Le traitement médicamenteux de la démence, en particulier de la maladie d'Alzheimer

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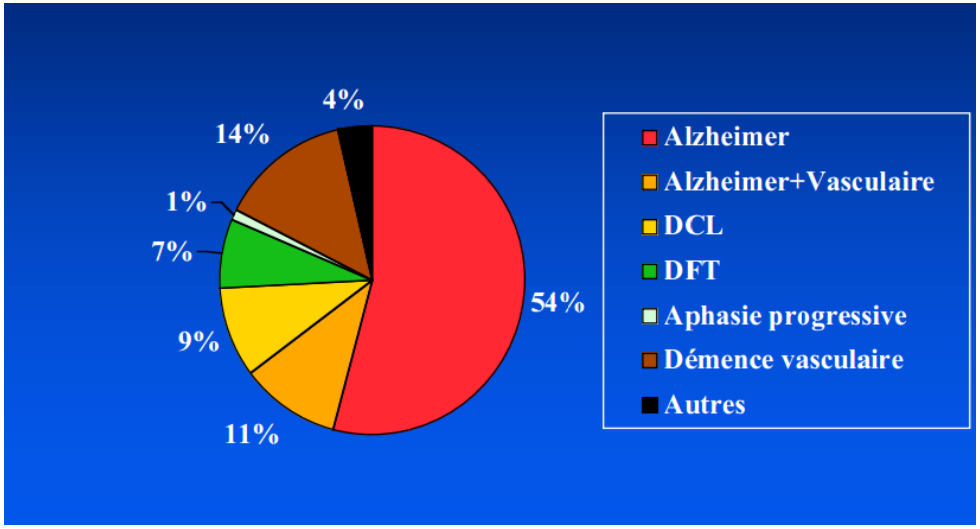
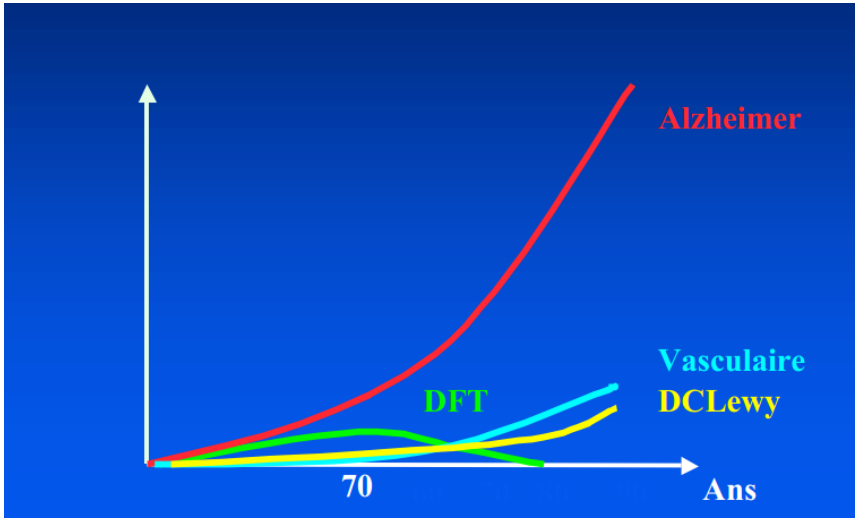
Conflits d'intérets : -

Les démences….

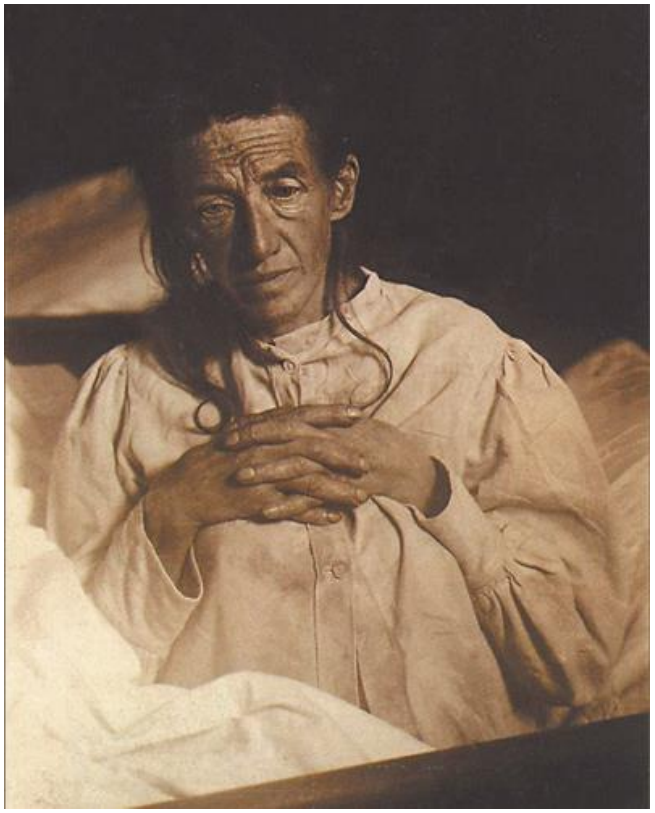
- Démence de type Alzheimer **
- Démence vasculaire
- Démence fronto-temporale (Pick)
- Démence à corps de Lewy (Parkinson)
- Démence sous corticale (Huntington, PSP…)
- Démence de type Creutzfeldt-Jakob
- ….

Incidence des principaux types de démences.



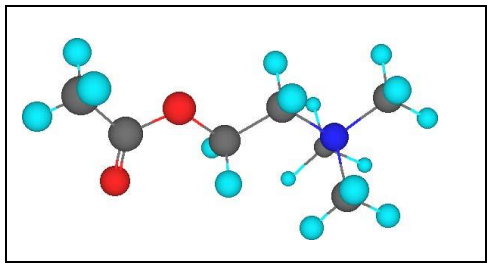


Alzheimer's disease…

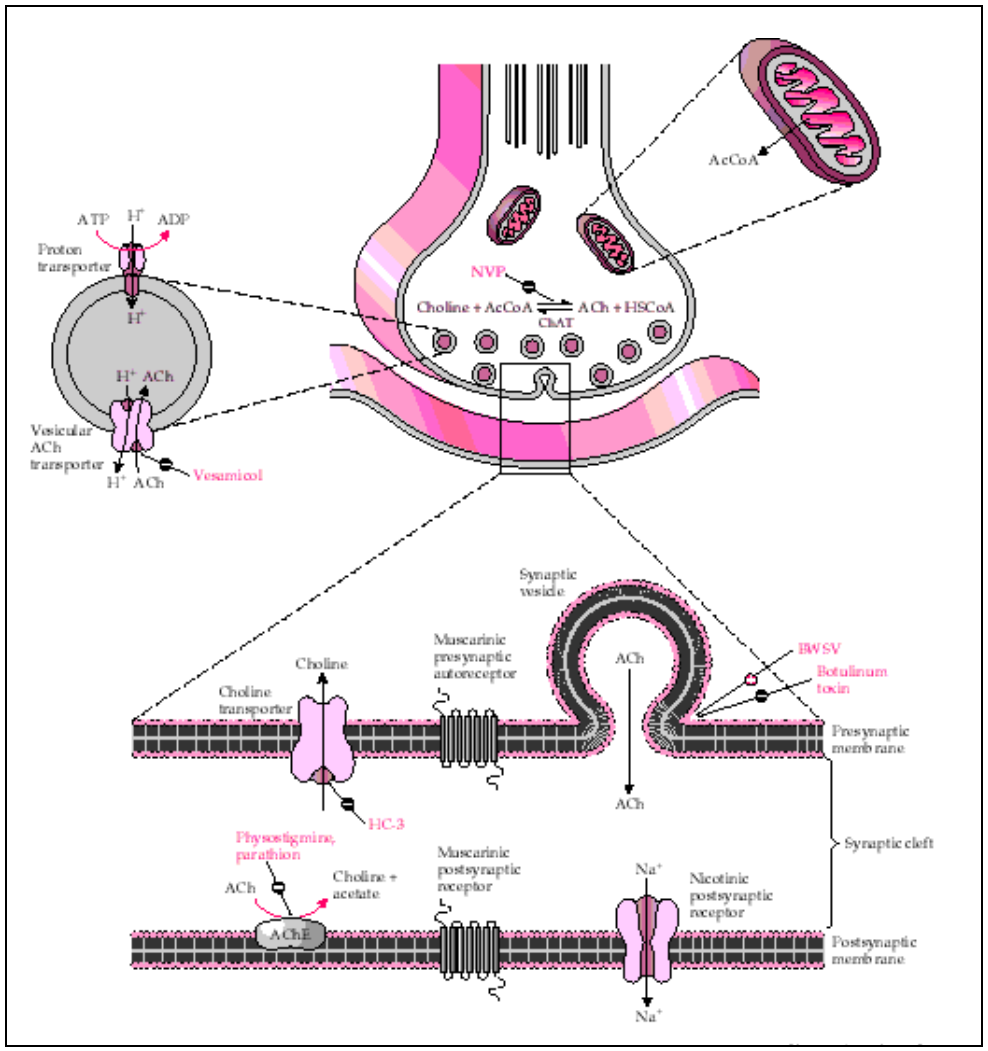


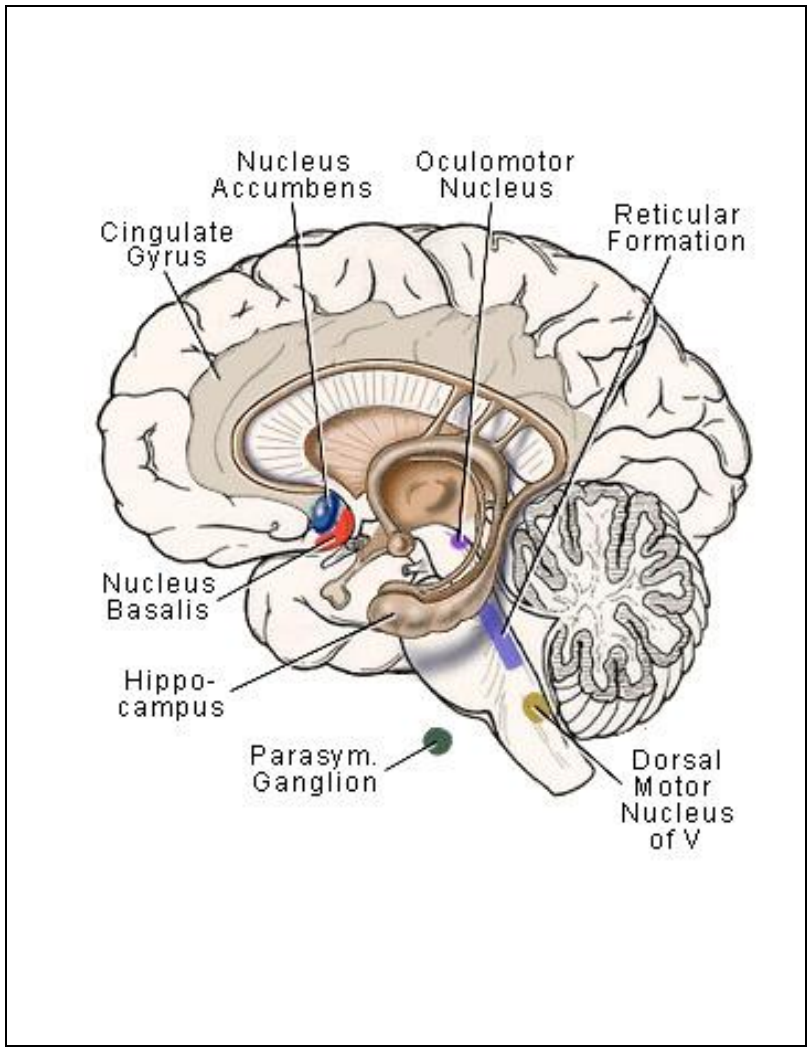
A **clinical syndrome** starting with memory impairment and leading to dementia

Memory, Dementia (Alzheimer) and drugs : neurotransmitters involved (1970,1997 -)



Memory, Dementia and the cholinergic system (1970-)

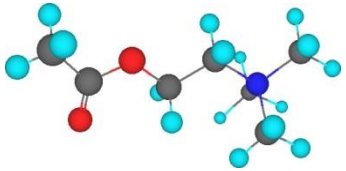




The cholinergic hypothesis of memory disorders and Alzheimer disease (AD) (since early 1970s)

- **Severe loss of choline acetyl-tranferase (CAT) in AD**
- **Reduced choline uptake, Ach levels and release in AD**

- Scopolamine-induced amnesia
- Lesions of the (cholinergic) basal nucleus of Meynert
- Reduction of Ach levels in transgenic APP mice models
- Cholinomimetic drug trials/treatments



- Acquisition is sensitive to muscarinic antagonists (and learning after repeated- acquisition procedure)

- Functional cholinergic neurotransmission is necessary for short term memory, not (less) for long-term memory

- Declarative memory (language) is affected by muscarinc antagonists, not the procedural memory (action)

– A higher level of acetylcholine during a learning task correlates with more details of the experience being remembered

N Engl J Med. 1986 Nov 13;315(20):1241-5.

Oral tetrahydroaminoacridine in long-term treatment of senile dementia, Alzheimer type.

Summers WK, Majovski LV, Marsh GM, Tachiki K, Kling A.

Pharmacotherapy of dementia ;

1996, *Répertoire commenté des médicaments(B) / Vidal(F)*

(B) Actébral®, Cerebroxine®, Cervoxan®, Complamin®, Cosaldon®, Cyclospasmol®, Duvadilan®, Encephabol®, Hydergine®, Lucidril®, Nootropil®, Nooxine®, Papavérine®, Pervincamine®, Stugeron® …

(F) Albatran®, Axonyl®, Capergyl®, Cervilane®, Cyclergyl®, Ergodose®, Iskedyl®, Lucidril®, Nootropyl®, Novodyl®, Oxovinca®, Sermion®, Stratene®, Sureptil®, Trivastal®, Validex®, Vasobral®, Vinca®…

1997; registration of the first anticholinesterase drug : tacrine, cognex®

Pharmacotherapy of dementia (1997, 2001-)

Table 1. Clinical Pharmacology of Agents Useful for Reducing the Signs of Dementia.*

Characteristic	Donepezil	Rivastigmine	Galantamine	Memantine
Time to maximal serum concentration (hr)	3–5	0.5–2	0.5–1	3–7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70–80	2†	5–7	60–80
Protein binding (%)	96	40	0–20	45
Metabolism	CYP2D6, CYP3A4	Nonhepatic	CYP2D6, CYP3A4	Nonhepatic
Dose (initial/maximal)	5 mg daily/ 10 mg daily	1.5 mg twice daily/ 6 mg twice daily	4 mg twice daily/ 12 mg twice daily	5 mg daily/ 10 mg twice daily
Mechanism of action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor antagonist

* CYP2D6 denotes cytochrome P-450 enzyme 2D6, CYP3A4 cytochrome P-450 enzyme 3A4, and NMDA *N*-methyl-D-aspartate.
† Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has an eight-hour half-life for the inhibition of acetylcholinesterase in the brain.

Treatment of AD: effect of Aricept

Effect of Aricept

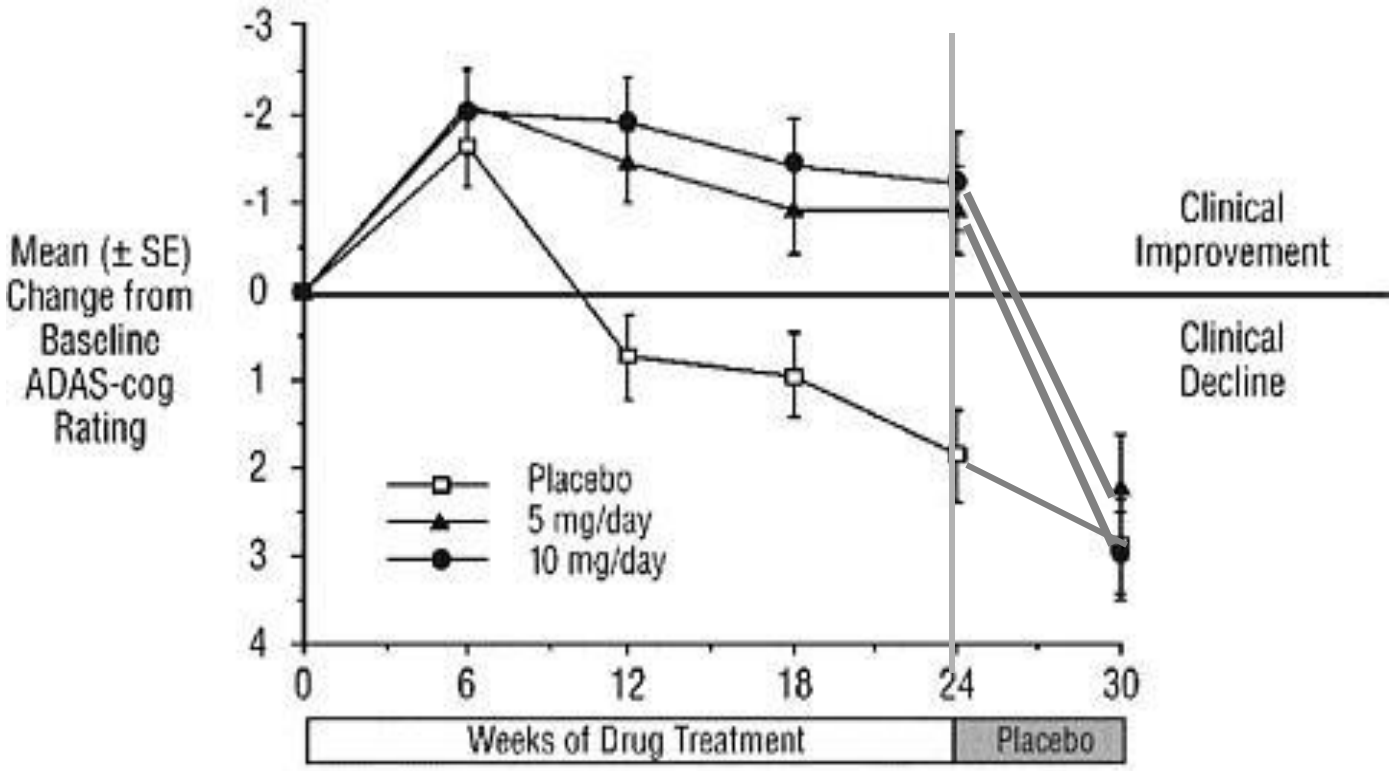


Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

Efficacy of cholinesterase inhibitors in Alzheimer disease

Large cohort study (Fl. Pasquier, Lille) :

-control group : MMSE : loss of 3.5 points/year

-ACE-inhibitors : MMSE : loss of 2 points/year

Long term survey, donepezil (S. Rogers, UK)

stable 24 to 38 weeks, MMSE results :

-0.81 (year1), -2.39(year2), -1.96(year3)

- Number needed to treat (NNT) : 9 (11)

afssaps
Agence française de sécurité sanitaire des produits de santé

Communiqué de presse
24 janvier 2005

Reminyl® (galantamine) et mortalité : Résultats de deux essais cliniques menés chez des patients atteints d'une altération modérée de la fonction cognitive

Reminyl® (galantamine) est un médicament indiqué uniquement dans le traitement des symptômes de la maladie d'Alzheimer, dans ses formes légères à modérées. Reminyl® bénéficie d'une Autorisation de Mise sur le Marché (AMM) européenne et est autorisé en France depuis octobre 2000.

Les résultats de deux essais cliniques viennent d'être portés à la connaissance des autorités sanitaires. Ceux-ci avaient pour objectif d'évaluer l'impact de la galantamine sur le délai d'apparition de la démence chez des patients souffrant d'une altération modérée de la fonction cognitive. Ces études, d'une durée de 2 ans, ont été menées chez 2048 patients (1026 recevant de la galantamine et 1022 patients recevant un placebo) en Europe, Australie, Argentine et aux Etats-Unis d'Amérique.

Ces deux études, dont les résultats n'ont pas été publiés à ce jour, montrent que la galantamine n'a pas allongé le délai de survenue de la démence, et a eu une action semblable au placebo. De plus, l'analyse préliminaire des résultats de ces deux essais montre une fréquence plus importante des décès dans le groupe de patients traité par galantamine (15 décès) comparativement au groupe placebo (5 décès). La cause des décès est variable, mais souvent de nature cardiovasculaire.

Il s'agit des deux premières études avec la galantamine dont la durée de traitement est longue (2 ans). Les essais cliniques, effectués précédemment dans le traitement de la maladie d'Alzheimer, ont été réalisés sur une période plus courte (6 mois). Il n'avait alors pas été observé d'augmentation de la mortalité dans les groupes galantamine comparativement au groupe placebo.

L'Agence française de sécurité sanitaire des produits de santé (Afssaps) en collaboration avec les autres Etats membres, procède à une réévaluation du médicament. Des données complémentaires issues des deux études sont attendues prochainement.
Dans l'attente de l'analyse de l'ensemble des données, l'Afssaps :

- rappelle que Reminyl n'est pas indiqué chez les patients atteints d'altération modérée de leur fonction cognitive (en particulier la mémoire),
- recommande le respect strict de l'indication autorisée.

National Institute for
Clinical Excellence

11 Strand
London
WC2N 5HR

Web: www.nice.org.uk

NHS
National Institute for
Clinical Excellence

Donepezil, rivastigmine, galantamine to treat Alzheimer's disease:

EU registration: 1998-2000

NICE 2001: « *recommends the use of these drugs for all patients ..*»

NICE 2005: « *these drugs should no longer be prescribed on the NHS..* »

inconclusive results, high cost

NICE 2006: « *is recommending that these drugs should be recommended as options for the treatment… moderate severity…* »

additionnal data (amended 2007):

NICE 2009: « *long term effectiveness is limited and largely inconclusive* »

NICE 2016 « *recommended for moderate severity AD* »

Maladie d'Alzheimer : trop de patients exposés à des risques médicamenteux

Une étude a montré des traitements médicamenteux dépassant 6 mois chez 3 patients traités sur 4. Pourtant, ces traitements prolongés exposent les patients à des risques injustifiés.

En 2011, la Commission de la transparence de la Haute autorité de santé a enfin reconnu que les 4 médicaments largement utilisés dans la maladie d'Alzheimer n'apportent pas de progrès pour les patients : le donépézil (Aricept° ou autre), la rivastigmine (Exelon° ou autre), la galantamine (Reminyl° ou autre), et la mémantine (Ebixa° ou autre). Ils exposent à des effets indésirables d'une gravité disproportionnée à leur efficacité minime et passagère.

L'Institut des données de santé a autorisé Prescrire à étudier des données de remboursement de la Sécurité sociale concernant ces médicaments (sur un échantillon représentatif qui respecte l'anonymat des patients et des prescripteurs).

Sur la période 2003-2011, 4 752 patients âgés de plus de 60 ans ont été exposés à au moins un des 4 médicaments étudiés. 19 % ont été exposés au moins une fois à l'association de 2 de ces médicaments. Or ces associations n'ont pas d'intérêt démontré. Seulement 24 % des 4 752 patients ont reçu un traitement de moins de 6 mois. 7 % ont reçu un traitement continu durant 6 mois à 12 mois, 9 % durant 1a n à 2 ans et 15 % durant plus de 2 ans. Environ 45 % ont reçu un traitement intermittent dont la durée cumulée dépassait 6 mois. Or les traitements prolongés n'ont pas d'efficacité démontrée et sont dangereux. Deux essais cliniques, d'une durée de 2 ans, ont en effet montré une mortalité plus élevée sous galantamine que sous placebo. La cause du décès a souvent été cardiovasculaire. Dans un essai à 3 ans, la mortalité est apparue plus élevée avec le donépézil qu'avec le placebo.

Ces données montrent qu'en France les traitements par ces médicaments dépassent 6 mois chez 3 patients traités sur 4 environ, alors qu'ils exposent les patients à des risques injustifiés. Mieux vaut écarter ces médicaments et se concentrer sur des mesures non médicamenteuses.

"Maladie d'Alzheimer : des patients trop exposés aux anticholinestérasiques et à la mémantine en France" Rev Prescrire 2014 ; 34 (363) : 23. (pdf, réservé aux abonnés)

Médicaments symptomatiques de la maladie d'Alzheimer : l'efficacité est prouvée !

Le 3 juin 2016 Dans Alzheimer et moi, L'actualité associative 2

Avis de neurologues-chercheurs sur ces médicaments

Avec l'existence sur le marché de 4 médicaments traitant les symptômes de la maladie d'Alzheimer, de nombreuses polémiques sont apparues au fil des ans remettant en cause leur efficacité et pointant du doigt leur prétendue dangerosité.

Des neurologues-chercheurs de Lyon, des CMRR (Centre Mémoire de Ressources et de Recherche) de Lille et Paris ont décidé de se tourner vers l'association LECMA-Vaincre Alzheimer pour faire entendre leur voix et celles de leurs confrères en contact chaque jour avec des patients atteints de la maladie.

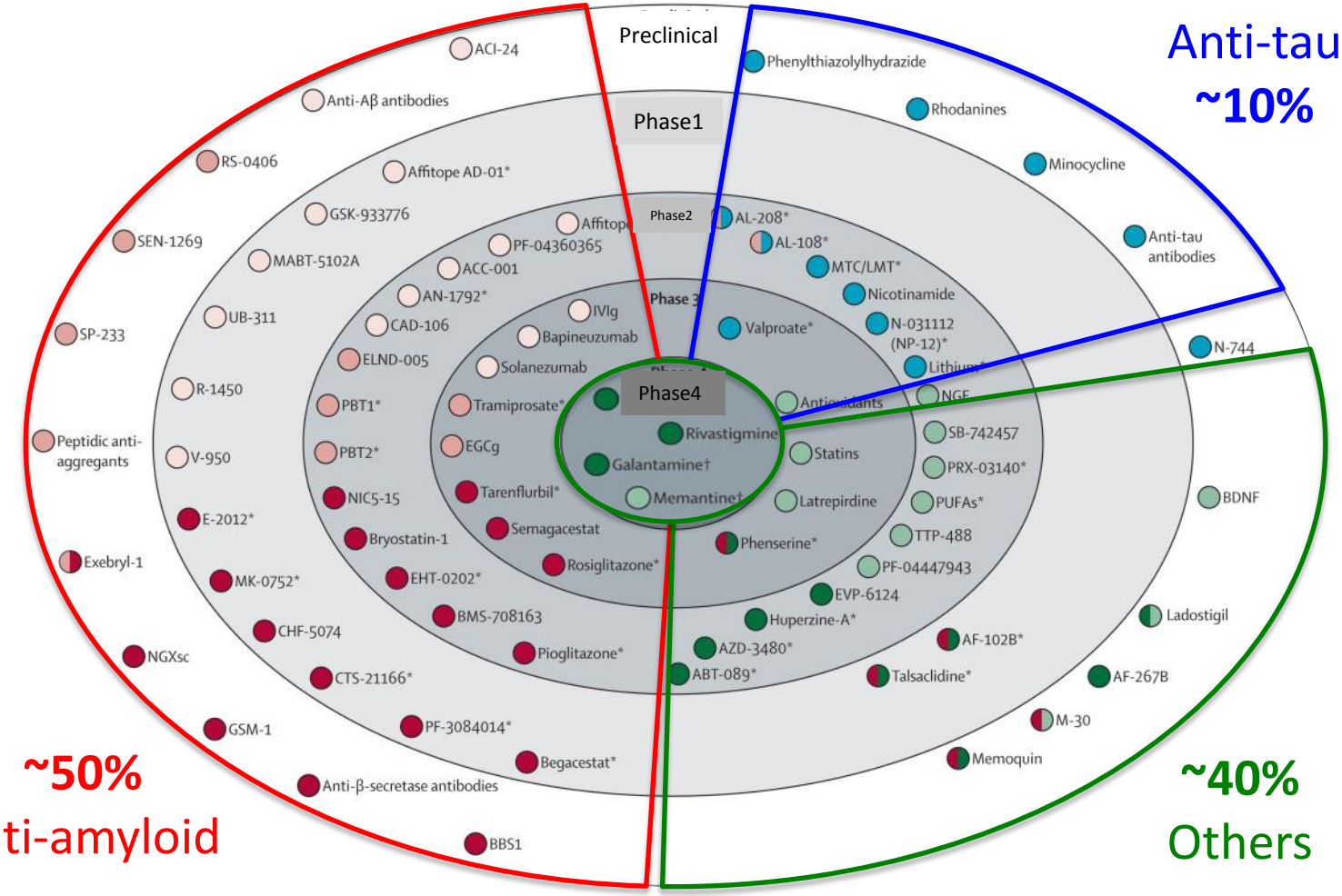
LECMA-Vaincre Alzheimer : « Les traitements dits anti-Alzheimer sont-ils efficaces ? »

Maintenir le remboursement de ces traitements, donc leur prescription par les médecins, c'est exposer les patients à des effets secondaires parfois très graves.

La ministre de la Santé vient d'annoncer, le 26 octobre sur RTL, qu'elle ne suivrait pas la Haute autorité de santé (HAS) dans sa recommandation de dérembourser les médicaments contre la maladie d'Alzheimer. La décision de Marisol Touraine peut passer, à première vue, pour une bonne nouvelle. Ce n'est pas cette fois qu'on réalisera des économies sur notre dos, se disent sans doute certains patients et leurs proches… En fait, ce qui se passe est bien pire. Le choix de la ministre revient à jouer dangereusement avec la santé des personnes touchées par cette maladie neurodégénérative.

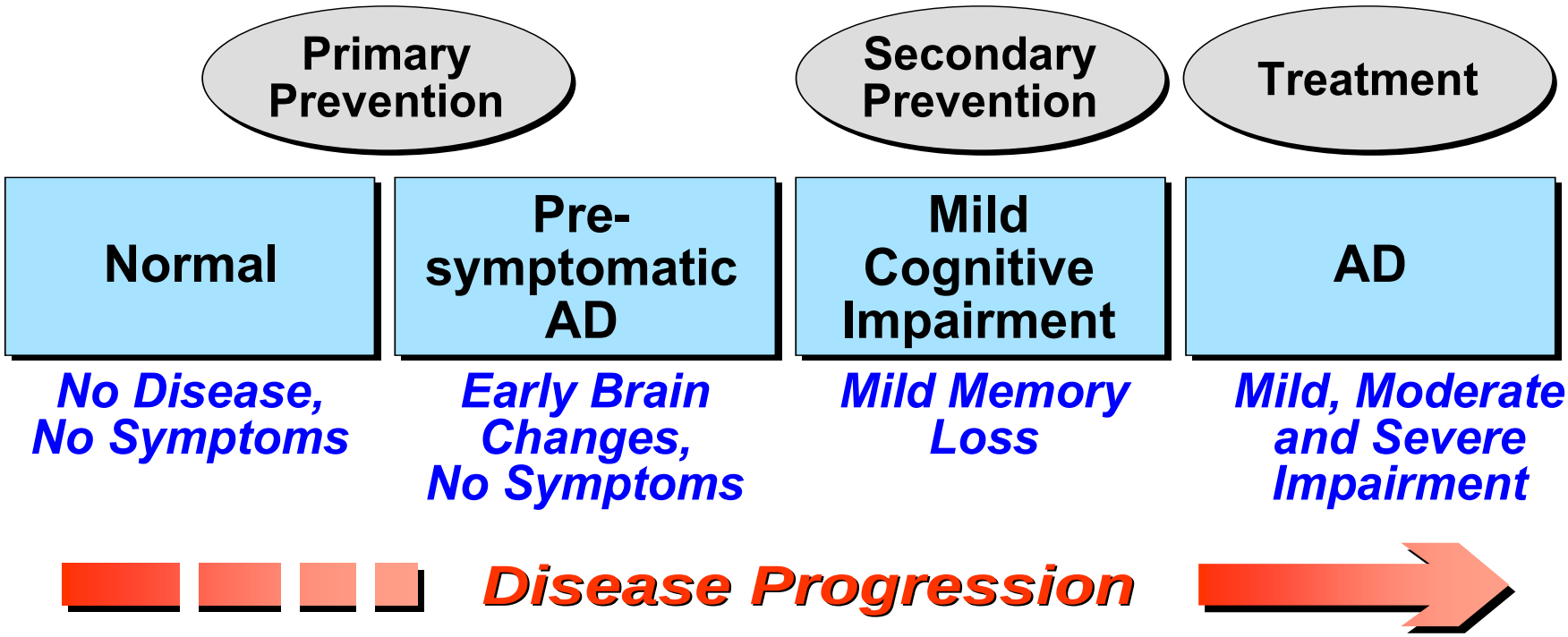
La HAS, autorité publique indépendante, a rendu le 21 octobre un verdict sans appel, via sa Commission de la transparence. Les quatre médicaments spécifiques de la maladie d'Alzheimer ont un service médical rendu «insuffisant», n'autorisant pas leur remboursement. Dit clairement : ils ne sont pas utiles car ils suscitent trop d'effets secondaires pour un bénéfice non avéré. Jusqu'ici, ces traitements bénéficiaient d'une cotation en service médical rendu (SMR) «faible», synonyme d'un remboursement à 15 % par l'Assurance maladie.

95% AD clinical trials have failed over the past 20 years…



Magialasche et al.,
Lancet Neurology 2012

Alzheimer's Disease Prevention Initiative

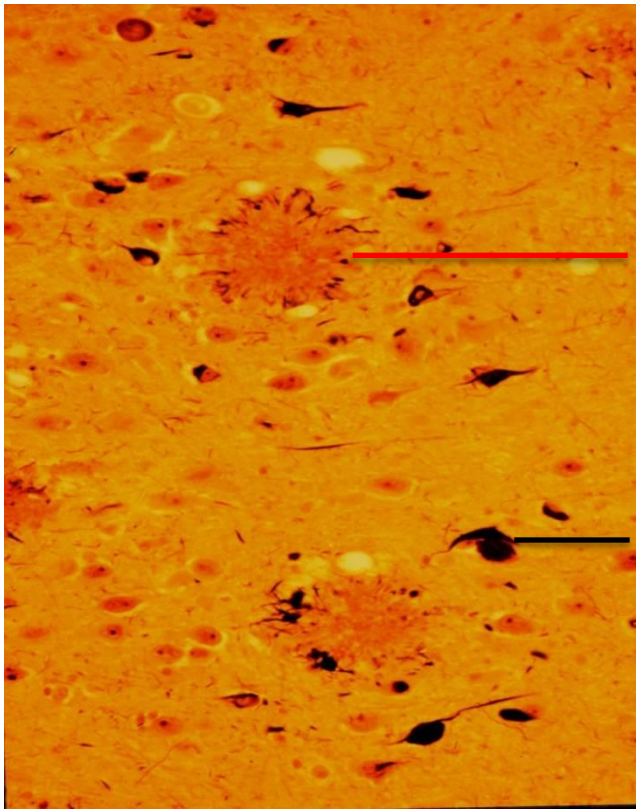


Recent approaches of Alzheimer disease treatment (*disease modifying drugs*)

- Development of markers (biological markers, imaging…)
- Possibility of treatment at an early stage of disease

Pathophysiology of Alzheimer's Disease

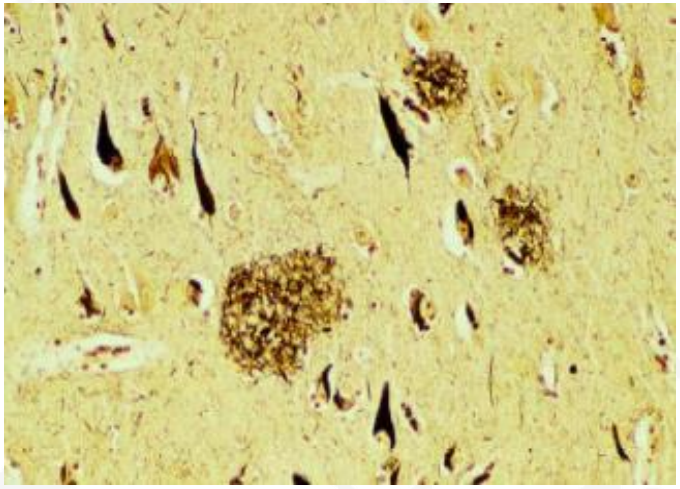
Alzheimer's disease…



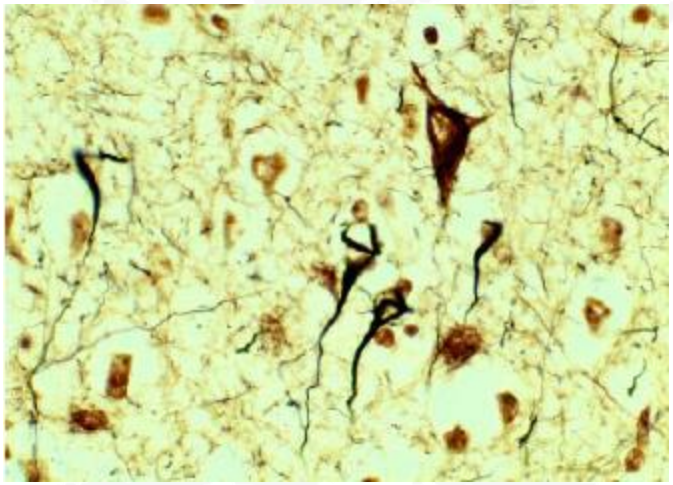
A **brain pathology** characterized by senile plaques (amyloid) and neurofibrillary tangles (tau)

Histological Hallmarks of AD

SENILE PLAQUES



NEUROFIBRILLARY TANGLES



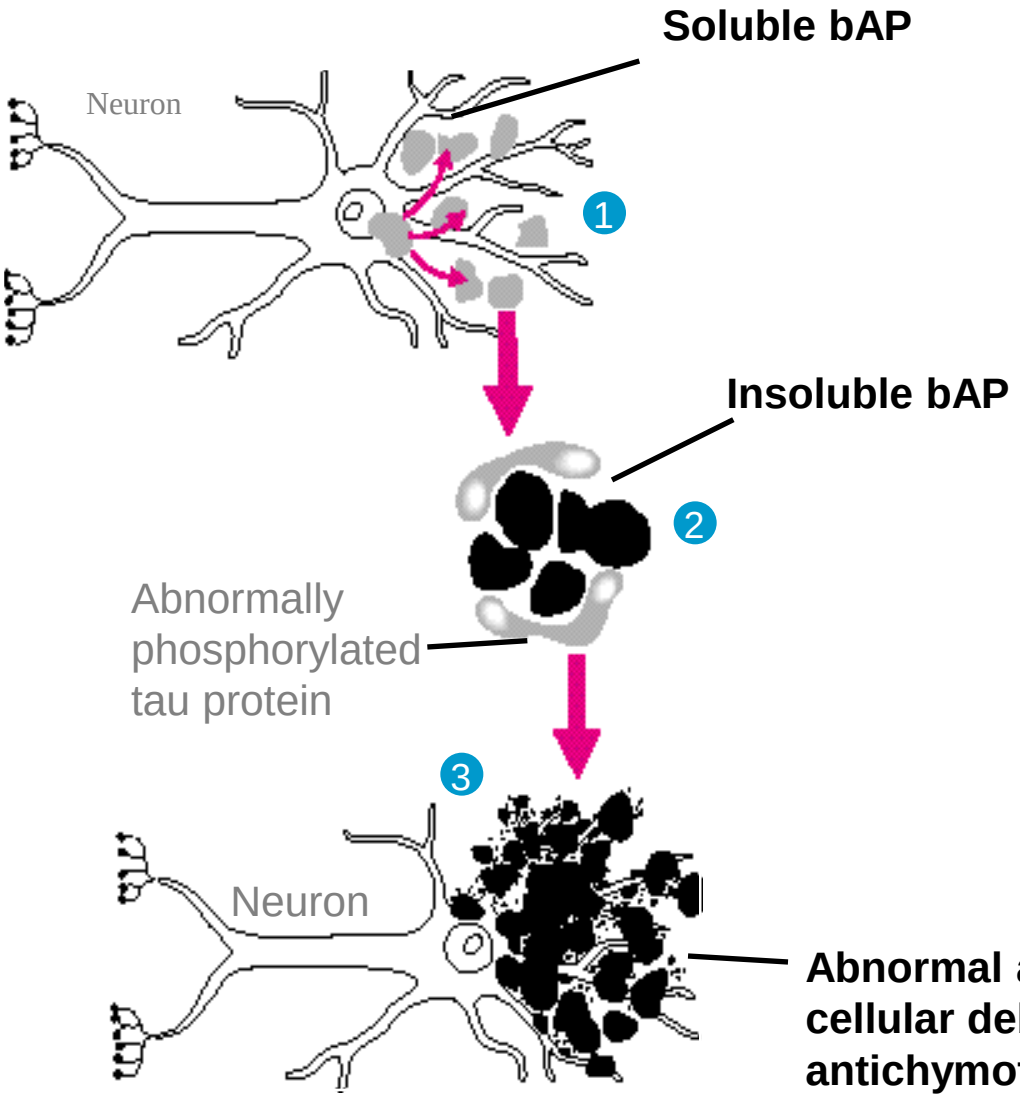
SENILE PLAQUES

In 1907, in the first report, Alois Alzheimer described senile plaques (SP) and neurofibrillary tangles (NFT)

SP are found in neocortex, hippocampus and in several subcortical areas

NFT density correlates with disease duration and severity of dementia.

Neuritic Plaques



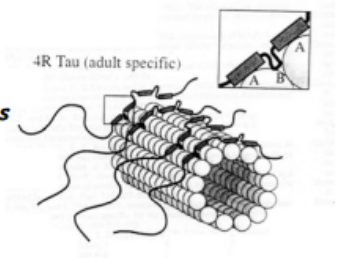
1. Soluble bAP formed inside cell and deposited outside of cell
2. Soluble bAP transformed to insoluble bAP by contact with abnormally phosphorylated tau protein
3. Insoluble bAP forms deposits that become dense neuritic plaques over time, trapping other plaque components

Tau proteins : role in stability of microtubules and in axonal transport (phosphorylation/dephosphorylation)

Protéines Tau et microtubules

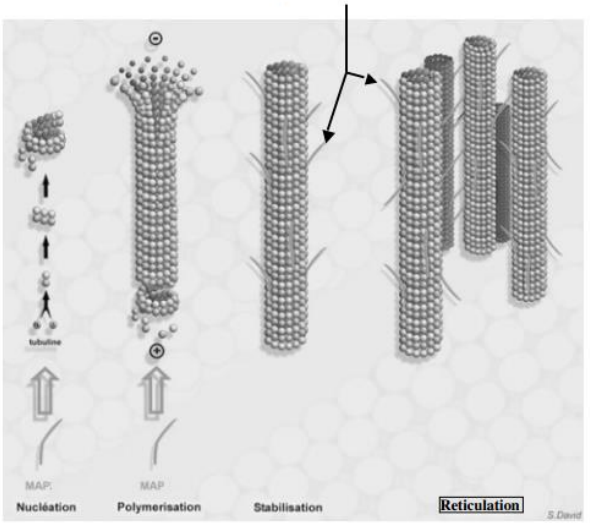
- Les microtubules sont des structures labiles qui nécessitent d'être stabilisées par les protéines tau

Modèle de liaison de tau à 4 domaines répétés sur un microtubule



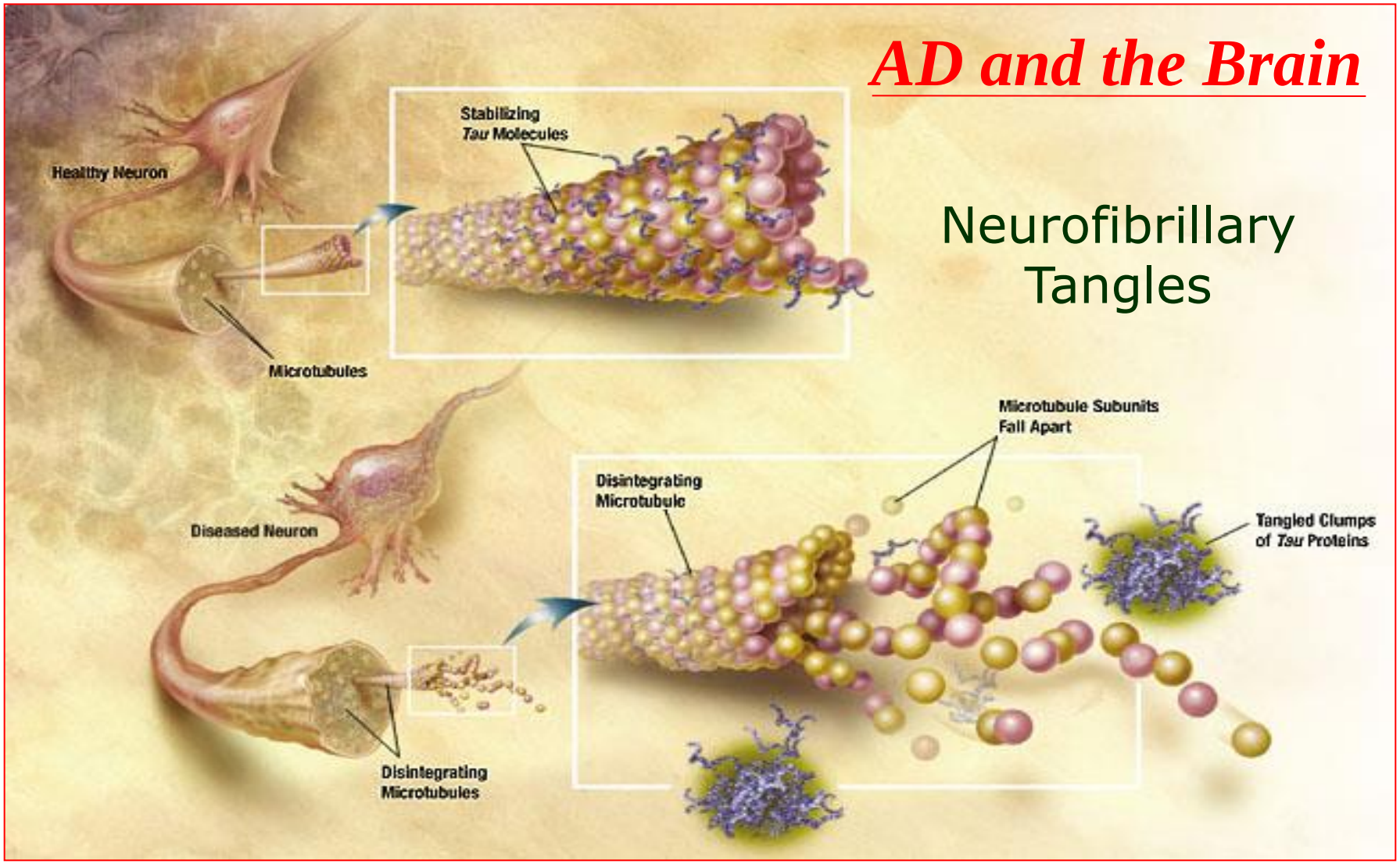
D'après Goode & Felstein, 1994

Cross-linking of microtubules by MAPs allows a better stability of microtubules

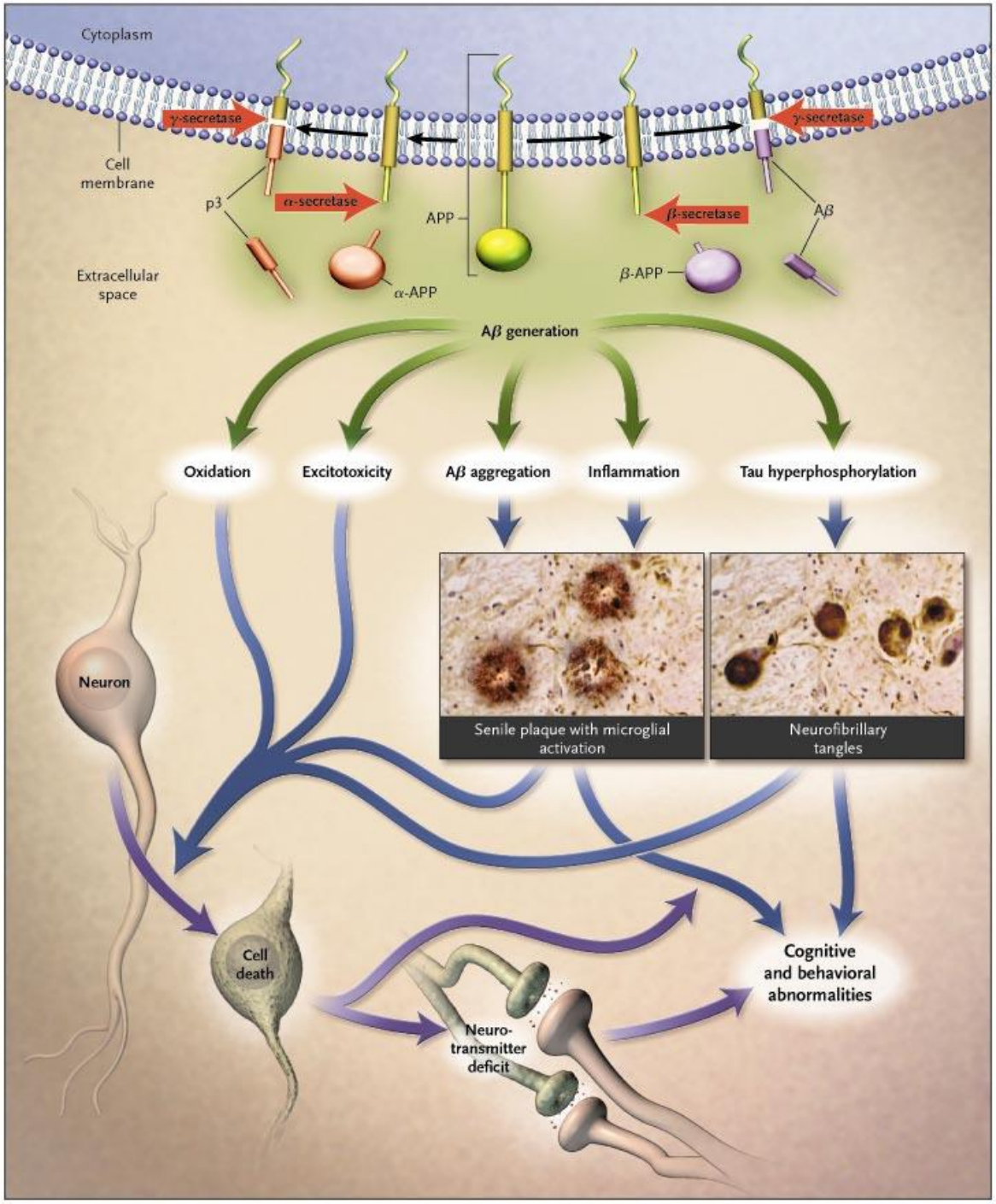


Tau hyperphosphorylation → AD pathology

AD and the Brain



Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps stabilize microtubules. In AD, *tau* changes, causing microtubules to collapse, and *tau* proteins clump together to form neurofibrillary tangles.



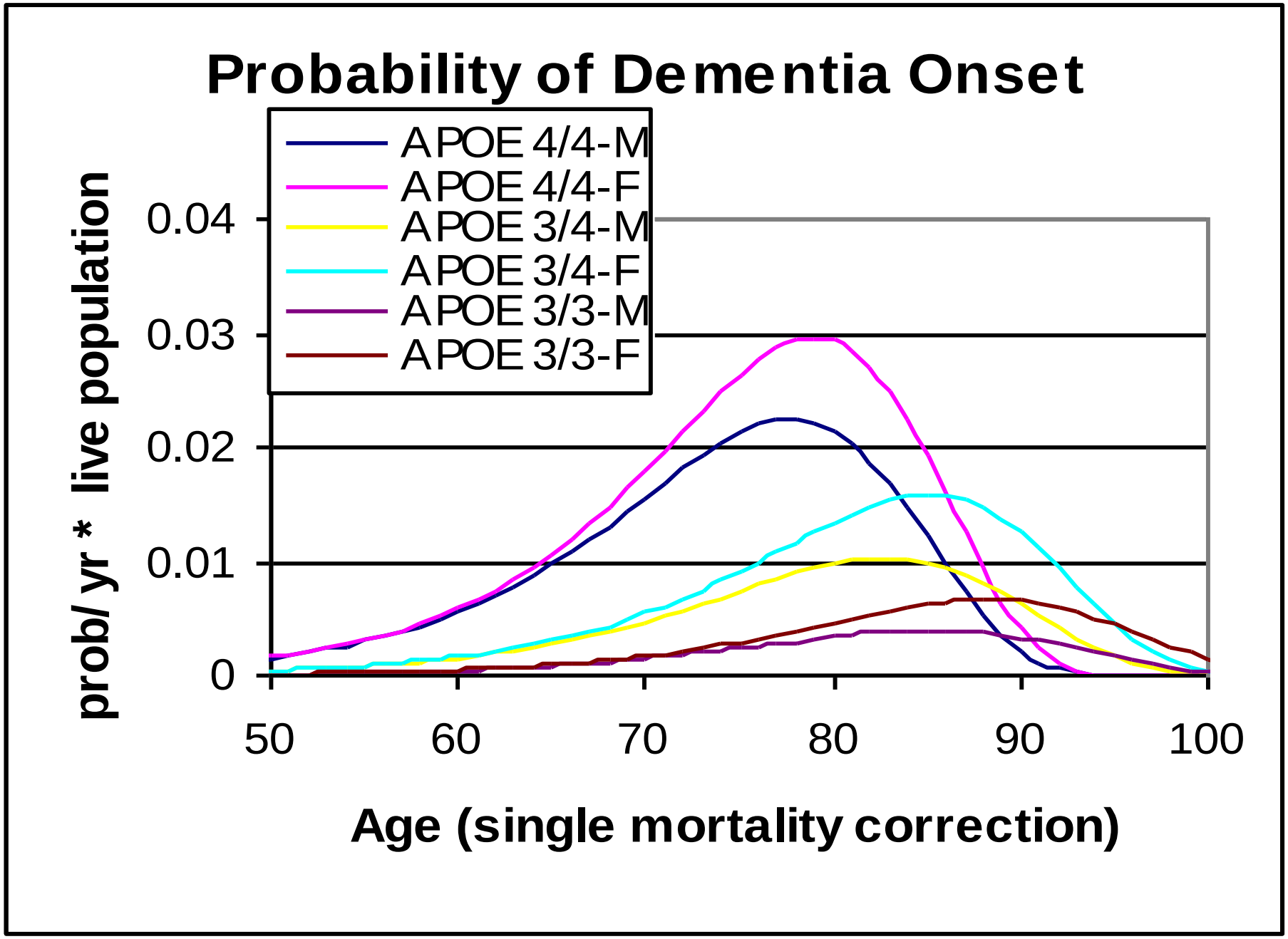
Putative Amyloid Cascade.

•This hypothesis of the amyloid cascade, which progresses from the generation of the beta-amyloid peptide from the amyloid precursor protein, through multiple secondary steps, to cell death, forms the foundation for current and emerging options for the treatment of Alzheimer's disease. APP denotes amyloid precursor protein, and AB beta-amyloid.

Risk Factors

- Age, Female sex
- Most potent risk factor - presence of the apolipoprotein ε4 (*APOE* ε4) allele.
  - Lifetime risk of AD for an individual
    - without the ε4 allele is approximately 9%
    - carrying at least 1 ε4 allele is 29%

ε4 genotype is not sufficiently specific or sensitive for the diagnosis of AD to allow its use as a diagnostic test


Probability of Dementia Onset
APOE 4/4-M
APOE 4/4-F
APOE 3/4-M
APOE 3/4-F
APOE 3/3-M
APOE 3/3-F
prob/ yr * live population
0.04
0.03
0.02
0.01
0
50
60
70
80
90
100
Age (single mortality correction)

CSF Tau and Amyloid-b42 levels

CSF markers in Alzheimer disease :

- decrease of amyloid levels
  (concentration in senile plaques,
  low excretion rate in CSF)
- increase of Tau and Phospo-Tau levels

Table 2 Summary of CSF biomarkers by diagnostic group as compared to patients with SMC[a]

	Aβ42	Tau	p-tau
SMC	Ref	Ref	Ref
AD	↓ ↓	↑ ↑	↑ ↑
FTLD	↓	↑	=
DLB	↓	↑	↑
VAD	↓	=	=
CBD	↓	=	=
CJD	=	↑ ↑ ↑	↑
PSP	=	=	=
PSY	=	=	=

Abbreviations: Aβ42 = amyloid β 42; AD = Alzheimer disease; CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; DLB = dementia with Lewy bodies; FTLD = fronto-temporal lobar degeneration; p-tau = phosphorylated tau; PSP = progressive supranuclear palsy; PSY = psychiatric disorder; SMC = subjective memory complaints; VaD = vascular dementia.

[a] ↓ ↓, Strongly decreased, compared to SMC and patients with other types of dementia (OD); ↑ ↑, strongly increased, compared to SMC and OD; ↓, decreased compared to SMC; ↑, increased compared to SMC; =, comparable with SMC; ↑ ↑ ↑, extremely increased, compared to all other groups.

Immunotherapy for Alzheimer disease shows promise

The amyloid hypothesis…

Trends Pharmacol Sci. 1991 Oct;12(10):383-8.

Amyloid deposition as the central event in the aetiology of Alzheimer's disease.

Hardy J[1], Allsop D.

Author information

Abstract

While there may be many causes of Alzheimer's disease (AD), the same pathological sequence of events, described here by John Hardy and David Allsop, is likely to occur in all cases. The recent discovery of a pathogenic mutation in the beta-amyloid precursor protein (APP) gene on chromosome 21 suggests that APP Mismetabolism and beta-amyloid deposition are the primary events in the disease process. The occurrence of AD in Down syndrome is consistent with this hypothesis. The pathological cascade for the disease process is most likely to be: beta-amyloid deposition----tau phosphorylation and tangle formation----neuronal death. The development of a biochemical understanding of this pathological cascade will facilitate rational design of drugs to intervene in this process.

Familial AD is caused by amyloid mutations but is amyloid the cause of sporadic AD ?

Anti-amyloid drugs…

Chen et al. Nature. 1999 Jul;400:173-7

1 year

Transgenic mice (amyloid mutation)

➔ unsuccessful in patients with sporadic AD dementia

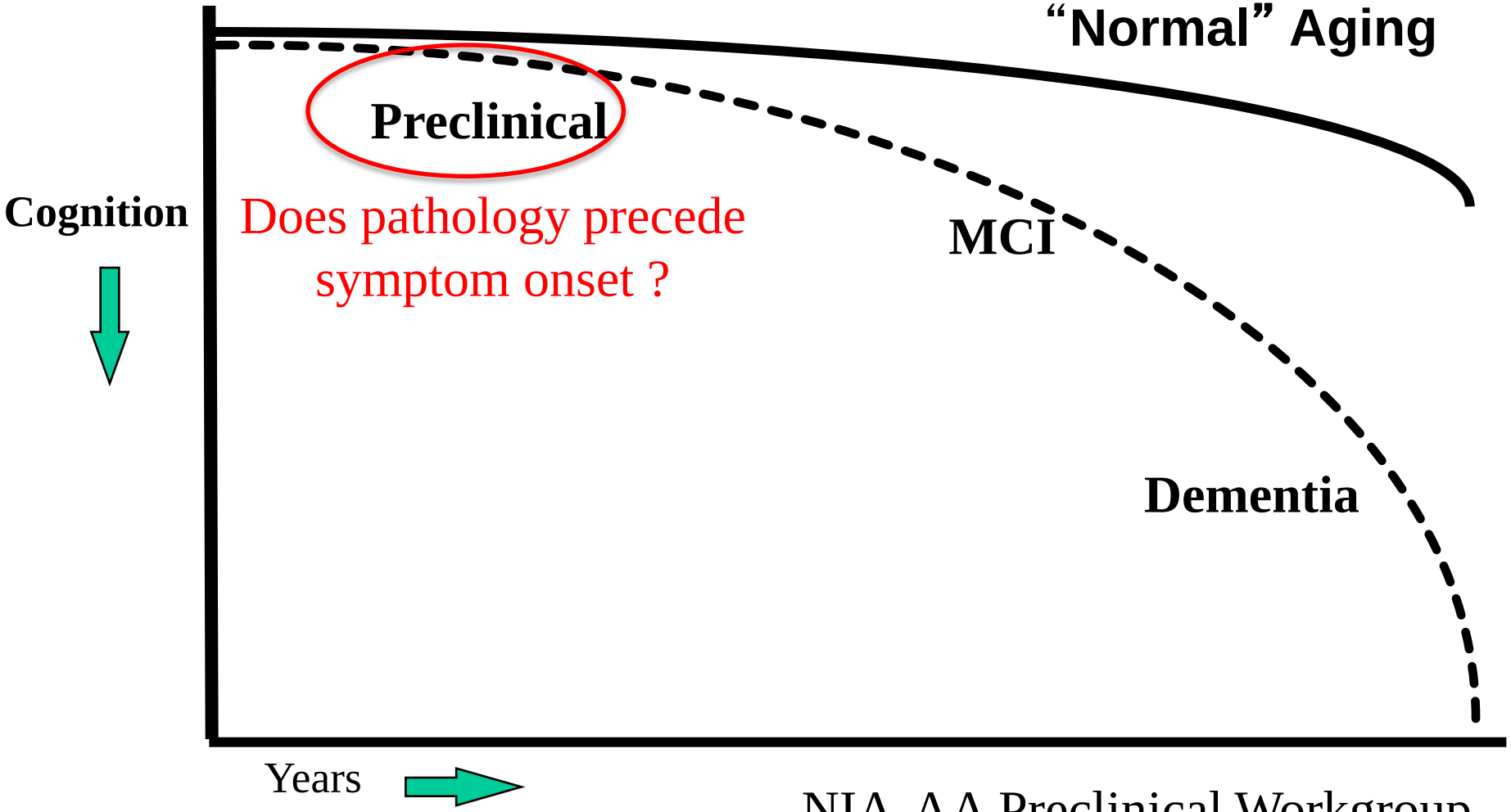
Clinical Trial AN-1792 in 2002 : Aβ42-immunization in Alzheimer's disease (clinical studies have been interrupted)

- Vaccination led to anti-Aβ antibodies and reduction of amyloid plaques and parenchymal Aβ load

- No reduction of the tangles
- No improvement of clinical state in vaccinated patients *
- No improvement nor stabilization on MRI (progression of hippocampal atrophy) *

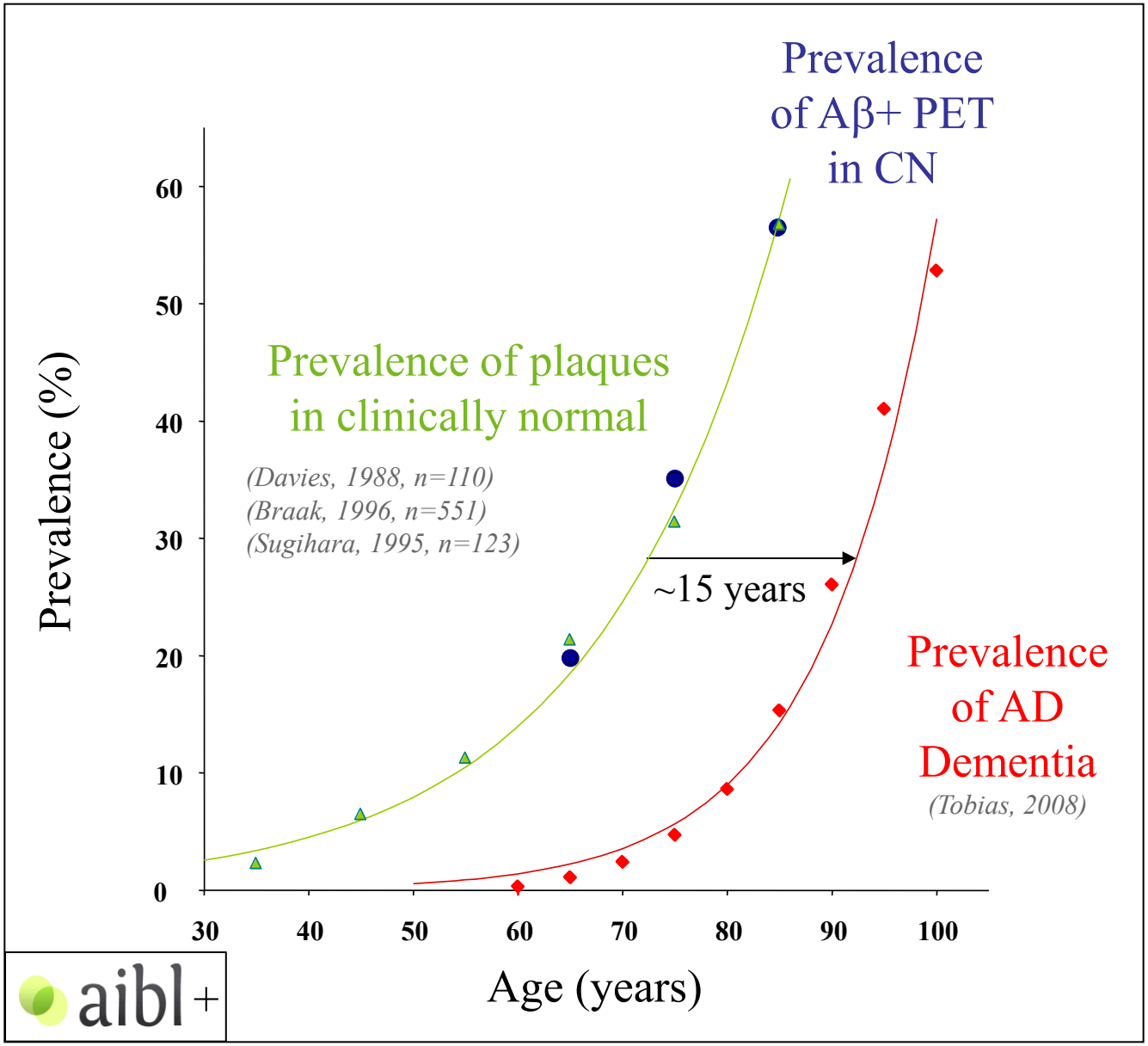
- Meningo-encephalitis in 6% of patients (2/3 reversible)
- Increase of cerebral amyloid angiopathy (redistribution)
- Cortical hemorrhages and hemosiderin deposits

The continuum of Alzheimer's disease



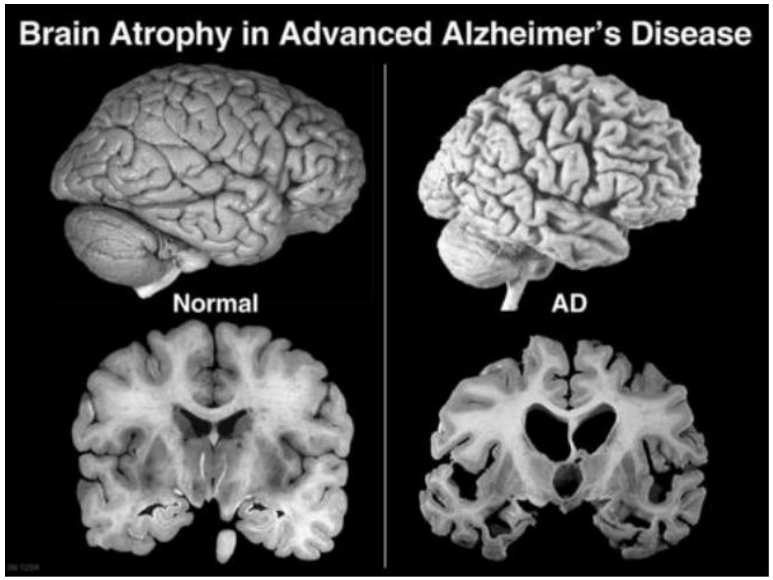
NIA-AA Preclinical Workgroup
Sperling R et al 2011

Preclinical Alzheimer's Disease



Slide courtesy of Victor Villemagne

Australian **I**maging **B**iomarkers and **L**ifestyle Study (**AIBL**)

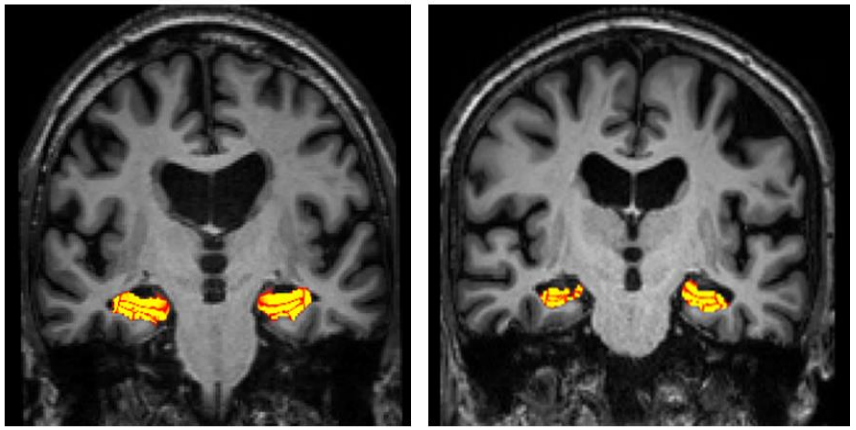


Hippocampe normal chez un patient sans troubles cognitifs

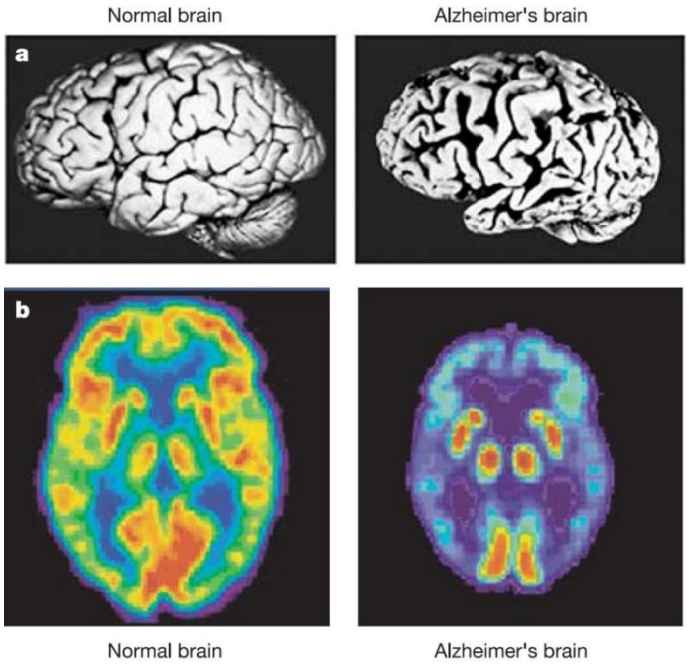
(3710,00 mm³ ; Z-score : 0,60)

Hippocampe atrophique chez un patient MCI

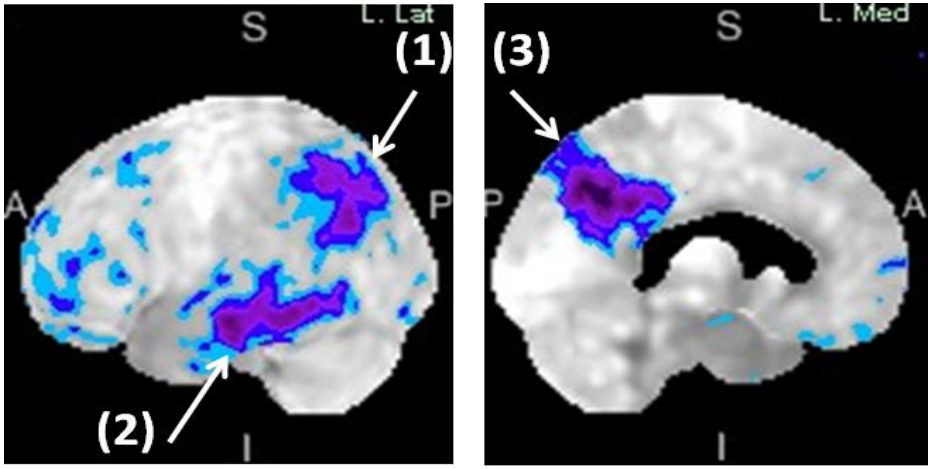
(2193,00 mm3 ; Z-score : -3,37)



Légende : sections coronales IRM 3 Tesla; la section de l'hippocampe est colorée en jaune



Pet scans (glucose utilization)



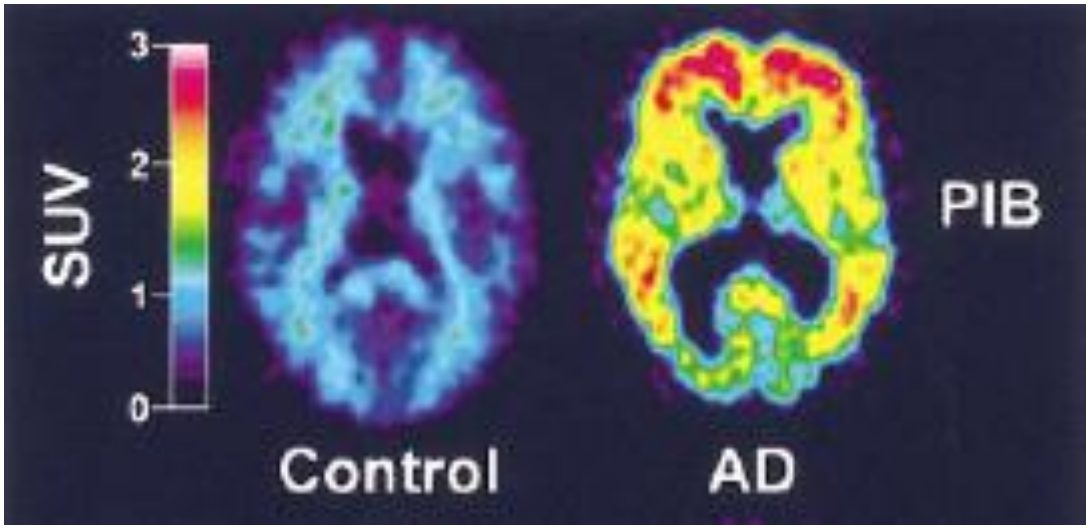
Légende : Les images sont des reconstructions du cerveau (face latérale et médiale de l'hémisphère gauche). Les zones colorées représentent les régions corticales montrant une diminution significative du métabolisme du glucose par rapport aux sujets contrôle : les aires associatives pariétales (1), temporales (2) ainsi que les régions cingulaires postérieures (3).

Amyloid Imaging

ORIGINAL ARTICLES

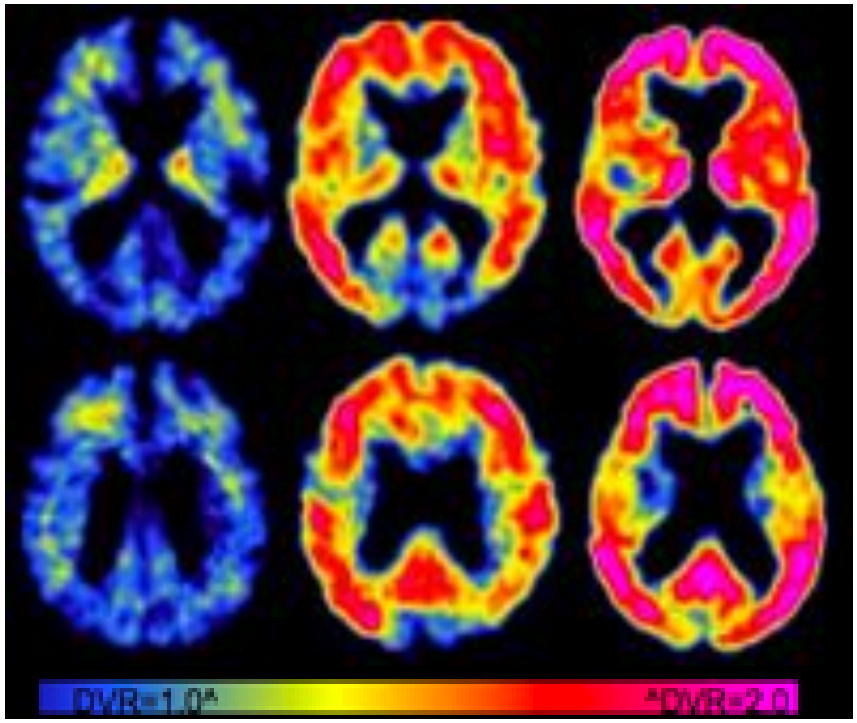
Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B

William E. Klunk, MD, PhD,[1] Henry Engler, MD,[2] Agneta Nordberg, MD, PhD,[3,4] Yanming Wang, PhD,[5] Gunnar Blomqvist, PhD,[2] Daniel P. Holt, BS,[5] Mats Bergström, PhD,[2] Irina Savitcheva, MD,[2] Guo-feng Huang, PhD,[5] Sergio Estrada, PhD,[2] Birgitta Ausén, MSCI,[4] Manik L. Debnath, MS,[1] Julien Barletta, BS,[6] Julie C. Price, PhD,[5] Johan Sandell, PhD,[2] Brian J. Lopresti, BS,[5] Anders Wall, PhD,[2] Pernilla Koivisto, PhD,[2] Gunnar Antoni, PhD,[2] Chester A. Mathis, PhD,[5] and Bengt Långström, PhD[2,6]



Ann Neurol 2004;55:306–319

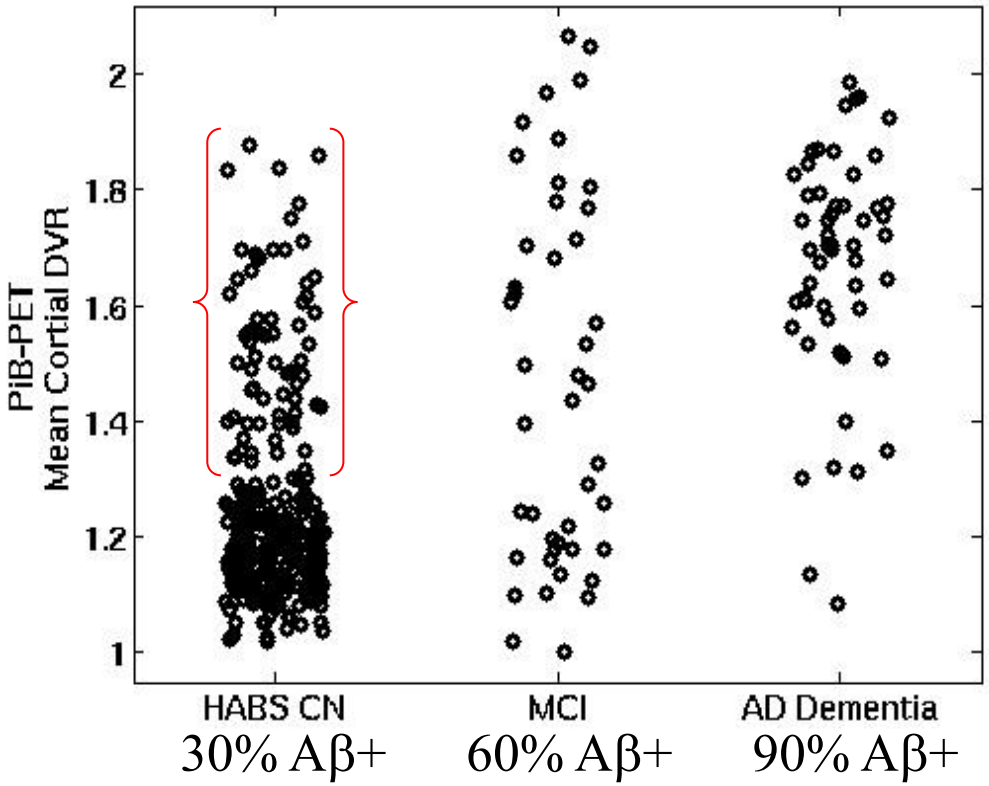
PET Amyloid (Aβ) Imaging in Clinically Normal (CN) Older Individuals



CN Aβ–

CN Aβ+

AD Aβ+



Harvard **A**ging **B**rain **S**tudy (**HABS**)

Sperling, Mormino, Johnson *Neuron* 2014

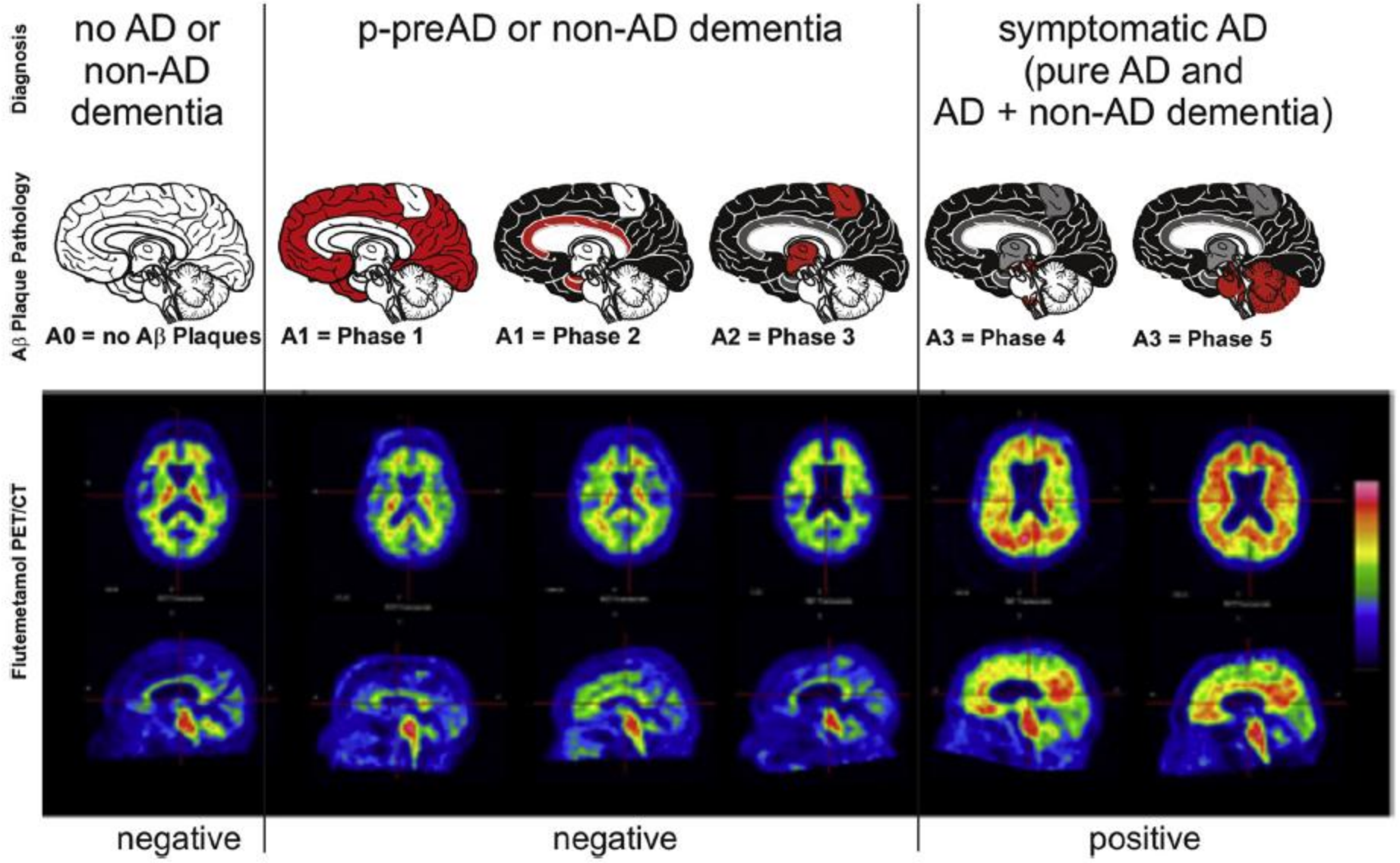
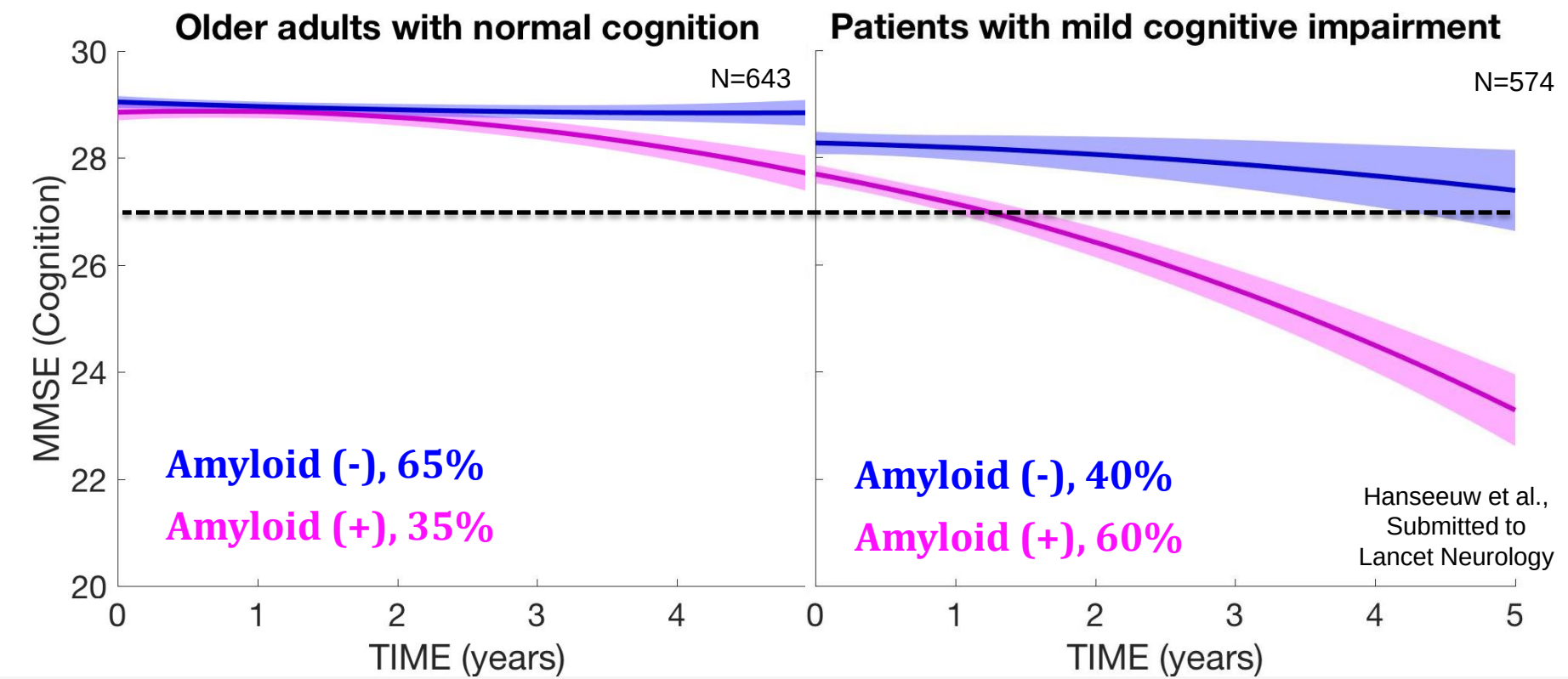


Fig. 4. Schematic representation of Aβ plaque pathology in different Aβ phases with corresponding [^{18}F]flutemetamol amyloid PET images. Cases with early Aβ phases 1–3 did not exhibit a significant [^{18}F]flutemetamol retention, whereas symptomatic or preclinical AD cases with Aβ phases 4 and 5 showed positive [^{18}F]flutemetamol retention. Parts of this figure are reproduced with permission from Thal DR, et al. Phases of Abeta-deposition in the human brain and its

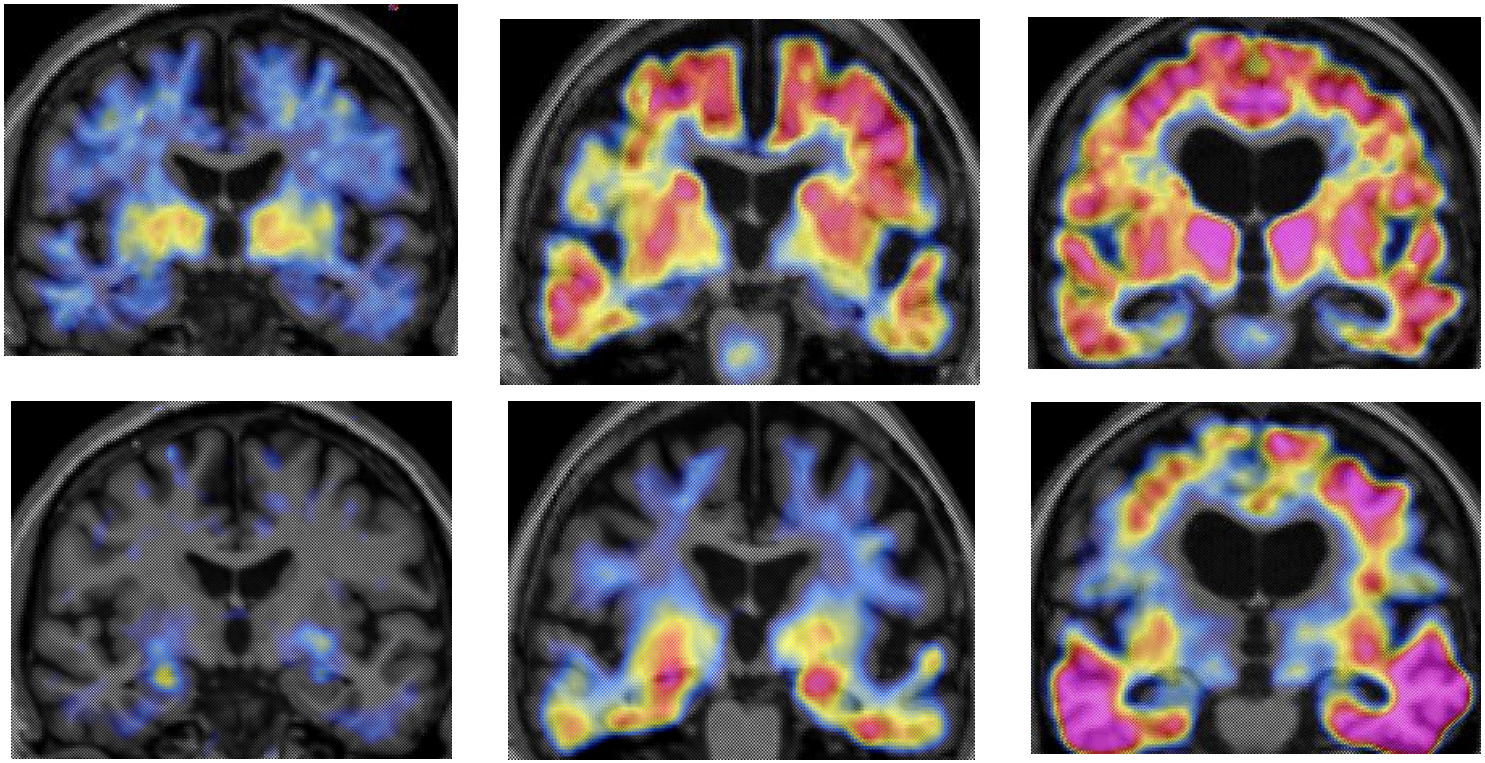
Brain amyloidosis measured using PET predicts cognitive decline



Data from the **H**arvard **A**ging **B**rain **S**tudy (**HABS**) : 276 CN + 51 MCI and the **A**lzheimer **D**isease **N**euroimaging **I**nitiative (**ADNI**): 367 CN + 523 MCI

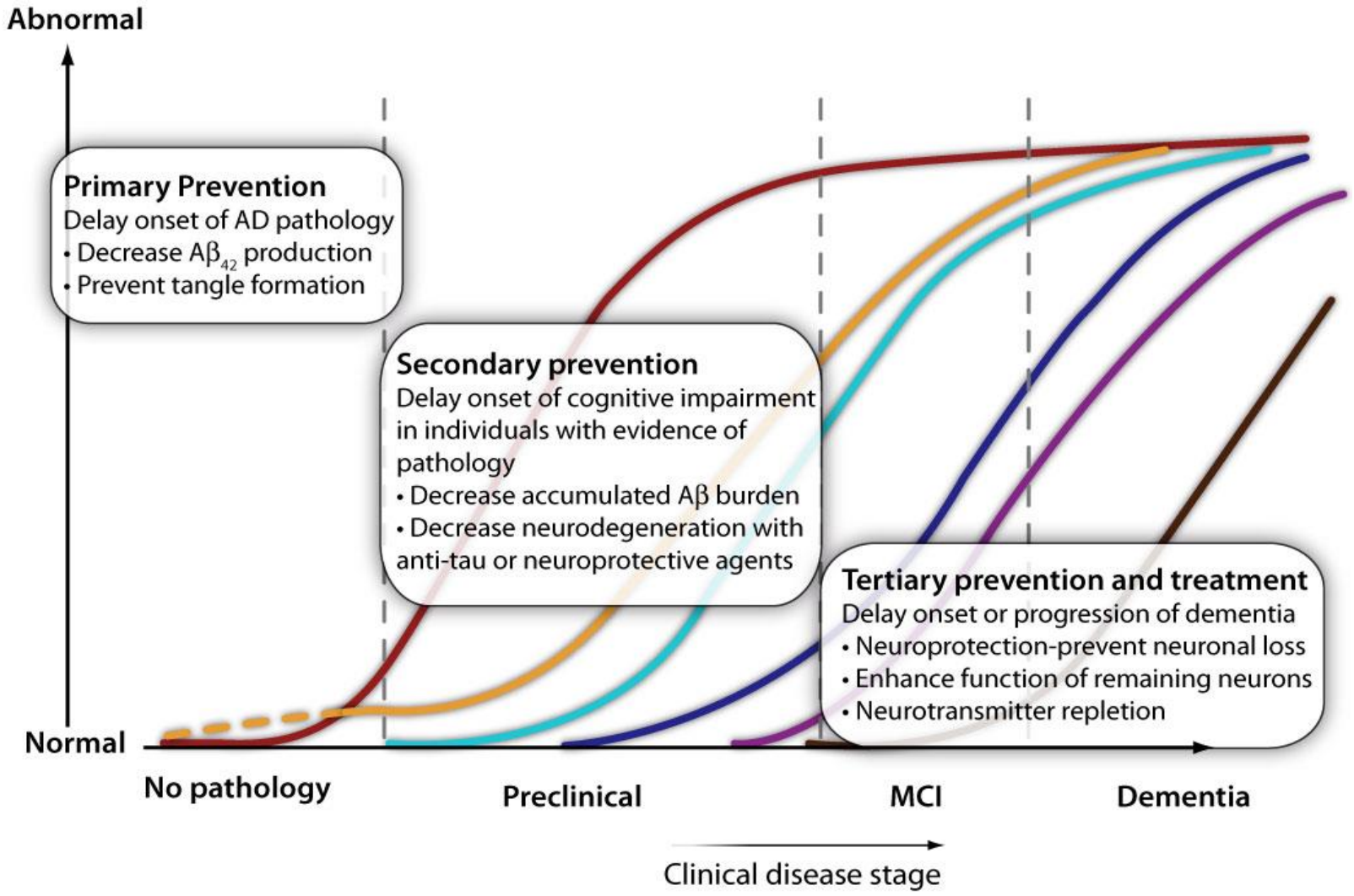
- Mutations disturbing amyloid metabolism are responsible for genetic Alzheimer's disease
- Brain amyloidosis is also frequently observed in older adults with normal cognition
- Brain amyloidosis is an important risk factor for subsequent cognitive decline
- Anti-amyloid drugs are currently used in preventive therapies to further test the "*amyloid hypothesis*"
- Evaluating amyloid expansion outside the neocortex can help better predict who will suffer from cognitive decline in the next few years

Amyloid **and** Tau PET Imaging



- All adults have tau pathology to some extent, but a few high-Aβ elders have increased tau
- Tau pathology correlates better with present and future cognitive performances than Aβ
- Cognitive changes seem to correlate tightly with the rates of tau accumulation
- Future clinical trials should target tau accumulation and/or the interaction between amyloid and tau

Testing the Right Target and the Right Drug at the Right Stage of Alzheimer's Disease



Sperling RA, Jack CR, Aisen P *Sci Transl Med* 2011

ARTICLE

doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

Adacanumab trial in AD (sept. 2016)

Table 1 | Baseline characteristics

Characteristic		Placebo ($n=40$)	Aducanumab 1 mg kg^{-1} ($n=31$)	Aducanumab 3 mg kg^{-1} ($n=32$)	Aducanumab 6 mg kg^{-1} ($n=30$)	Aducanumab 10 mg kg^{-1} ($n=32$)	Total ($n=165$)*
Years of age (mean ± s.d.)		72.8 ± 7.2	72.6 ± 7.8	70.5 ± 8.2	73.3 ± 9.3	73.7 ± 8.3	72.6 ± 8.1
Female sex (*n* (%))		23 (58)	13 (42)	17 (53)	15 (50)	15 (47)	83 (50)
ApoE ε4 (*n* (%))	Carriers	26 (65)	19 (61)	21 (66)	21 (70)	20 (63)	107 (65)
	Non-carriers	14 (35)	12 (39)	11 (34)	9 (30)	12 (38)	58 (35)
Clinical stage (*n* (%))	Prodromal	19 (48)	10 (32)	14 (44)	12 (40)	13 (41)	68 (41)
	Mild	21 (53)	21 (68)	18 (56)	18 (60)	19 (59)	97 (59)
MMSE (mean ± s.d.)		24.7 ± 3.6	23.6 ± 3.3	23.2 ± 4.2	24.4 ± 2.9	24.8 ± 3.1	24.2 ± 3.5
Global CDR (*n* (%))	0.5	34 (85)	22 (71)	22 (69)	25 (83)	24 (75)	127 (77)
	1	6 (15)	9 (29)	10 (31)	5 (17)	8 (25)	38 (23)
CDR-SB (mean ± s.d.)		2.66 ± 1.50	3.40 ± 1.76	3.50 ± 2.06	3.32 ± 1.54	3.14 ± 1.71	3.18 ± 1.72
FCSRT sum of free recall score (mean ± s.d.)		15.2 ± 8.5	13.2 ± 9.0	13.8 ± 8.0	14.4 ± 8.3	14.6 ± 8.3	14.3 ± 8.3
PET SUVR composite score (mean ± s.d.)		1.44 ± 0.17	1.44 ± 0.15	1.46 ± 0.15	1.43 ± 0.20	1.44 ± 0.19	1.44 ± 0.17
AD medications use† (*n* (%))		24 (60)	19 (61)	28 (88)	20 (67)	17 (53)	108 (65)

Percentages are rounded to the nearest integer. AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4 allele; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating—Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation; SUVR, standard uptake value ratio.
*Number of patients dosed.
†Cholinesterase inhibitors and/or memantine.

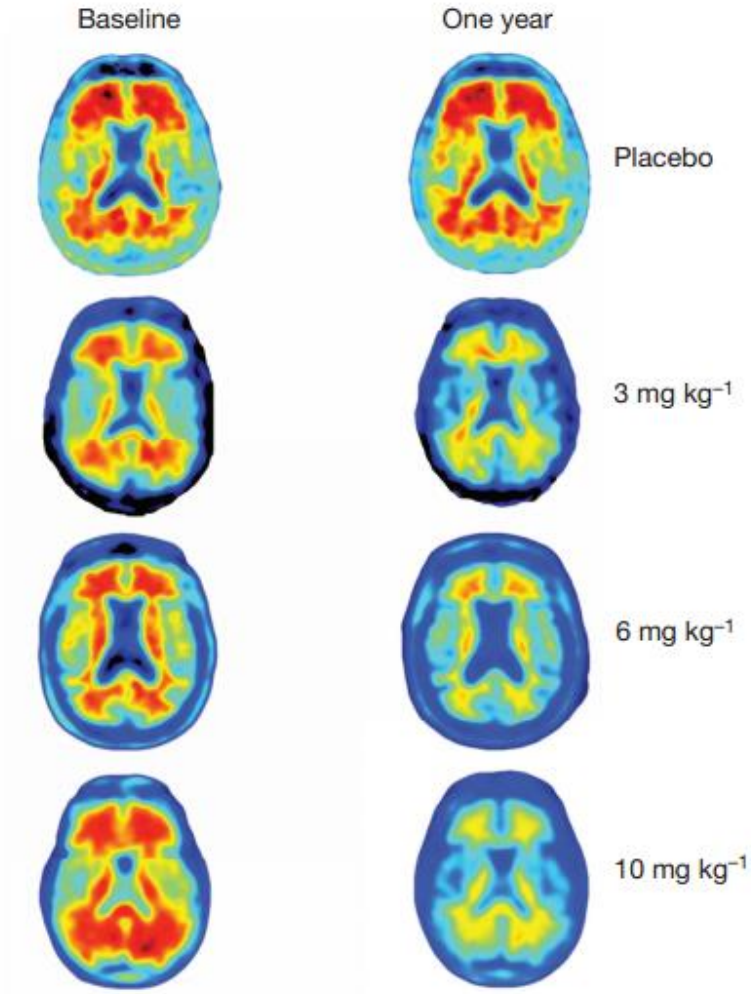


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40$, 32, 30 and 32, respectively). Axial slice shows anatomical regions in posterior brain putatively related to AD pathology. SUVR, standard uptake value ratio.

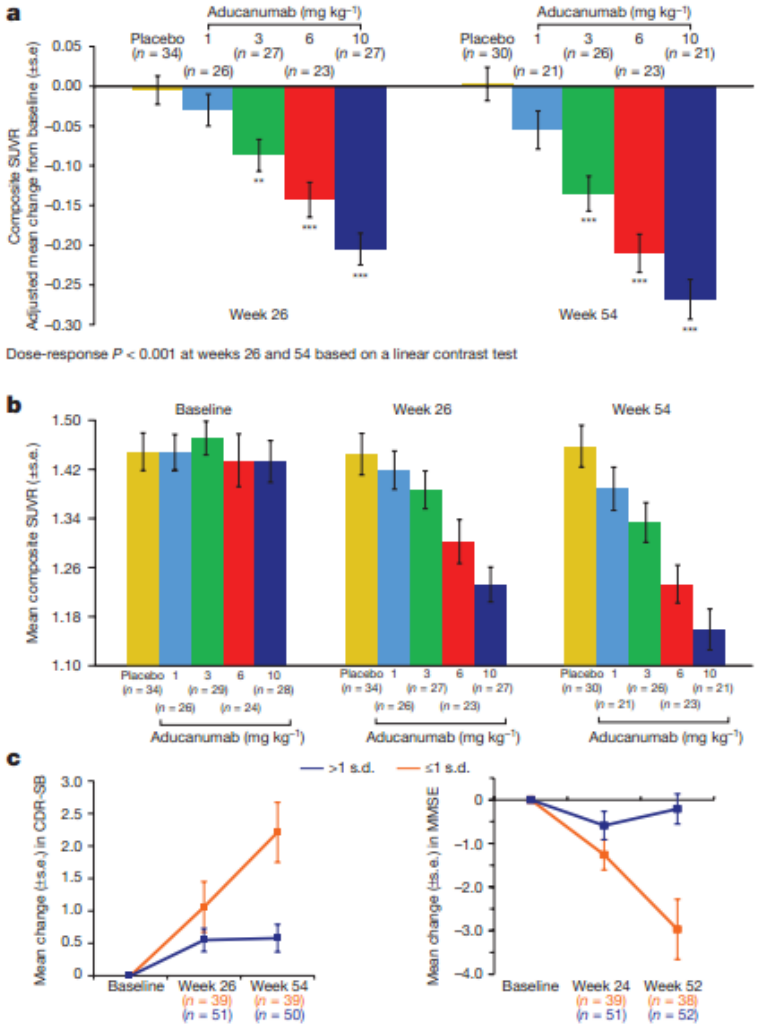


Figure 2 | Amyloid plaque reduction with aducanumab. a–c, Change from baseline (**a**, analyses using ANCOVA), SUVR values (**b**), and categorization of change in amyloid PET (**c**) at week 54 and associated change from baseline CDR-SB and MMSE in aducanumab-treated patients (post hoc analysis). Categorization of amyloid PET at week 54 based on s.d. of change from baseline in placebo-treated patients. $^{**}P < 0.01$; $^{***}P < 0.001$ versus placebo; two-sided tests with no adjustments for multiple comparisons. Mean ± s.e. ANCOVA, analysis of covariance; CDR-SB, Clinical Dementia Rating—Sum of Boxes; MMSE, Mini Mental State Examination; SUVR, standard uptake value ratio.

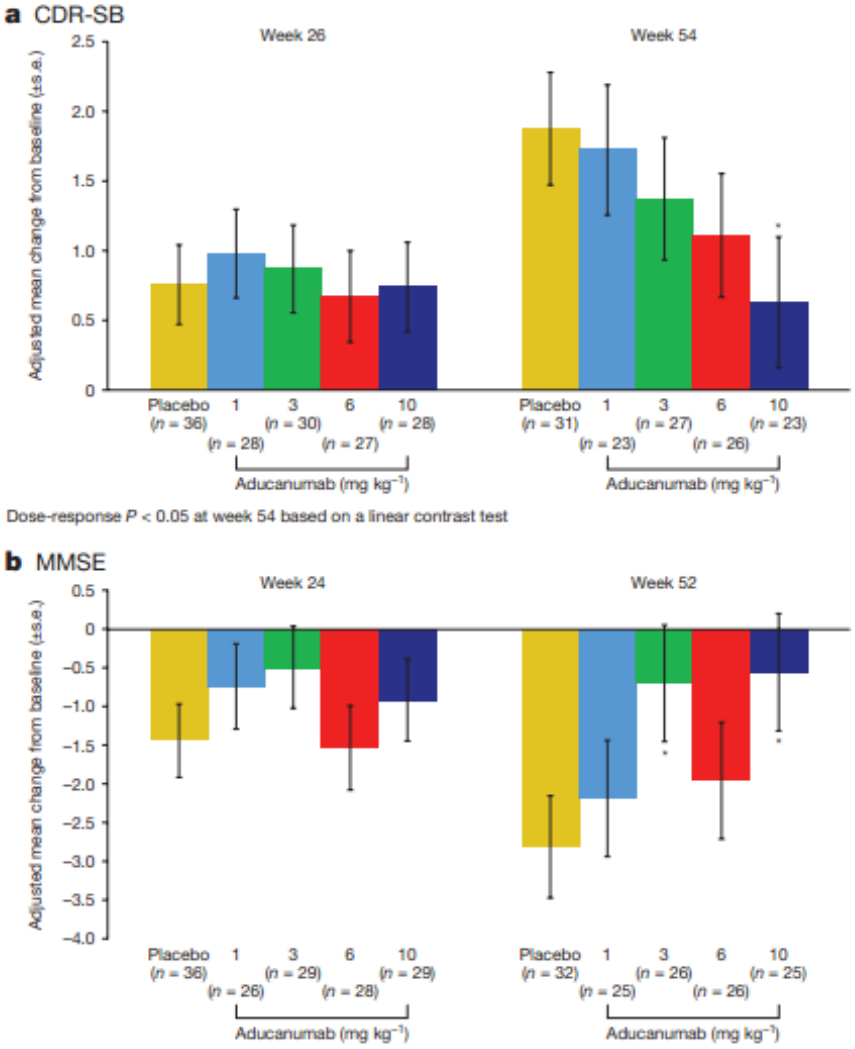


Figure 3 | Aducanumab effect (change from baseline) on CDR-SB and MMSE. a, **b**, Aducanumab effect on CDR-SB (**a**) and MMSE (**b**). *$P < 0.05$ versus placebo; two-sided tests with no adjustments for multiple comparisons. CDR-SB and MMSE were exploratory endpoints. Adjusted mean ± s.e. Analyses using ANCOVA. CDR-SB, Clinical Dementia Rating—Sum of Boxes; MMSE, Mini Mental State Examination.

Table 2 | Summary of adverse events and most common adverse events

Adverse event (*n* (%))	Placebo (*n* = 40)	Aducanumab			
		1 mg kg^{-1} (*n* = 31)	3 mg kg^{-1} (*n* = 32)	6 mg kg^{-1} (*n* = 30)	10 mg kg^{-1} (*n* = 32)
Any adverse event	39 (98)	28 (90)	27 (84)	28 (93)	29 (91)
Serious event	15 (38)	3 (10)	4 (13)	4 (13)	12 (38)
Discontinuing treatment due to an adverse event	4 (10)	3 (10)	2 (6)	3 (10)	10 (31)
Common adverse events					
ARIA	2 (5)	2 (6)	4 (13)	11 (37)	15 (47)
Headache	2 (5)	5 (16)	4 (13)	8 (27)	8 (25)
Urinary tract infection	4 (10)	3 (10)	2 (6)	4 (13)	5 (16)
Upper respiratory tract infection	6 (15)	2 (6)	2 (6)	2 (7)	6 (19)
Diarrhoea	3 (8)	0	6 (19)	1 (3)	3 (9)
Arthralgia	2 (5)	0	6 (19)	2 (7)	1 (3)
Fall	8 (20)	3 (10)	2 (6)	2 (7)	2 (6)
Superficial siderosis of CNS	0	2 (6)	1 (3)	2 (7)	4 (13)
Constipation	0	3 (10)	1 (3)	1 (3)	3 (9)
Nausea	2 (5)	2 (6)	5 (16)	0	1 (3)
Anxiety	4 (10)	4 (13)	1 (3)	1 (3)	1 (3)
Nasopharyngitis	0	1 (3)	5 (16)	0	1 (3)
Cough	2 (5)	3 (10)	1 (3)	0	1 (3)
Alanine aminotransferase increased	0	3 (10)	0	1 (3)	0
Aspartate aminotransferase increased	0	3 (10)	0	0	1 (3)

Common adverse events are those with an incidence of ≥10% in any aducanumab treatment group. Incidence of ARIA based on adverse event reporting. Adverse events of ARIA-E (oedema) and ARIA-H (micro-haemorrhage) are both coded to the MedDRA preferred term of amyloid-related imaging abnormalities, and ARIA-H (superficial siderosis) codes to the MedDRA preferred term of superficial siderosis of the CNS. ARIA, amyloid-related imaging abnormalities; CNS, central nervous system; MedDRA, Medical Dictionary for Regulatory Activities.

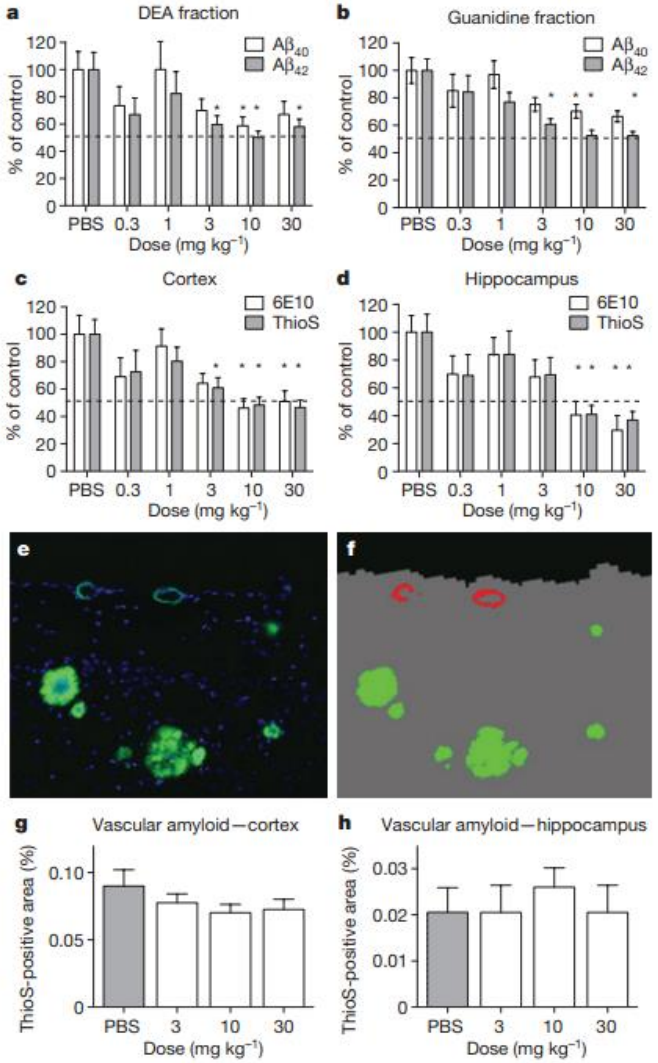


Figure 4 | Reduction of amyloid burden following weekly dosing with ^{ch}aducanumab in 9.5- to 15.5-month-old Tg2576 transgenic mice. **a**, **b**, $A\beta_{40}$ and $A\beta_{42}$ levels in soluble DEA (**a**) and insoluble GuHCl (**b**) brain fractions. **c**, **d**, Total brain Aβ (6E10) and compact amyloid plaques (ThioS) in cortex (**c**) and hippocampus (**d**) (mean ± s.e.; $n = 20–55$; dotted line 50% reduction; $^*P < 0.05$ versus control). **e**–**h**, ThioS staining of amyloid deposits (**e**) and Visiopharm software (**f**) differentiated parenchymal deposits (green) from vascular deposits (red) (representative pictures 10× magnification), and quantified area of vascular amyloid

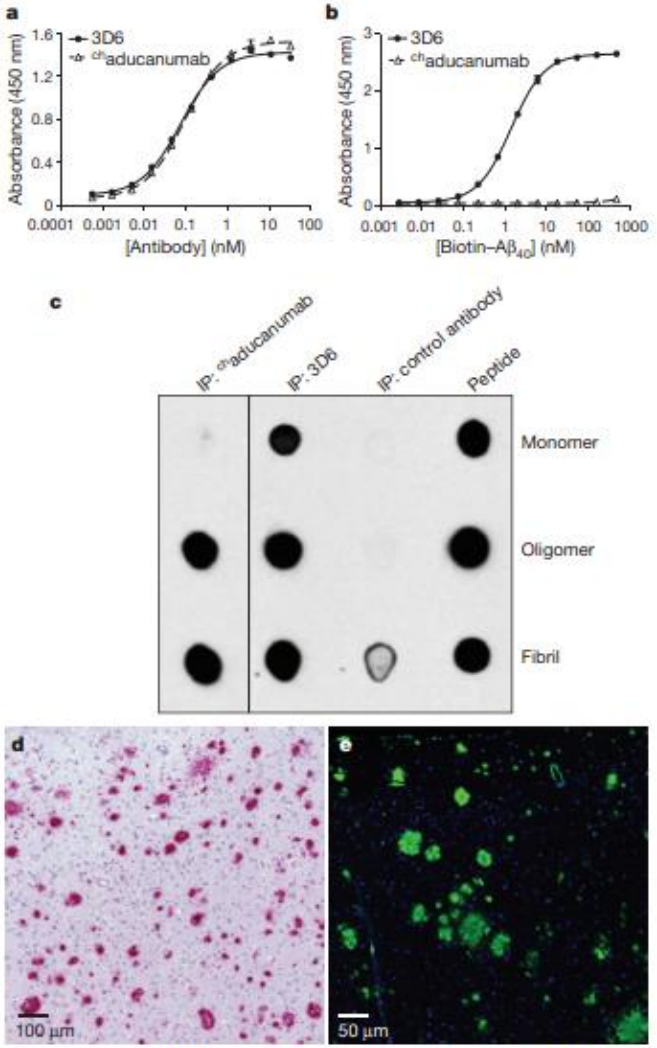


Figure 5 | Aducanumab binds selectively to insoluble fibrillar and soluble oligomeric Aβ aggregates. **a**, Binding of ^{ch}aducanumab or 3D6 to immobilized fibrillar $A\beta_{42}$. Mean ± s.d., in triplicate. **b**, Capture of soluble monomeric $A\beta_{40}$ with immobilized ^{ch}aducanumab or 3D6. Mean ± s.d., in triplicate. **c**, Dot blots of $A\beta_{42}$ monomer, soluble oligomers, or insoluble fibrils immunoprecipitated with ^{ch}aducanumab, 3D6, or irrelevant antibody control. Equivalent concentrations confirmed by direct dot blotting (Peptide). **d**, **e**, Immunostaining of Aβ in autopsy brain tissue from a patient with AD with ^{ch}aducanumab (0.2 μg ml^{-1}) (**d**) and 22-month-old Tg2576 transgenic mouse brain tissue with aducanumab (60 ng ml^{-1}) (**e**).

Les anticorps monoclonaux (immunothérapie) ; l' espoir dans le traitement des maladies neurodégénératives ?

- maladie d'Alzheimer (anti-amyloide)
- maladie d'Alzheimer et tau-pathies (anti-tau)
- démence à corps de Lewy, Parkinson (antisynucléine)
- ALS, subcortical dementia (MSA, SNP, …)

Against amyloid…

ClinicalTrials.gov

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Text Size

221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE)

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2017 by Biogen

Sponsor:
Biogen

Information provided by (Responsible Party):
Biogen

ClinicalTrials.gov Identifier:
NCT02477800

First received: June 18, 2015
Last updated: January 19, 2017
Last verified: January 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score as compared with placebo in participants with early AD. Secondary objectives are to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by Mini-Mental State Examination (MMSE), AD Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], and AD Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI].

Against Tau…

CellPress

Article

Antibody-Mediated Targeting of Tau In Vivo Does Not Require Effector Function and Microglial Engagement

Seung-Hye Lee,[1,3] Claire E. Le Pichon,[1,3,4] Oskar Adolfsson,[2] Valérie Gafner,[2] Maria Pihlgren,[2] Han Lin,[1] Hilda Solanoy,[1] Robert Brendza,[1] Hai Ngu,[1] Oded Foreman,[1] Ruby Chan,[1,5] James A. Ernst,[1] Danielle DiCara,[1] Isidro Hotzel,[1] Karpagam Srinivasan,[1] David V. Hansen,[1] Jasvinder Atwal,[1] Yanmei Lu,[1] Daniela Bumbaca,[1] Andrea Pfeifer,[2] Ryan J. Watts,[1] Andreas Muhs,[2,*] Kimberly Scearce-Levie,[1,*] and Gai Ayalon[1,*]

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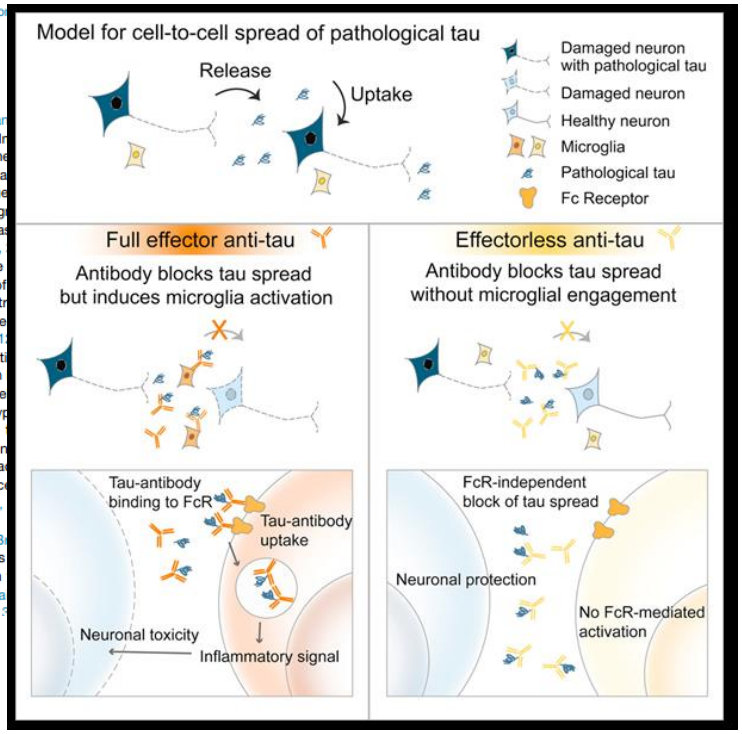
http://dx.doi.org/10.1016/j.celrep.2016.06.099

SUMMARY

The spread of tau pathology correlates with cognitive decline in Alzheimer's disease. In vitro, tau antibodies can block cell-to-cell tau spreading. Although mechanisms of anti-tau function in vivo are unknown, effector function might promote microglia-mediated clearance. In this study, we investigated whether antibody effector function is required for targeting tau. We compared efficacy in vivo and in vitro of two versions of the same tau antibody, with and without effector function, measuring tau pathology, neuron health, and microglial function. Both antibodies reduced accumulation of tau pathology in Tau-P301L transgenic mice and protected cultured neurons against extracellular tau-induced toxicity. Only the full-effector antibody enhanced tau uptake in cultured microglia, which promoted release of proinflammatory cytokines. In neuron-microglia co-cultures, only effectorless anti-tau protected neurons, suggesting full-effector tau antibodies can induce indirect toxicity via microglia. We conclude that effector function is not required for efficacy, and effectorless tau antibodies may represent a safer approach to targeting tau.



Against alpha-synuclein…

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society
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Research Article

First-in-human assessment of PRX002, an anti–α-synuclein monoclonal antibody, in healthy volunteers

Dale B. Schenk PhD, Martin Koller MD, MPH, Daniel K. Ness DVM, PhD, Sue G. Griffith MD, PhD, MRCP, Michael Grundman MD, MPH, Wagner Zago PhD, Jay Soto BS, George Atiee MD, Susanne Ostrowitzki MD, PhD, Gene G. Kinney PhD

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Volume 32, Issue 2
February 2017
Pages 211–218

First published: 25 November 2016 Full publication history

DOI: 10.1002/mds.26878 View/save citation

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Funding information

The copyright line for this article was changed on 10 December 2016 after original online publication.

Funding agencies: This study was sponsored by Prothena Biosciences Limited (South San Francisco, CA, USA) and F. Hoffmann-La Roche Ltd. (Basel, Switzerland).

Relevant conflicts of interests/financial disclosures: D.B.S. reported employment, leadership, stock ownership, intellectual property, and travel for Prothena. M.K. reports employment, leadership, stock ownership, and travel for Prothena. D.K.N. reports employment, stock ownership, and travel for Prothena. S.G.G. is a consultant for Prothena. M.G. is a consultant and reports stock ownership in Prothena. W.Z. reports employment, stock ownership, and travel for Prothena. J.S. reports employment, stock ownership, and travel for Prothena. G.A. has nothing to disclose. S.O. reports employee status and stock ownership in F. Hoffmann-La Roche Ltd. G.G.K. reports employment, leadership, stock ownership, travel, and patents/intellectual property with Prothena.

ABSTRACT

Background: α-Synuclein is a major component of pathologic inclusions that characterize Parkinson's disease. PRX002 is an antibody that targets α-synuclein, and its murine parent antibody 9E4 has been shown in preclinical studies to reduce α-synuclein pathology and to protect against cognitive and motor deteriorations and progressive neurodegeneration in human α-synuclein transgenic mice. **Methods**: This first-in-human, randomized, double-blind, placebo-controlled, phase 1 study assessed the impact of PRX002 administered to 40 healthy participants in 5 ascending-dose cohorts (n = 8/cohort) in which participants were randomly assigned to receive a single intravenous infusion of study drug (0.3, 1, 3, 10, or 30 mg/kg; n = 6/cohort) or placebo (n = 2/cohort). **Results**: PRX002 demonstrated favorable safety, tolerability, and pharmacokinetic profiles at all doses tested, with no immunogenicity. No serious adverse events, discontinuations as a result of adverse events, or dose-limiting toxicities were reported. Serum PRX002 exposure was dose proportional; the average terminal half-life across all doses was 18.2 days. A significant dose-dependent reduction in free serum α-synuclein (unbound to PRX002) was apparent within 1 hour after PRX002 administration, whereas total α-synuclein (free plus bound) increased dose-dependently, presumably because of the expected change in kinetics following antibody binding.

Against Nogo-A…

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PLOS ONE

Safety, Pharmacokinetic, and Functional Effects of the Nogo-A Monoclonal Antibody in Amyotrophic Lateral Sclerosis: A Randomized, First-In-Human Clinical Trial

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Abstract

The neurite outgrowth inhibitor, Nogo-A, has been shown to be overexpressed in ske… sclerosis (ALS); it is both a potential biomarker and therapeutic target. We perform… escalation study, in subjects with ALS, assessing safety, pharmacokinetics (PK) and fi… humanized monoclonal antibody against Nogo-A. In Part 1, 40 subjects were rando… intravenous ozanezumab (0.01, 0.1, 1, 5, or 15 mg/kg) or placebo. In Part 2, 36 subjects w… repeat doses of intravenous ozanezumab (0.5, 2.5, or 15 mg/kg) or placebo, approxi… endpoints were safety and tolerability (adverse events [AEs], vital signs, electrocardio… tests). Secondary endpoints included PK, immunogenicity, functional endpoints (clin… biomarker parameters. Overall, ozanezumab treatment (0.01–15 mg/kg) was well tolera… the repeat dose 2.5 mg/kg and 15 mg/kg ozanezumab groups was higher than in th… repeat dose 0.5 mg/kg ozanezumab group. The majority were considered not related to… serious AEs were reported in three subjects receiving ozanezumab; none were conside… drug-related patterns were identified for ECG, laboratory, or vital signs parameters. C… ozanezumab) showed a weak, positive anti-ozanezumab-antibody result. PK result… monoclonal antibody treatments. No apparent treatment effects were observed fo… biomarkers. Immunohistochemical staining showed dose-dependent co-localization of c… muscle. In conclusion, single and repeat dose ozanezumab treatment was well tolerate… at the site of action. These findings support future studies with ozanezumab in ALS.

Trial Registration: ClinicalTrials.gov NCT00875446 GSK-ClinicalStudyRegister.com GSK

Safety and efficacy of ozanezumab in patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled, phase 2 trial

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Lancet Neurol 2017; 16: 208–16

Published Online January 27, 2017 http://dx.doi.org/10.1016/S1474-4422(16)30399-4

See Comment page 175

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Summary

Background Neurite outgrowth inhibitor A (Nogo-A) is thought to have a role in the pathophysiology of amyotrophic lateral sclerosis (ALS). A monoclonal antibody against Nogo-A showed a positive effect in the *SOD1*^{G93A} mouse model of ALS, and a humanised form of this antibody (ozanezumab) was well tolerated in a first-in-human trial. Therefore, we aimed to assess the safety and efficacy of ozanezumab in patients with ALS.

Methods This randomised, double-blind, placebo-controlled, phase 2 trial was done in 34 centres in 11 countries. Patients aged 18–80 years with a diagnosis of familial or sporadic ALS were randomly assigned (1:1), centrally according to a computer-generated allocation schedule, to receive ozanezumab (15 mg/kg) or placebo as intravenous infusions over 1 h every 2 weeks for 46 weeks, followed by assessments at week 48 and week 60. Patients and study personnel were masked to treatment assignment. The primary outcome was a joint-rank analysis of function (ALS Functional Rating Scale-Revised) and overall survival, analysed at 48 weeks in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01753076, and with GSK-ClinicalStudyRegister.com, NOG112264, and is completed.

Findings Between Dec 20, 2012, and Nov 1, 2013, we recruited 307 patients, of whom 303 were randomly assigned to receive placebo (n=151) or ozanezumab (n=152). The adjusted mean of the joint-rank score was –14·9 (SE 13·5) for the ozanezumab group and 15·0 (13·6) for the placebo group, with a least squares mean difference of –30·0 (95% CI –67·9 to 7·9; p=0·12). Overall, reported adverse events, serious adverse events, and adverse events leading to permanent discontinuation of study drug or withdrawal from study were similar between the treatment groups, except for dyspepsia (ten [7%] in the ozanezumab group *vs* four [3%] in the placebo group), depression (11 [7%] *vs* five [3%]), and diarrhoea (25 [16%] *vs* 12 [8%]). Respiratory failure was the most common serious adverse event (12 [8%] *vs* seven [5%]). At week 60, the number of deaths was higher in the ozanezumab group (20 [13%]) than in the placebo group (16 [11%]), mainly as a result of respiratory failure (ten [7%] *vs* five [3%]). Two deaths were considered related to the study drug (bladder transitional cell carcinoma in the ozanezumab group and cerebrovascular accident in the placebo group).

Interpretation Ozanezumab did not show efficacy compared with placebo in patients with ALS. Therefore, Nogo-A does not seem to be an effective therapeutic target in ALS.

Particular aspects of AD drug treatment

- elderly patients (and more than in clinical studies)
- patients with high comorbidities
- combined therapies needed (various targets)
- high cost of immunotherapy,
- ethical problems

preclinical diagnosis,

patient selection for treatment,

side effects in asymptomatic patients,

distributive justice (socially just allocation, cost of other diseases)

The age gap between patients in clinical studies and in the general population : the example in dementia research

The Lancet *Neurology*, 3, 627, 2004

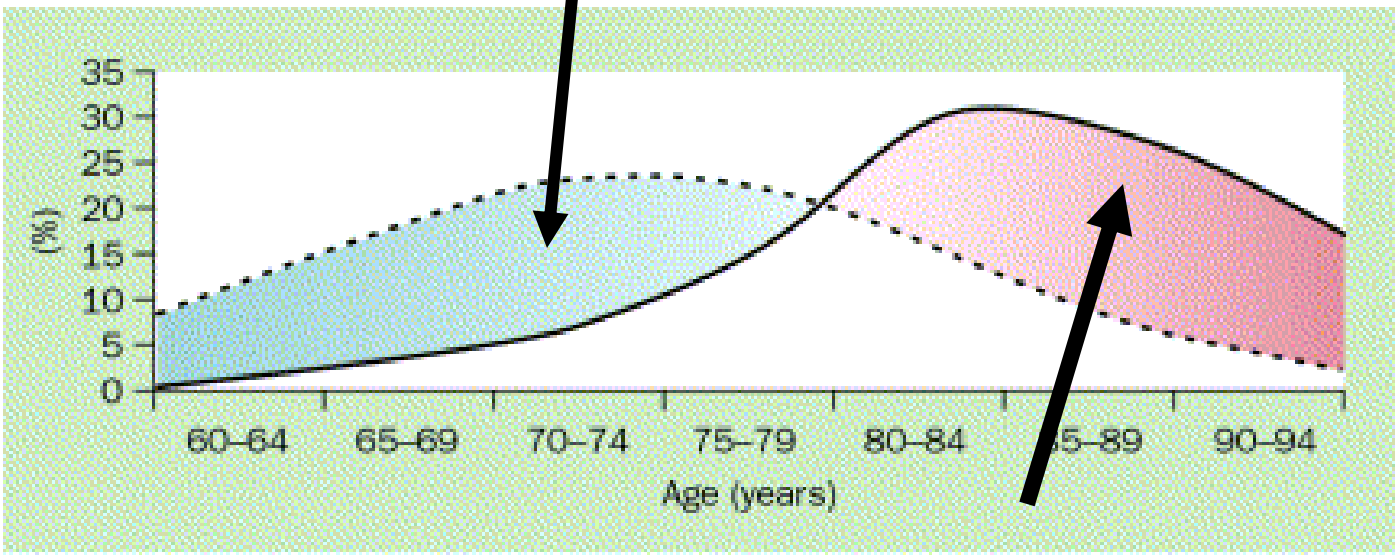
Clinical studies in dementia (n: 6.953 ; publications 2000-2003):

mean age : 74.5 years

Age distribution of patients with dementia from the general population (n: 180.961):

mean age : 83 years

Patients below age 70 y. are over-represented in research on dementia



Patients > 80 y.o., who represent 75% of the demented subjects in the general population are largely under-represented

Dementia research is systematically biased towards patients who are young relative to many who have dementia.

Maladie d'Alzheimer, Conclusion

Lésions protéiques

Lésions

Perte neuronale

Clinic

MA pré-symptomatique … MA prédémentielle … Démence de type MA …

Aβ LCR ……

… TEP avec traceur amyloïde……

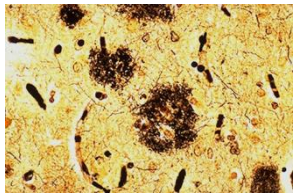
Marqueurs

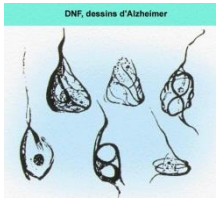
… + protéine tau LCR……

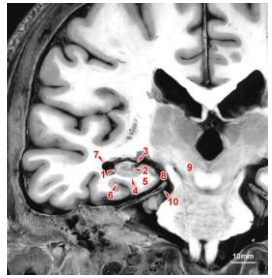
… TEP glucose / SPECT ……

… Atrophie hippocampique …

Maladie d'Alzheimer
Conclusion







Lésions protéiques

Lésions

Perte neuronale

Clinique

MA pré-symptomatique … MA prédémentielle … Démence de type MA …

Diagnostic « actuel » de MA

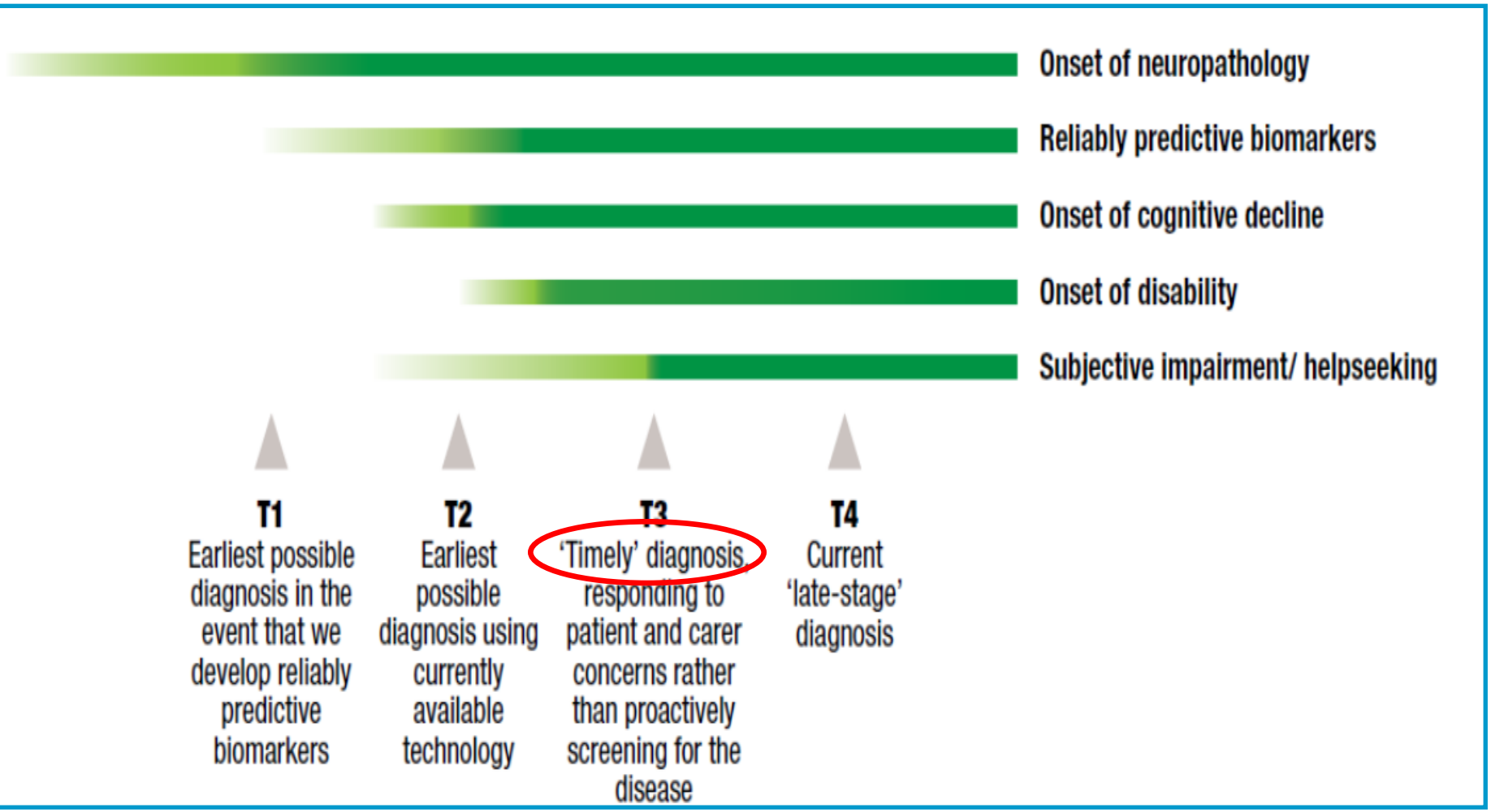
Traitements symptomatiques

Traitements étio-pathogéniques

Diagnostic de MA pré-démentielle

Albert et al., Mc Kahn et al., Alzheimer's and Dementia, 2011

Opportunités diagnostiques & Evolution de la maladie



Cummings et al. Alzheimer's Research & Therapy (2016) 8:39
DOI 10.1186/s13195-016-0207-9

Alzheimer's
Research & Therapy

REVIEW Open Access

Drug development in Alzheimer's disease: the path to 2025

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Abstract

The global impact of Alzheimer's disease (AD) continues to increase, and focused efforts are needed to address this immense public health challenge. National leaders have set a goal to prevent or effectively treat AD by 2025. In this paper, we discuss the path to 2025, and what is feasible in this time frame given the realities and challenges of AD drug development, with a focus on disease-modifying therapies (DMTs). Under the current conditions, only drugs currently in late Phase 1 or later will have a chance of being approved by 2025. If pipeline attrition rates remain high, only a few compounds at best will meet this time frame. There is an opportunity to reduce the time and risk of AD drug development through an improvement in trial design; better trial infrastructure; disease registries of well-characterized participant cohorts to help with more rapid enrollment of appropriate study populations;
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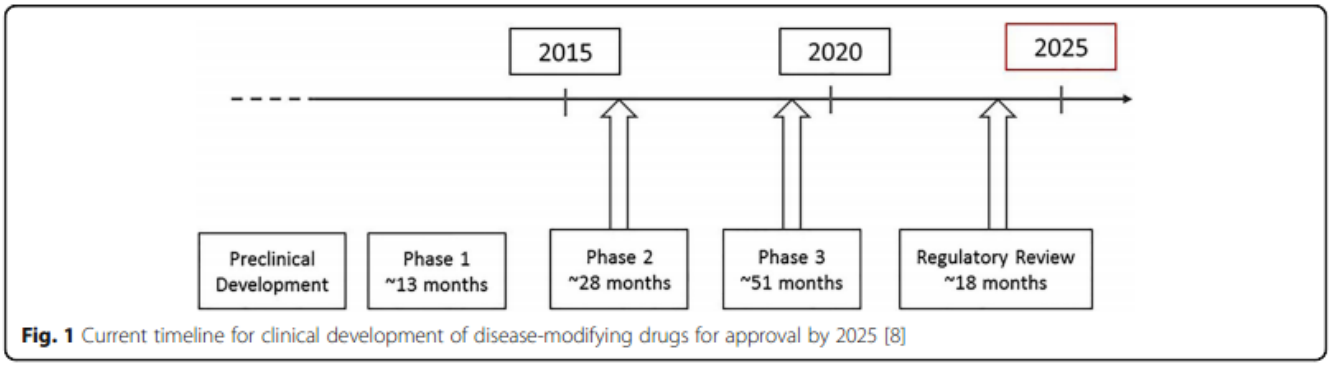

Fig. 1 Current timeline for clinical development of disease-modifying drugs for approval by 2025 [8]