XXXII Congreso Nacional de la SEMI
XIV Congreso de la Sociedad Canaria de Medicina Interna
26-28 Octubre 2011

MESA REDONDA 32: EL INTERNISTA ANTE EL RETO DE LA DEMENCIA

Perspectivas diagnósticas y terapéuticas futuras en la enfermedad de Alzheimer

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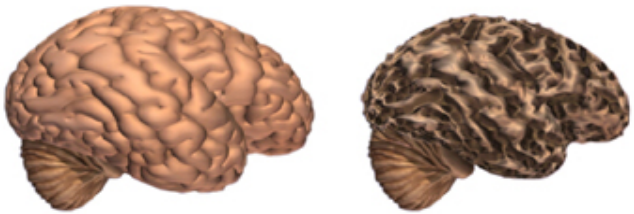
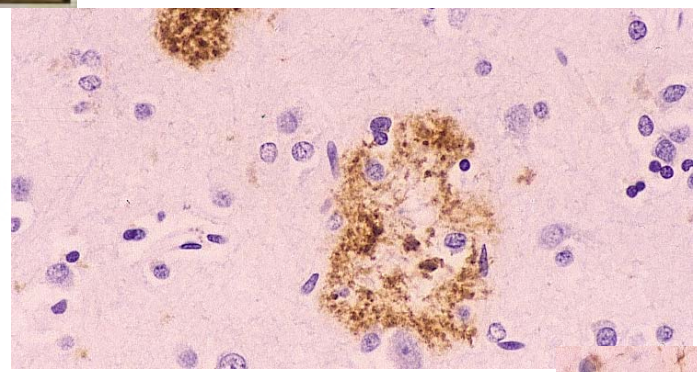
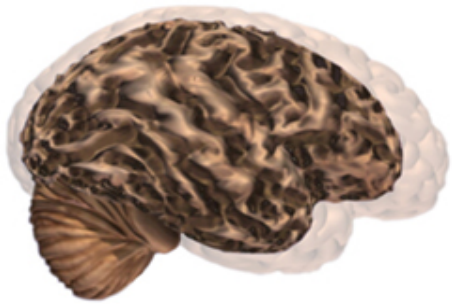
Enfermedad de Alzheimer

Dr Alois Alzheimer describió en 1906 el caso de la Sra Auguste D. que había desarrollado deterioro cognitivo y alteraciones conductuales de inicio a los **51** años

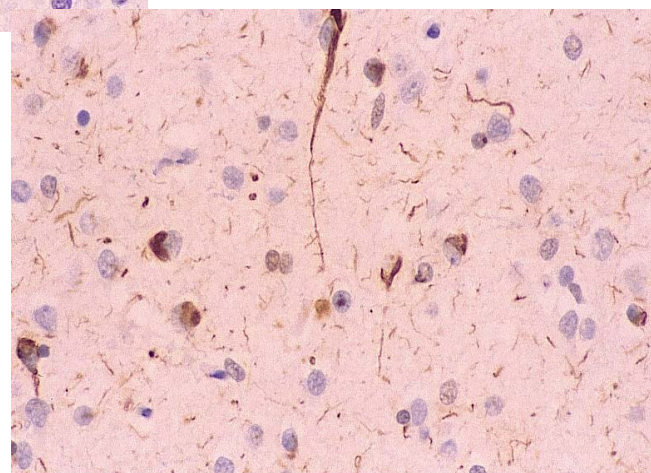




Placas extracelulares β- amyloid +



Ovillos neurofibrilares y Hebras neuríticas Tau + (hiperfosforilada)



Epidemiología de la enfermedad de Alzheimer

- Hasta los años 60, la enfermedad de Alzheimer (EA) se consideraba una enfermedad neurodegenerativa rara y de presentación a edades preseniles (<65 años), frente a la mucho más frecuente "demencia senil" que se consideraba una parte del proceso de "envejecimiento"

- En los años 60s del sXX, se demonstró que la mayor parte de los casos de demencia senil presentaban los típicos cambios patológicos de la EA y que por otra parte, la EA no era consustancial al proceso de envejecimiento

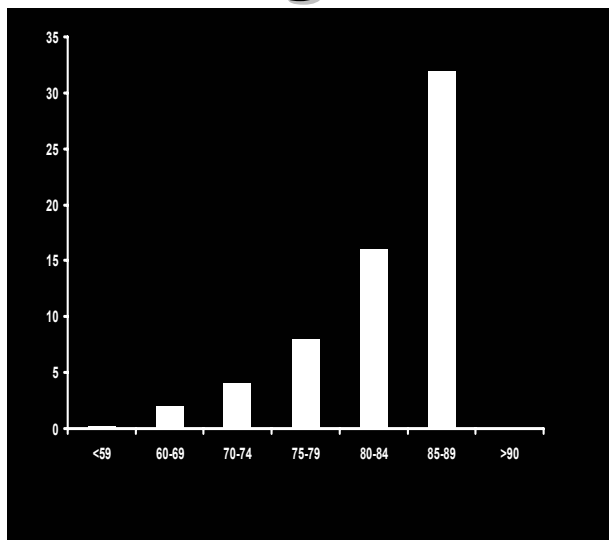
→ EA es la causa más frecuente de demencia (60-70%), siendo los casos seniles >> los preseniles

→17–25 millones de afectados a nivel mundial
400.000 casos en España

→ 3ª enfermedad en costes económicos
(después de la enfermedad cardíaca y el cáncer)

→Se calcula que un retraso de 5 años en el inicio de los síntomas de EA, reduciría su prevalencia un 50% (Kachaturian, 2009)

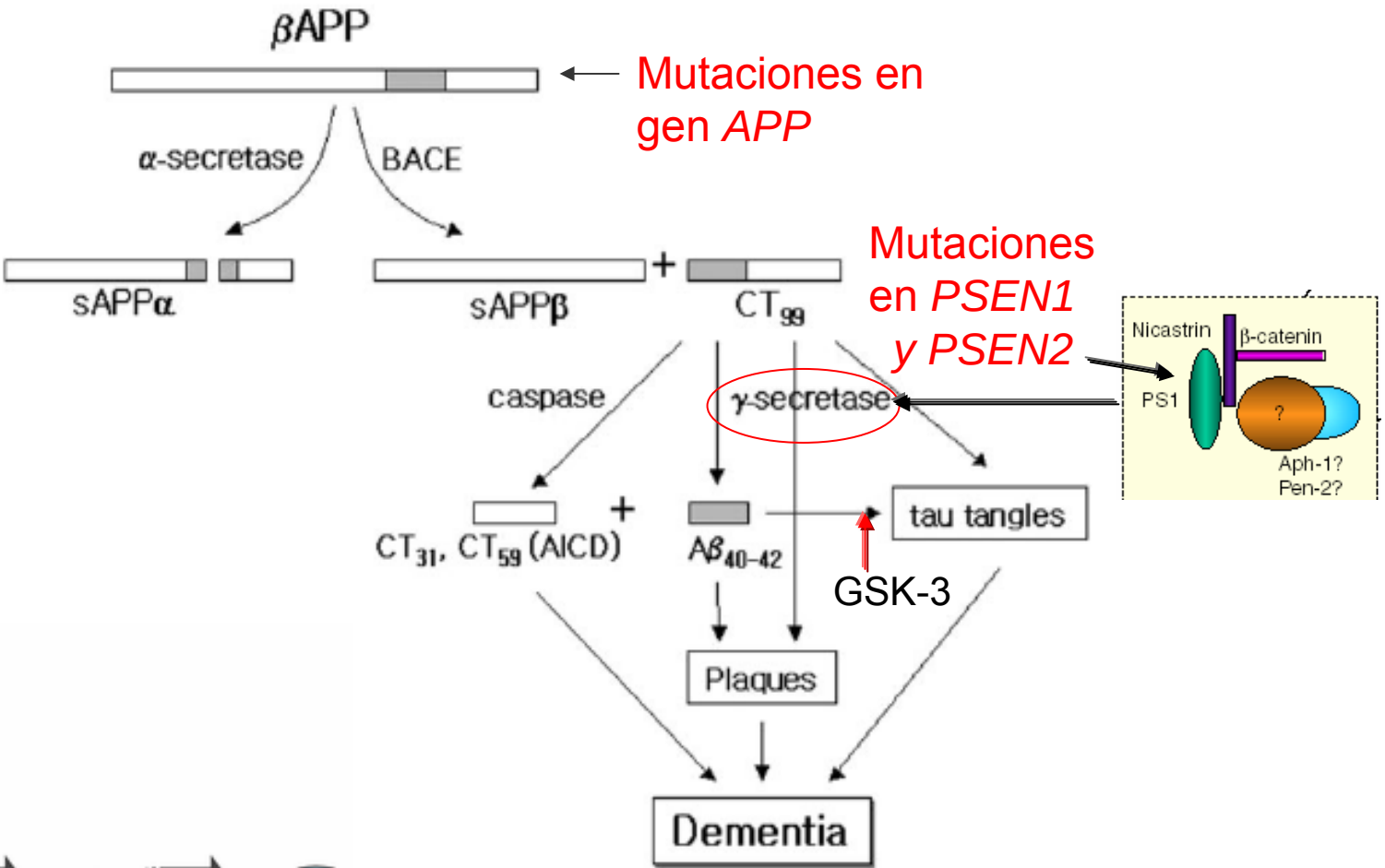
Factores/marcadores de riesgo

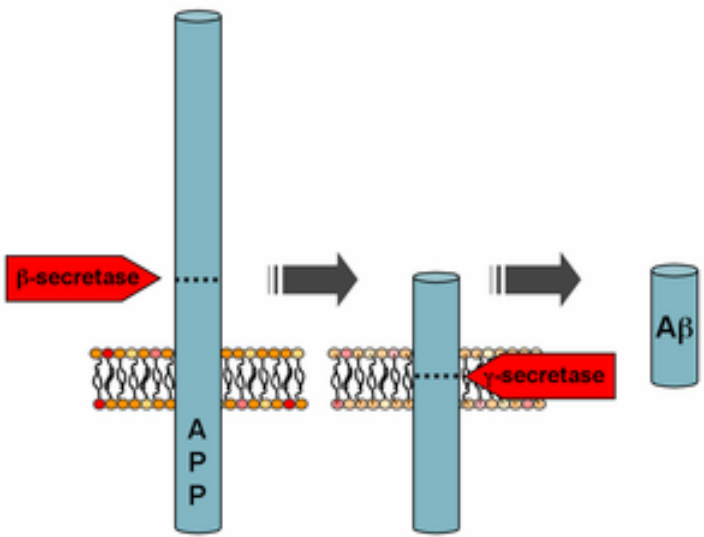


Eurodem

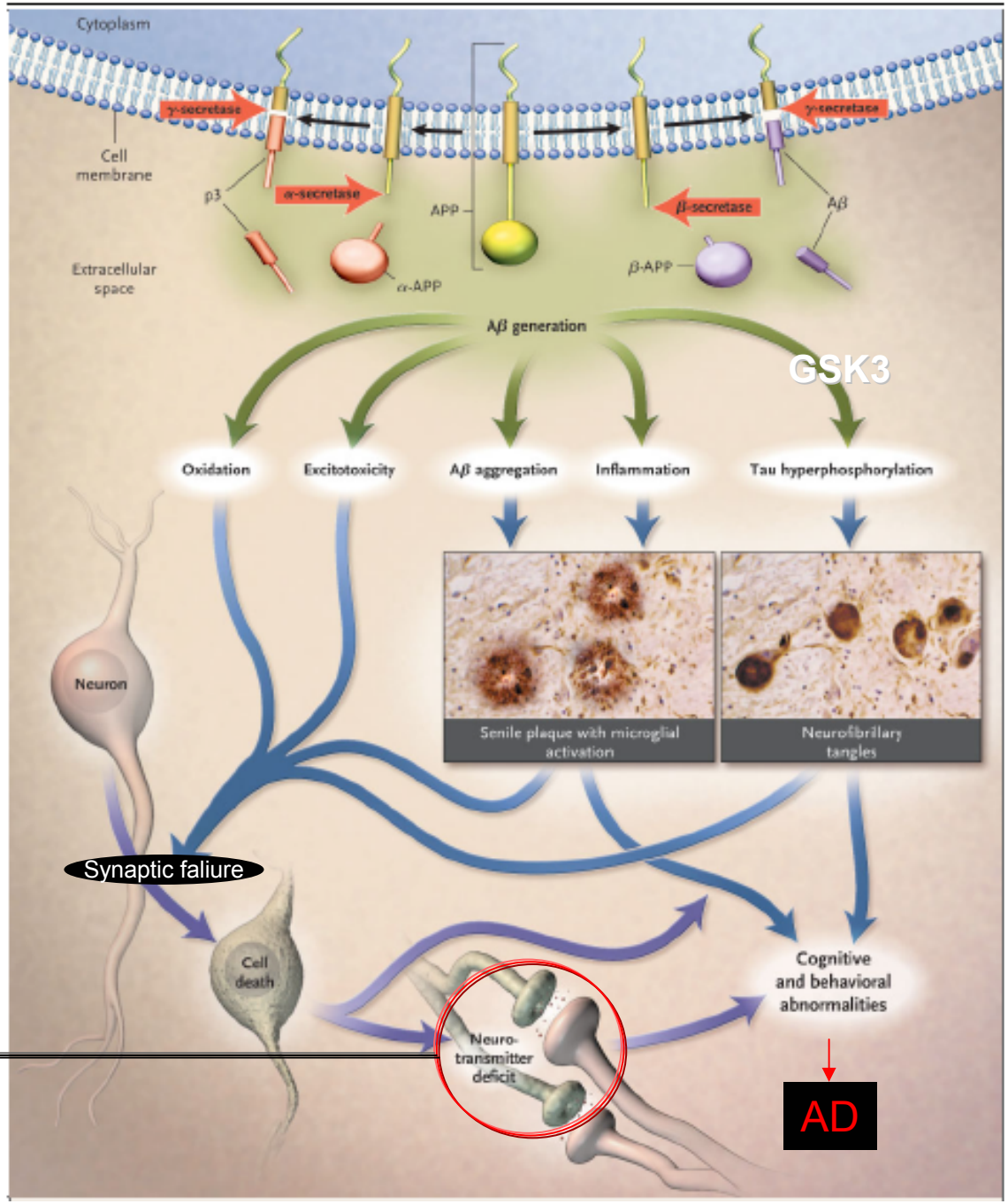
- Edad (prev x 2 cada 5 años > 60 años)
- Sexo femenino
- Historia familiar
- Factores genéticos
  - "herabilidad EA" 60-70% : 50% atribuible a *APOE*
  - << 0,5% casos herencia mendeliana
- Factores ambientales
  - bajo nivel educacional/ reserva cognitiva
  - traumatismos craneoencefálicos repetidos
  - factores de riesgo cardiovascular: diabetes, tabaquismo activo
  - efecto protector: AINEs en edades medias de la vida
  - dieta (discutido)
  - actividad física /actividades sociales de ocio

Mutaciones y cascada amiloide en la enf Alzheimer





Formas genéticas: ↑Aβ42 / Aβ40
Formas esporádicas: reducción del aclaramiento



Tratamientos Actuales

Cummings, 2004

Tratamientos actuales para la EA

a) Inhibidores de la acetilcolinesterasa:

↑ Ach a nivel cerebral y pretenden suplir los déficits existentes

b) Memantina: antagonista del receptor N-metyl- D- aspartate (NMDA) glutamato: mecanismo poco conocido

	Donepezilo	Rivastigmina	Galantamina	Memantina
Comercialización	2/1998	1/1999	9/2001	3/2003
Mecanismo de acción	Inhibición enzimática de la AChE	Inhbición enzimática de la AChE y BuChE	Inhibición enzimática de la AChE + modulación alostérica	Antagonista de los receptores NMDA del glutamato
Tipo de inhibición	Rápidamene reversible	Pseudo-irreversible	Rápidament e reversible	-
Selectividad cerebral vs periférica	SI / NO	SI (afinidad G1)	NO	NO
Semivida (h)	+/- 70	+/- 1,5	+/- 6	60 - 80
Eliminación	Hepática	Renal	Hepática Renal 50%	Renal
Metabolización CYP450	CYP450	Por sus enzimas diana	CYP450	80% sin metabolizar
Unión a proteínas	96	40	18	
Interacciones	moderado	muy bajo	moderado	bajo

ADAS-cog: donepezilo superior al placebo en cognición

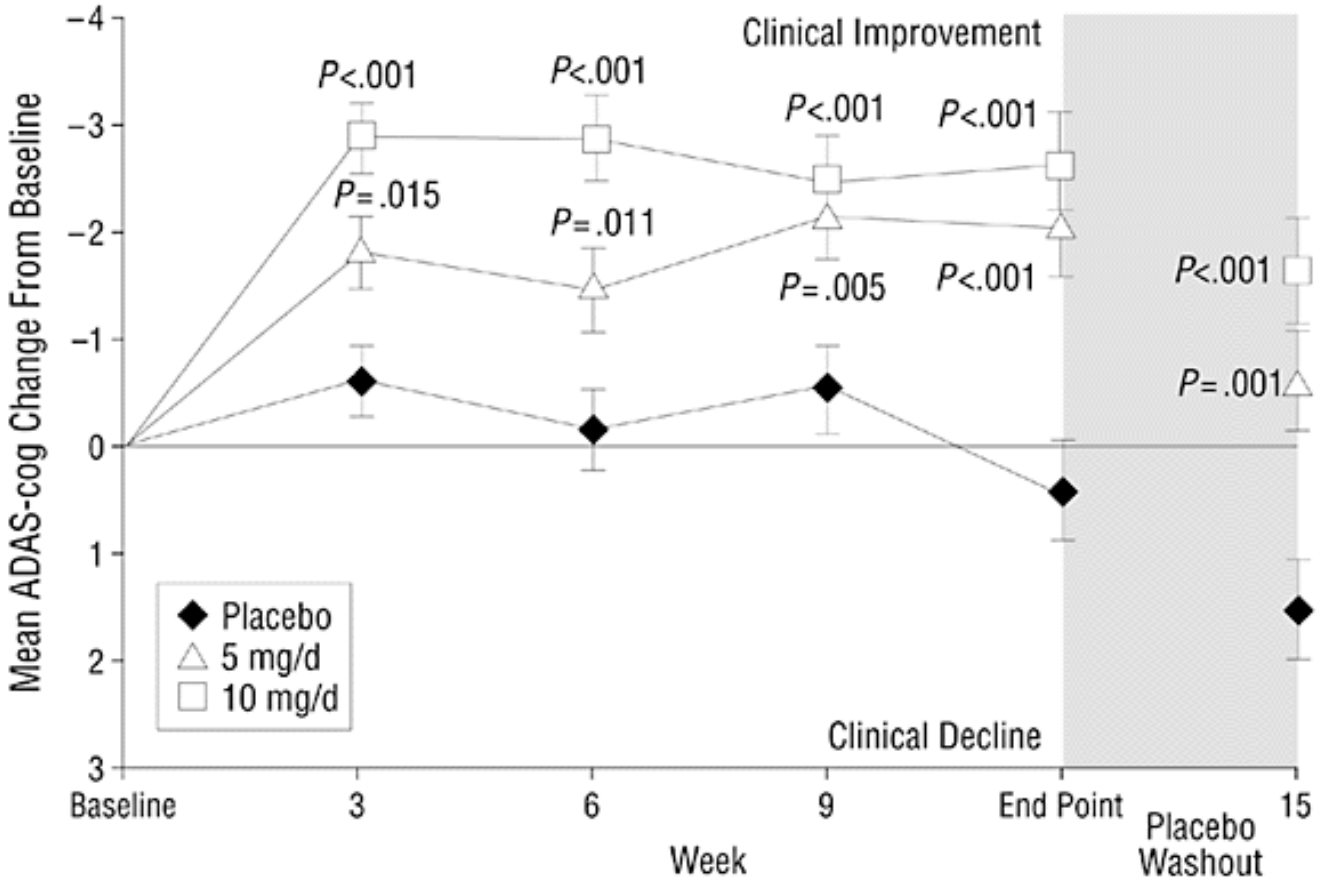
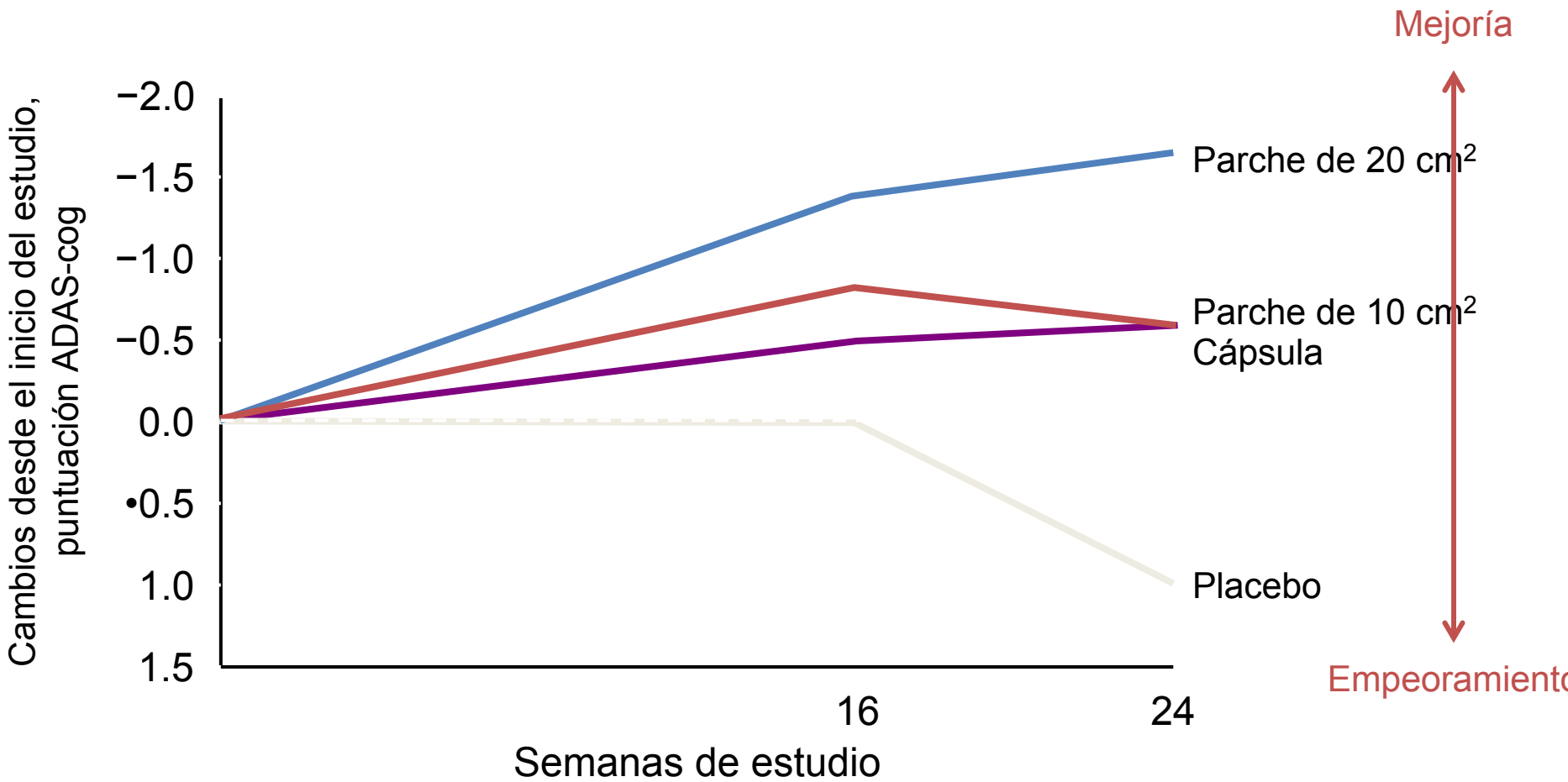


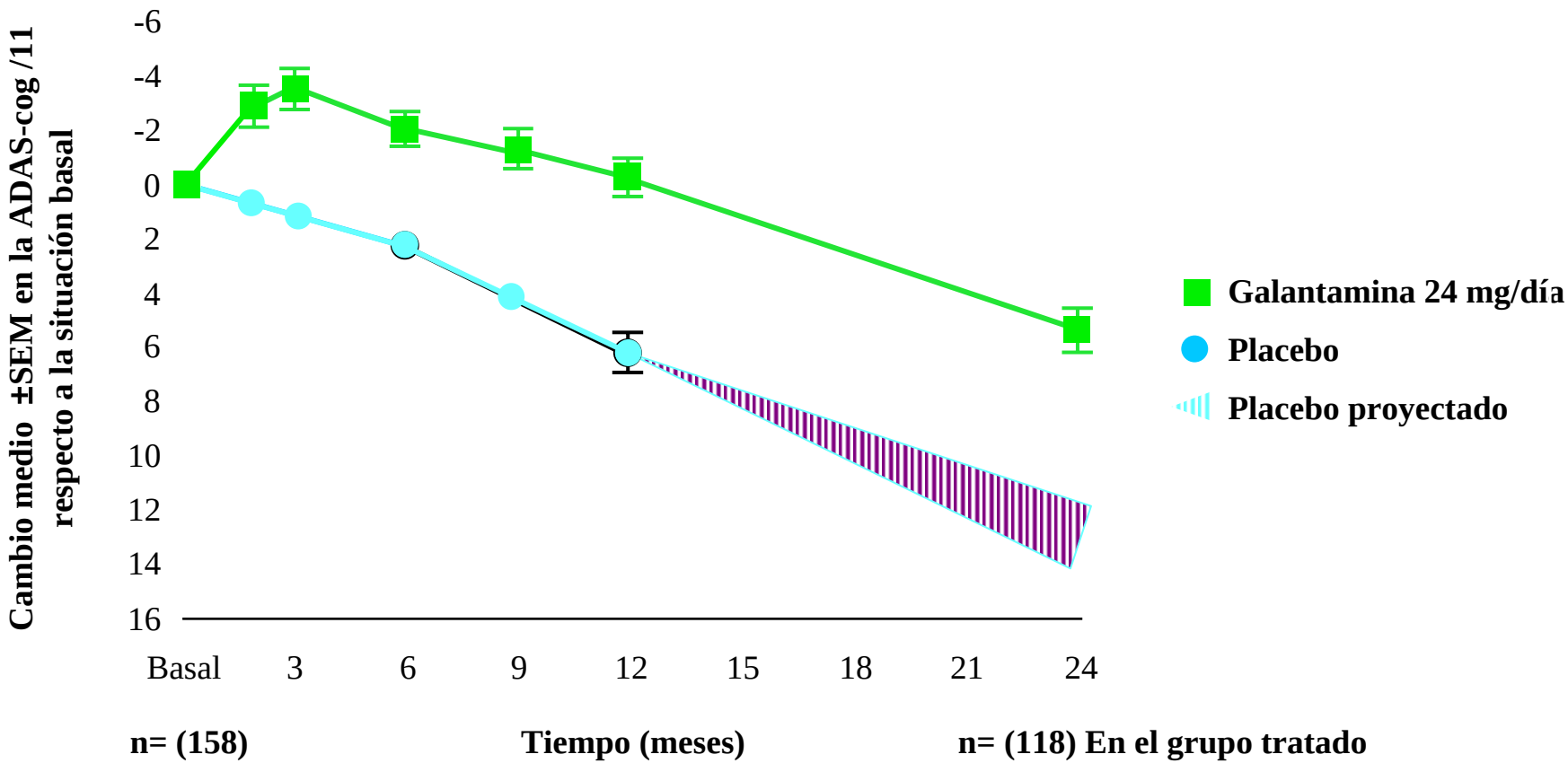
Figure 1. Least squares mean (± SEM) change from baseline in the Alzheimer's Disease Assessment Scale–Cognitive Subscal (ADAS-cog) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 457 were included in the intention-to-treat analysis at end point. Rogers,1998

ADAS-cog: rivastigmina es superior al placebo en cognición (estudio IDEAL)



*p < 0,05 *versus* placebo
†p = 0,09 *versus* placebo
Análisis ITT-LOCF

Estudio abierto a largo plazo (GAL-USA-9)



Doody R, et al. Neurology 2001; 56(suppl 3): A456

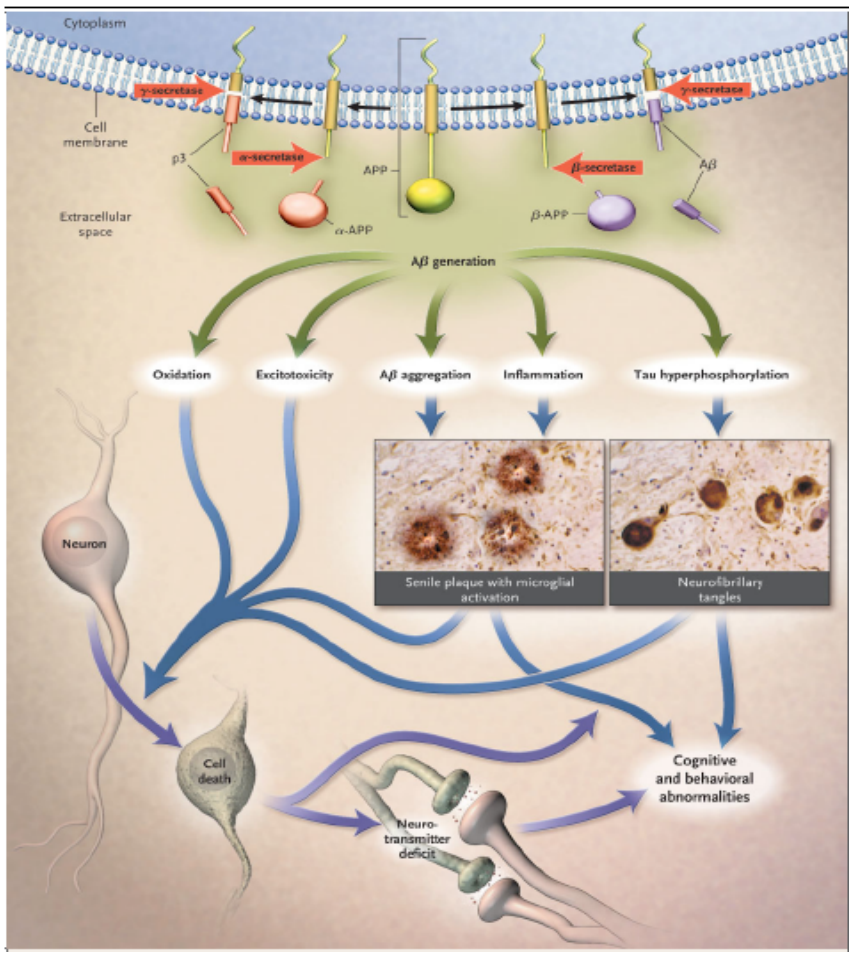
Indicaciones aprobadas

	Demencia Leve	Demencia Moderada	Demencia moder.severa	Demencia severa
Donepezilo				
Rivastigmina				
Galantamina				
Memantina				

A	Se recomienda el tratamiento con IACE (donepezilo 5-10mg/día, galantamina 16-24mg/día o rivastigmina 6-12mg/día oral/4,6-9,5mg/día transdérmica) en pacientes con EA leve o moderada.
B	Puede utilizarse un IACE (donepezilo o galantamina) en la EA grave, aunque la evidencia de su beneficio es menor.
A	Se recomienda tratamiento con memantina a dosis de 20mg/día en pacientes con EA moderada a grave.
A	Se recomienda el tratamiento con IACE en pacientes con EA leve a moderada, para el manejo de síntomas cognitivos y funcionales
A	Se recomienda el tratamiento con IACE en pacientes con EA leve a moderada, para el manejo de las alteraciones conductuales (apatía, ansiedad y depresión), a pesar de que el beneficio es modesto.
A	Se recomienda el tratamiento con memantina de pacientes con EA moderada a grave, para el manejo de los síntomas cognitivos y funcionales.

GPC Alzheimer, GuíaSalud, MSyC

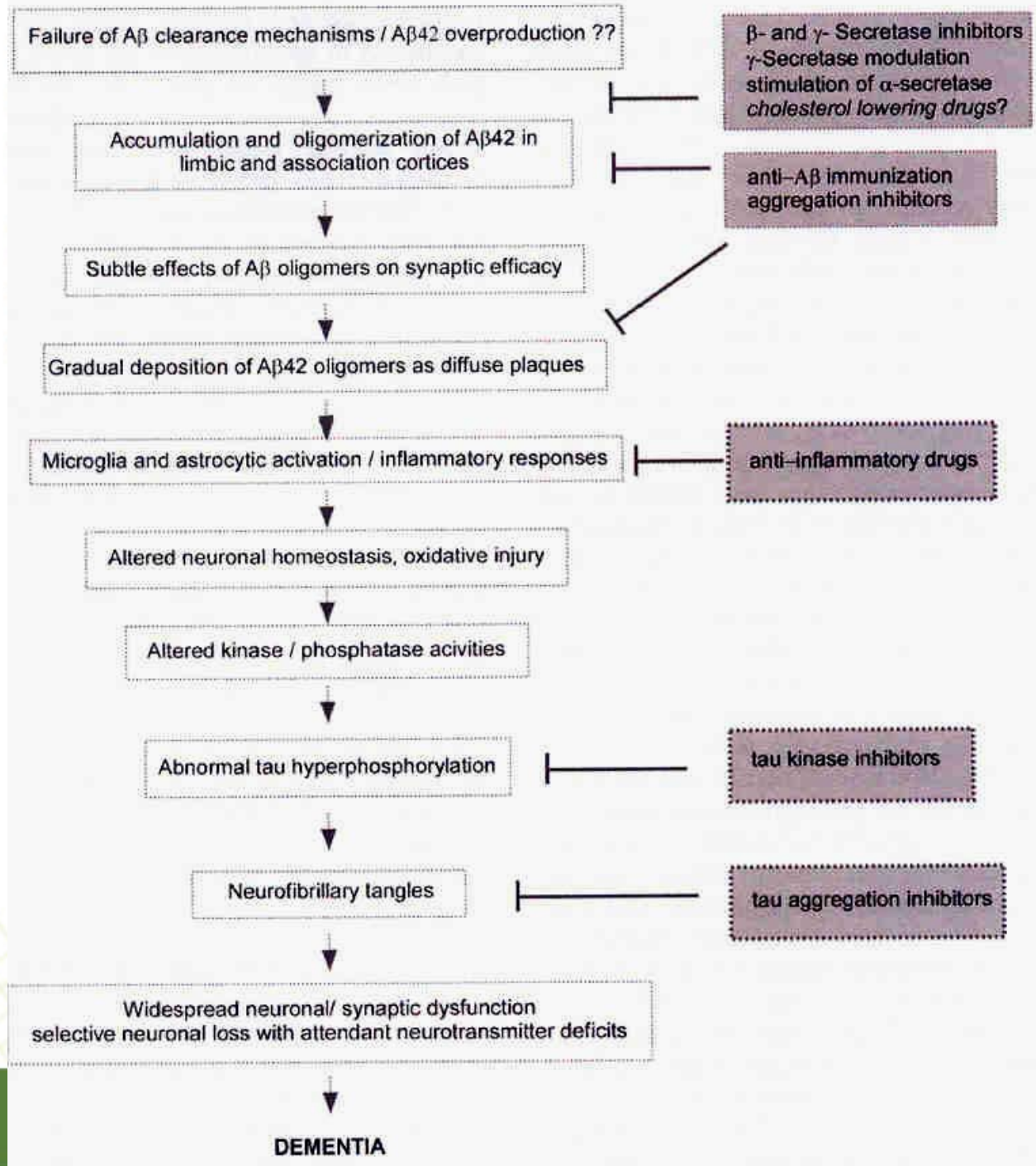
¿Tratamientos futuros ?



http://clinicaltrials.gov/ (11-jul-11)

940 ensayos clínicos en marcha (farmacológicos y no farmacológicos) para la investigación en enfermedad de Alzheimer

Klafki H-W. Brain 2006;129:2840-2855



Terapias anti-amiloide

- *Modulación de la producción de Aβ42*

Estimulador α secretasa
- Epigalocatechin
- ESPRIT Simvastaina (fase II)

Inhibidores β secretasa
- DR9.

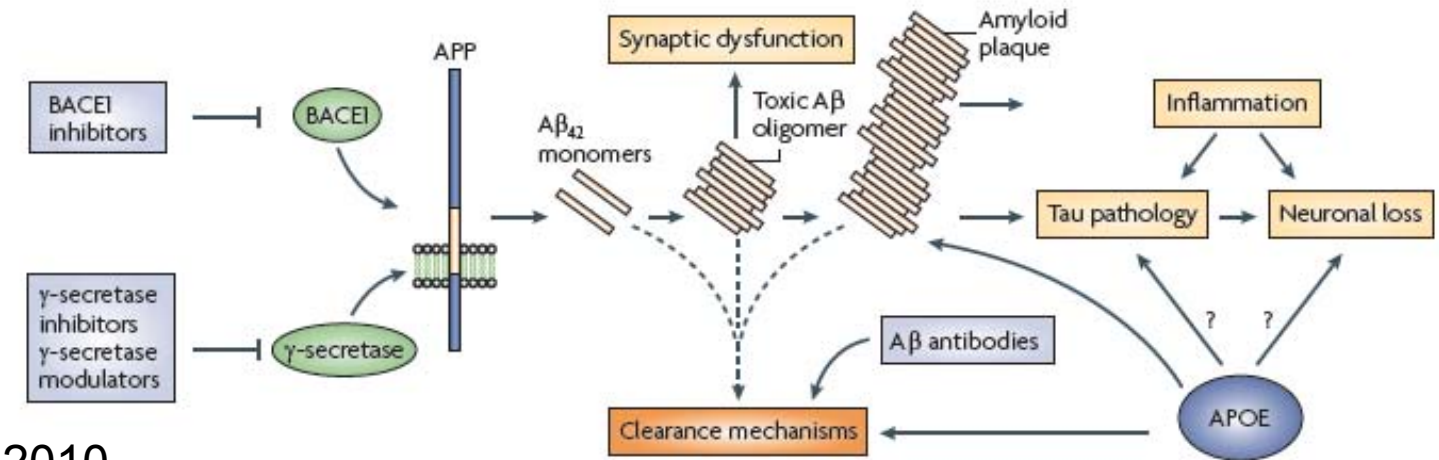
Inhibidor/modulación de γ secretasa
- R-Flurbiprofen-Flurizan (fase III)
- Semagacestat (fase III)
- Otros en fase I

- *Inhibiendo la agregación de Aβ42:*

Tramiprosate; ELND005; Clioquinol; PBT

- *Promoviendo la eliminación de Aβ42*

Neprilysin; Insulin degrading enzyme
Plasmin ;RAGE inhibitors
Inmunoterapias (activa-pasiva)

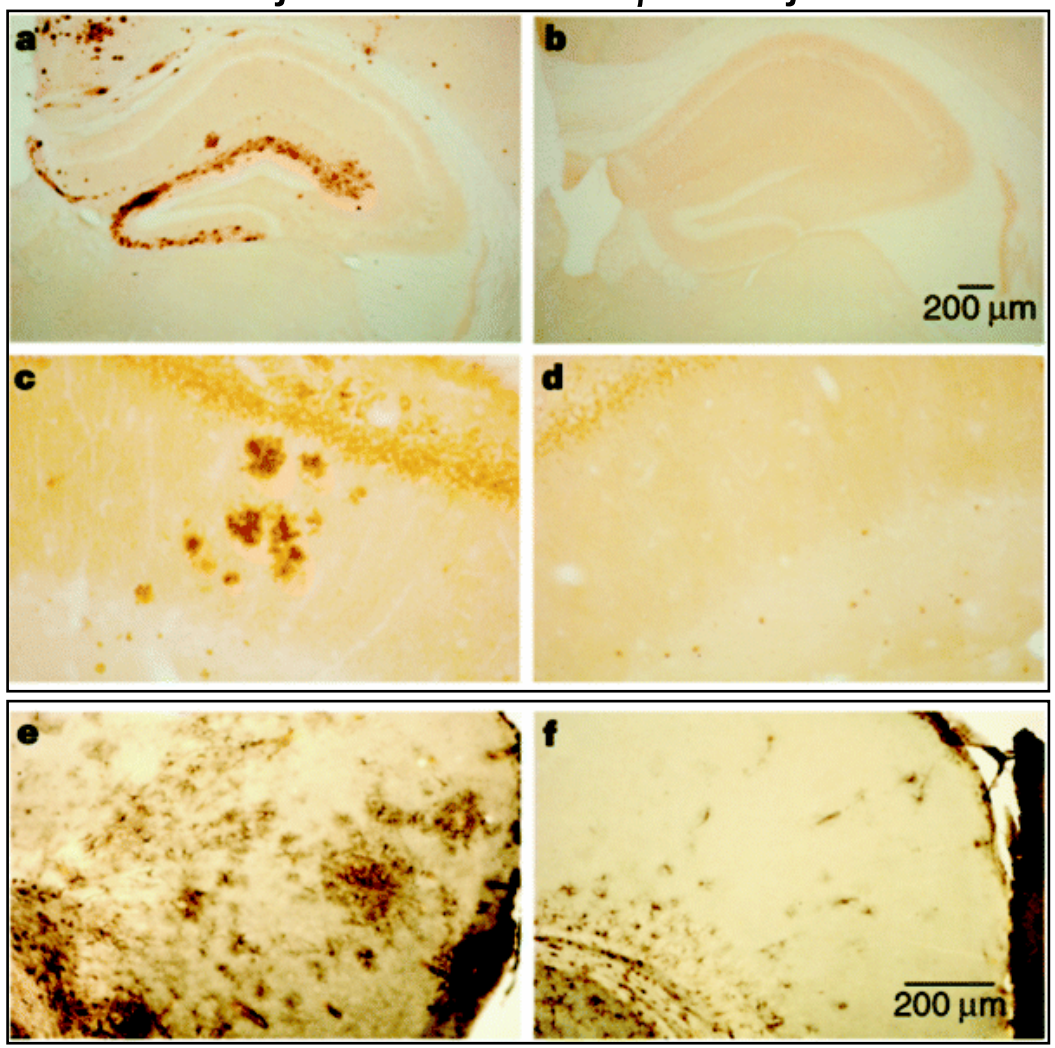


Citron, 2010

Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Schenk et al., Nature (1999) 400: 173-177. Elan Pharmaceuticals, San Francisco, California

PBS-injected Aβ42-injected



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

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Abstract—*Background:* AN1792 (beta-amyloid [Aβ]1–42) immunization reduces Aβ plaque burden and preserves cognitive function in APP transgenic mice. The authors report the results of a phase IIa immunotherapy trial of AN1792(QS-21) in patients with mild to moderate Alzheimer disease (AD) that was interrupted because of meningoencephalitis in 6% of immunized patients. *Methods:* This randomized, multicenter, placebo-controlled, double-blind trial of IM AN1792 225 μg plus the adjuvant QS-21 50 μg (300 patients) and saline (72 patients) included patients aged 50 to 85 years with probable AD, Mini-Mental State Examination (MMSE) 15 to 26. Injections were planned for months 0, 1, 3, 6, 9, and 12. Safety and tolerability were evaluated, and pilot efficacy (AD Assessment Scale–Cognitive Subscale [ADAS–Cog], MRI, neuropsychological test battery [NTB], CSF tau, and Aβ42) was assessed in anti-AN1792 antibody responder patients (immunoglobulin G titer ≥ 1:2,200). *Results:* Following reports of meningoencephalitis (overall 18/300 [6%]), immunization was stopped after one (2 patients), two (274 patients), or three (24 patients) injections. Of the 300 AN1792(QS-21)-treated patients, 59 (19.7%) developed the predetermined antibody response. Double-blind assessments were maintained for 12 months. No significant differences were found between antibody responder and placebo groups for ADAS–Cog, Disability Assessment for Dementia, Clinical Dementia Rating, MMSE, or Clinical Global Impression of Change, but analyses of the z-score composite across the NTB revealed differences favoring antibody responders (0.03 ± 0.37 vs -0.20 ± 0.45; $p = 0.020$). In the small subset of subjects who had CSF examinations, CSF tau was decreased in antibody responders (n = 11) vs placebo subjects (n = 10; $p < 0.001$). *Conclusion:* Although interrupted, this trial provides an indication that Aβ immunotherapy may be useful in Alzheimer disease.

NEUROLOGY 2005;64:1553–1562

ARTICLES

A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease

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R. Black, MD
M. Grundman, MD, MPH
For the Bapineuzumab 201 Clinical Trial Investigators*

ABSTRACT

Background: Bapineuzumab, a humanized anti-amyloid-beta (Aβ) monoclonal antibody for the potential treatment of Alzheimer disease (AD), was evaluated in a multiple ascending dose, safety, and efficacy study in mild to moderate AD.

Methods: The study enrolled 234 patients, randomly assigned to IV bapineuzumab or placebo in 4 dose cohorts (0.15, 0.5, 1.0, or 2.0 mg/kg). Patients received 6 infusions, 13 weeks apart, with final assessments at week 78. The prespecified primary efficacy analysis in the modified intent-to-treat population assumed linear decline and compared treatment differences within dose cohorts on the Alzheimer's Disease Assessment Scale–Cognitive and Disability Assessment for Dementia. Exploratory analyses combined dose cohorts and did not assume a specific pattern of decline.

Results: No significant differences were found in the primary efficacy analysis. Exploratory analyses showed potential treatment differences ($p < 0.05$, unadjusted for multiple comparisons) on cognitive and functional endpoints in study "completers" and *APOE* ε4 noncarriers. Reversible vasogenic edema, detected on brain MRI in 12/124 (9.7%) bapineuzumab-treated patients, was more frequent in higher dose groups and *APOE* ε4 carriers. Six vasogenic edema patients were asymptomatic; 6 experienced transient symptoms.

Conclusions: Primary efficacy outcomes in this phase 2 trial were not significant. Potential treatment differences in the exploratory analyses support further investigation of bapineuzumab in phase 3 with special attention to *APOE* ε4 carrier status.

Classification of evidence: Due to varying doses and a lack of statistical precision, this Class II ascending dose trial provides insufficient evidence to support or refute a benefit of bapineuzumab.

Neurology® 2009;73:2061–2070

A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease

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For the ELND005-AD201 Investigators

ABSTRACT

Objective: This randomized, double-blind, placebo-controlled, dose-ranging phase 2 study explored safety, efficacy, and biomarker effects of ELND005 (an oral amyloid anti-aggregation agent) in mild to moderate Alzheimer disease (AD).

Methods: A total of 353 patients were randomized to ELND005 (250, 1,000, or 2,000 mg) or placebo twice daily for 78 weeks. Coprimary endpoints were the Neuropsychological Test Battery (NTB) and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale. The primary analysis compared 250 mg (n = 84) to placebo (n = 82) after an imbalance of infections and deaths led to early discontinuation of the 2 higher dose groups.

Results: The 250 mg dose demonstrated acceptable safety. The primary efficacy analysis at 78 weeks revealed no significant differences between the treatment groups on the NTB or ADCS-ADL. Brain ventricular volume showed a small but significant increase in the overall 250 mg group ($p = 0.049$). At the 250 mg dose, scyllo-inositol concentrations increased in CSF and brain and CSF Aβx-42 was decreased significantly compared to placebo ($p = 0.009$).

Conclusions: Primary clinical efficacy outcomes were not significant. The safety and CSF biomarker results will guide selection of the optimal dose for future studies, which will target earlier stages of AD.

Classification of evidence: Due to the small sample sizes, this Class II trial provides insufficient evidence to support or refute a benefit of ELND005. **Neurology® 2011;77:1253–1262**

- **Anti-tau**

  Inhibidores de GSK3β: Tideglusib (on-going)

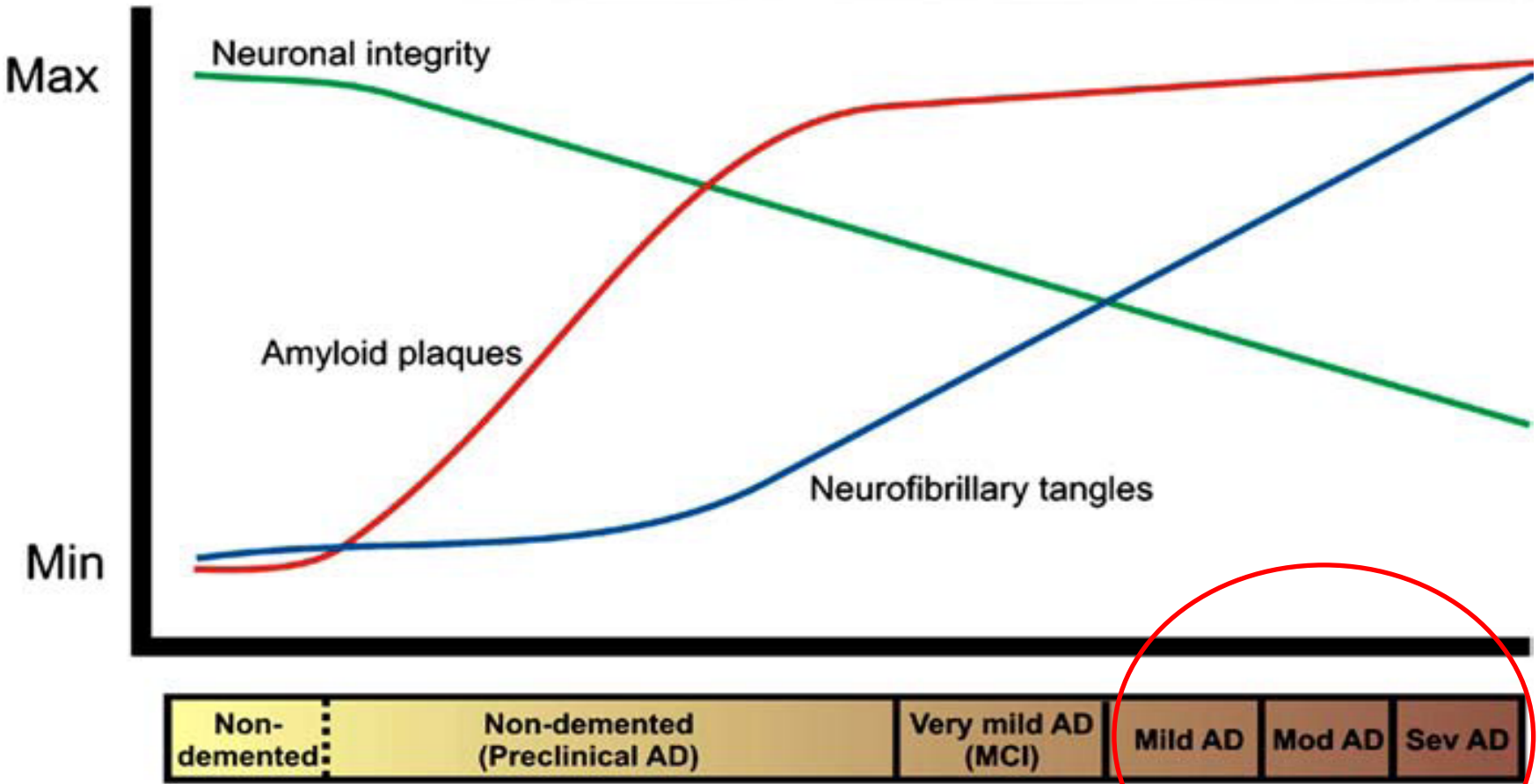
  Inhibidores de la agregación de tau: methylthioninium chloride (*Rember)* (FIIb)

- Antiinflamatorio-antioxidantes
  - Vit E (f III), C,ac. lipoico, coQ
  - Revestrarol (fase II)
  - AINEs: naproxeno (fase III)
  - Lipopolisacaridos
  - Curcumina (fIII)

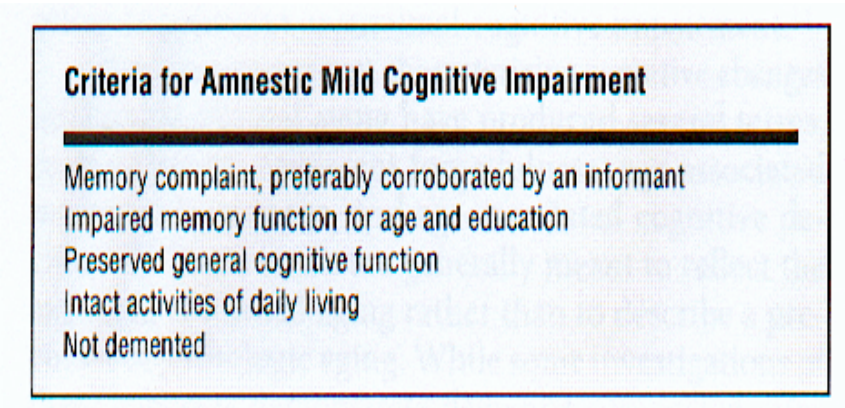
- Neurotróficos
- Modificadores de la neurotransmisión
  - Dimebon (F III)
  - PRX-03140 Aumenta niveles Ach (fase II)
  - Lecozotan Agonista serotoninérgico
    Modula Ach y glutamato (fase II,III)
  - Huperzina A Inhibidor de la Ach natural
  - AC3933 Aumenta la liberación Ach (fase II)
  - MK-0952 Inhibe fosfodiesterasa, aumenta liberación ÁCh, serotonina (fase II)

- Modulación hormonal
  - 17α y 17β estradiol Remplazamiento hormonal
  - Leuprorelina Agonista GH-Rh
  - Raloxifeno Modulador receptor estrogénico (fase II)

La enfermedad de Alzheimer empieza en el cerebro décadas antes del inicio de los síntomas



Deterioro cognitivo leve



Petersen, 2001

- 3-19% > 65 años
- 10% /anual-> demencia

Todos los enfermos de EA pasan por una fase de deterioro cognitivo leve
pero 30-40% de sujetos con deterioro cognitivo leve se mantienen estables o mejoran en 5 años

Nuevos criterios de investigación para la EA

Panel 2: Diagnostic criteria for AD

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment that includes the following features:

1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features

B. Presence of medial temporal lobe atrophy

- Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C. Abnormal cerebrospinal fluid biomarker

- Low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
- Other well validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET

- Reduced glucose metabolism in bilateral temporal parietal regions
- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

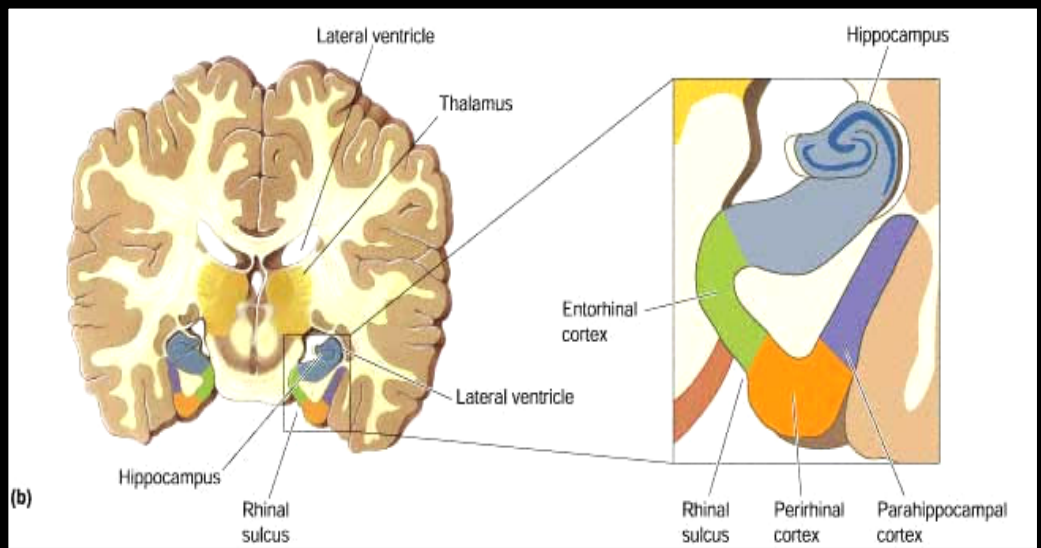
E. Proven AD autosomal dominant mutation within the immediate family

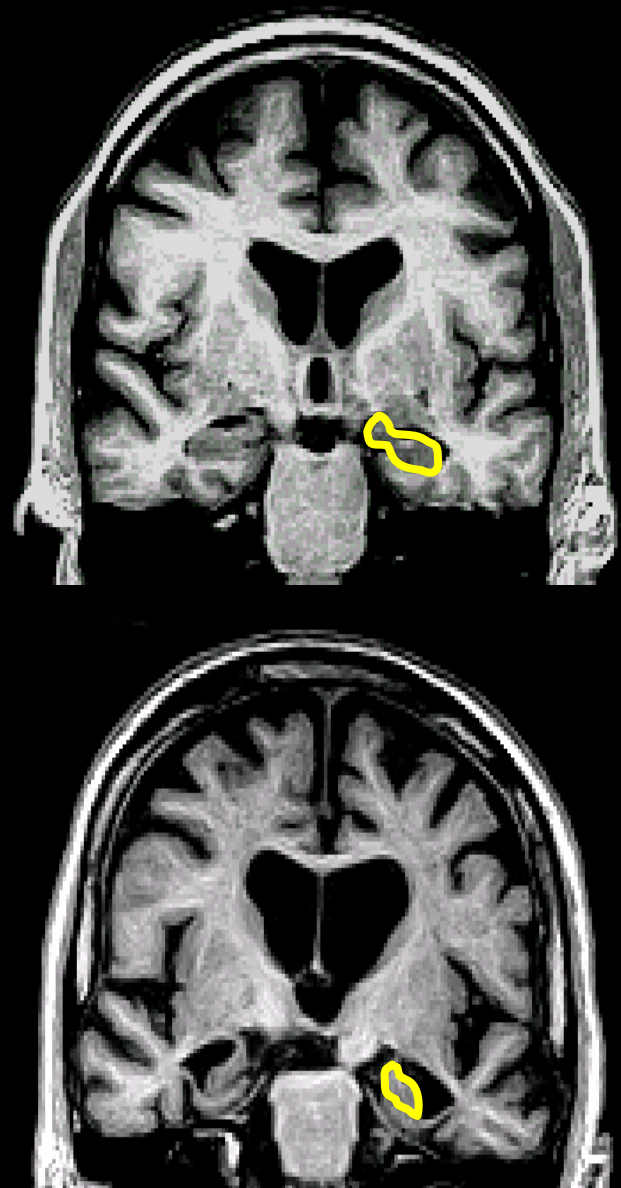
Prodromal AD (also called "predementia stage of AD")

This term refers to the early symptomatic, predementia phase of AD in which (1) clinical symptoms including episodic memory loss of the hippocampal type (characterised by a free recall deficit on testing not normalised with cueing) are present, but not sufficiently severe to affect instrumental activities of daily living and do not warrant a diagnosis of dementia; and in which (2) biomarker evidence from CSF or imaging is supportive of the presence of AD pathological changes. This phase is now included in the new definition of AD. The term of prodromal AD might disappear in the future if AD is considered to encompass both the predementia and dementia stages.

Lancet Neurology 2007

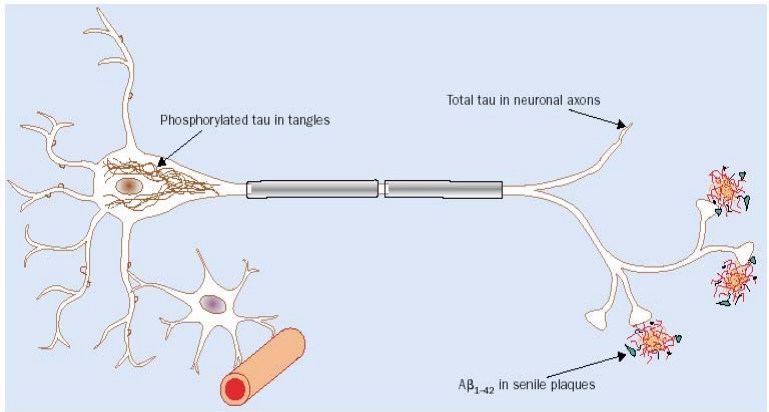
B) Neuroimagen estructural :
Atrofia hipocampal



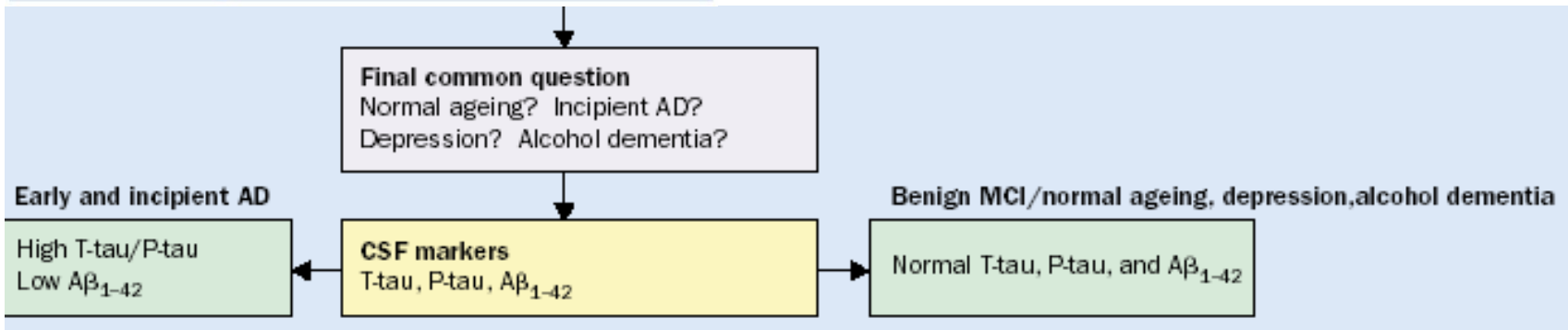


Medial temporal lobe (MTL)

C) Marcadores bioquímicos en LCR



Blennow, Lancet Neurol 2003



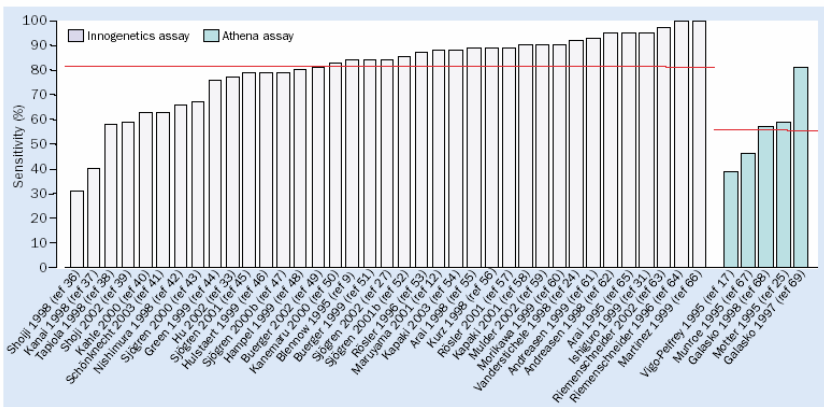


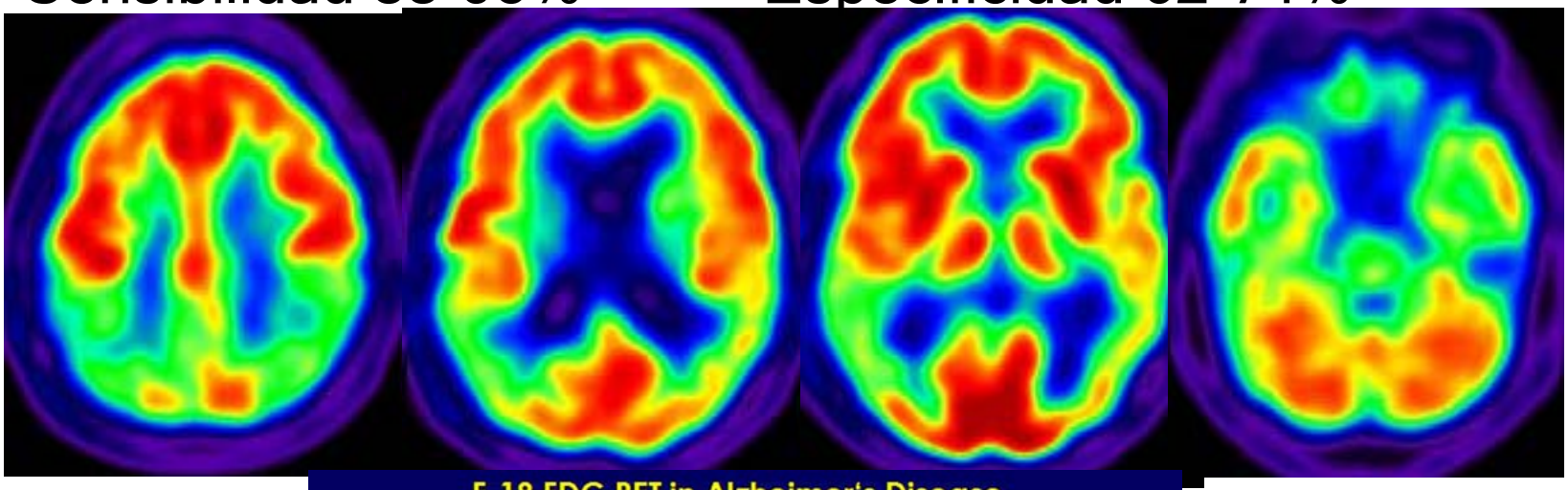
Figure 4. CSF total tau (T-tau) as a diagnostic marker for AD. Bars represent sensitivity figures for the two most commonly used ELISAs, the

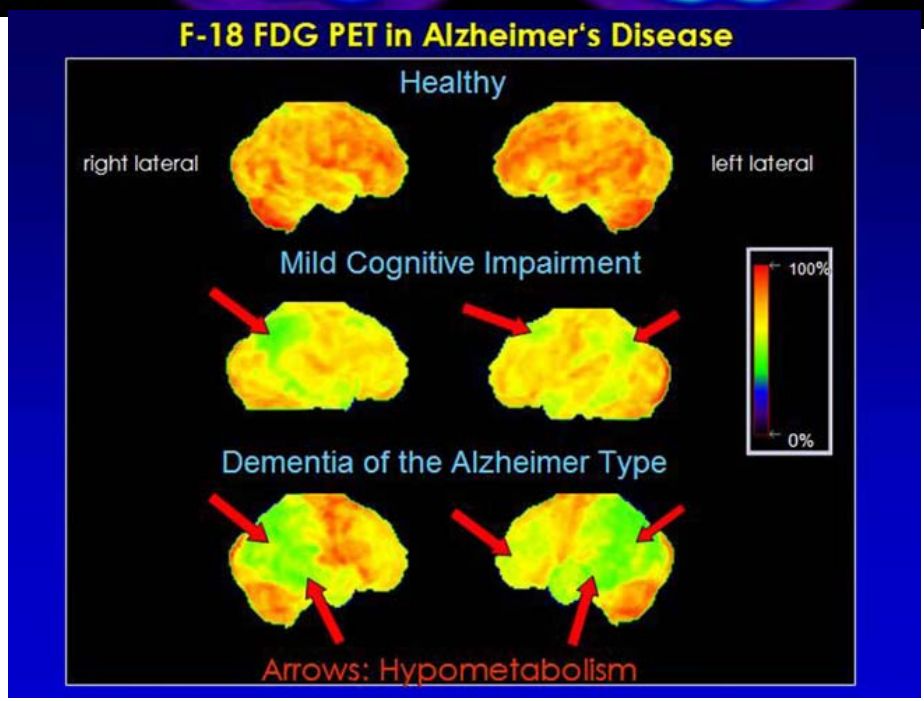
Combinaciones de biomarcadores:
↓Aβ42 + ↑tau total o↑ fosfo-tau
Sensibilidad 85-94%, especificidad 83-100%
EA frente a controles

Tau LCR

D) F-18 FDG-PET

Sensibilidad 88-95% Especificidad 62-74%



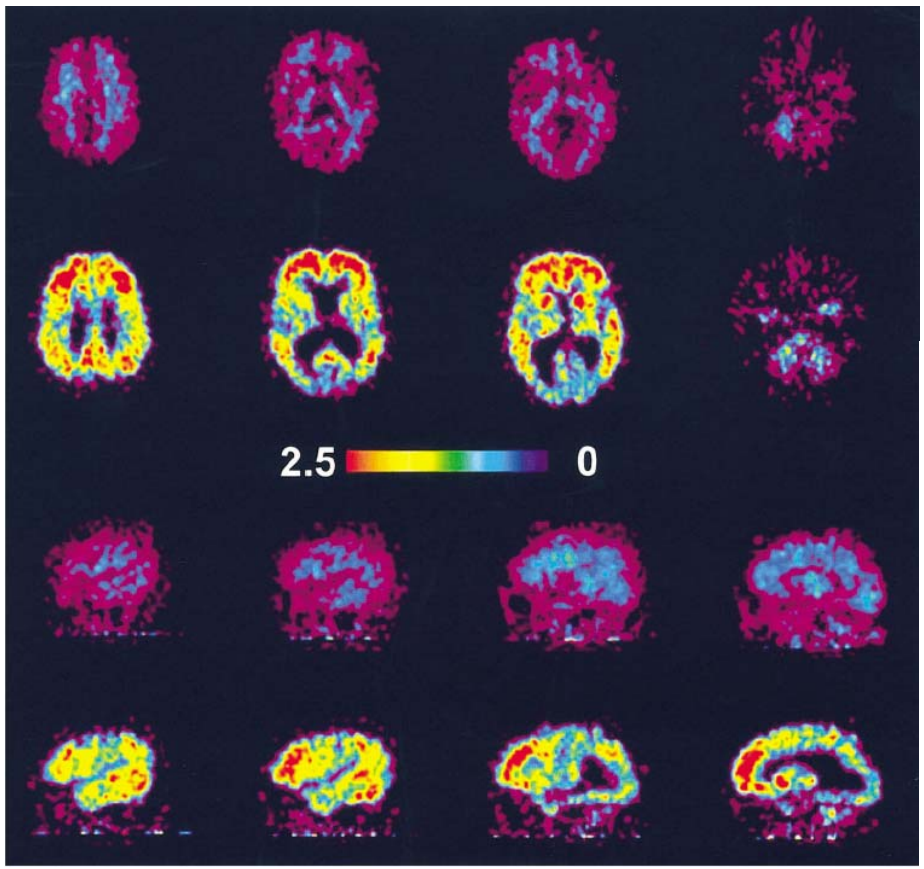


ORIGINAL ARTICLES

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



control

AD

Herholz, Lancet Neurol 11

	Pittsburgh compound B	Flutemetamol	Florbetapir	Florbetaben
Synonyms	PiB	GE-067, 3'-fluoro-PIB	AV-45	BAY-94-9172, AV-1
Chemical group	Benzothiazole	Benzothiazole	Styrylpyridine	Stilbene
Isotope label	Carbon-11	Fluorine-18	Fluorine-18	Fluorine-18
Amyloid affinity (Ki, nM)	0·9	0·7	2·2	2·4
Plasma metabolites	Polar	Polar	Polar and non-polar	Polar and non-polar
Typical injected dose (MBq)	250–450	185	300	300
Typical imaging time (min)	40–90	80–100	50–70	90–130
Effective radiation dose (mSv; μSv/MBq)	1·3–2·4 (5·3)	6·3 (33·8)	5·8 (19·3)	4·4 (14·7)

Data from references 20–26.

Table: PET tracer characteristics

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Alzheimer's & Dementia ■ (2011) 1–10

Alzheimer's & Dementia

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup

Marilyn S. Albert[a,*], Steven T. DeKosky[b,c], Dennis Dickson[d], Bruno Dubois[e],

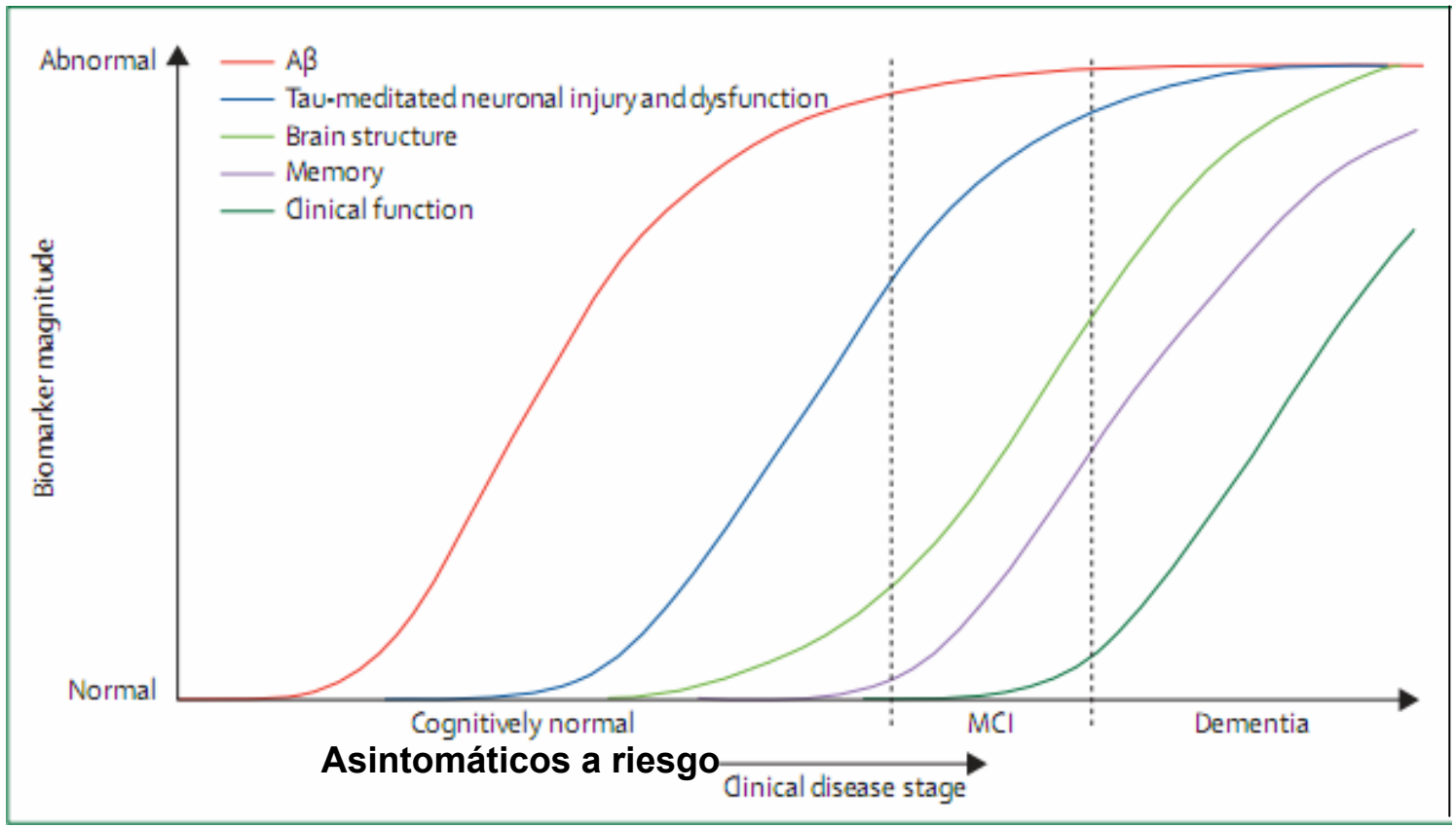
Table 3
MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI–core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

Table 2
Biomarkers under examination for AD

Biomarkers of Aβ deposition
CSF $A\beta_{42}$
PET amyloid imaging
Biomarkers of neuronal injury
CSF tau/phosphorylated-tau
Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
Rate of brain atrophy
FDG-PET imaging
SPECT perfusion imaging
Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures
Associated biochemical change
Inflammatory biomarkers (cytokines)
Oxidative stress (isoprostanes)
Other markers of synaptic damage and neurodegeneration such as cell death

X → Aß → Tau → RM → NPS → Clínica



Jack *et al.* Lancet Neurol 2010;9:119-28

ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–13

Alzheimer's & Dementia

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r], Creighton H. Phelps[r]

[a]*Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

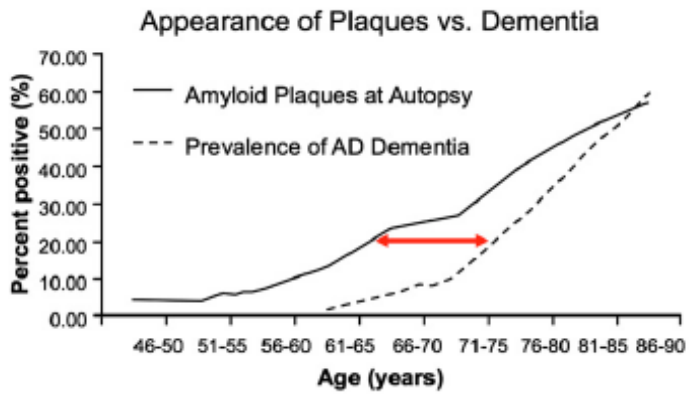
is detectable before myocardial infarction. It is widely acknowledged that symptoms are not necessary to diagnose human disease. Type II diabetes, hypertension, renal insufficiency, and osteoporosis are frequently detected through laboratory tests (i.e., biomarkers), and effective treatment can prevent the emergence of symptoms. Thus, we should be open to the idea that AD could one day be diagnosed preclinically by the presence of biomarker evidence of AD-P, which may eventually guide therapy before the onset of symptoms.

Stage 1
Asymptomatic amyloidosis
-High PET amyloid tracer retention
-Low CSF $A\beta_{1-42}$

Stage 2
Amyloidosis + Neurodegeneration
-Neuronal dysfunction on FDG-PET/fMRI
-High CSF tau/p-tau
-Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
-Evidence of subtle change from baseline level of cognition
-Poor performance on more challenging cognitive tests
-Does not yet meet criteria for MCI

MCI ➔AD dementia



Can Alzheimer disease be prevented by amyloid-β immunotherapy?

Cynthia A. Lemere and Ellezer Masliah

Abstract | Alzheimer disease (AD) is the most common form of dementia. The amyloid-β (Aβ) peptide has become a major therapeutic target in AD on the basis of pathological, biochemical and genetic evidence that supports a role for this molecule in the disease process. Active and passive Aβ immunotherapies have been shown to lower cerebral Aβ levels and improve cognition in animal models of AD. In humans, dosing in the phase II clinical trial of the AN1792 Aβ vaccine was stopped when ~6% of the immunized patients developed meningoencephalitis. However, some plaque clearance and modest clinical improvements were observed in patients following immunization. As a result of this study, at least seven passive Aβ immunotherapies are now in clinical trials in patients with mild to moderate AD. Several second-generation active Aβ vaccines are also in early clinical trials. On the basis of preclinical studies and the limited data from clinical trials, Aβ immunotherapy might be most effective in preventing or slowing the progression of AD when patients are immunized before or in the very earliest stages of disease onset. Biomarkers for AD and imaging technology have improved greatly over the past 10 years and, in the future, might be used to identify presymptomatic, at-risk individuals who might benefit from Aβ immunization.

Lemere, C. A. & Masliah, E. *Nat. Rev. Neurol.* 6, 108–119 (2010); doi:10.1038/nrneurol.2009.219

Iniciativas en marcha:

- Dominantly Inherited Alzheimer Network (DIAN)
- Alzheimer's Prevention Initiative
- Alzheimer's Disease Cooperative Study’s Anti-Amyloid Treatment in Asymptomatic (A4) trial

Conclusiones

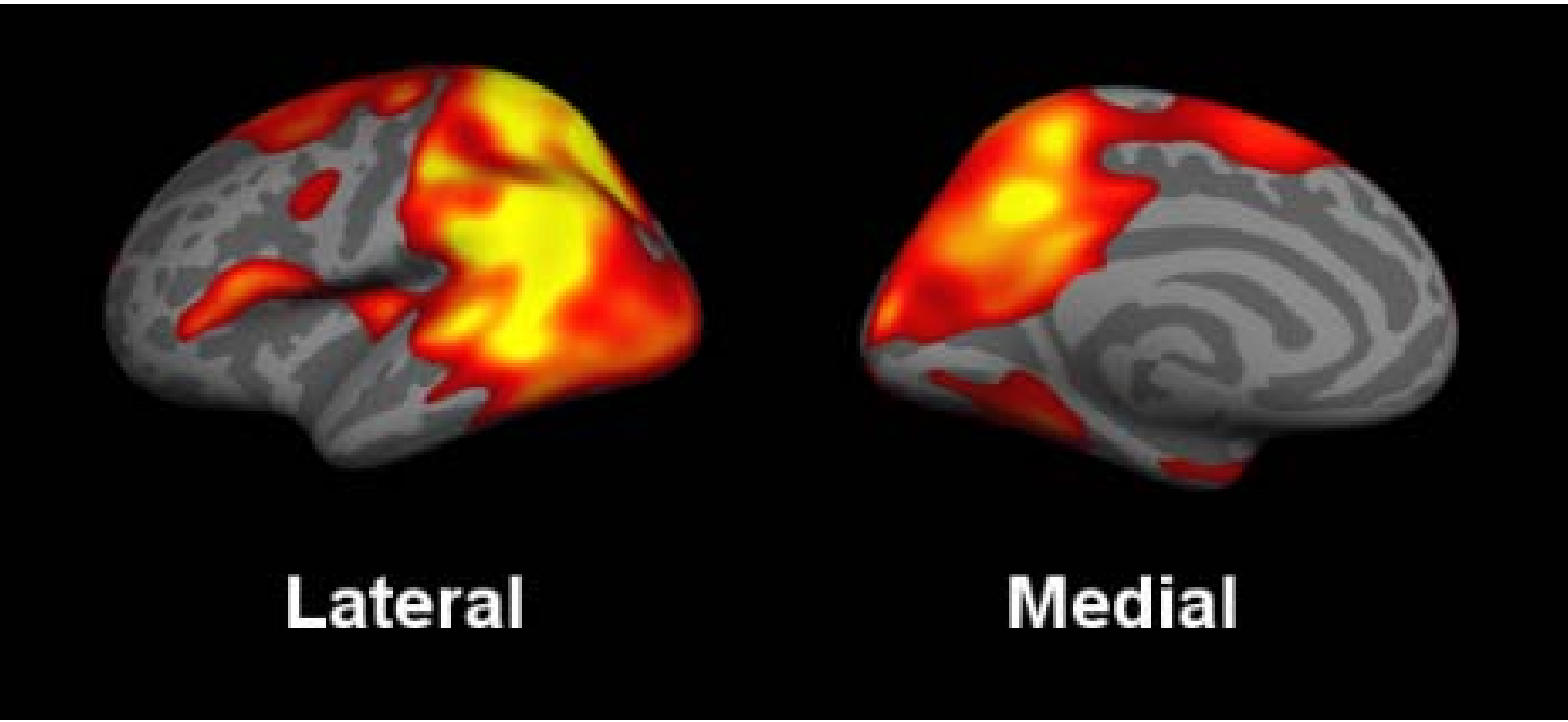
- Los tratamientos actualmente autorizados para la enfermedad de Alzheimer tienen un efecto sintomático y de “baja” magnitud

- Datos preliminares sobre tratamientos anti-amiloide sugieren que, si bien son eficaces en su función anti-amiloidogénica, ello no conlleva mejorías relevantes en la evolución cognitiva en pacientes con demencia leve o moderada

- Existe consenso entre investigadores en que para conseguir modificar el curso de la enfermedad, los tratamientos habrán de ser aplicados en fases más precoces de la enfermedad de Alzheimer: ¿predemencia? ¿preclínica?

- Se necesitan más datos sobre el comportamiento de los biomarcadores en la enfermedad de Alzheimer y su relación con la sintomatología clínica para establecer “endpoints” válidos para estudios farmacológicos

Gracias por vuestra atención



Para saber más: www.alzforum.org