lomen-Hoerth*** at the University of California, San Francisco intend to explore imaging techniques that might allow clinicians to predict the disease progression for patients who start out with signs of damage to the upper motor neurons, the nerves from the brain to the spinal cord, and those patients who will have only upper motor neuron disease but will not progress to ALS.

New Models of ALS Disease Processes

Axon transport is the process by which motor neurons handle their internal supply lines. ***Morfini*** at the University of Illinois in Chicago will study processes relevant to ALS by manipulating the molecular controls within the axons that make up nerve fibers. ALS appears to affect various enzymes that regulate the structural and functional proteins that keep the axon intact and moving materials properly. Drugs that change these enzymes will be tested to help find new treatment approaches.

The gene Hn1 is a newly identified player in the survival of motor neurons. ***Harrison and Streit*** at the University of Florida in Gainesville will see if the gene is important for survival of the motor neurons in the rat model of ALS with an eye toward eventual treatment.

Vascular endothelial growth factor, VEGF, can protect motor neurons and when administered to SOD1 mutant mice can delay the disease onset. ***Keshet*** at the Hebrew University in Jerusalem plans to determine how local exposure to VEGF or its lack influences the development of motor neurons in a transgenic mouse model for ALS.

Cell Basis of ALS Toxicity: Progress Reported at Neuroscience Meeting

Scientists are making progress in clarifying the role of each cell in the nervous system in producing ALS (amyotrophic lateral sclerosis), also known as Lou Gehrig's disease. At the annual meeting of the Society for Neuroscience in Washington, D.C., researchers working with ***Don Cleveland, Ph.D.*** report that the action in glial cells of a mutant protein linked to some inherited forms of ALS could be key for progression of the disease, while its presence in the motor neurons might be the trigger.

If the microglial cells do not make the mutant copper-zinc superoxide dismutase (SOD1), the later stage of the mouse disease is prolonged.

Cleveland's group defines an early and a later stage in the disease of the mice that express mutant SOD1. The early phase is defined as when the mutant mice reach a peak weight and then start losing weight, up until a ten percent weight loss. The later phase is when the mice lose further weight until they are at end stage. This later stage of disease lasts longer in mice that do not express the mutant protein in the microglia cells. In fact, reducing production of mutant SOD1 in microglia cells extends lifespan in the mice by 99 days, that is, by a third of their lifespan, according to findings in a poster by Severine Boillee, Ph.D.

Other findings reported by the investigators at the Ludwig Institute at the University of California, San Diego, suggested that lowering the production of mutant protein in the motor neurons can also extend survival of the ALS mice. The later stage of the rodent disease and the early phase were both prolonged by cutting mutant SOD1 production within motor neurons, according to results in the poster by Koji Yamanaka, M.D.

The fact that the disease still progresses suggests that other cells besides the motor neuron are involved in the process of ALS. Further experiments will seek to determine how other cell types, such as muscle and astrocytes, contribute to the disorder.

Life is not measured by the number of breaths we take,
but the moments that take our breaths away.
Author Unknown