



La
Psychiatrie
dans TOUS ses états

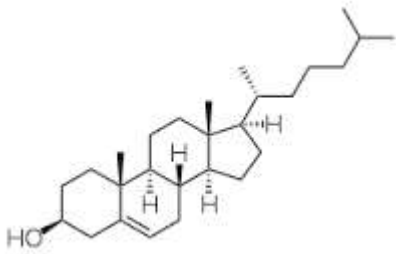
Cholestérol et apolipoprotéine E (APOE) dans la maladie d'Alzheimer.

Equipe Maladie d'Alzheimer et maladies à prions.
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CNRS UMR7225, INSERM U1127, UPMC, Hôpital de la Pitié-Salpêtrière

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LIPIDES ET CERVEAU

- Les lipides sont essentiels au fonctionnement du cerveau
- Le cerveau est l'un des tissus les plus riches en lipides (60 % de la matière sèche)
- On distingue différentes catégories de lipides :
 - les lipides simples ou acides gras
 - les lipides complexes comme les phospholipides et le cholestérol.
- Les membranes des neurones contiennent des acides gras et des lipides complexes



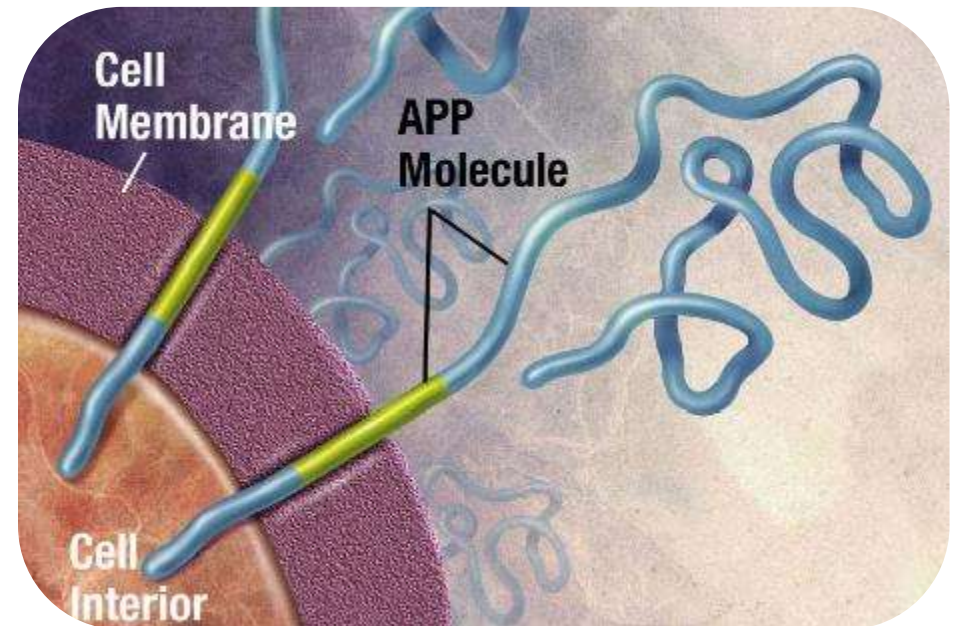
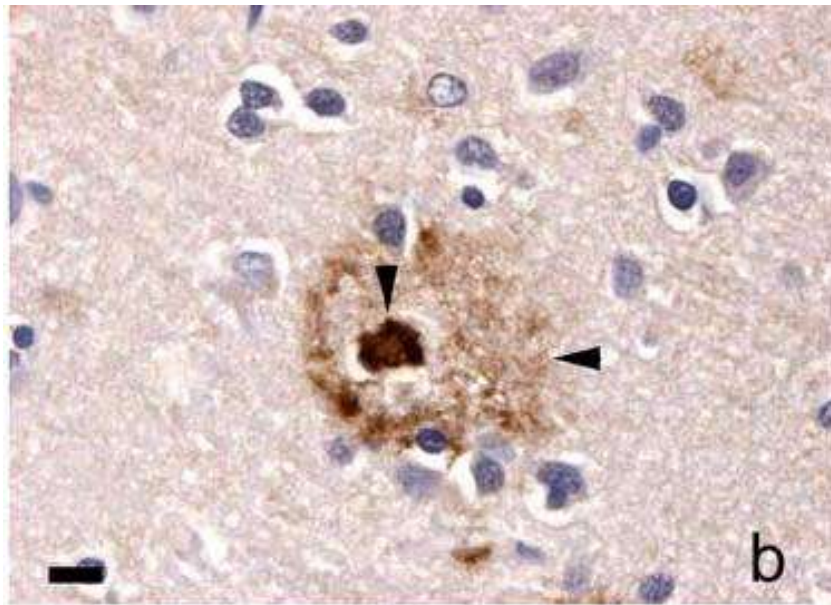
CHOLESTEROL ET CERVEAU

- Composant majeur des membranes cellulaires assurant stabilité et maintien des structures en s'intercalant entre les phospholipides (bicouche de la membrane).
- Il fluidifie la membrane évitant la cristallisation des acides gras, diminue la perméabilité membranaire aux molécules hydrosolubles.
- Il a un rôle de « tampon thermique » : à 37 °C, il limite le mouvement des phospholipides, donc la fluidité membranaire diminue ; à des températures plus basses, il empêche l'entassement des phospholipides.
- Dans la membrane, il permet la formation de radeaux lipidiques, zones essentielles à l'ancrage de protéines fonctionnelles.
- Dans les neurones, il est enrichi dans les gaines de myéline et permet la propagation de l'influx nerveux.

La maladie d'Alzheimer

Les principales lésions

Lésions extracellulaires: pathologie amyloïde



Progression des lésions amyloïdes

STADES
DE
THAL

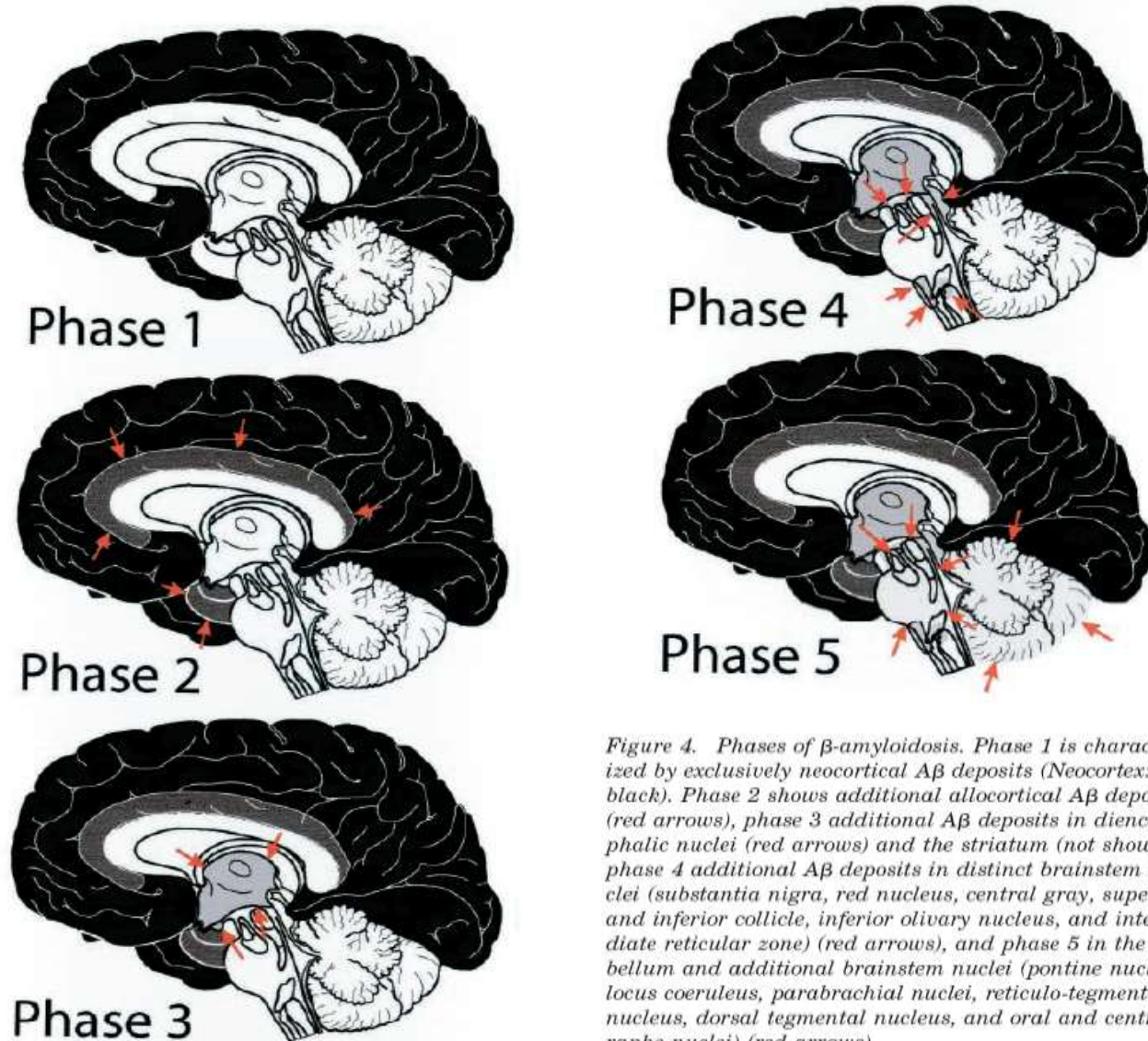
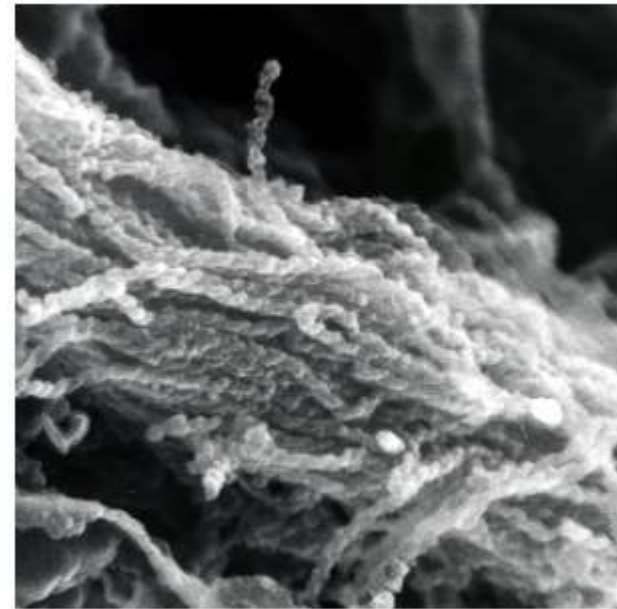
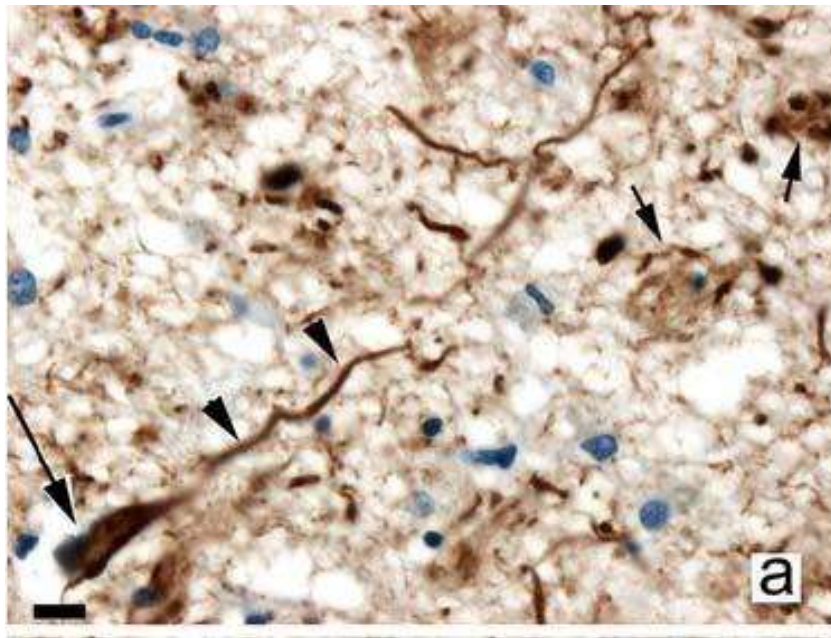


Figure 4. Phases of β -amyloidosis. Phase 1 is characterized by exclusively neocortical $A\beta$ deposits (Neocortex: black). Phase 2 shows additional allocortical $A\beta$ deposits (red arrows), phase 3 additional $A\beta$ deposits in diencephalic nuclei (red arrows) and the striatum (not shown), phase 4 additional $A\beta$ deposits in distinct brainstem nuclei (substantia nigra, red nucleus, central gray, superior and inferior collicle, inferior olivary nucleus, and intermediate reticular zone) (red arrows), and phase 5 in the cerebellum and additional brainstem nuclei (pontine nuclei, locus coeruleus, parabrachial nuclei, reticulo-tegmental nucleus, dorsal tegmental nucleus, and oral and central raphe nuclei) (red arrows).

La maladie d'Alzheimer

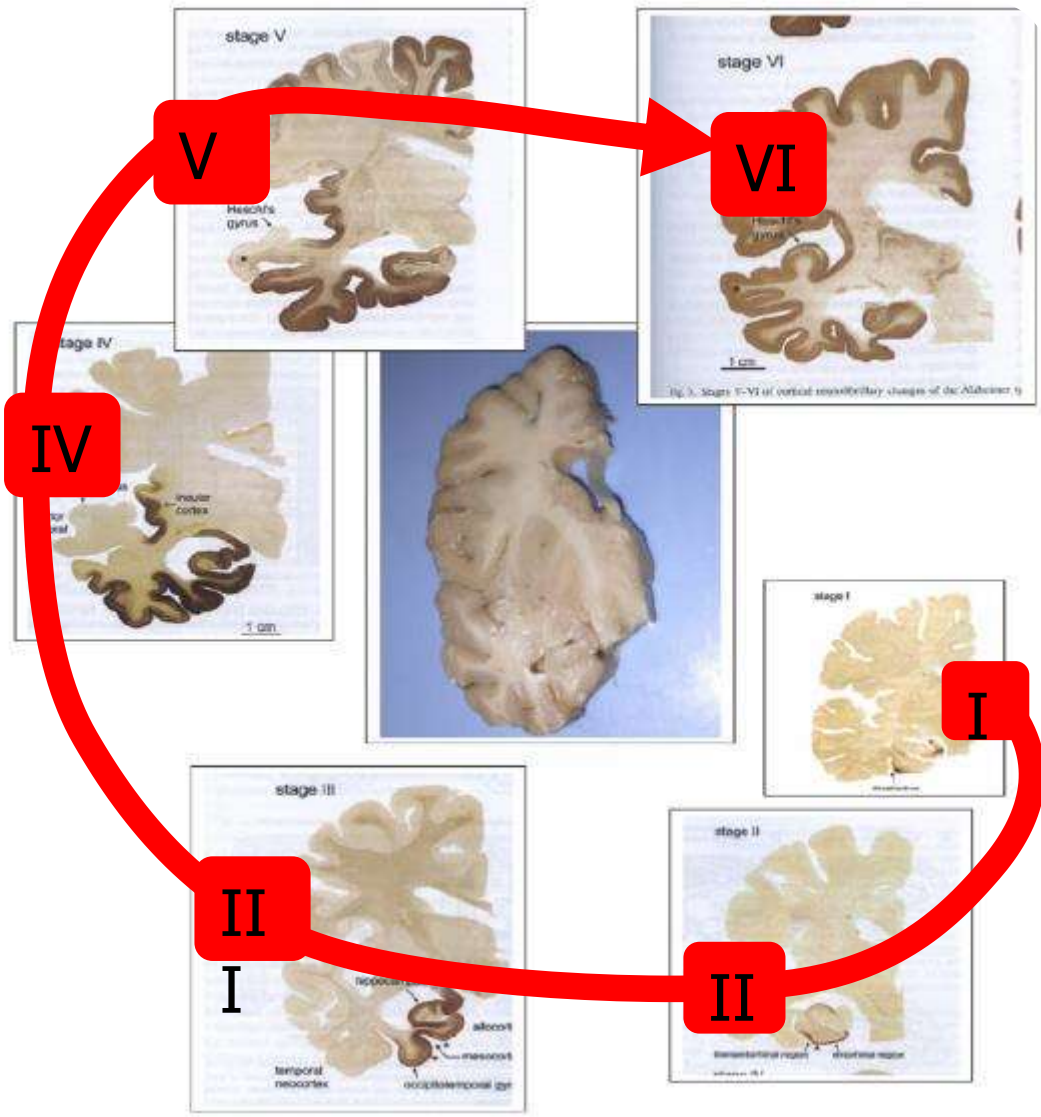
Les principales lésions

Lésions intracellulaires: pathologie tau



Duyckaerts *et al.* Acta Neuropath. 2009

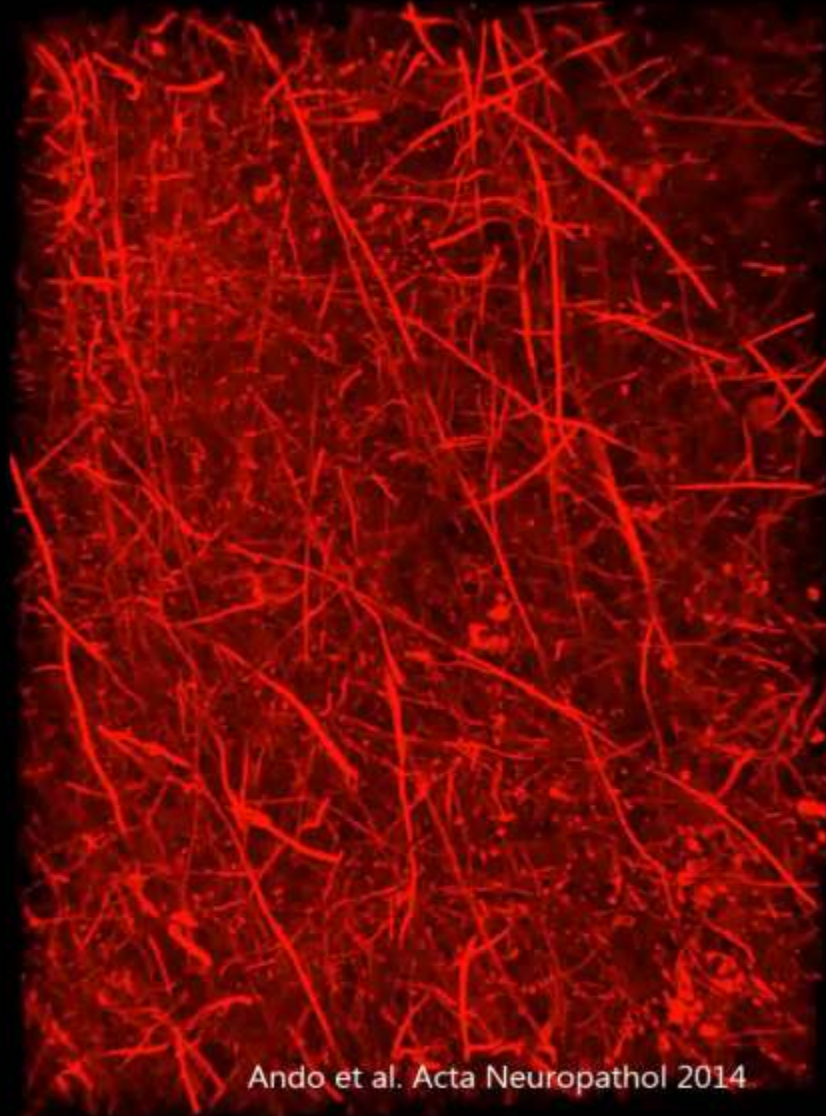
Progression des lésions tau



STADES
DE
BRAAK



CLARITY dans un cerveau postmortem (cortex) de patient Alzheimer
A β en **BLEU**, tau en **VERT**, neurofilaments en **ROUGE**



Ando et al. Acta Neuropathol 2014

Formes familiales de la Maladie d'Alzheimer

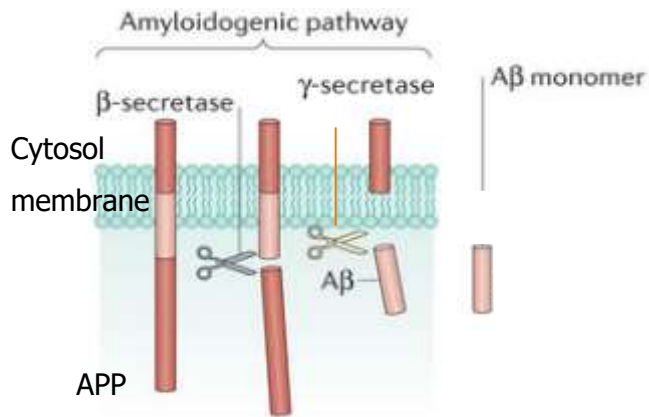
<1% des cas

Table 1 | Summary of genetic findings for early-onset autosomal-dominant forms of AD

Gene (and protein)	Chromosomal location	Total number of pathogenic mutations (affected families)	Relevance to AD pathogenesis	Initial study references
APP (amyloid precursor protein)	<u>21q21.3</u>	29 (78)	Increase in A β production or A β_{42} /A β_{40} ratio; mutations in the A β sequence or close to the β - and γ -secretase site of APP; locus duplications	98
PSEN1 (presenilin 1)	<u>14q24.3</u>	166 (362)	Increase in A β_{42} /A β_{40} ratio; mutations throughout molecule; enzymatic role in γ -secretase complex	99
PSEN2 (presenilin 2)	<u>1q31-42</u>	10 (18)	Increase in A β_{42} /A β_{40} ratio; mutations throughout molecule; enzymatic role in γ -secretase complex	100,101

The data in the 'Total number of pathogenic mutations' column is from the [AD & FTD Mutation Database](#). The 'Initial study references' column lists the first publication(s) to describe Alzheimer's disease (AD)-causing mutations in the respective genes. A β , amyloid- β ; APP, amyloid precursor protein. Table modified, with permission, from REF. 102 © (2001) Current Science Inc.

Peptide A β



PERSPECTIVE

Alzheimer's Disease: The Amyloid Cascade Hypothesis

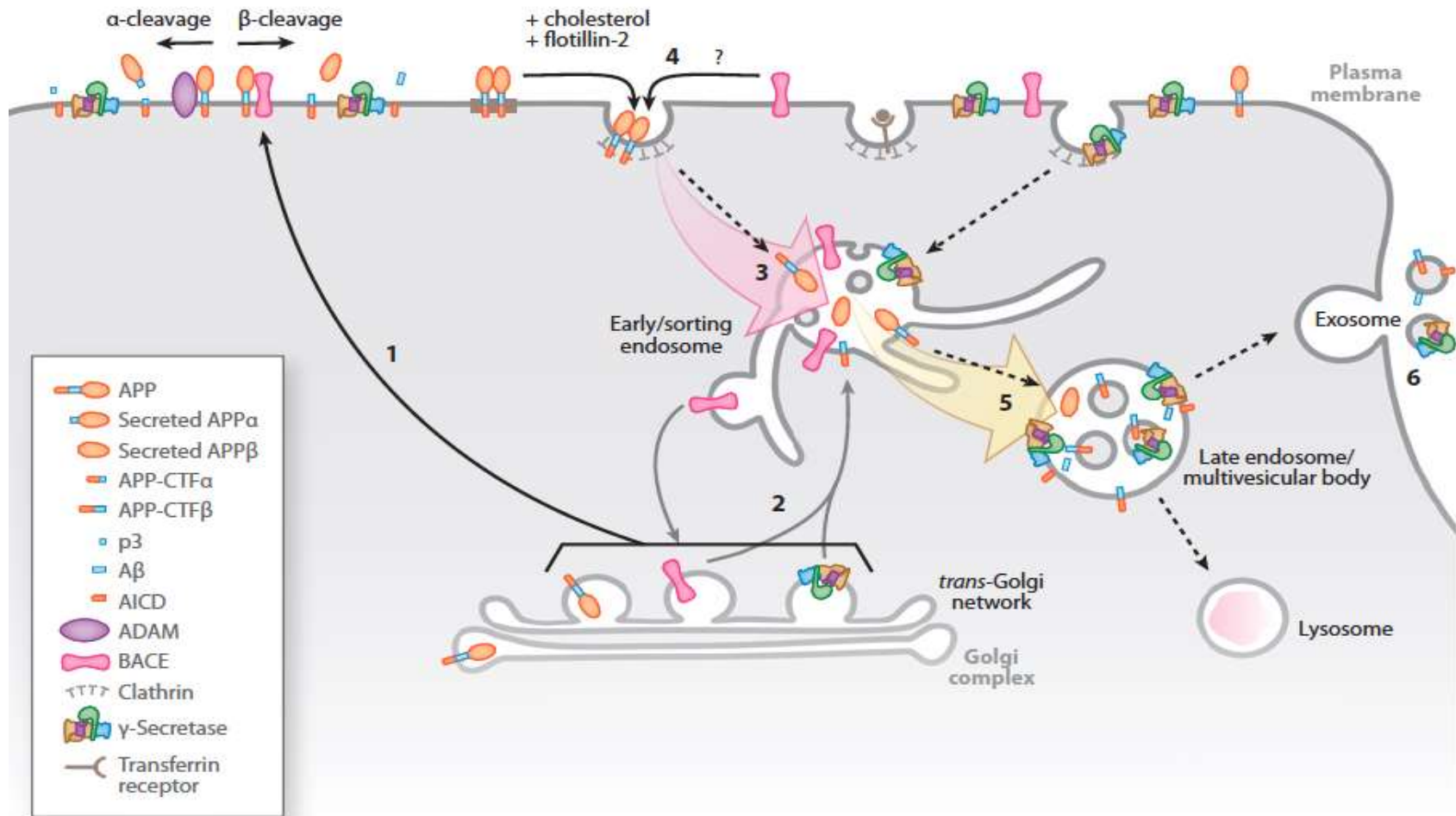
John A. Hardy and Gerald A. Higgins

- DNFs (tau)
- Perte neurones
- Perte synapses
- Dommages vasculaires, inflammation

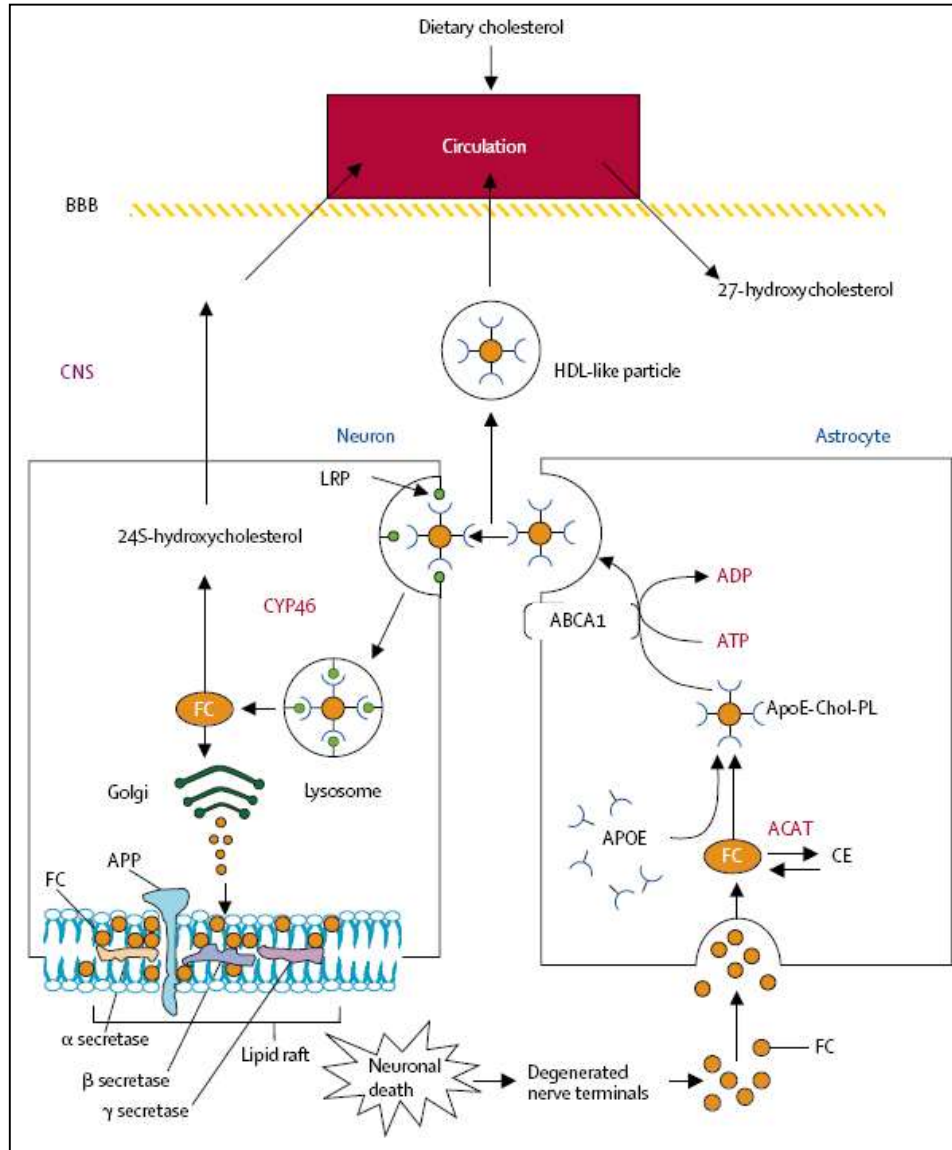
Troubles cognitifs

Démence

Clivage de l'APP dans le compartiment endo-lysosomal.



Cholestérol et maladie d'Alzheimer



Genétique facteurs de risque génétiques
ApoE, ABCA7

Neuropathologie le cholestérol cérébral est augmenté dans la MA
(Cutler *et al.*, 2004; Xiong *et al.*, 2008; Panchal *et al.* 2010 JLR; Lazar *et al.* 2012)

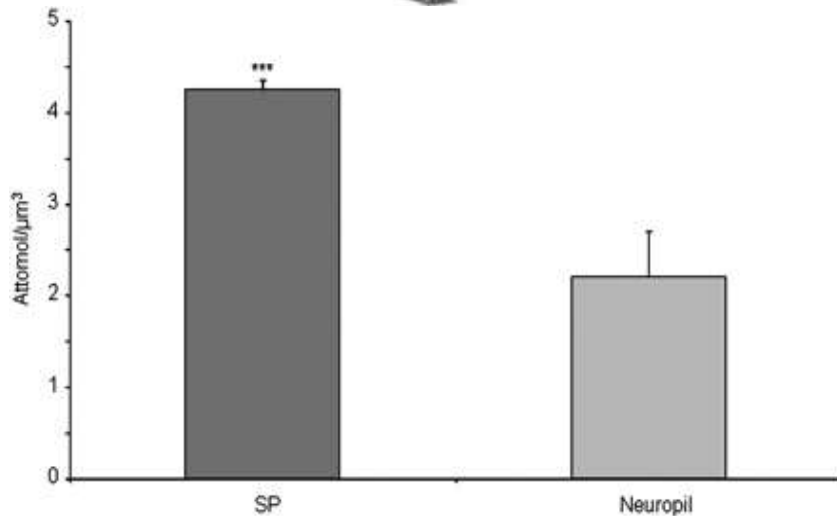
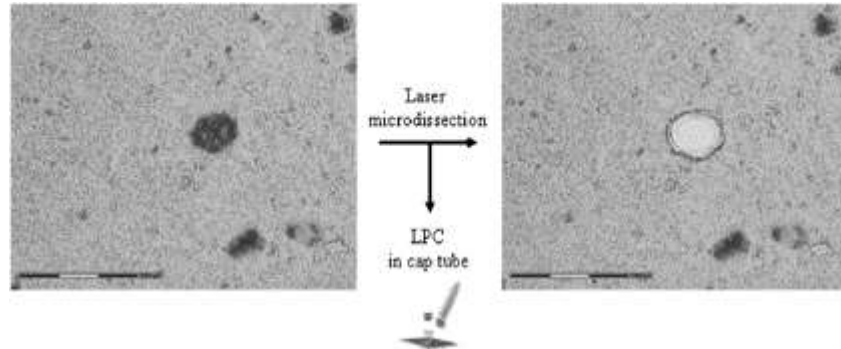
In vitro APP et les enzymes de clivage sont localisées dans les radeaux lipidiques
(Bouillot *et al.*, 1996; Cordy *et al.*, 2003; Marquer *et al.* 2011)

In vivo
⊙ Augmentation de CYP46 dans le cerveau de souris TgAPP ou un traitement avec des cyclodextrines corrigent la pathologie amyloïde et les déficits cognitifs
⊙ Tg APP/PS1 et SREBP ont les pathologies amyloïde et tau
(Hudry *et al.* 2009; Jiaqi *et al.* 2012; Barbero-Camps *et al.* HMG 2013)

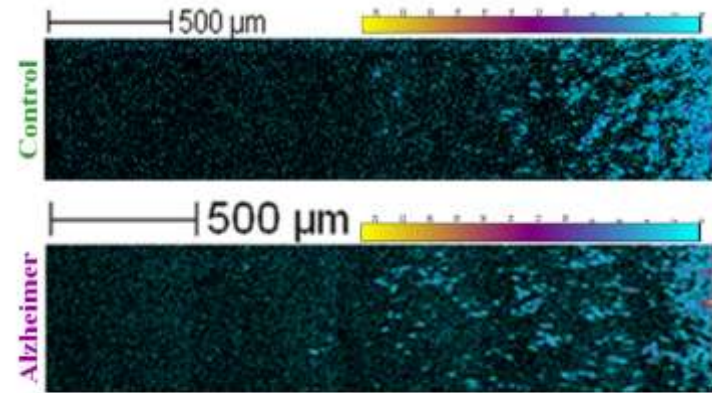


Identification of lipids in senile plaques

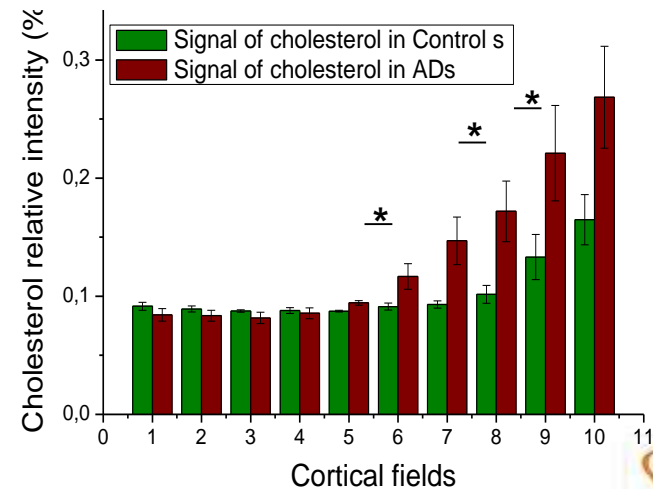
Microdissected plaques



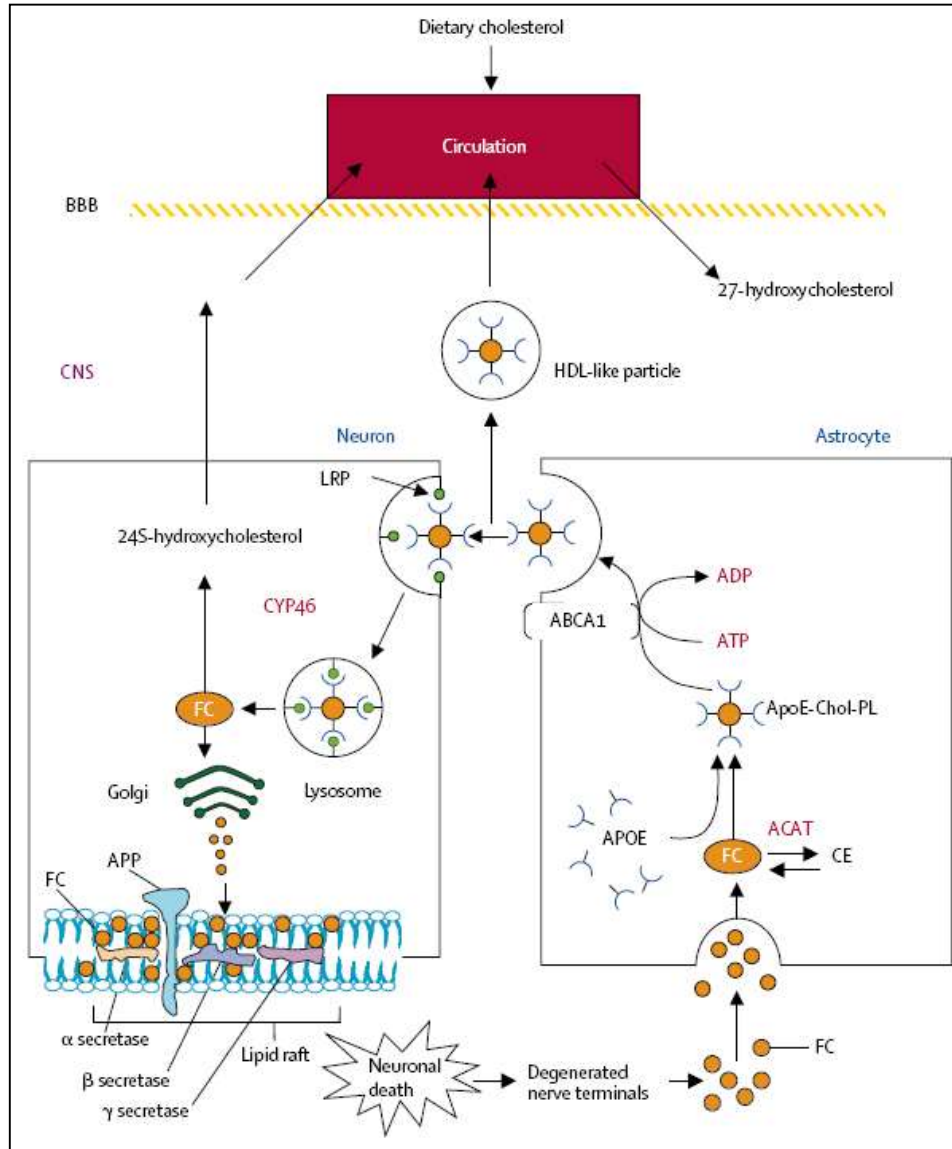
Imaging lipids



a



Cholestérol et maladie d'Alzheimer



Genétique facteurs de risque génétiques
ApoE, ABCA7

Neuropathologie le cholestérol cérébral est augmentés dans la MA
(Cutler *et al.*, 2004; Xiong *et al.*, 2008; Panchal *et al.* 2010 JLR; Lazar *et al.* 2012)

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CYP46A1 inhibition, brain cholesterol accumulation and neurodegeneration pave the way for Alzheimer's disease

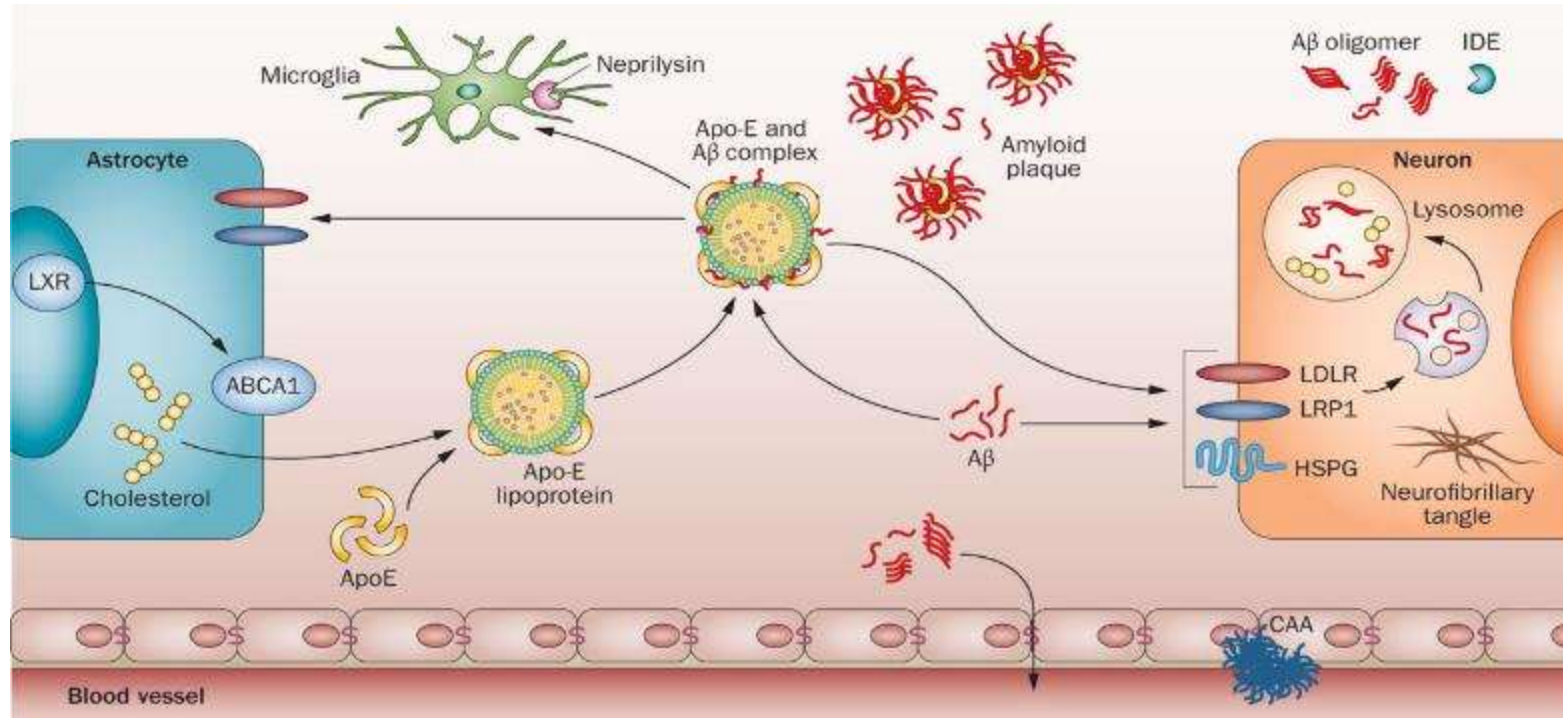
Fathia Djelti,¹ Jerome Braudeau,^{1,*} Eloise Hudry,^{1,*} Marc Dhenain,² Jennifer Varin,³ Ivan Bièche,³ Catherine Marquer,⁴ Farah Chali,⁴ Sophie Ayciriex,⁵ Nicolas Auzeil,⁵ Sandro Alves,¹ Dominique Langui,⁴ Marie-Claude Potier,⁴ Olivier Laprevote,⁵ Michel Vidaud,³ Charles Duyckaerts,⁴ Richard Miles,⁴ Patrick Aubourg^{1,*} and Nathalie Cartier^{1,*}

ORIGINAL ARTICLE

Cholesterol 24-hydroxylase defect is implicated in memory impairments associated with Alzheimer-like Tau pathology

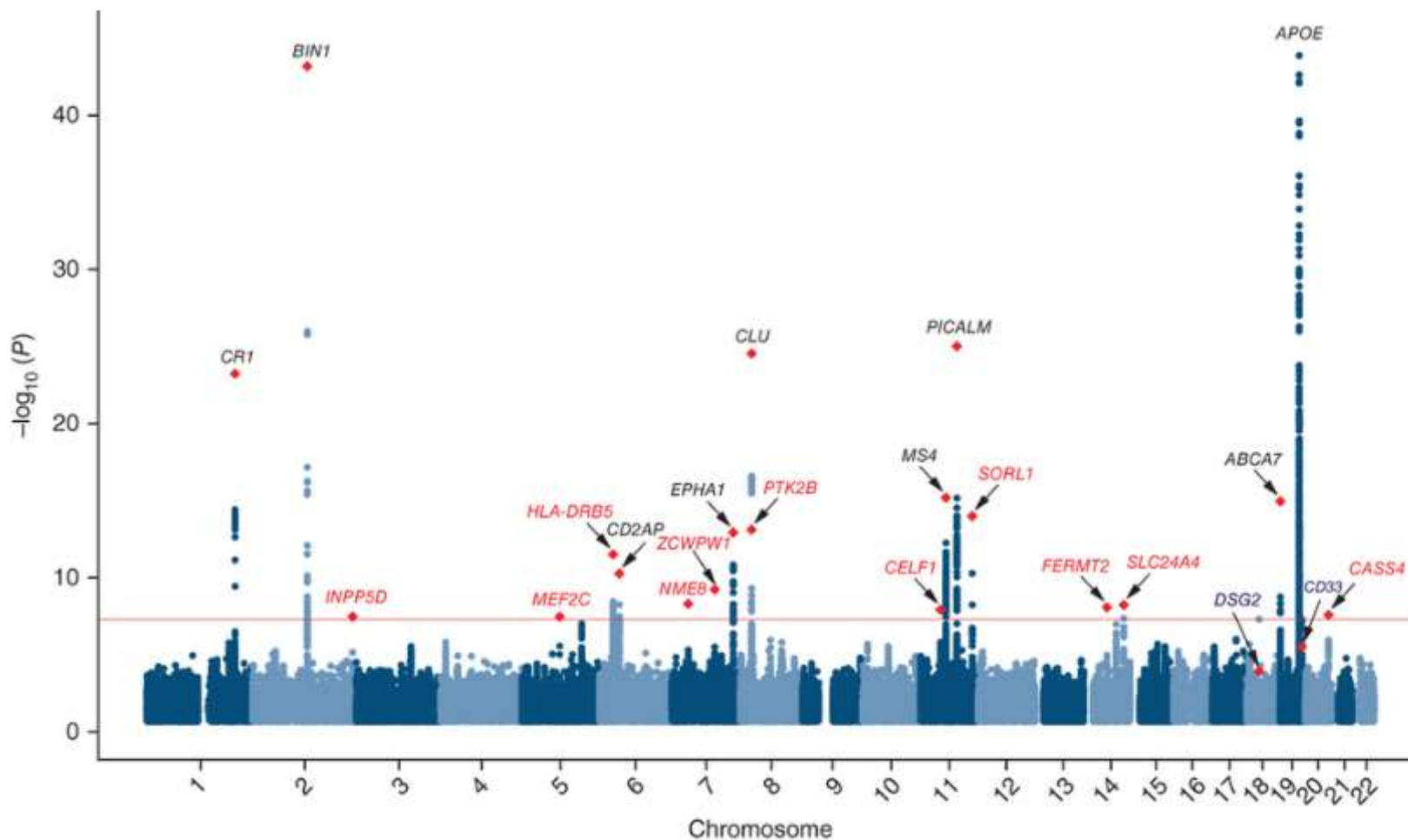
Marie-Anne Burlot^{1,2,3}, Jérôme Braudeau^{1,2}, Kristin Michaelsen-Preusse^{4,5}, Brigitte Potier⁶, Sophie Ayciriex⁷, Jennifer Varin⁸, Benoit Gautier^{1,2}, Fathia Djelti^{1,2,3}, Mickael Audrain^{1,2,3}, Luce Dauphinot⁹, Francisco-Jose Fernandez-Gomez^{10,11}, Raphaëlle Caillierez^{10,11}, Olivier Laprévôte⁷, Ivan Bièche⁸, Nicolas Auzeil⁷, Marie-Claude Potier⁹, Patrick Dutar⁶, Martin Korte^{4,5}, Luc Buée^{10,11,12}, David Blum^{10,11,12} and Nathalie Cartier^{1,2,*}

L'ApoE et le métabolisme de l'Aβ dans le cerveau.

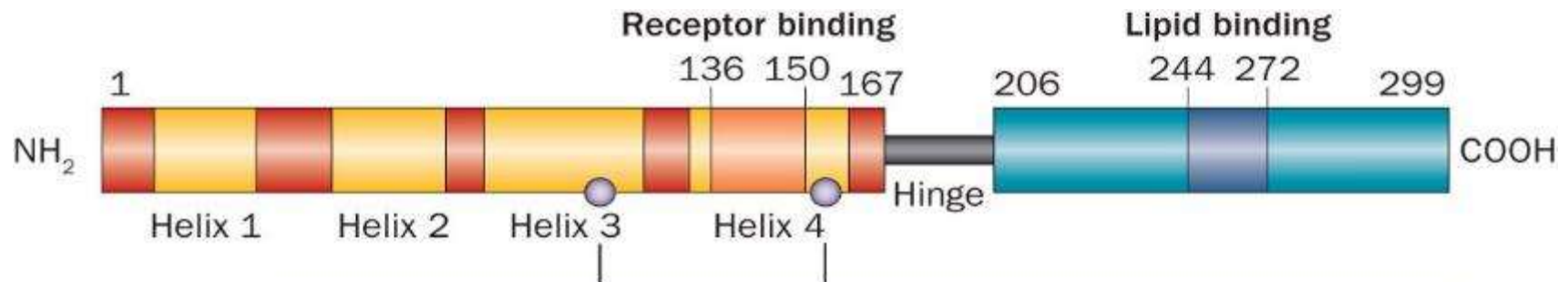


Liu, C.-C. *et al.* (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy
Nat. Rev. Neurol. doi:10.1038/nrneurol.2012.263

Métanalyse génétique de 74 046 individus: identification de 11 facteurs de risque



APOE ϵ 4 est le facteur de risque majeur pour la maladie d'Alzheimer



	Isoform-specific amino acid difference		Allele frequency (%)	
	112	158	General	AD
Apo-E2	Cys	Cys	8.4	3.9
Apo-E3	Cys	Arg	77.9	59.4
Apo-E4	Arg	Arg	13.7	36.7

Liu, C.-C. *et al.* (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy
Nat. Rev. Neurol. doi:10.1038/nrneurol.2012.263

Effets de l'*APOE* ϵ 4 sur la fréquence et l'âge d'apparition de la maladie d'Alzheimer

Table 1 | The effect of *APOE* ϵ 4 on AD frequency and age at onset⁷

Characteristic	<i>APOE</i> ϵ 4 noncarrier	<i>APOE</i> ϵ 4 heterozygous	<i>APOE</i> ϵ 4 homozygous
AD frequency (%)	20	47	91
Mean age of clinical onset (years)	84	76	68

Abbreviations: AD, Alzheimer disease; *APOE* ϵ 4, ϵ 4 allele of the apolipoprotein E gene.

Liu, C.-C. *et al.* (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy
Nat. Rev. Neurol. doi:10.1038/nrneurol.2012.263

La cohorte INSIGHT de l'ICM/IHU/IM2A

INveStIGATION of AlzHeimer's predicTors

321 sujets de plus de 70 ans suivis 7 ans

Etude monocentrique

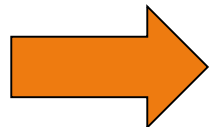
Sujets sans déficit cognitif

Imagerie (IRM, PET FDG et amyloïde)

EEG

Biomarqueurs LCR et sang

Génétique



1. Trouver les profils de conversion
2. Réaliser des études clinique dur les sujets à risque

INSIGHT - APOE

	Number individuals	% INSIGHT cohort
E2/E2	1	0,3%
E2/E3	44	13,7%
E2/E4	4	1,2%
E3/E3	217	67,6%
E3/E4	52	16,2%
E4/E4	3	0,9%
Total	321	

Amyloïde positifs PET (28 %)
37,5% are APOE4

Amyloïde négatifs PET (72 %)
12,6% are APOE4

17% APOE4

Nouveaux essais cliniques chez les sujets à risque

Table 1 | New trials in patients with preclinical AD

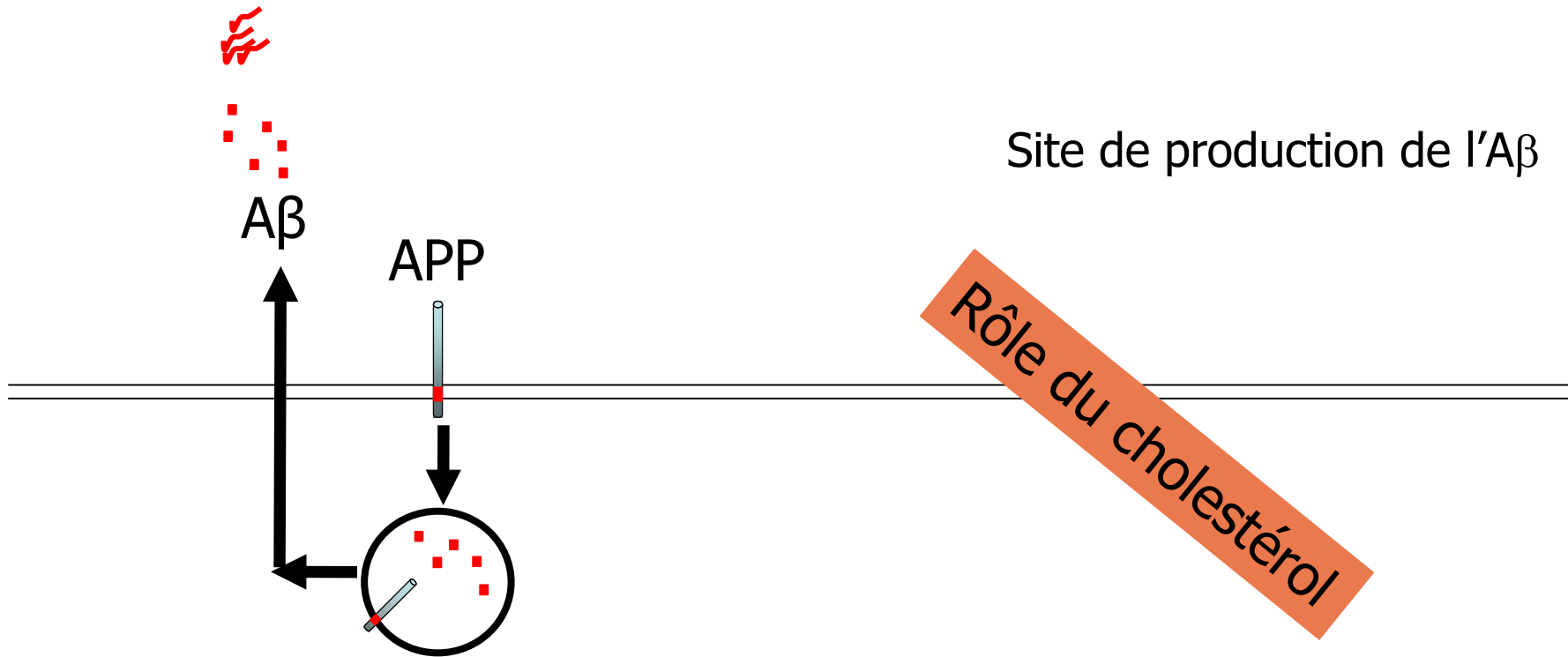
Trial	Participants	Trial duration	Compound and administration	Targeted A β species	Primary outcomes	Biomarker measures	Interim analysis
ADCS A4	1,000 amyloid-positive adults aged 65–85 years (500 per treatment arm)	168 weeks	Solanezumab IV every 4 weeks	Monomer	ADCS Preclinical Alzheimer Cognitive Composite	Florbetapir PET, MRI, CSF analyses, tau PET	Blinded sample size re-estimation
API ADAD	200 ADAD mutation carriers (100 per treatment arm) and 100 kindred non-carriers (placebo arm) aged 30–60 years without MCI or dementia	260 weeks	Crenezumab SQ every 2 weeks	Monomeric, oligomeric and fibrillar	API ADAD composite cognitive test score	Florbetapir PET, ¹⁸ F-FDG-PET, MRI, CSF analyses	After last participant enrolled completes 104 weeks of treatment
API APOE4*	Approximately 1,340 APOE ϵ 4 homozygotes aged 60–75 years without MCI or dementia	260 weeks	CAD106 IM quarterly, CNP50 (oral pill) daily	Multiple species	API composite cognitive test score, time to diagnosis of MCI or dementia due to AD	Florbetapir PET, ¹⁸ F-FDG-PET, MRI, CSF analyses, tau PET	TBD
DIAN-TU Biomarker	138 ADAD mutation carriers (52 per active treatment arm, 34 pooled placebo) and 77 kindred non-carriers (placebo arm) –15 years to +10 years from parental age of symptom onset	Up to 104 weeks	Solanezumab IV every 4 weeks, gantenerumab SQ every 4 weeks	Monomer (solanezumab), aggregated (gantenerumab)	CSF A β (solanezumab), PIB-PET (gantenerumab)	CSF and plasma analyses, florbetapir PET, PIB-PET, ¹⁸ F-FDG-PET, MRI, tau PET	Biomarker interim analyses based on adaptive design
DIAN-TU Adaptive Prevention Trial	266 ADAD mutation carriers (133 per treatment arm) and 133 kindred non-carriers (placebo arm) –15 years to +10 years from parental age of symptom onset	208 weeks	TBD from DIAN-TU Biomarker	TBD from DIAN-TU Biomarker	Cognitive measure or composite TBD	CSF and plasma analyses, florbetapir PET, PIB-PET, ¹⁸ F-FDG-PET, MRI, tau PET	TBD
TOMMORROW	4,622 APOE/TOMM40 high-risk (2311 per treatment arm) and 600 low-risk (placebo arm) individuals aged 65–83 years without MCI or dementia	260 weeks [†]	Pioglitazone daily	Not applicable	Time to diagnosis of MCI due to AD	MRI volumetrics in subset	Futility analysis once 50% (205/410) of the anticipated events have occurred

*Subject to regulatory authority approval. [†]Estimate. Exact duration depends on the number of progression events. Abbreviations: A β , amyloid- β ; AD, Alzheimer disease; ADAD, autosomal dominant AD; ADCS, Alzheimer's Disease Cooperative Study; API, Alzheimer's Prevention Initiative; APOE, apolipoprotein E; CSF, cerebrospinal fluid; DIAN-TU, Dominantly Inherited Alzheimer Network Trials Unit; IM, intramuscularly; IV, intravenously; MCI, mild cognitive impairment; PIB, Pittsburgh compound B; SQ, subcutaneously; TBD, to be determined.

Reiman, E. M. *et al.* (2015) CAP—advancing the evaluation of preclinical Alzheimer disease treatments
Nat. Rev. Neurol. doi:10.1038/nrneuro.2015.177



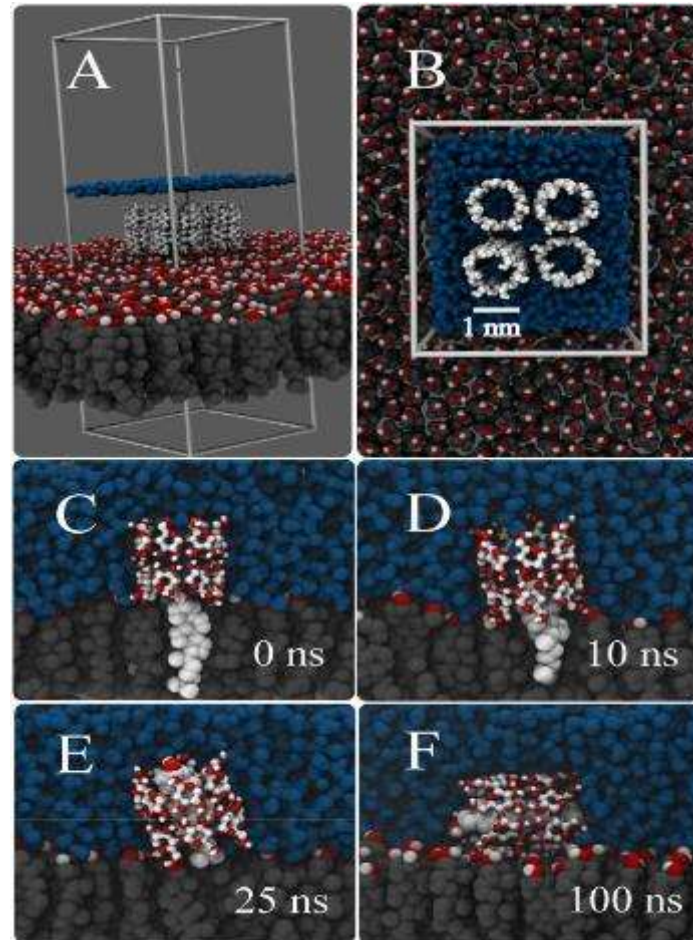
Rôle du cholestérol sur la pathologie amyloïde



Modulation du cholestérol membranaire

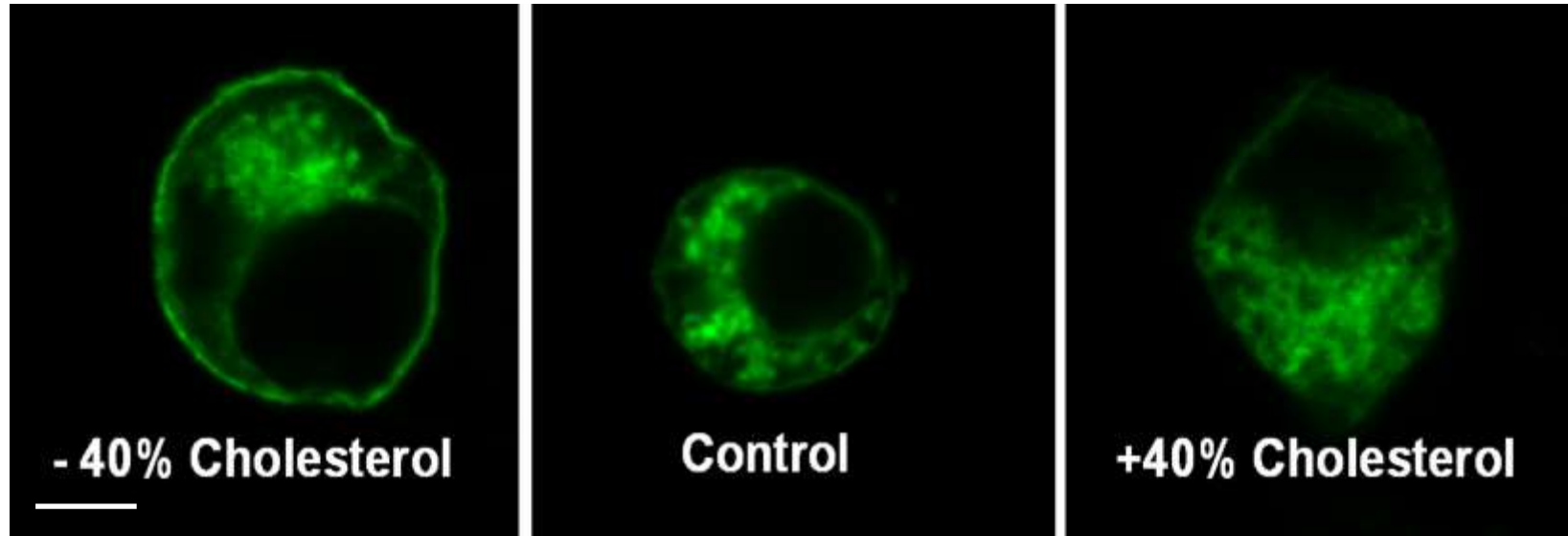
Diminution avec la MBCD
(Lopez et al. PLoS Comput.
Biol. 2011)

Augmentation avec le
complexe MBCD-cholestérol

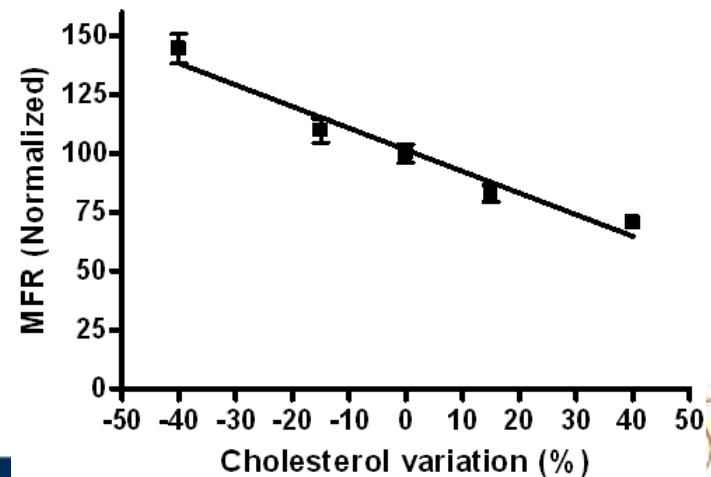


Molecular dynamic studies

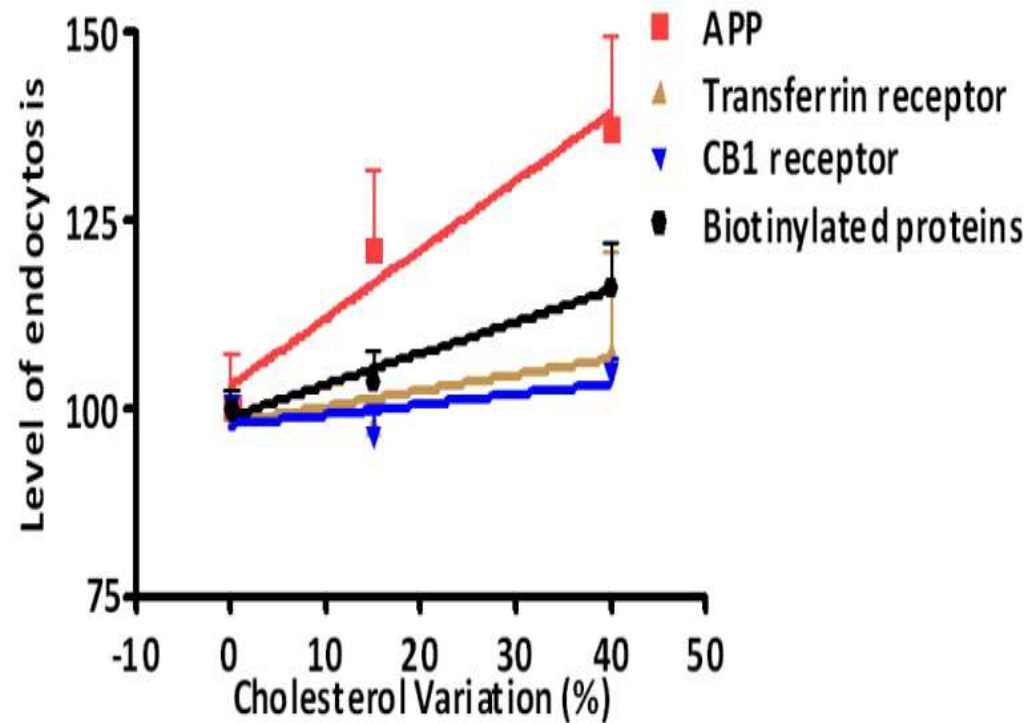
Le cholestérol membranaire contrôle l'endocytose d'APP.



MFR=Membrane/Intracellular
Fluorescence Ratio

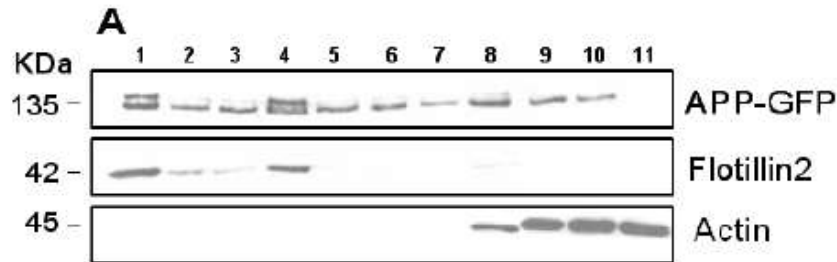


Le cholestérol membranaire contrôle l'endocytose d'APP.

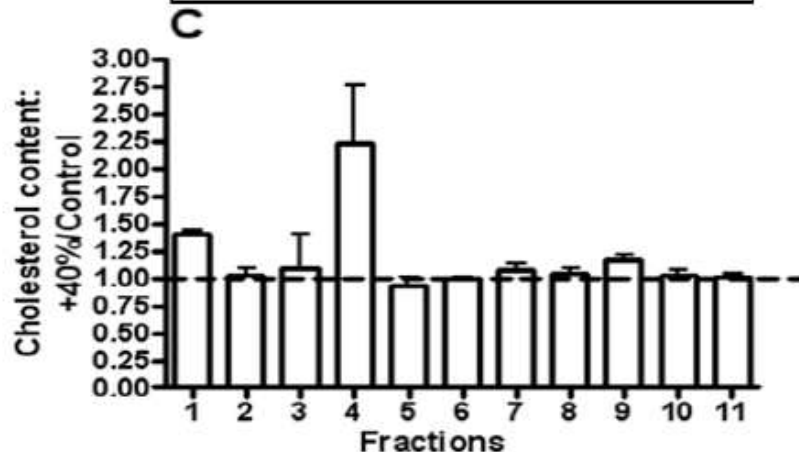
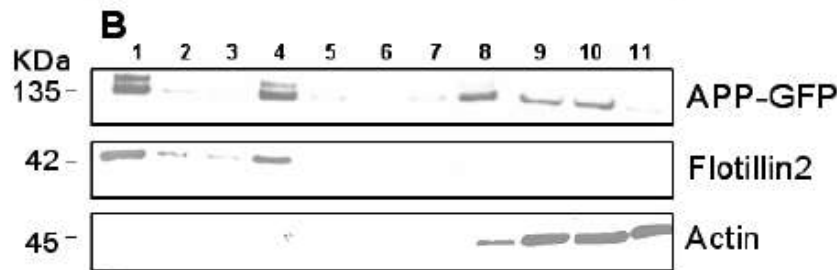


Le cholestérol membranaire contrôle l'endocytose d'APP.

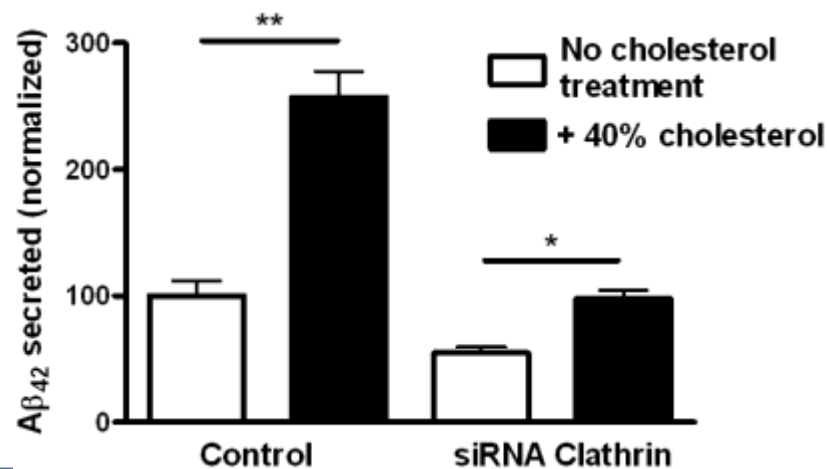
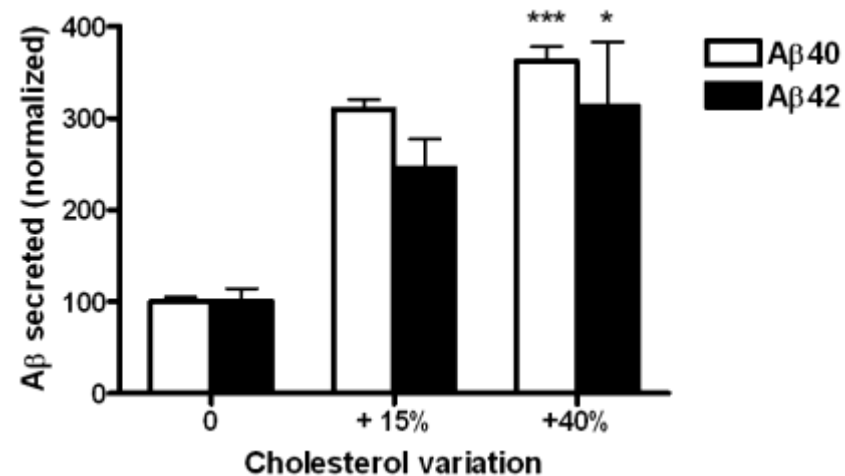
contrôle



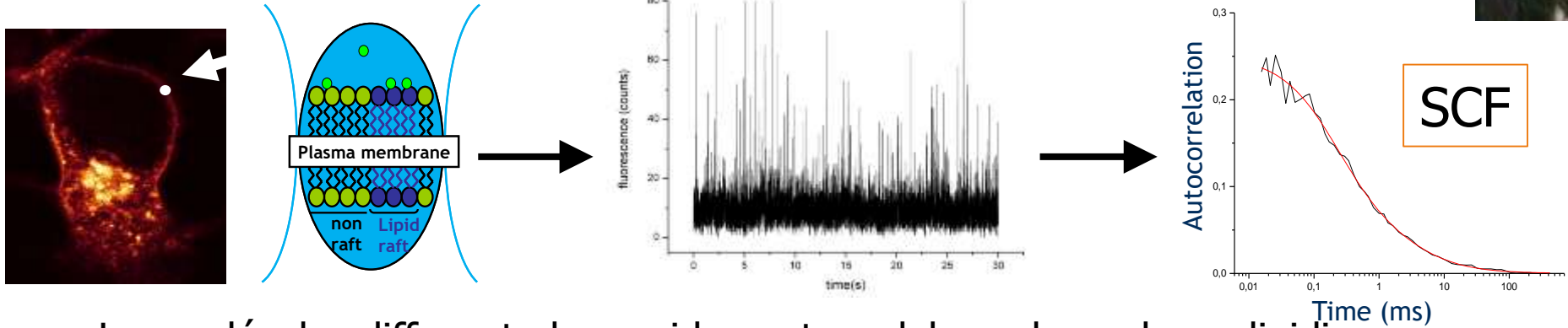
+ 40% cholestérol



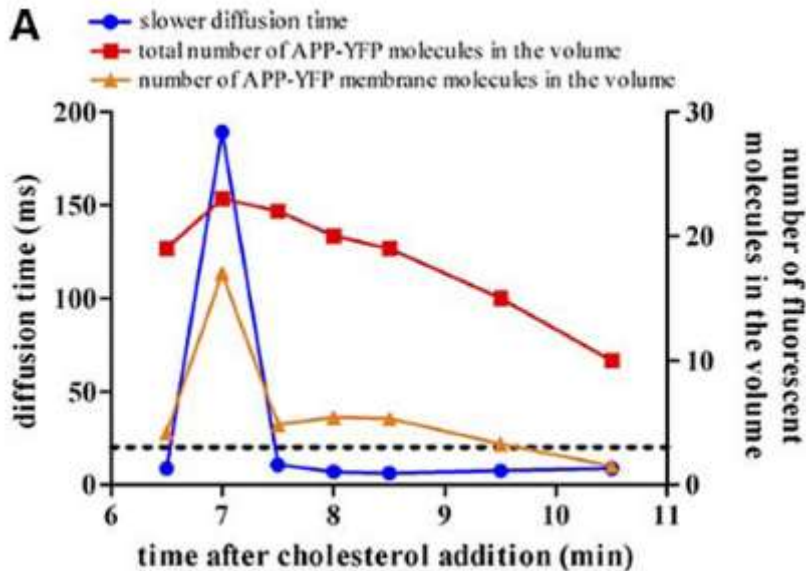
L'augmentation de cholestérol induit une sécrétion d'A β .



Le cholestérol membranaire contrôle la localisation d'APP dans les radeaux lipidiques.

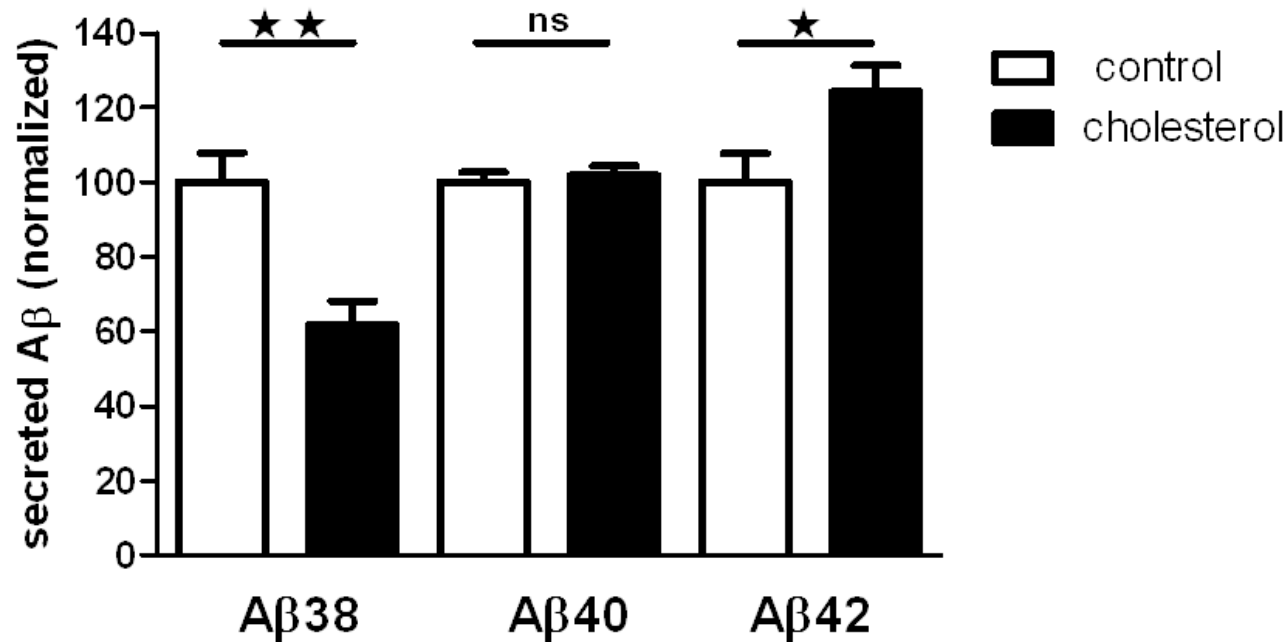


Les molécules diffusent plus rapidement en dehors des radeaux lipidiques.



Relocalisation de l'APP-YFP dans les radeaux lipidiques après ajout de cholestérol

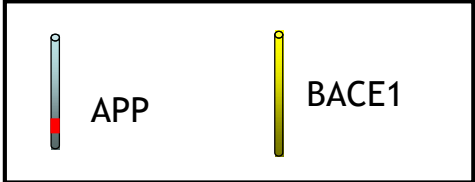
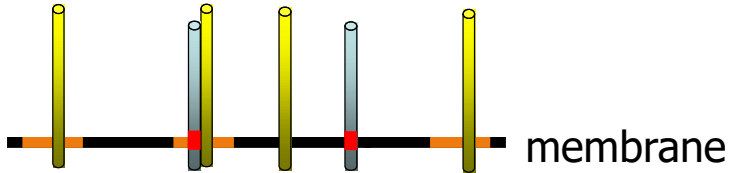
Augmentation de la production d'A β



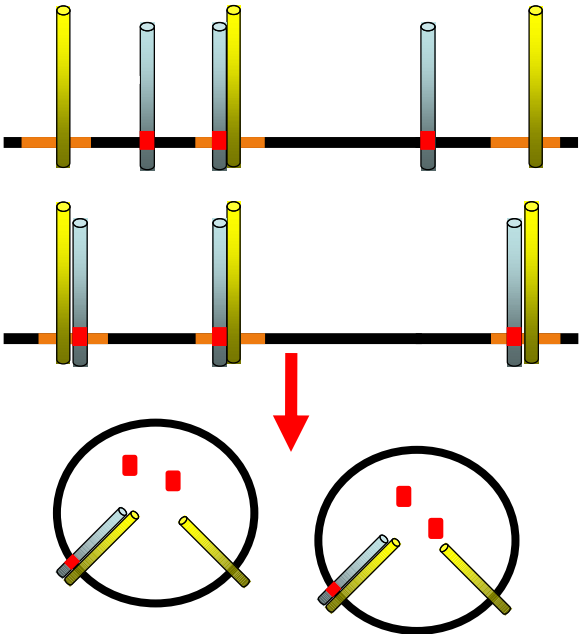
Effets du cholestérol sur la pathologie amyloïde dans la MA



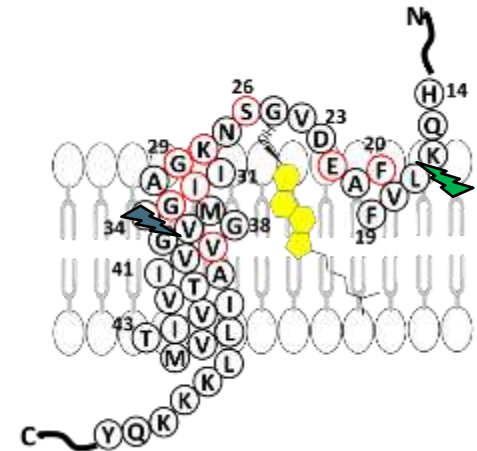
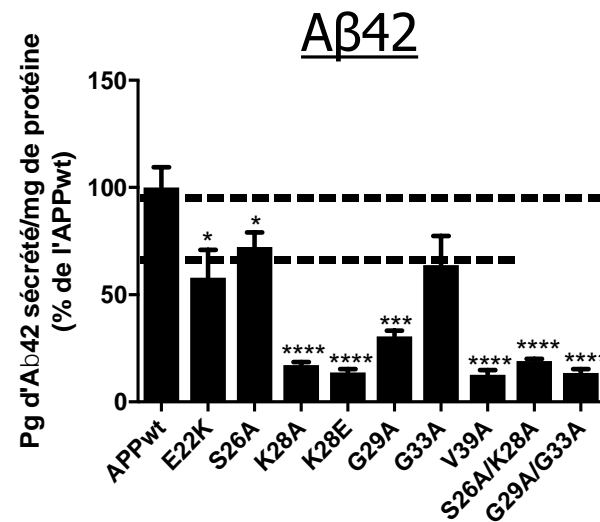
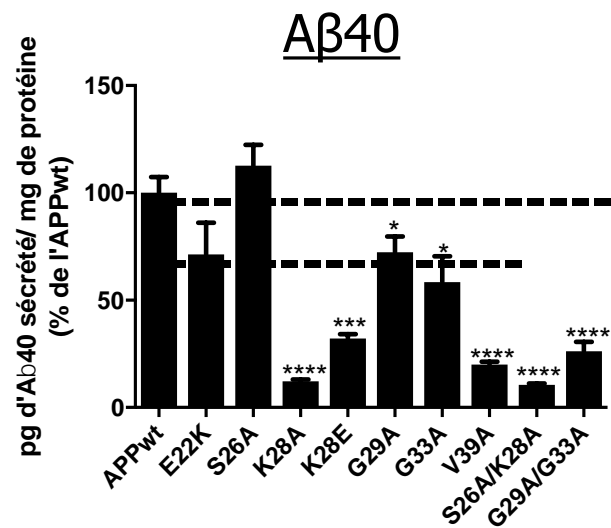
Contrôle



+ Cholestérol
(0-10 min)

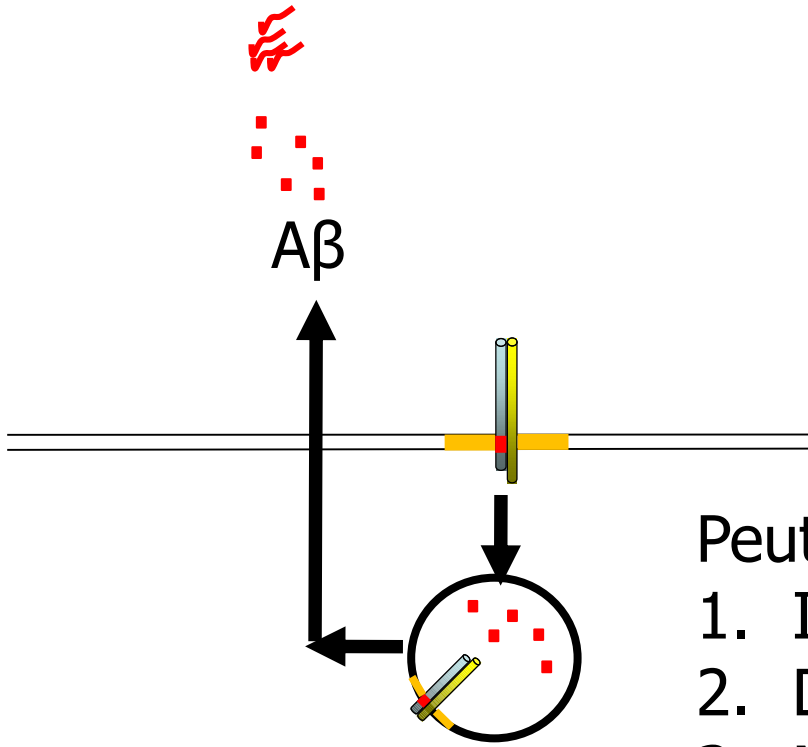


Mutation du site de liaison du cholestérol sur l'APP



t test, moyenne +/- SEM, * : p<0.05, ** : p<0,01, *** : p<0,001, **** : p<0 ,0001, comparaison avec l'APPwt, 3 expériences indépendantes avec 6<n<8

Rôle du cholestérol sur la pathologie amyloïde



Peut-on:

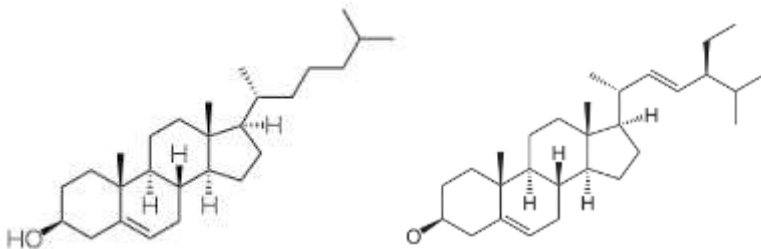
1. Inhiber la liaison du cholestérol sur l'APP?
2. Diminuer el cholestérol membranaire?
3. Modifier le trafic endosomal?

Role of cholesterol metabolism in the pathogenesis of Alzheimer's disease

Bernadette Allinquant^a, Christine Clamagirand^a, and Marie-Claude Potier^b

27. Burg VK, Grimm HS, Rothhaar TL, *et al*. **Plant sterols** the better cholesterol in Alzheimer's disease? A mechanistical study. *J Neurosci* 2013; 33:16072 – 16087.

First time of ex-vivo and in-vivo studies of different phytosterols for the generation of A β peptides showing that the stigmasterol-enriched diets are efficient in decreasing A β generation.



Le **stigmastérol** est un phytostérol présent dans un grand nombre d'aliments, notamment dans les huiles de soja, de colza.

ICM, Hôpital de la Pitié-Salpêtrière, Paris

Charles Duyckaerts

Benoit Delatour, Serge Marty

Jean Delabar

Catherine Marquer

Linda Hanbouch

Kunie Ando, **Lydie Boussicaut**

Adina Lazar

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CHERCHER, TROUVER, GUÉRIR, POUR VOUS & AVEC VOUS.

LLA Lipid lowering agents

Preclinical studies of the efficacy of LLAs for the treatment and prevention of AD and dementia

Both *in vitro* and *in vivo* studies are summarized.

First Author	Model System	LLA(s) Used	Outcome Measure(s)	Effective?	BBB-Permeable?
Buxbaum ³¹	Cultured cells/tissue	Lovastatin	Levels of secreted A β	Yes	Yes
Chauhan ³⁴	Transgenic mouse	Lovastatin, pravastatin	Levels of A β and APP α in brain	Yes, yes	Yes, no
Fassbender ³³	Cultured cells/tissue; guinea pig	Lovastatin (<i>in vitro</i> only), simvastatin (<i>in vitro</i> and <i>in vivo</i>)	Levels of extracellular and intracellular A β (<i>in vitro</i>); levels of A β in CSF and brain homogenate (<i>in vivo</i>)	Yes, yes	Yes, yes
Kojro ²²	Cultured cells/tissue	lovastatin	Levels of APP α and A β	Yes	Yes
Li ³⁵	Transgenic mouse	simvastatin	Learning and memory, as assessed by Morris water maze; brain Abeta levels	Yes, no	Yes
Paris ³²	Cultured cells/tissue	Mevinolin, mevastatin	Rescuing A β 's stimulation of pro-inflammatory molecules (mevinolin); LDH release (mevastatin)	Yes, yes	Yes, unknown
Simons ²⁴	Cultured cells/tissue	lovastatin	Levels of full-length APP; APP α , and A β	Yes (A β), no (APP and APP α)	Yes

Use of statins in AD

We identify several confounding factors among the human studies, including differing blood-brain barrier permeabilities among statins, the stage in AD at which statins were administered, and the drugs' pleiotropic metabolic effects, all of which contribute to the substantial variability observed to date.

We recommend that future human studies of this important therapeutic topic

- (1) take the blood-brain barrier permeabilities of statins into account when analyzing results,
- (2) include specific analyses of the effects on low- and high-density lipoprotein cholesterol, and, most important,
- (3) conduct statin treatment trials solely in patients with mild AD, who have the best chance for disease modification.

Shepardson et al. Ann. Neurol. 2011