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Compound Blocks Brain Cell Destruction in Parkinson's Disease; Findings May Open Door to First Protective Therapy

Scientists from the Florida campus of The Scripps Research Institute have produced the first known compound to show significant effectiveness in protecting brain cells directly affected by Parkinson's disease, a progressive and fatal neurodegenerative disorder.

Although the findings were in animal models of the disease, the effectiveness of the compound, combined with its potential to be taken orally, offers the tantalizing possibility of a potentially useful future therapy for Parkinson's disease patients. The results were published in two separate studies in the journal ACS Chemical Neuroscience.

"These studies present compelling data on the first oral, brain-penetrating inhibitor to show significant efficacy in preventing neurodegeneration in both mouse and rat models of Parkinson's disease," said team leader Philip LoGrasso, a Professor in the Department of Molecular Therapeutics and Senior Director for Drug Discovery at Scripps Florida. "The compound offers one of the best opportunities we have for the development of an effective neuroprotective treatment."

The new small molecule -- labeled SR-3306 -- is aimed at inhibiting a class of enzymes called c-jun-N-terminal kinases (JNK). Pronounced "junk," these enzymes have been shown to play an important role in neuron (nerve cell) survival. As such, they have become a highly viable target for drugs to treat neurodegenerative disorders such as Parkinson's disease.

"A drug like SR-3306 that prevents neurodegeneration would be a quantum leap in the clinical treatment of Parkinson's because all current therapies treat only the symptoms of the disease, not the underlying pathologies," LoGrasso said.

Patients with Parkinson's disease suffer from the loss of a group of neurons in the substantia nigra pars compacta (SNpc), part of the midbrain involved in motor control.

These cells produce dopamine, a neurotransmitter that plays a key role in motor reflexes and cognition. The disease also affects projecting nerve fibers in the striatum, a part of the forebrain filled with cells that interact with dopamine. Stopping the Progression of Neuron Destruction in Animal Models.

The SR-3306 compound, which has been in development at Scripps Florida for several years, performed well in both cell culture and animal models. In cell culture, the compound showed greater than 90 percent protection against induced cell death of primary dopaminergic neurons, while in mouse models of induced neuron death, the compound showed protective levels of approximately 72 percent.

The scientists went one step further, testing the new compound in a rat model, which duplicates the physical symptoms often seen with the human disease -- a pronounced and progressive loss of motor skills. The results showed SR-3306 provided a protection level of approximately 30 percent in the brain, a level that reduced the dysfunctional motor responses by nearly 90 percent.

"It was a surprise that level of neuroprotection reduced the behavioral impact so strongly," LoGrasso said, "but it's indicative of how it might perform in human patients. While SR-3306 doesn't represent a cure, it does appear to have the potential of stopping the progression of the disease."

The new studies are part of a \$7.6 million multiyear grant awarded to LoGrasso in 2008 by the National Institutes of Neurological Disorders and Stroke. The grant will enable Scripps Research and potential partners to file an application for an investigational new drug -- the first step in the lengthy clinical trials process required by the

U.S. Food and Drug Administration before a new drug can be brought to market.

The first authors of the study, "Small Molecule c-jun-N-terminal Kinase Inhibitors Protect Dopaminergic Neurons in a Model of Parkinson's Disease," are Jeremy W. Chambers and Alok Pachori of Scripps Research. Other authors include Shannon Howard, Michelle Ganno, Donald Hansen Jr., Ted Kamenecka, Xinyi Song, Derek Duckett, Weimin Chen, Yuan Yuan Ling, Lisa Cherry, Michael D. Cameron, Li Lin, and Claudia H. Ruiz, also of Scripps Research.

The first author of the study, "JNK Inhibition Protects Dopamine Neurons and Provides Behavioral Improvement in a Rat 6-hydroxydopamine Model of Parkinson's Disease," is Candice E. Crocker of Dalhousie University, Halifax, Nova Scotia, Canada. Other authors include Susan Khan and Michael D. Cameron of Scripps Research, and Harold A. Robertson and George S. Robertson of Dalhousie.

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Sources: Jeremy W. Chambers, Alok Pachori, Shannon Howard, Michelle Ganno, Donald Hansen, Ted Kamenecka, Xinyi Song, Derek Duckett, Weimin Chen, Yuan Yuan Ling, Lisa Cherry, Michael D. Cameron, Li Lin, Claudia H. Ruiz, Philip LoGrasso. Small Molecule c-jun-N-Terminal Kinase Inhibitors Protect Dopaminergic Neurons in a Model of Parkinson's Disease. ACS Chemical Neuroscience, 2011; 110207090626012 DOI: 10.1021/cn100109k

Candice E. Crocker, Susan Khan, Michael D. Cameron, Harold A. Robertson, George S. Robertson, Philip LoGrasso. JNK Inhibition Protects Dopamine Neurons and Provides Behavioral Improvement in a Rat 6-Hydroxydopamine Model of Parkinson's Disease. ACS Chemical Neuroscience, 2011; DOI: 10.1021/cn1001107