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Miller School Study Points to Innovative Epigenetic Strategy for Alzheimer's Disease

A University of Miami Miller School of Medicine research team has identified an innovative epigenetic strategy using a single molecule to turn off multiple genes that drive Alzheimer's disease.

Brain scans.

In a study published October 9 in the *Proceedings of the National Academy of Sciences (PNAS)*, the researchers demonstrated that an epigenetic molecule called M344 penetrates the brain, targets the buildup of beta-amyloid peptides associated with Alzheimer's disease, increases neuroprotective genes and increases memory.

"One can think of this as re-programming of gene expression to simultaneously restore multiple deficits that have been observed in the brains of Alzheimer's sufferers," said senior author Claes Wahlestedt, M.D., Ph.D., professor of psychiatry and behavioral sciences, associate dean for therapeutic

innovation, and director of the Center for Therapeutic Innovation. His laboratory conducted the new study, which was supported by the National Institutes of Health and the State of Florida Department of Health (the Ed and Ethel Moore Alzheimer's Disease Research Program).

Alzheimer's disease (AD) is the most common form of dementia in the elderly, and 16 million people in the U.S. are expected to have the condition by 2050, according to the Alzheimer's Association. However, today there are only a few FDA-approved treatments, and they are modestly palliative at best, said Wahlestedt.

"Experts in the field now agree that Alzheimer's is a multifactorial disease and that fundamentally new therapeutic approaches must be tested, such as drug cocktails that target the multiple aspects of the disease," he said.

"Knowing that epigenetic molecules can regulate multiple phenomena, we looked for a single drug that could simultaneously affect the expression of a number of defined Alzheimer's-related genes in both early- and late-onset AD," said Claude-Henry Volmar, Ph.D., senior scientist at the Center for Therapeutic Innovation and associate director of Molecular Therapeutics Shared Resource at Sylvester Comprehensive Cancer Center.

Volmar was the first author of the study, "M344 Promotes Nonamyloidogenic Amyloid Precursor Protein Processing While Normalizing Alzheimer's Disease Genes and Improving Memory."

"We examined all known epigenetic compounds in human cells that show characteristics of Alzheimer's disease," Volmar said. "Through a series of screenings and tests, we discovered

that M344 normalizes Alzheimer's-like pathology in a mouse model, resulting in significant reversal of cognitive impairment in different behavioral tasks." Analysis of concentrations of M344 in the brain and plasma demonstrated that sufficient but transient brain exposure can prevent memory impairment, Volmar added.

"Most importantly, this work endorses a shift to a multi-targeted approach to the treatment of AD, supporting the broad therapeutic potential of a single epigenetic small molecule," said Wahlestedt. "We have also learned that a new drug of this type may only have to be present in the brain for a short time period every day. This would make it possible to reduce potential side effects."

Based on these new insights, the University of Miami team is now working on strategies to bring similar treatments from the laboratory into clinical testing.

Miller School co-authors were Shaun Brothers, Ph.D., Hasib Salah-Uddin, Ph.D., Karolina J. Janczura, M.S., Paul Halley, Ph.D., Guerline Lambert, M.P.H., Andrew Wodrich, Sivan Manoah, Nidhi Patel, Gregory C. Sartor, Ph.D., Neil Mehta, Nancy T.H. Miles, Sachi Desse and David Dorcius. Michael D. Cameron, Ph.D., in the Department of Molecular Medicine at Scripps Florida, also contributed to the study.