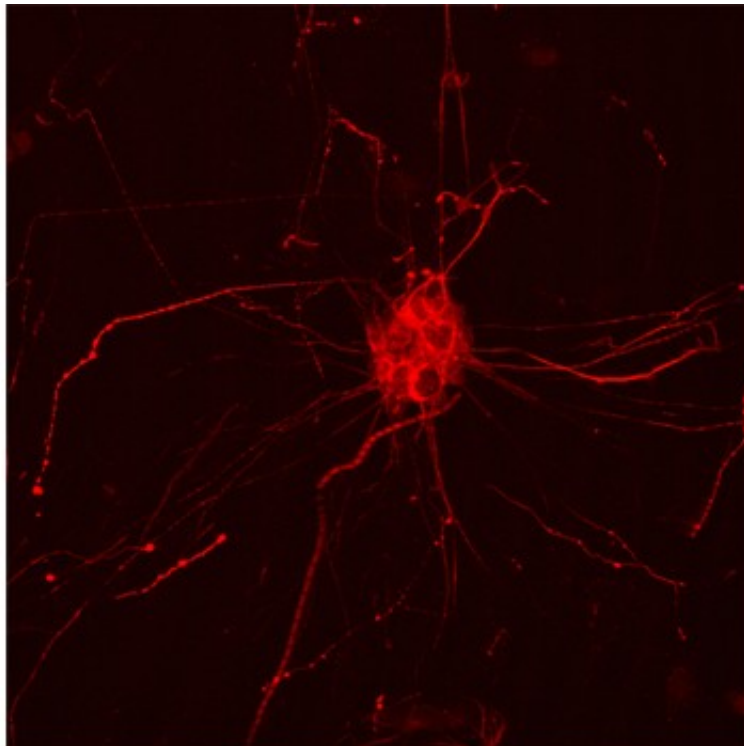


Modulation of brain cholesterol: A new line of research in Alzheimer's disease treatment?

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Fluorescent labelling of the Tau protein in a hNT human cell. Credit:
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We have known for some years that Alzheimer's disease is characterised by two types of lesions, amyloid plaques and degenerated tau protein. Cholesterol plays an important role in the physiopathology of this disease. Two French research teams (Inserm/CEA/University of Lille/University of Paris-Sud) have just shown, in a rodent model, that

overexpressing an enzyme that can eliminate excess cholesterol from the brain may have a beneficial action on the tau component of the disease, and completely correct it. This is the first time that a direct relationship has been shown between the tau component of Alzheimer's disease and cholesterol. This work is published in the 10 September 2015 issue of *Human Molecular Genetics*.

Excess brain cholesterol cannot freely cross the blood-brain barrier; to be eliminated it must be converted into 24-hydroxycholesterol (24-OHC) by the enzyme CYP46A1 (cholesterol-24-hydroxylase). At Inserm Unit 1169, Nathalie, Cartier, coordinator of this work, and Patrick Aubourg, director of the unit, proposed the hypothesis that increasing the efflux of cholesterol from the brain by overexpressing CYP46A1 might have a beneficial effect on the elements of Alzheimer pathology.

The first step in this work made it possible to show that injecting a viral vector, AAV-CYP46A1, effectively corrects a mouse model of amyloid pathology of the disease, the APP23 mouse. CYP46A1 thus appears to be a therapeutic target for Alzheimer's disease.

Conversely, in vivo inhibition of CYP46A1 in the mice, using antisense RNA molecules delivered by an AAV vector administered to the hippocampus, induces an increase in the production of A β peptides, abnormal [tau protein](#), neuronal death and hippocampal atrophy, leading to memory problems. Together these elements reproduce a phenotype mimicking Alzheimer's disease.

These results demonstrate the key role of cholesterol in the disease, and confirm the relevance of CYP46A1 as a potential [therapeutic target](#) (work published in *Brain* on 3 July 2015).

Taken together, this work now enables the research team coordinated by Nathalie Cartier, Inserm Research Director, to propose a gene therapy

approach for Alzheimer's [disease](#): intracerebral administration of a vector, AAV-CYP46A1, in patients with early and severe forms (1% of patients, familial forms) for whom there is no available treatment.

"To achieve this objective, we are carrying out all the preclinical steps of development and validation of the tools (vector, neurosurgical protocol, elements of monitoring) for demonstrating the efficacy and tolerance of the strategy, in order to submit an application for authorisation of a clinical trial," explains Nathalie Cartier.

More information: *Human Molecular Genetics*,
[dx.doi.org/10.1093/hmg/ddv268](https://doi.org/10.1093/hmg/ddv268)

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