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One step closer toward a treatment for Alzheimer's disease?

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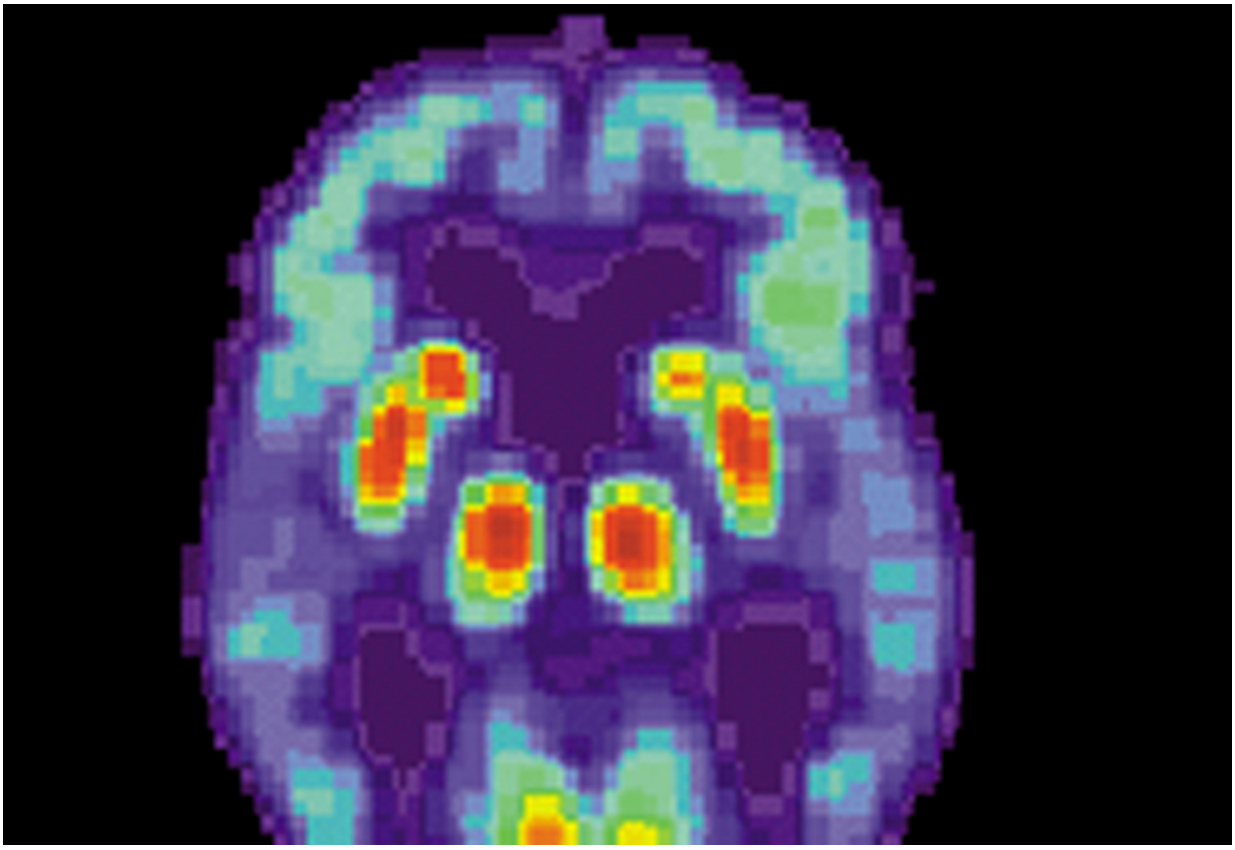

PET scan of a human brain with Alzheimer's disease. Credit: public domain

Scientists at the Massachusetts General Hospital (MGH), in collaboration with colleagues at the University California, San Diego (UCSD), have characterized a new class of drugs as potential therapeutics for

Alzheimer's disease and discovered a piece in the puzzle of how they would work. Their study, using disease-related animal and cellular models, shows that treatment with a representative compound of this class of gamma-secretase modulators leads to a reduction of the Alzheimer's-associated beta-amyloid. The study has been online published in *EBioMedicine*, an open-access journal jointly published by Cell Press and The Lancet.

"Our study explores the mechanism by which gamma-secretase modulators reduce levels of amyloid-beta 42, the primary pathological driver of Alzheimer's disease," says Can (Martin) Zhang, MD, PhD, of the Genetics and Aging Research Unit in the MassGeneral Institute for Neurodegenerative Disease (MGH-MIND), co-corresponding author of the *EBioMedicine* paper. "These findings will be useful in the ongoing effort to develop molecules that may be effective for the treatment and prevention of Alzheimer's disease."

The most common neurodegenerative disorder, Alzheimer's disease is characterized by the buildup of amyloid plaques and neurofibrillary tangles in several brain regions. The leading hypothesis for its pathogenesis is the amyloid cascade - which suggests that the amyloid beta-protein, and particularly the amyloid-beta 42 peptide, initiates the disease process. An imbalance between the production and clearance of amyloid-beta results in the protein's aggregation into larger plaques that lead to the death of brain cells and the cognitive symptoms seen in Alzheimer patients. Several potential treatments have been developed that specifically target amyloid, but none have been effective in halting disease progression.

Amyloid-beta is produced by the cleavage of the larger amyloid precursor protein (APP) by an enzyme called gamma-secretase. Previous research led to the development of gamma-secretase inhibitors that totally block the function of the enzyme, but in clinical trials these drugs

produced serious side effects through their effects on the processing of other proteins.

Rudolph Tanzi, PhD, director of the MGH Genetics and Aging Research Unit, and Steven Wagner, PhD, of the USCD Department of Neurosciences - co-corresponding authors of the current study - first developed the concept of gamma-secretase modulators (GSMs), which change but do not totally suppress the enzyme's activity, back in 2000. More recently their teams developed a group of soluble GSMs, one of which - SGSM-36 - appeared to be a promising candidate for clinical development.

In the current study, the researchers showed that three days of treatment with SGSM-36 reduced levels of amyloid-beta 42 in the brains and plasma of a validated mouse model of inherited Alzheimer's without affecting the processing of APP by other enzymes. In cellular models - including the three-dimensional "Alzheimer's in a dish" system developed by Tanzi's team - they compared the action of SGSM-36 to that of the semagacestat, one of the gamma-secretase inhibitors that failed in clinical trials. While SGSM-36 treatment only reduced levels of the toxic amyloid-beta 40 and 42 peptides, semagacestat reduced all form of amyloid as well as gamma-secretase processing of other proteins, including the important signaling protein Notch, reduction of which may have caused the toxic effects of gamma-secretase inhibitor treatment.

In order to better understand how SGSM-36 alters the gamma-secretase enzyme and its function. The team used fluorescence lifetime imaging microscopy to examine the molecule, identifying a site where SGSM-36 enlarges the space between three characteristic loops of the protein, conferring a more open conformation that has been shown to be associated with lowering production of the toxic forms of amyloid-beta.

"Genetic, biochemical, molecular biological and pathological evidence all support the hypothesis that excessive accumulation of amyloid-beta - particularly amyloid-beta 42 - is the primary event leading to Alzheimer's related pathology," says Zhang, who is an assistant professor of Neurology at Harvard Medical School (HMS). "In our future studies, we will be testing SGSM-36 against similar molecules that may have equal or higher potency in reducing amyloid-beta 42 and further investigating its molecular mechanisms in animal models, with the eventual goal of testing its potential in clinical trials."

More information: Frank Raven et al, Soluble Gamma-secretase Modulators Attenuate Alzheimer's β-amyloid Pathology and Induce Conformational Changes in Presenilin 1, *EBioMedicine* (2017). DOI: 10.1016/j.ebiom.2017.08.028

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