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A new line of research in the fight against Alzheimer's disease and dementia

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A team at Inserm, directed by Etienne-Emile Baulieu (Inserm research unit 788 "Steroids, neuroprotection et neuroregeneration", Paris XI University), has just characterised, at the cellular and molecular level, the interaction between the Tau protein (in which an abnormal form is implicated in many neurodegenerative diseases) and a protein known as FKBP52 which is very abundant in the brain. A better understanding of the biochemical and functional basis of this interaction will enable the neurodegenerative mechanisms brought about by the Tau protein, involved in many forms of dementia generally associated with ageing of the brain, to be better resolved. This work has been published in the *Proceedings of the National Academy of Science (PNAS)*.

Alzheimer's disease is one of the primary causes of dementia among the aged, and manifests itself in loss of mental faculties, including memory. This disease of the brain, like other illnesses which bring about very severe dementia among many of the elderly, currently affects more than 25 million people worldwide (1) and more than 800,000 in France. These are categorised as diseases whose treatment is among the most costly to society in the developed nations.

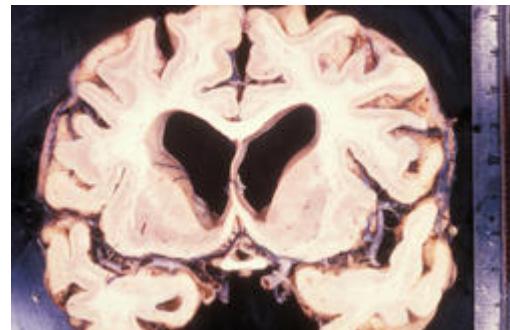
The Tau protein is one of the major factors in many dementias known as Tauopathies. Occurring naturally in the central nervous system, Tau plays a significant role in proper neurone function. In its abnormal, hyperphosphorylated form, the Tau protein disturbs the working of neuronal cells, leading not only to the development of Alzheimer's disease but also to several other forms of neurodegenerative ailment.

The mass of Tau protein in an abnormal brain manifests itself in particular in the form of "tangles".

Etienne-Emile Baulieu's research team (at Research unit 788, directed by Michael Schumacher), in collaboration with Michel Goedert (who originally characterised the Tau protein in Alzheimer's disease in 1998) have just identified an interaction between the dysfunctional Tau protein and another protein, FKBP52.

Using tools from biochemistry and molecular biology, the researchers established that there was a specific physical link between these two proteins in the brain. They demonstrated *in vitro* that the FKBP52 protein suppressed activity of the Tau protein, and hence prevented its role in the assembly of microtubules, known for their role in transporting nutrient and information-bearing molecules into the cell. The researchers observed that a strong expression of FKBP52 prevents the accumulation of Tau protein in nerve cells.

This work extends the research carried out by M. Baulieu over many years on steroids in the nervous system ("neurosteroids"), and which led to his interest in their mechanisms and in ageing of the brain. Furthermore, it was in this context that in 1992 his team revealed the FKBP52 protein without, however, elucidating its function. FKBP52 is a protein belonging to the family of immunophilins, which are intracellular receptors of immunosuppressor compounds. This protein family, which has the special characteristic of possessing immunomodulatory properties, has been found in many neurological disorders: in this context this suggests new and distinct functions.



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Alzheimer's disease. Cross-section of the human brain, cortical atrophy and ventricular dilation.

"This new FKBP52 'anti-Tau' work means that we have to re-examine the functions of this protein, initially identified as a modulator for steroid hormone receptors" the authors write. "The interaction described in this article deserves rapid further detailed study" they conclude. Several national and international collaborative studies are about to be undertaken to validate the therapeutic and diagnostic approaches for Alzheimer's disease. This research work will be supported financially by the Vivre longtemps foundation (the "Long Life" Foundation) and the Institut Baulieu.

(1) Source : OMS Report– Troubles neurologiques, défis pour la santé publique (2007)
(2) Medical Research Council Laboratory of Molecular Biology, Cambridge, UK

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["A Role for FKBP52 in Tau Protein Function"](#)
PNAS, early edition 25 January 2010

Researcher contact

[Etienne Emile Baulieu](#), Member of the Académie des sciences, President 2003-2004
Tel :01 49 59 18 82
[Béatrice Chamraud](#)
Tel : 01 49 59 18 91

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