Tractament de la malaltia d'Alzheimer en un futur proper

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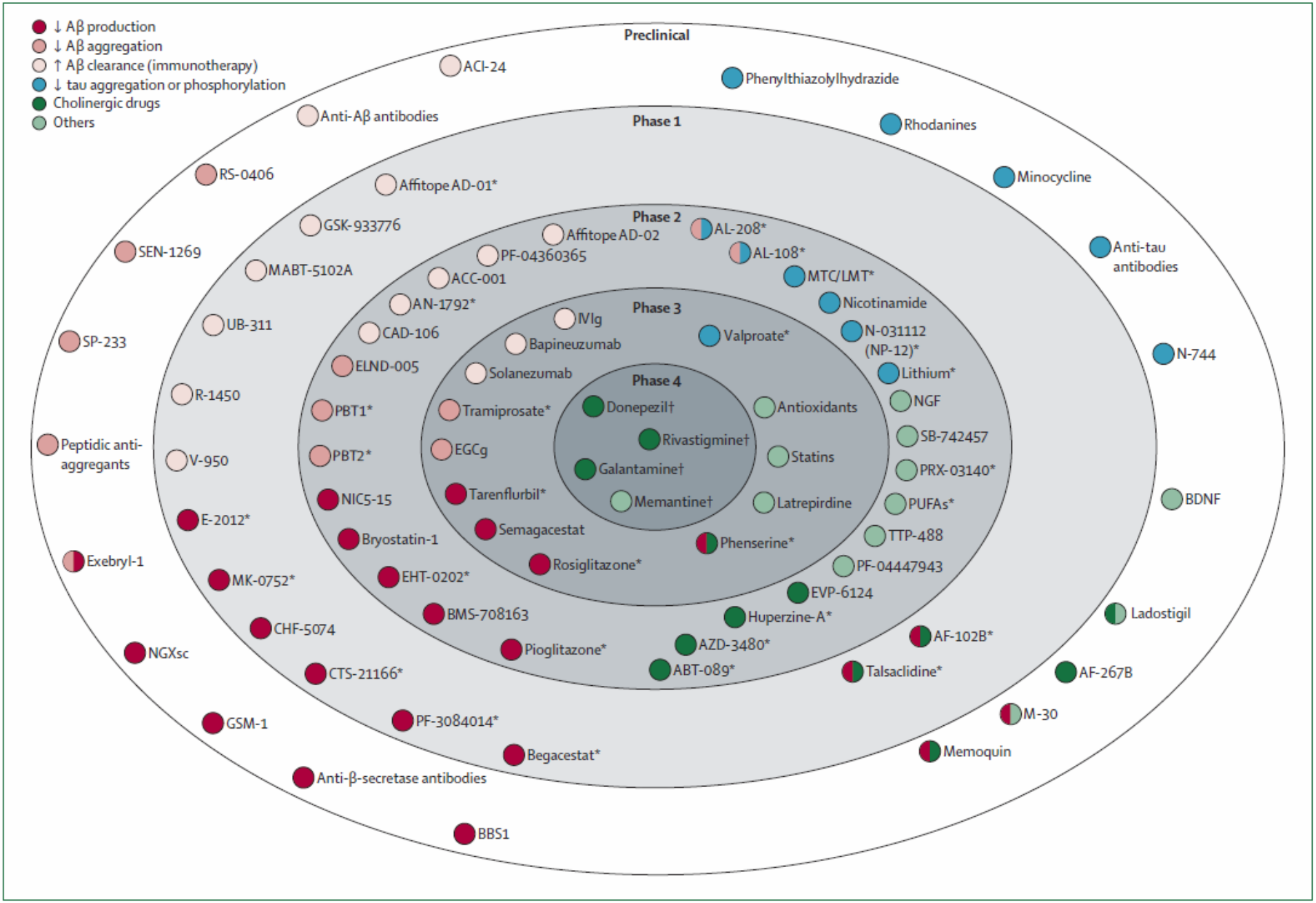
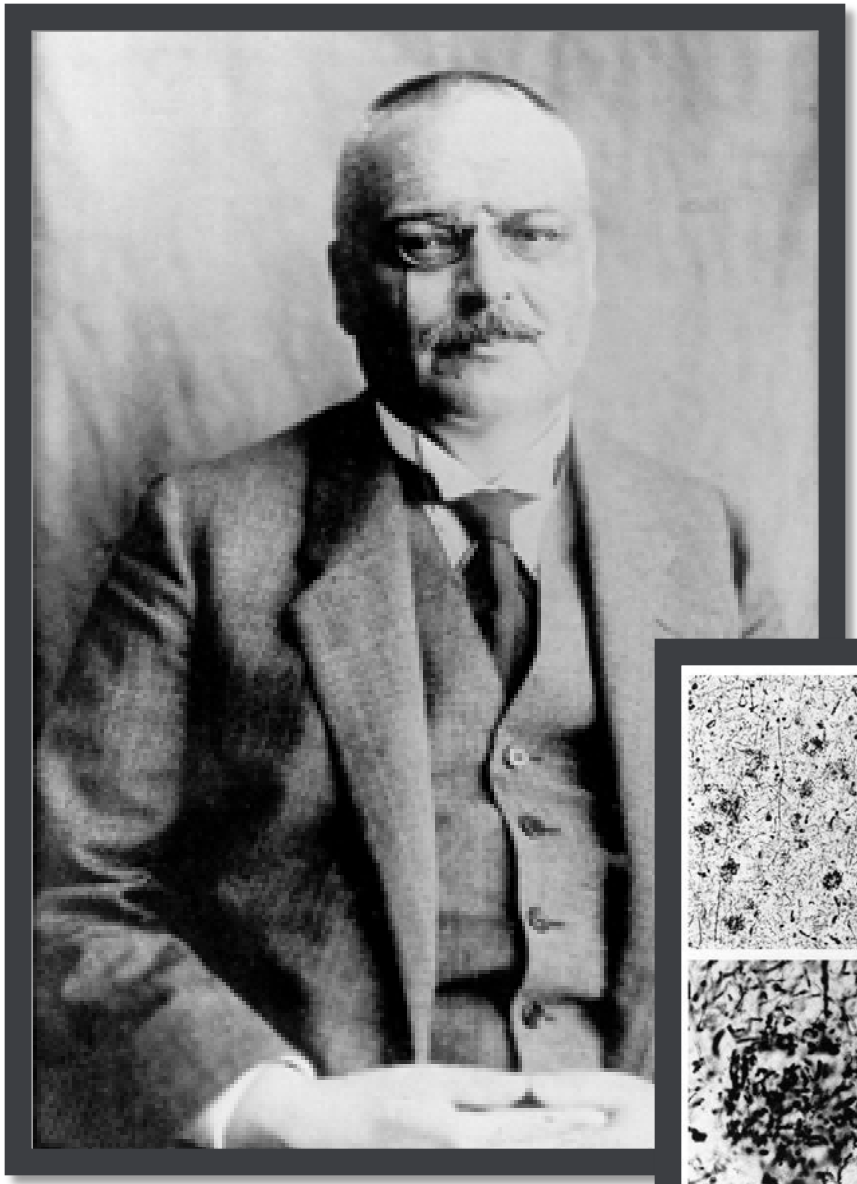
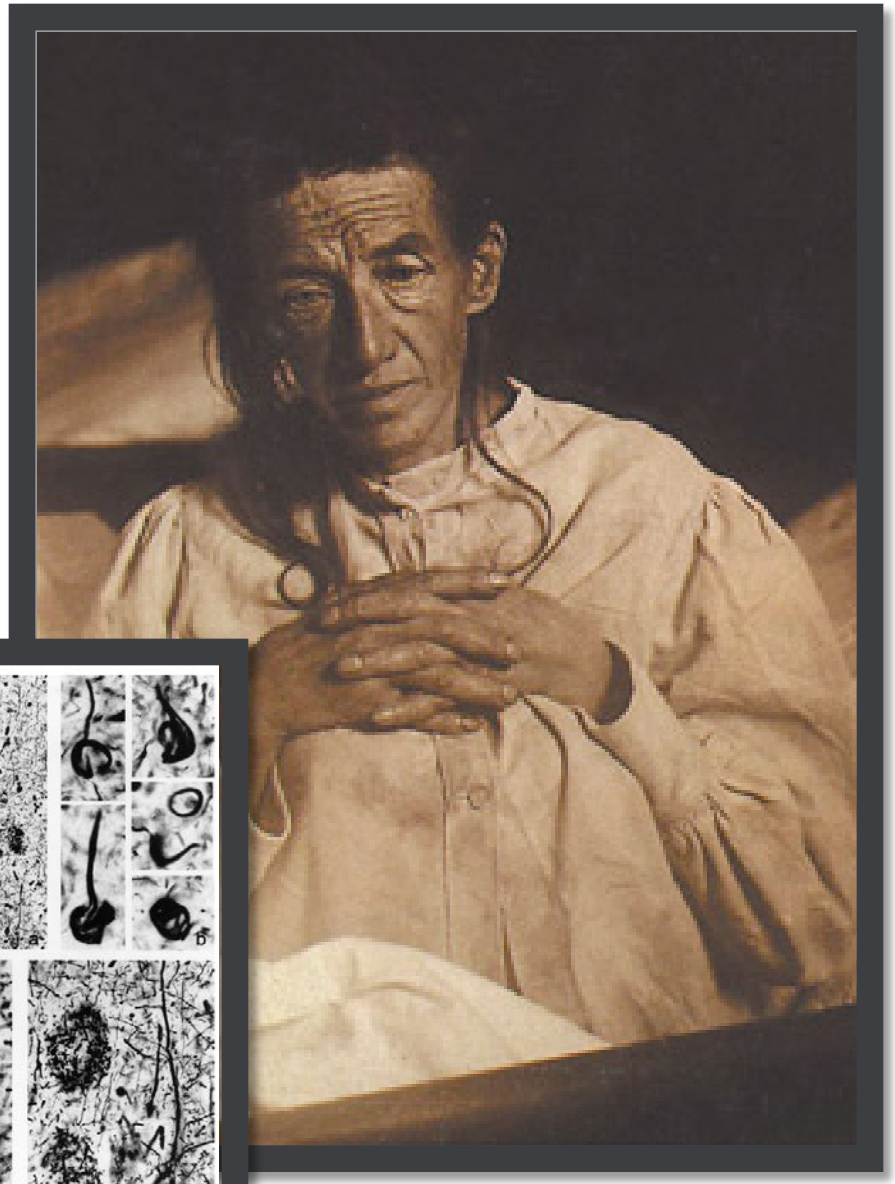
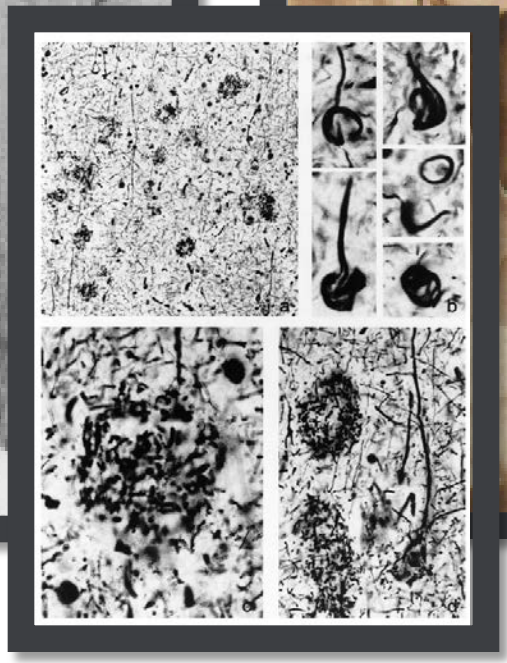


Mangialasche et al, Lancet Neurol 2010







Compendium

der

PSYCHIATRIE.

Zum Gebrauche

für

Studirende und Aerzte

von

Dr. Emil Kraepelin,
Docent an der Universität Leipzig.

Leipzig,
Verlag von Ambr. Abel.
1883.

The Prevalence and Malignancy of Alzheimer Disease

A Major Killer

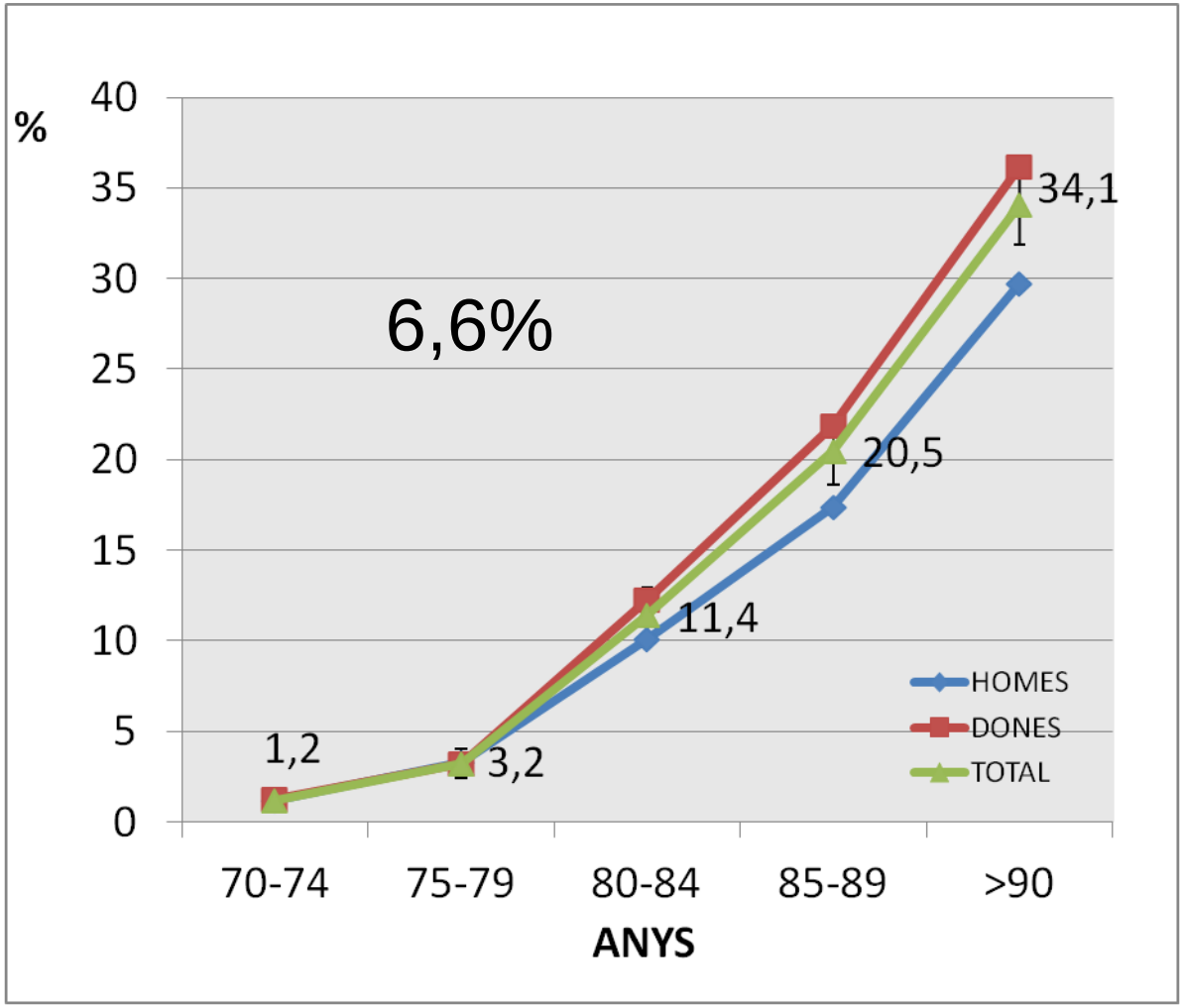
An accompanying letter to the editor (p 304) provides another illustration of the malignancy of Alzheimer disease, a phenomenon well known to neurologists. Katzman and Karasu[1] estimate that the senile form of Alzheimer disease may rank as the fourth or fifth most common cause of death in the United States. Yet the US vital statistics tables do not list "Alzheimer disease," "senile dementia," or "senility" as a cause of death, even in the extended list of 263 causes of death.

The argument that Alzheimer disease is a major killer rests on the assumption that Alzheimer disease and senile dementia are a single process and should, therefore, be considered a single disease. Both Alzheimer disease and senile dementia are progressive dementias with similar changes in mental and neurological status that are indistinguishable by careful clinical analyses.[2,3] The pathological findings are identical—atrophy of the brain, marked loss of neurons, neurofibrillary tangles, granulovacuolar changes, and neuritic (senile) plaques. Ultrastructural studies have established the identity of the neurofibrillary tangle with its twisted tubule and the senile plaque with its amyloid core and degenerating neurites in the brains of patients with Alzheimer disease (under age 65) and senile dementia (over age 65). Most recent ultrastructural and neurochemical studies indicate that the neurofibrillary tangle in both disorders is characterized by the twisted tubule that represents two neurofilaments joined together in a helical fashion with a period of 800 Angstroms. The studies of Tomlinson et al[4] and Blessed et al[5] have established a quantitative correlation between the degree of dementia and the number of neurofibrillary tangles and senile plaques in the cerebral cortex. The evidence on which a distinction between senile dementia and Alzheimer disease can still be argued is the genetic analysis of Larsson et al.[6] In their analysis of the kindred of patients with senile dementia, numerous relatives were found with senile dementia, but none with a diagnosis of Alzheimer disease. However, the incidence of the Alzheimer senile dementia complex is strongly age-related, even among the elderly. Larsson et al[6] had suggested a predisposing, autosomal dominant gene with age-related penetrance, reaching a penetrance of 40% at age 90. Therefore, the absence of any relative with "Alzheimer disease" might be related to its relative infrequency in patients under 65. Moreover, in a genetic study carried out in Switzerland, Constantinidis et al[7] encountered the two diseases in the same family. Although further studies are clearly indicated, the fact remains that neither the clinician, the neuropathologist, nor the electron microscopist can distinguish between the two disorders, except by the age of the patient. Today, the majority of workers in the field accept the identity of the two disease.[8] We believe that it is time to drop the arbitrary age distinction and adopt the single designation, Alzheimer disease.

Precise epidemiological information is not available concerning the prevalence of Alzheimer disease in the United States. However, several excellent community surveys of the prevalence of organic dementias in persons over age 65 have been carried out in northern Europe.[9-13] In these series, care has been taken to include persons living at home as well as those receiving institutional care. The prevalence of "severe dementia" or organic "psychosis," terms used to describe patients in whom, in addition to intellectual deterioration, there was evidence of disorganization of the personality and inability to carry out the normal tasks of daily living, averaged 4.1%. The prevalence of "mild dementia" and "mild mental deterioration" or "chronic brain syndrome without psychosis," terms used to describe individuals with intellectual impairment who are still able to carry out activities of daily living, averaged 10.8%. Estimates of the incidence of Alzheimer disease (senile dementia) among patients over age 65 with organic dementia vary between 40%[14] and 58%.[4] Applying these figures to the United States, the prevalence of Alzheimer disease in persons

Robert Katzman, MD. The Prevalence and Malignancy of Alzheimer Disease: A Major Killer.
***Arch Neurol* 1976;33(4):217-218.**

PREVALÈNCIA DE LA MALALTIA D'ALZHEIMER



Gascón-Bayarri J., Reñé R., Del Barrio J.L., et al. **Prevalence of dementia subtypes in El Prat de Llobregat, Catalonia, Spain: the PRATICON study.** Neuroepidemiology. 2007; 28(4):224-34.

Població per grups d'edat i sexe. Total Catalunya. 2010. Font: Idescat

Rang d'edat	(n) Població Catalunya	% Demència	(n) Demència	% MA	(n) Malaltia d'Alzheimer
65-69	330.759	1	3.307	0,5	1653
70-74	267.164	2,8	7.481	1,2	3.206
75-79	271.132	5,9	15.997	3,2	8.676
80-84	199.608	14,3	28.544	11,4	22.755
85-89	117.201	26,5	31.058	20,5	24.026
≥ 90	53.299	46,3	24.677	34,1	18.175
Total	**1.639.143**		**111.064**		**77.491**

La magnitud del problema

- 4ª- 5ª causa de mort
- 1ª - 2ª causa d' atenció PADES
- 55% d' augment risc d' anar a l' hospital
- 67% pateix al menys 3 co-morbilitats
- 64% dels cuidadors pateixen sobrecàrrega, 33% consumeixen psicofàrmacs
- Augment de morbilitat i mortalitat dels cuidadors
- 1r – 2n motiu de consulta a l' AE
- Consum de recursos econòmics

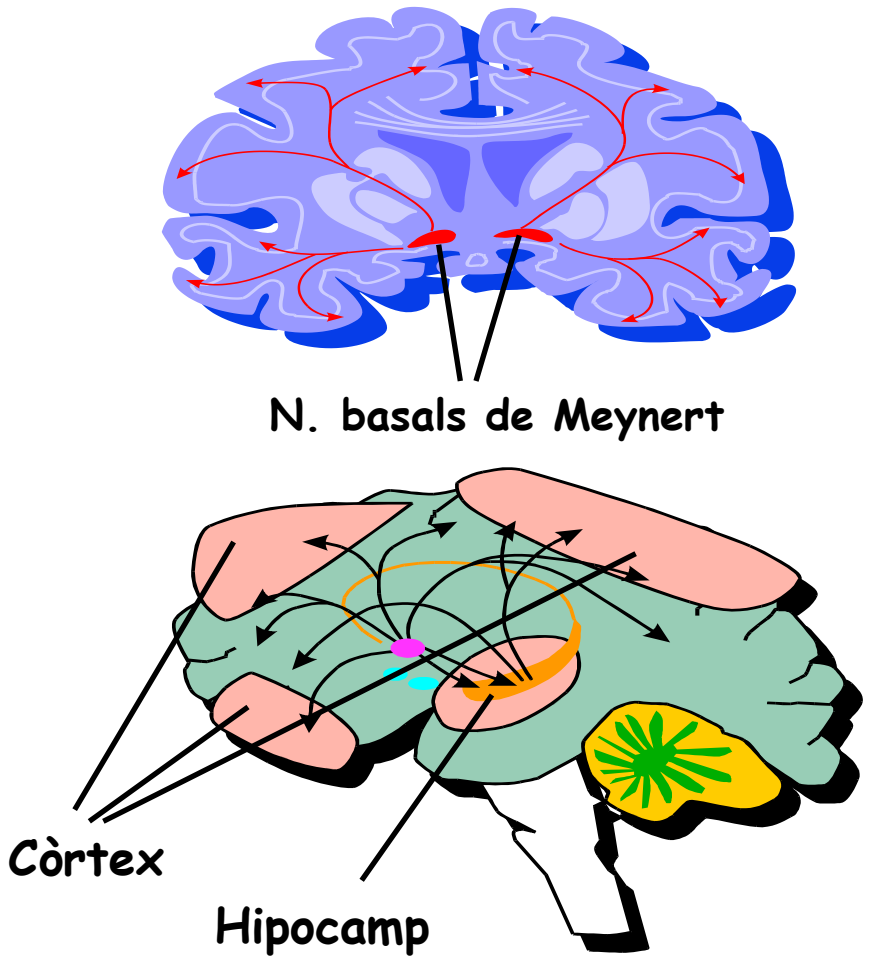
Dèficit colinèrgic a la MA

Dèficit colinèrgic

Pèrdua progressiva de neurones colinèrgiques

Disminució progressiva de l'Ach disponible

Deteriorament cognitiu i conductual de les AVD



Tacrina

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

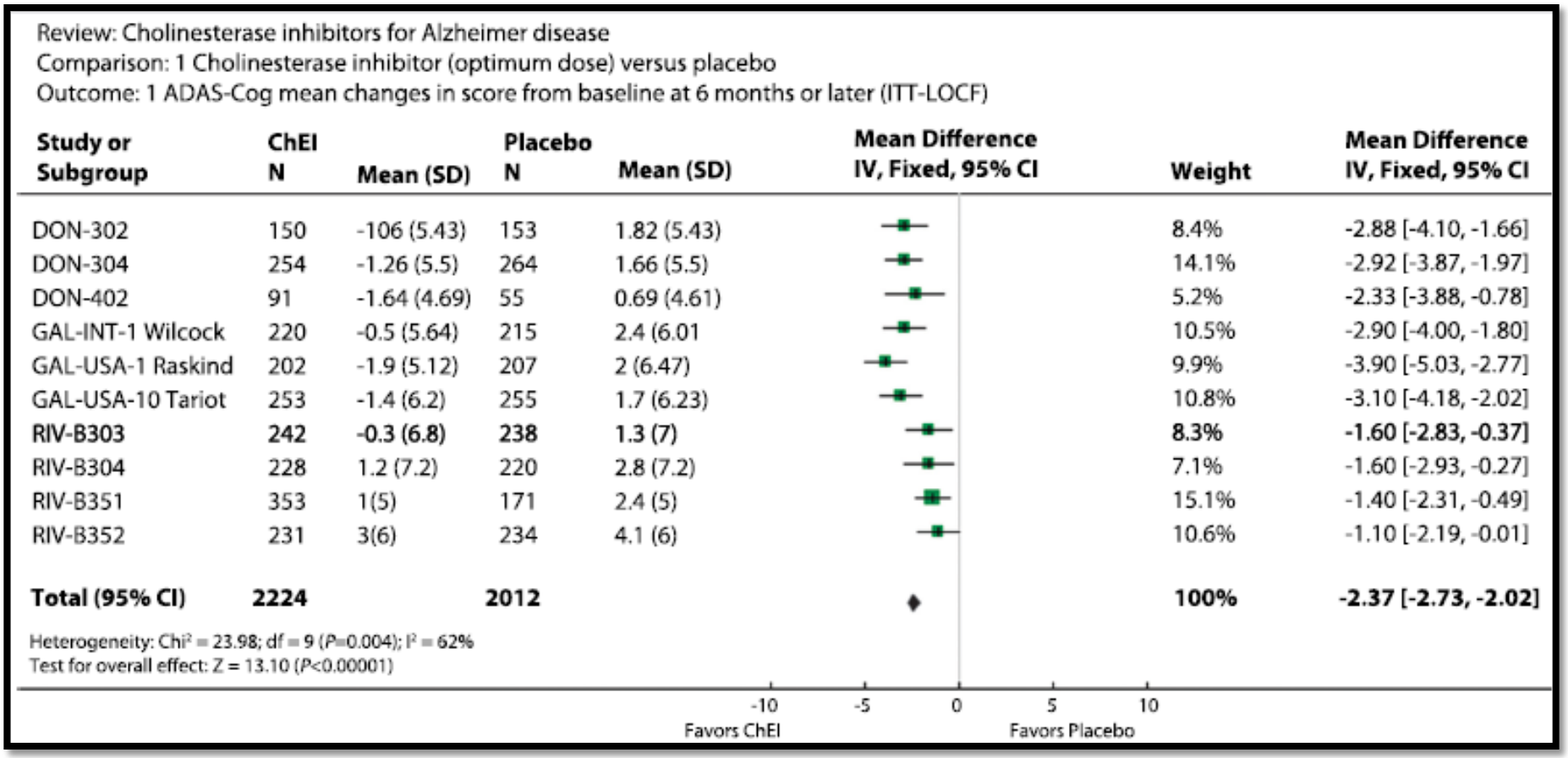
Summers, W. K., Majovski, L. V., Marsh, G. M., Tachiki, K., & Kling, A. (1986).

The New England Journal of Medicine, *315*(20), 1241-1245.

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.



Cholinesterase inhibitors, optimum dose versus placebo. **The figure shows the mean drug-placebo difference on the ADAS-Cog from several clinical trials** along with 95% confidence interval widths displayed as horizontal lines. The overall mean effect is -2.37 points with 95% confidence intervals of -2.73 to -2.03.

Lon S. Schneider, Continuum (Minneap Minn) 2013;19(2):339–357. Review. Data from Birks J, Cochrane Database Syst Rev.13 2006.

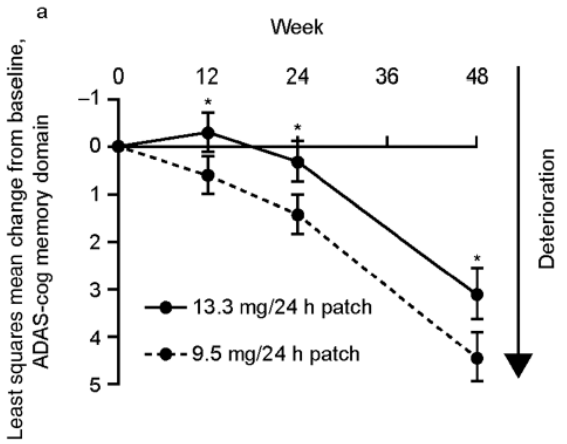
RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Efficacy of higher-dose 13.3 mg/24 h (15 cm²) rivastigmine patch on the Alzheimer's Disease Assessment Scale–cognitive subscale: domain and individual item analysis

Gustavo Alva[1], Richard Isaacson[2], Carl Sadowsky[3], George Grossberg[4], Xiangyi Meng[5] and Monique Somogyi[5]

Results: Numerically, less decline was displayed with 13.3 mg/24 h versus 9.5 mg/24 h patch in the total ADAS-cog score at all time points (significant at Week 24, $p = 0.027$). Factor analysis identified two domains: memory and language. Significantly, less decline was observed on the memory domain with 13.3 mg/24 h versus 9.5 mg/24 h patch at Weeks 12, 24, and 48 ($p < 0.05$; observed cases). Three items (following commands, orientation, and word recognition) displayed numerically less decline with 13.3 mg/24 h versus 9.5 mg/24 h patch at all time points. No significant between-group differences were observed on the language domain.



Neuroscience and Biobehavioral Reviews 37 (2013) 2676–2688

Contents lists available at ScienceDirect

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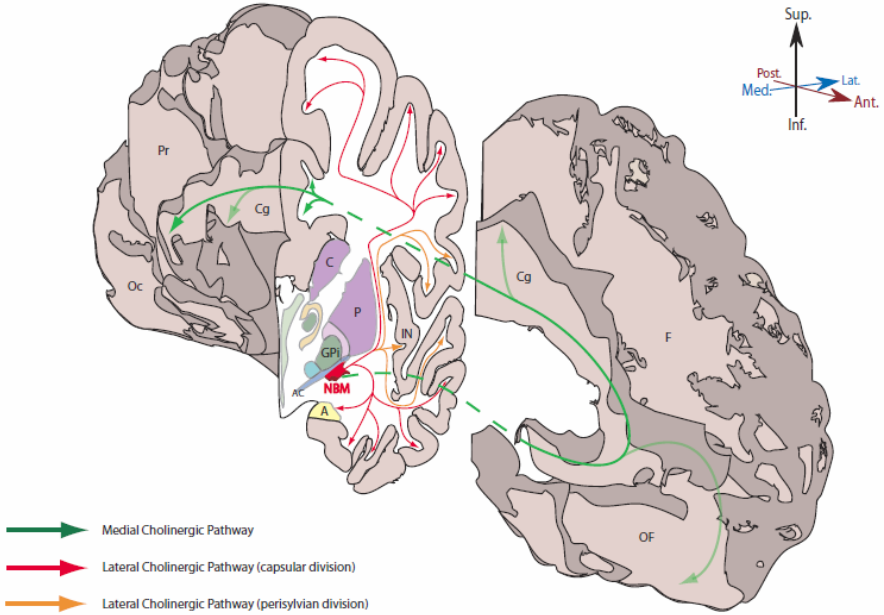
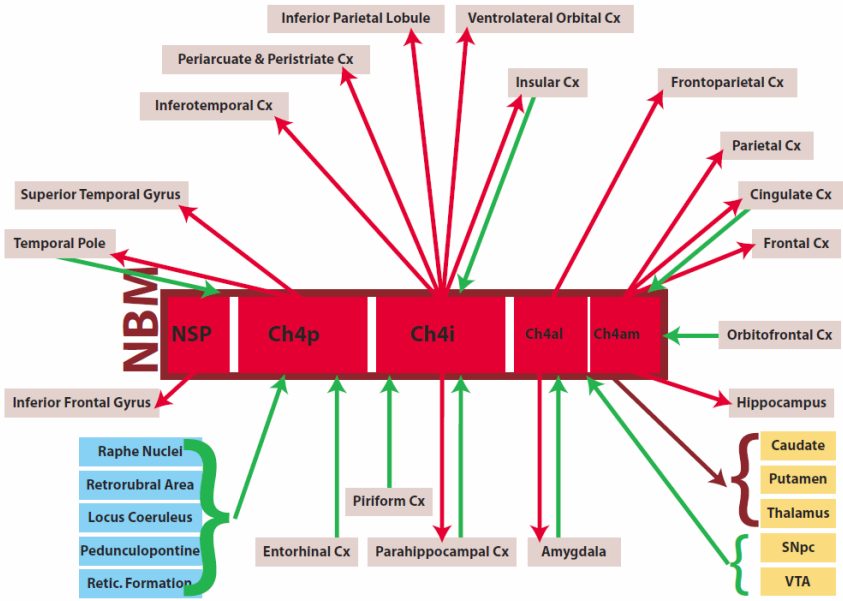
journal homepage: www.elsevier.com/locate/neubiorev

Review

The nucleus basalis of Meynert: A new target for deep brain stimulation in dementia?

James Gratwicke, Joshua Kahan, Ludvic Zrinzo, Marwan Hariz, Patricia Limousin, Thomas Foltynie*, Marjan Jahanshahi

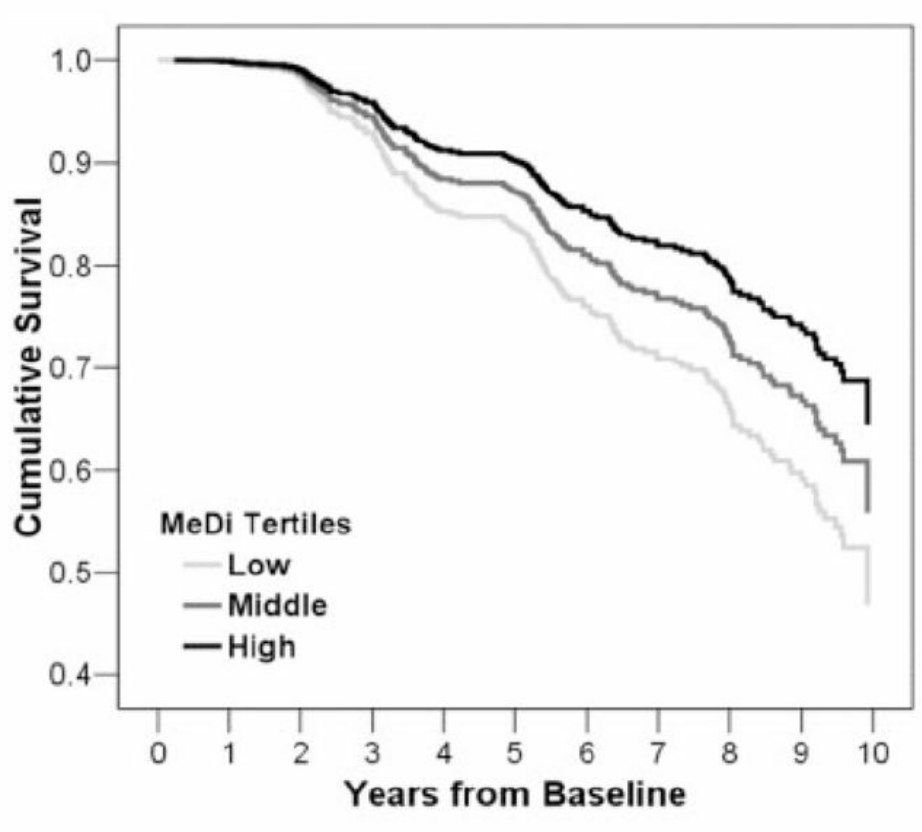




Ann Neurol. 2006 June ; 59(6): 912–921. doi:10.1002/ana.20854.

Mediterranean Diet and Risk for Alzheimer's Disease

Nikolaos Scarmeas, MD[1,2,3], **Yaakov Stern, PhD**[1,2,3], **Ming-Xin Tang, PhD**[1,4], **Richard Mayeux, MD**[1,2,3], and **Jose A. Luchsinger, MD**[1,5]



Cicle de Kennedy

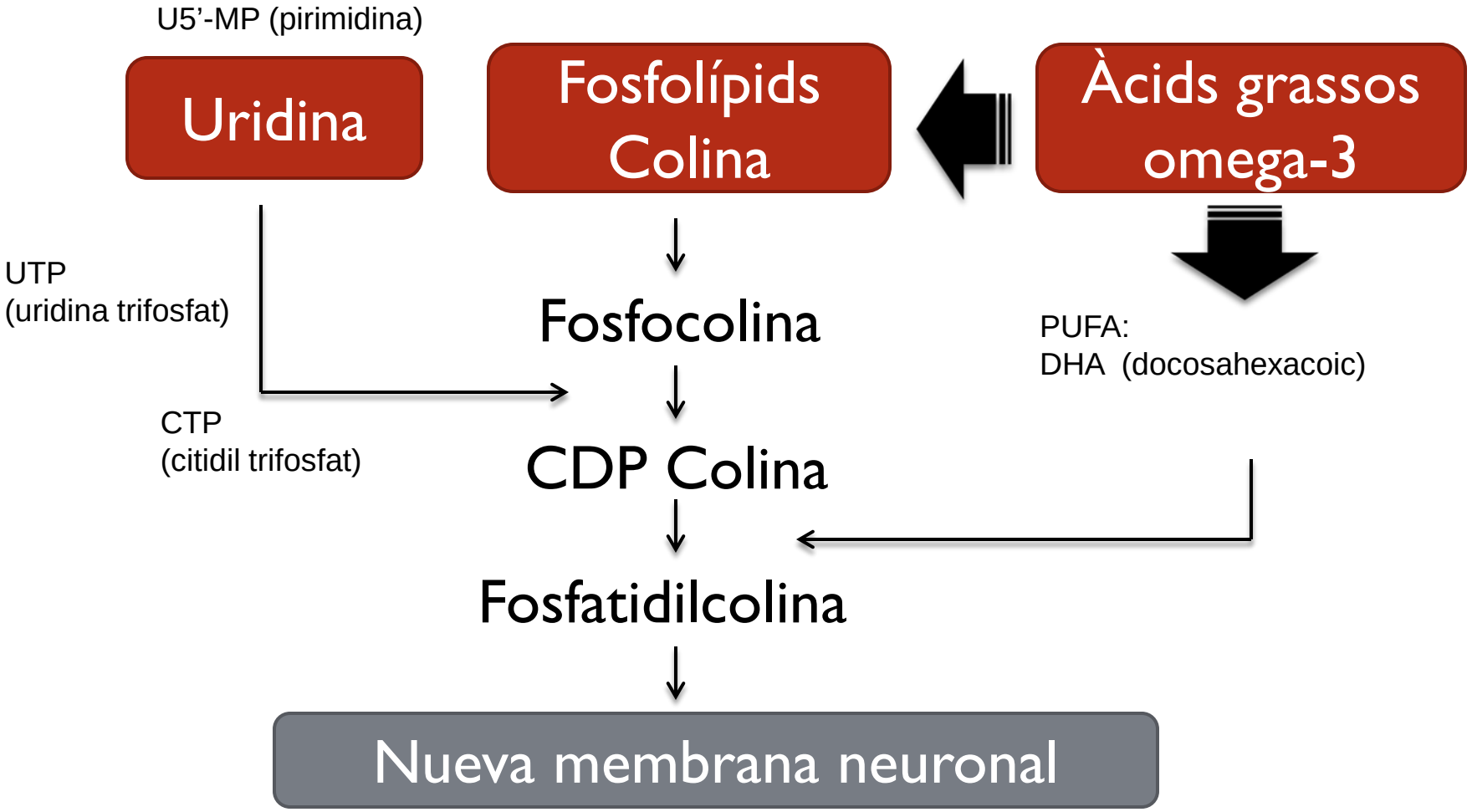
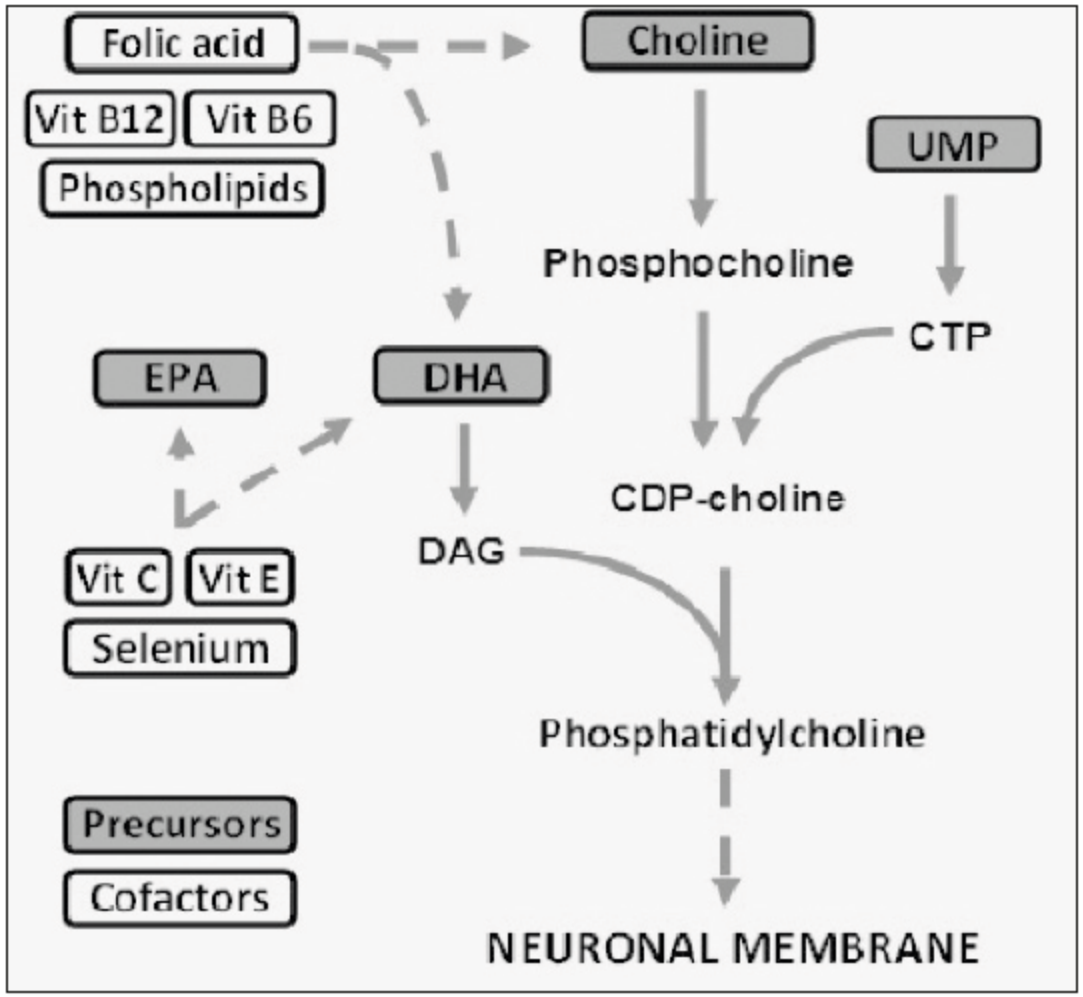


Figure 1

The synthesis of phosphatidylcholine, a major phospholipid found in synaptic membranes



CDP, cytidine diphosphate; CTP, cytidine triphosphate; DAG, diacylglycerol; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; UMP, uridine monophosphate

Table 1

Composition of Fortasyn™ Connect, the nutrient combination in Souvenaid®

Component	Amount per daily intake of Souvenaid®
Eicosapentaenoic acid (EPA)	300 mg
Docosahexaenoic acid (DHA)	1200 mg
Uridine monophosphate (UMP)	625 mg
Choline	400 mg
Phospholipids	106 mg
Folic acid	400 µg
Vitamin B6	1 mg
Vitamin B12	3 µg
Vitamin C	80 mg
Vitamin E	40 mg
Selenium	60 µg

Journal of Alzheimer's Disease 31 (2012) 225–236
DOI 10.3233/JAD-2012-121189
IOS Press

Efficacy of Souvenaid in Mild Alzheimer's Disease: Results from a Randomized, Controlled Trial

Philip Scheltens[a,*], Jos W.R. Twisk[b], Rafael Blesa[c], Elio Scarpini[d], Christine A.F. von Arnim[e], Anke Bongers[f], John Harrison[g,h], Sophie H.N. Swinkels[f], Cornelis J. Stam[i], Hanneke de Waal[a], Richard J. Wurtman[j], Rico L. Wieggers[f], Bruno Vellas[k] and Patrick J.G.H. Kamphuis[f]

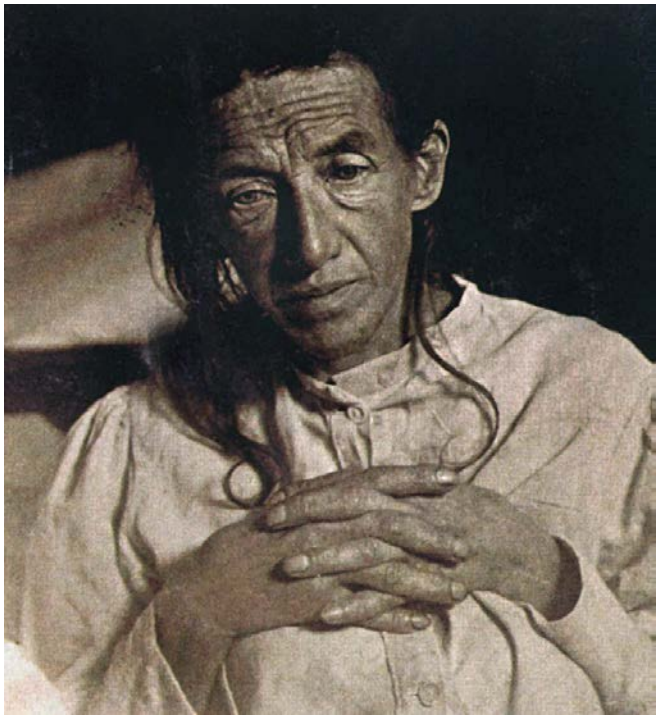
Abstract. Souvenaid aims to improve synapse formation and function. An earlier study in patients with Alzheimer's disease (AD) showed that Souvenaid increased memory performance after 12 weeks in drug-naïve patients with mild AD. The Souvenir II study was a 24-week, randomized, controlled, double-blind, parallel-group, multi-country trial to confirm and extend previous findings in drug-naïve patients with mild AD. Patients were randomized 1 : 1 to receive Souvenaid or an iso-caloric control product once daily for 24 weeks. The primary outcome was the memory function domain Z-score of the Neuropsychological Test Battery (NTB) over 24 weeks. Electroencephalography (EEG) measures served as secondary outcomes as marker for synaptic connectivity. Assessments were done at baseline, 12, and 24 weeks. The NTB memory domain Z-score was significantly increased in the active *versus* the control group over the 24-week intervention period ($p = 0.023$; Cohen's d = 0.21; 95% confidence interval [−0.06]–[0.49]). A trend for an effect was observed on the NTB total composite z-score ($p = 0{\cdot}053$). EEG measures of functional connectivity in the delta band were significantly different between study groups during 24 weeks in favor of the active group.

The Journal of Nutrition, Health & Aging©
Volume 18, Number 3, 2014

Table 2
Overview of completed and ongoing clinical trials with Souvenaid®

	Souvenir I	S-Connect	Souvenir II	LipiDiDiet
N	225	527	259	300 (target)
Alzheimer's disease type	Mild	Mild-moderate	Mild	Prodromal
Mean MMSE	20-26	14-24	>20	>24
Acetylcholinesterase inhibitors and/or memantine	No	Yes	No	No
Duration	12 weeks	24 weeks	24 weeks	24 months
Primary endpoint	WMS-r (delayed verbal recall) ADAS-Cog (13 item)	ADAS-Cog (11 item)	NTB memory domain (z-scores)	NTB (z-scores)
Results	Improved memory No improvement in cognition	No improvement in cognition	Improved memory	Ongoing

ADAS-Cog, Alzheimer's Disease Assessment Scale–cognitive subscale; MMSE, Mini-Mental State Examination; NTB, Neuropsychological Test Battery; WMS-r, Wechsler Memory Scale-revised



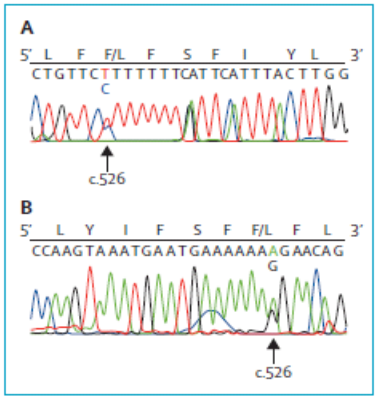


Figure: **Sequence chromatograms of 28 bp of exon 6 of *PSEN1* in DNA extracted from brain samples of Auguste Deter**

Sequencing detected a c.526T→C substitution. Both the sequence of the forward DNA strand (A) and the sequence of the reverse strand (B) are shown. The resulting aminoacid change, Phe176Leu, is indicated (F/L). The slight compressions at positions c.533 and c.537 were resolved on the reverse strand.

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December 14, 2012
http://dx.doi.org/10.1016/
S1474-4422(12)70307-1

www.thelancet.com/neurology **Vol 12 February 2013**

*Ulrich Müller, Pia Winter,
Manuel B Graeber
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Institute of Human Genetics, Justus Liebig University, 35392 Giessen, Germany (UM, PW); and The Brain and Mind Research Institute, University of Sydney, Sydney, Australia (MBG)

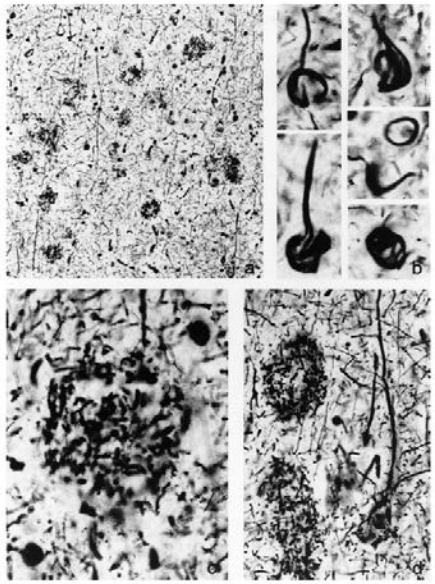
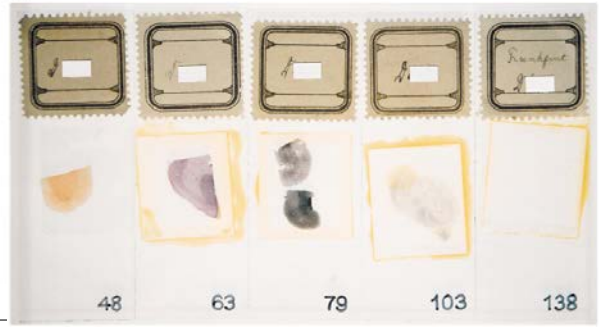


Fig. 2a–d Bielschowsky-stained tissue sections. **a** Numerous amyloid plaques and neurofibrillary tangles are visible in the cerebral cortex of Auguste D. Examples of tangles are shown in **b**, whereas amyloid plaques containing abnormal neurites are depicted in **c** and **d**. Primary magnification: ×20 (**a**), ×63 (**b–d**)

Fig. 1a Tissue sections from Auguste D.'s brain stained according to Herxheimer (*48*), Mallory? (*63*), Bielschowsky (*79*), Nissl (*103*) and Nissl (faded)? (*138*). The slide on the very right also shows "Frankfurt" on its label. All sections are marked "D...". **b** Entry no. 181 in the autopsy book of Kraepelin's clinic shows a date, "28 April 06", "Frankfurt" followed by the last name "D...", and the source of the tissue, i.e., "Frankfurt". "D..." is the last name of Auguste D., who died in Frankfurt on 8 April 1906

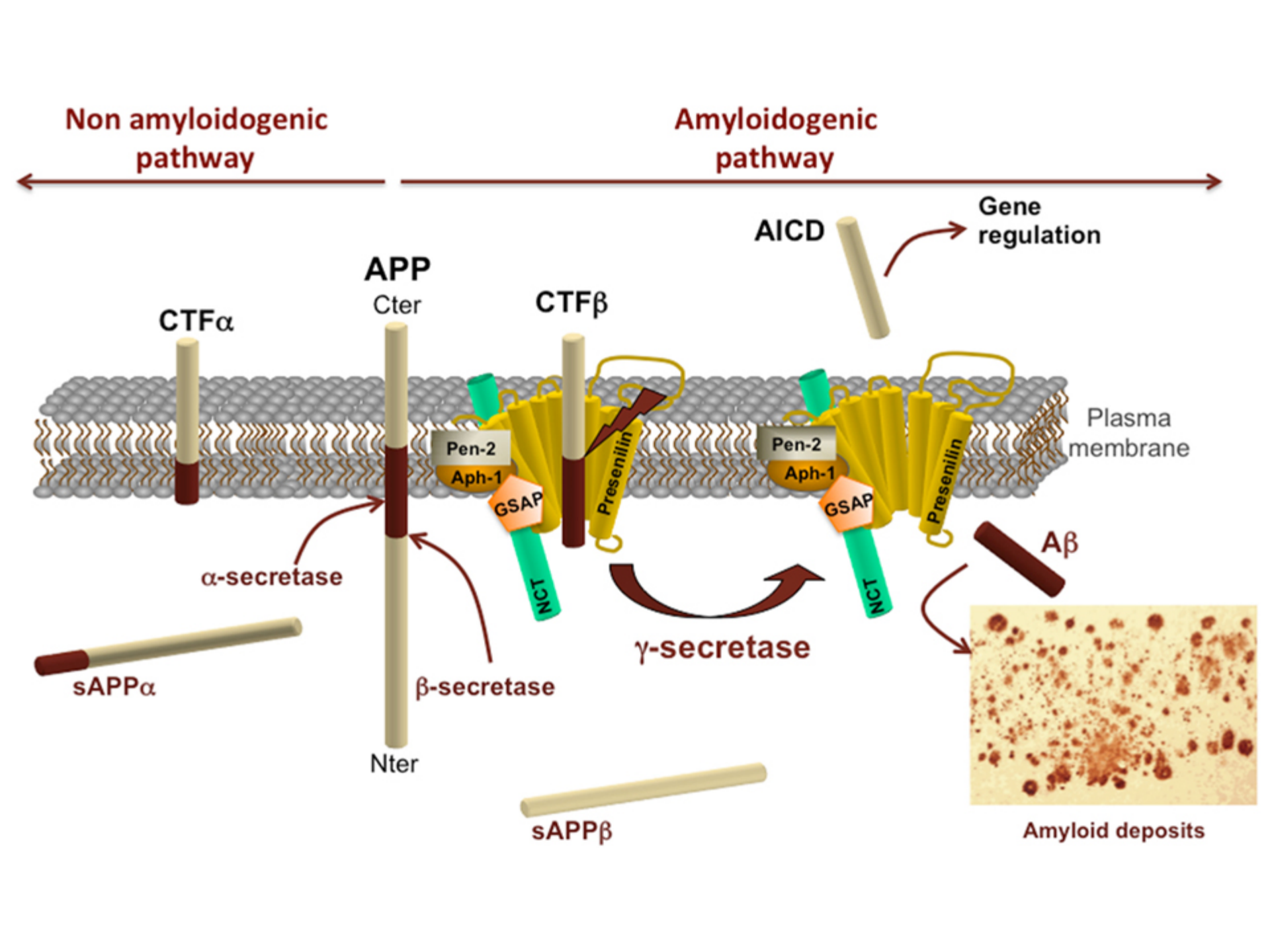


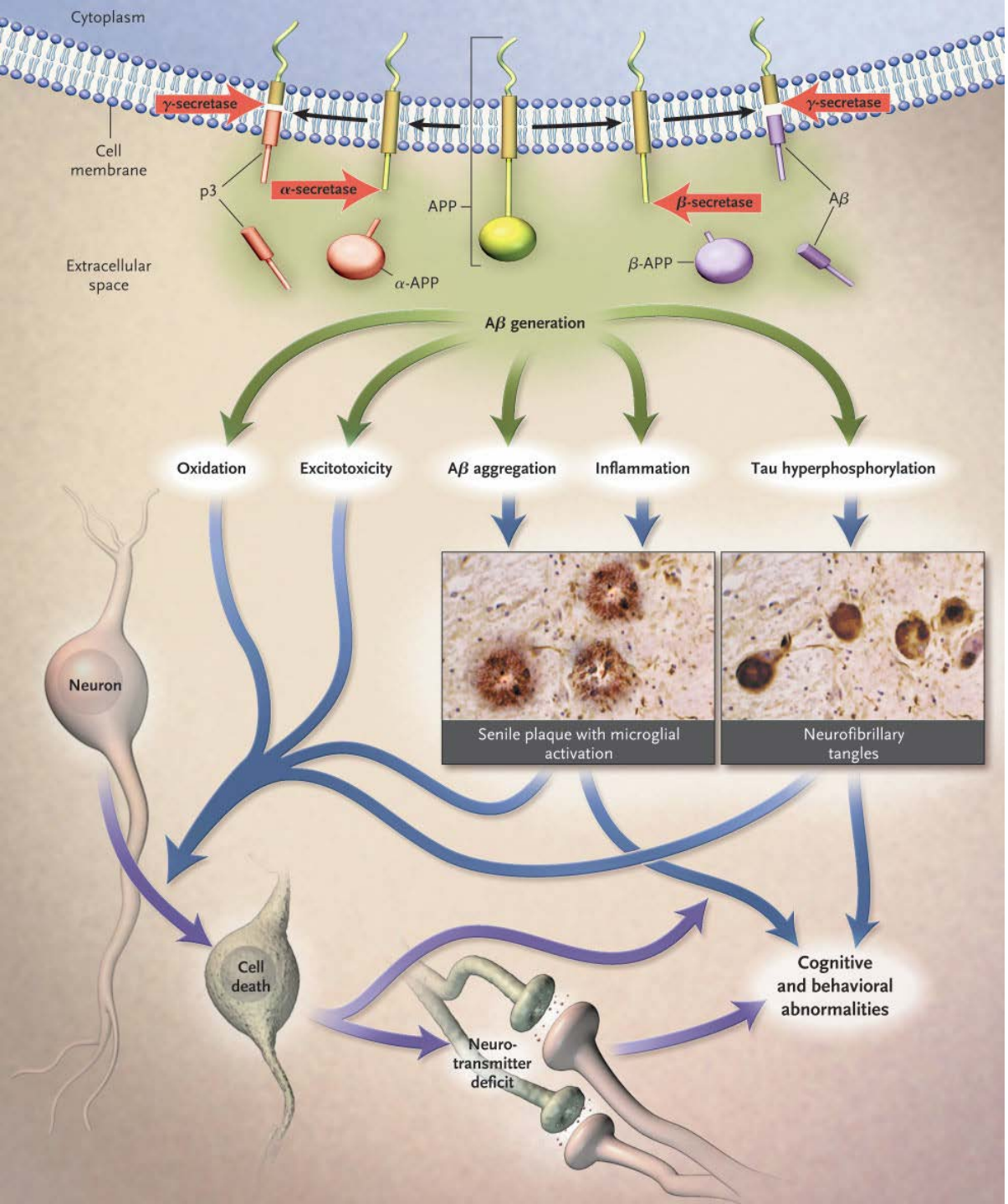
Neurogenetics (1998) 1:223–228

Original article

Histopathology and *APOE* genotype of the first Alzheimer disease patient, Auguste D.

M.B. Graeber · S. Kösel · E. Grasbon-Frodl · H.J. Möller · P. Mehraein


Non amyloidogenic pathway
Amyloidogenic pathway
AICD
Gene regulation
APP
Cter
CTFβ
CTFα
Plasma membrane
Pen-2
Aph-1
GSAP
Presenilin
NCT
Aβ
α-secretase
γ-secretase
sAPPα
β-secretase
Nter
sAPPβ
Amyloid deposits



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.

IMMUNITY & AGEING

REVIEW Open Access

Passive anti-amyloid immunotherapy in Alzheimer's disease: What are the most promising targets?

Jens Moreth, Chrystelle Mavoungou and Katharina Schindowski*

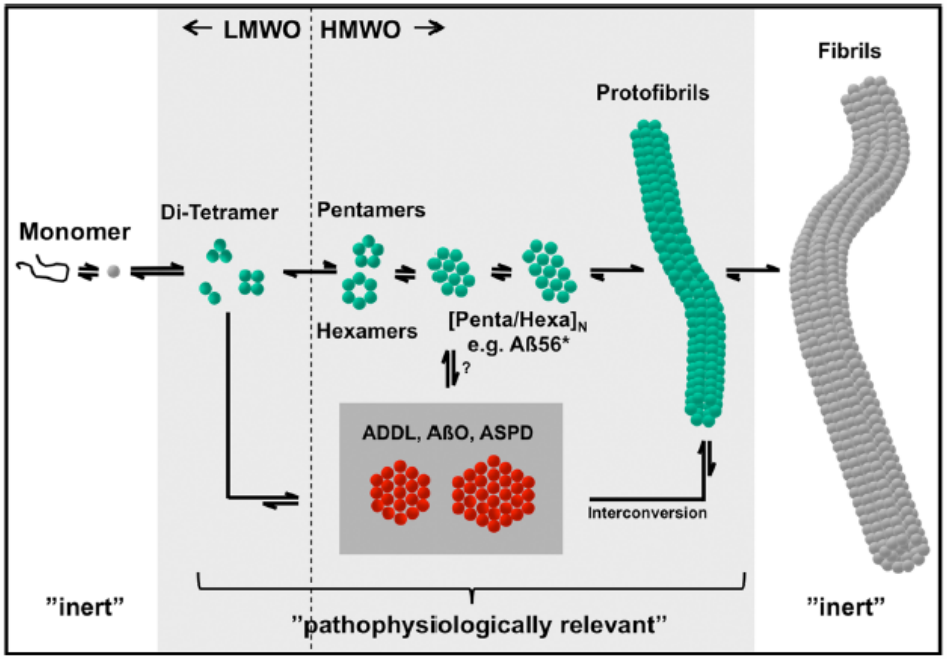


Figure 1 Pathways of aggregation and observed Aß-aggregate intermediates. Monomeric Aß folds to the activated state and then exists in rapid equilibrium with low molecular weight oligomers, which aggregate over various transient high molecular weight intermediates to matured fibrils. The definition of LMW and HMW oligomers is related to the elution profile of Aß-aggregates in size exclusion chromatography, revealing two predominant peaks at the exclusion limit (>60 kDa) and at the void volume (4-20 kDa), respectively. The HMW intermediates comprise pentamers, hexamers and multiples thereof, finally forming protofibrils, which are the precursors for multi-stranded ribbons of matured fibrils. Further neurotoxic aggregate species e.g. AßO, ADDL and ASPD are believed to aggregate over alternative pathways but preliminary data revealed that these are able to converge into the other pathways of aggregation (inter-conversion). Interestingly, every change in the experimental paradigm can provoke this aggregate conversion. Therefore, one might assume that many different aggregates coexist and, thus, neurotoxicity can be attributed to several pathogenic modes of action. Monomers and fibrils are believed to be biologically inert; however fibrils are able to collapse into protofibrils and then also reveal toxicity. The broad range of prefibrillar aggregates have been reported as pathophysiologically relevant in AD.

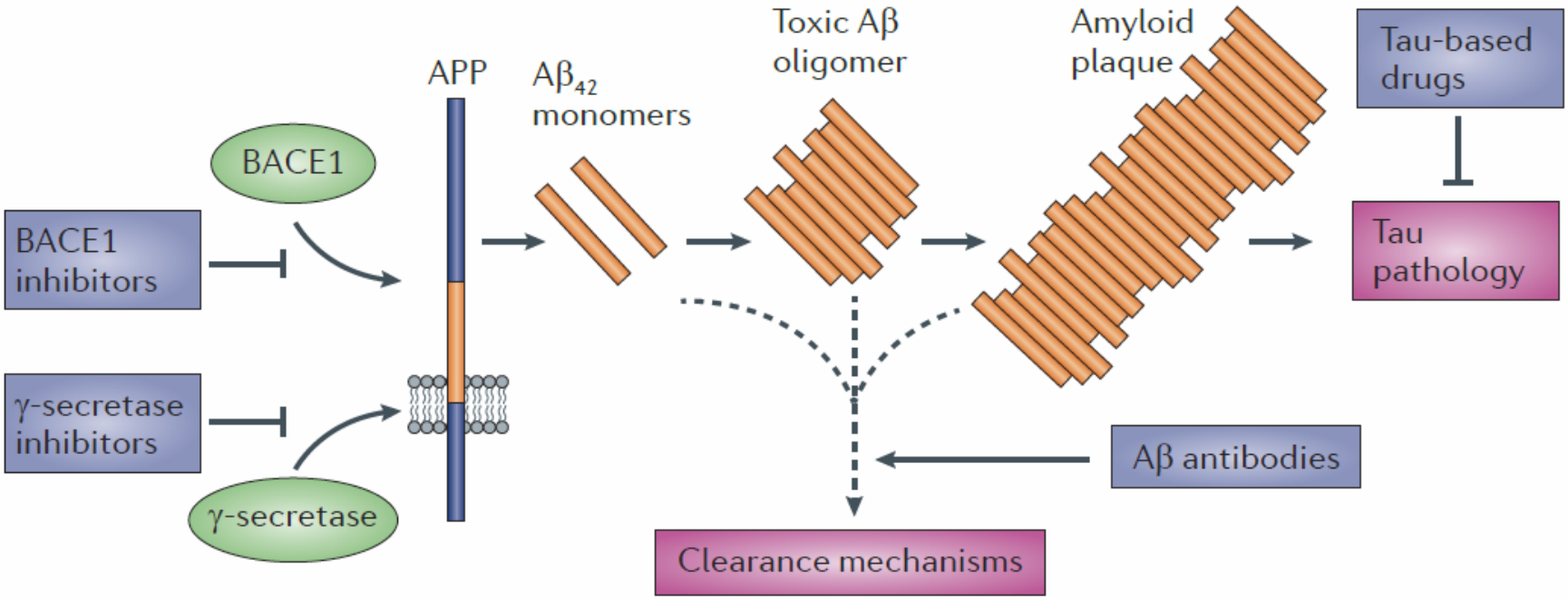


Figure 1 | **The amyloid cascade and therapeutic points of intervention.** The amyloid precursor protein (APP) is cleaved sequentially by β-secretase (also known as BACE1) and γ-secretase, releasing various amyloid-β (Aβ) peptides. The aggregation-prone $A\beta_{42}$ isoform can exist as monomers, oligomers and as amyloid plaques, which trigger downstream effects including tau hyperphosphorylation. BACE1 and γ-secretase inhibitors prevent the production of Aβ, whereas monoclonal antibodies (mAbs) — which can target different isoforms of Aβ — promote clearance. Vaccines could drive an immune system response that would clear Aβ, and tau-based therapies may moderate downstream effects of toxic build-up. Figure modified, with permission, from Citron, M. Alzheimer's disease: strategies for disease modification. *Nature Rev. Drug Discov.* **9**, 387–398

Teràpia antiamiloide

- Reducció APP:↓ modulació de la síntesi RNAm APP
- Activació α-secretasa
- Inhibició BACE-1 (β-secretasa)
- Inhibició γ-secretasa
- Antiagregació monòmers Aβ
- Immunoteràpia:
  - vacunació
  - anticossos monoclonals
  - Immunoglobulines

Inhibició β-secretasa

- Inhibició de BACE 1 (β-site APP cleaving enzime).
- Regulació negativa de β-secretasa, enzim que inicia la via amiloidogènica.
- Estudis fase III amb tiazolidinediones: Rosiglitazona i Pioglitazona (ADO-tipo 2). No eficàcia.

- Estimulació del receptor PPAR-gamma (nuclear peroxisome proliferator-activated receptor) que promou degradació de PPA per augment de la seva ubiquitinització.
- Redueixen la concentració d'insulina perifèrica (hiperinsulinèmia) que competeix amb Aβ per la seva degradació per *insulin degrading enzyme*.

Inhibició γ-secretasa

- R-flurbiprofèn (MPC-7869) (Tarenflurbil)
  - Selective Aβ42 lowering agent . Modula activitat γ-secretasa i redueix producció Aβ42 però no Aβ40
  - Fase II: "Efecte modest" sobre les AVD a dosis de 800 mg (Wilcock, Lancet Neurology, 2008)
  - Fase III: MA lleu, n=1700, 18 mesos, 800 mg, ADAS-Cog, ADCS-ADL, NR (Green, JAMA, 2009)

- Semagacestat LY450139
  - Fase II segur a dosis 140 mg/24 h. ADAS-Cog NR (Fleisher, Arch Neurology, 2008)
  - Fase III: n=1537 (100-140 mg/d). ADAS-Cog , ADCS-ADL, NR (càncer pell, infeccions (Doody et al, NEJM 2013)

- Avagacestat (BMS-78163)
  - Fase 2 safety trial (Dockens, Clin Pharmacokinet, 2012)

Antioligomerització.
Antiagregació de fibril.les.

- Tramiprosat (Homotaurina, Alzhemed)
  - Fase 3. MA lleu-moderada, n=1052, ADAS-Cog. NR.
    (Alphase Study, USA. Aisen, Arch Med Sci, 2011)

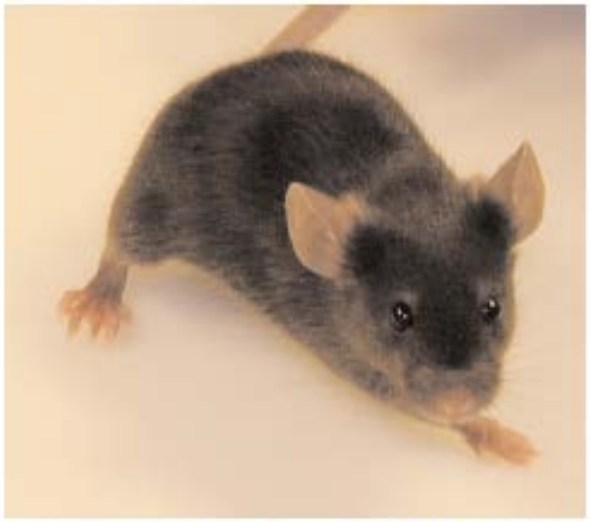
- PBT2-metal protein attenuating compound
  - Cu^{2+}/Zn^{2+} mediated toxic oligomerisation
  - Fase 2 (Lannfelt, Lancet Neurol, 2008)

- ELND005 scyllo inositol
  - Inhibition of Aβ42 peptide aggregation and formation of Aβ fibrils
  - Fase 2 (Salloway , Neurology, 2011). Alta tasa d'infeccions.

Amyloid β vaccination: reduced plaques and improved cognition

Studies in three different transgenic mouse models suggest that the amyloid β-protein contributes to memory loss in Alzheimer disease. Immunization with an amyloid β-peptide fragment reduces learning and memory impairments in mice, and this approach may eventually be used to prevent and/or treat this disease in people.

STEVEN G. YOUNKIN



Memory deficits in Tg2576 transgenic mice, which overexpress mutant APP, can be reversed by $A\beta_{42}$ vaccination.

NATURE MEDICINE • VOLUME 7 • NUMBER 1 • JANUARY 2001

Vacuna

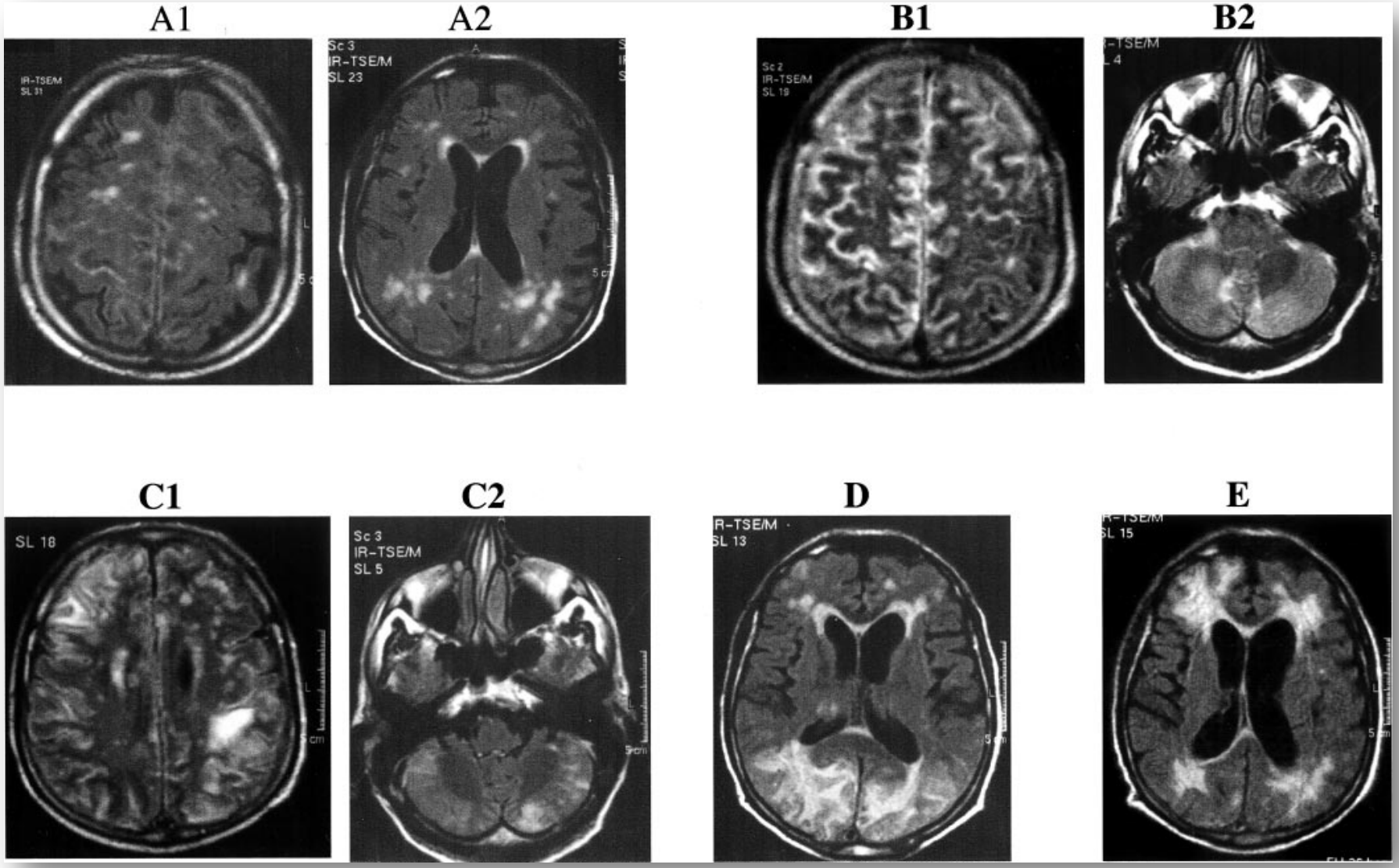
Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial

by S. Gilman, M. Koller, R. S. Black, L. Jenkins, S. G. Griffith, N. C. Fox, L. Eisner, L. Kirby, M. Boada Rovira, F. Forette, and J. -M. Orgogozo

- Fase IIa. Immunització activa amb Aβ 1-42 humana (AN 1792) + QS 21
- MA lleu (ADAS-Cog, DAD, CDR, MMSE, CGI-C)
- Els pacients amb títols elevats d'anticossos van millorar la memòria (NTB) y van tenir descens de tau a LCR
- No resposta clínica
- Meningoencefalitis (6%)

Neurology
Volume 64(9):1553-1562
May 10, 2005

AMERICAN ACADEMY OF NEUROLOGY



Orgogozo et al. (2003) Neurology, 61, 46-54

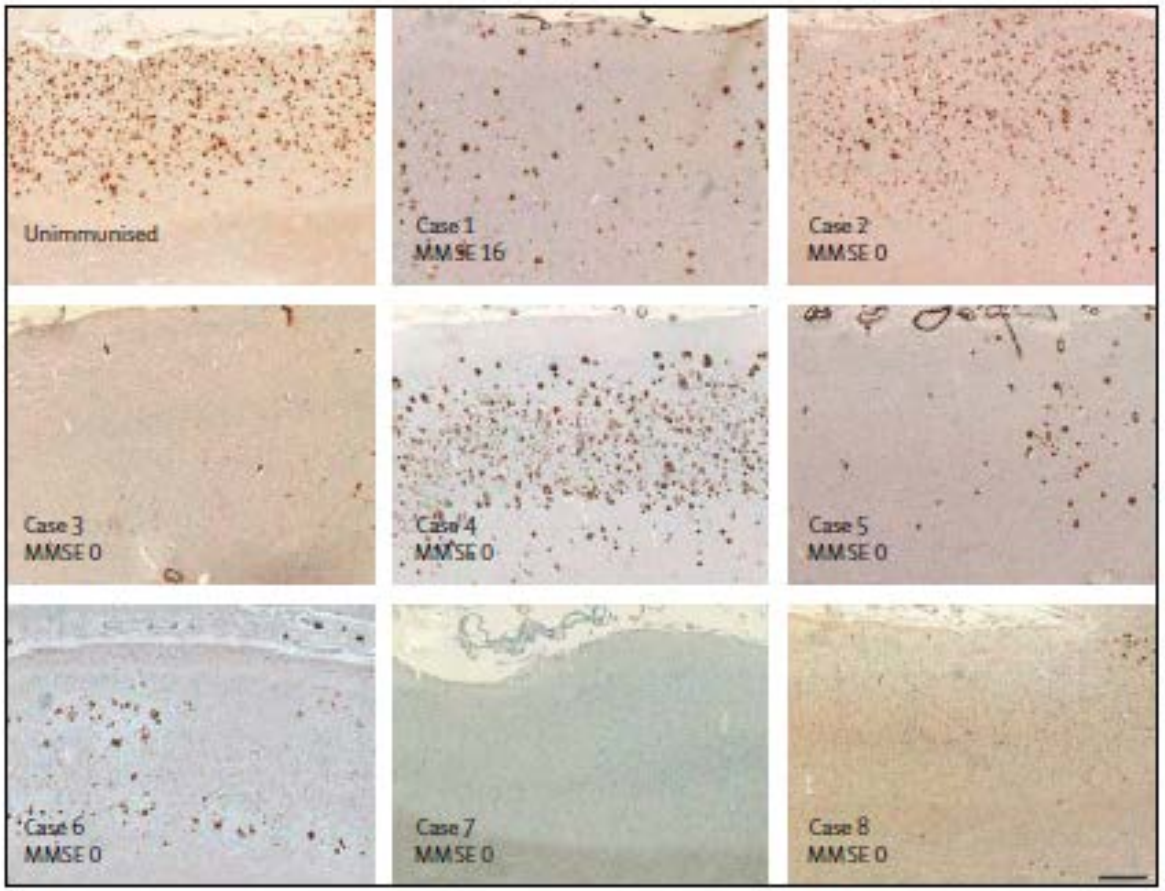


Figure 2: **Histological patterns of Aβ in the temporal lobe neocortex after immunisation with AN1792**
An unimmunised control (top left) has a high density of plaques. Cases 1–8 are all patients who were immunised with $Aβ_{42}$. Case 1 died 4 months after the first immunisation dose and showed an early stage of Aβ removal. Cases 2–8 survived 20–64 months after first immunisation dose. Case 2 did not develop anti-Aβ antibodies and showed no evidence of plaque clearance. Cases 3–6 showed an intermediate range of plaque clearance. Cases 7 and 8 showed very extensive (case 8) to nearly complete (case 7) removal of Aβ plaques throughout the cerebral cortex. All the long-term survivors (ie, cases 2–8) continued to have progressive dementia with cognitive function declining to an unrecordable level (ie, MMSE=0) before death. Scale bar=0·5 mm.

Holmes et al., Lancet 2008; 372: 216-23

Noves vacunes en estudi

- Dissenyades per reduir la resposta immunitària cel.lular Th1
- Modificacions en la presentació de l'antigen Aβ (immunògens alternatius)
  - Formes solubles d'Aβ (immunògens no fibril.lars)
  - Codificació vial del fragment Nt d'Aβ
  - Pèptids similars a epítops d'Aβ
- Noves vies d'administració (oral, nasal, transcutània)

Noves vacunes en estudi

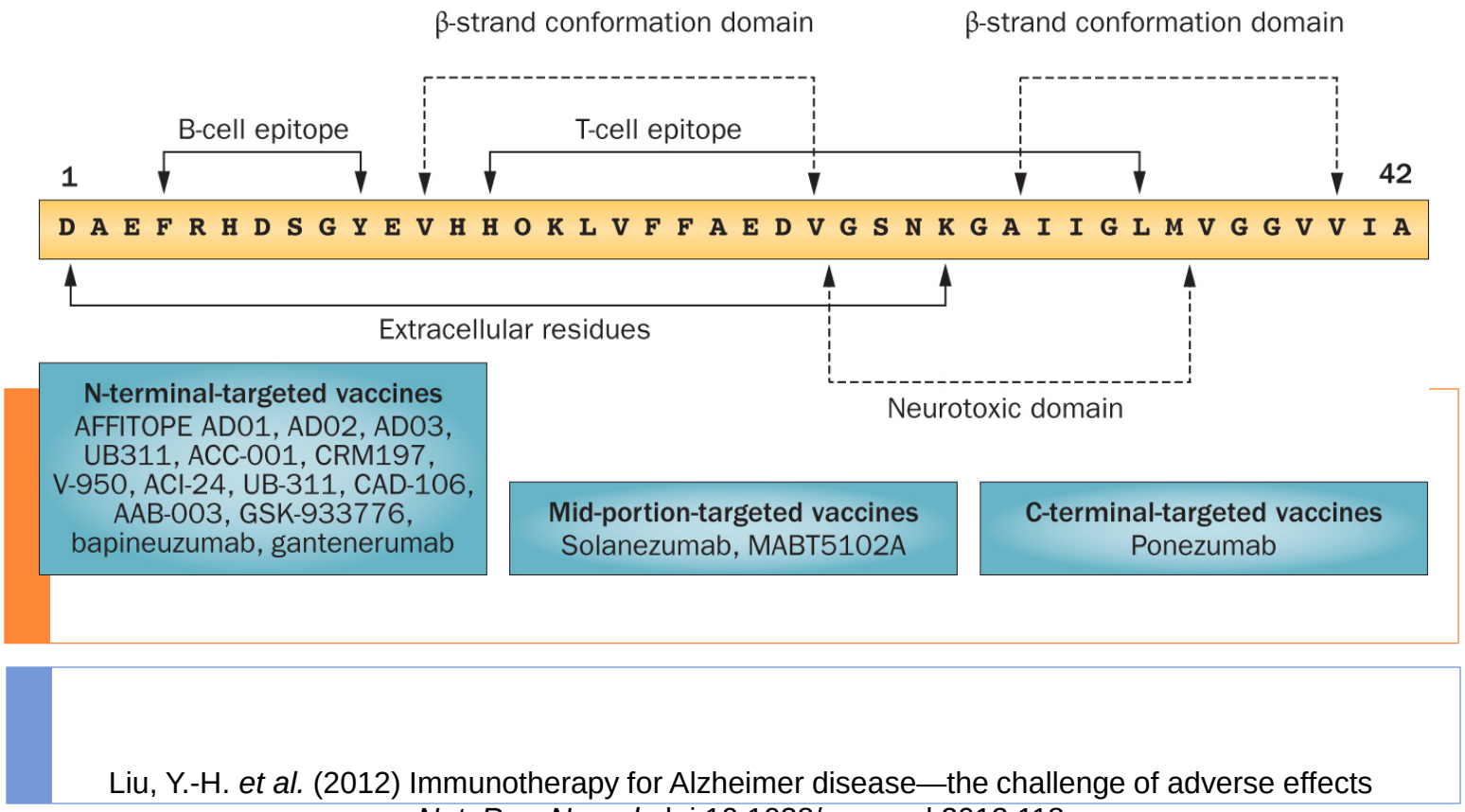
- CAD 106 (Novartis) Aβ 1-16: fase II
- ACI 24 (AC Immune) Aβ 1-15: fase II
- AFFITOPE AD-02 (GSK): fase II (finalitzat, no resultats)
- ACC-001 (Pfizer): fase II
- UB-311 (United Biomedical): fase II
- V950 (Merck): fase II
- ACI24: fase II, LuAF20513: fase I

Anticossos monoclonals

- Els ratolins transgènics tractats amb m-ab antiAβ mostren reducció de nivells cerebrals d'Aβ, de plaques senils i millora cognitiva respecta a placebo.
- m-ab evadeixen resposta Th1.
- Difereixen en l'epítop reconegut de l'Aβ (regió N-terminal 1-10, central 17-32 i C-terminal 32-42).
- Mecanisme d'acció no ben conegut:
  - Desagregació dels agregats Aβ
  - Activació de FC → activació microglial → destrucció PS
  - Unió perifèrica a Aβ (*peripheral sink*)

Primera generació (Bapineuzumab) va causar ARIA (Amyloid related imaging abnormalities), més freqüents a ApoE4.

Figure 2 Epitopes of the amyloid-β (Aβ) peptide sequence



Liu, Y.-H. *et al.* (2012) Immunotherapy for Alzheimer disease—the challenge of adverse effects
Nat. Rev. Neurol. doi:10.1038/nrneurol.2012.118

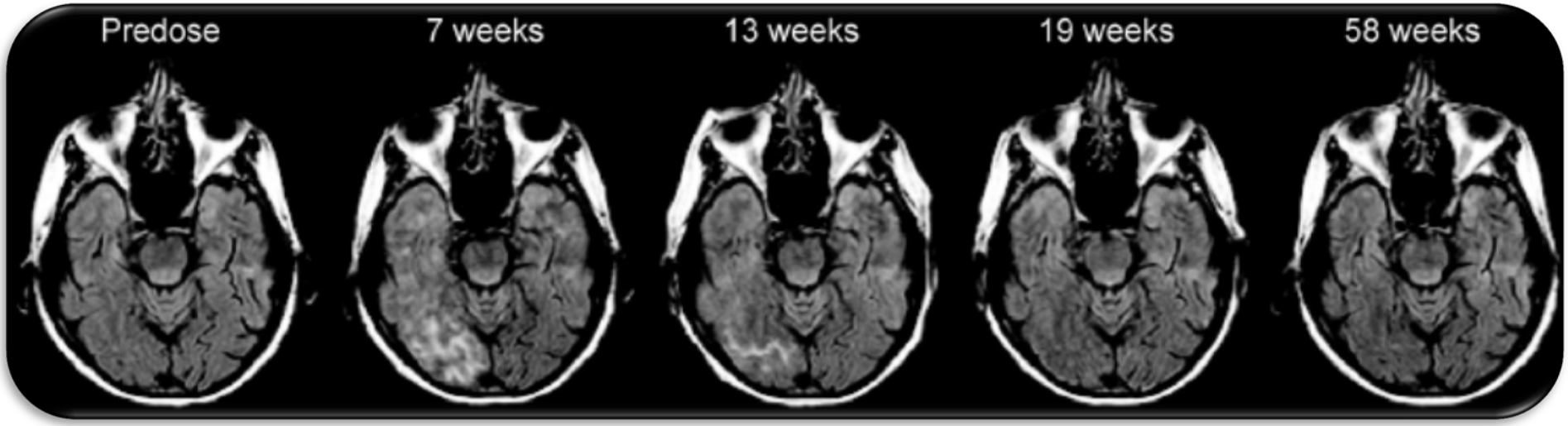
nature REVIEWS NEUROLOGY

Anticossos monoclonals

- Bapineuzumab (AAB-001, Pfizer)
  - IgG_1 humanitzada contra Nt (Aβ 1-5). Fibril.lar > soluble.
  - Fase II: aparició d'ARIA (edema vasogènic i microhemorràgies, sobretot portadors E4) (Salloway 2009)
  - Fase III: estudis descontinuats el 2012 per NR primary endpoints
  - AAB-003 en MA lleu-moderada, fase I (NCT01193608, NCT01369225; finalitzats, no resultats)

- Solanezumab (Lilly)
  - m-ab contra epítop central (Aβ13-28). Aβ soluble.
  - Fase II: NR en ADAS-Cog, CSF-tau i PET-PiB
  - No ARIA
  - TRIAL PROGRAM. Fase III EXPEDITION 1,2: n=2050, MA lleu-moderada. Primary endpoints: NR (subanàlisi grup MMSE 20-26: 34% millora f. cognitiva però ↑Aβ plasma, CSF-tau, volum hipocampal, PET-PiB). Letàrgia, exantema, malestar (no edema vasogènic)
  - Fase III ongoing en MMSE>20 (EXPEDITION-EXT NCT01127633 / EXPEDITION 3 NCT01900665) Nov 2018
  - A4 Study

Edema vasogènic en pacients tractats amb bapineuzumab



)

This 69-year-old woman is an APOE 4 homozygote who was treated with bapineuzumab 1.0 mg/kg IV. She remained asymptomatic despite the appearance of multiple areas of VE evident on the MRI. The VE was apparent on MRI by 7 weeks after her first infusion and resolved by 19 weeks. The patient was redosed at 0.5 mg/kg of bapineuzumab IV and followed for over 2 years without recurrence of VE.

Salloway et al., Neurology 2009; 73: 261-70

Anticossos monoclonals

- Gantenerumab (Hoffman-La Roche)
  - m-ab amb afinitat subnanomolar a epítop conformacional de fibril.les (3-11 i 19-28, no soluble)
  - Fase I: reducció AB a PET - PiB fins 30%, dosi-dependent (Ostrowizki, Arch Neurol 2012)
  - Fase III: MA prodròmica, PET+, ongoing (Scarlet RoAD trial) NCT01224106
  - DIAN TU Study

- Crenezumab MABT5102A (Genentech)
  - IgG_4 anti Aβ42 (12-23)
  - Fase II 2011-2014. MA lleu - moderada (NCT 01343966)
  - API Study

IgG intravenosa

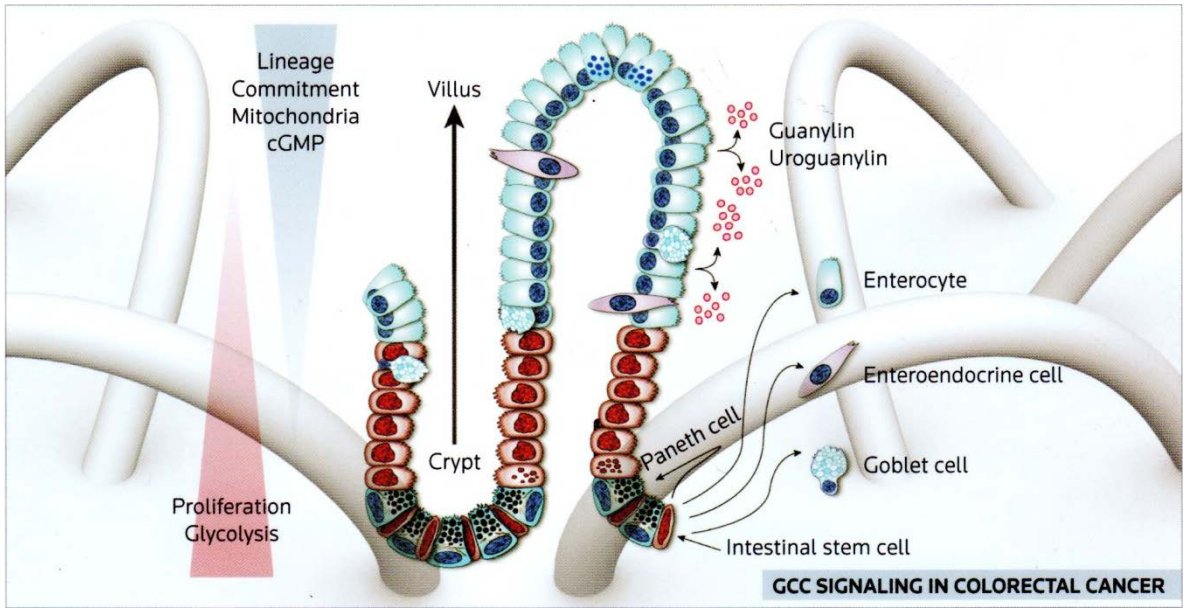
Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial

Dodel R., Rominger A., Bartenstein P., Barkhof F., Blennow K., et al.

Lancet Neurology 2013; 12: 233–43

- Fase 2. n: 89; 58 inclosos. Ac naturals anti Aβ
  - MA lleu (MMSE 16-26)
    - IgG iv 0.2-0.5-0.8 g /kg/4 setmanes
    - IgG iv 0.1-0.25-0.4 g/kg/2 setmanes
  - OOSS: ADAS-Cog, CDR, ADCS-ADL.
    12 i 24 setmanes. NR.

Fase 2: NewGam 10% IVIG (MCI) ongoing (NCT01300728)



DRUG NEWS & PERSPECTIVES

THE INTERNATIONAL DRUG NEWSMAGAZINE

REPRINTED FROM DRUG NEWS & PERSPECTIVES 2009; VOL 22(6): 325-339

AMYLOID-TARGETED THERAPEUTICS IN ALZHEIMER'S DISEASE: USE OF HUMAN ALBUMIN IN PLASMA EXCHANGE AS A NOVEL APPROACH FOR Aβ MOBILIZATION

Boada, M., Ortiz, P., Anaya, F., Hernandez, I.

(AMBAR study NCT01561053)

HEALTHCARE & SCIENCE

THOMSON REUTERS

PERSPECTIVE

Resolving controversies on the path to Alzheimer's therapeutics

nature medicine

Dennis J Selkoe

Alzheimer's disease constitutes a personal and societal tragedy of immense proportions. Since 1960, research in laboratories and clinics worldwide has elucidated many features of this insidious and ultimately fatal syndrome, and this progress has led to initial human trials of potentially disease-modifying agents. However, some of these agents have already failed. Gnawing controversies and important gaps in our knowledge seem to cast additional doubt on the ability of the field to move forward effectively. Here I discuss some of these looming concerns and offer possible explanations for the major trial failures that suggest they are not predictive of the future. Rigorous preclinical validation of mechanism based therapeutic agents followed by meticulously designed trials that focus on the cardinal cognitive symptoms and their associated biomarkers in the mild or presymptomatic phases of Alzheimer's disease are likely to lead to success, perhaps in the not-too-distant future.

Biochemical Pharmacology 85 (2013) 289–305

Contents lists available at SciVerse ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

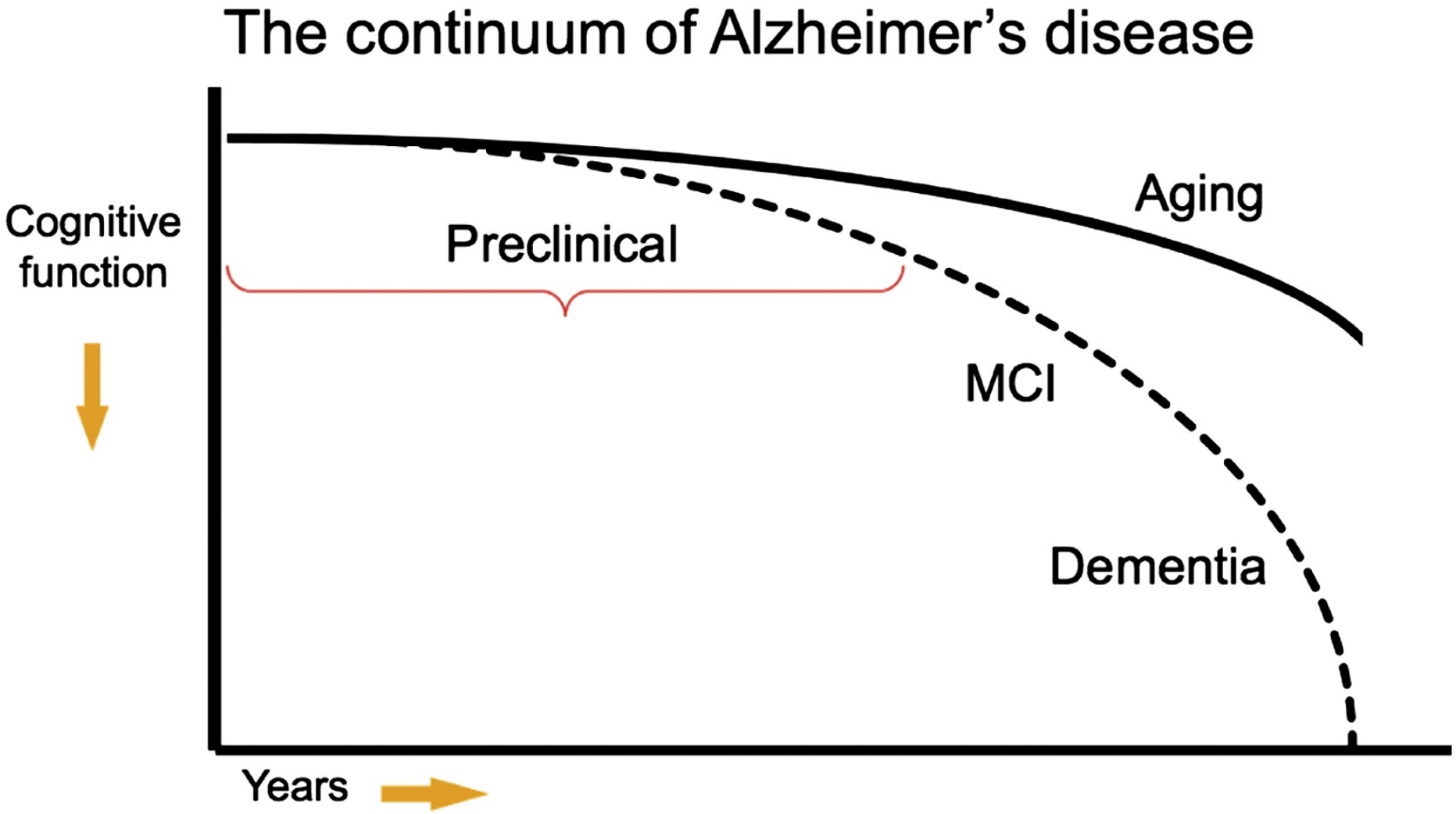
Alzheimer's therapeutics: Continued clinical failures question the validity of the amyloid hypothesis—but what lies beyond?

Kevin Mullane [a], Michael Williams [b,*]

No resposta a la immunoteràpia

- Motius:

1. No es produeix una eliminació prou important d'Aβ del SNC.
2. La hipòtesi de la cascada és falsa.
3. El dipòsit d'Aβ és molt precoç, comença molts anys abans de la clínica.



The hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. ***C. Jack et al.***, *Lancet Neurology 2010; 9: 119–28*

ELSEVIER

Alzheimer's & Dementia 9 (2013) 123–131

Alzheimer's & Dementia

Perspectives

Can we prevent Alzheimer's disease? Secondary "prevention" trials in Alzheimer's disease

Maria C. Carrillo[a,*], H. Robert Brashear[b], Veronika Logovinsky[c], J. Michael Ryan[d], Howard H. Feldman[e], Eric R. Siemers[f], Susan Abushakra[g], Dean M. Hartley[a], Ronald C. Petersen[h], Ara S. Khachaturian[i], Reisa A. Sperling[j]

Table 2

Upcoming Trials for Preventive Immunotherapies.

Name	Drug Used vs. Placebo	Patient Group	Trial Start Date	Responsible Party
Dominantly Inherited Alzheimer Network (DIAN)	Use of three different dugs: gantenerumab *, solanezumab *, beta-secretase (BACE) inhibitor	Families with carriers for autosomal dominant Alzheimer's disease	Early 2013	Washington University School of Medicine
Treatment of Asymptomatic Alzheimer (A4)	Solanezumab *	Clinically older individuals with amyloid positive PET scan	Mid 2013	Harvard Medical School and Brigham and Women's Hospital, Boston, MA
Alzheimer Prevention Initiative (API)	Crenezumab *	cognitively healthy individuals who are cariers for genes causing familial Alzheimer's disease	Early 2013	Banner Alzheimer's Institute, Phoenix, AZ

Anti-Amyloid treatment for Asymptomatic AD (A4)

- Pacients de més de 65 a
- N: 1.000
- PET-PIB +
- MMSE : 27-30, cognitivament normals CDR: 0
- Solanezumab
- Primary Outcome: avaluació cognitiva
- 2014-2020

Dominanty Inherited Alzheimer Network (DIAN-TU)

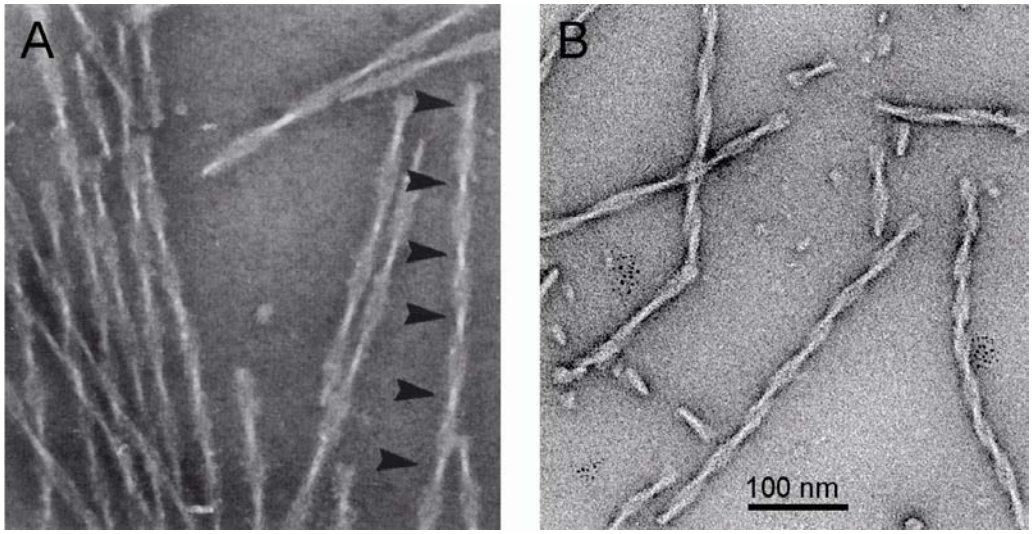
- Pacients de 18 – 80 a.
- N: 160
- Portadors de mutacions genètiques AD o al 50% de risc.
- -15 a +10 anys de l' inici parental
- CDR: 0-1
- Solanezumab, ganterezumab, inh. BACE1
- 2012-2017

Alzheimer Preventive Therapy API

- N: 300
- Edad > 30 a.
- PS1 E280A, Antioquía (Colombia)
- Cognitivament normals
- Ac monoclonal: Crenezumab
- 5 a de tractament
- Biomarcadors i clínica
- Ongoing, set 2020

Patologia tau i Malaltia d'Alzheimer

- Tau és una proteïna soluble citoplasmàtica que està unida a la tubulina durant la seva polimerització, estabilizant els microtúbuls
- Hi han 6 isoformes de tau en el SNC, de 352 a 441 residus
- La seva funció és estabilitzar els microtúbuls pel transport axonal i en el citoesquelet pel seu creixement
- Major correlació amb el dèficit cognitiu que la patologia Aβ
- Pocs estudis terapèutics sobre tau

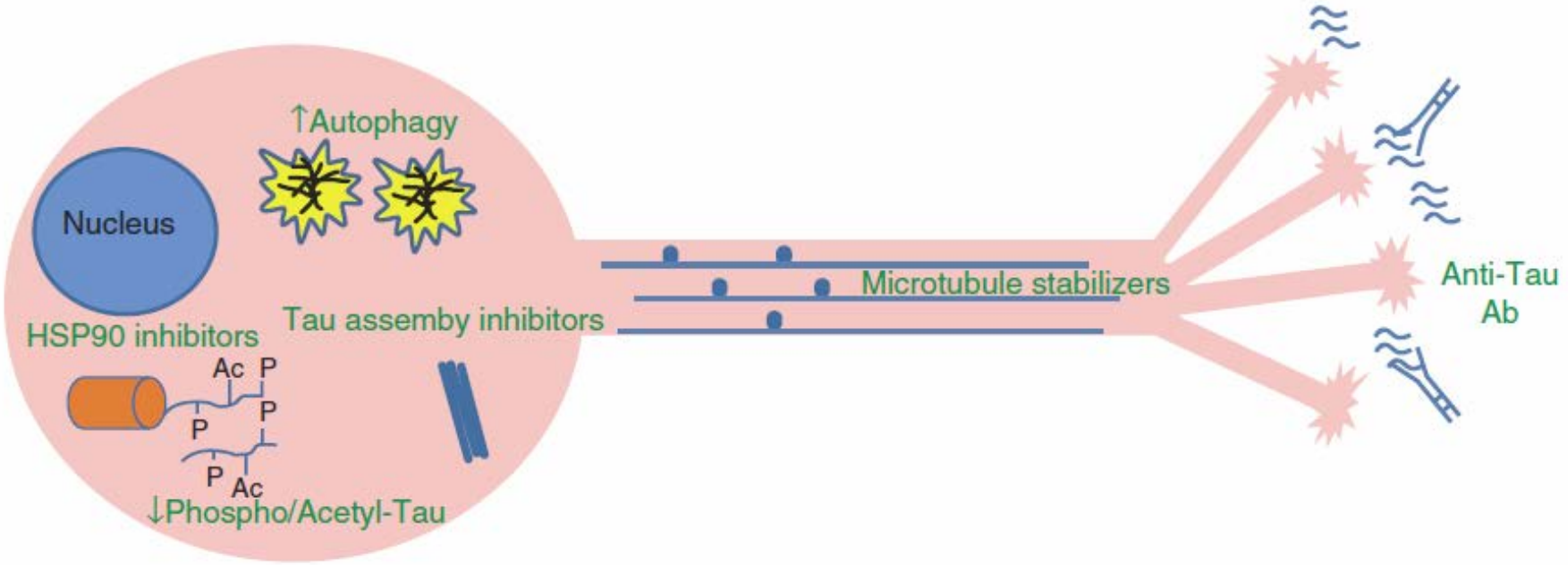


Developing Therapeutic Approaches to Tau, Selected Kinases, and Related Neuronal Protein Targets

Virginia M-Y. Lee[1], Kurt R. Brunden[1], Michael Hutton[2], and John Q. Trojanowski[1]

[1]Center for Neurodegenerative Disease Research, Institute on Aging, Department of Pathology and Laboratory Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

[2]Eli Lilly and Co., Indianapolis, Indiana 46285



Cold Spring Harbor Perspectives in Medicine

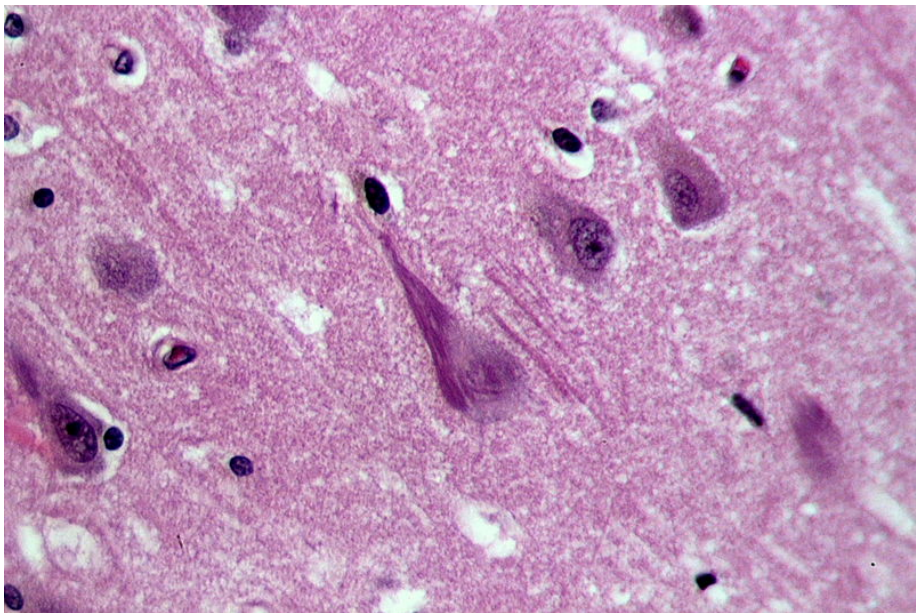
www.perspectivesinmedicine.org

Estratègies sobre tau

- 1. Modulació de la fosforil.lació

  Inhibidors de les fosforil.lases (tau-kinases)

  Activadors de les fosfatases
- 2. Antiagregant de tau
- 3. Estabilizadors dels microtúbuls
- 4. Immunoteràpia

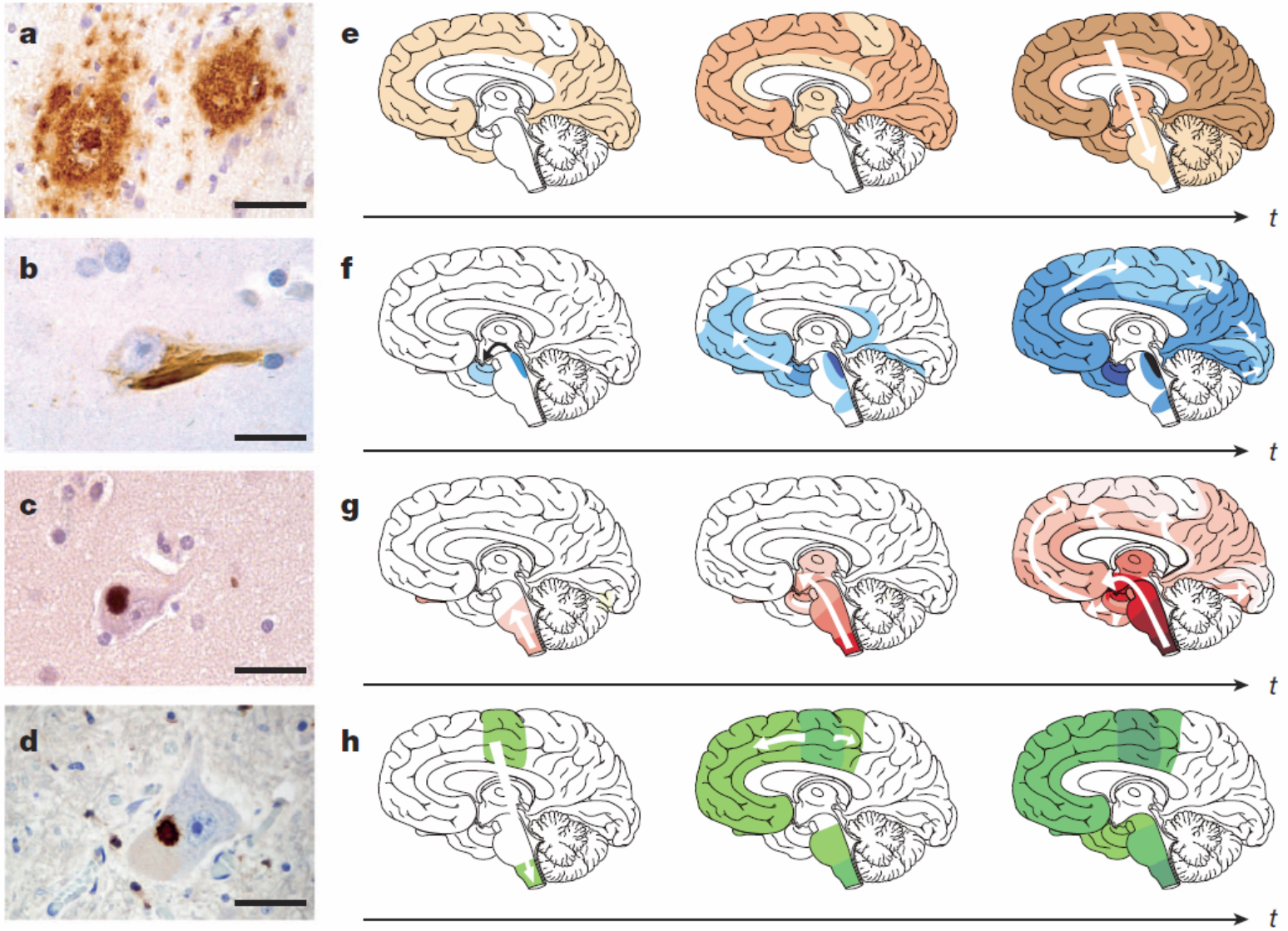


Immunoteràpia anti-tau

- Primera vacunació en el model de ratolí JNPL3-P301L amb tau fosfopèptid de 30 aa incloent PSer 396 i 404 (Asuni 2007)
- Immunització passiva amb m-Ab PHF1, que reconeix PSer 396 i 404 de tau
- AADvac1: vacuna contra epítops de tau que regulen interacció tau-tau (interregulatory domains tau-tau interaction) o punts d'unió entre oligòmers de tau evitant la seva agregació o polimerització (NCT02031198,
- NCT01850238: fase I, ongoing)

Self-propagation of pathogenic protein aggregates in neurodegenerative diseases

Mathias Jucker[1,2] & Lary C. Walker[3,4]



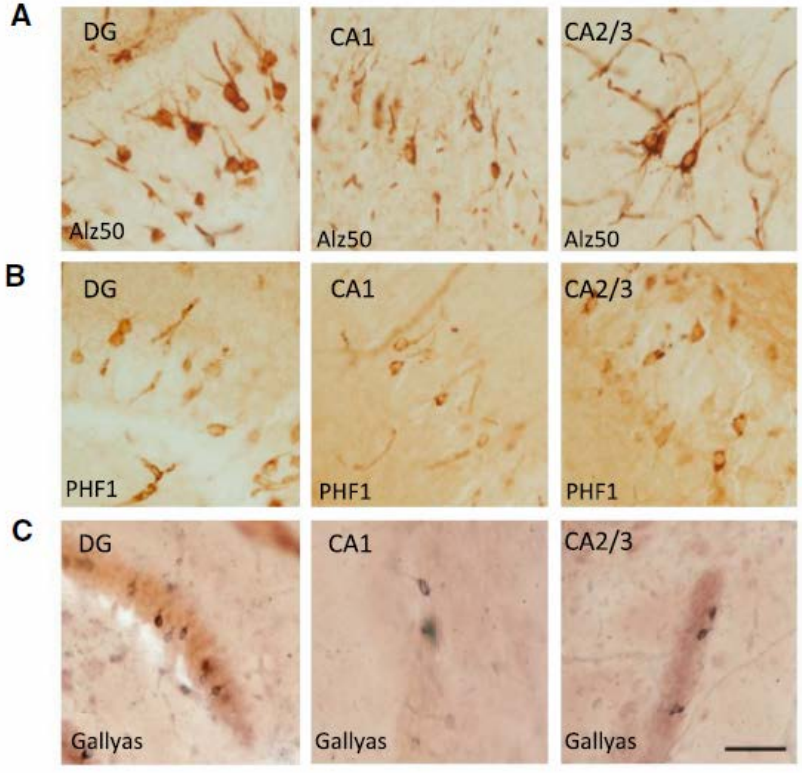
Nature 2013

Neuron
Article

Propagation of Tau Pathology in a Model of Early Alzheimer's Disease

Alix de Calignon,[1,2,8] Manuela Polydoro,[1,8] Marc Suárez-Calvet,[1,3] Christopher William,[1] David H. Adamowicz,[1] Kathy J. Kopeikina,[1,4] Rose Pitstick,[5] Naruhiko Sahara,[6] Karen H. Ashe,[7] George A. Carlson,[5] Tara L. Spires-Jones,[1] and Bradley T. Hyman[1,*]

Neuron 73, 685–697, February 23, 2012



Neuron
Article

Anti-T
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Kiran Yanam
David F. Woz

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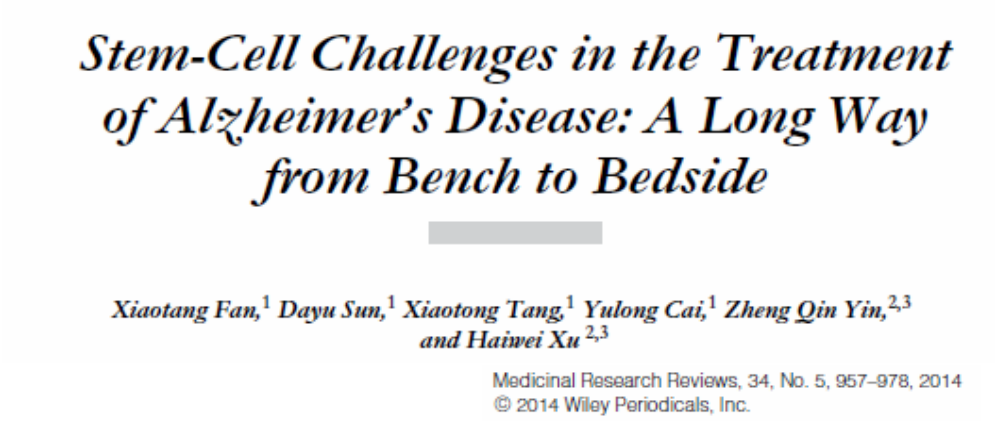
athology

gmei Ma,[1,2,3] Susan E. Maloney,[4]

Neuron 80, 402–414, October 16, 2013



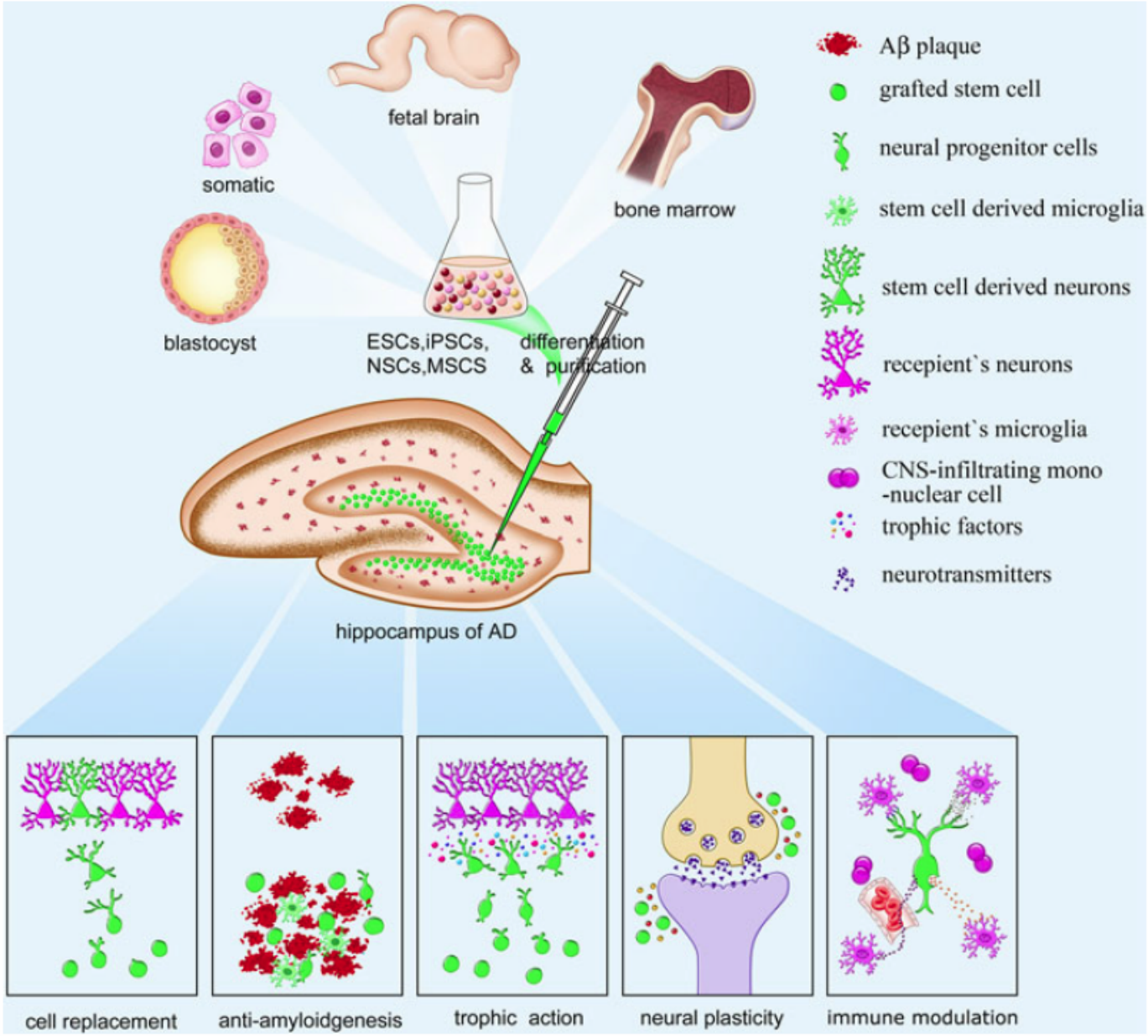
Stem-Cell Challenges in the Treatment of Alzheimer's Disease: A Long Way from Bench to Bedside

Xiaotang Fan,[1] Dayu Sun,[1] Xiaotong Tang,[1] Yulong Cai,[1] Zheng Qin Yin,[2,3] and Haiwei Xu [2,3]

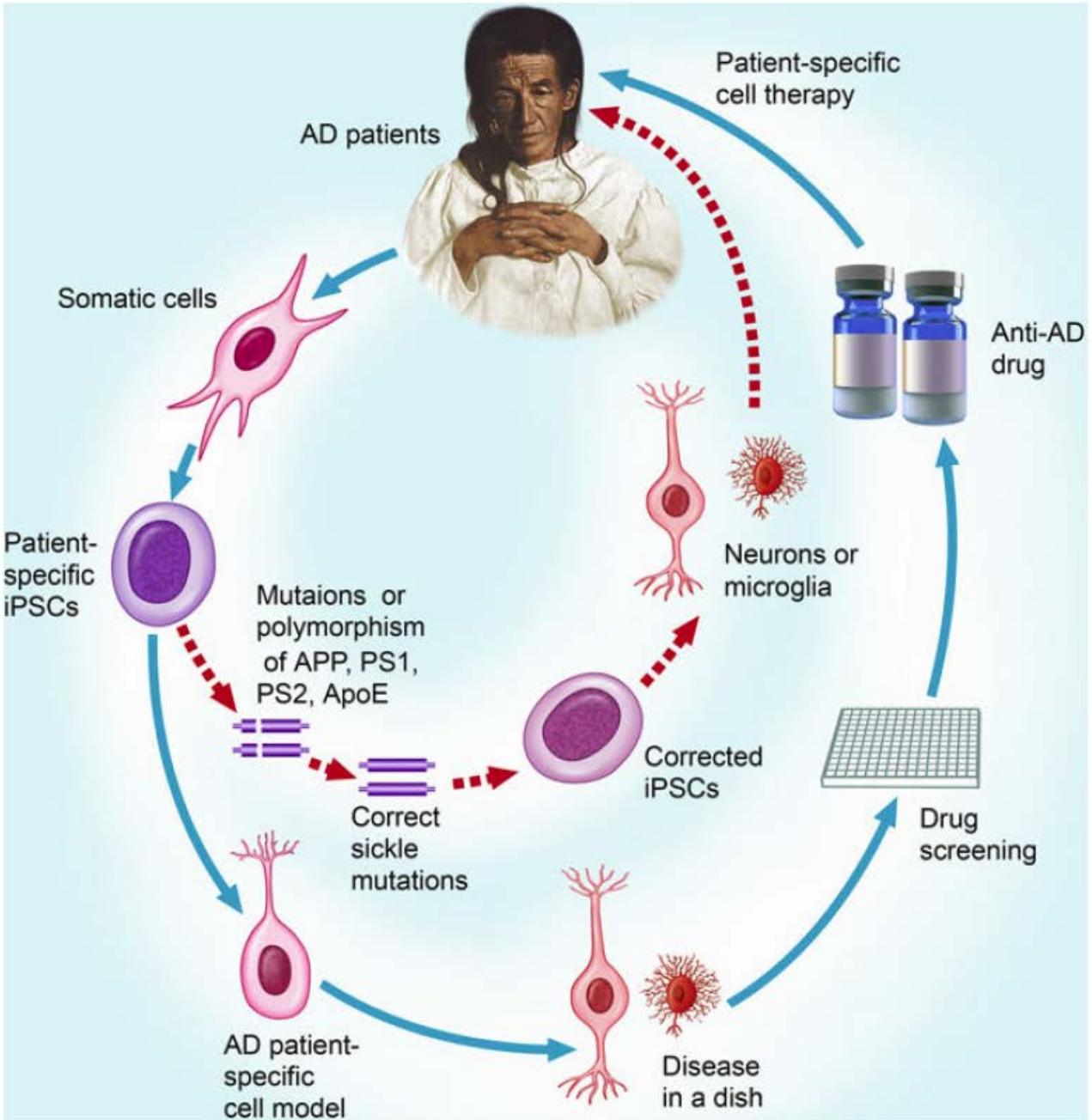
Medicinal Research Reviews, 34, No. 5, 957–978, 2014

- CM específiques de teixit
  - Neuronals
  - Mesenquimals (medul.la òssia, cordó umbilical)
  - Embrionàries (blastocists)

- CM pluripotencials induïdes(iPSC) reprogramades des de cèl.lules somàtiques:
  - Es poden obtenir de fibroblasts autòlegs
  - Poden generar tipus cel.lulars de les 3 capes germinals
  - Gran capacitat de proliferació amb menor tumorigènesi


fetal brain
somatic
bone marrow
blastocyst
ESCs,iPSCs,
NSCs,MSCS
differentiation
& purification
hippocampus of AD
Aβ plaque
grafted stem cell
neural progenitor cells
stem cell derived microglia
stem cell derived neurons
recepient`s neurons
recepient`s microglia
CNS-infiltrating mono
-nuclear cell
trophic factors
neurotransmitters
cell replacement
anti-amyloidgenesis
trophic action
neural plasticity
immune modulation

STEM-CELL CHALLENGES IN AD



Resum

- Estudi LipidiDiet (Souvenaid®) en MA prodròmica (juny 2015).
- Scarlet RoAD (Gantenerumab) en MA prodròmica (des 2015).
- Estudi AMBAR (plasmafèresi + Ig) (des 2016).
- Estudis EXPEDITION EXT i EXPEDITION 3 (Solanezumab). MA amb MMSE >20 (nov 2018).
- Prevention Trial Studies DIAN-TU (2017), A4 (2020), API (2020).
- Vacunes anti-Aβ (fases I i II). Vacuna anti-tau AADvac1 (fase I).
- Bloqueig transinàptic de tau, cèl.lules mare… (animals)

A practical algorithm for managing Alzheimer's disease: what, when, and why?

Jeffrey L. Cummings[1], Richard S. Isaacson[2], Frederick A. Schmitt[3] & Drew M. Velting[4]

Box 1. *Recommendations for maintaining brain health in elderly patients with and without AD*

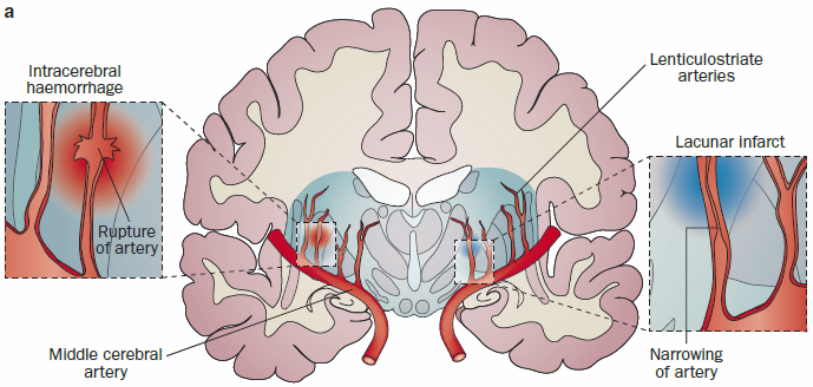
- Consider following a Mediterranean-style diet, with fish, vegetables, legumes, fruit, cereals, unsaturated fatty acids (e.g., olive oil), and a limited amount of meat or dairy products.
- Consider taking supplements containing omega-3 (particularly docosahexaenoic acid), B-complex vitamins (including B12, B6, folic acid), and vitamin E.
- Keep alcohol intake to a low-to-moderate level (e.g., one glass of wine per day with dinner).
- Engage in regular physical activity.
- Maintain leisure and social activities – keep socially engaged.
- Continue or take up activities that help to stimulate the brain, e.g., Tai Chi, dancing, puzzles.
- Become educated about AD and seek support from others with AD, e.g., the Alzheimer's Association, Alzheimer's Foundation of America, Keep Memory Alive, and other community groups.
- Include music in daily life – listening to music, playing an instrument, singing.
- Maintain regular sleep patterns.
- Manage stress – stop doing things if they are becoming too stressful (e.g., volunteer work, answering the telephone), keep to a regular daily schedule, include relaxing activities (e.g., playing with pets, massage, and aromatherapy).

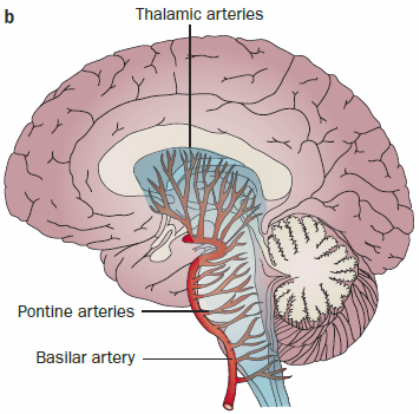
OPINION

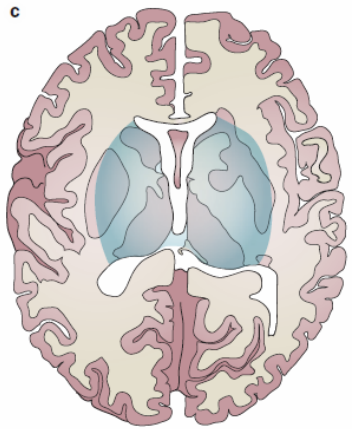
Antihypertensive treatment can prevent stroke and cognitive decline

Peter Sörös, Shawn Whitehead, J. David Spence and Vladimir Hachinski

Sörös, P. *et al. Nat. Rev. Neurol.* 9, 174–178 (2013)







The NEW ENGLAND JOURNAL of MEDICINE

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Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

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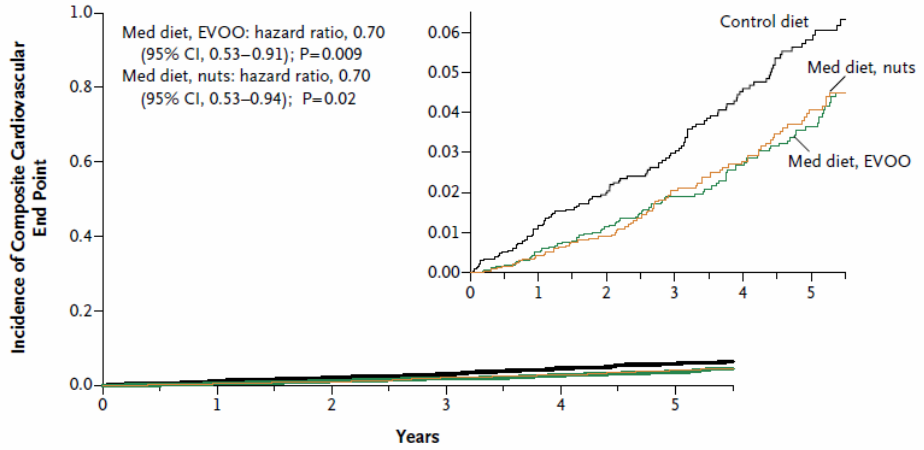
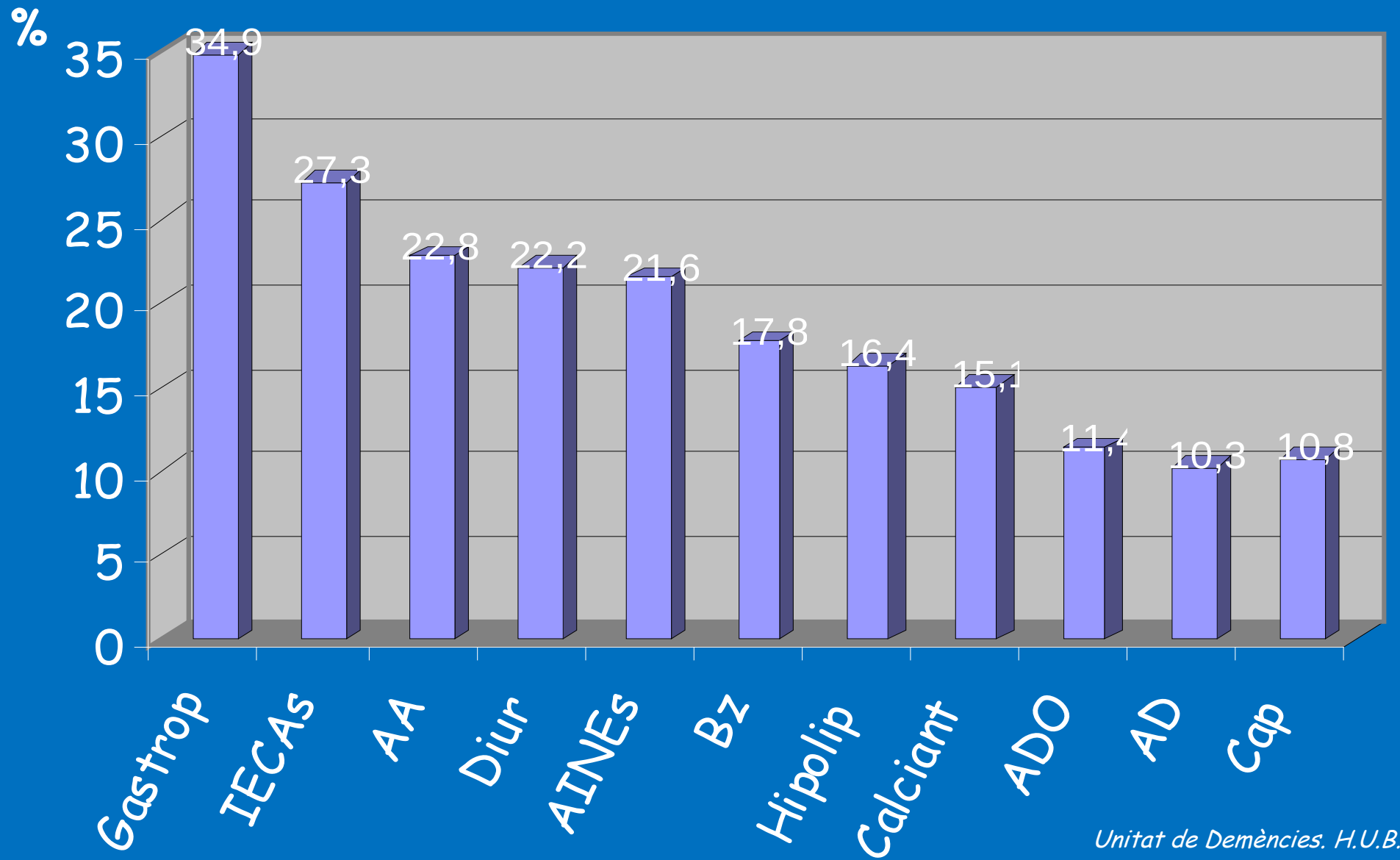
A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



No. at Risk						
Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

Dades Sociosanitàries

Consum de fàrmacs en població ≥70 anys



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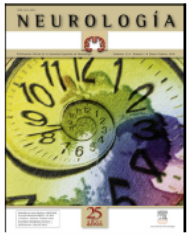

ORIGINAL

Estadio evolutivo de los pacientes con enfermedad de Alzheimer que acuden a la consulta especializada en España. Estudio EACE☆

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PALABRAS CLAVE
Enfermedad de Alzheimer;
Demencia;
Diagnóstico;
Estadio evolutivo;
Estado cognitivo;
Atención especializada

Resumen

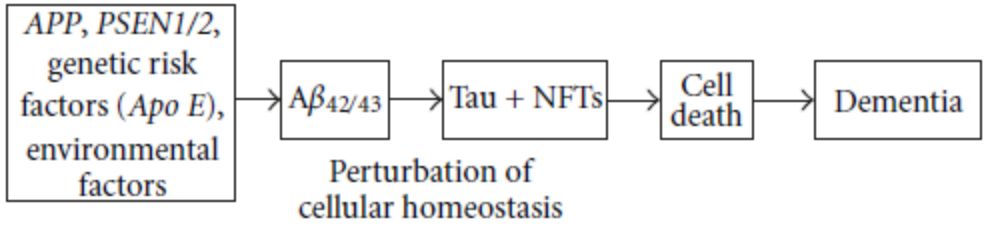
Introducción: Estamos asistiendo a un cambio en el paradigma del diagnóstico de la enfermedad de Alzheimer (EA), de modo que tiende a realizarse en fases más precoces de la evolución, incluso antes de la aparición del síndrome completo de demencia. En nuestro entorno no se conoce en qué situación clínica se está realizando el diagnóstico de la EA. Por ese motivo, se ha llevado a cabo este estudio, para describir el estadio evolutivo de los pacientes con EA en el momento del diagnóstico.

Métodos: Estudio multicéntrico, observacional y transversal. Se incluyeron pacientes que cumplían criterios NINCDS-ARDRA de EA probable, atendidos en consultas de Atención Especializada en España. Se recogieron los datos sobre los tiempos asistenciales y de evolución de la EA según el MMSE, el cuestionario NPI y la escala CDR.

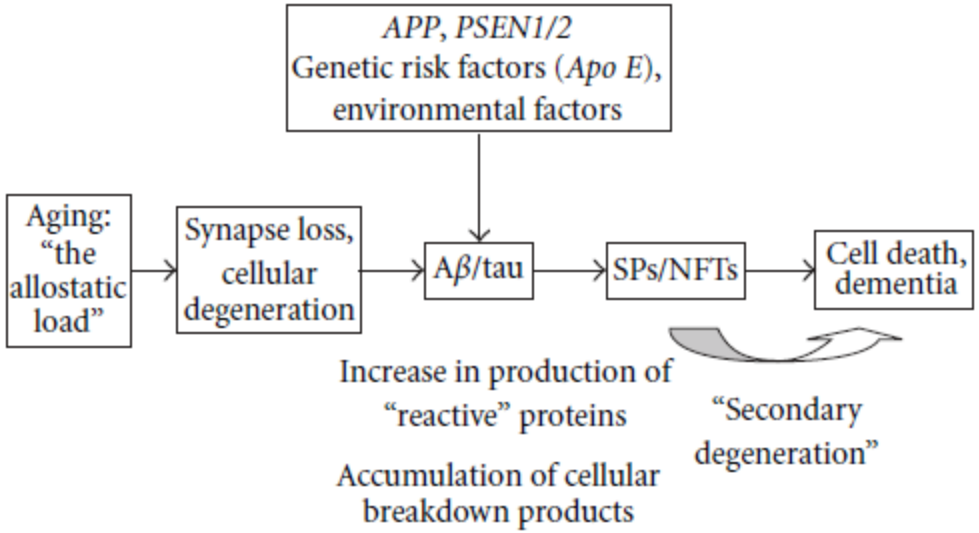
Resultados: Participaron 437 especialistas de todas las Comunidades Autónomas, que incluyeron un total de 1.707 pacientes, de los cuales 1.694 fueron incluidos en el análisis. La puntuación media del MMSE fue de 17,6 ± 4,8 (IC 95%: 17,4-17,9). El 64% de los pacientes presentaban deterioro cognitivo moderado (MMSE entre 10 y 20) y el 6% grave (MMSE < 10). El tiempo medio desde los primeros síntomas hasta la primera consulta a Atención Primaria fue de 10,9 ± 17,2 meses (IC 95%: 9,9-11,8), y hasta el diagnóstico de la EA fue de 28,4 ± 21,3 meses.

Conclusiones: Los resultados del EACE ponen de manifiesto que en nuestro entorno la mayor parte de los pacientes con EA acuden a Atención especializada en un estado evolutivo moderado.

"Amyloid cascade hypothesis" (ACH): original formulation



"Amyloid cascade hypothesis" (ACH): modified scheme



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