

# Study points to novel epigenetic target for Alzheimer's Disease

6 November 2018



From left, Karolina J. Janczura, Claes Wahlestedt, M.D., Ph.D., and Claude-Henry Volmar, Ph.D. Credit: University of Miami

A research team at the University of Miami Miller School of Medicine's Center for Therapeutic Innovation (CTI) has identified a novel epigenetic drug target to simultaneously normalize multiple deficits in Alzheimer's disease (AD), the most common form of dementia in the elderly and the sixth leading cause of death in the U.S., according to the Alzheimer's Association.

The study, titled "Inhibition of HDAC3 Reverses Alzheimer's Disease-related Pathologies in vitro and in the 3xTg-AD Mouse Model," was published on November 5 in the *Proceedings of the National Academy of Sciences* (PNAS). The researchers demonstrated that epigenetic "eraser" enzyme, histone deacetylase 3 (HDAC3) is connected to multiple Alzheimer's disease hallmarks, including beta-amyloid (A $\beta$ ), hyperphosphorylated tau and several other aberrant genes.

"Importantly, none of the FDA-approved treatments available to date are efficacious at addressing these hallmarks, let alone multiple hallmarks," 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).

Karolina J. Janczura, first author of the study, a Ph.D. candidate at the Center for Therapeutic Innovation and an American Heart Association predoctoral fellowship recipient, stated: "This was an incredibly rewarding experience. We were able to demonstrate that it is possible to re-program neuronal cell gene expression and thereby achieve a very striking reversal of deteriorating memory in our Alzheimer's disease model."

Claude-Henry Volmar, Ph.D., co-corresponding author, director of research laboratory at the Center for Therapeutic Innovation and associate director of Molecular Therapeutics Shared Resource at the Sylvester Comprehensive Cancer Center, added: "We discovered that treatment with RGFP-966, an experimental HDAC3 inhibitor drug, normalizes Alzheimer's-like pathology in multiple cellular and animal models. Considering that the majority of clinical trials focused on traditional AD targets have failed to date, our group focused on the multifactorial aspect of the disease, and we hope our recent discovery will guide the development of AD therapeutics."

"Further support of the potential role of HDAC3 in Alzheimer's in this work comes from the fact that its inhibition in AD patient-derived neurons also resulted in reversal of AD phenotype," Janczura said.

"Interestingly, a novel interaction between the protein tau and HDAC3 was discovered in this project, suggesting a possible role of HDAC3 in

other tau-related pathologies in addition to AD," Volmar said.

"Most importantly, this work endorses a multipronged approach to the treatment of AD and supports the broad therapeutic potential of a single epigenetic small molecule, bypassing the need for developing multiple drugs to be used in combination," Wahlestedt said.

**More information:** Karolina J. Janczura et al. Inhibition of HDAC3 reverses Alzheimer's disease-related pathologies in vitro and in the 3xTg-AD mouse model, *Proceedings of the National Academy of Sciences* (2018). [DOI: 10.1073/pnas.1805436115](https://doi.org/10.1073/pnas.1805436115)

Provided by University of Miami

APA citation: Study points to novel epigenetic target for Alzheimer's Disease (2018, November 6) retrieved 13 April 2021 from <https://medicalxpress.com/news/2018-11-epigenetic-alzheimer-disease.html>

*This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.*