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Rejected Alzheimer's drug shows new potential

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An international team of scientists led by researchers at Mount Sinai School Medicine have discovered that a drug that had previously yielded conflicting results in clinical trials for Alzheimer's disease effectively stopped the progression of memory deterioration and brain pathology in mouse models of early stage Alzheimer's disease. The findings, published July 31, 2012 in *Molecular Psychiatry*, demonstrate renewed potential for this compound and could lead to clinical trials in patients with early stages of the disease.

Latrepirdine, known commercially as Dimebon, was initially sold as an antihistamine in Russia, approved for use there in 1983. In the 1990s, researchers at the Institute of Physiologically Active Compounds in Moscow determined that the compound appeared effective in treating Alzheimer's disease in animals. They continued their research in humans and performed several studies, including Phase I and II trials, all of which showed significant and sustained improvement in cognitive behavior with minimal side effects. The Phase II trials, performed in Russia, were overseen by U.S. Alzheimer's researchers, including Mary Sano, PhD, Director of the Mount Sinai Alzheimer's Disease Research Center.

However, when research was continued in the United States in a Phase III trial, the drug did not demonstrate any improvement in people with the disease, causing the sponsors to halt further clinical study of the drug in Alzheimer's disease. Some researchers have speculated that the Russian patients might have had different disease stage or subtype of

Alzheimer's, and therefore were more responsive to treatment than the patients in the Phase III trials in the United States.

Before the failed trials were announced, researchers at Mount Sinai School of Medicine, led by Sam Gandy, MD, PhD, Professor of Neurology, and Psychiatry, and Director of the Mount Sinai Center for Cognitive Health, began studying the mechanism of action behind latrepirdine in the current study, which is supported by the Cure Alzheimer's Fund.

Dr. Gandy's team randomly administered either latrepirdine or placebo to mice engineered to present the early stages of Alzheimer's disease and found that the drug halted both behavioral decline and progression of neuropathology. In evaluating how latrepirdine improved memory, John Steele, PhD, a neuroscience graduate student working with Dr. Gandy, and Lenard Lachenmayer, MD, a postdoctoral fellow working under the supervision of Zhenyu Yue, PhD, Associate Professor of Neurology at Mount Sinai, found that the drug enhanced autophagy, the so-called "self-eating" process of cells that protects the brain from neurodegeneration.

"When we learned that latrepirdine failed in patients in the United States in 2010, scientists around the world were disappointed and perplexed," Dr. Gandy said. "We wanted to find out why the drug did so well in Russia but then showed no effect in the global studies. The findings from our animal model studies indicated that this drug should not be discarded, and that, if its mechanism of action can be optimized, it still has potential."

Dr. Sano points out that not only did latrepirdene have significant and sustained effect in the Russian study but it also showed a mild effect in one study of patients with Huntington's disease.

"Since cognitive benefit is what really matters to patients and families, it

is critical that we explore every mechanism by which it might occur," Dr. Sano said.

"While this is just the beginning, our research shows that this previously cast-off drug still has strong therapeutic promise," Dr. Gandy said. "Autophagy drugs are believed to hold great promise for a range of neurodegenerative diseases, and these data raise the question of whether further basic science work on latrepirdine might lead to optimization of the drug so that a more potent drug could be developed, and subsequently tested in human clinical trials.

"This is especially true since we know that latrepirdine is an extremely safe drug and in view of the recent failure of the first key trial of the drug bapineuzumab," Dr. Gandy added. "Also, as may be the case with all amyloid-lowering drugs, initiating latrepirdine trials before amyloid deposition begins may be the key. Now, with the new brain amyloid scans that began at Mount Sinai in June, we can easily establish who those patients are."

Looking ahead, Drs. Gandy, Yue, and their collaborators are planning to test latrepirdine in mouse models of other protein buildup diseases such as Parkinson's disease, Lewy body dementia, and chronic traumatic encephalopathy, the Alzheimer's-like condition athletes endure from boxing, football and hockey. Dr. Sano notes that so few agents show any improvement in cognition that it is critical that to exhaust every potential lead.

Mount Sinai has a long-standing legacy of critical breakthroughs in team research in Alzheimer's disease. Dr. Gandy is an internationally-renowned expert in understanding the amyloid plaques characteristic of Alzheimer's disease, and he led a team of researchers to the discovery of the first drugs that reduced amyloid buildup. Dr. Sano is a world leader in designing clinical trials to find treatments and preventions for

cognitive loss and Alzheimer's disease. Together, their labs and the Mount Sinai Alzheimer's Disease Research Center and Center for Cognitive Health are focused on a strategic approach to translating clinical challenges into bench investigations and back.

Provided by The Mount Sinai Hospital

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