MedicalXpress

Scientists discover drug candidate for Alzheimer's, Huntington's disease

June 2 2011

Scientists at the Gladstone Institutes have identified a drug candidate that diminishes the effects of both Alzheimer's disease and Huntington's disease in animal models, offering new hope for patients who currently lack any medications to halt the progression of these two debilitating illnesses.

Gladstone Investigator Paul Muchowski, PhD, has identified a new compound called JM6 in experiments done in collaboration with an international team of researchers, and which are being published today in an online article in *Cell*. In laboratory tests involving mice genetically engineered to model one or the other of the two diseases, Dr. Muchowski's team found that JM6 blocks kynurenine 3-monooxygenase (KMO), an enzyme that has long been speculated to play a role in neurodegenerative diseases.

In mice modeling Alzheimer's disease, the novel compound prevented memory deficits and the loss of synaptic connections between brain cells—both of which are key features of the human disease. In mice modeling Huntington's disease, JM6 prevented brain inflammation and the loss of synaptic connections between brain cells, while also extending lifespan.

The need for a therapeutic breakthrough for diseases that degrade the brain over time is great. Alzheimer's disease—the most common form of dementia—afflicts an estimated 5.4 million people in the United States alone, at an annual cost of $183 billion, according to the Alzheimer's

Association. Without a therapeutic breakthrough, the number of Americans with Alzheimer's disease is expected to double by 2050, as a new case will develop every 33 seconds. Huntington's disease, meanwhile, is the most common inherited neurodegenerative brain disorder, diminishing the ability of some 30,000 Americans to walk, talk and reason.

"This discovery has significant implications for two devastating diseases and suggests that the KMO enzyme is a good protein for us to target with medications in diverse neurodegenerative disorders," said Lennart Mucke, MD, who oversees all neurological research at Gladstone and who won the prestigious Potamkin Prize last year for developing experimental strategies to make the brain more resistant to Alzheimer's. "With any luck, Dr. Muchowski and his colleagues could begin testing this drug in patients within the next two years."

Remarkably, JM6 does not penetrate into the brain, but works by inhibiting KMO in the blood. The blood cells then send a protective signal to the brain, to stabilize brain-cell function and prevent neurodegeneration. The fact that the compound does not pass the so-called blood-brain barrier will facilitate testing in patients, as JM6's potential impact could be confirmed with a simple blood test.

JM6 was named for Dr. Muchowski's father, Dr. Joseph Muchowski, Ph.D., a retired medicinal chemist who helped his son devise the novel KMO inhibitor. The study was carried out in collaboration with the laboratories of Dr. Robert Schwarcz, a University of Maryland School of Medicine professor who pioneered studies linking KMO and metabolically related enzymes to nerve-cell loss, and Professor Eliezer Masliah at the University of California, San Diego, an expert in neuropathology.

These findings are further bolstered by research also being published

online today in *Current Biology*. Led by Flaviano Giorgini, PhD, of the University of Leicester—and a former postdoc of Dr. Muchowski's—the other study provides compelling genetic and pharmacological evidence of KMO's importance in fruit flies genetically modified to mimic Huntington's disease.

"In a world where there is such vacuum of hope about Huntington's disease, I am thrilled that someone of Dr. Muchowski's caliber has suggested the possibility of imminent clinical trials," said Charles Sabine, a former NBC correspondent who watched Huntington's disease kill his father. Both Mr. Sabine and his brother currently have Huntington's. "I believe that families with Huntington's disease should jump at the opportunity of being involved in those trials."

Gladstone, together with the University of Maryland School of Medicine, is currently considering a variety of ways to get JM6 into Phase 1 safety trials in humans—hopefully sometime in 2013—including the spinout of a venture-capital-backed startup or collaboration with a large pharmaceutical company. Gladstone also has a grant application pending with the National Institute of Neurological Disorders and Stroke to help fund safety tests required for initiating human trials. Gladstone, the National Institutes of Health and the Taube-Koret Center for Huntington's Disease Research at Gladstone all provided funding for this study.

Dr. Paul Muchowski, an associate investigator at Gladstone, specializes in neurodegenerative diseases. He is also an associate professor in the Departments of Biochemistry and Biophysics, and Neurology, at the University of California, San Francisco (UCSF).

Provided by Gladstone Institutes