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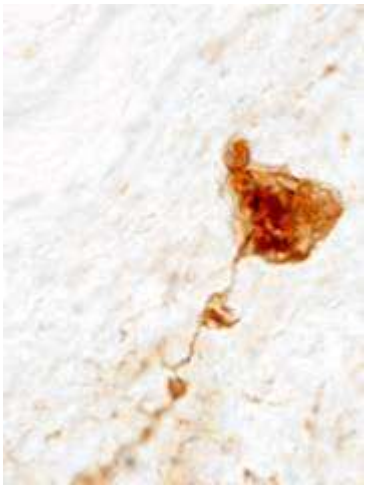
Mice With Parkinson's Disease Gene May Point the Way to New Treatments

Mouse Model Offers Scientists a Powerful New Way to Understand the Disease and Evaluate Treatments



An abnormal, swollen dopamine axon in the brain of a mutant LRRK2 transgenic mouse model created by Weill Cornell's Dr. Chenjian Li and colleagues.

NEW YORK (June 7, 2009) — Scientists at Weill Cornell Medical College have developed a new mouse model of Parkinson's disease (PD) that successfully reproduces the impairments of movement and the degenerative brain changes that occur in the human disease. Their research, performed in collaboration with investigators at Columbia University Medical Center, appears in the June 7 issue of the journal Nature Neuroscience.

"Because this new mouse model replicates the pathogenesis of human Parkinson's disease so closely, it promises to be a major boon to Parkinson's research, both in terms of basic science and drug development," says Dr. M. Flint Beal, study co-author and professor of neurology and neuroscience at Weill Cornell Medical College. "While there are many treatments for the symptoms of PD, no current therapies prevent the inevitable progression of the disease. One reason for the inability to develop such therapies is that there has been no truly workable animal model of the human disease. This new model will now address this critical need."

Earlier attempts to create a mouse model for Parkinson's continually fell short due to technological limitations. Using a new transgenesis technology called BAC (bacterial artificial chromosome) that allows researchers to insert large DNA fragments into the genome, senior author Dr. Chenjian Li, assistant professor of neurology at Weill Cornell Medical College, and his colleagues were able to introduce into the mouse's genome a mutant form of the LRRK2 gene — the most common genetic cause of PD.

The Weill Cornell team observed that the mice expressing the mutant form of the gene became very slow to move as they became older, just like human PD patients. Remarkably, the mice became able to move normally when treated with levodopa, the same drug that is commonly used to treat human patients.

Further research by Drs. Beal and Li and their labs revealed that the mice with impaired movement also had impaired release of the brain neurotransmitter dopamine, just as it occurs in the human disease. Dr. Robert Burke, the Alfred and Minnie Bressler Professor of Neurology (in Pathology) at Columbia University Medical Center, and his colleague Ms. Tinmarla Francis Oo, senior staff associate at Columbia University Medical Center, further discovered that the dopamine deficit came from disintegration, not of the dopamine neurons themselves, but of their axons, the long, filament-like structures responsible for transmitting dopamine to distant targets in the brain. Their insights, says Dr. Li, are helping us understand the disease at a deeper level — something that will lead us to better treatments and possibly even a cure for Parkinson's disease.

There are currently two standard types of treatment for Parkinson's: medication and a surgical technique called deep brain stimulation, which achieves similar results for some patients. Neither approach, however, stops the progression of the disease as it lays waste to the brain's dopamine system and inexorably erodes key physical, cognitive and psychological functions.

Says Dr. Li: "The new model will provide scientists with an appropriate 'stage' on which to screen for effective medications. It will also show us the disease in real time, allowing us to track its progression at a cellular and molecular level. What we learn will then feed back into the drug development process.

"From a longer-term perspective, this also gives us a picture-window into normal biology," he continues. "The new mouse model will provide an opportunity to investigate the brain's dopaminergic system, a brain circuit critical to movement, emotions and drug addition."

The study's co-first authors were Yanping Li and Wencheng Liu of Weill Cornell Medical College. Additional co-authors included Kindiya Geghman and Yi Tang of Weill Cornell; Lei Wang and Mikhail Bogdanov of Weill Cornell and Bedford VA Medical Center, Bedford, Mass.; and Vernice Jackson-Lewis, Chun Zhou and Serge Przedborski of Columbia University Medical Center.

The study was supported by the National Institute of Neurologic Disorders and Stroke, the Michael J. Fox Foundation and the Parkinson's Disease Foundation.

Parkinson's is the second most common neurodegenerative disease after Alzheimer's. In its later stages, it can be extremely disabling, both physically and mentally. The disorder not only impairs the ability to initiate and sustain movement, but affects cognition and mood as well. Aging, genetics, and environmental toxins are the main risk factors for a disease whose prevalence is slated to rise dramatically as the population ages. About 90 percent of the time, Parkinson's is sporadic in origin, meaning its cause is unknown. But 10 percent of cases run in families.

Columbia University Medical Center
Columbia University Medical Center provides international leadership in basic, pre-clinical and clinical research, in medical and health sciences education, and in patient care. The Medical Center trains future leaders and includes the dedicated work of many physicians, scientists, public health professionals, dentists, and nurses at the College of Physicians & Surgeons, the Mailman School of Public Health, the College of Dental Medicine, the School of Nursing, the biomedical departments of the Graduate School of Arts and Sciences, and allied research centers and institutions. Established in 1767, Columbia's College of Physicians and Surgeons was the first institution in the country to grant the M.D. degree and is now among the most selective medical schools in the country. Columbia University Medical Center is home to the largest medical research enterprise in New York City and state and one of the largest in the United States. For more information, please visit **www.cumc.columbia.edu**.

Weill Cornell Medical College
Weill Cornell Medical College, Cornell University's medical school located in New York City, is committed to excellence in research, teaching, patient care and the advancement of the art and science of medicine, locally, nationally and globally. Weill Cornell, which is a principal academic affiliate of NewYork-Presbyterian Hospital, offers an innovative curriculum that integrates the teaching of basic and clinical sciences, problem-based learning, office-based preceptorships, and primary care and doctoring courses. Physicians and scientists of Weill Cornell Medical College are engaged in cutting-edge research in areas such as stem cells, genetics and gene therapy, geriatrics, neuroscience, structural biology, cardiovascular medicine, transplantation medicine, infectious disease, obesity, cancer, psychiatry and public health — and continue to delve ever deeper into the molecular basis of disease and social determinants of health in an effort to unlock the mysteries of the human body in health and sickness. In its commitment to global health and education, the Medical College has a strong presence in places such as Qatar, Tanzania, Haiti, Brazil, Austria and Turkey. Through the historic Weill Cornell Medical College in Qatar, the Medical College is the first in the U.S. to offer its M.D. degree overseas. Weill Cornell is the birthplace of many medical advances — including the development of the Pap test for cervical cancer, the synthesis of penicillin, the first successful embryo-biopsy pregnancy and birth in the U.S., the first clinical trial

of gene therapy for Parkinson's disease, the first indication of bone marrow's critical role in tumor growth, and most recently, the world's first successful use of deep brain stimulation to treat a minimally conscious brain-injured patient. For more information, visit **www.med.cornell.edu**.

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