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16 novembre 2017

Le demenze: aspetti clinici, etici e medico-legali

LA SFIDA TERAPEUTICA TRA PASSATO E FUTURO

Dott. Andrea Arighi

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - Milano

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[Alzheimer disease therapy--moving from amyloid- \$\beta\$ to tau.](#)
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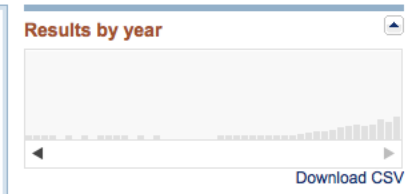
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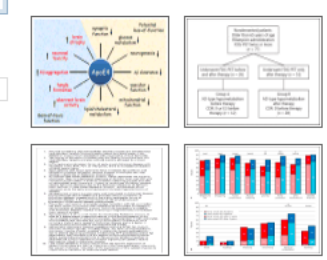
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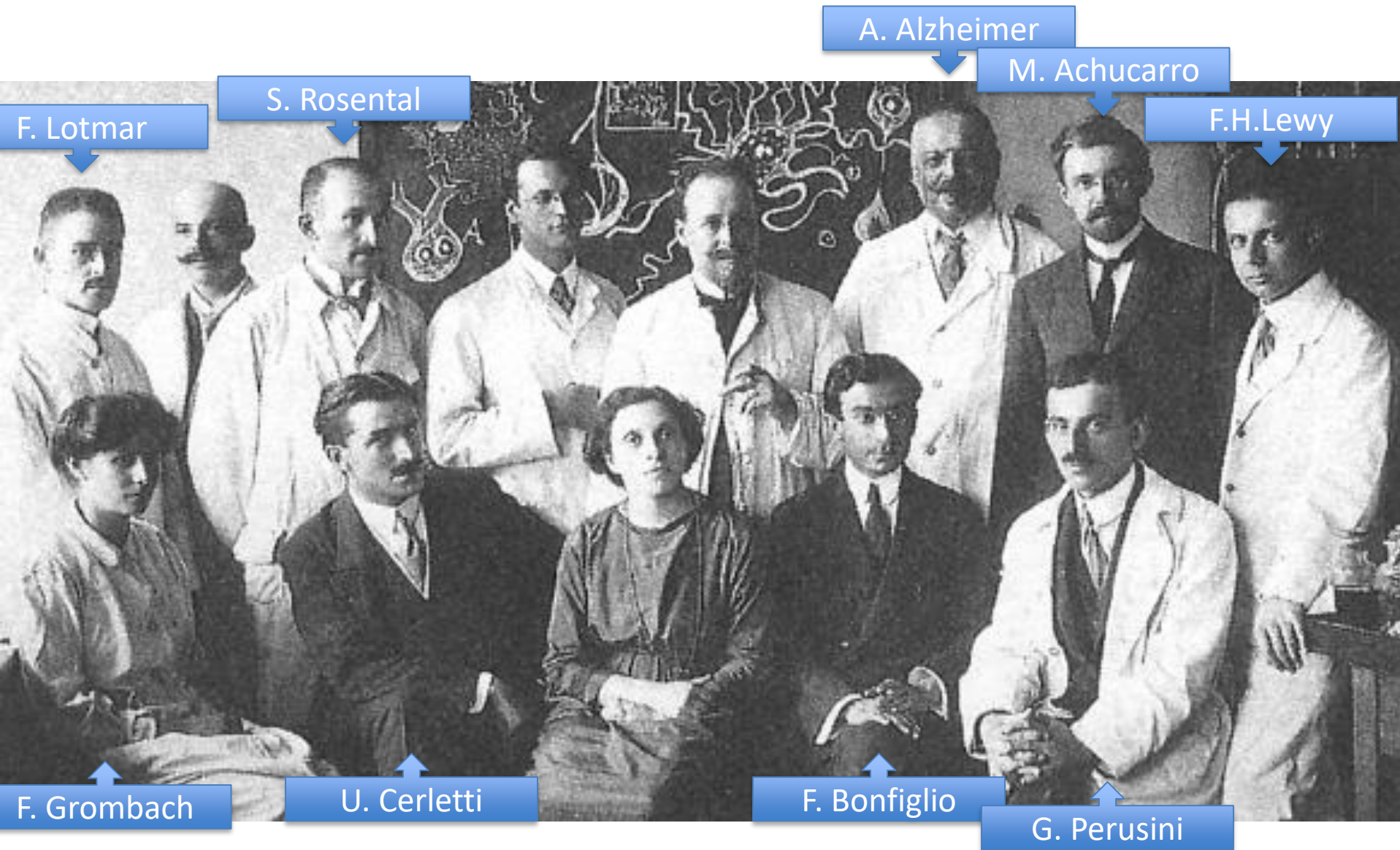
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Laboratorio neuro-patologico

Clinica psichiatrica di Monaco diretta da Emil Kraepelin

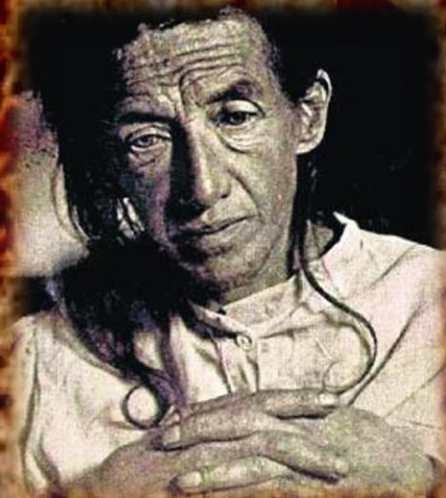




Alois Alzheimer
(1863-1915)

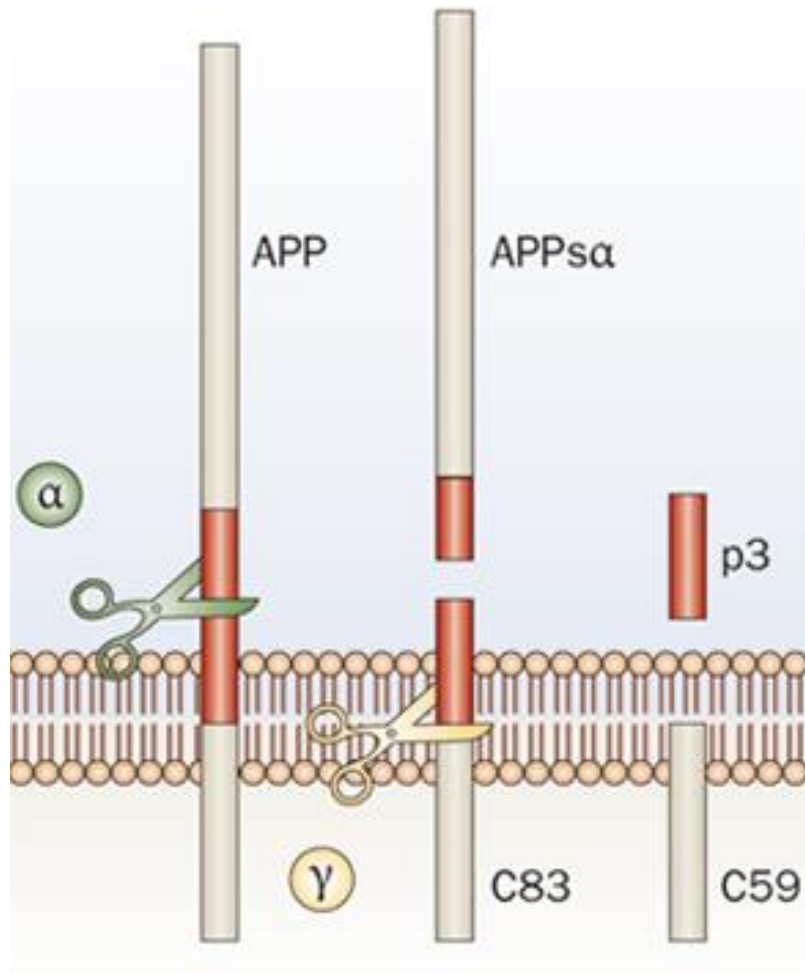


Gaetano Perusini
(1879-1915)

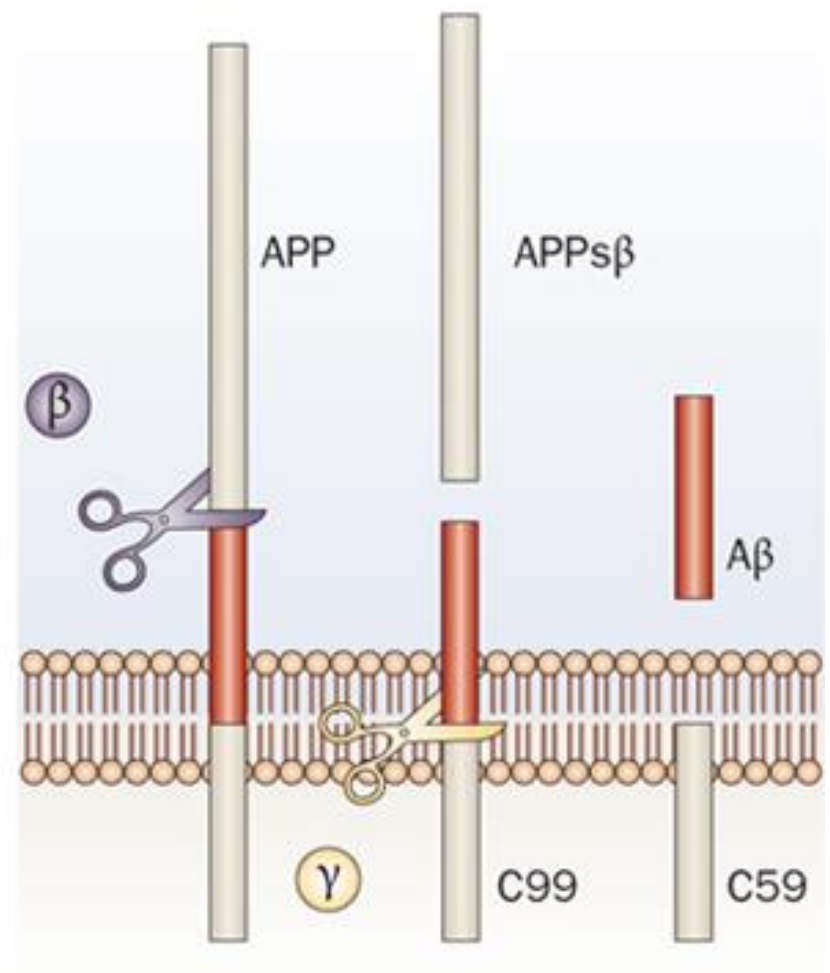


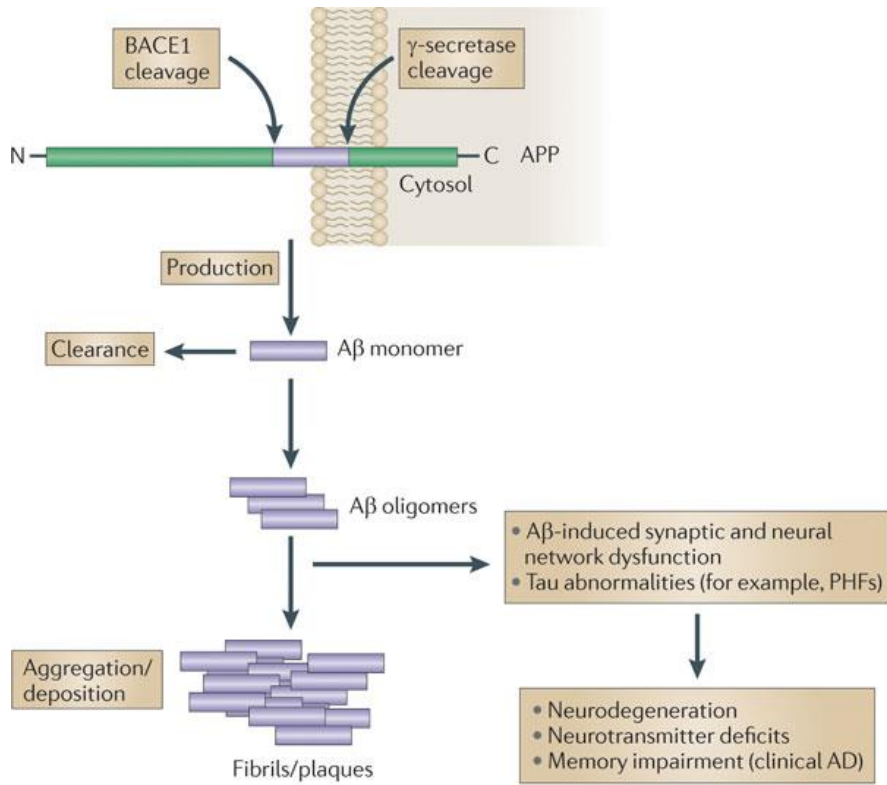
1906: Auguste Deter, 51 aa

Nonamyloidogenic pathway



Amyloidogenic pathway





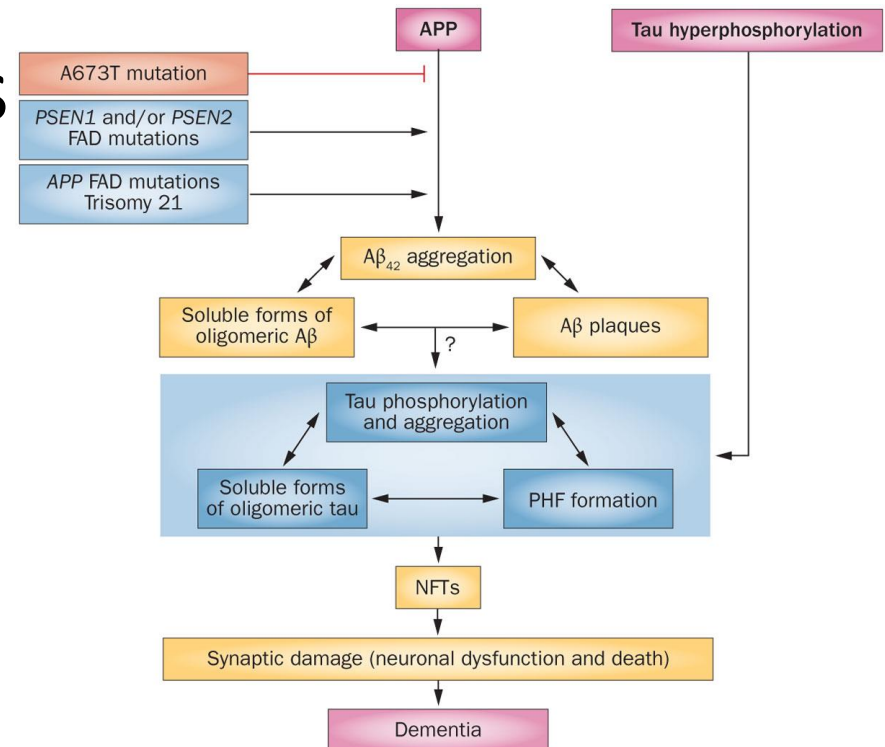
Nature Reviews | Neuroscience

Alzheimer disease therapy—moving from amyloid-β to tau

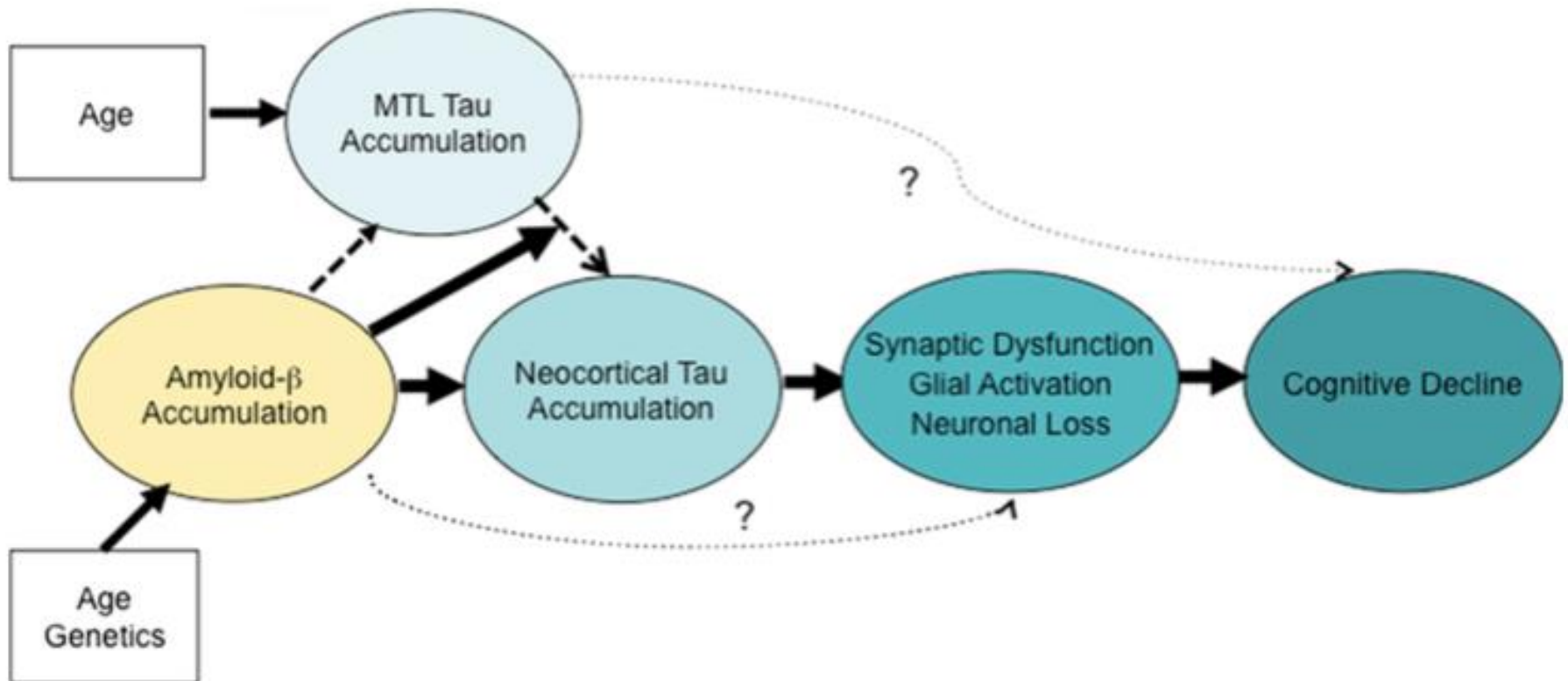
Ezio Giacobini and Gabriel Gold

Tau

VS



Hypothetical Model of the Interaction of Ab and Tau Accumulation

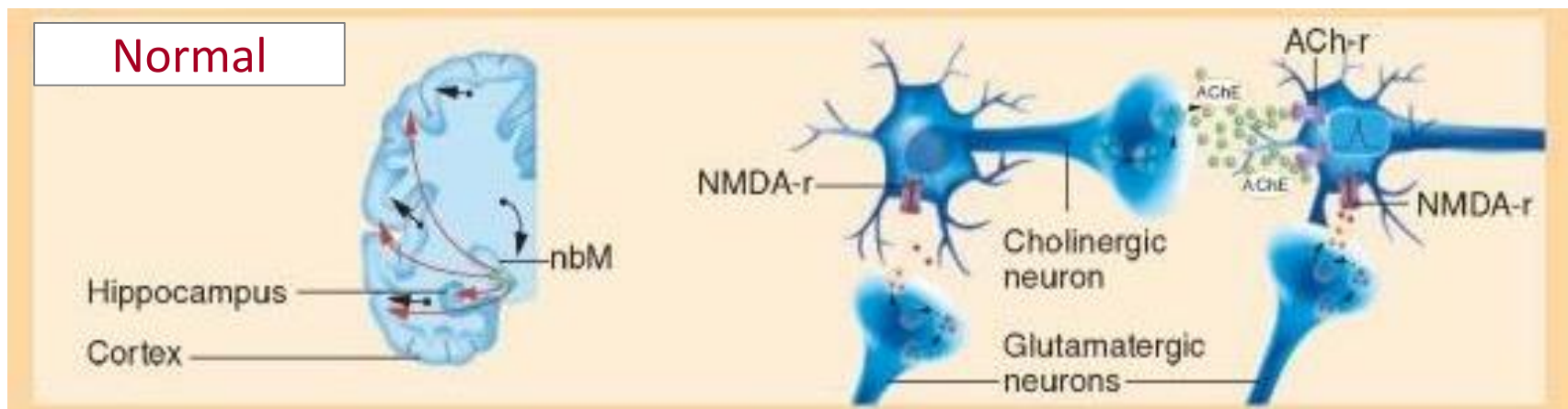




Il passato

Ipotesi colinergica e glutamatergica

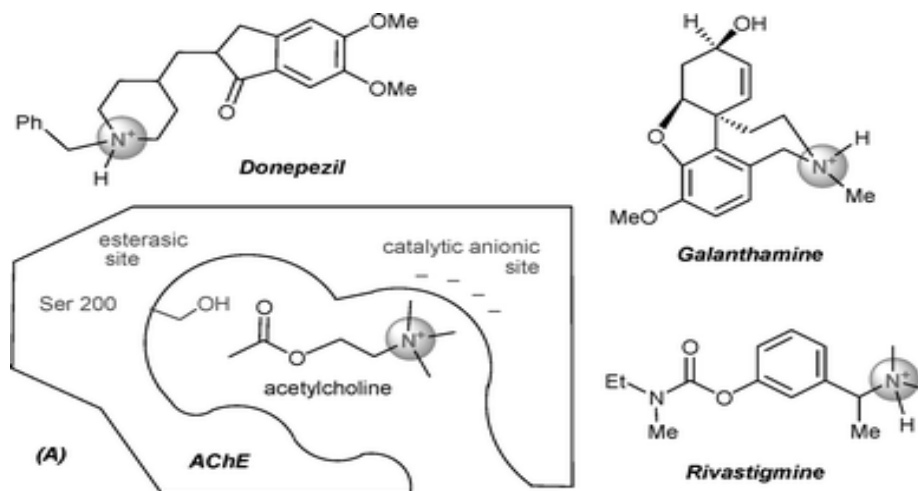
Nella patogenesi dell'AD uno dei primi eventi è la compromissione e la degenerazione dei **neruoni glutamatergici e GABAergici dell'ippocampo** (Revett et al., 2012; Tiwari and Patel, 2012) e la degenerazione dei **neuroni colinergici del proencefalo basale**, in particolare del NBM (Francis et al., 1999); inoltre sono state descritte anche alterazioni dei neuroni noradrenergici del locus coeruleus e dei neuroni serotoninergici del nucleo dorsale del rafe (Trillo et al., 2013).



L'approccio farmacologico

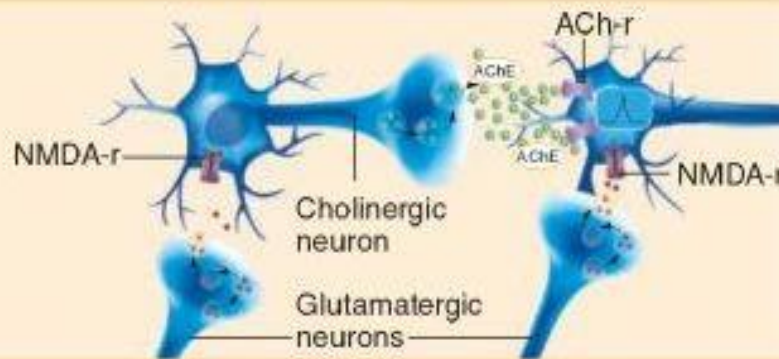
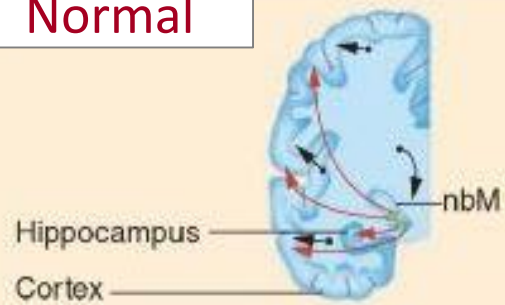
30 anni di storia

- Only **four** drugs (**cholinesterase inhibitors and memantine**) have been marketed for the treatment of AD (since 1996) and **none** since 2002 in Europe and 2003 in the USA
- Other cholinesterase inhibitors such as tacrine, velnacrine, physostigmine, eptastigmine and metrifonate showed efficacy as well, but were **not marketed** because of adverse events, safety and patent issues
- Drug discovery in neuroscience in general:
 - complicated, lengthy and uncertain, with an overall **failure rate greater than 95%**.
 - any given development programme may continue for **10–15 years from discovery to marketing approval**

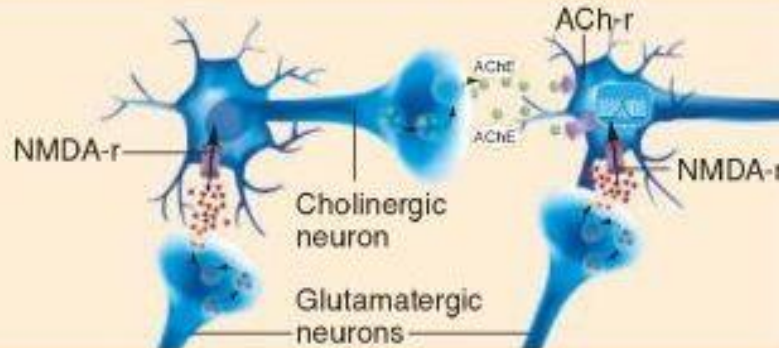
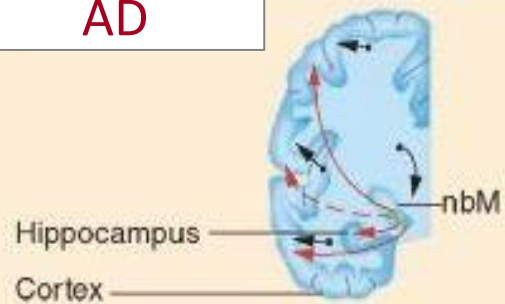


Pharmaceutical Research and Manufacturers of America
 Researching Alzheimer's medicines: setbacks and stepping stones, 2012

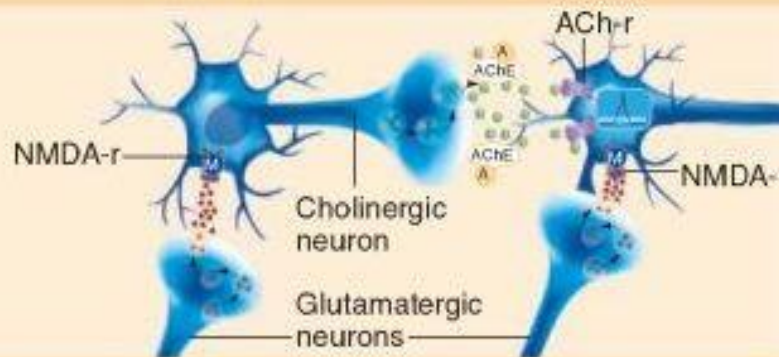
Normal



AD



Therapy



- Cholinergic input
- Glutamatergic input
- Acetylcholine
- Glutamate
- ACh-r
- NMDA-r
- AChEI
- Memantine
- AChE

Review: Cholinesterase inhibitors for Alzheimer's disease

Comparison: 1 Cholinesterase inhibitor (optimum dose) vs placebo

Outcome: 1 ADAS-Cog mean changes in score from baseline at 6 months or later (ITT-LOCF)

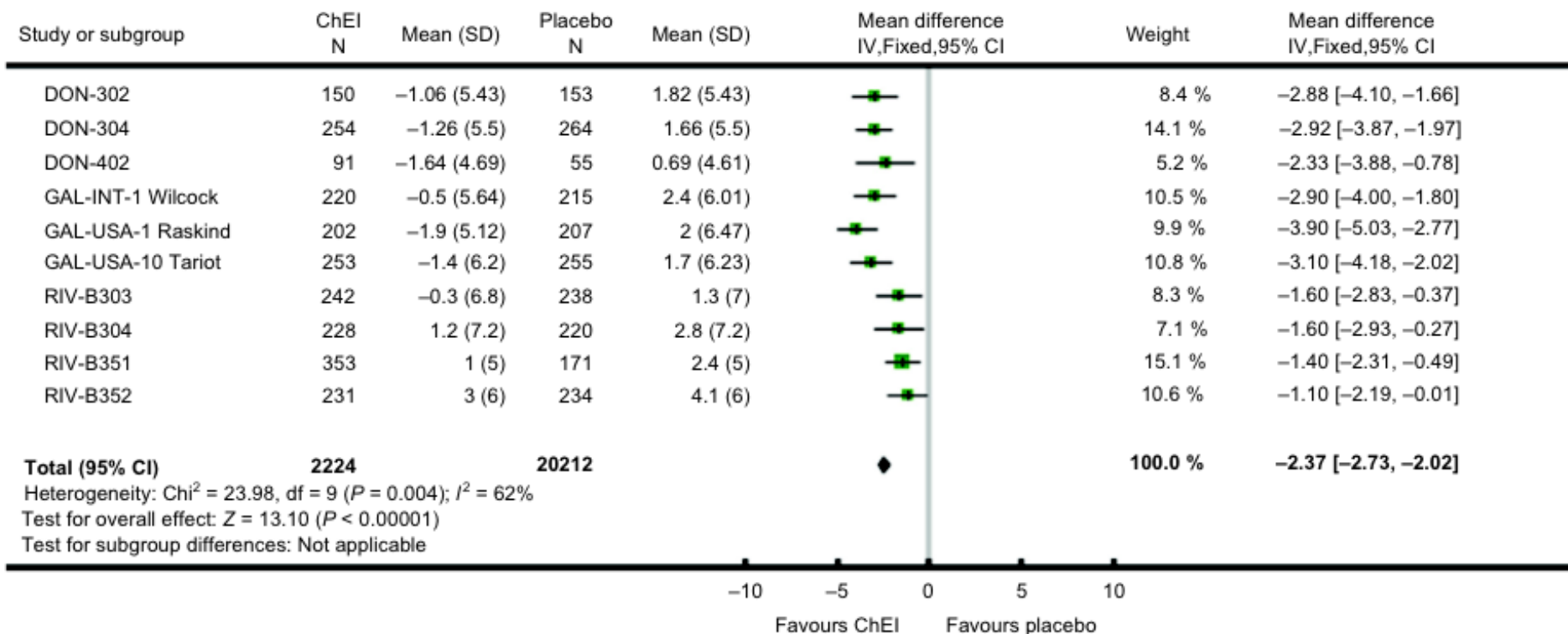


Fig. 1 Forestplots for 6-month trials of the three currently marketed cholinesterase inhibitors showing the general consistency of effect, mean drug-placebo differences on the ADAS-cog and 95% confidence intervals. The overall mean effect is 2.37 ADAS-cog points. Reproduced with permission from Birks [39].

Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis

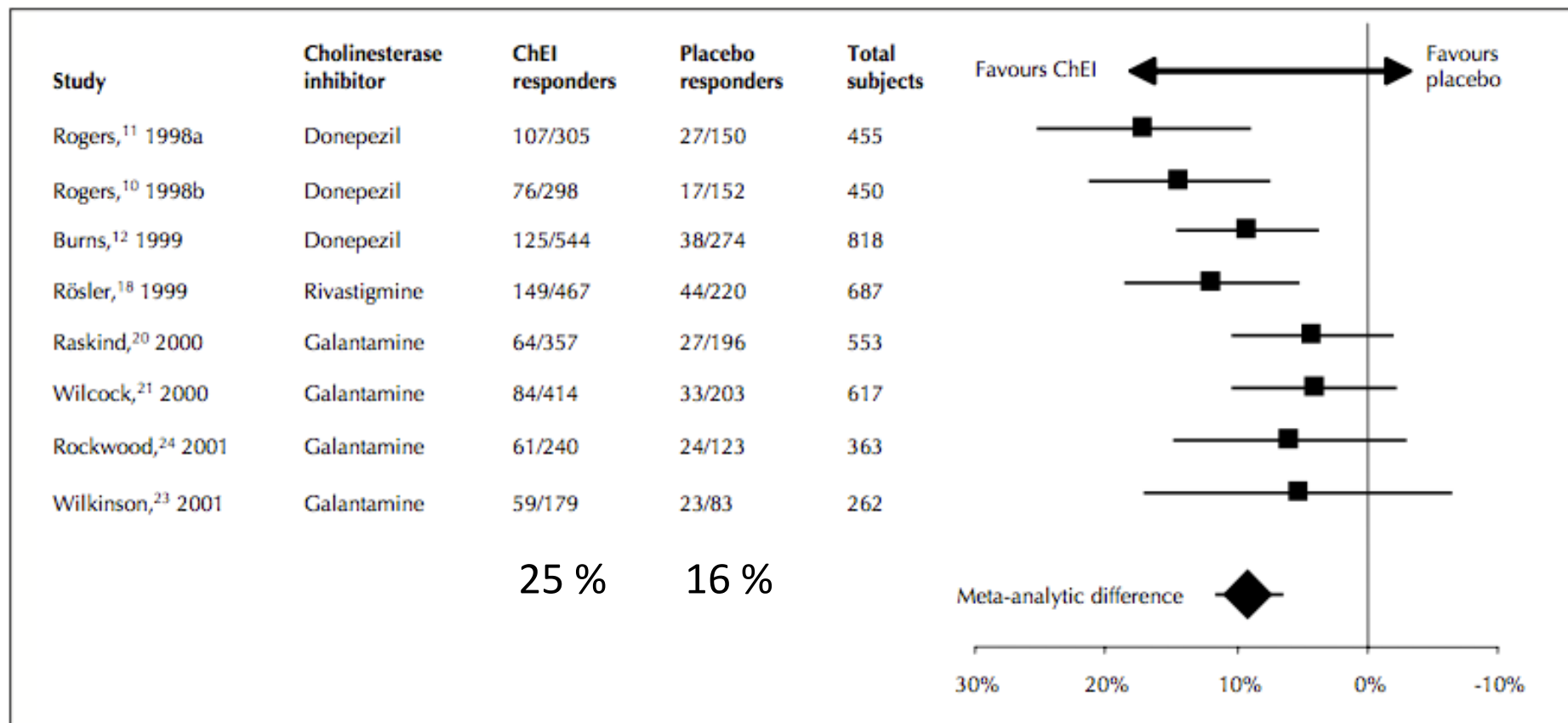


Fig. 1: Global response to treatment with cholinesterase inhibitors (ChEIs) in 8 randomized, double-blind, placebo-controlled, parallel-group trials. The graph indicates the proportions of global responders to ChEI treatment in excess of the proportions responding to placebo for each of the studies and overall, when the data were pooled, with 95% confidence intervals.

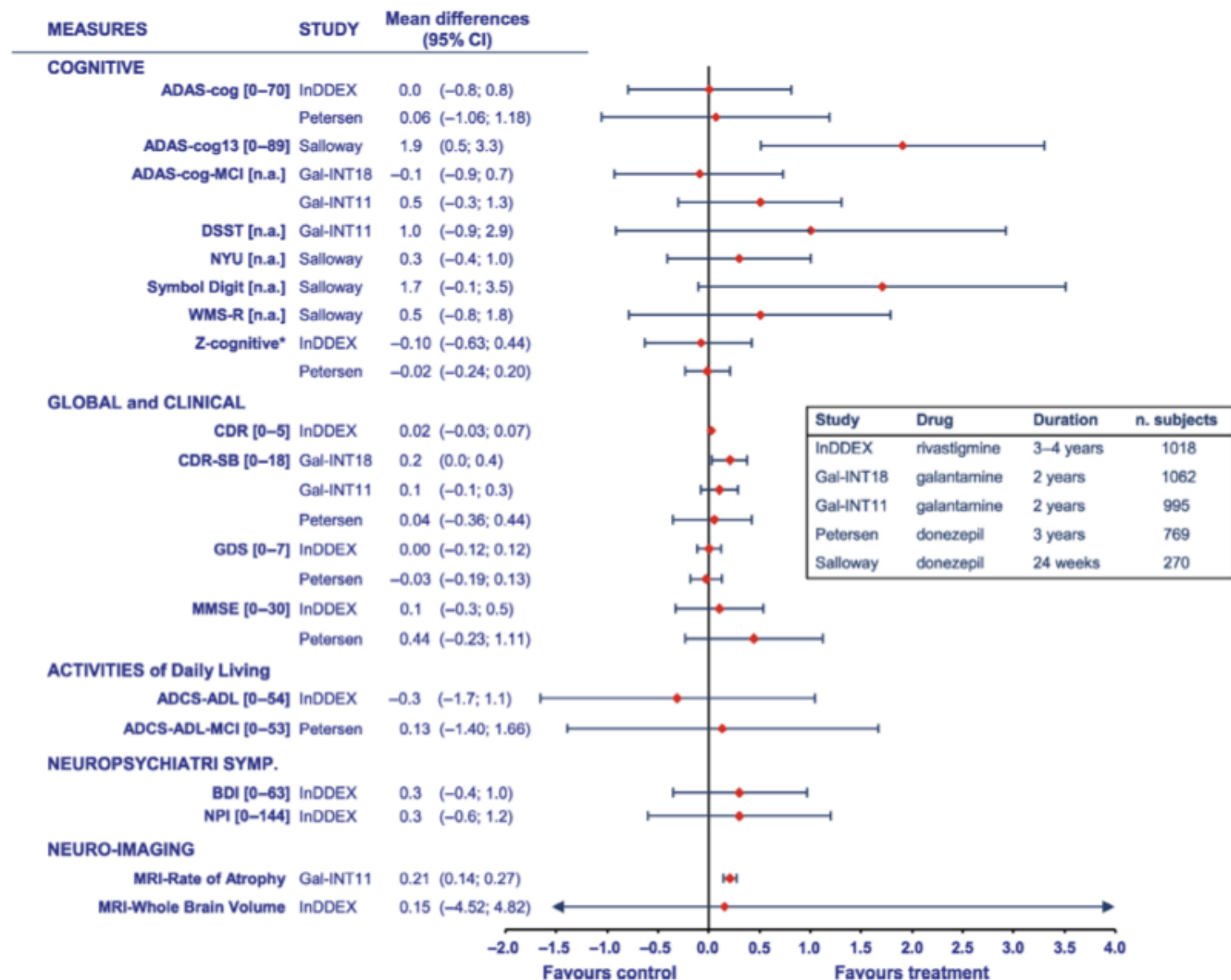


Fig. 2 Outcomes of clinical trials of cholinesterase inhibitors for mild cognitive impairment showing a general lack of cognitive and global effects in trials from 2 to 4 years in duration (except for one 24-week trial). The data show the point estimates and 95% confidence intervals of the drug-placebo differences. The Z-cognitive is a composite of the neuropsychological test battery used in the rivastigmine trial. Reproduced with permission from Raschetti et al. [76].

Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (2012)

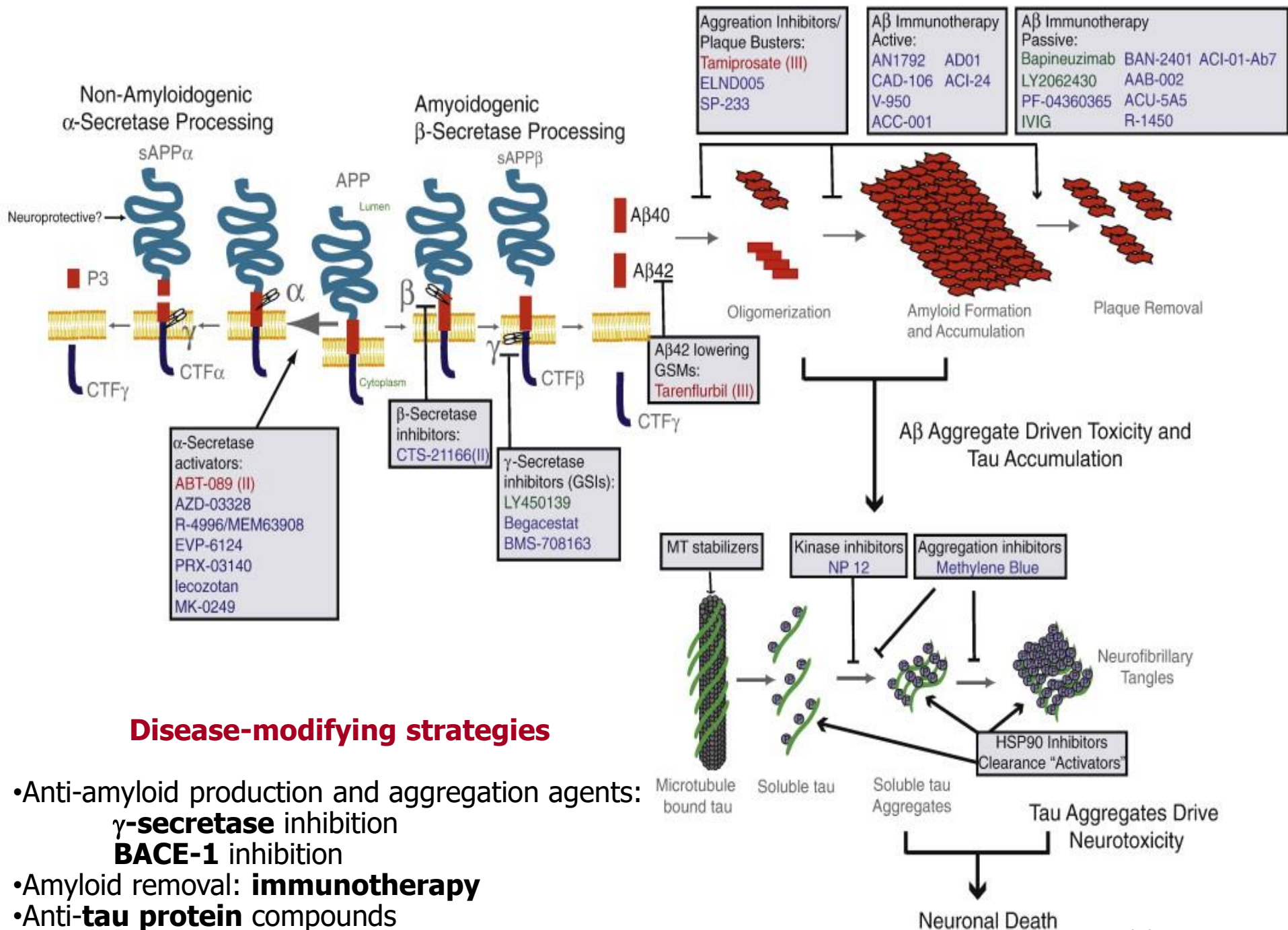
Serge Gauthier, MD, Christopher Patterson, MD, Howard Chertkow, MD, Michael Gordon, MD, Nathan Herrmann, MD, Kenneth Rockwood, MD, Pedro Rosa-Neto, md, phd, Jean-Paul Soucy, MD on behalf of the cccdt4 participants* *McGill Center for Studies in Aging, Montreal, QC*

Donepezil	Aricept	Cholinesterase Inhibition	FDA: 1996, EMEA: 1997; QD dosing; for mild, mod, severe AD
Rivastigmine	Exelon	Cholinesterase Inhibition	BID; patch formulation released; for mild to mod AD
Galantamine	Reminyl	Cholinesterase Inhibition	BID; XR formulation released; for mild to mod AD

- **all three** ChEIs have demonstrated **efficacy** for mild to severe AD
- improvement is **statistically significant** but **clinically marginal**
 - a trial for most patients is recommended (**Grade 1A**)
 - direct comparisons do **not suggest differences** (**Grade 2B**)



Il presente



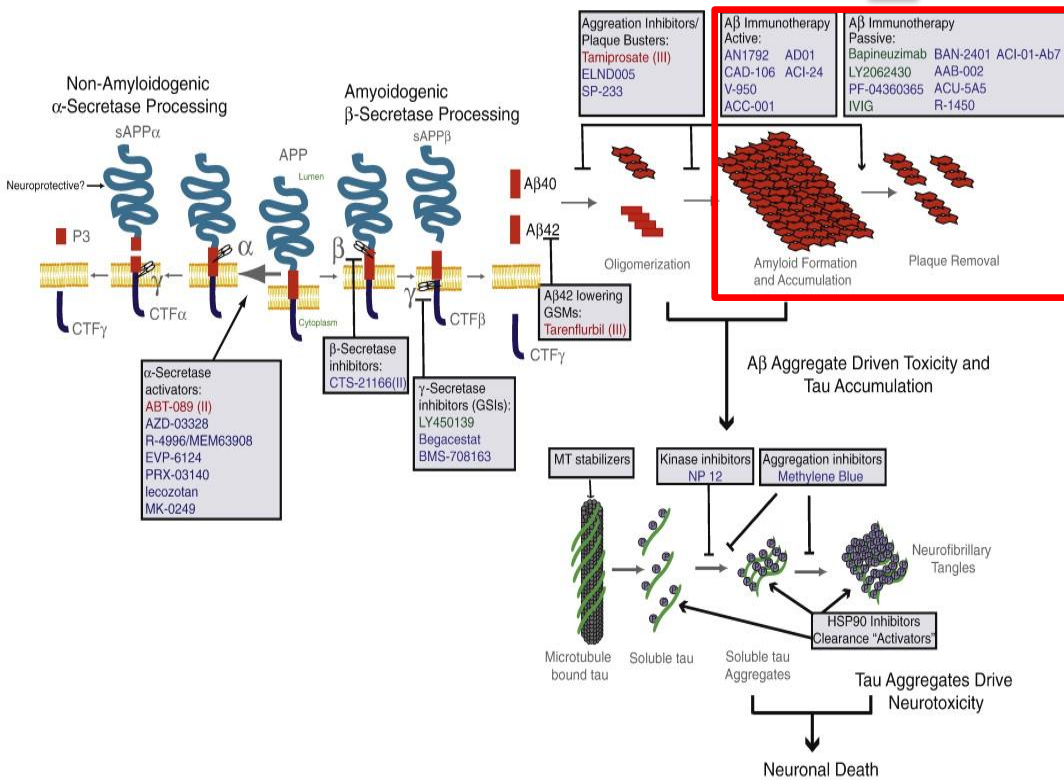
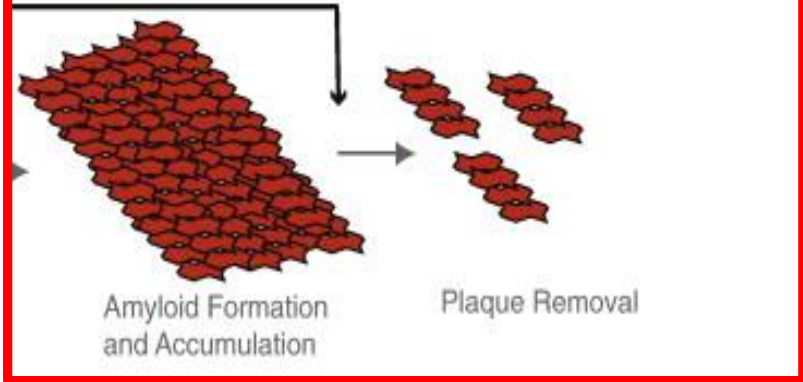
Disease-modifying strategies

- Anti-amyloid production and aggregation agents:
 - γ -secretase inhibition
 - BACE-1** inhibition
- Amyloid removal: **immunotherapy**
- Anti-**tau protein** compounds

Immunotherapy

A β Immunotherapy Active:
 AN1792 AD01
 CAD-106 ACI-24
 V-950
 ACC-001

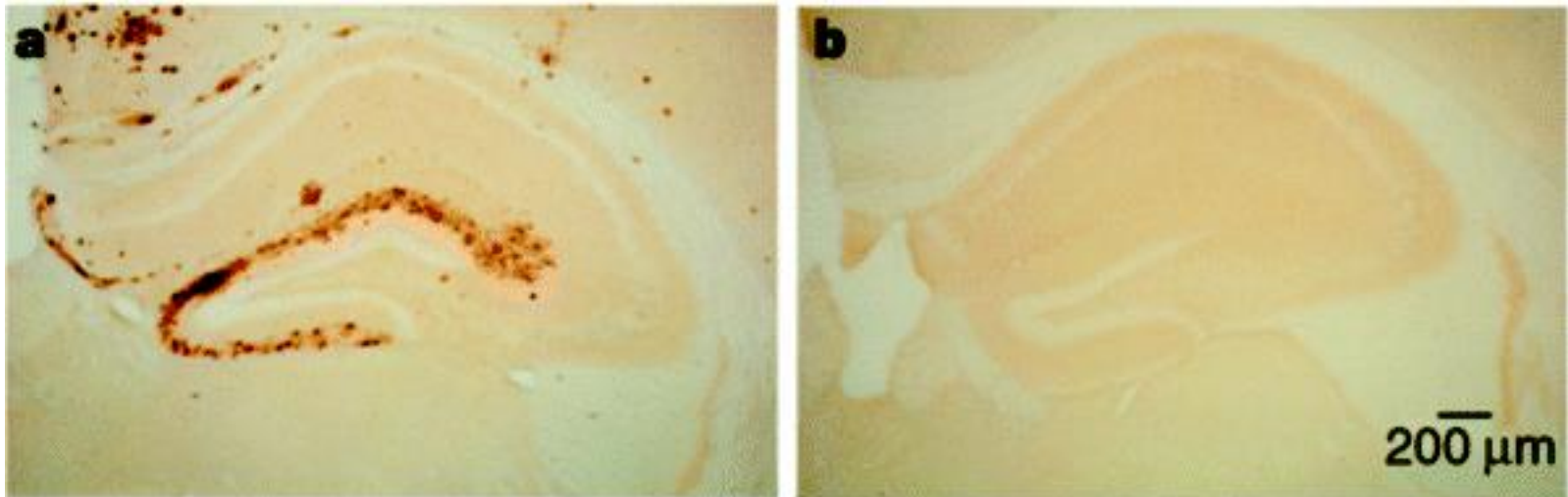
A β Immunotherapy Passive:
 Bapineuzimab BAN-2401 ACI-01-A β 7
 LY2062430 AAB-002
 PF-04360365 ACU-5A5
 IVIG R-1450



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

Dale Schenk, Robin Barbour, Whitney Dunn, Grace Gordon, Henry Grajeda, Teresa Guido, Kang Hu, Jiping Huang, Kelly Johnson-Wood, Karen Khan, Dora Kholodenko, Mike Lee, Zhenmei Liao, Ivan Lieberburg, Ruth Motter, Linda Mutter, Ferdie Soriano, George Shopp, Nicki Vasquez, Christopher Vandever, Shannan Walker, Mark Wogulis, Ted Yednock, Dora Games & Peter Seubert

Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA



Active immunization

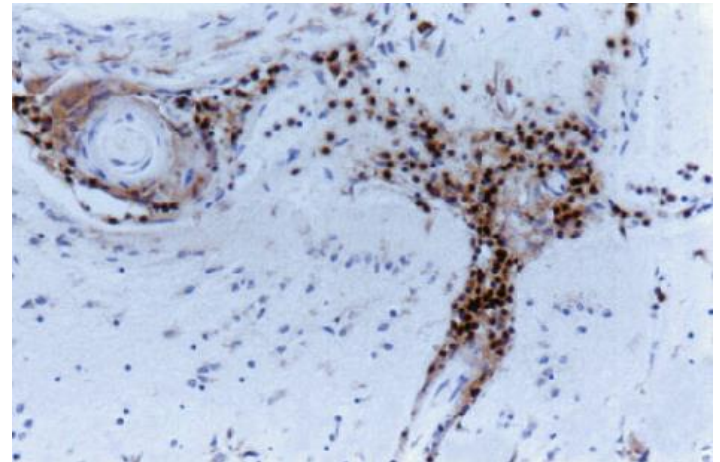
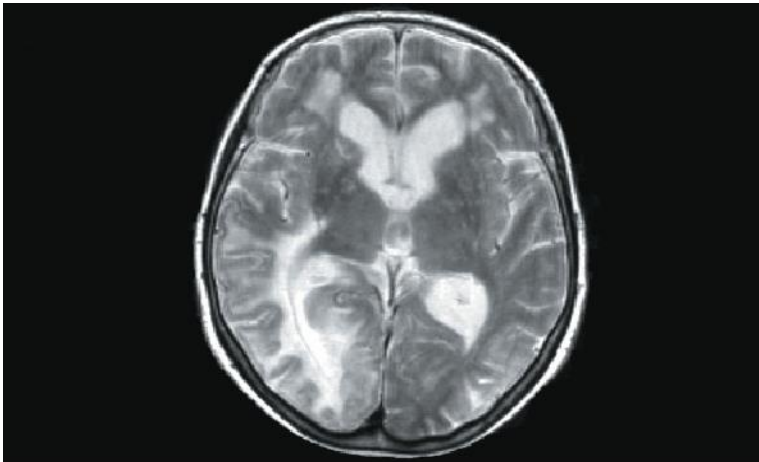
HUMAN TRIAL: AN1792 + AS21 adjuvant

in 2001 **phase IIa** study
372 probable AD (mild to moderate)

Study discontinuation!

Aseptic meningoencephalitis in **18** of 300 (**6%**) immunized patients

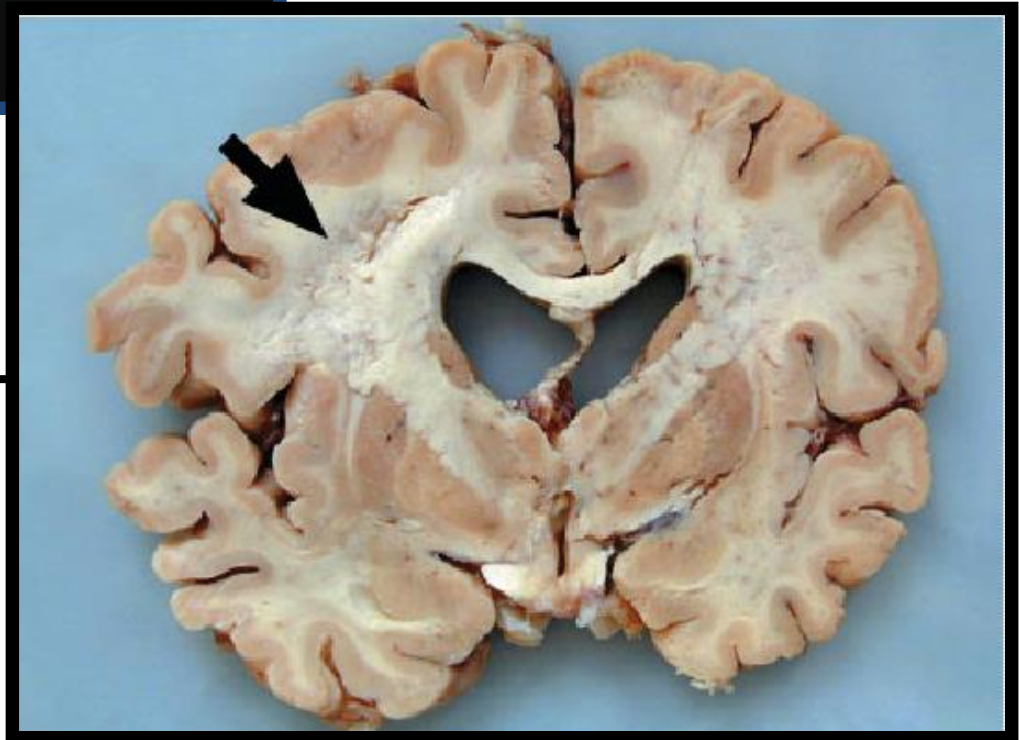
By the time of discontinuation:
24 patients received 3 immunizations
274 received 2 immunizations

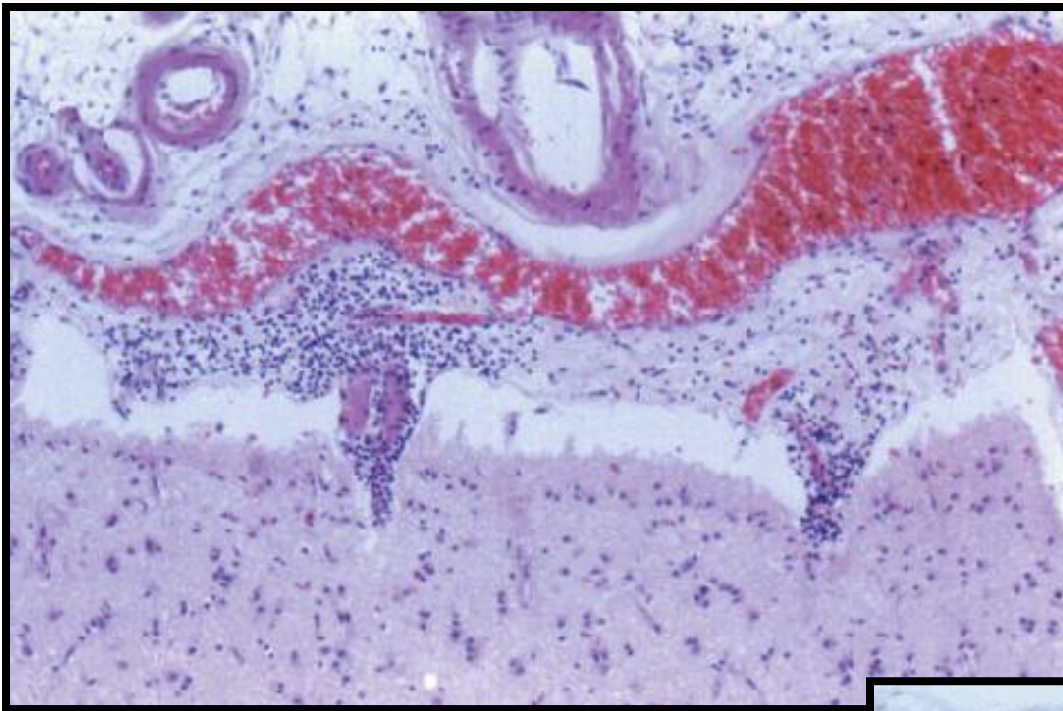




**MRI (T2):
WIDESPREAD SIGNAL
ALTERATION IN
CEREBRAL WHITE
MATTER**

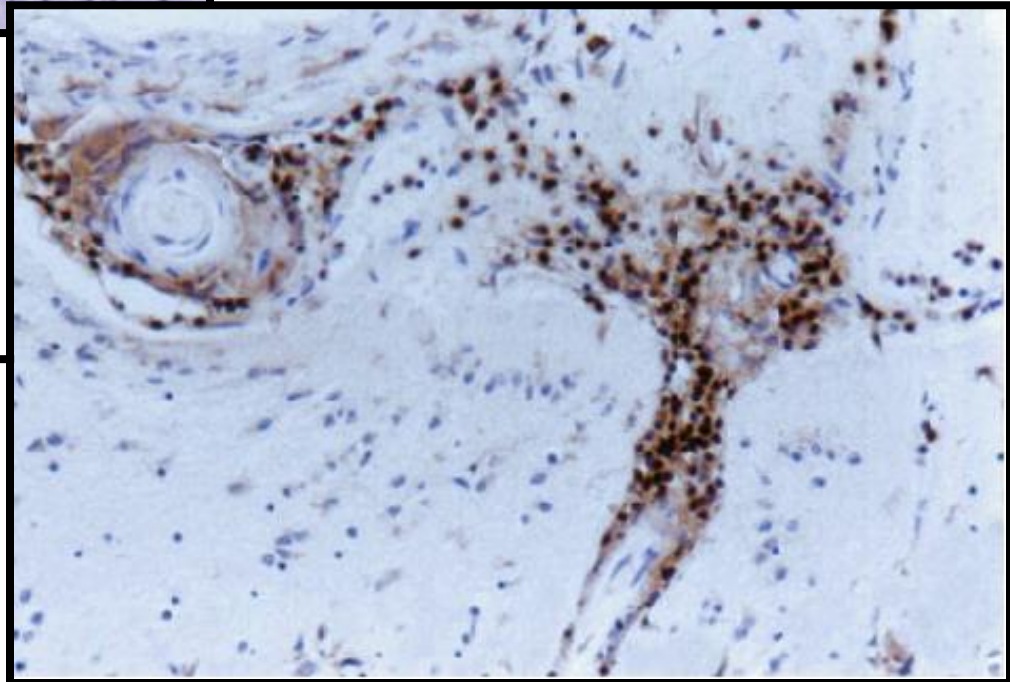
**GRANULAR CHANGES IN
CEREBRAL WHITE MATTER**





LEPTOMENINGEAL
INFILTRATE OF
LYMPHOCYTES
STAINED WITH
H&E...

...AND IMMUNO-STAINED
WITH A **T-LYMPHOCYTE**
ANTIBODY (CD3)





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

S. Gilman, MD, FRCP; M. Koller, MD, MPH; R.S. Black, MD; L. Jenkins, PhD;
S.G. Griffith, MD, PhD, MRCP; N.C. Fox, MD, FRCP; L. Eisner, MD; L. Kirby, MD; M. Boada Rovira, MD;
F. Forette, MD; and J.-M. Orgogozo, MD, for the AN1792(QS-21)-201 Study Team*

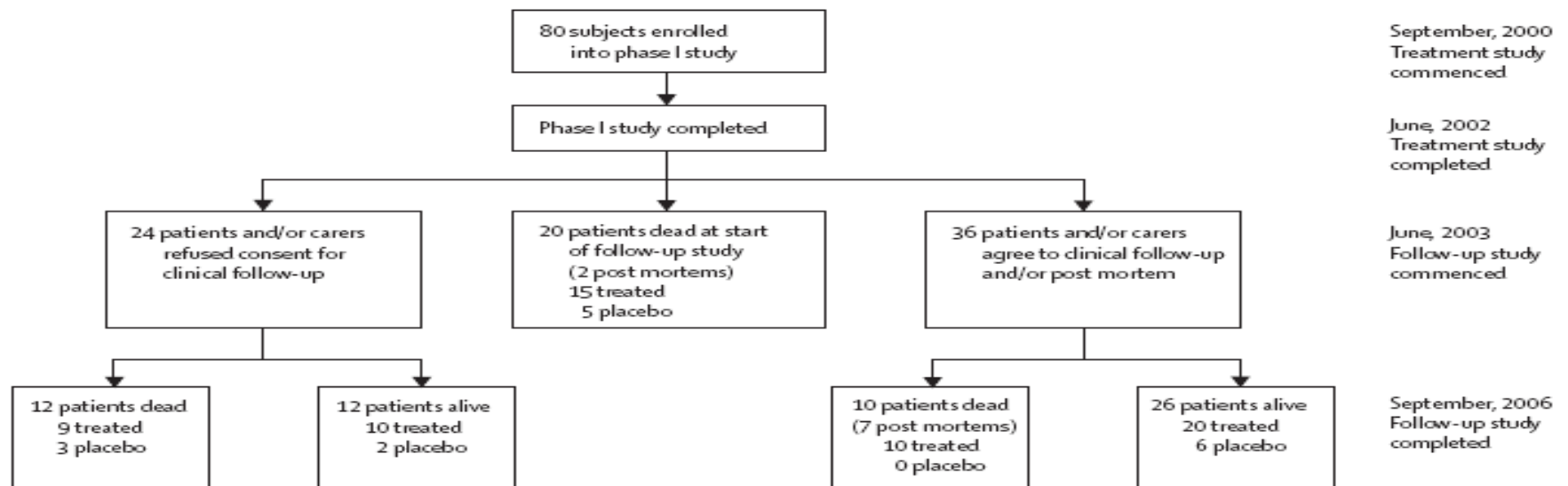
Double-blind clinical assessment maintained for
12 months:

significant differences in cognition favouring
antibody responders compared to placebo group

Long-term effects of A β_{42} immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial

Clive Holmes, Delphine Boche, David Wilkinson, Ghasem Yadegarfar, Vivienne Hopkins, Anthony Bayer, Roy W Jones, Roger Bullock, Seth Love, James W Neal, Elina Zotova, James A R Nicoll

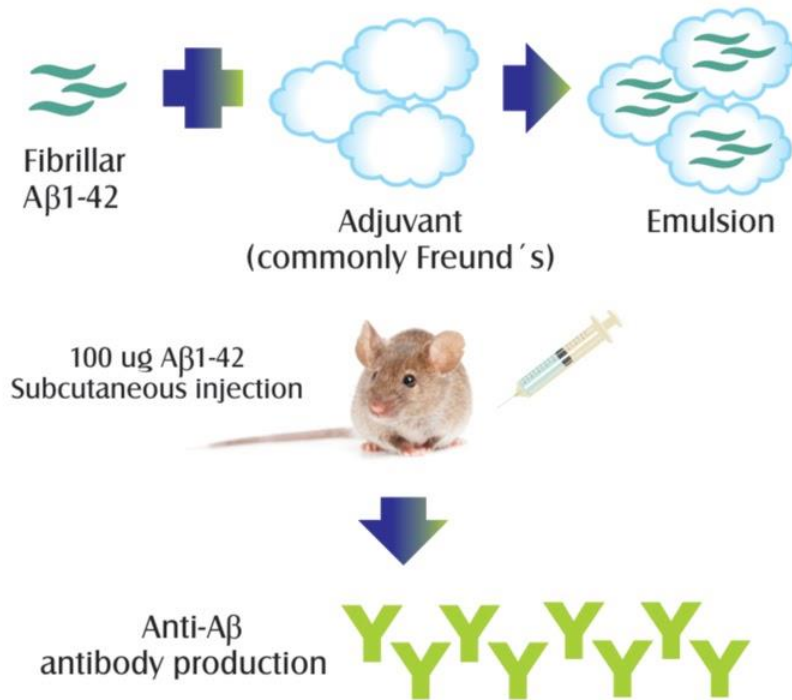
Lancet 2008; 372: 216–23



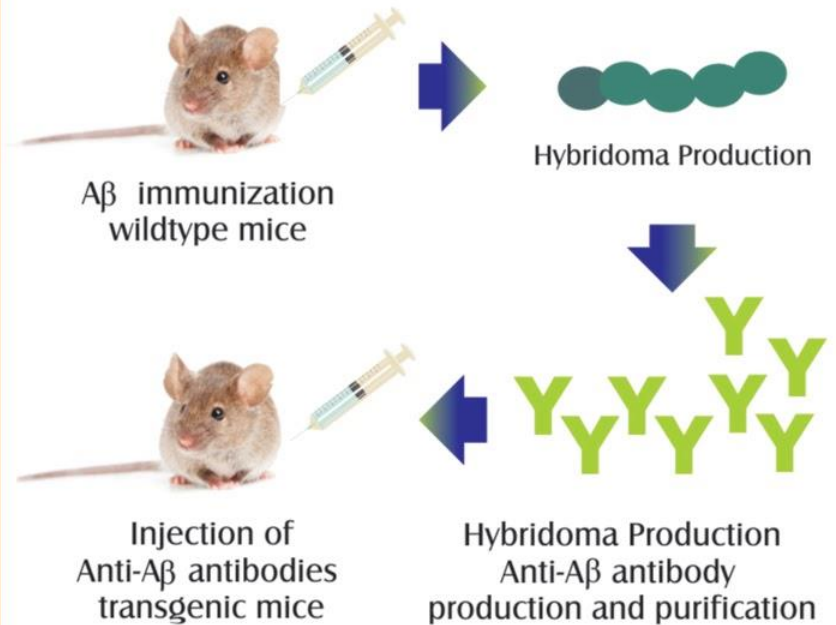
Results after 6 yrs: clearance of amyloid plaques, but no evidence of increased survival and no improvement in the time to severe dementia!

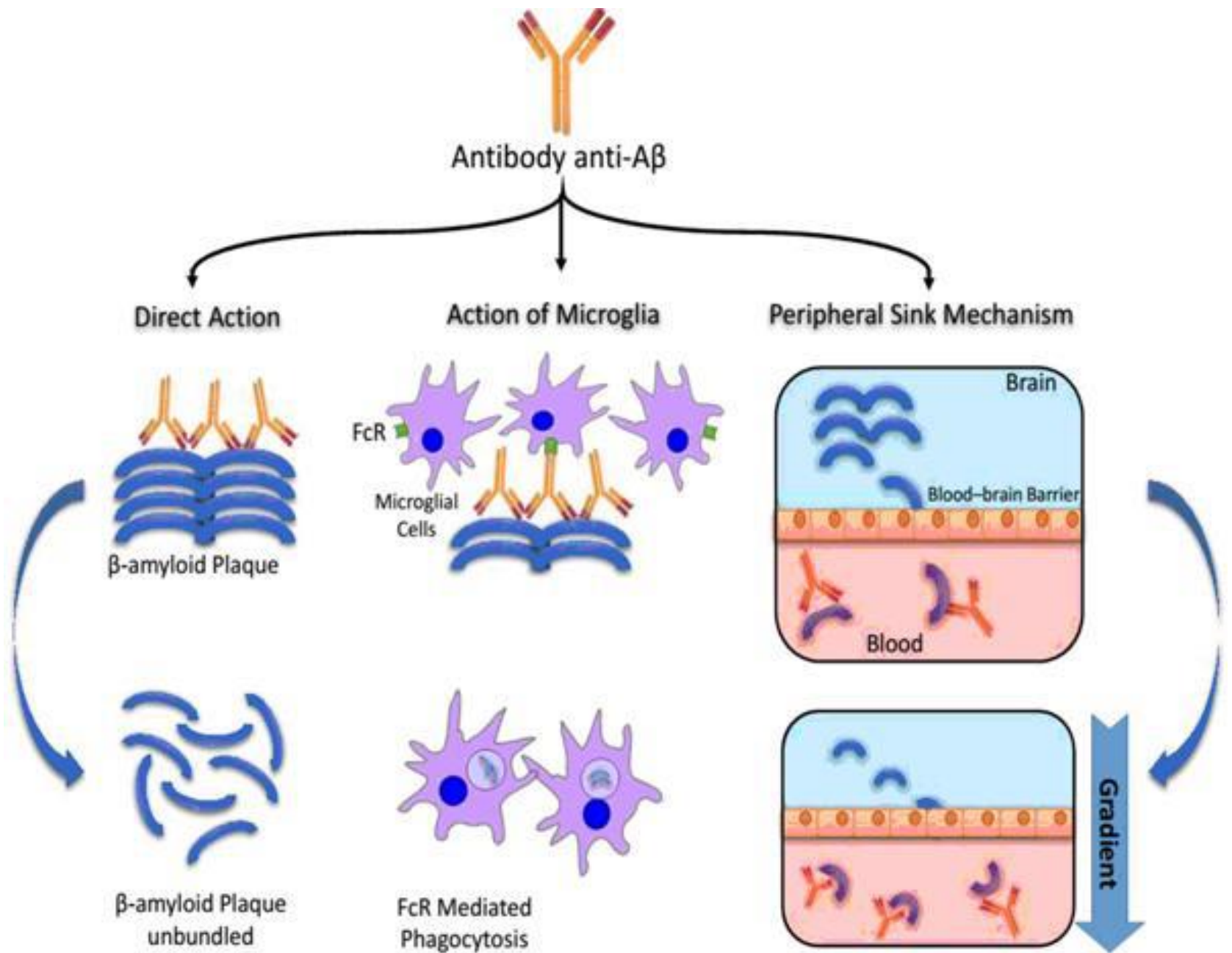
New approach: passive immunization

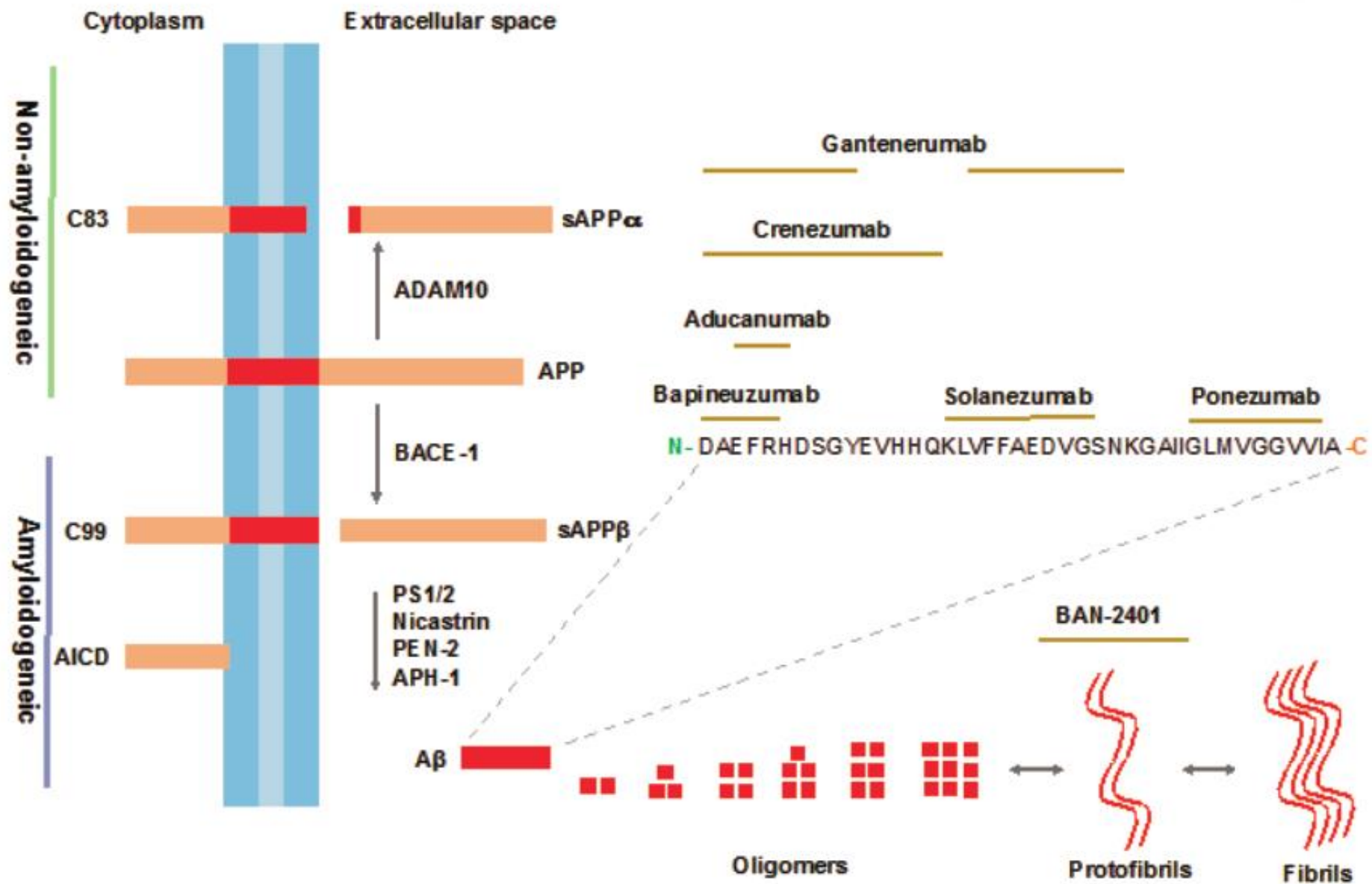
A Active Immunization



B Passive Immunization







^{11}C -PiB PET assessment of change in fibrillar amyloid- β load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

Juha O Rinne, David J Brooks, Martin N Rossor, Nick C Fox, Roger Bullock, William E Klunk, Chester A Mathis, Kaj Blennow, Jerome Barakos, Aren A Okello, Sofia Rodriguez Martinez de Llano, Enchi Liu, Martin Koller, Keith M Gregg, Dale Schenk, Ronald Black, Michael Grundman

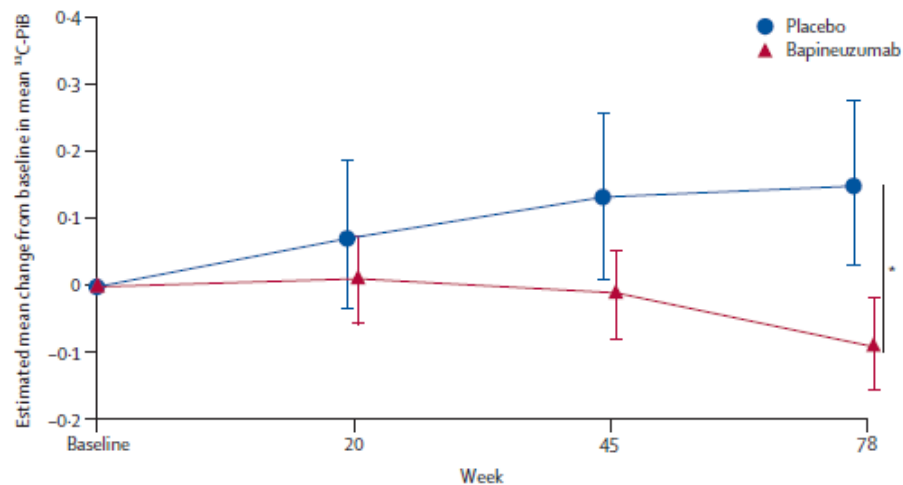


Figure 2: Estimated change from baseline over time in mean ^{11}C -PiB PET
Data are least squares means and 95% CIs. *Difference between patients in the placebo group and those in the bapineuzumab group at week 78 = -0.24 ($p=0.003$). PiB=Pittsburgh compound B.

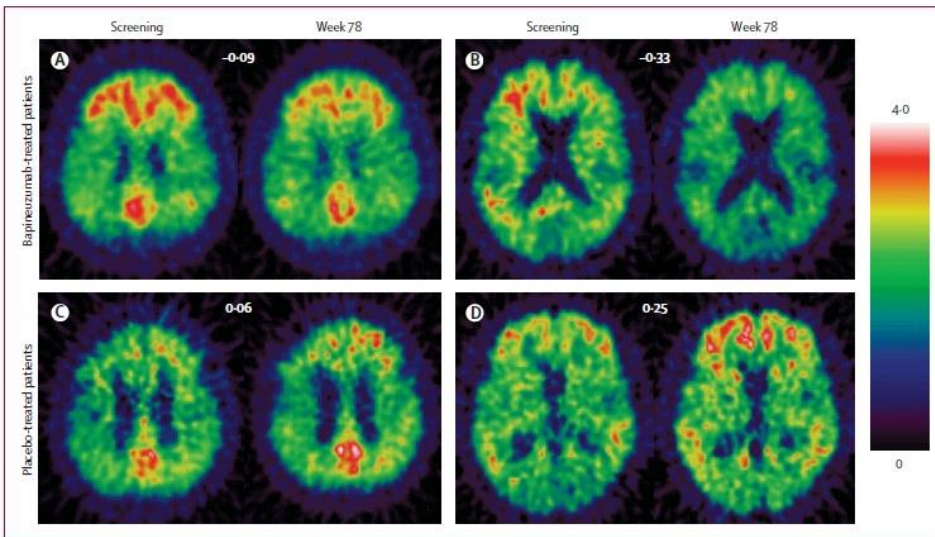
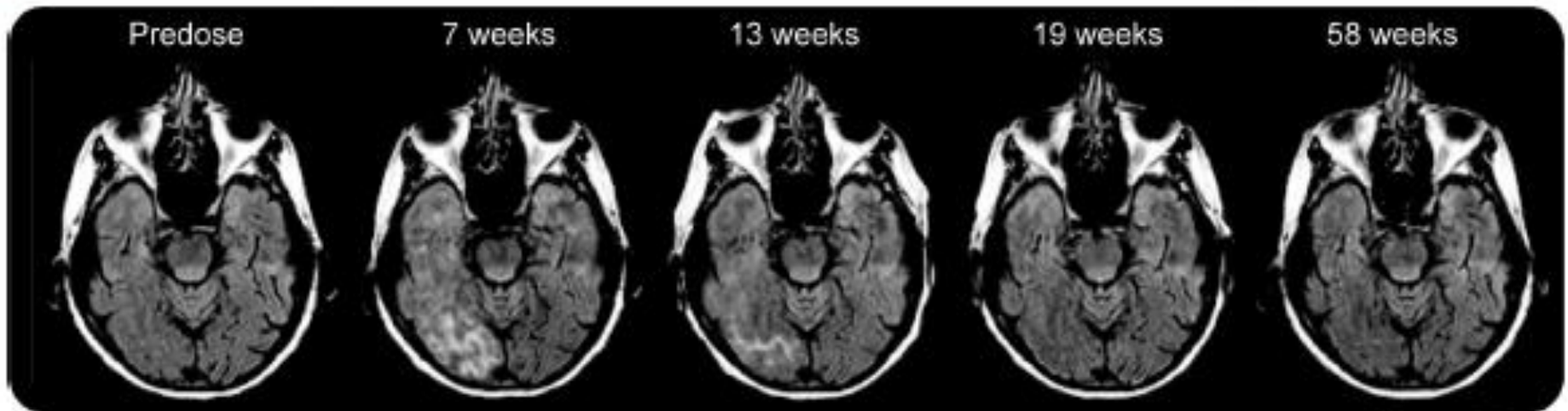


Figure 4: ^{11}C -PiB PET images from patients treated with bapineuzumab and those given placebo
Changes from screening to week 78 in patients treated with bapineuzumab (A,B) and in patients treated with placebo (C,D). Mean ^{11}C -PiB PET changes are shown at the top centre of each panel for each patient. The scale bar shows the PiB uptake ratios relative to cerebellum by colour. The scans before and after treatment are from MRI co-registered images in the same plane. PiB=Pittsburgh compound B.

Bapineuzumab:

VASOGENIC OEDEMA - MICROHEMORRHAGES

- detected on **MRI** in 12/124 patients (**9.7%**)
- **symptomatic** patients: headache, confusion, vomiting, and gait disturbance
- cessation of dosing → symptoms resolved over several weeks; MRI findings resolved over several months

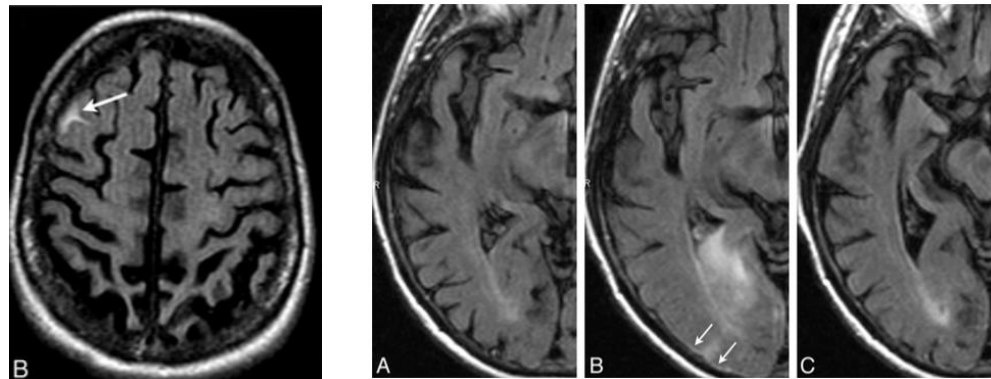


Appeared on the FLAIR MRI sequence with **high signal intensity** in the white matter, leptomeninges, or sulci, frequently associated with gyral swelling and cortical T2 hyperintensity in the adjacent cortex

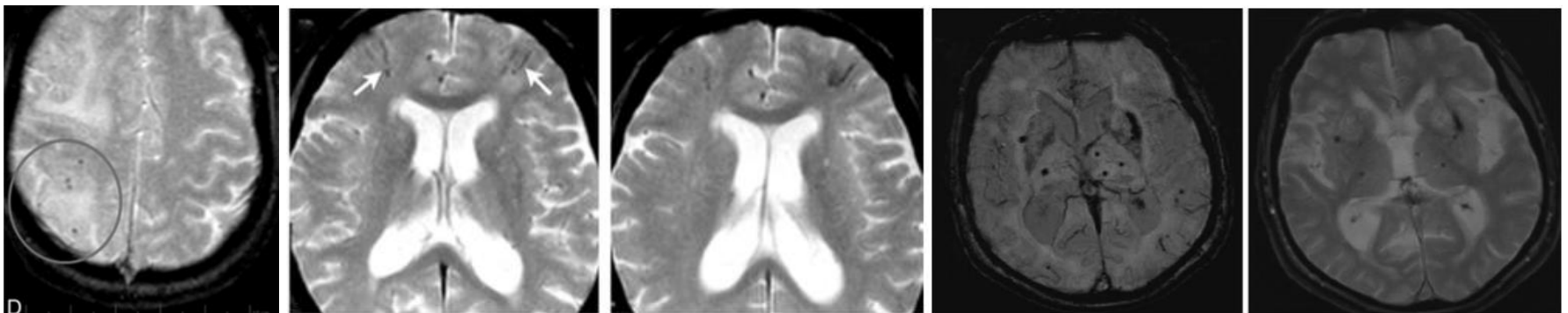
ARIA

Amyloid-Related Imaging Abnormalities

- **ARIA-E** → parenchymal or sulcal hyperintensities on FLAIR indicative of parenchymal edema or sulcal effusions



- **ARIA-H** → hypointense regions on gradient recalled-echo/T2* indicative of hemosiderin deposition



ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

Stephen Salloway, M.D., Reisa Sperling, M.D., Nick C. Fox, M.D., Kaj Blennow, M.D., William Klunk, M.D., Murray Raskind, M.D., Marwan Sabbagh, M.D., Lawrence S. Honig, M.D., Ph.D., Anton P. Porsteinsson, M.D., Steven Ferris, Ph.D., Marcel Reichert, M.D., Nzeera Ketter, M.D., Bijan Nejadnik, M.D., Volkmar Guenzler, M.D., Maja Miloslavsky, Ph.D., Daniel Wang, Ph.D., Yuan Lu, M.S., Julia Lull, M.A., Iulia Cristina Tudor, Ph.D., Enchi Liu, Ph.D., Michael Grundman, M.D., M.P.H., Eric Yuen, M.D., Ronald Black, M.D., and H. Robert Brashear, M.D., for the Bapineuzumab 301 and 302 Clinical Trial Investigators*

RESULTS

There were no significant between-group differences in the primary outcomes. At week 78, the between-group differences in the change from baseline in the ADAS-cog11 and DAD scores (bapineuzumab group minus placebo group) were -0.2 ($P=0.80$) and -1.2 ($P=0.34$), respectively, in the carrier study; the corresponding differences in the noncarrier study were -0.3 ($P=0.64$) and 2.8 ($P=0.07$) with the 0.5-mg-per-kilogram dose of bapineuzumab and 0.4 ($P=0.62$) and 0.9 ($P=0.55$) with the 1.0-mg-per-kilogram dose. The major safety finding was amyloid-related imaging abnormalities with edema among patients receiving bapineuzumab, which increased with bapineuzumab dose and $APOE\epsilon 4$ allele number and which led to discontinuation of the 2.0-mg-per-kilogram dose. Between-group differences were observed with respect to PIB-PET and cerebrospinal fluid phospho-tau concentrations in $APOE\epsilon 4$ allele carriers but not in noncarriers.

CONCLUSIONS

Bapineuzumab did not improve clinical outcomes in patients with Alzheimer's disease, despite treatment differences in biomarkers observed in $APOE\epsilon 4$ carriers.

(Funded by Janssen Alzheimer Immunotherapy and Pfizer; Bapineuzumab 301 and 302 ClinicalTrials.gov numbers, NCT00575055 and NCT00574132, and EudraCT number, 2009-012748-17.)

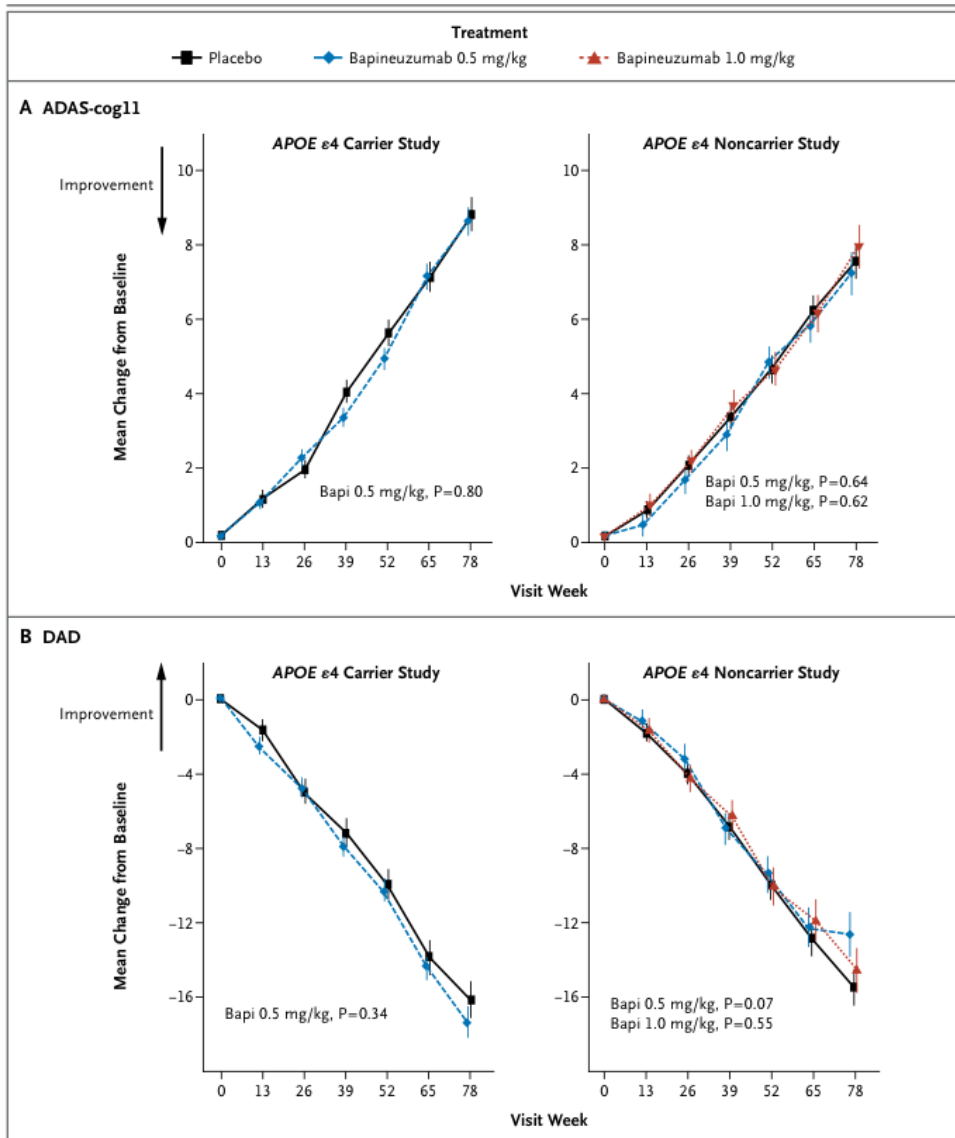
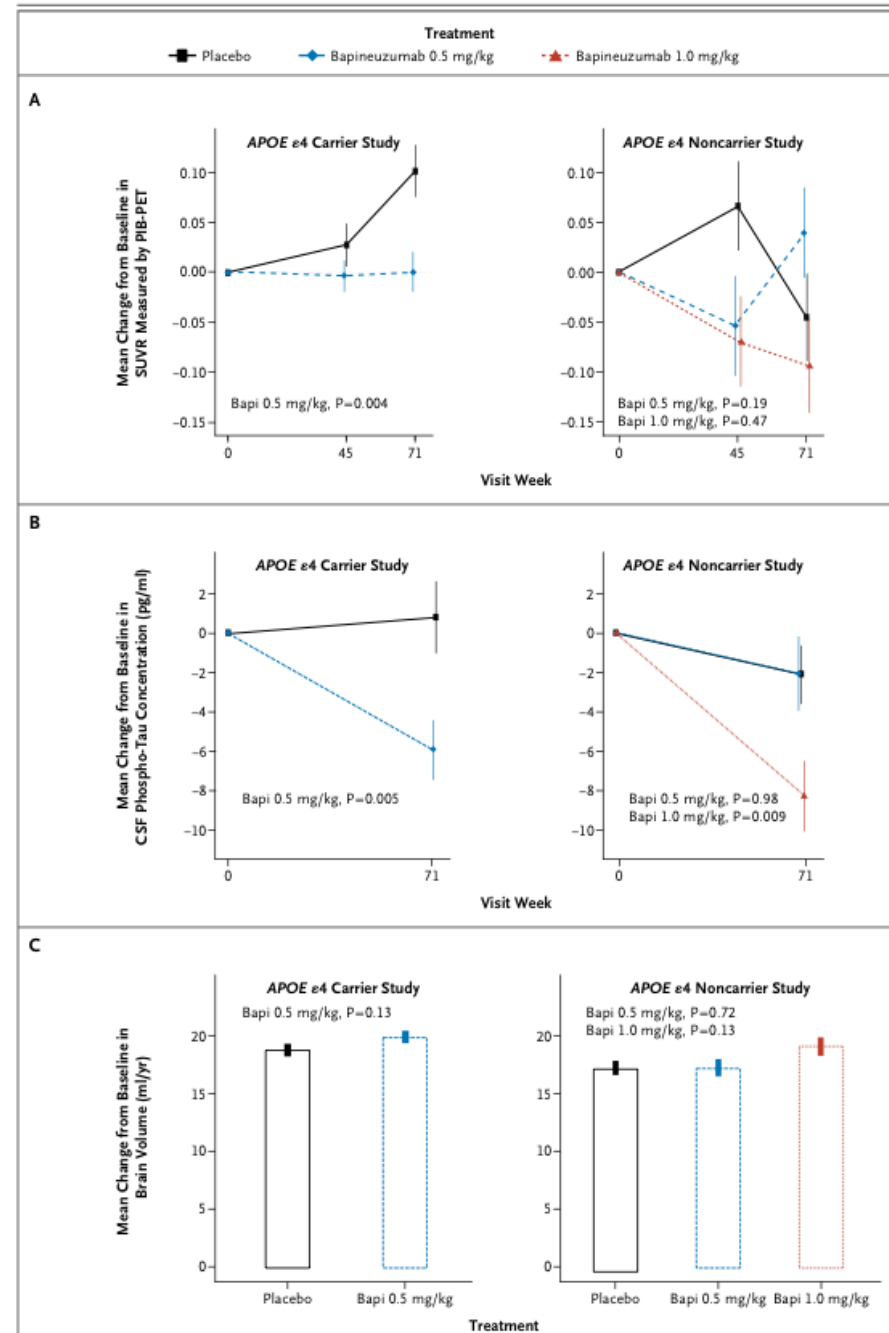


Figure 1. Primary Outcome.

Panel A shows the estimated mean change from baseline to week 78 in scores on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11, with scores ranging from 0 to 70 and higher scores indicating greater impairment), and Panel B the estimated mean change from baseline to week 78 in the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 100 and higher scores indicating less impairment) among APOE ε4 carriers and noncarriers, according to study regimen. The P values that are shown are unadjusted. Bapi denotes bapineuzumab.



ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Ronald G. Thomas, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Rema Raman, Ph.D., Xiaoying Sun, M.S., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Hong Liu-Seifert, Ph.D., and Richard Mohs, Ph.D., for the Solanezumab Study Group

RESULTS

Neither study showed significant improvement in the primary outcomes. The modeled difference between groups (solanezumab group minus placebo group) in the change from baseline was -0.8 points for the ADAS-cog11 score (95% confidence interval [CI], -2.1 to 0.5 ; $P=0.24$) and -0.4 points for the ADCS-ADL score (95% CI, -2.3 to 1.4 ; $P=0.64$) in EXPEDITION 1 and -1.3 points (95% CI, -2.5 to 0.3 ; $P=0.06$) and 1.6 points (95% CI, -0.2 to 3.3 ; $P=0.08$), respectively, in EXPEDITION 2. Between-group differences in the changes in the ADAS-cog14 score were -1.7 points in patients with mild Alzheimer's disease (95% CI, -3.5 to 0.1 ; $P=0.06$) and -1.5 in patients with moderate Alzheimer's disease (95% CI, -4.1 to 1.1 ; $P=0.26$). In the combined safety data set, the incidence of amyloid-related imaging abnormalities with edema or hemorrhage was 0.9% with solanezumab and 0.4% with placebo for edema ($P=0.27$) and 4.9% and 5.6% , respectively, for hemorrhage ($P=0.49$).

CONCLUSIONS

Solanezumab, a humanized monoclonal antibody that binds amyloid, failed to improve cognition or functional ability. (Funded by Eli Lilly; EXPEDITION 1 and 2 ClinicalTrials.gov numbers, NCT00905372 and NCT00904683.)

Table 2. Primary and Secondary Outcomes in EXPEDITION 1, Intention-to-Treat Population.*

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	4.5 (3.3 to 5.8)	3.8 (2.5 to 5.0)	-0.8 (-2.1 to 0.5)	0.24
ADAS-cog14 score‡	5.8 (4.3 to 7.3)	4.5 (2.9 to 6.0)	-1.4 (-2.9 to 0.2)	0.09
ADCS-ADL score†	-8.7 (-10.4 to -7.0)	-9.1 (-10.9 to -7.4)	-0.4 (-2.3 to 1.4)	0.64
CDR-SB score§	1.8 (1.3 to 2.3)	2.0 (1.5 to 2.4)	0.1 (-0.3 to 0.6)	0.51
NPI score¶	0.6 (-1.5 to 2.6)	-0.3 (-2.4 to 1.7)	-0.9 (-2.6 to 0.8)	0.29
MMSE score	-2.0 (-2.8 to -1.2)	-1.4 (-2.2 to -0.6)	0.6 (0.0 to 1.2)	0.06
Free A β_{40} in CSF — pg/ml	80.9 (-2100.5 to 2262.3)	-1127.3 (-3272.4 to 1017.9)	-1208.2 (-2132.4 to -283.9)	0.01
Free A β_{42} in CSF — pg/ml	-28.5 (-160.0 to 102.9)	-54.4 (-186.7 to 77.9)	-25.8 (-88.3 to 36.6)	0.41
Total A β_{40} in CSF — pg/ml	-1902.1 (-6660.1 to 2855.8)	1325.4 (-3162.0 to 5812.9)	3227.6 (1253.6 to 5201.5)	0.002
Total A β_{42} in CSF — pg/ml	-242.3 (-1144.4 to 659.7)	471.4 (-436.0 to 1378.8)	713.7 (309.1 to 1118.4)	<0.001

Table 3. Primary and Secondary Outcomes in EXPEDITION 2, Intention-to-Treat Population.*

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	6.6 (5.2 to 7.9)	5.3 (4.0 to 6.7)	-1.3 (-2.5 to 0.3)	0.06
ADAS-cog14 score†	7.5 (5.8 to 9.1)	5.9 (4.3 to 7.5)	-1.6 (-3.1 to 0.1)	0.04
ADCS-ADL score†	-10.9 (-12.7 to -9.1)	-9.3 (-11.2 to -7.5)	1.6 (-0.2 to 3.3)	0.08
CDR-SB score	1.9 (1.4 to 2.4)	1.6 (1.2 to 2.1)	-0.3 (-0.7 to 0.2)	0.17
NPI score	3.0 (0.8 to 5.1)	2.8 (0.7 to 5.0)	-0.2 (-1.8 to 1.5)	0.85
MMSE score	-2.8 (-3.6 to -2.0)	-2.1 (-2.8 to -1.3)	0.8 (0.2 to 1.4)	0.01
Free A β_{40} in CSF — pg/ml	-649.0 (-2139.5 to 841.5)	-1258.1 (-2695.8 to 179.7)	-609.1 (-1228.4 to 10.2)	0.05
Free A β_{42} in CSF — pg/ml	-35.1 (-129.5 to 59.3)	1.0 (-94.1 to 96.2)	36.1 (-1.0 to 73.3)	0.06
Total A β_{40} in CSF — pg/ml	-876.4 (-4342.5 to 2589.8)	2156.8 (-1211.9 to 5525.4)	3033.1 (1628.4 to 4437.9)	<0.001
Total A β_{42} in CSF — pg/ml	323.8 (86.2 to 561.5)	726.6 (489.4 to 963.9)	402.8 (307.7 to 497.8)	<0.001

Immunization: direct comparison

	Active	Passive (full IgG)
Safety	Encephalitis	Microhemorrhages, edema
T 1/2	Up to years	2-4 weeks
Titer control	Low T 1/2 up to years	High T 1/2 2-4 weeks
Immune response	Polyclonal humoral and cellular	Monoclonal
Responders	20-80%	Less than 100%: antidiotypic antibodies
Dosing	Prime and boosts	4-12 times per year
Administration	i.m.	i.v. and s.c.
Costs	Low	High

Active VS Passive immunization

NO

- Meningoencephalitis

YES

- Fewer doctor visit
 - Less costly
- Long lasting effect

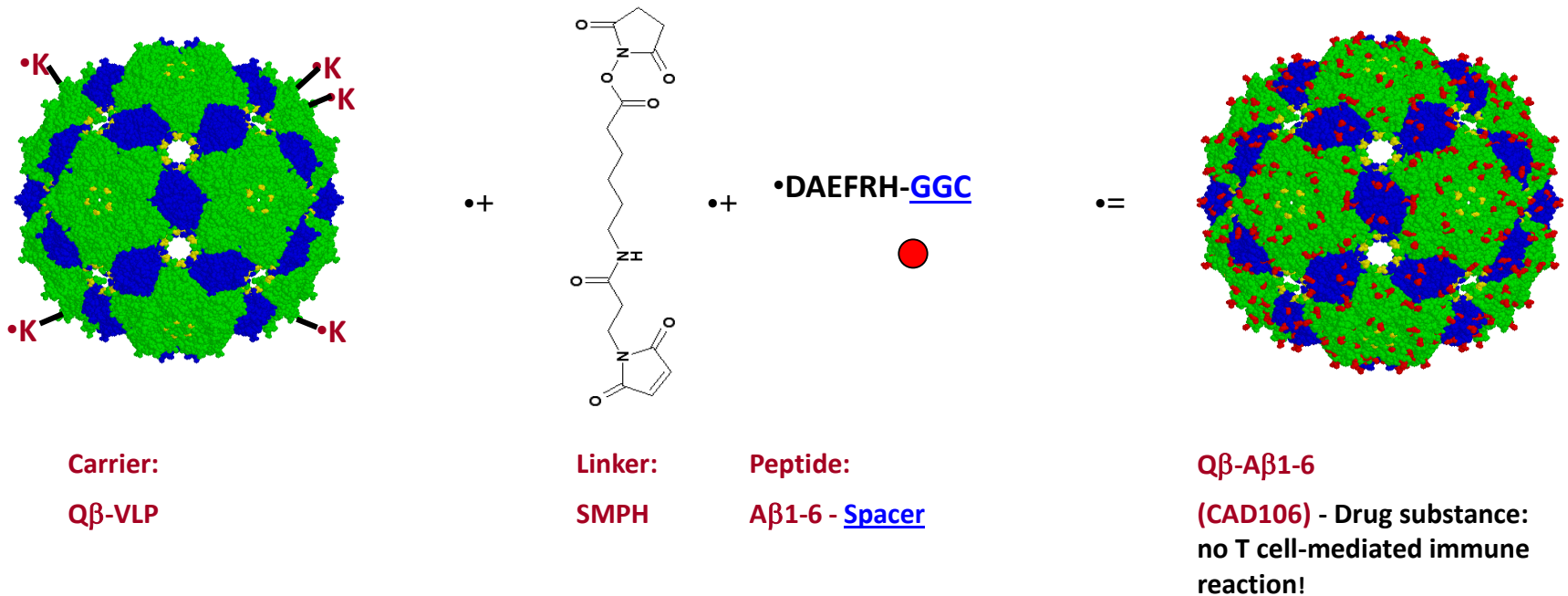
MORE FEASIBLE



Back to vaccination!

Active immunotherapy second generation

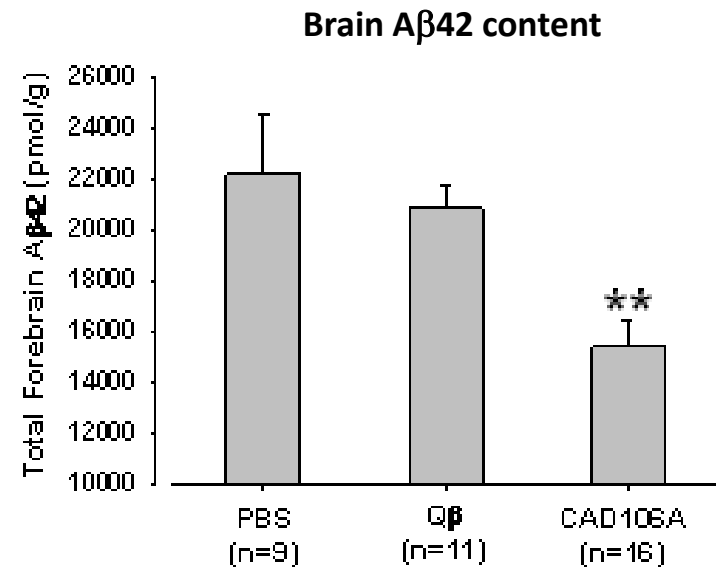
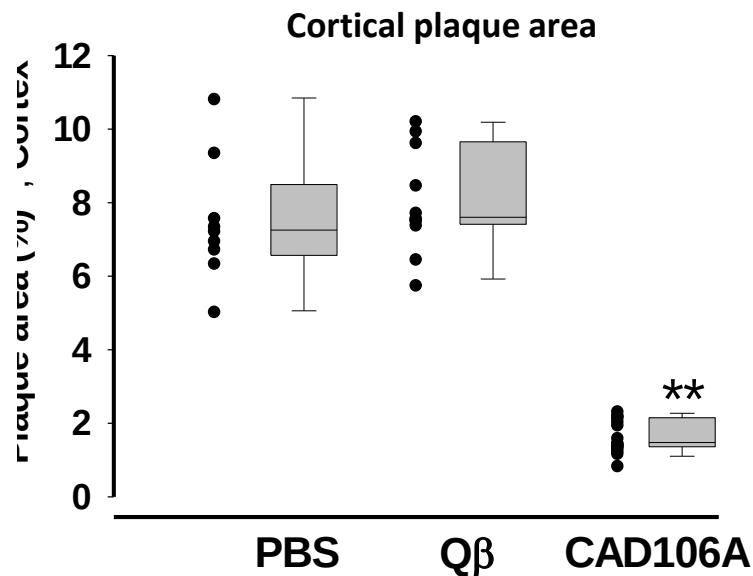
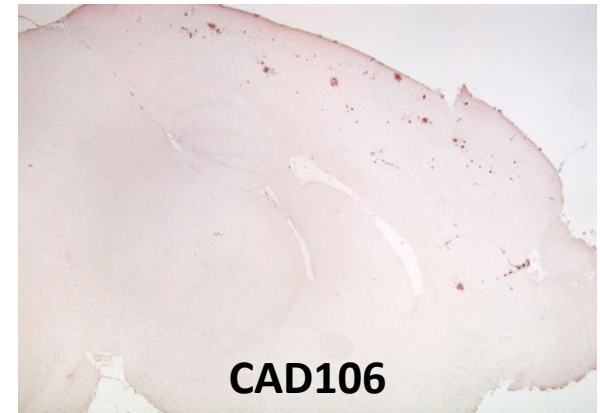
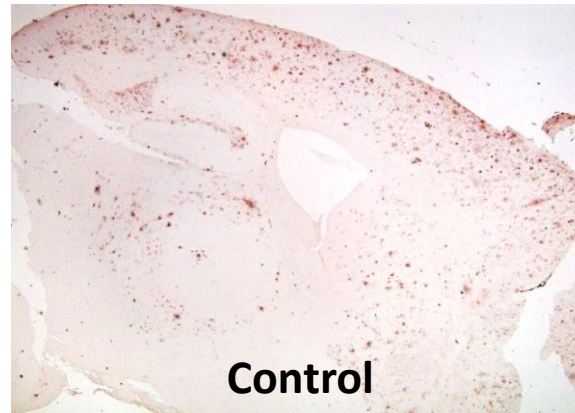
CAD106



New **antigen** designed to generate high **Aβ antibody** titers without inducing **Ab-reactive T-cells**

- Abeta 1-6 peptide, shorter than known human T-cell epitopes
- Its sequence is predicted not to activate T-cell responses
- Experimentally it contains B-cell but not T-cell epitopes

Reduction of amyloid accumulation



Amyloid plaque area: **~80 % lower** than in control mice

Longer treatment and **start** at **earlier age**: increased effect!

Active immunotherapy: CAD106 first study in AD patients

Safety, tolerability, and antibody response of active A β immunotherapy with CAD106 in patients with Alzheimer's disease: randomised, double-blind, placebo-controlled, first-in-human study

Bengt Winblad, Niels Andreasen, Lennart Minthon, Annette Floesser, Georges Imbert, Thomas Dumortier, R Paul Maguire, Kaj Blennow, Joens Lundmark, Matthias Staufenbiel, Jean-Marc Orgogozo, Ana Graf

- phase I, 52-ws study in **58** mild to moderate AD pts (2 cohorts), aged 50-80 yrs, randomly allocated to receive either CAD 106 or placebo
- primary objectives: safety and tolerability and to identify A β -antibody response (**responders**: patients with Ab-IgG serum titers >16 units at least once during the study)
- 56/58 reported minor adverse events. **No cases of meningoencephalitis**
- **67%** of treated patients in cohort I and **82%** in cohort 2 developed A β **antibody response**.

CTAD 2016 (Clinical Trials on Alzheimer's Disease), San Diego, USA: Addendum

EXPEDITION3: A Phase 3 Trial of Solanezumab in Mild Dementia due to Alzheimer's disease

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R. Dean², R. DeMattos², M. Mintun^{2,3},
R. Khanna², K.J. Selzler², E. Siemers²

(1. Columbia University Medical Center, New York, NY; 2. Eli Lilly and Company, Indianapolis, IN, USA; 3. Avid Radiopharmaceuticals Inc., a wholly owned subsidiary of Eli Lilly and Company, Philadelphia, PA, USA)

Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid beta (A β) plaques, neurofibrillary tangles, and neuronal loss with clinical symptoms including cognitive and functional impairment. Solanezumab, a humanized monoclonal antibody, was studied to determine if it would slow the progression of AD by increasing clearance of soluble A β from the brain. **Methods:** EXPEDITION3 was a double-blind, placebo-controlled, Phase 3 global study conducted in 11 countries at 210 sites in patients age 55 to 90 years with mild dementia due to AD (mild AD) (Mini-Mental State Examination [MMSE] score of 20 through 26), with confirmed amyloid pathology based on biomarkers (amyloid positive by F18 florbetapir PET or CSF A β 1-42), with an optional open-label extension. Patients were randomized to 400-mg solanezumab (N=1057) or placebo (N=1072) administered intravenously every 4 weeks. The primary efficacy outcome was change on the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog14) from baseline to Week 80. Key functional measures assessed included the Instrumental Activities of the Alzheimer's Disease Cooperatives Study Activities of Daily Living Inventory (ADCS-iADL) and the Functional Activities Questionnaire (FAQ). Additional efficacy measures assessed included the MMSE and the Clinical Dementia Rating scale-Sum of Boxes (CDR-

SB). Key safety assessments included adverse event (AE) reporting and magnetic resonance imaging (MRI). Biomarkers included plasma changes in A β 1-40 and A β 1-42, CSF changes in total and phosphorylated tau (p-tau), and neuroimaging measures including positron emission tomography (PET) scans using florbetapir F18 and F18 flortaucipir, and volumetric MRI.

Results: There was no statistically significant difference between treatment groups for the primary endpoint, ADAS-Cog14 (p=.095); numerically there was 11% less decline in cognition in the solanezumab-treated group compared with placebo.

For the key secondary endpoints, treatment effects favoring solanezumab were seen on cognitive and functional measures, including 13% less decline on the MMSE (p=.014), 15% less decline on the CDR-SB (p=.004), and 14% less decline on the ADCS-iADL (p=.019). FAQ did not show statistically significant differences (7% less decline, p=.140). Solanezumab-treated patients showed a statistically significant greater increase in plasma A β 1-40 and A β 1-42 compared with placebo-treated patients (p<.001 for each biomarker), confirming peripheral target engagement. Changes between treatment groups for florbetapir PET, CSF total tau and p-tau, and flortaucipir PET did not show significant treatment differences. Whole brain atrophy and ventricular enlargement were not statistically different between treatment groups, as demonstrated by volumetric MRI. Safety findings were comparable across study treatment groups with respect to deaths, serious AEs (SAEs), discontinuations due to an AE and treatment-emergent AEs (TEAEs). There were few statistically significant treatment group differences at the individual Preferred Term level for TEAEs and none for any SAEs. **Conclusions:** EXPEDITION3, a Phase 3 trial of solanezumab initiated in a mild AD patient population, did not meet the primary objective of decreasing cognitive decline. Several secondary clinical endpoints, including both cognitive and functional measures, directionally favored solanezumab, but the effect sizes were small. Factors possibly relevant to interpretation of the study results include drug target, disease stage studied, and drug dosage delivered. Solanezumab had a favorable safety profile at the dose studied.

The antibody aducanumab reduces A β plaques in Alzheimer's disease

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Alzheimer's disease (AD) is characterized by deposition of amyloid- β (A β) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against A β 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 A β . In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal A β , and reduce soluble and insoluble A β in a dose-dependent manner.

In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain A β 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.

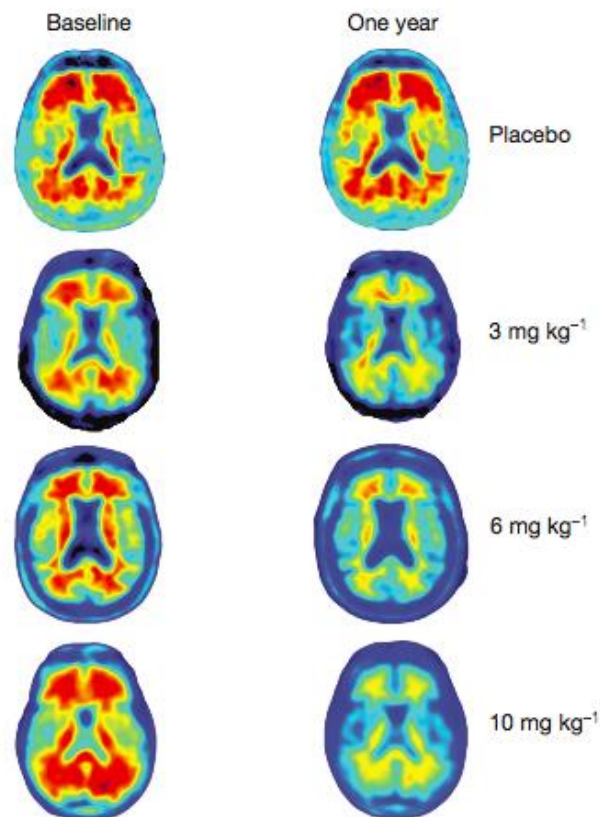
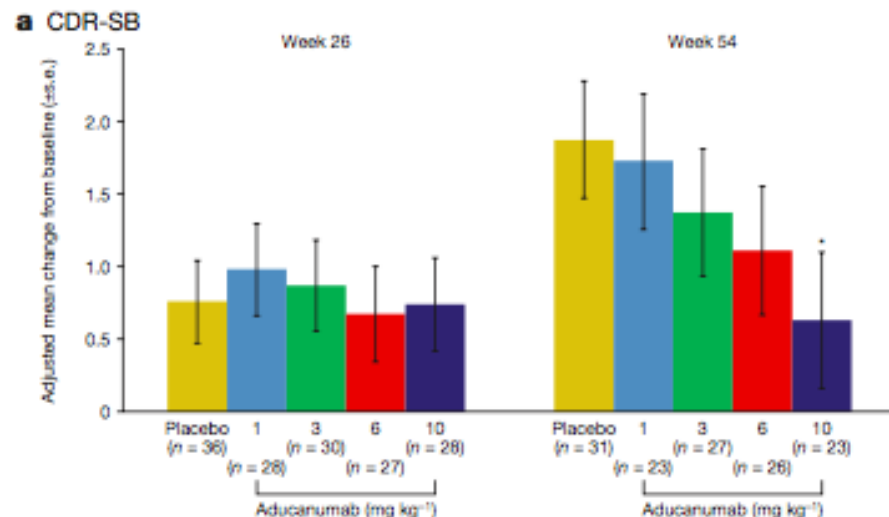
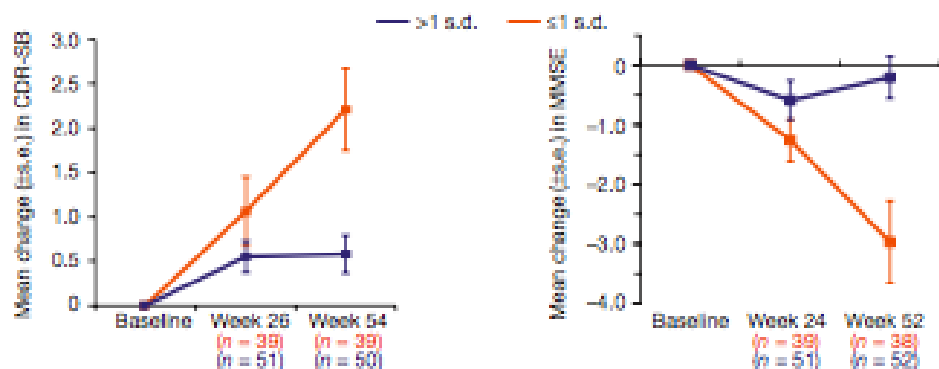
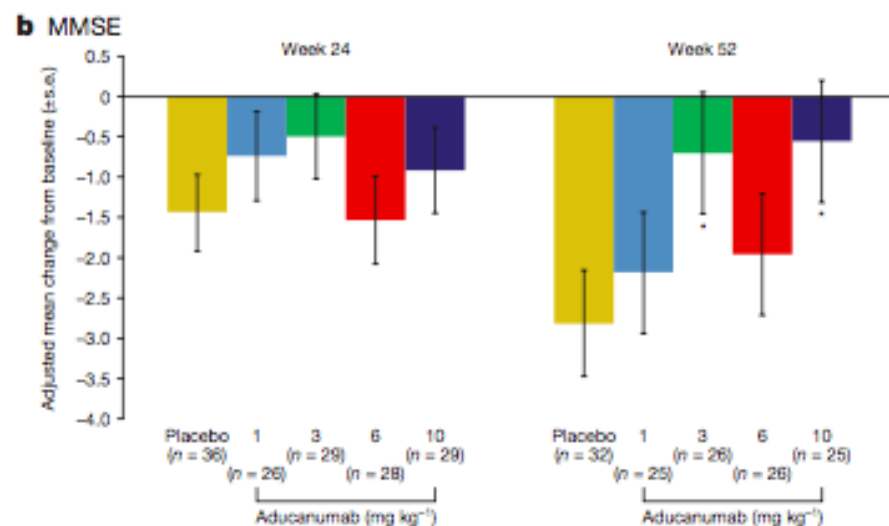


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40, 32, 30$ and 32 , respectively). Axial slice shows anatomical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

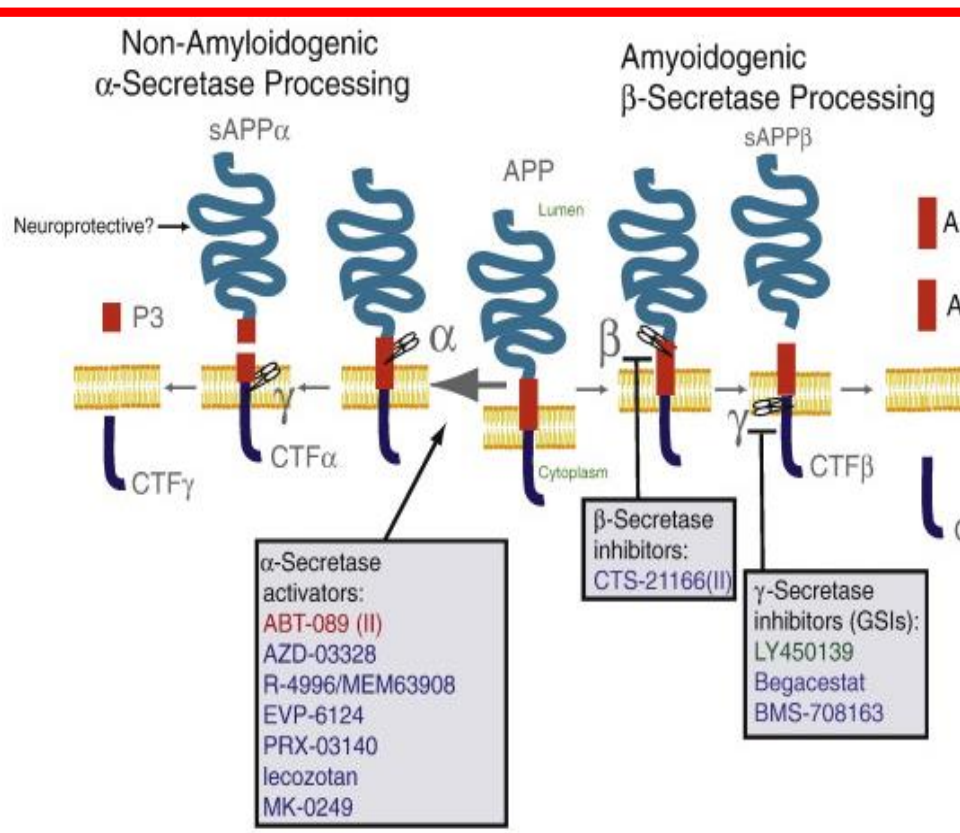
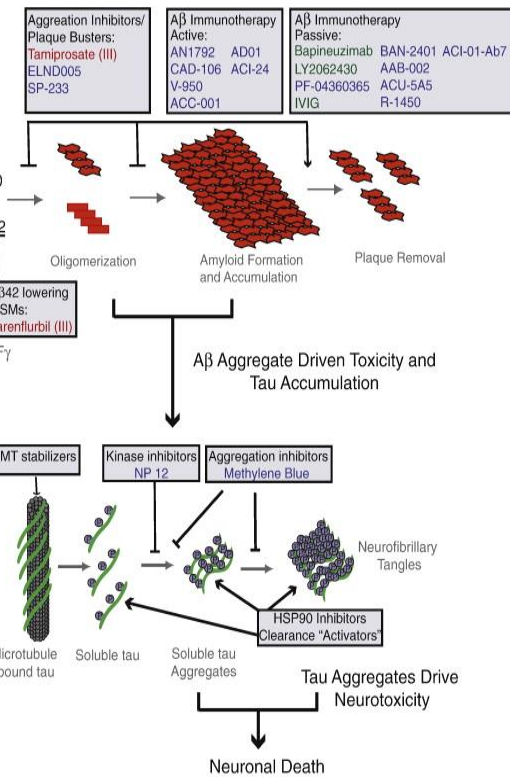
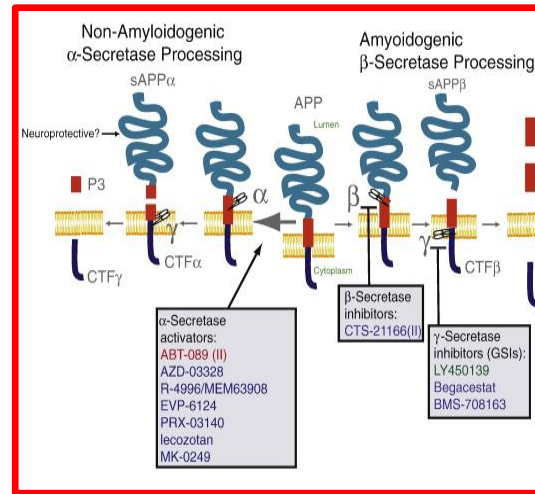


Dose-response $P < 0.05$ at week 54 based on a linear contrast test



Dose-response $P < 0.05$ at week 52 based on a linear contrast test

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 $\pm$ s.e. Analyses using ANCOVA. CDR-SB, Clinical Dementia Rating—Sum of Boxes; MMSE, Mini Mental State Examination.



Secretase modulation

A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Rema Raman, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Feng He, M.S., Xiaoying Sun, M.S., Ronald G. Thomas, Ph.D., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Gopalan Sethuraman, Ph.D., and Richard Mohs, Ph.D., for the Semagacestat Study Group

RESULTS

The trial was terminated before completion on the basis of a recommendation by the data and safety monitoring board. At termination, there were 189 patients in the group receiving placebo, 153 patients in the group receiving 100 mg of semagacestat, and 121 patients in the group receiving 140 mg of semagacestat. The ADAS-cog scores worsened in all three groups (mean change, 6.4 points in the placebo group, 7.5 points in the group receiving 100 mg of the study drug, and 7.8 points in the group receiving 140 mg; $P=0.15$ and $P=0.07$, respectively, for the comparison with placebo). The ADCS-ADL scores also worsened in all groups (mean change at week 76, -9.0 points in the placebo group, -10.5 points in the 100-mg group, and -12.6 points in the 140-mg group; $P=0.14$ and $P<0.001$, respectively, for the comparison with placebo). Patients treated with semagacestat lost more weight and had more skin cancers and infections, treatment discontinuations due to adverse events, and serious adverse events ($P<0.001$ for all comparisons with placebo). Laboratory abnormalities included reduced levels of lymphocytes, T cells, immunoglobulins, albumin, total protein, and uric acid and elevated levels of eosinophils, monocytes, and cholesterol; the urine pH was also elevated.

CONCLUSIONS

As compared with placebo, semagacestat did not improve cognitive status, and patients receiving the higher dose had significant worsening of functional ability. Semagacestat was associated with more adverse events, including skin cancers and infections. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT00594568.)

Table 3. Summary of Adverse Events Occurring during the Study Treatment, According to the MedDRA System or Organ Class and Preferred Term.*

Event	Placebo (N = 501)	Semagacestat			Total (N = 1534)
		100 mg (N = 506)	140 mg (N = 527)	Combined (N = 1033)	
		percent of participants			
System or organ class					
Neoplasms — benign, malignant, or unspecified	5	15	16	15	12
Skin or subcutaneous-tissue disorders	21	45	52	48	39
Preferred term					
Alopecia	0	1	5	3	2
Basal-cell carcinoma	1	3	5	4	3
Decreased appetite	3	7	11	9	7
Epistaxis	1	3	3	3	2
Eyelash discoloration	0	2	5	3	2
Hair-color changes	1	13	19	16	11
Nausea	5	11	12	11	9
Pruritus	2	3	4	3	3
Rash					
Erythematous	2	5	5	5	4
Macular	4	7	8	8	6
Maculopapular	1	3	5	4	3
Papular	1	3	4	4	3
Skin lesion	1	3	3	3	2
Squamous-cell carcinoma of skin	1	6	5	5	4
Syncope	1	3	3	3	3
Vomiting	4	10	9	9	7
Weight decrease	3	5	9	7	6

* The listed adverse events are those with an incidence of at least 2% in any one group and a rate in the combined semagacestat groups that was at least two times as high as the rate in the placebo group. MedDRA denotes *Medical Dictionary for Regulatory Activities*, version 13.1.

Targeting Prodromal Alzheimer Disease With Avagacestat

A Randomized Clinical Trial

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RESULTS Of the 263 participants in the treatment phase, 132 were randomized to avagacestat and 131 to placebo; an additional 102 participants were observed in an untreated observational cohort. Avagacestat was relatively well tolerated with low discontinuation rates (19.6%) at a dose of 50 mg/d, whereas the dose of 125 mg/d had higher discontinuation rates (43%), primarily attributable to gastrointestinal tract adverse events. Increases in nonmelanoma skin cancer and nonprogressive, reversible renal tubule effects were observed with avagacestat. Serious adverse event rates were higher with avagacestat (49 participants [37.1%]) vs placebo (31 [23.7%]), attributable to the higher incidence of nonmelanoma skin cancer. At 2 years, progression to dementia was more frequent in the PDAD cohort (30.7%) vs the observational cohort (6.5%). Brain atrophy rate in PDAD participants was approximately double that of the observational cohort. Concordance between abnormal amyloid burden on positron emission tomography and pathologic CSF was approximately 87% ($\kappa = 0.68$; 95% CI, 0.48-0.87). No significant treatment differences were observed in the avagacestat vs placebo arm in key clinical outcome measures.

CONCLUSIONS AND RELEVANCE Avagacestat did not demonstrate efficacy and was associated with adverse dose-limiting effects. This PDAD population receiving avagacestat or placebo had higher rates of clinical progression to dementia and greater brain atrophy compared with CSF biomarker-negative participants. The CSF biomarkers and amyloid positron emission tomography imaging were correlated, suggesting that either modality could be used to confirm the presence of cerebral amyloidopathy and identify PDAD.

Coric V, 2015

Table 2. Summary of AEs

Characteristic	Placebo (n = 131)	Avagacestat (n = 132)
Any SAE, No. (%)	31 (23.7)	49 (37.1)
Cardiac disorders	1 (0.8)	3 (2.3)
GI tract disorders	1 (0.8)	6 (3.5)
Neoplasms	12 (9.2)	23 (17.4)
Injury, poisoning, and procedural complications	4 (3.1)	7 (5.3)
Any AE leading to treatment discontinuation, No. (%)	13 (9.9)	46 (34.8)
Any GI tract AE	3 (2.3)	19 (14.4)
Any skin AE	1 (0.8)	7 (5.3)
Any nervous system disorder	2 (1.5)	8 (6.1)
Any AE, No. (%)	110 (84.0)	126 (95.5)
Any GI tract AE	48 (36.6)	87 (65.9)
Diarrhea	24 (18.3)	41 (31.1)
Nausea	4 (3.1)	35 (26.5)
Vomiting	2 (1.5)	14 (10.6)
Any skin AE	50 (38.2)	72 (54.5)
Rash	8 (6.1)	27 (20.5)
Any neoplasms	20 (15.3)	25 (18.9)
BCC	5 (3.8)	8 (6.1)
SCC skin	1 (0.8)	8 (6.1)
SCC	0	8 (6.1)
Malignant melanoma	1 (0.8)	0
Other AEs		
Fatigue	9 (6.8)	24 (18.2)
Weight decreased	2 (1.5)	14 (10.6)
Appetite decreased	3 (2.3)	14 (10.6)
Dizziness	13 (9.9)	20 (15.2)
Depression	11 (8.4)	7 (5.3)
Anxiety	12 (9.2)	4 (3.0)
Cerebral microbleed	2 (1.5)	4 (3.0)
Vasogenic edema	1 (0.8)	3 (2.3)

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; GI, gastrointestinal; SAE, serious AE; SCC, squamous cell carcinoma.

Merck ends trial of potential Alzheimer's drug verubecestat

Nigel Hawkes

London

The drug giant Merck has pulled the plug on a trial of an Alzheimer's drug, verubecestat, after early data showed "virtually no chance" that it would work. But a second trial of the same drug continues in patients at an earlier stage of the disease.

Verubecestat was seen as a promising candidate in a field littered with failures, after data published last November showed that the drug reduced the levels of amyloid protein in the spinal fluid of patients and healthy controls who took it for short periods.¹

The build-up of amyloid is one of the signatures of Alzheimer's, and various drugs have been designed to reduce it, using different approaches. Verubecestat is a small molecule taken orally that targets an enzyme, BACE-1 (beta site amyloid precursor protein cleaving enzyme 1), involved in the creation of amyloid. By attaching itself to the enzyme, verubecestat inhibits its ability to slice up amyloid precursor protein, a key step in producing amyloid.

Merck started two large trials: one in patients with mild to moderate disease, due to last 18 months; and a second in patients at an earlier stage of the disease, due to last two years. The first of these has now been halted after the data monitoring committee concluded that it would not produce positive clinical effects. However, the side effects were mild enough to justify continuing the second trial in patients at an earlier stage of amyloid build-up. Results are expected in February 2019 if the trial runs its full course.

This latest disappointment follows the abandonment by Lilly in November 2016 of its anti-amyloid drug, solanezumab.² That

drug's mode of operation was different, but the results were equally bleak. Since 2000 around 250 compounds designed as treatments for Alzheimer's have been tested, and only one has been granted a licence.

While some experts now believe that attempts to target amyloid are doomed, hopes are being kept alive by another candidate, Biogen's drug aducanumab. In trials involving 165 patients with either mild Alzheimer's or preliminary evidence of amyloid in brain scans, aducanumab reduced levels of amyloid and showed some slowing in the decline of memory and thinking skills, but the trial was too small to generate statistically significant results.³ Bigger trials are ongoing.

Verubecestat's failure is disappointing, said Bryce Vissel, director of the Centre for Neuroscience and Regenerative Medicine at the University of Technology in Sydney, Australia. Although this was not the end for amyloid theory, he said, "It is my strong view that new approaches need to be developed and new directions of research need to be supported."

- 1 Kennedy ME, Stamford AW, Chen X, et al. The BACE1 inhibitor verubecestat (MK-8931) reduces CNS β -amyloid in animal models and in Alzheimer's disease patients. *Sci Transl Med* 2016;356:363ra150. doi:10.1126/scitranslmed.aad9704. pmid:27807285.
- 2 Hawkes N. Promise of new Alzheimer's drug is dashed after lack of evidence. *BMJ* 2016;356:l6362. doi:10.1136/bmj.l6362 pmid:27884817.
- 3 Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature* 2016;356:50-6. doi:10.1038/nature19323. pmid:27582220.

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2017 Alzheimer's Drug Development Pipeline

Disease-Modifying Immunotherapy

Subject Characteristics (Shape)

- △ Healthy Volunteers
- ▽ Preclinical
- Prodromal/ Prodromal - Mild
- Mild - Moderate
- ◇ Severe

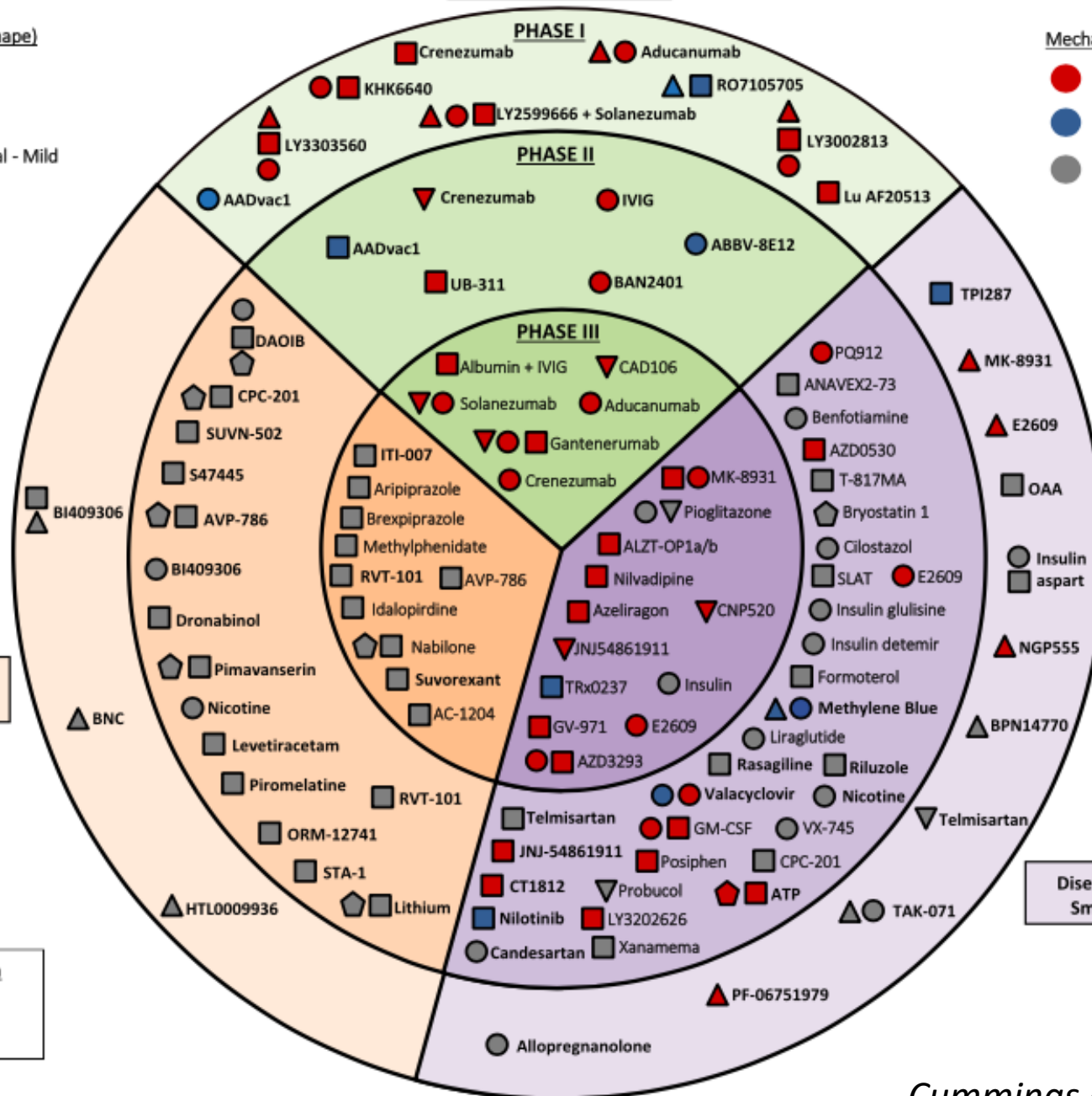
Mechanism of Action (Color)

- Amyloid-related
- Tau-related
- Others

Symptom-Reducing Small Molecule

Undisclosed Mechanism

- △ RGN1016 (Phase I)
- BAC (Phase II)



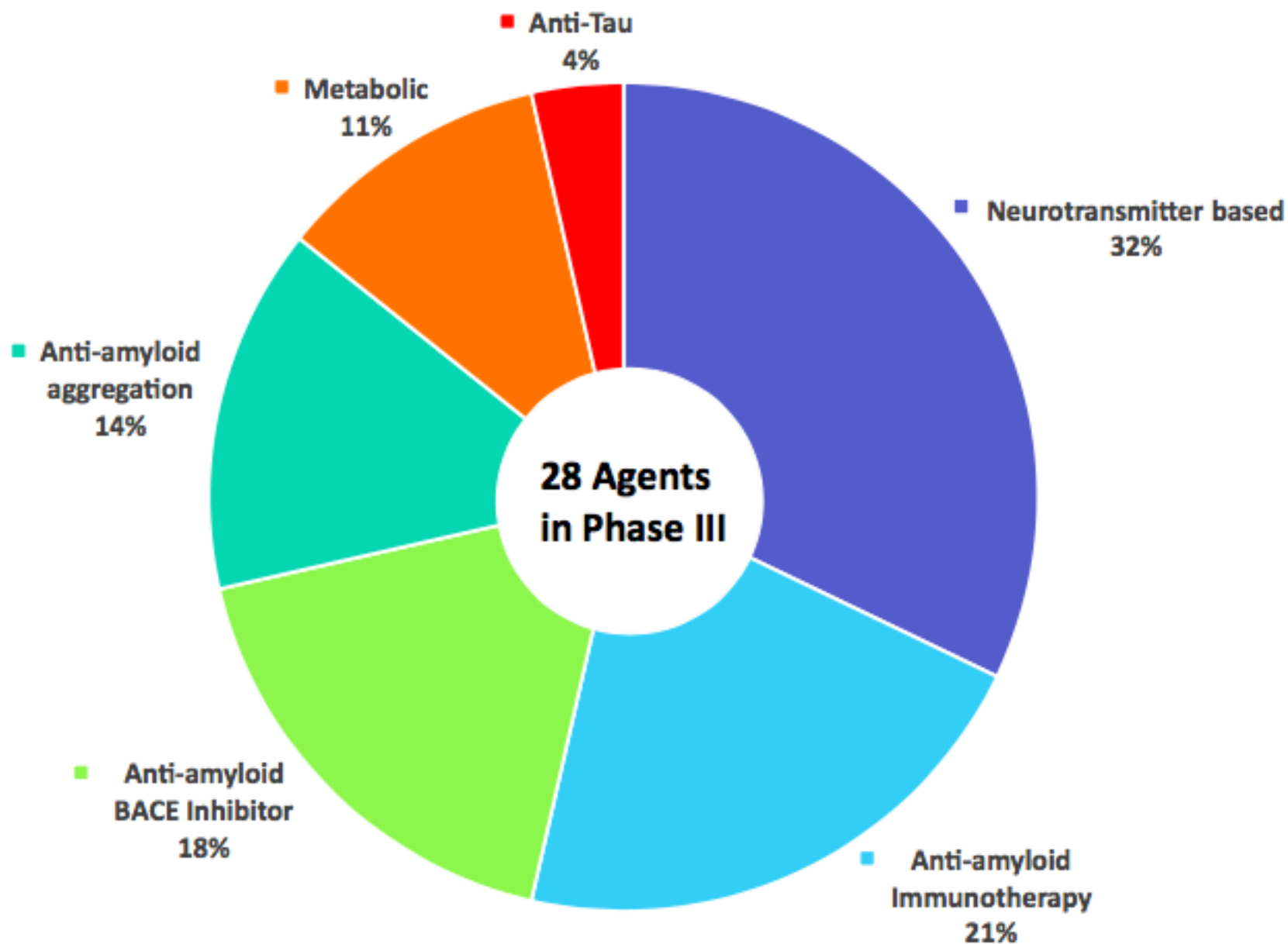


Fig. 3. Mechanisms of action of agents in phase III. Abbreviation: BACE, β -site amyloid precursor protein cleaving enzyme.

Cummings et al., 2016

Table 6
 BACE inhibitors in clinical trials for AD

BACE inhibitors currently in phase II or III of development					
Agent (sponsor)	Clinicaltrials.gov identifier (trial name)	Phase	Population	Start date	Estimated end date
CNP520 (Novartis)	NCT02565511 (GENERATION)	II/III	Asymptomatic (homozygote <i>APOE</i> <i>e4/e4</i>)	11/2015	08/2023
E2609 (Eisai)	NCT02322021	II	MCI to moderate AD	11/2014	01/2018
	NCT02956486 (MISSION-AD1)	III	MCI to mild AD	10/2016	06/2020
JNJ54861911 (Janssen)	NCT02406027	II	MCI to mild AD	07/2015	10/2022
	NCT02569398	II/III	Preclinical (amyloid positive)	11/2015	05/2023
LY3202626 (Lilly)	NCT02791191 (NAVIGATE-AD)	II	Mild AD	06/2016	08/2018
LY3314814 (Lilly)	NCT02245737 (AMARANTH)	II/III	MCI to mild AD	9/2014	8/2019
	NCT02783573 (DAYBREAK ALZ)	III	Mild AD	7/2016	08/2021
Verubecestat (Merck)	NCT01739348 (EPOCH)	II/III	Mild to moderate AD	11/2012	06/2017

Abbreviations: AD, Alzheimer’s disease; BACE, β -site amyloid precursor protein cleaving enzyme; MCI, mild cognitive impairment.

Table 7

Immunotherapies in clinical trials for AD (clinicaltrials.gov accessed 1/5/2017)

Agent	Sponsor	Target	Trial phase	Population
AADvac1	Axon Neuroscience	Anti-tau mAb	1	AD
AADvac1	Axon Neuroscience	Anti-tau mAb	2	Mild-moderate AD
ABBV-8E12	AbbVie	Anti-tau mAb	2	Early AD
Aducanumab	Biogen	mAb targeting multiple forms of A β	1	Healthy volunteers
Aducanumab	Biogen	mAb targeting multiple forms of A β	1	Prodromal-mild AD
Aducanumab	Biogen	mAb targeting multiple forms of A β	1	Mild-moderate AD
Aducanumab	Biogen	mAb targeting multiple forms of A β	3	Early AD
Aducanumab	Biogen	mAb targeting multiple forms of A β	3	Early AD
Albumin and immunoglobulin	Grifols	Polyclonal antibody targeting multiple forms of A β	3	Mild-moderate AD
BAN2401	Eisai	mAb targeting N terminal protofibrils	2	Early AD
CAD106	Novartis, NIA	A β ₁₋₆ , active vaccine	2	AD, at risk
Crenezumab	Genentech	mAb targeting soluble oligomer and fibrillar A β	1	Mild-moderate AD
Crenezumab	Genentech, NIA, Academic	mAb targeting soluble oligomer and fibrillar A β	2	ADAD
Crenezumab	Genentech	mAb targeting soluble oligomer and fibrillar A β	3	Prodromal-mild AD
Gantenerumab	Roche	mAb targeting aggregated A β	3	Mild AD
Gantenerumab	Roche	mAb targeting aggregated A β	3	Prodromal AD
Gantenerumab	Roche, Lilly, Alzheimer's Association	mAb targeting aggregated A β	2/3	AD, at risk
Solanezumab	Lilly, Roche, Alzheimer's Association	mAb targeting monomeric A β	2/3	AD, at risk
KH6640	Kyowa Hakko Kirin	mAb targeting aggregated A β	1	AD
Lu AF20513	Lundbeck		1	Mild AD
NewGam 10% IVIG	Sutter Health	Polyclonal antibody targeting multiple forms of A β	2	Amnesic MCI
LY2599666 & solanezumab	Lilly	Combination of BACE inhibitor and MAb targeting monomeric A β	1	MCI due to AD
LY3303560	Lilly		1	MCI due to AD-mild AD
LY30032813	Lilly		1	MCI due to AD
LY30032813	Lilly		1	Mild-moderate AD
RO7105705	Genentech	Anti-tau mAb	1	Mild-moderate AD
Solanezumab	Lilly	mAb targeting monomeric A β	3	Prodromal AD
Solanezumab	Lilly	mAb targeting monomeric A β	3	Preclinical AD
Solanezumab	Lilly	mAb targeting monomeric A β	3	AD
Solanezumab	Lilly	mAb targeting monomeric A β	3	Mild AD
UB-311	United Neuroscience	mAb targeting N terminal A β ₁₋₁₄	2	Mild AD

Abbreviations: AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer's disease; mAb, monoclonal antibody; MCI, mild cognitive impairment. Yes, the expansion is correct.; IVIG, intravenous immunoglobulin; NIA, National Institute on Aging.



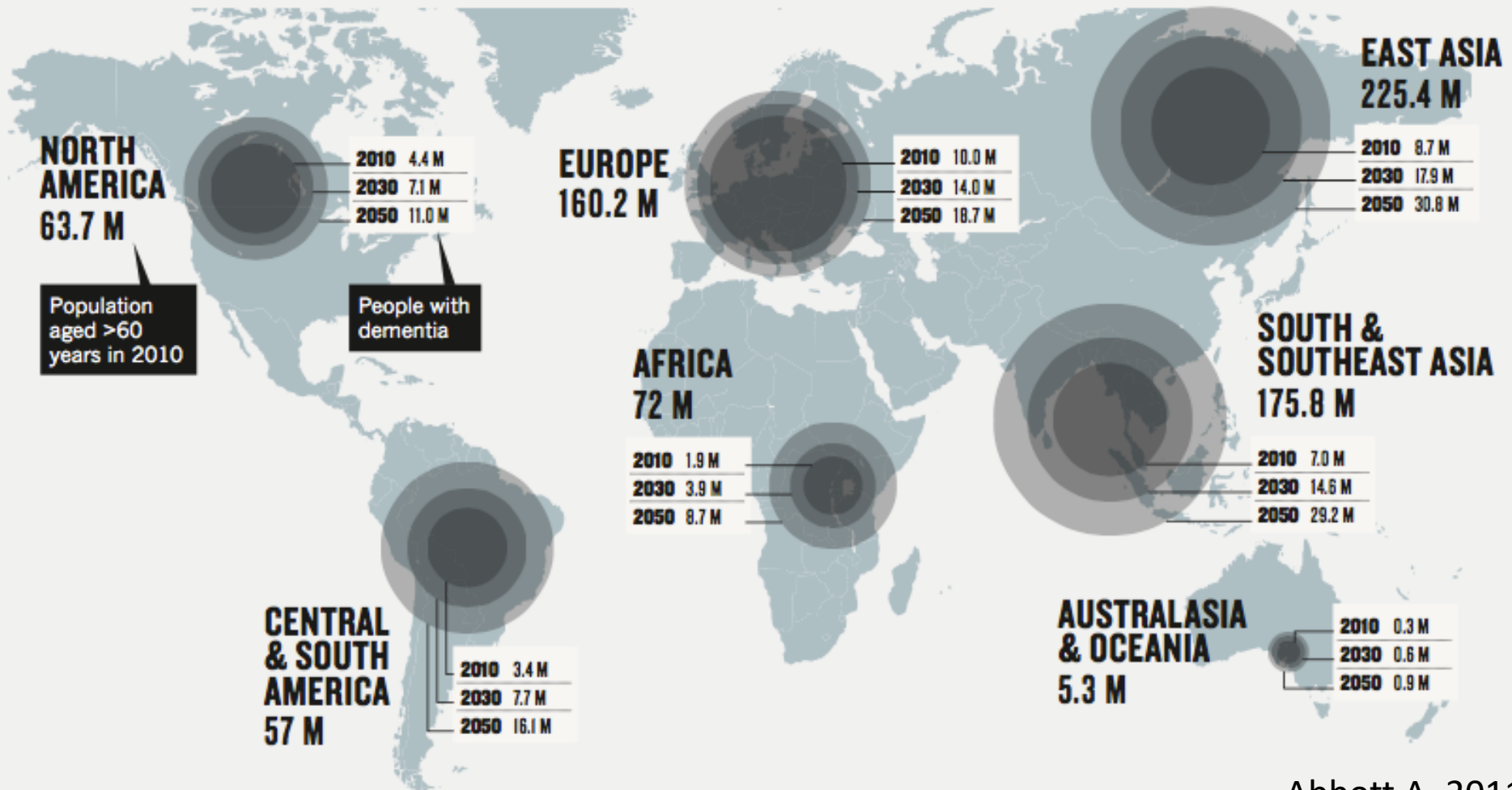
Il futuro

A problem for our age

As the number of Alzheimer's cases rises rapidly in an ageing global population, the need to understand this puzzling disease is growing.

ESTIMATED GROWTH OF DEMENTIA

The number of people with dementia will roughly double every 20 years, with the biggest increases in developing countries.



Why did so many trials fail?

- **Preclinical models:**
the gap between mice and humans
- **Population:**
patient may not have AD but other dementias instead + too late treatment
- **Amyloid cascade:**
removal of plaques is not sufficient to halt the disease progression

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removal of plaques is not sufficient to halt the disease progression



Successful therapies for Alzheimer's disease: why so many in animal models and none in humans?

Rafael Franco^{1,2 *} and *Angel Cedazo-Minguez*³

Ann. Hum. Genet. (1989), **53**, 89–140

Printed in Great Britain

89

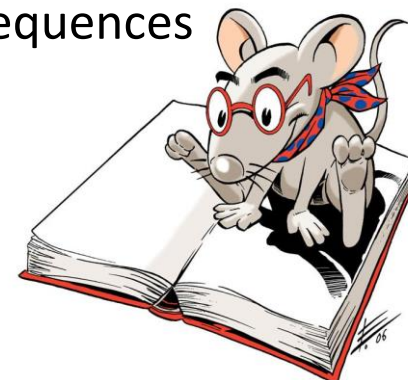
Chromosome maps of man and mouse. IV

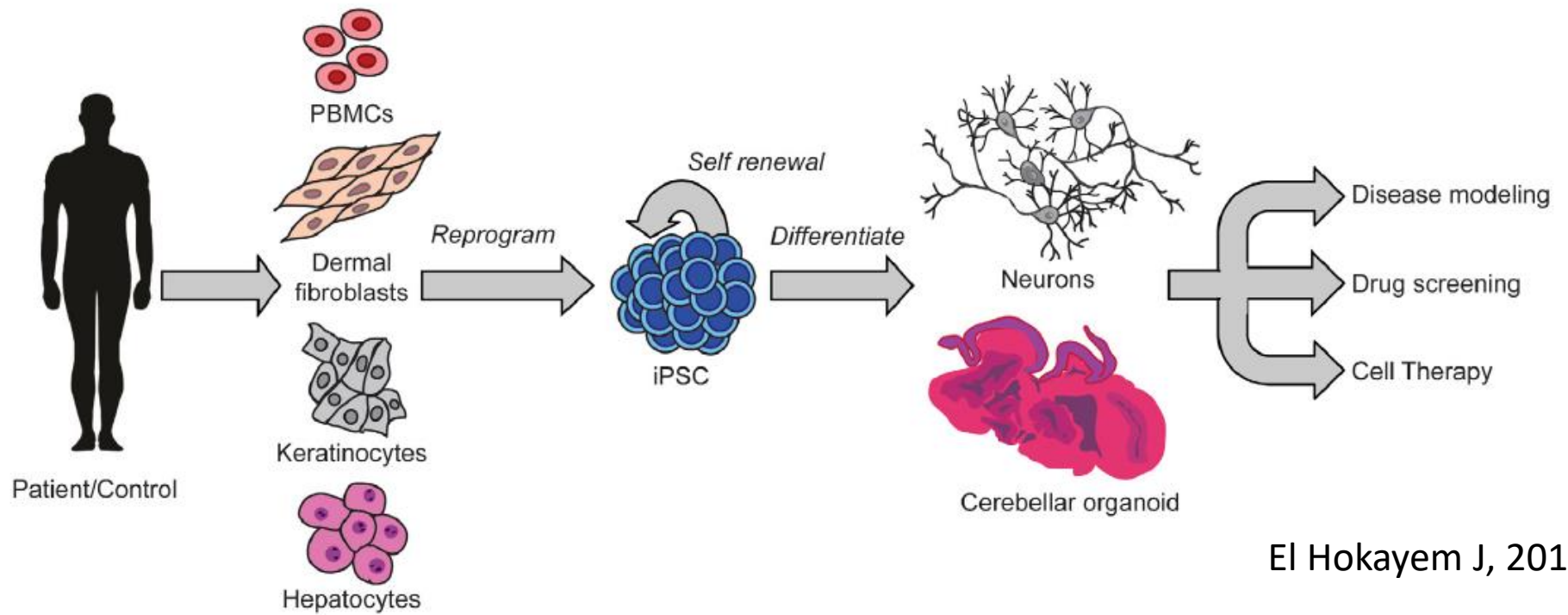
A. G. SEARLE,* J. PETERS,* M. F. LYON,* J. G. HALL,†|| E. P. EVANS,‡
J. H. EDWARDS† AND V. J. BUCKLE§

Mice

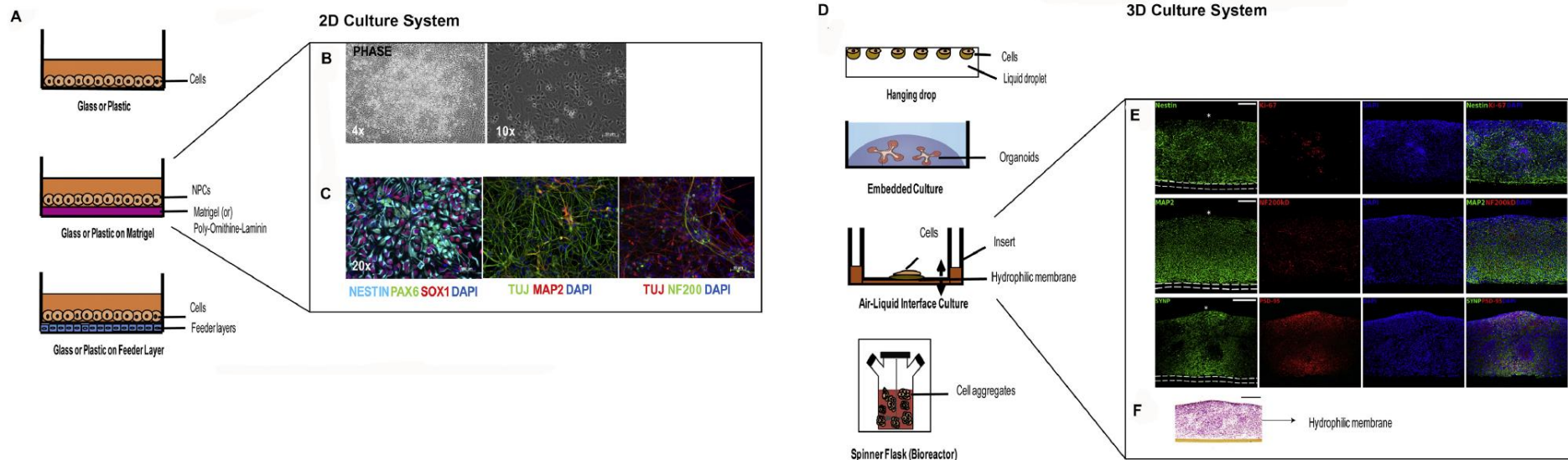
chosen because of the **high degree of homology** between coding sequences
but **low homology** in terms non-coding/intronic DNA

Similar proteins, but completely **different regulation**
miRNA, methylation, etc → epigenetics!





El Hokayem J, 2016



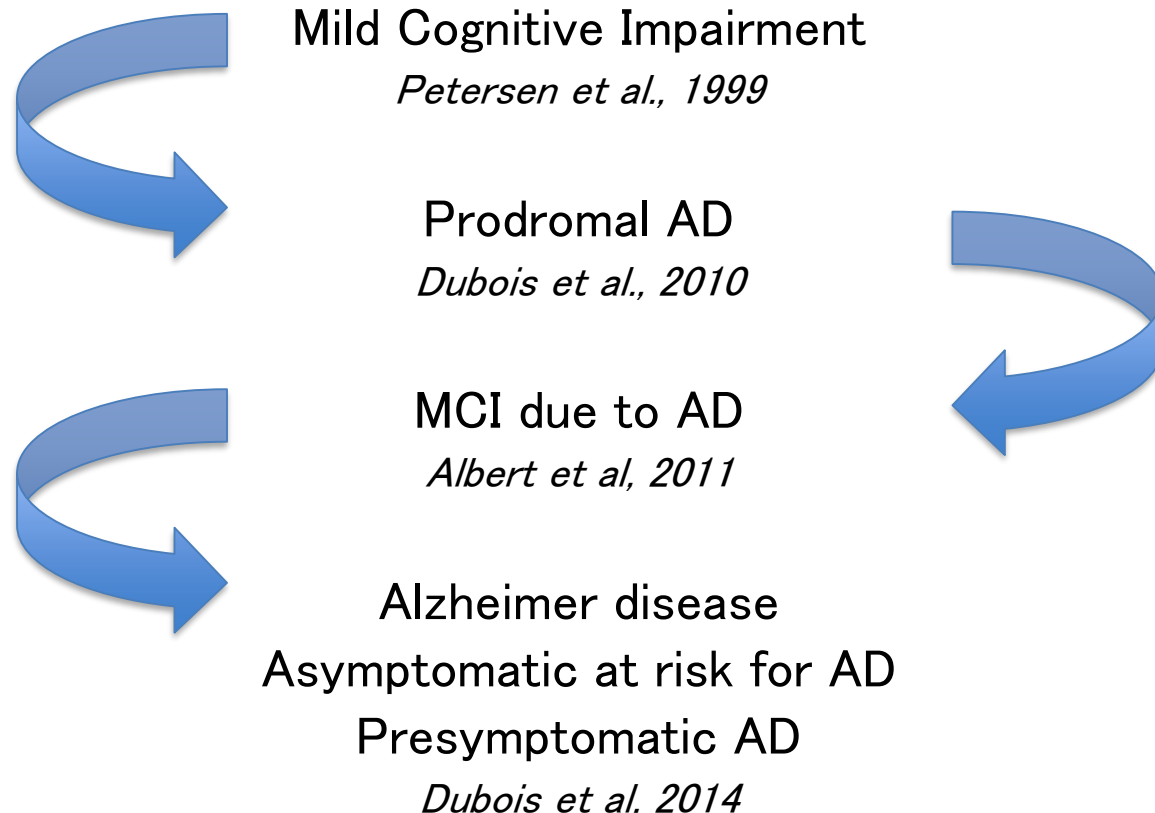
Poon A, 2017

Why did so many trials fail?

- **Preclinical models:**
the gap between mice and humans
- **Population:**
patient may not have AD but other dementias instead + too late treatment
- **Amyloid cascade:**
removal of plaques is not sufficient to halt the disease progression

Pre-dementia phase

Lack of effective treatments: need to develop new strategies to prevent the progression of the disease



I biomarcatori

NIA-AA criteria 2011

The rationale for including biomarkers for the pathophysiological process of AD in the diagnostic criteria is summarized in the Introduction to this series of articles [3]. The major AD biomarkers that have been widely investigated at this time (see [21] for review) may be broken into two classes based on the biology which they measure. Biomarkers of brain amyloid-beta ($A\beta$) protein deposition are low CSF $A\beta_{42}$ and positive PET amyloid imaging [22,23]. The second category is that of biomarkers of downstream neuronal degeneration or injury. The three major bio-markers in this category are elevated CSF tau, both total tau and phosphorylated tau (p-tau); decreased ^{18}F fluorodeoxyglucose (FDG) uptake on PET in temporo-parietal cortex; and disproportionate atrophy on structural magnetic resonance imaging in me-dial, basal, and lateral temporal lobe, and medial parietal cortex. Total tau and p-tau are treated equivalently in this study, although p-tau may have more specificity for AD than other dementing diseases.

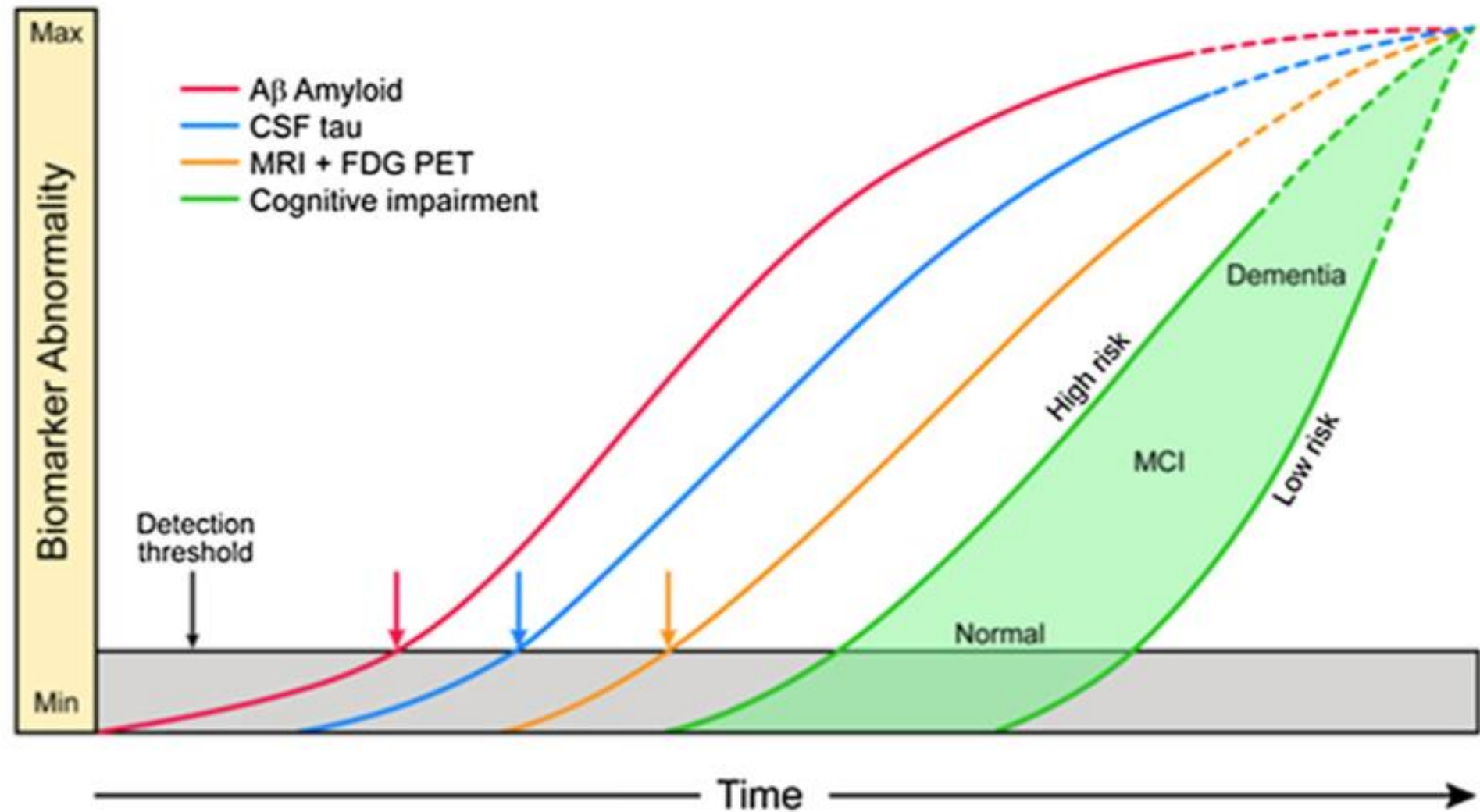
McKhann GM, 2011

IWG-2 criteria 2014

In conclusion, Alzheimer's pathology can be suspected in vivo at any stage of the disease, including preclinical states, by a CSF signature of low $A\beta_{1-42}$ and high T-tau or P-tau concentrations, or by evidence of significant PET amyloid retention (either by visual assessment in advanced cases or by assessment of global cortical threshold in intermediate or difficult cases).

Dubois B, 2014

Biomarker model of pure AD



I biomarcatori

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes	No
Total tau, phospho-tau	Yes	No
PET		
Amyloid tracer uptake	Yes	No
Fluorodeoxyglucose	No	Yes
Structural MRI		
Medial temporal atrophy	No	Yes
AD=Alzheimer's disease.		
Table 1: Categorisation of the current, most-validated AD biomarkers		

Cerebrospinal fluid

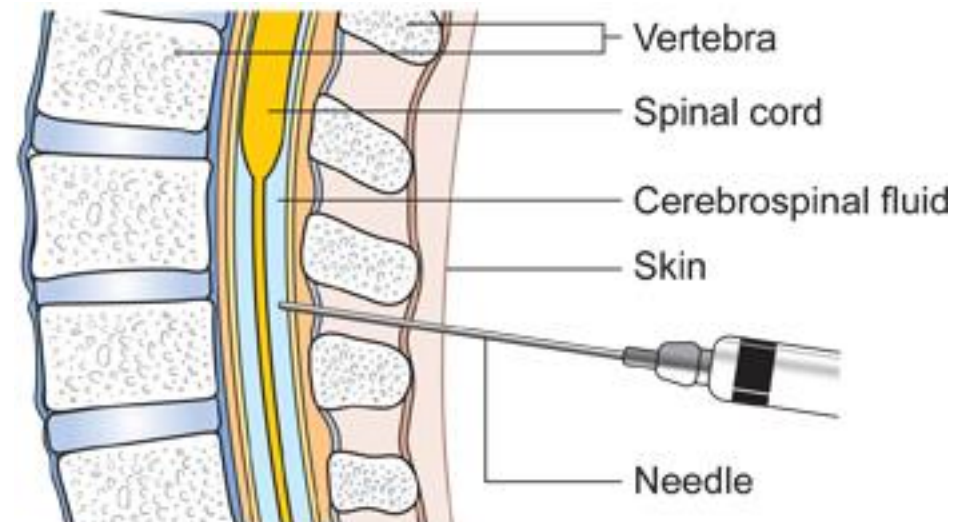
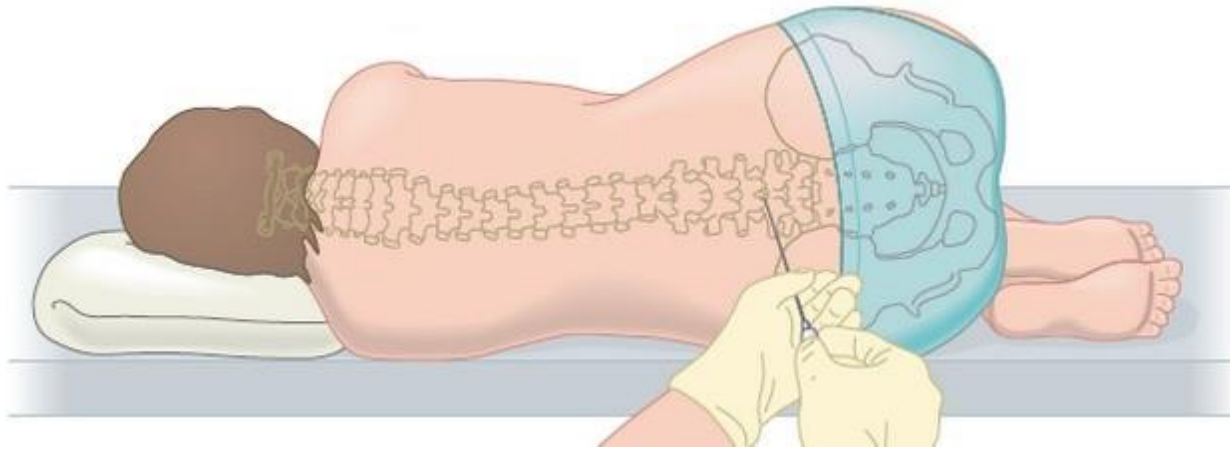


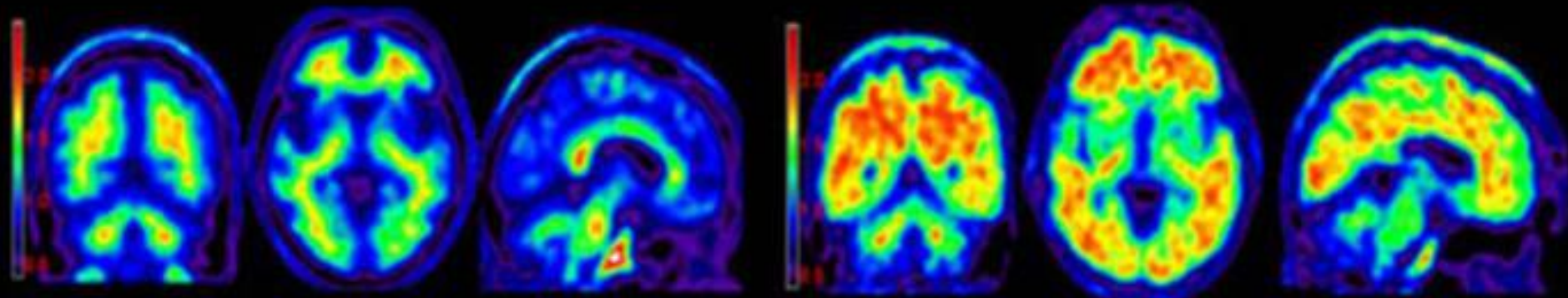
Diagram showing how you have a lumbar puncture
© Copyright CancerHelp UK

Beta amiloide ↓

Tau ↑

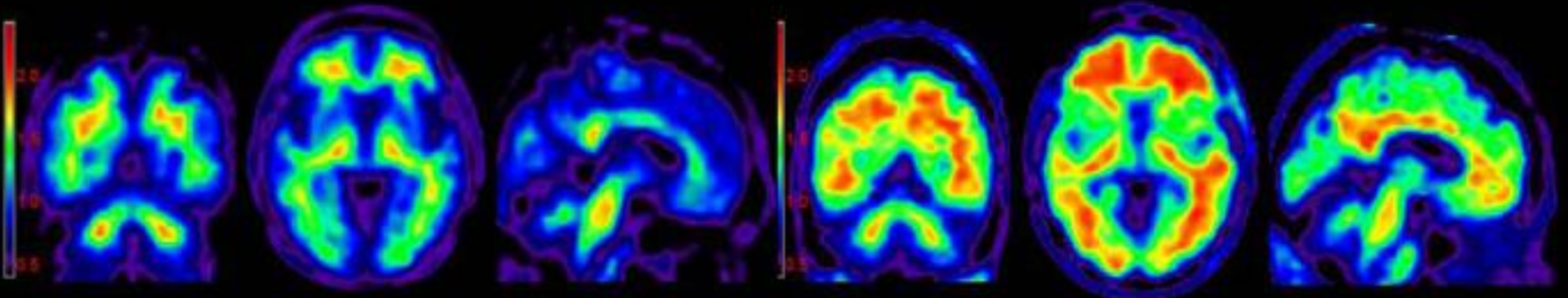
P-Tau ↑

Amyloid PET



Cognitively Normal

A β + AD



A β - MCI

A β + MCI

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings

Panel 1: IWG-2 criteria for typical AD (A plus B at any stage)

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
 - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
 - Objective evidence of an amnesic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

Panel 5: Definition of AD biomarkers

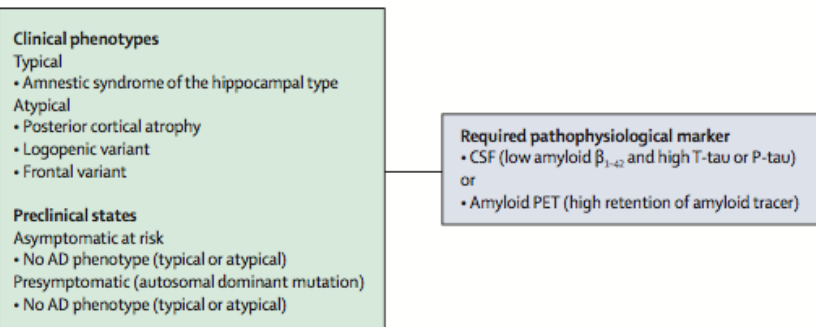
Diagnostic marker

- Pathophysiological marker
- Reflects in-vivo pathology
- Is present at all stages of the disease
- Observable even in the asymptomatic state
- Might not be correlated with clinical severity
- Indicated for inclusion in protocols of clinical trials

Progression marker

- Topographical or downstream marker
- Poor disease specificity
- Indicates clinical severity (staging marker)
- Might not be present in early stages
- Quantifies time to disease milestones
- Indicated for disease progression

AD=Alzheimer's disease.



Why did so many trials fail?

- **Preclinical models:**
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- **Amyloid cascade:**
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Amyloid hypothesis

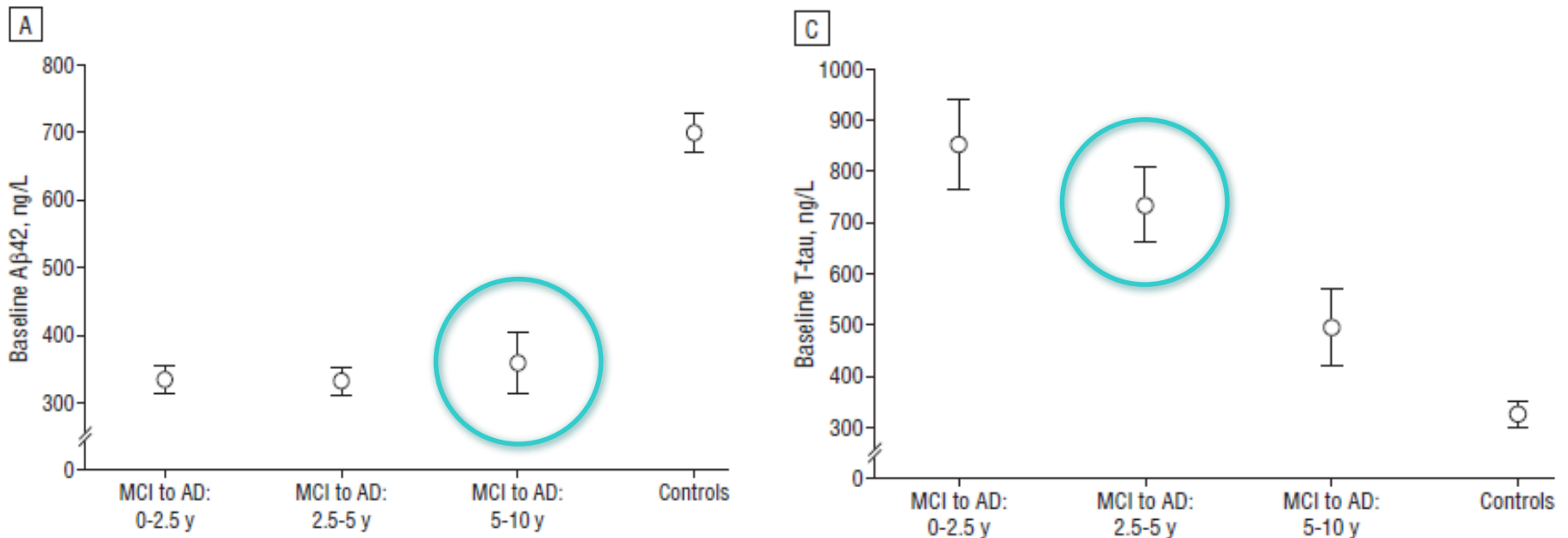
Does $A\beta$ accumulation **correlate** well with the extent of neuronal loss or cognitive dysfunction?

NO, because:

Cerebrospinal Fluid Levels of β -Amyloid 1-42, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia

Peder Buchhave, MD, PhD; Lennart Minthon, MD, PhD; Henrik Zetterberg, MD, PhD;
Åsa K. Wallin, MD, PhD; Kaj Blennow, MD, PhD; Oskar Hansson, MD, PhD

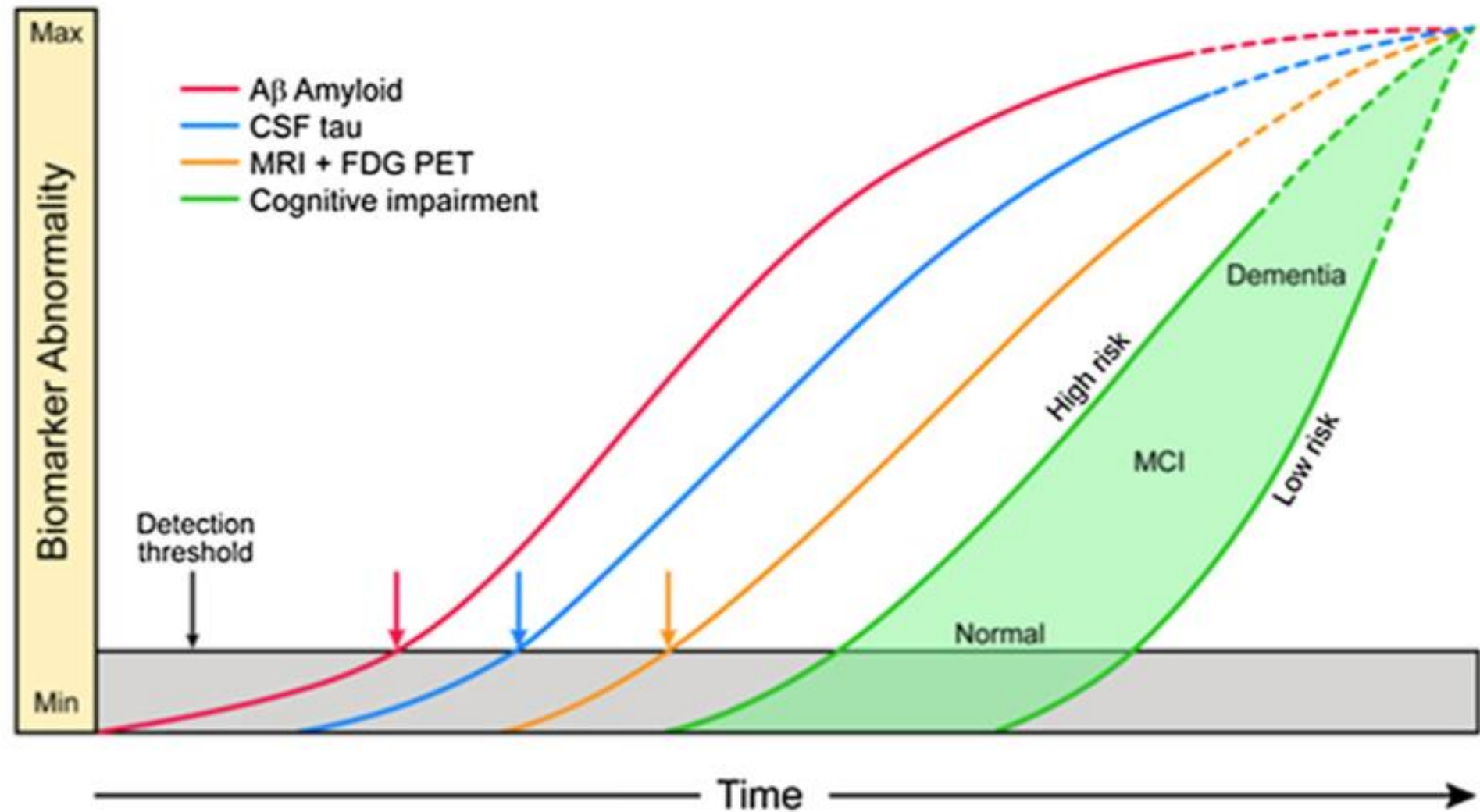
Arch Gen Psychiatry. 2012;69(1):98-106



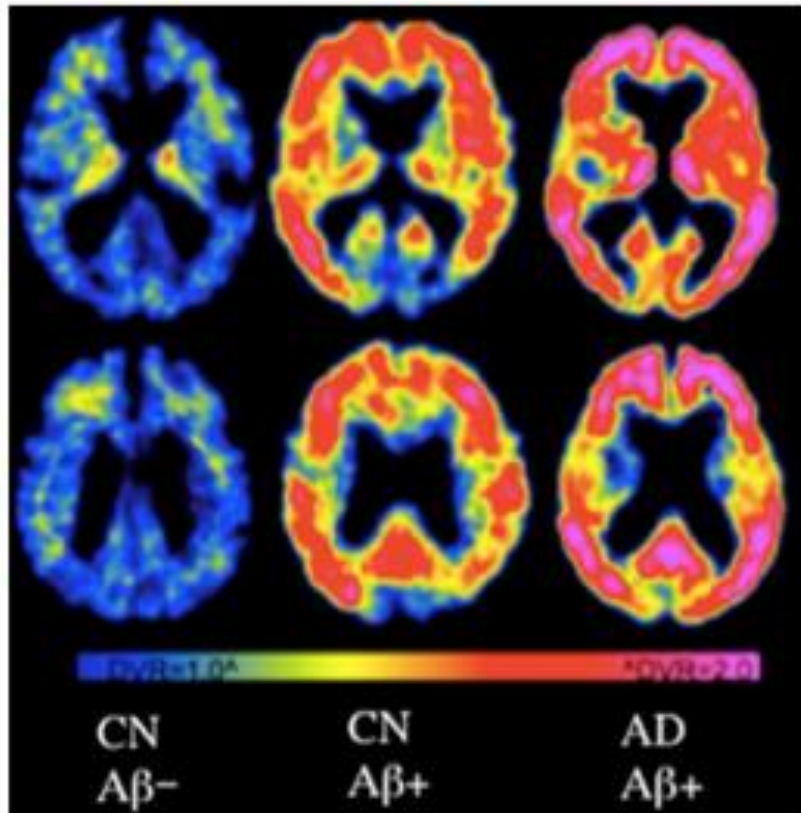
Amyloid CSF levels: changed **10 years** before symptoms appearance

Tau CSF levels: changed **5 years** before symptoms appearance

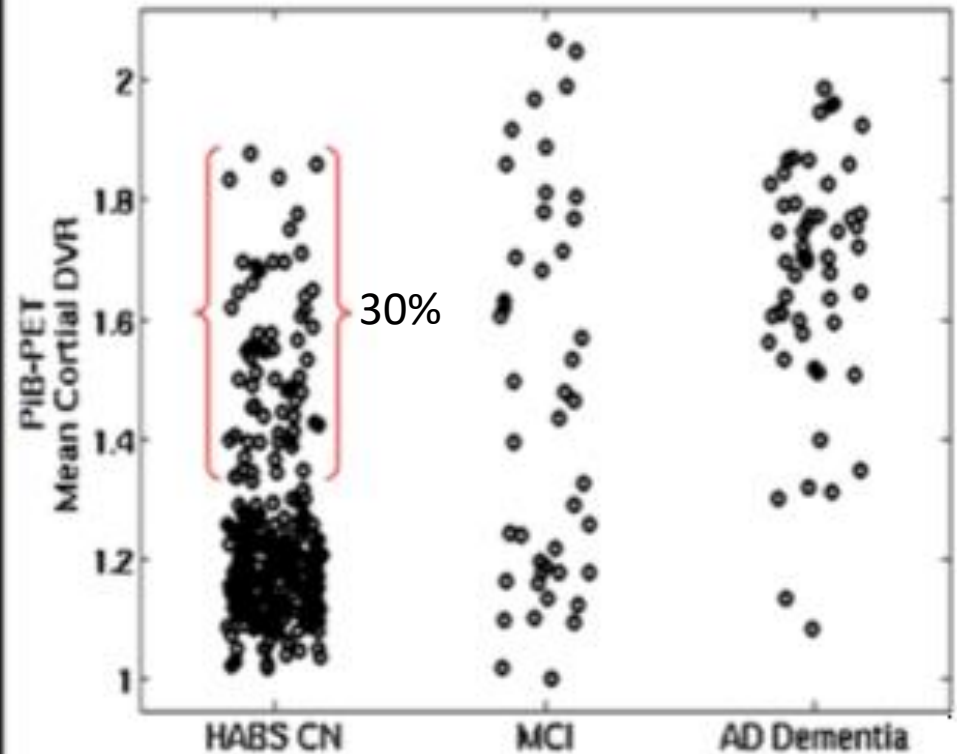
Biomarker model of pure AD



PET Amyloid Imaging with ^{11}C -PiB

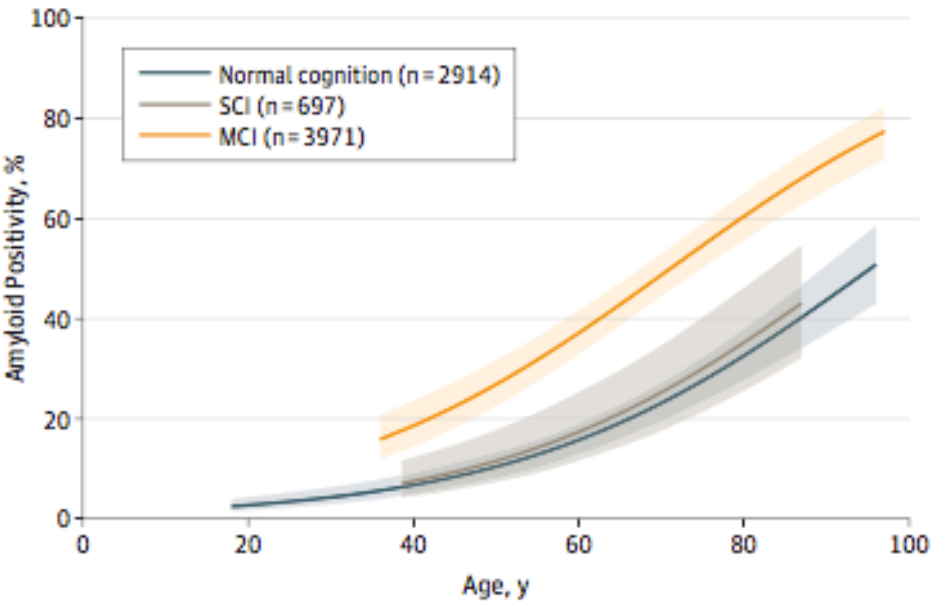


normal
older
individuals



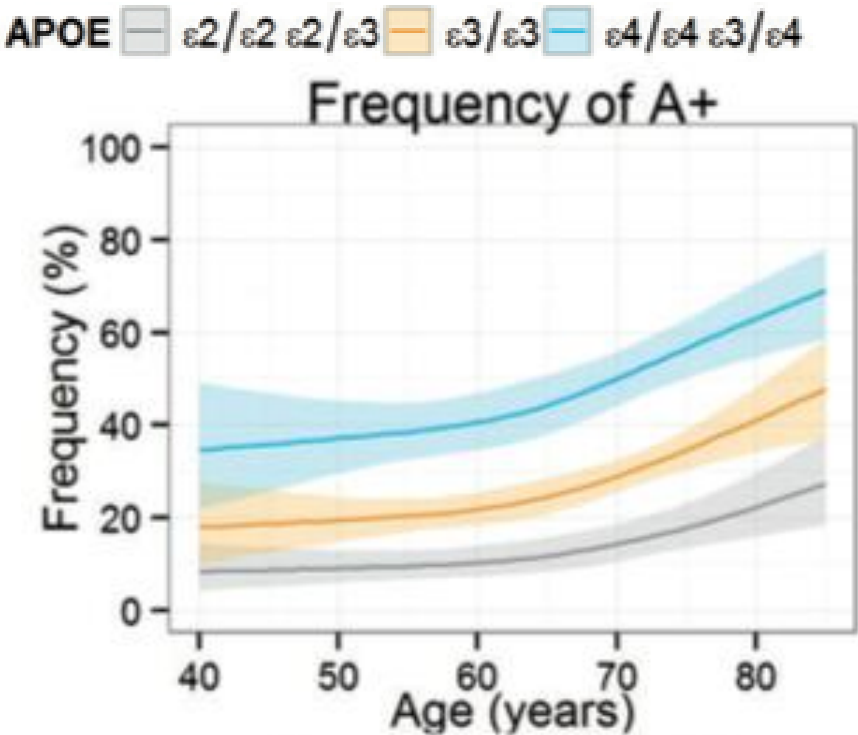
Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia

A Meta-analysis



Amy-PET

Alzheimer's disease cerebrospinal fluid biomarker in cognitively normal subjects

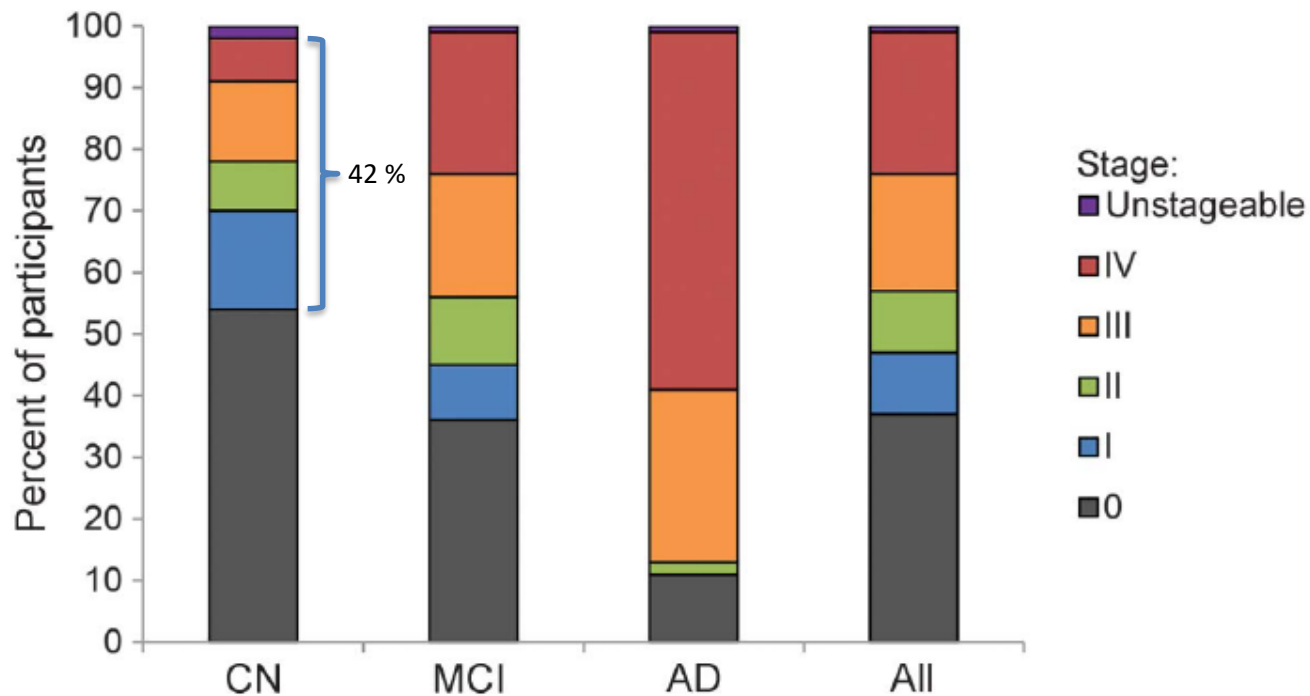


CSF

In vivo staging of regional amyloid deposition

[OPEN](#)

Figure 3 Proportions of in vivo amyloid stages by clinical diagnosis



Use of BMs in clinical trials

Ideally

treat subjects with low CSF A β but normal tau
(no cell death yet) → prevent all pathogenic
mechanisms related to A β deposition,
responsible for neurodegeneration

But

Tau is a **symptom proximity marker**, therefore should
be used (together with amyloid) to evaluate conversion
proximity in clinical trials (2-3 years follow-up)



CrossMark

Tau imaging: early progress and future directions

Victor L Villemagne, Michelle T Fodero-Tavoletti, Colin L Masters, Christopher C Rowe



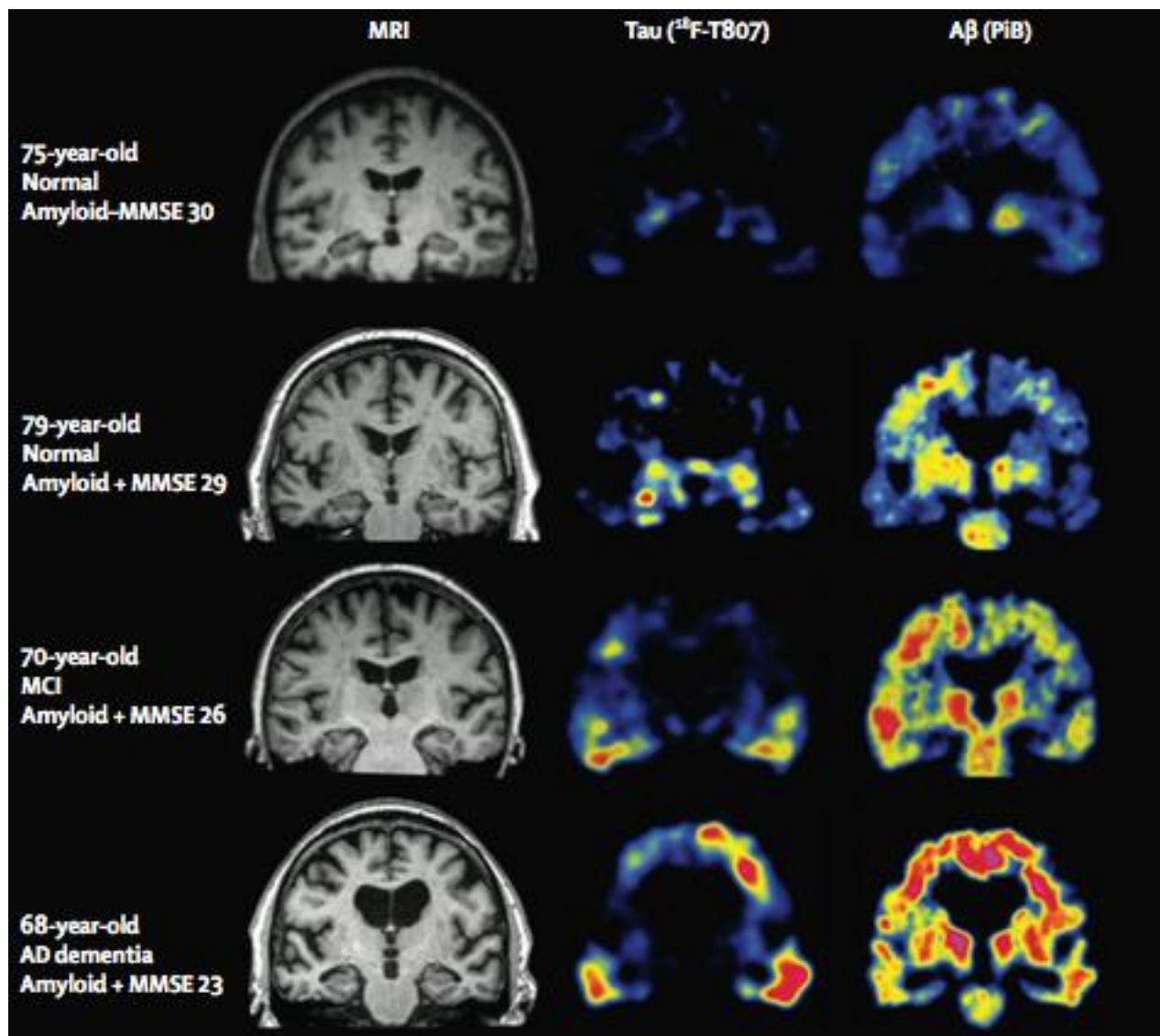
Transentorhinal
stages I-II



Limbic
stages III-IV



Isocortical
stages V-VI



PET TAU tracers: [^{18}F]AV-1451

Tau, Amyloid, and Hypometabolism in a Patient with Posterior Cortical Atrophy

Rik Ossenkoppele, PhD,^{1,2}

Daniel R. Schonhaut, BA,^{1,2}

Suzanne L. Baker, PhD,³

James P. O'Neil, PhD,³

Mustafa Janabi, PhD,³

Pia M. Ghosh, BA,¹ Miguel Santos, MD,¹

Zachary A. Miller, MD,¹

Brianne M. Bettcher, PhD,¹

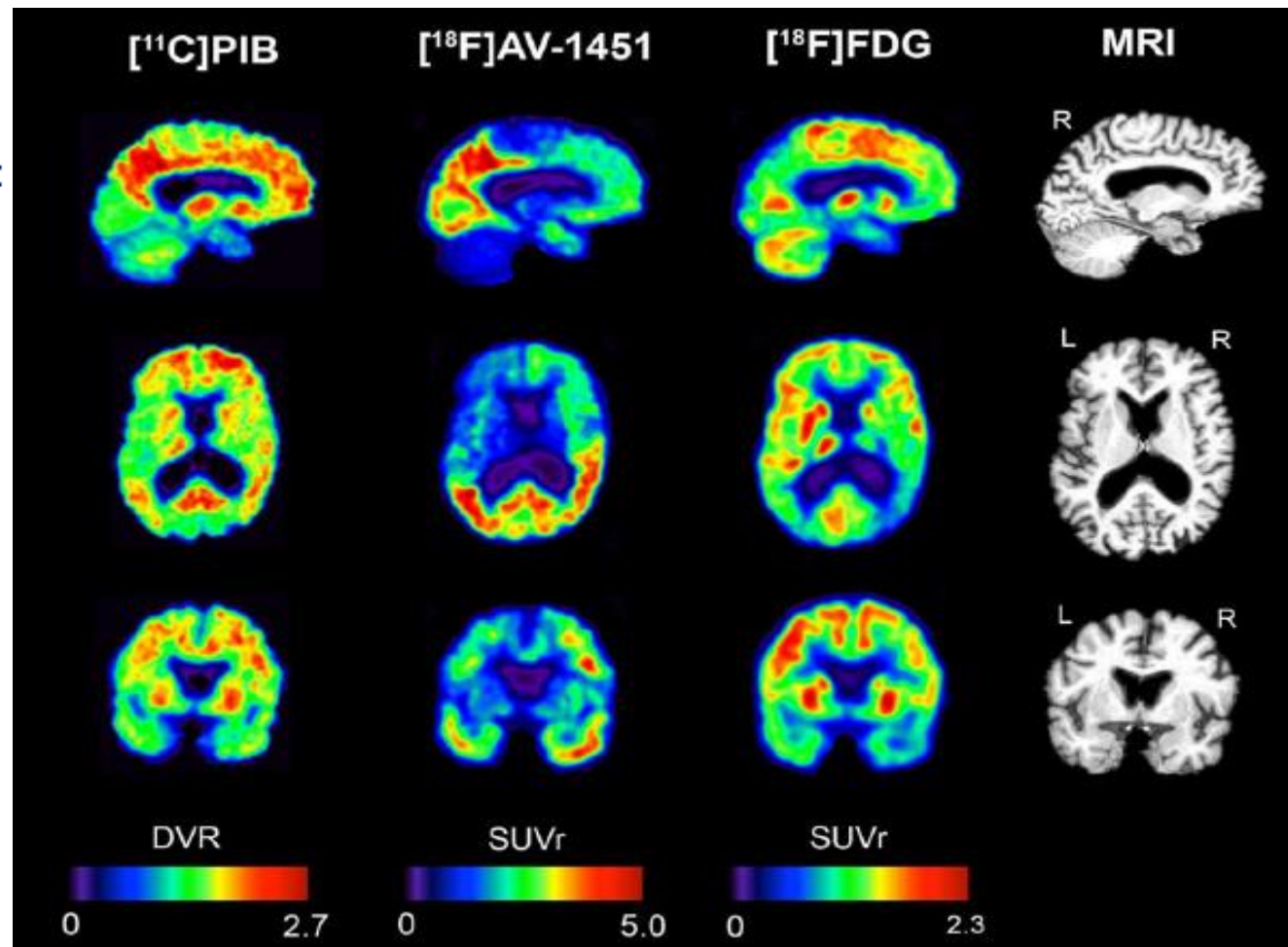
Maria L. Gorno-Tempini, MD, PhD,¹

Bruce L. Miller, MD,¹

William J. Jagust, MD,^{2,3} and

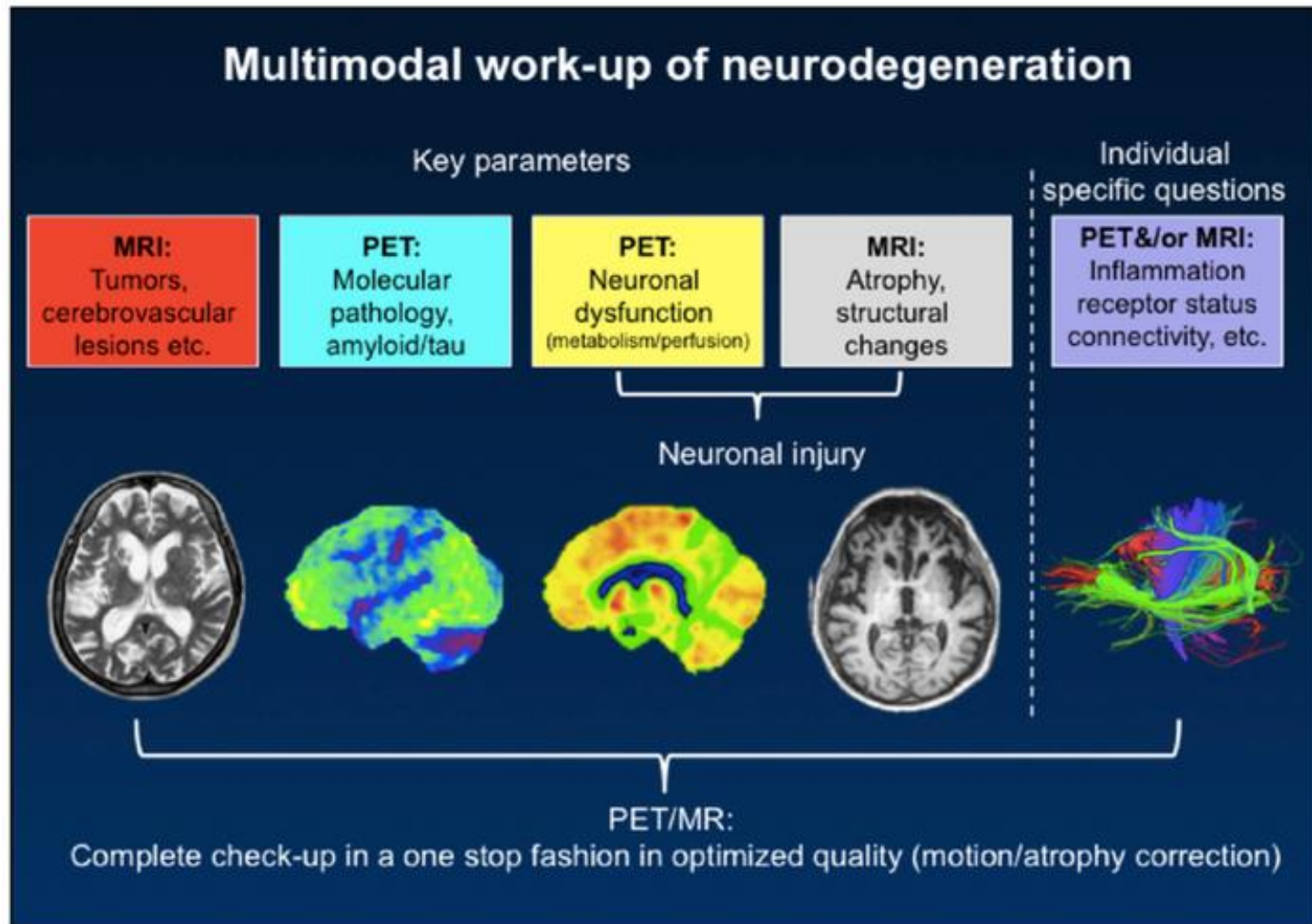
Gil D. Rabinovici, MD^{1,2}

ANN NEUROL 2015;77:338–342

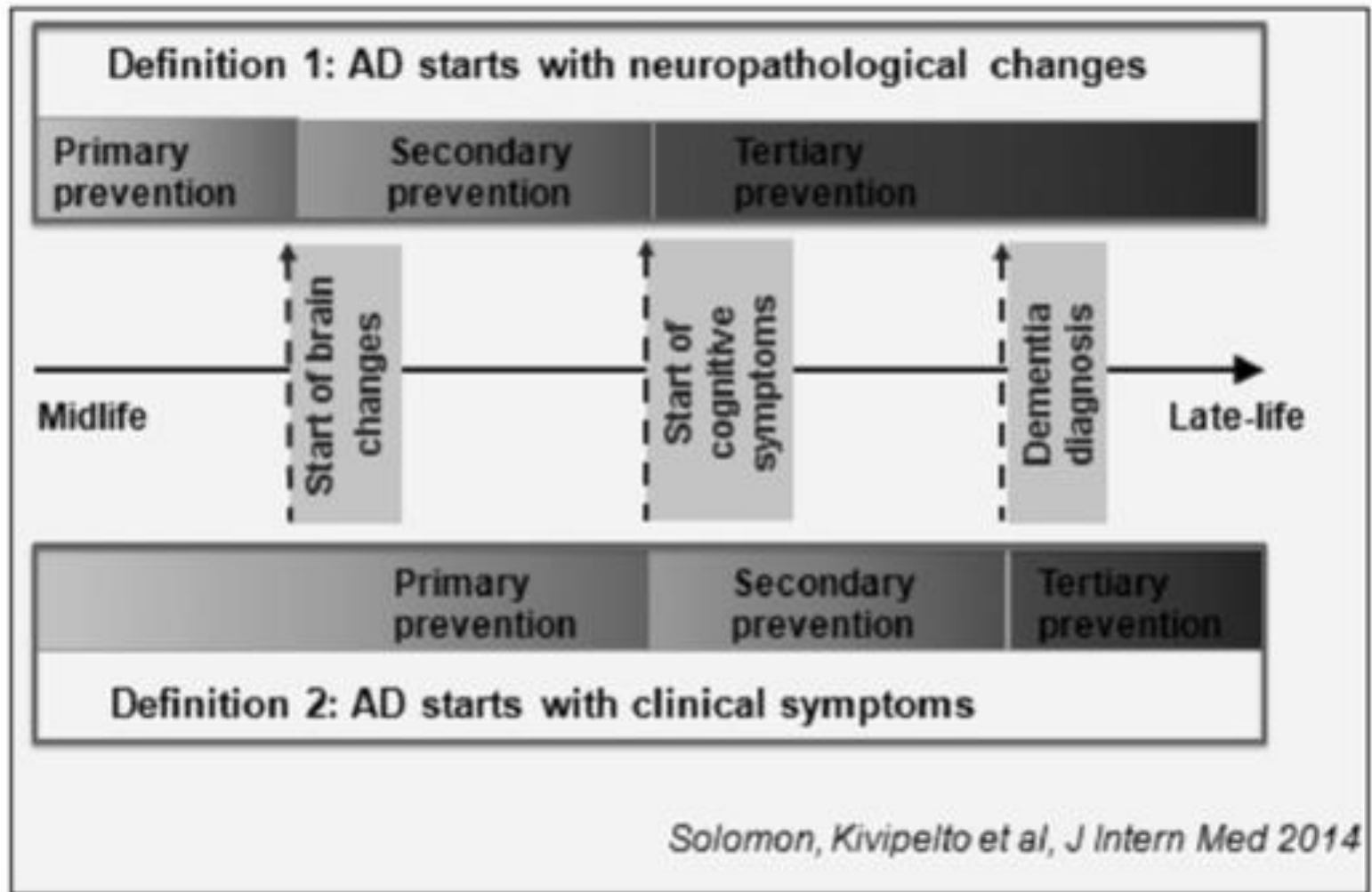


The pattern of increased [^{18}F]AV-1451 retention highly overlapped with regions that showed decreased [^{18}F]FDG uptake → **hypometabolism** and **symptomatology** are more closely **linked to tau** than to A β

PET / MR



How disease definition affects prevention



The Evolution of Preclinical Alzheimer's Disease: Implications for Prevention Trials

Reisa Sperling,^{1,2,4,*} Elizabeth Mormino,² and Keith Johnson^{2,3,4}

¹Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA 02115, USA

²Harvard Aging Brain Study, Department of Neurology

³Department of Radiology

Massachusetts General Hospital, Boston, MA 02114, USA

⁴Harvard Medical School, Boston, MA 02115, USA

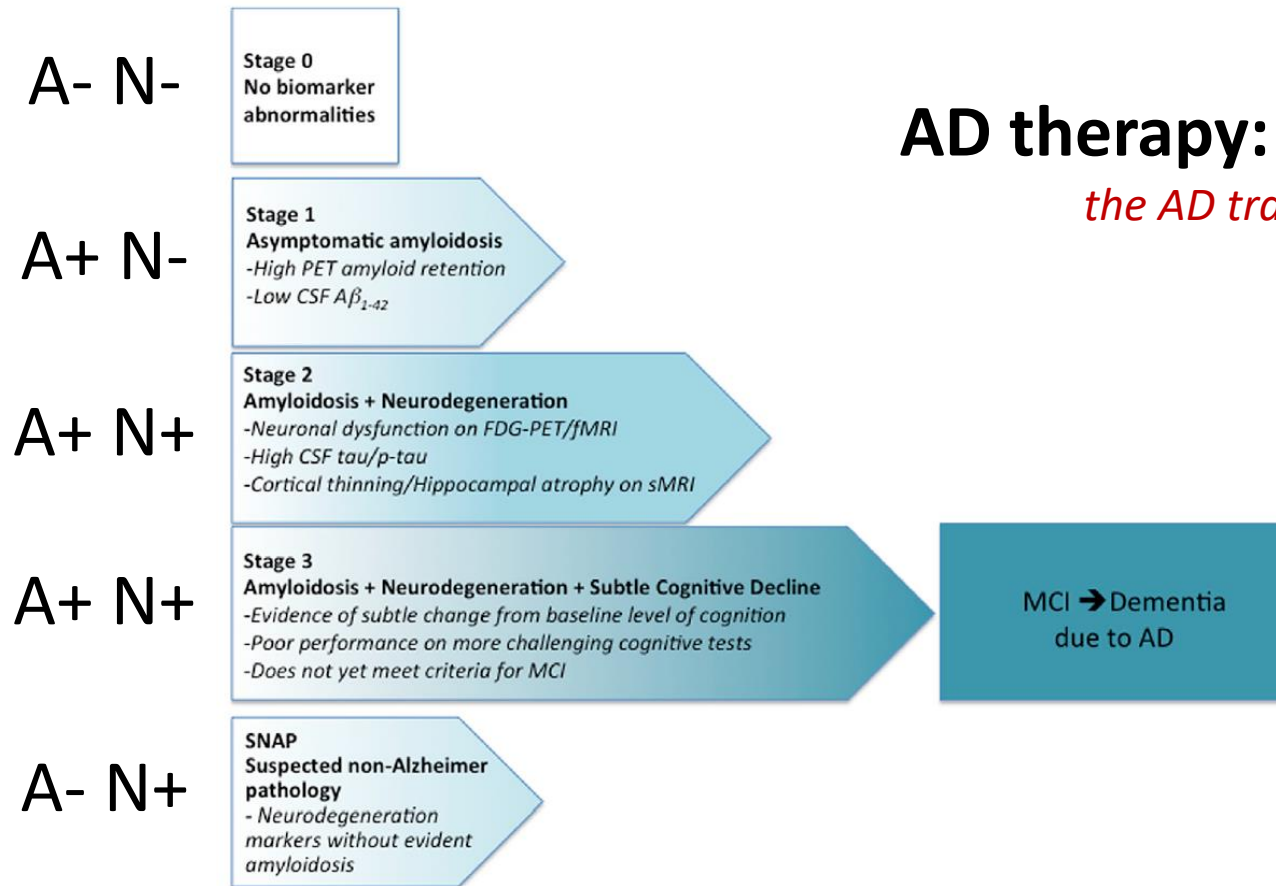
*Correspondence: reisa@rics.bwh.harvard.edu

<http://dx.doi.org/10.1016/j.neuron.2014.10.038>

As the field begins to test the concept of a “preclinical” stage of neurodegenerative disease, when the pathophysiological process has begun in the brain, but clinical symptoms are not yet manifest, a number of intriguing questions have already arisen. In particular, in preclinical Alzheimer's disease (AD), the temporal relationship of amyloid markers to markers of neurodegeneration and their relative utility in the prediction of cognitive decline among clinically normal older individuals remains to be fully elucidated. Secondary prevention trials in AD have already begun in both genetic at-risk and amyloid at-risk cohorts, with several more trials in the planning stages, and should provide critical answers about whether intervention at this very early stage of disease can truly bend the curve of clinical progression. This review will highlight recent progress in cognitive, imaging, and biomarker outcomes in the field of preclinical AD, and the remaining gaps in knowledge.

AD therapy: the future

the AD trajectory



- Stage 0: **no biomarker abnormalities**, people not thought to be on the AD trajectory
- Stage 1: cerebral **amyloidosis**
- Stage 2: **amyloidosis** plus markers of **neurodegeneration**
- Stage 3: **amyloidosis + neurodegeneration** + subtle **cognitive** and behavioral **decline**
- SNAP (Suspected Non-Alzheimer Pathology): **neurodegeneration without amyloidosis**

Stage 0: primary prevention



Stage 0
No biomarker abnormalities

Stage 1
Asymptomatic amyloidosis
-High PET amyloid 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

SNAP
Suspected non-Alzheimer pathology
- Neurodegeneration markers without evident amyloidosis

- Cardiovascular risk factors
- Mediterranean diet
- Physical activity

MCI → Dementia
due to AD

Average Daily Food Intake of Homer Simpson

Suggested Daily Cals: 2,774
HOMER'S ESTIMATED CALS: 24,929

Snacks:

1 Family-Size Chippos
1 Can Nuts and Gum
1 Powersauce Bar
1 Hot Dog
64 Slices of Cheese
11,239 estimated cals.

Lunch:

2 Krusty Burgers
3 Orders of Fries
2 Large Squishees
2,360 estimated cals.

Throughout Day:

12 Duff Beers
1,740 estimated cals.

Dinner:

1/2 whole pig
1 bowl mashed potatoes
1 bowl green moosh
2 pieces floor pie
5,340 estimated cals.

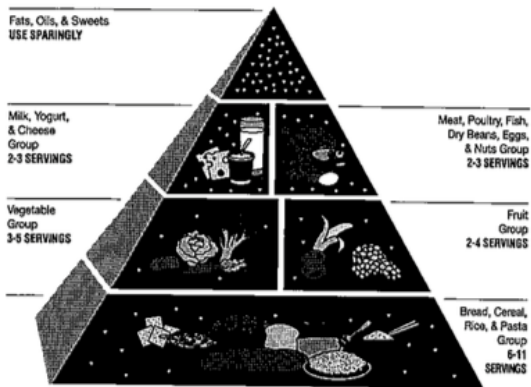
Breakfast:

13 Donuts
4,250 estimated cals.

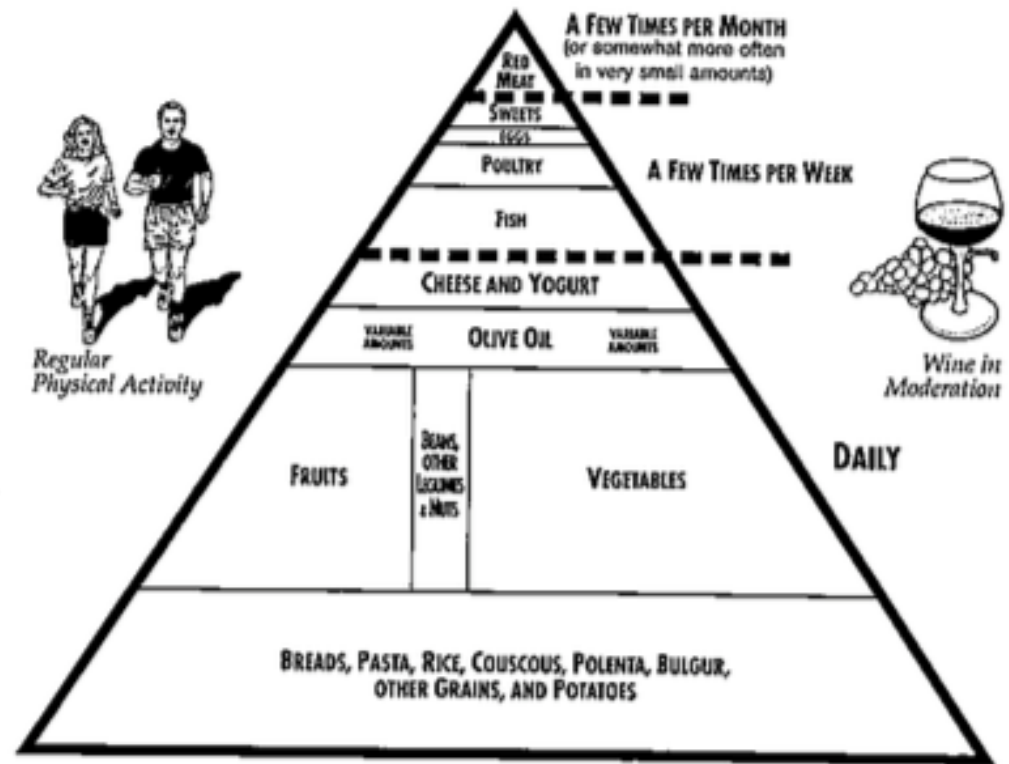
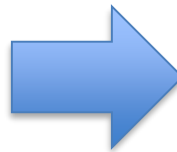


La dieta mediterranea

- 1993 – International Conference on the Diet of the Mediterranean

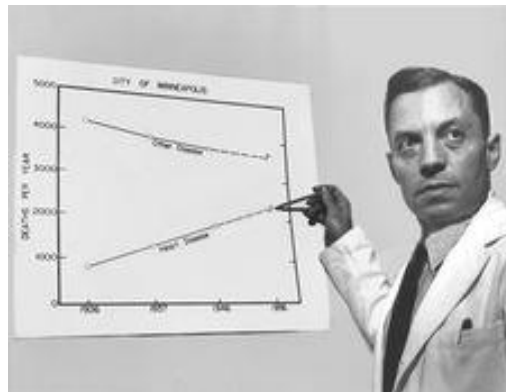


1992 – US Department of Agriculture food guide pyramid

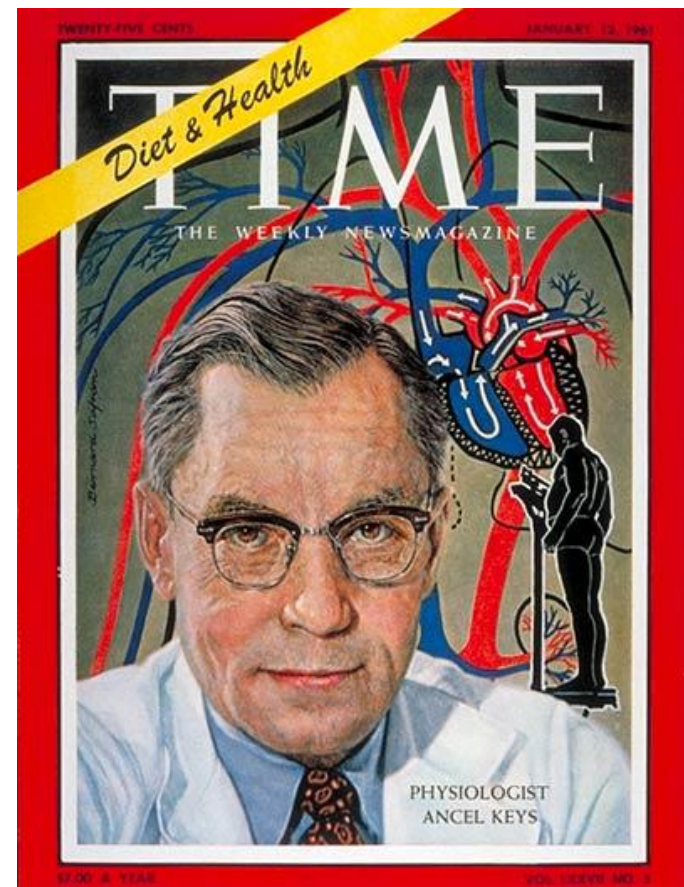


1994 – Mediterranean diet pyramid

The 7 Seven Countries Study



Ancel Keys in 1947





USO LIMITATO:

Carni rosse e Burro
Cereali raffinati: pane, pasta e riso
Patate
Bevande gassate e Dolci
Sale

Alcol con moderazione
(ma non per tutti)



Multivitaminici
con extra Vitamina D
(per molte persone)



Latticini (1 o 2 porzioni al giorno)
o supplementi di Calcio + vitamina D



Noci, Semi, Legumi e Tofu



Pesce Pollame e Uova



Frutta e Verdura



Grassi e oli salutari



Cereali integrali

Mediterranean Diet and Risk for Alzheimer's Disease

Nikolaos Scarmeas, MD,¹⁻³ Yaakov Stern, PhD,¹⁻³ Ming-Xin Tang, PhD,^{1,4} Richard Mayeux, MD,¹⁻³
and Jose A. Luchsinger, MD^{1,5}

Objective: Previous research in Alzheimer's disease (AD) has focused on individual dietary components. There is converging evidence that composite dietary patterns such as the Mediterranean diet (MeDi) is related to lower risk for cardiovascular disease, several forms of cancer, and overall mortality. We sought to investigate the association between MeDi and risk for AD.

Methods: A total of 2,258 community-based nondemented individuals in New York were prospectively evaluated every 1.5 years. Adherence to the MeDi (zero- to nine-point scale with higher scores indicating higher adherence) was the main predictor in models that were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, medical comorbidity index, and body mass index.

Results: There were 262 incident AD cases during the course of 4 (± 3.0 ; range, 0.2–13.9) years of follow-up. Higher adherence to the MeDi was associated with lower risk for AD (hazard ratio, 0.91; 95% confidence interval, 0.83–0.98; $p = 0.015$). Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had a hazard ratio of 0.85 (95% confidence interval, 0.63–1.16) and those at the highest tertile had a hazard ratio of 0.60 (95% confidence interval, 0.42–0.87) for AD (p for trend = 0.007).

Interpretation: We conclude that higher adherence to the MeDi is associated with a reduction in risk for AD.

Ann Neurol 2006;59:912–921

Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population¹⁻³

Christine C Tangney, Mary J Kwasny, Hong Li, Robert S Wilson, Denis A Evans, and Martha Clare Morris

ABSTRACT

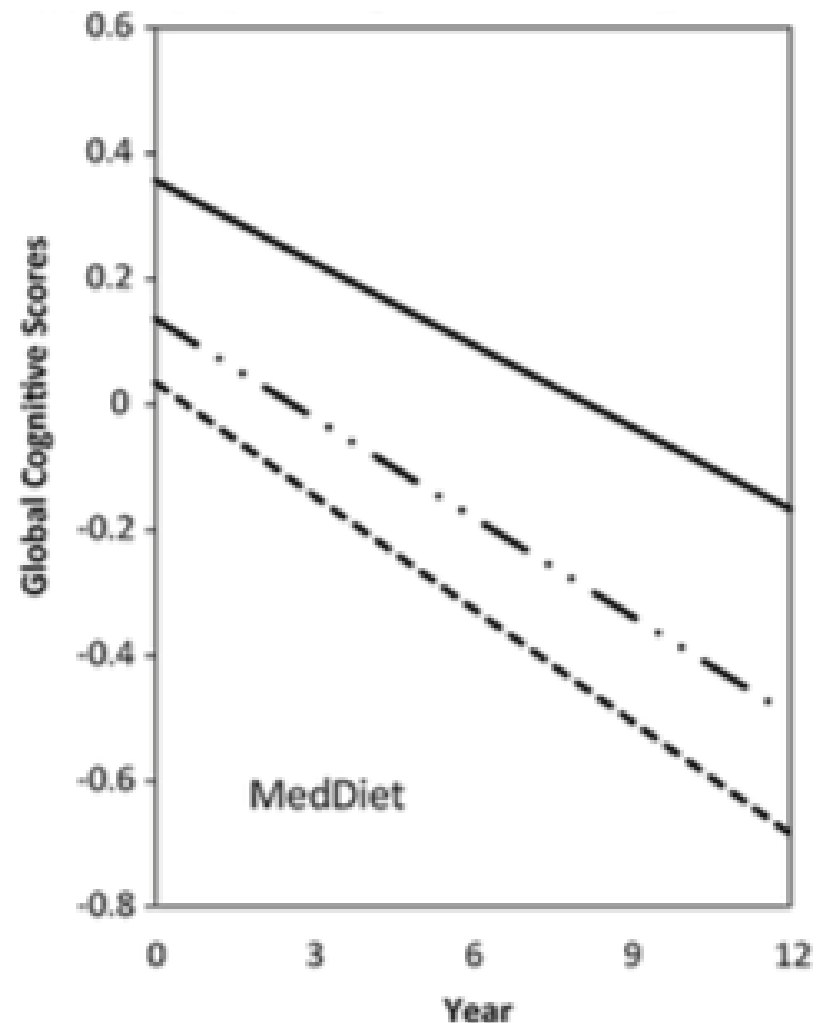
Background: Many of the foods abundant in the traditional Mediterranean diet, such as vegetables and fish, have been associated with slower cognitive decline.

Objective: We investigated whether adherence to a Mediterranean dietary pattern or to the Healthy Eating Index–2005 (HEI-2005) is associated with cognitive change in older adults.

Design: This article is based on analyses of data from an ongoing longitudinal study in adults aged ≥ 65 y known as the Chicago Health and Aging Project (CHAP). CHAP participants (2280 blacks and 1510 whites) with ≥ 2 cognitive assessments were evaluated for adherence to 1) the Mediterranean dietary pattern (MedDiet; maximum score: 55) and 2) the HEI-2005 (maximum score: 100). For both scoring systems, higher scores connote greater adherence. Cognitive function was assessed at 3-y intervals on the basis of a composite measure of global cognition. Linear mixed models were used to examine the association of dietary scores to change in cognitive function. Mean follow-up time was 7.6 y.

Results: Mean ($\pm$ SD) scores for participants were 28.2 ± 0.1 for the MedDiet and 61.2 ± 9.6 for the HEI-2005. White participants had higher energy-adjusted MedDiet scores but lower HEI-2005 scores than did black participants. Higher MedDiet scores were associated with slower rates of cognitive decline ($\beta = +0.0014$ per 1-point increase, SEE = 0.0004, $P = 0.0004$) after adjustment for age, sex, race, education, participation in cognitive activities, and energy. No such associations were observed for HEI-2005 scores.

Conclusion: The Mediterranean dietary pattern as captured by the MedDiet scoring system may reduce the rate of cognitive decline with older age. *Am J Clin Nutr* 2011;93:601–7.



Mediterranean Diet, Stroke, Cognitive Impairment, and Depression: A Meta-Analysis

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Demosthenes B. Panagiotakos, PhD,² Ioannis N. Sergentanis, MD,^{1,3}
Rena Kosti, PhD,¹ and Nikolaos Scarmeas, MD, MSc, PhD^{4,5}

Objective: This meta-analysis aims to quantitatively synthesize all studies that examine the association between adherence to a Mediterranean diet and risk of stroke, depression, cognitive impairment, and Parkinson disease.

Methods: Potentially eligible publications were those providing effect estimates of relative risk (RR) for the association between Mediterranean diet and the aforementioned outcomes. Studies were sought in PubMed up to October 31, 2012. Maximally adjusted effect estimates were extracted; separate analyses were performed for high and moderate adherence.

Results: Twenty-two eligible studies were included (11 covered stroke, 9 covered depression, and 8 covered cognitive impairment; only 1 pertained to Parkinson's disease). High adherence to Mediterranean diet was consistently associated with reduced risk for stroke (RR = 0.71, 95% confidence interval [CI] = 0.57–0.89), depression (RR = 0.68, 95% CI = 0.54–0.86), and cognitive impairment (RR = 0.60, 95% CI = 0.43–0.83). Moderate adherence was similarly associated with reduced risk for depression and cognitive impairment, whereas the protective trend concerning stroke was only marginal. Subgroup analyses highlighted the protective actions of high adherence in terms of reduced risk for ischemic stroke, mild cognitive impairment, dementia, and particularly Alzheimer disease. Meta-regression analysis indicated that the protective effects of Mediterranean diet in stroke prevention seemed more sizeable among males. Concerning depression, the protective effects of high adherence seemed independent of age, whereas the favorable actions of moderate adherence seemed to fade away with more advanced age.

Interpretation: Adherence to a Mediterranean diet may contribute to the prevention of a series of brain diseases; this may be of special value given the aging of Western societies.

ANN NEUROL 2013;74:580–591

Psaltopoulou T, 2013

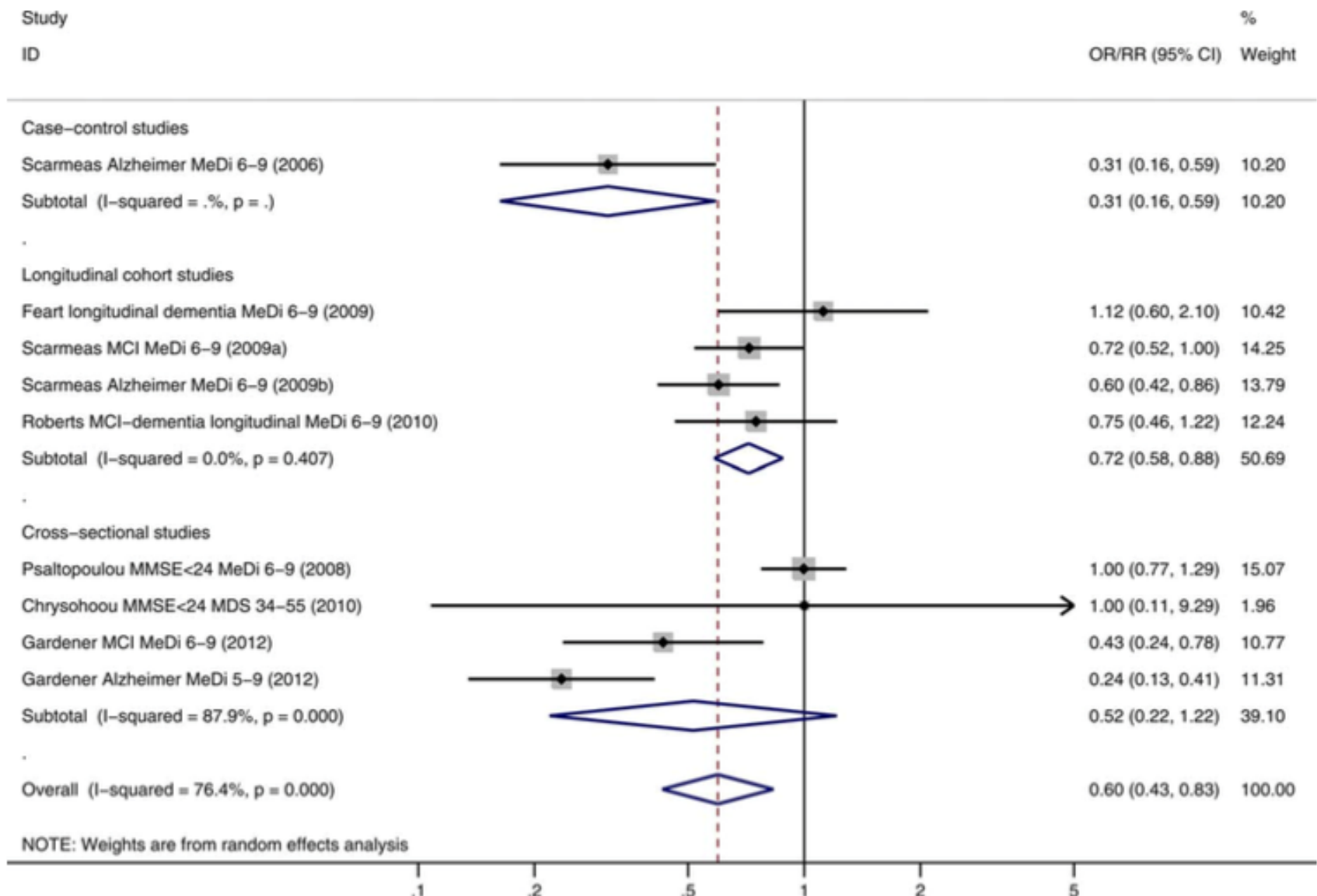
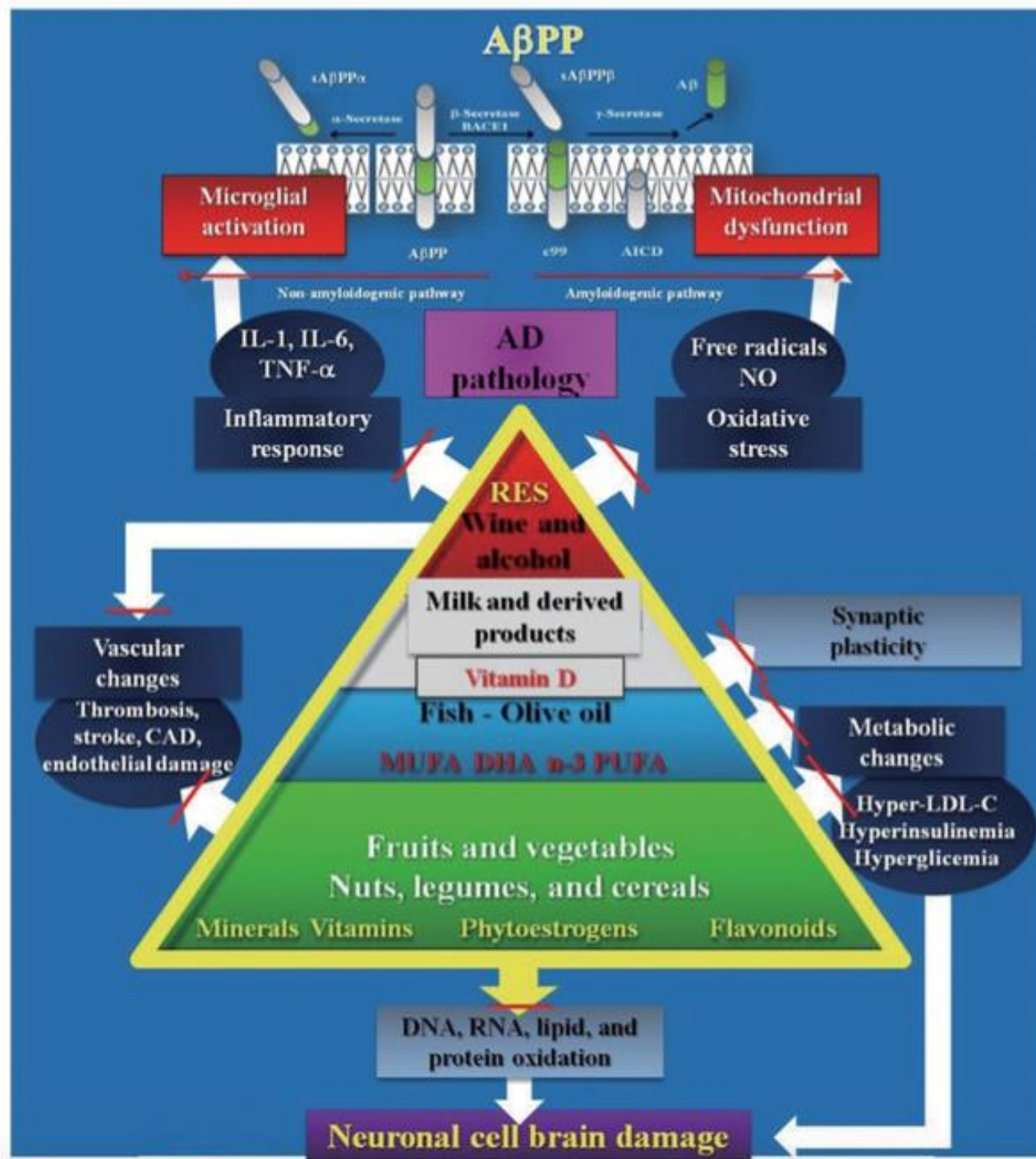
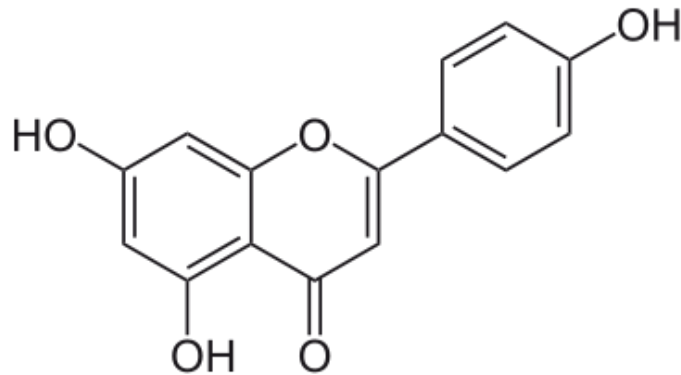


FIGURE 3: Forest plot describing the association between high adherence to Mediterranean diet and risk for cognitive impairment. Apart from the overall analysis, the subanalyses on case-control (upper panels), longitudinal cohort (middle panels), and cross-sectional studies (lower panels) are presented. CI = confidence interval; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; OR = odds ratio; RR = relative risk. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

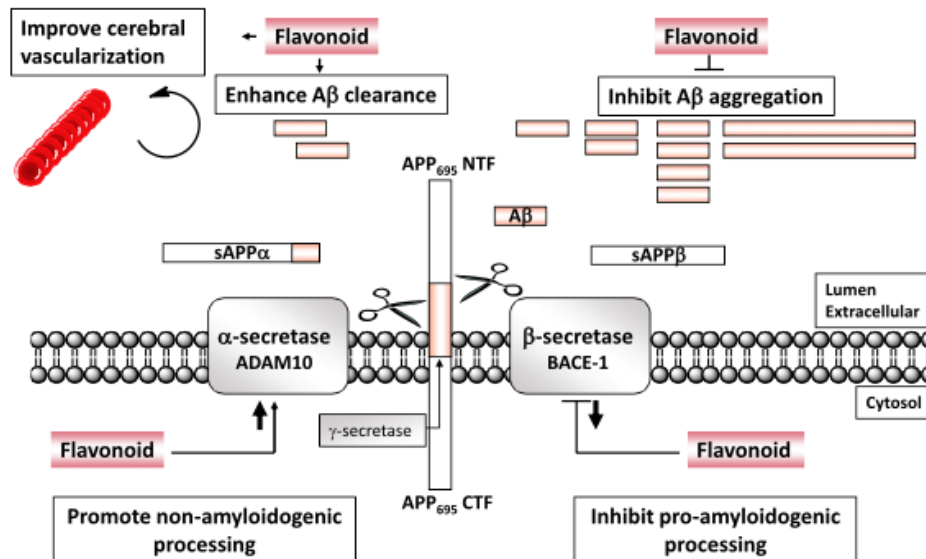
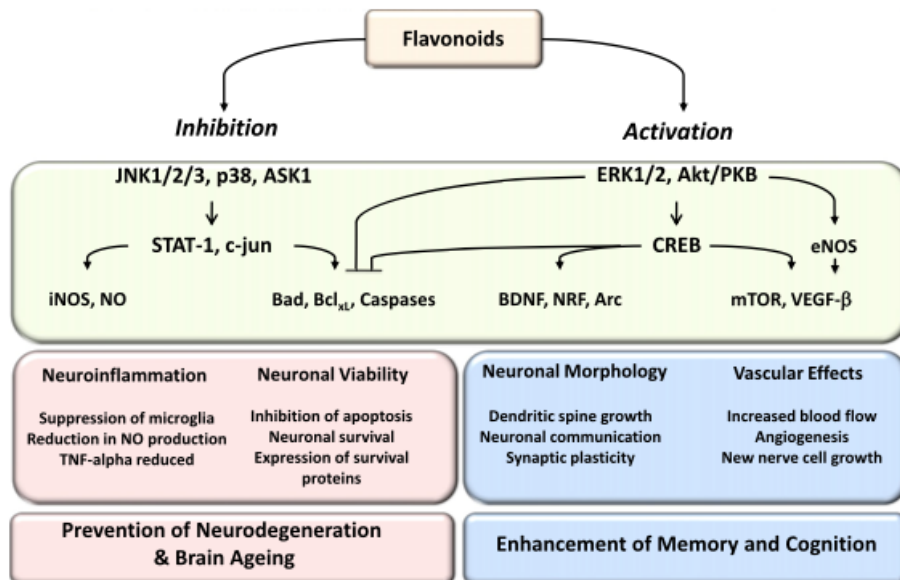


Flavonoids, cognition, and dementia: Actions, mechanisms, and potential therapeutic utility for Alzheimer disease

Robert J. Williams ^a, Jeremy P.E. Spencer ^{b,*}



- prezzemolo
- cipolle
- mirtilli e altri frutti di bosco
- il tè nero, verde e oolong,
- banane
- agrumi
- Ginkgo biloba
- vino rosso
- cioccolato fondente

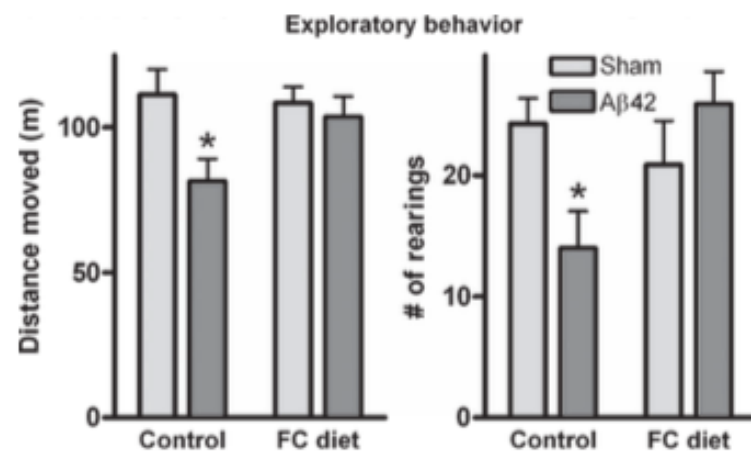




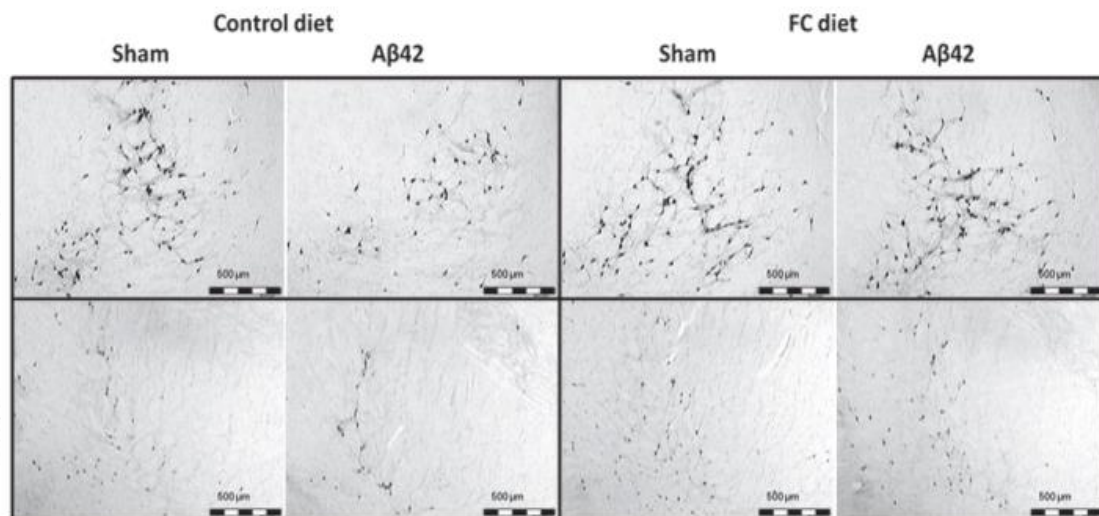
...shakeriamo!

Neuroprotective Effects of a Specific Multi-Nutrient Intervention Against A β_{42} -Induced Toxicity in Rats

Martijn C. de Wilde^{a,*}, Botond Penke^b, Eline M. van der Beek^a, Almar A.M. Kuipers^a, Patrick J. Kamphuis^{a,c} and Laus M. Broersen^a



Nutrient	Control	FC diet
Weat	25.9	25.9
Barley	25.0	23.0
Semolina	25.0	25.0
Soybean meal	8.5	8.5
Whey	5.0	5.0
Bentonite (binder)	1.0	1.0
CaCO ₃	1.40	1.40
Dicalciumphosphate	0.30	0.30
NaCl	0.50	0.50
L-lysine HCl	0.18	0.18
DL-methionine	0.05	0.05
Oil	5.0	5.0
C-18 : 1n9	1.13	0.83
C-18 : 2n6 (LA)	2.22	1.42
C-20 : 4n6 (AA)	0.00	0.04
total n6*	2.22	1.46
C-18 : 3n3 (ALA)	0.23	0.04
C-22 : 6n3 (DHA)	0.00	0.40
C-20 : 5n3 (EPA)	0.00	0.40
total n3*	0.23	0.96
UMP	–	1.000
Soy lecithin	–	0.400
Vitamin/mineral premix	2.20	2.20
Choline	–	0.313
Folic acid	–	0.00070
Vitamin B6	–	0.003
Vitamin B12	–	0.0000011
Vitamin C	–	0.160
Vitamin E	–	0.157
Selenium	–	0.0001110
*n3/n6 ratio	0.10	0.65



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

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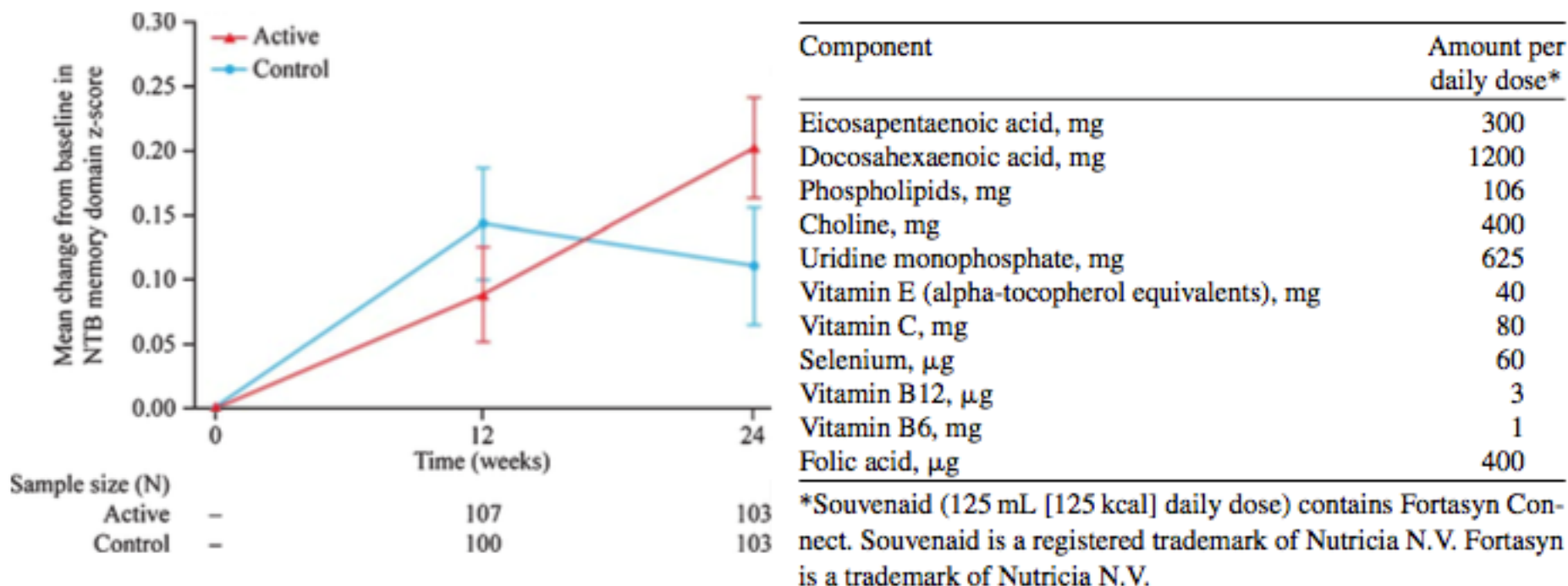


Fig. 2. Mean change from baseline in the Neuropsychological Test Battery (NTB) memory composite score. Error bars represent standard errors. The difference in trajectories over time between active and control groups during the 24-week intervention period: $p = 0.023$ (mixed model for repeated measures, 2 degrees of freedom contrast).



Non solo dieta...

Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease

A Randomized Trial

Context Many observational studies have shown that physical activity reduces the risk of cognitive decline; however, evidence from randomized trials is lacking.

Objective To determine whether physical activity reduces the rate of cognitive decline among older adults at risk.

Design and Setting Randomized controlled trial of a 24-week physical activity intervention conducted between 2004 and 2007 in metropolitan Perth, Western Australia. Assessors of cognitive function were blinded to group membership.

Participants We recruited volunteers who reported memory problems but did not meet criteria for dementia. Three hundred eleven individuals aged 50 years or older were screened for eligibility, 89 were not eligible, and 52 refused to participate. A total of 170 participants were randomized and 138 participants completed the 18-month assessment.

Intervention Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity.

Main Outcome Measure Change in Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) scores (possible range, 0–70) over 18 months.

Results In an intent-to-treat analysis, participants in the intervention group improved 0.26 points (95% confidence interval, –0.89 to 0.54) and those in the usual care group deteriorated 1.04 points (95% confidence interval, 0.32 to 1.82) on the ADAS-Cog at the end of the intervention. The absolute difference of the outcome measure between the intervention and control groups was –1.3 points (95% confidence interval, –2.38 to –0.22) at the end of the intervention. At 18 months, participants in the intervention group improved 0.73 points (95% confidence interval, –1.27 to 0.03) on the ADAS-Cog, and those in the usual care group improved 0.04 points (95% confidence interval, –0.46 to 0.88). Word list delayed recall and Clinical Dementia Rating sum of boxes improved modestly as well, whereas word list total immediate recall, digit symbol coding, verbal fluency, Beck depression score, and Medical Outcomes 36-Item Short-Form physical and mental component summaries did not change significantly.

Conclusions In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.

Trial Registration anzctr.org.au Identifier: ACTRN12605000136606

Exercise and Alzheimer's Disease Biomarkers in Cognitively Normal Older Adults

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Alison M. Goate, PhD,^{2,4,5,6,7} Julie M. Bugg, PhD,⁸ David M. Holtzman, MD,^{2,4,5}

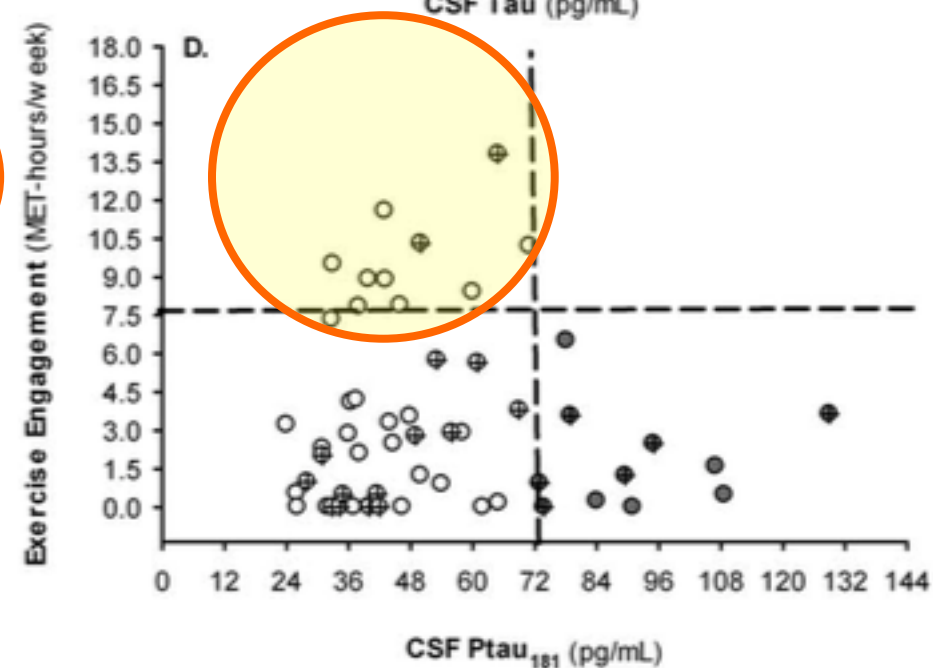
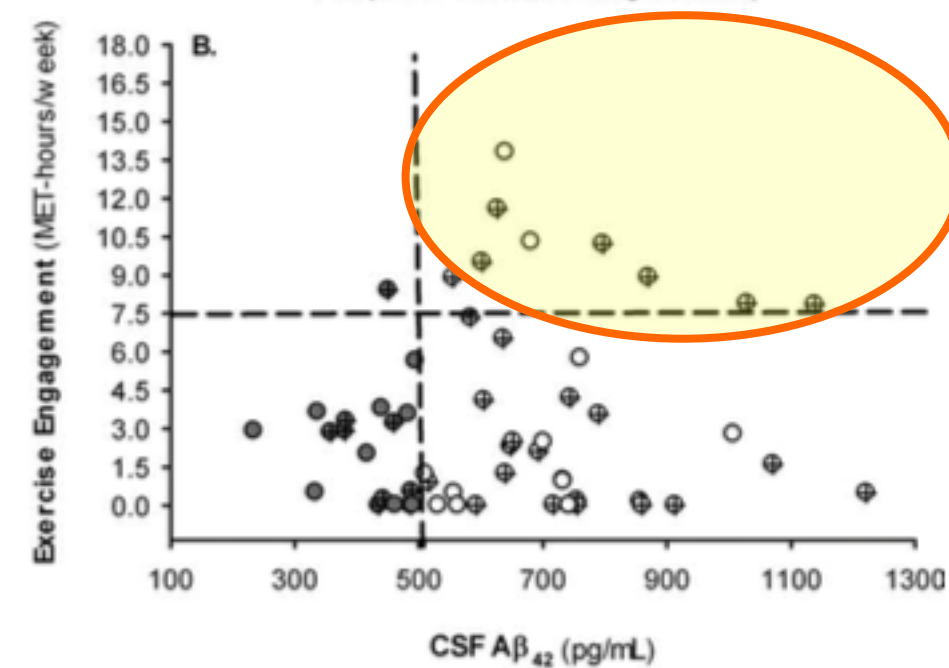
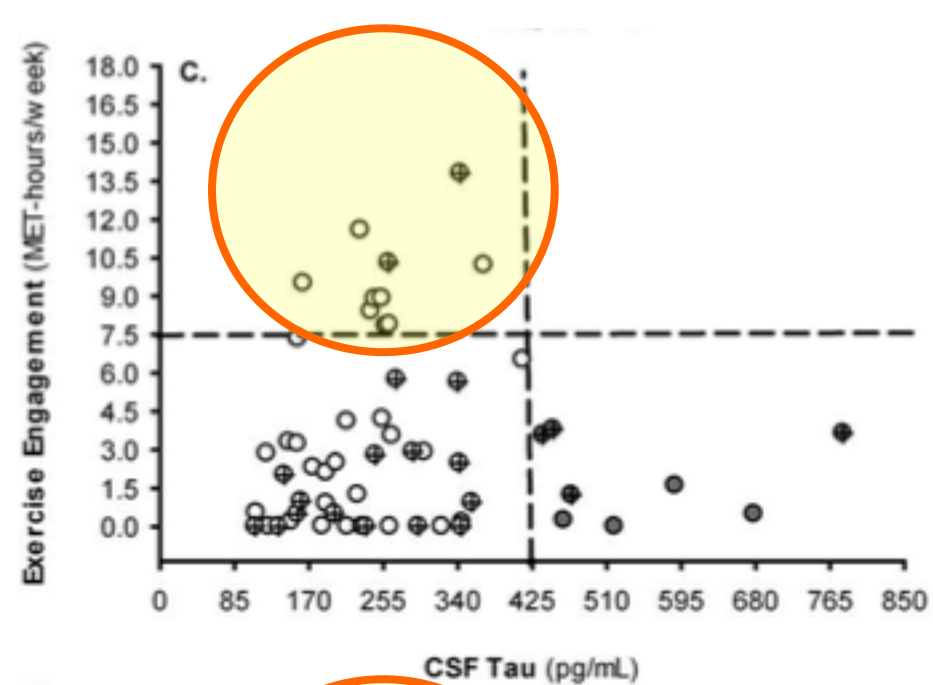
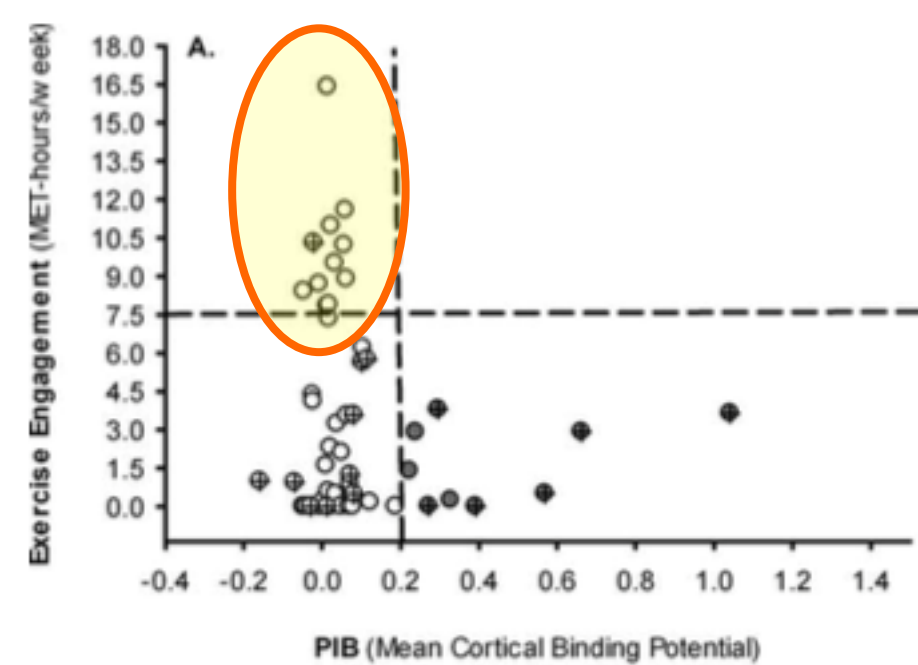
John C. Morris, MD,^{2,5} and Denise Head, PhD^{1,2,3,8}

Objective: In addition to the increasingly recognized role of physical exercise in maintaining cognition, exercise may influence Alzheimer's disease (AD) pathology, as transgenic mouse studies show lowered levels of AD pathology in exercise groups. The objective of this study was to elucidate the association between exercise and AD pathology in humans using Pittsburgh compound-B (PIB), amyloid- β ($A\beta$)₄₂, tau, and phosphorylated tau (ptau)₁₈₁ biomarkers.

Methods: Sixty-nine older adults (17 males, 52 females) aged 55 to 88 years, were recruited and confirmed to be cognitively normal. A questionnaire on physical exercise levels over the past decade was administered to all. Cerebrospinal fluid samples were collected from 56 participants, and amyloid imaging with PIB was performed on 54 participants.

Results: Participants were classified based on biomarker levels. Those with elevated PIB ($p = 0.030$), tau ($p = 0.040$), and ptau₁₈₁ ($p = 0.044$) had significantly lower exercise, with a nonsignificant trend for lower $A\beta$ ₄₂ ($p = 0.135$) to be associated with less exercise. Results were similar for PIB after controlling for covariates; tau ($p = 0.115$) and ptau₁₈₁ ($p = 0.123$) differences were reduced to nonsignificant trends. Additional analyses also demonstrated that active individuals who met the exercise guidelines set by the American Heart Association had significantly lower PIB binding and higher $A\beta$ ₄₂ levels with and without controlling for covariates (PIB: $p = 0.006$ and $p = 0.001$; $A\beta$ ₄₂: $p = 0.042$ and $p = 0.046$). Last, the associations between exercise engagement and PIB levels were more prominent in APOE epsilon 4 noncarriers.

Interpretation: Collectively, these results are supportive of an association between exercise engagement and AD biomarkers in cognitively normal older adults.



Physical Activity, Diet, and Risk of Alzheimer Disease

Context Both higher adherence to a Mediterranean-type diet and more physical activity have been independently associated with lower Alzheimer disease (AD) risk but their combined association has not been investigated.

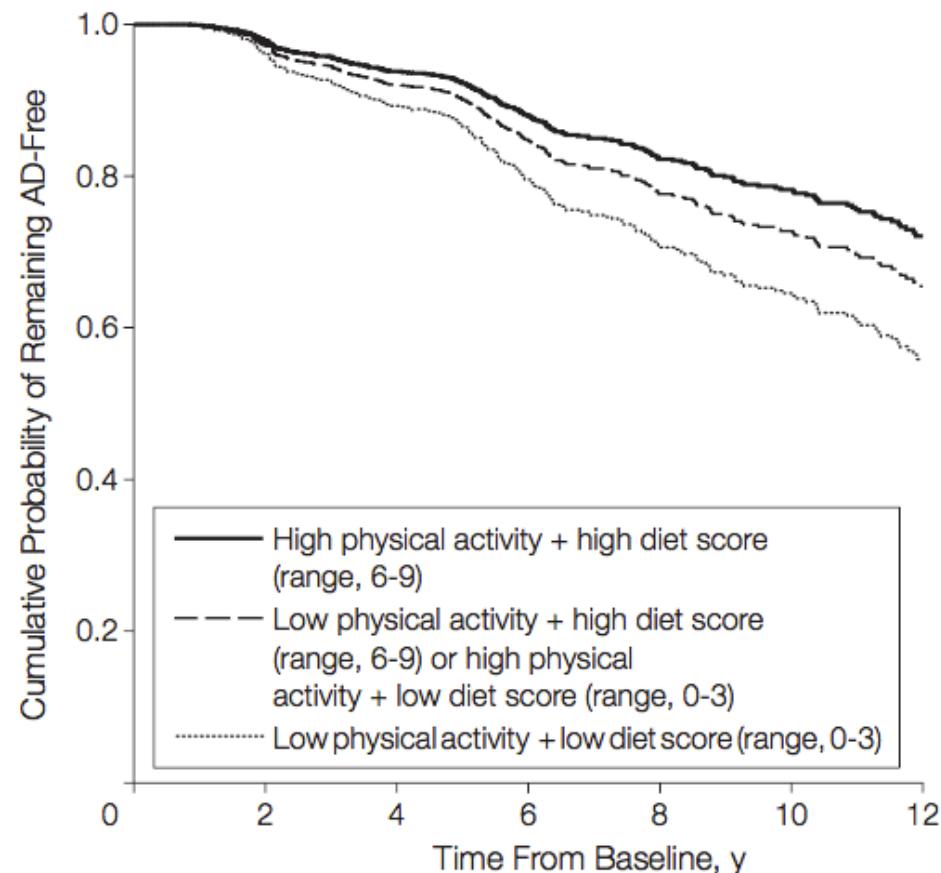
Objective To investigate the combined association of diet and physical activity with AD risk.

Design, Setting, and Patients Prospective cohort study of 2 cohorts comprising 1880 community-dwelling elders without dementia living in New York, New York, with both diet and physical activity information available. Standardized neurological and neuropsychological measures were administered approximately every 1.5 years from 1992 through 2006. Adherence to a Mediterranean-type diet (scale of 0-9; trichotomized into low, middle, or high; and dichotomized into low or high) and physical activity (sum of weekly participation in various physical activities, weighted by the type of physical activity [light, moderate, vigorous]; trichotomized into no physical activity, some, or much; and dichotomized into low or high), separately and combined, were the main predictors in Cox models. Models were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, body mass index, smoking status, depression, leisure activities, a comorbidity index, and baseline Clinical Dementia Rating score.

Main Outcome Measure Time to incident AD.

Results A total of 282 incident AD cases occurred during a mean (SD) of 5.4 (3.3) years of follow-up. When considered simultaneously, both Mediterranean-type diet adherence (compared with low diet score, hazard ratio [HR] for middle diet score was 0.98 [95% confidence interval {CI}, 0.72-1.33]; the HR for high diet score was 0.60 [95% CI, 0.42-0.87]; $P = .008$ for trend) and physical activity (compared with no physical activity, the HR for some physical activity was 0.75 [95% CI, 0.54-1.04]; the HR for much physical activity was 0.67 [95% CI, 0.47-0.95]; $P = .03$ for trend) were associated with lower AD risk. Compared with individuals neither adhering to the diet nor participating in physical activity (low diet score and no physical activity; absolute AD risk of 19%), those both adhering to the diet and participating in physical activity (high diet score and high physical activity) had a lower risk of AD (absolute risk, 12%; HR, 0.65 [95% CI, 0.44-0.96]; $P = .03$ for trend).

Conclusion In this study, both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD.



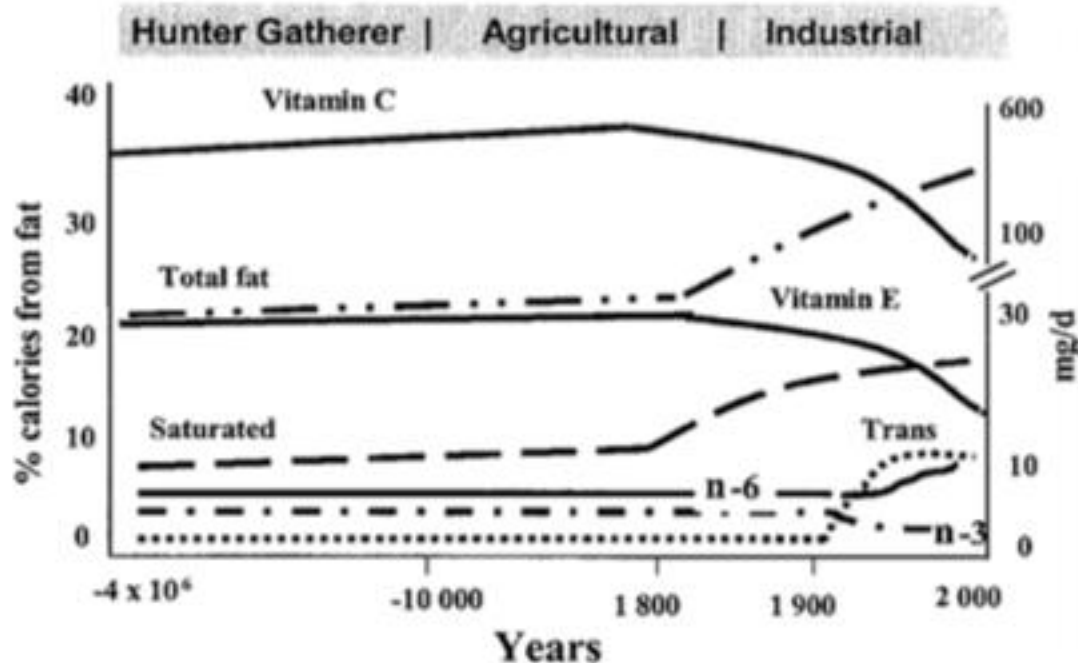


FIGURE 1 Hypothetical scheme of fat, fatty acid (n-6, n-3, *trans* and total) intake (as percentage of energy from fat) and intake of vitamins E and C (mg/d). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 y (12).

Ratios of (n-6) to (n-3) fatty acids in various populations

Population	(n-6):(n-3)	Reference
Paleolithic	0.79	8
Greece before 1960	1.00–2.00	9
Current United States	16.74	8
Current United Kingdom and northern Europe	15.00	10
Current Japan	4.00	11

Industrialized societies diet:

- an increase in energy intake and decrease in energy expenditure
- an increase in saturated fat, (n-6) fatty acids and *trans* fatty acids and a decrease in (n-3) fatty acid intake
- a decrease in fiber intake
- an increase in cereal grains
- a decrease in fruit and vegetable intake
- a decrease in protein, anti-oxidant and calcium intake

Primate aging in the mammalian scheme: the puzzle of extreme variation in brain aging

Caleb E. Finch • Steven N. Austad

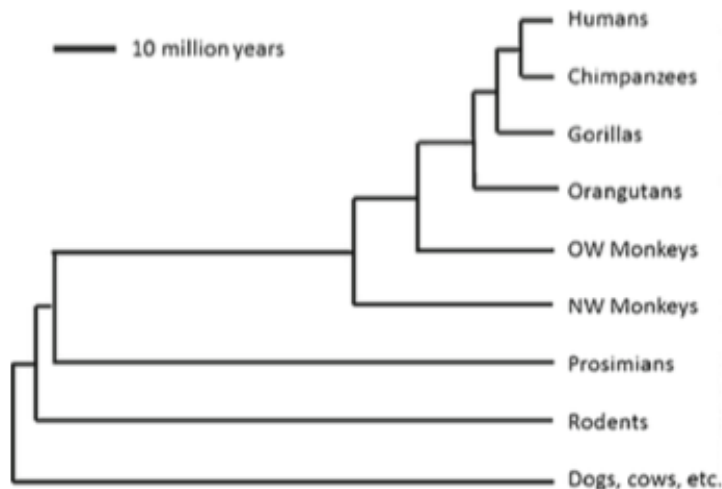
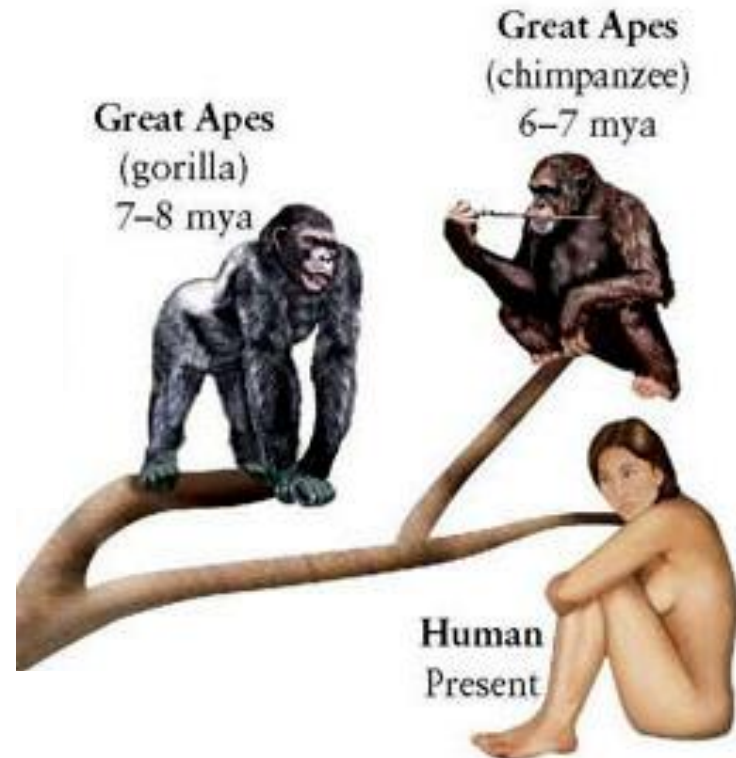


Fig. 1 Phylogeny of some relevant mammal groups (after Bininda-Emonds et al. 2007). Note that branch lengths are proportional to estimated time of divergence



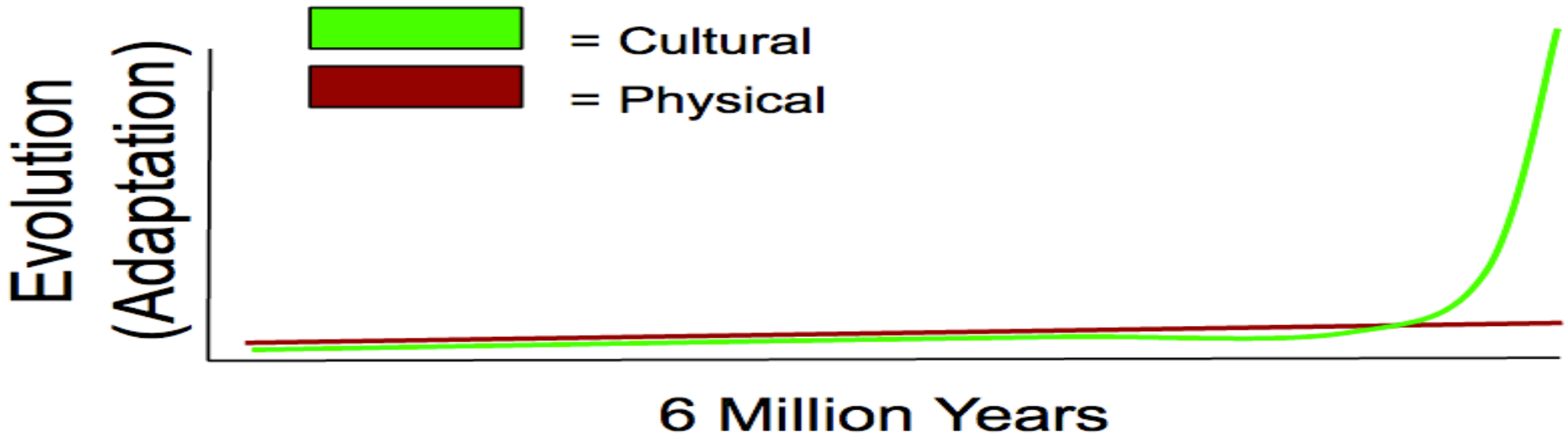
	Dendritic atrophy	Neuron loss	Diffuse amyloid	Tauopathy	AD
Human, clinically normal	++	±	+	++ after 80	+++ after 80
Great ape ^a	?	?	+	±	—

Tauopathy With Paired Helical Filaments in an Aged Chimpanzee

REBECCA F. ROSEN,¹ AARON S. FARBERG,¹ MARLA GEARING,^{2,3}
JEROMY DOOYEMA,¹ PATRICK M. LONG,¹ DANIEL C. ANDERSON,¹
JEREMY DAVIS-TURAK,⁴ GIOVANNI COPPOLA,⁴ DANIEL H. GESCHWIND,⁴
JEAN-FRANCOIS PARÉ,¹ TIMOTHY Q. DUONG,^{1,5} WILLIAM D. HOPKINS,¹
TODD M. PREUSS,^{1,2} AND LARY C. WALKER^{1,5*}



There is also no presence of tauopathic abnormalities in primates, except for one 41 year old female chimpanzee, who also suffered from obesity and hypercholesterolemia.



Le patologie da mismatch evolutivo

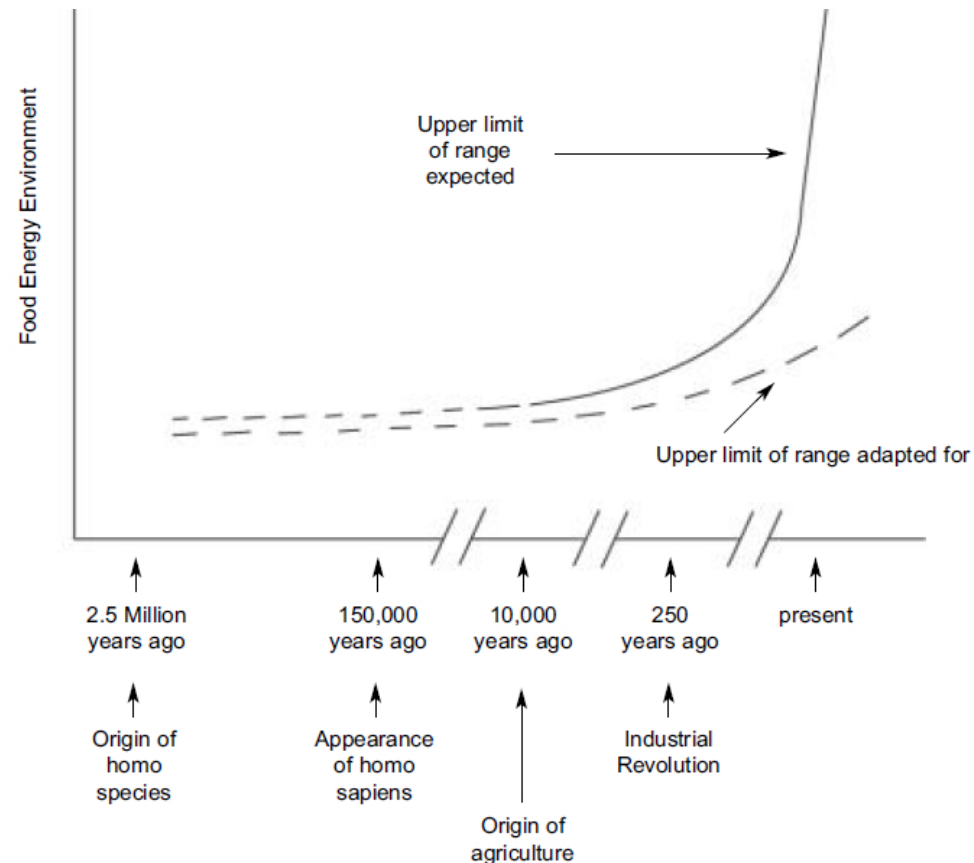
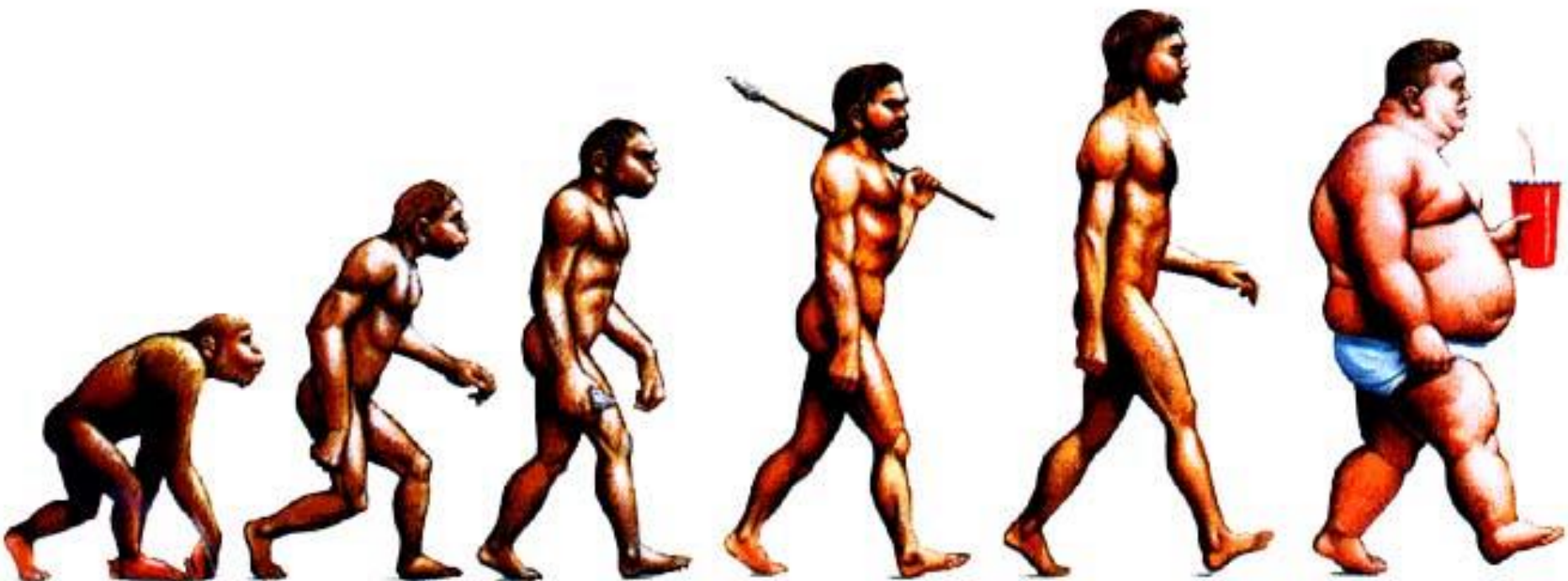


Figure 2. Relationship between the upper limit of the food-energy environment that the evolving hominid/human was exposed to (solid line) and the upper limit of environments, which adaptive responses acting in early life allow an individual to tolerate, without an increased risk of disease in middle age (dashed line). The slow increase in the slope of the dashed line since the development of agriculture and particularly over the last 200 years is due to the reduction in maternal constraint as maternal stature and general health improved. The rapid recent rise in the food-energy environment has exaggerated the risk of disease due to mismatch.



La prevenzione

Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions

Sandrine Andrieu, Nicola Coley*, Simon Lovestone, Paul S Aisen, Bruno Vellas*

The projected effects of preventive interventions with even quite modest effects at the individual level are impressive, dramatically reducing the future burden of dementia. For example, an intervention that delays disease onset and progression by 1 year, or a reduction in the prevalence of several modifiable lifestyle risk factors of 10% per decade, could potentially reduce the number of Alzheimer's disease dementia cases worldwide in 2050 by around 9 million.^{5,6}

Andrieu S, 2015

Potential for primary prevention of Alzheimer's disease: an analysis of population-based data

Sam Norton, Fiona E Matthews, Deborah E Barnes, Kristine Yaffe, Carol Brayne

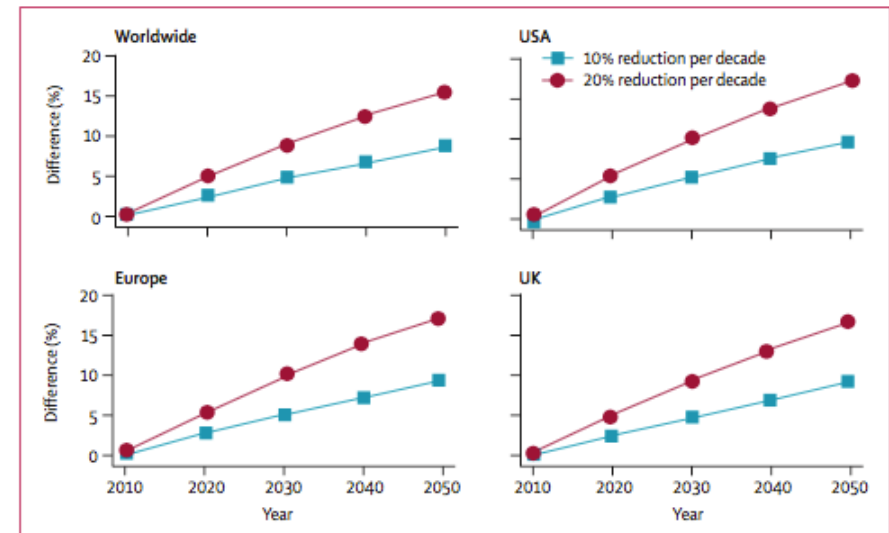


Figure: Projected percentages of Alzheimer's disease cases that could be prevented, with 10% or 20% reductions per decade in each risk factor

Norton S, 2014



Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions

Sandrine Andrieu*, Nicola Coley*, Simon Lovestone, Paul S. Aisen, Bruno Vellas

Interventions that have even quite modest effects at the individual level could drastically reduce the future burden of dementia associated with Alzheimer's disease at the population level. In the past three decades, both pharmacological and lifestyle interventions have been studied for the prevention of cognitive decline or dementia in randomised controlled trials of individuals mostly aged older than 50–55 years with or without risk factors for Alzheimer's disease. Several trials testing the effects of physical activity, cognitive training, or antihypertensive interventions showed some evidence of efficacy on a primary cognitive endpoint. However, most of these trials had short follow-up periods, and further evidence is needed to confirm effectiveness and establish the optimum design or dose of interventions and ideal target populations. Important innovations in ongoing trials include the development of multidomain interventions, and the use of biomarker or genetic inclusion criteria. Challenges include the use of adaptive trial designs, the development of standardised, sensitive outcome measures, and the need for interventions that can be implemented in resource-poor settings.

Introduction

Dementia, of which Alzheimer's disease is the most common cause, affects an estimated 36 million people worldwide.¹ Although the prevalence of dementia might be decreasing, especially in Europe and North America,² we face a huge increase in the absolute number of individuals affected by age-related diseases such as Alzheimer's disease, because of demographic ageing.^{3,4} Evidence-based interventions are needed to prevent the onset of Alzheimer's disease, or to slow or stop the progression of the disease, to tackle the growing burden of cognitive decline and dementia. The ability of such interventions to prevent a substantial number of cases of Alzheimer's disease dementia will depend on careful testing in well-designed studies and successful implementation at the levels of individuals and populations.

The projected effects of preventive interventions with even quite modest effects at the individual level are impressive, dramatically reducing the future burden of dementia. For example, an intervention that delays disease onset and progression by 1 year, or a reduction in the prevalence of several modifiable lifestyle risk factors of 10% per decade, could potentially reduce the number of Alzheimer's disease dementia cases worldwide in 2050 by around 9 million.^{5,6} However, this projection is based on findings from observational studies and assumes that a causal association exists between lifestyle risk factors and Alzheimer's disease dementia onset. Moreover, the overall effect of lifestyle changes that encompass behaviours such as dietary habits or physical exercise would depend on such changes being acceptable to many individuals throughout their lifespan. A large gap exists between the fairly consistent findings of observational studies of preventive interventions and the generally inconclusive or negative results of clinical trials,⁷ which is troublesome both for decision makers, in terms of promoting public health messages at the collective level, and for physicians, in terms of delivering

clear messages at the individual level. This situation has led to controversy within the scientific community. Some researchers conclude that no reliable evidence exists for any kind of recommendations,⁸ whereas others assess in quantitative terms the expected effect on the future number of Alzheimer's disease cases of the removal of one or more risk factors.^{9,10}

The aim of this Review is to summarise the findings of and lessons learned from completed randomised prevention trials that have tested either pharmacological interventions, lifestyle interventions, or a combination of these in Alzheimer's disease, to draw attention to innovative ongoing trials, and to underline research priorities for the future. Our definition of prevention trials is given in panel 1.

Prevention studies

Initial prevention trials, which were ancillary studies of large trials testing pharmacological interventions for other conditions, began from the early 1990s onwards and measured dementia incidence as their primary cognitive endpoint (figure 1). Then, in the late 1990s and early 2000s, drugs that had recently been approved as symptomatic treatments for patients with Alzheimer's disease dementia were tested for the prevention of dementia, cognitive decline, or both in the then newly defined entity of mild cognitive impairment. In view of the widespread failure of trials that aimed to prevent dementia, attention in the following decade (the early to mid-2000s) turned to the prevention of cognitive decline, especially in studies testing the effectiveness of lifestyle interventions. In parallel, several phase 3 trials testing specific Alzheimer's disease treatments were initiated in patients with Alzheimer's disease dementia with the hope of finding a disease-modifying agent able to slow or stop the disease process,¹¹ but all went on to fail, perhaps because intervention at the dementia stage was too late to stop or slow the disease process.^{12,13} Thus, trials testing pharmacological interventions for the

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Articles

Non-invasive ventilation and diaphragm pacing in ALS

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Articles

Home-based constraint-induced movement therapy after stroke

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Review

Prevention of Alzheimer's disease

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Stage 1: secondary prevention

Stage 0
No biomarker
abnormalities



Stage 1
Asymptomatic amyloidosis
-High PET amyloid 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

SNAP
**Suspected non-Alzheimer
pathology**
- Neurodegeneration
markers without evident
amyloidosis

secondary prevention with a treatment
interfering with $A\beta$ deposition

Immunization

from treatment for symptomatics to
prevention in asymptomatics

MCI → Dementia
due to AD

Stopping Alzheimer's Before It Starts

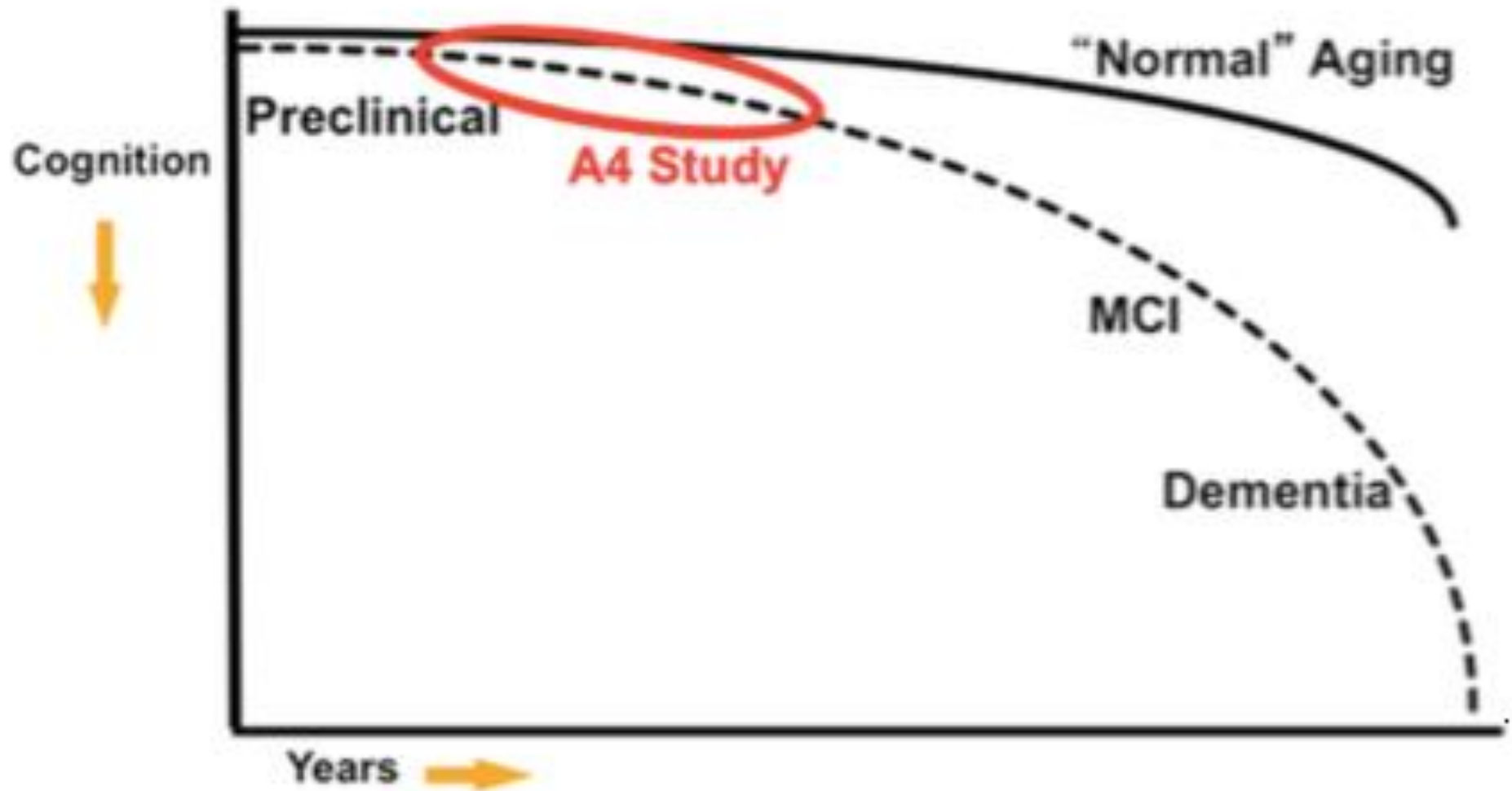
Three new clinical trials expected to begin next year will attempt to prevent dementia by treating people at risk for the disease before they develop symptoms

—GREG MILLER 17 AUGUST 2012 VOL 337 SCIENCE

Alzheimer's Prevention Trials at a Glance

Trial	Participants	Treatment	Outcome Measures
API: Alzheimer's Prevention Initiative	300 members of Colombian families, including 100 carriers of a mutated <i>PSEN1</i> gene	Crenezumab (Genentech)	Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy
DIAN: Dominantly Inherited Alzheimer Network	240 members of families with early-onset Alzheimer's; 60 have a mutation in one of three genes	Three anti-amyloid therapies to be determined	An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects
A4: Anti-Amyloid Treatment of Asymptomatic Alzheimer's	1500 healthy seniors, including 500 with amyloid-positive brain scans	One anti-amyloid therapy to be determined	Primary: Cognitive Secondary: Biomarkers

Secondary prevention in Alzheimer's disease:



Alzheimer Prevention Initiative (API)

Phase II

Crenezumab

in a large Colombian *PSEN1* cohort

Dominantly Inherited Alzheimer Network (DIAN)

Phase II

Solanezumab vs Gantenerumab

in carriers of mutations in *APP*, *PSEN1* and *PSEN2*

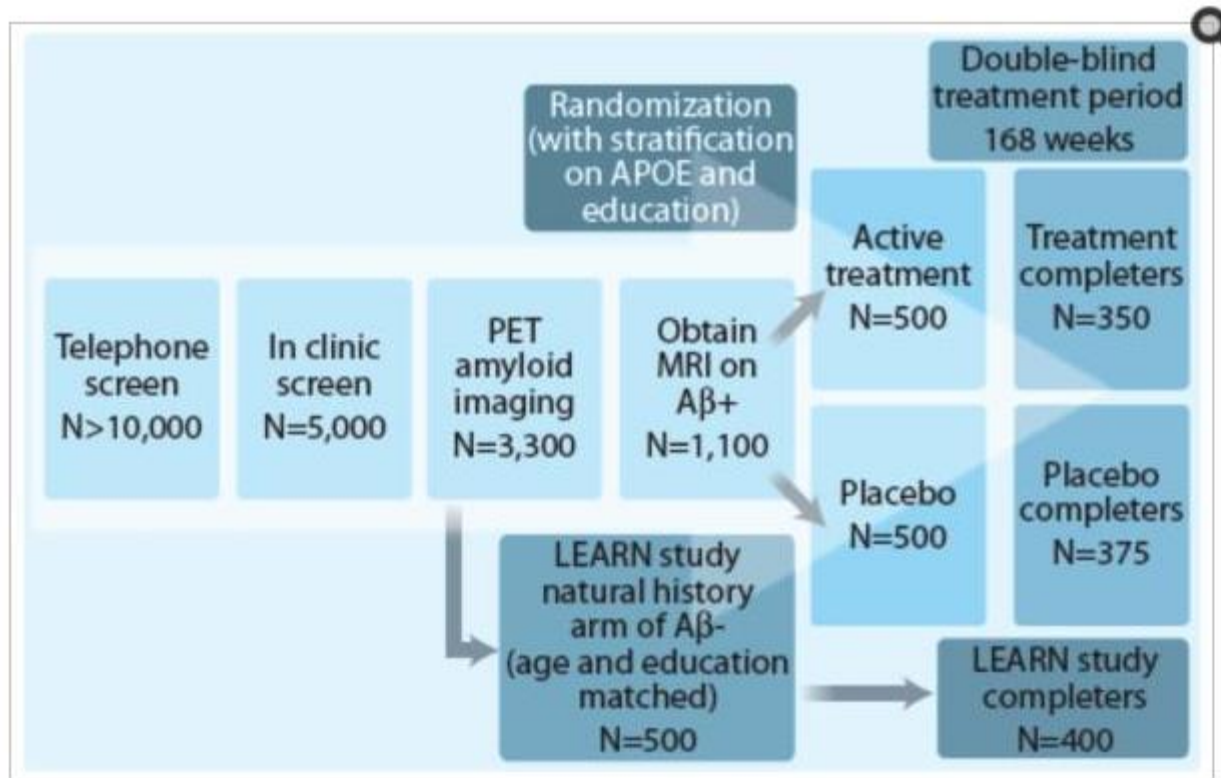
Anti-Amyloid Treatment in Asymptomatic Alzheimer' s disease (A4)

Phase III

Solanezumab vs placebo

in cognitively normal people (65-85 years) with A β accumulation

The A4 study



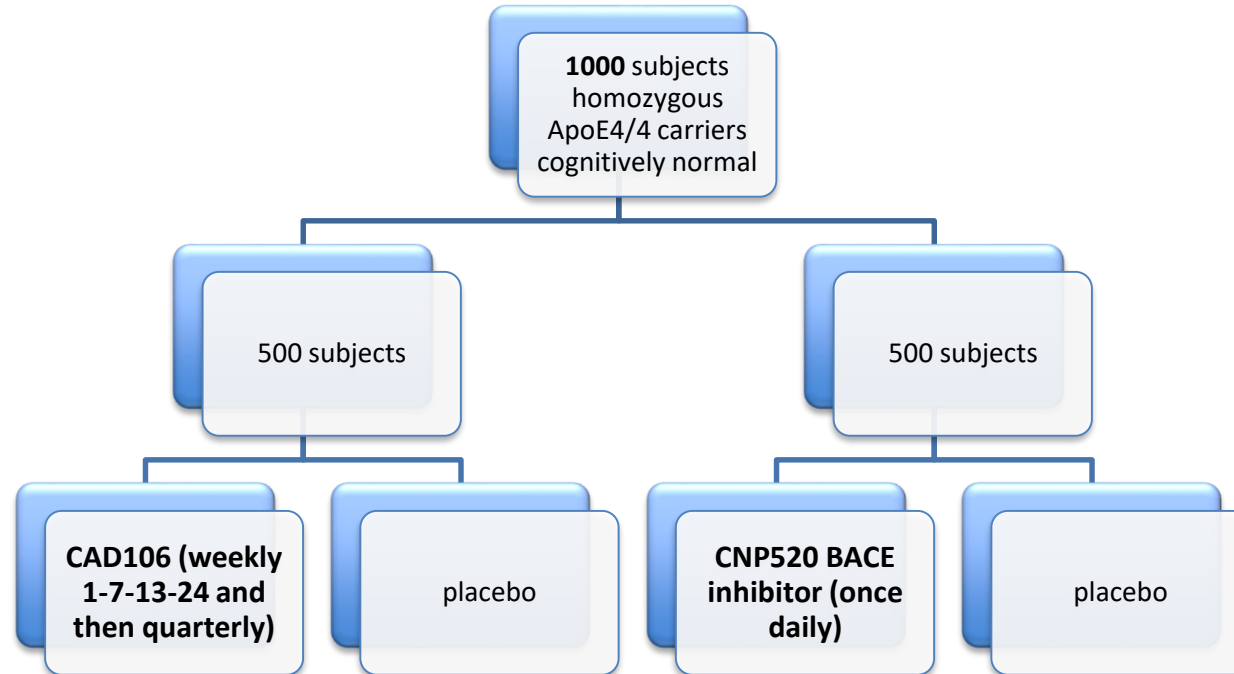
2017: study extended to 240 weeks

Screening and Randomization Algorithm for the A4 Study

The A4 trial will enroll clinically **normal older individuals with amyloid accumulation**, who are at increased risk for cognitive decline due to AD. Five thousand clinically normal older individuals will be screened to identify those with increased amyloid accumulation on PET imaging; those individuals will be randomized into the anti-amyloid treatment arm with solanezumab or placebo arm. Individuals who do not show evidence of elevated amyloid accumulation may be eligible to participate in the **LEARN study**, a companion natural history observation arm that will run parallel to the A4 treatment arm with identical cognitive assessments. A4 and LEARN study participants will be followed for 168 week treatment and observation periods.

2014

CAD106 and CNP520 in ApoE4/4 carriers



- **Secondary** prevention trial → **ApoE4/4 carriers**
- Phase 2/3 trial began in November 2015 and set to run until 2023, with a **5-year** treatment period
- **Primary outcome:** delay diagnosis to Mild Cognitive Impairment (MCI) or AD dementia
- **Secondary outcomes:** change on the Clinical Dementia Rating Scale sum of boxes (CDR-SB) along with other cognitive/functional scales, fluid biomarkers including CSF A β and tau, brain imaging including volumetric MRI plus amyloid PET and tau PET

Stages 2-3: acting on tau

Stage 0
No biomarker abnormalities

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

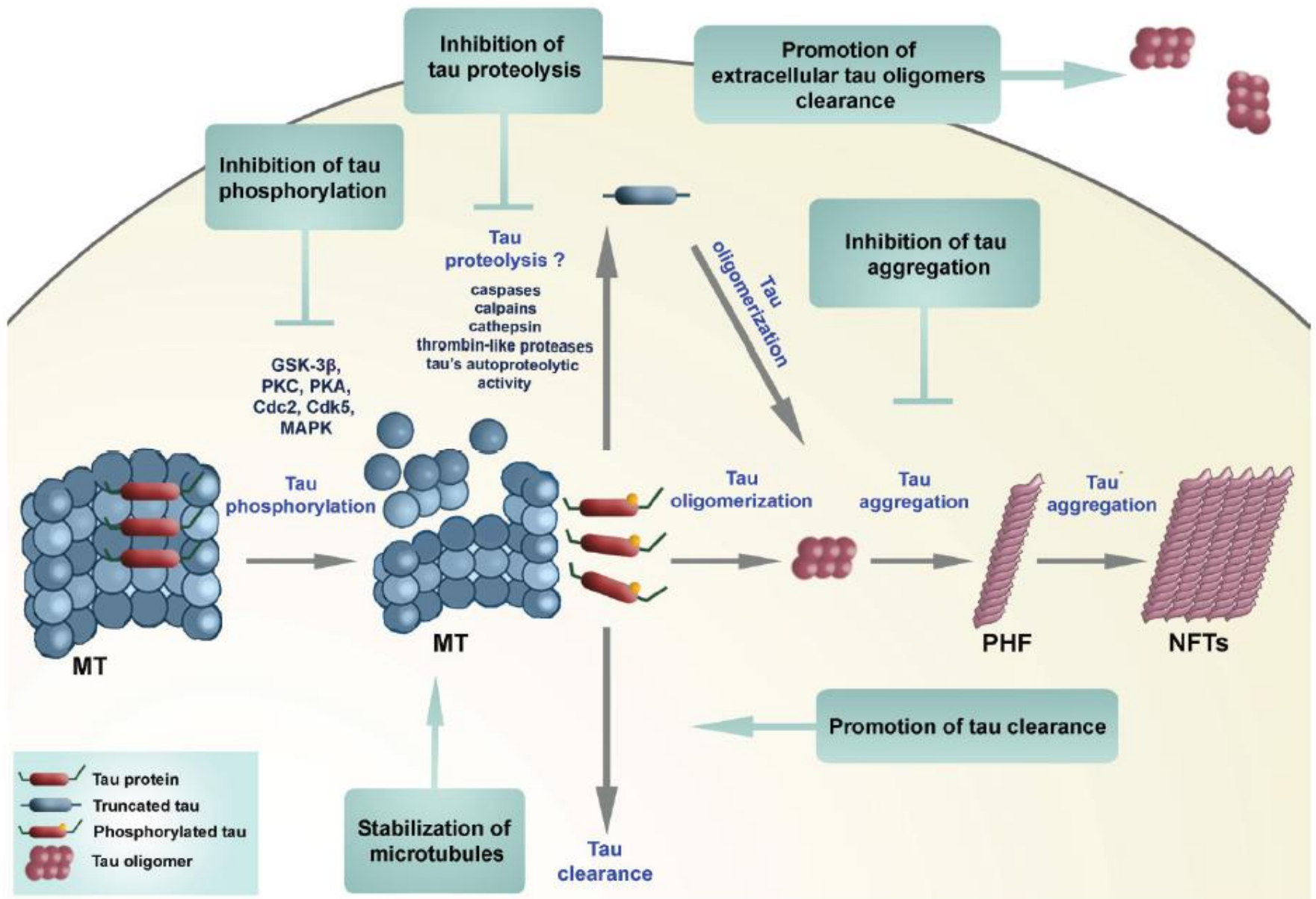
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-Does not yet meet criteria for MCI

SNAP
Suspected non-Alzheimer pathology
- Neurodegeneration markers without evident amyloidosis

- Inhibition kinase phosphorylating tau
- Aggregation inhibition with small molecules
- Microtubule stabilization
- Vaccination

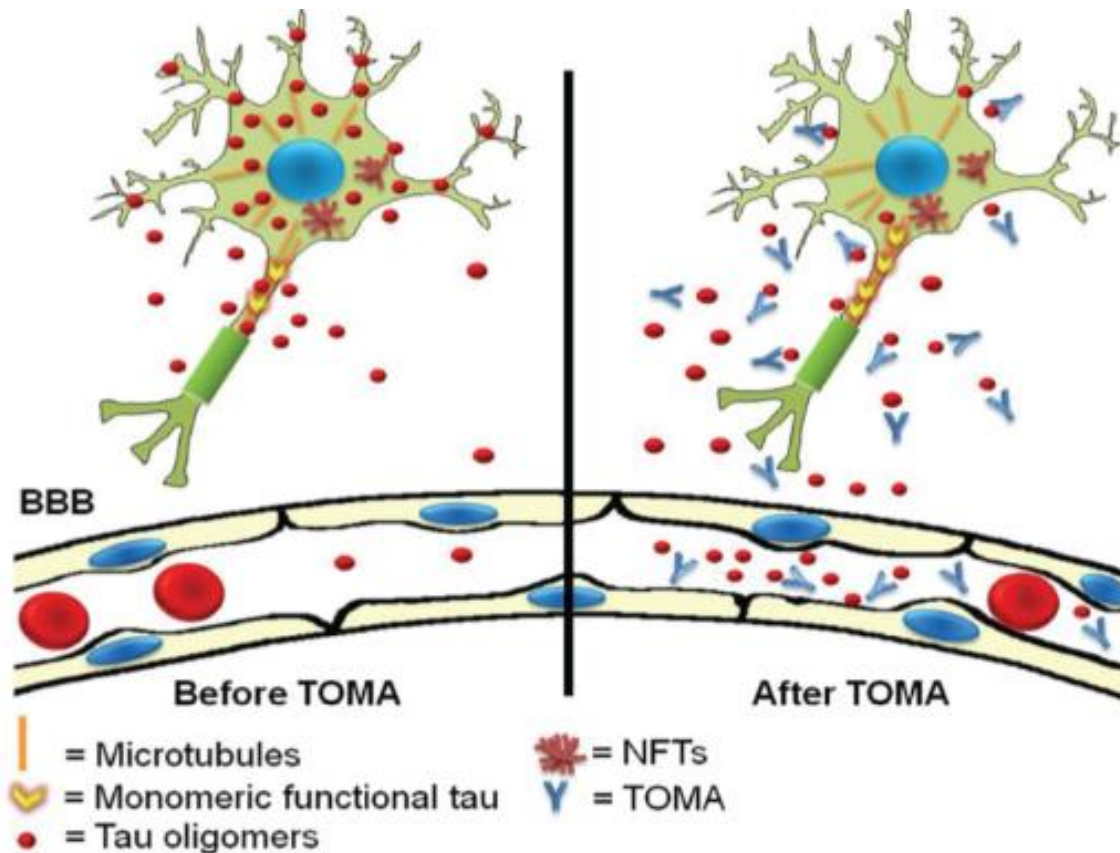
MCI → Dementia
due to AD



Passive Immunization with Tau Oligomer Monoclonal Antibody Reverses Tauopathy Phenotypes without Affecting Hyperphosphorylated Neurofibrillary Tangles

Diana L. Castillo-Carranza,^{1,2} Urmi Sengupta,^{1,2} Marcos J. Guerrero-Muñoz,^{1,2} Cristian A. Lasagna-Reeves,^{1,2} Julia E. Gerson,^{1,2} Gurpreet Singh,^{1,2} D. Mark Estes,³ Alan D. T. Barrett,^{3,4} Kelly T. Dineley,^{1,2} George R. Jackson,^{1,2,3} and Rakez Kaye^{1,2,3}

¹Mitchell Center for Neurodegenerative Diseases, ²Departments of Neurology, Neuroscience, and Cell Biology, ³Sealy Center for Vaccine Development, University of Texas Medical Branch, and ⁴Department of Pathology, University of Texas Medical Branch, Galveston, Texas 77555



Name	Synonyms	FDA Status	Company	Target Type	Therapy Type	Approved For
LMTM	TRx0237, LMT-X, Methylene Blue, Tau aggregation inhibitor (TAI)	Alzheimer's Disease (Phase 3), Frontotemporal Dementia (Phase 3)	TauRx Therapeutics Ltd	Tau	Small Molecule	Methylene Blue predates FDA. Used for treatment of malaria and methemoglobinemia.

Name	Synonyms	FDA Status	Company	Target Type	Therapy Type	Approved For
AADvac-1	Axon peptide 108 conjugated to KLH	Alzheimer's Disease (Phase 2)	Axon Neuroscience SE	Tau	Immunotherapy (active)	
ACI-35		Alzheimer's Disease (Phase 1)	AC Immune SA, Janssen	Tau	Immunotherapy (active)	
C2N 8E12	ABBV-8E12	Progressive Supranuclear Palsy (Phase 1), Alzheimer's Disease (Phase 2)	AbbVie, C2N Diagnostics, LLC	Tau	Immunotherapy (passive)	
RG7345	RO6926496	Alzheimer's Disease (Discontinued)	Roche	Tau	Immunotherapy (passive)	
RO 7105705	RG 6100	Alzheimer's Disease (Phase 1)	AC Immune SA, Genentech, Hoffmann-La Roche	Tau	Immunotherapy (passive)	

Stages 3

Stage 0
No biomarker
abnormalities

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Stage 2
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Deep Brain Stimulation

La DBS

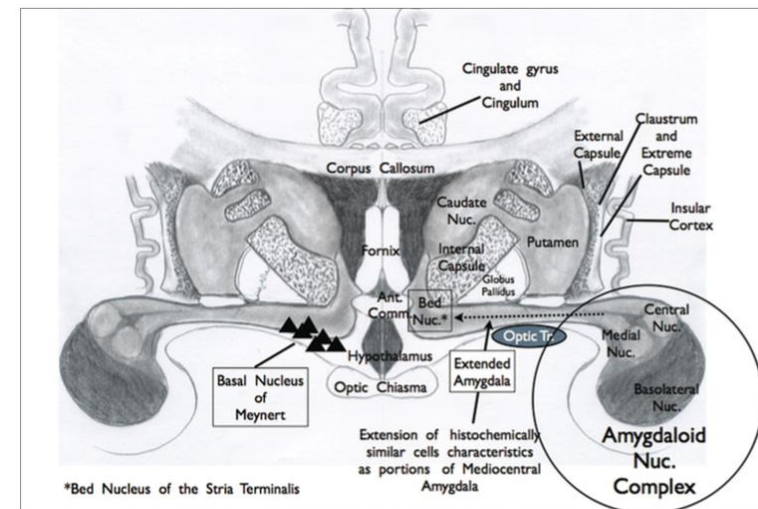
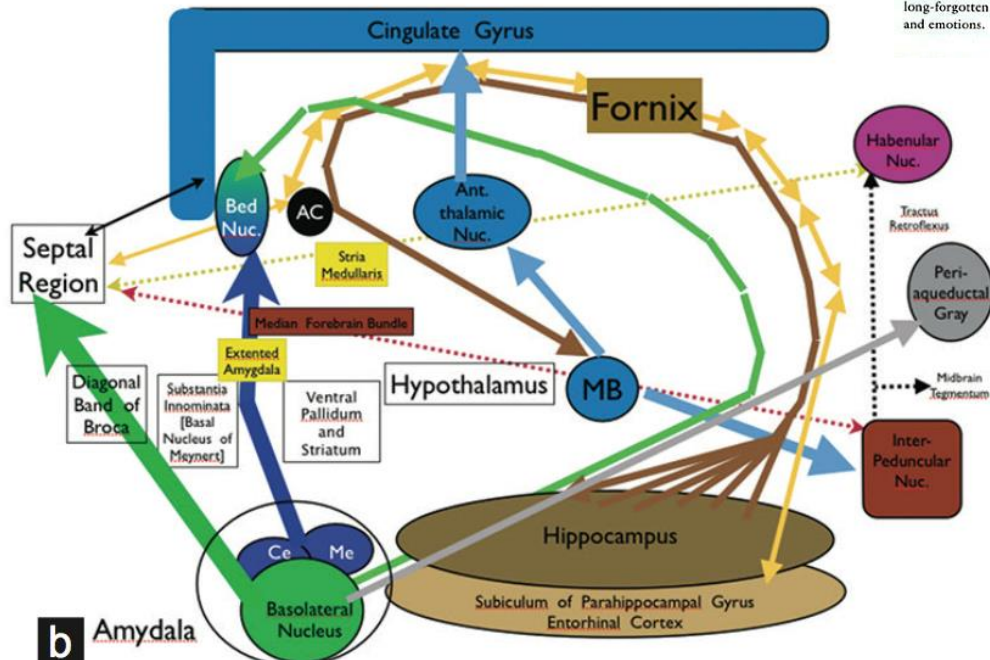
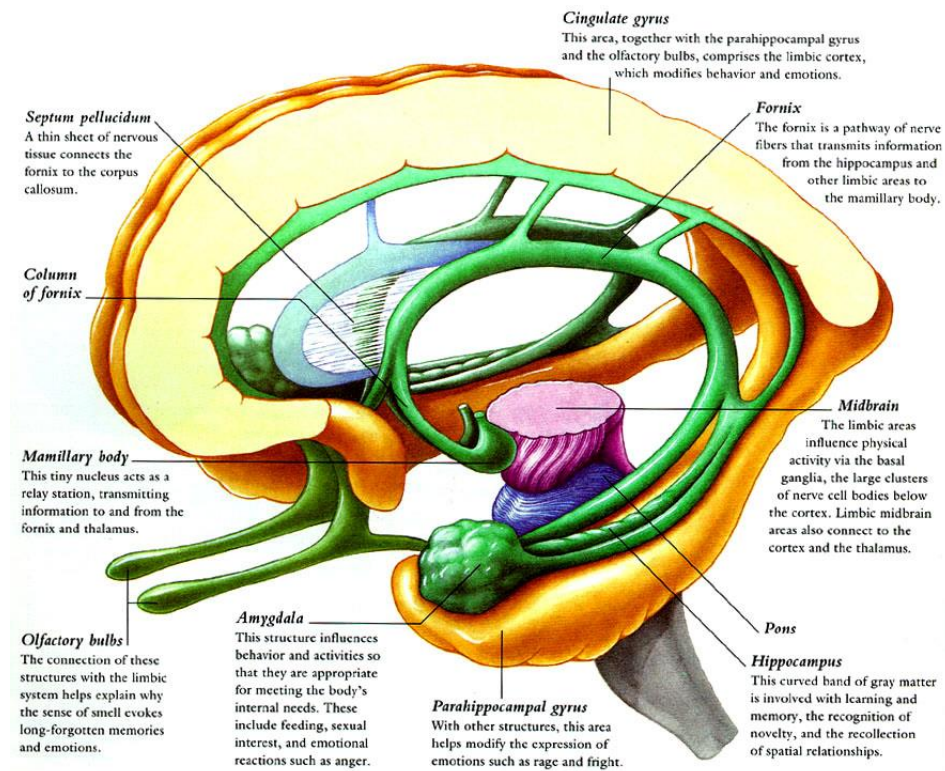
- Terapia chirurgica minimamente invasiva che consiste nell'impianto di elettrodi all'interno del cervello, che stimolano con impulsi elettrici specifiche aree cerebrali.
- Effetti terapeutici sostanziali in diverse patologie neurologiche: malattia di Parkinson, la sindrome di Tourette e diverse forme gravi di epilessia (Andrade et al., 2006; Houeto et al., 2005; Savica et al., 2012; Temel and Visser-Vandewalle, 2006; Wichmann and DeLong, 2006)
- Effetti terapeutici sostanziali in diverse patologie psichiatriche: sindromi depressive non rispondenti a terapia (Bewernick et al., 2010; Lozano et al., 2008; Malone et al., 2009) e disturbo ossessivo-compulsivo (Denys et al., 2010).

Ad oggi in pochi studi si è provato a stimolare le strutture dei circuiti della memoria.

Sono stati trovati effetti benefici con l'applicazione della DBS

- al fornice (Fontaine et al., 2013; Hamani et al., 2008; Heschem et al., 2013; Laxton et al., 2010; Smith et al., 2012)
- alla corteccia entorinale (Stone et al., 2011; Suthana et al., 2012)
- al nucleo basale di Meynert (NBM) (Kuhn et al., 2014; Freund et al., 2009; Turnbull et al., 1985)

Sistema limbico



DBS in AD

Structure	Subject	Type of stimulation	Memory task	Effect	Reference
Ncl. Basalis Meynert (NBM)	Human (senile dementia of Alzheimer's type patient) N = 1	Unilateral, 3 V, 50 Hz and 210 μ s pulse width, cycling between 15 s on and 12 min off throughout the day and night, repetitive for 9 months		No clinical effect, but increased cerebral glucose metabolism	Turnbull et al. (1985)
	Human (Parkinson patient) N = 1	NBM: Bilateral, 1 V, 20 Hz, and 120 μ s pulse width STN: bilateral, 3.5–4.2 V, 130 Hz and 60 μ s pulse width	Neuropsychological tests, e.g. clock drawing, letter-number-span, auditory verbal learning, etc.	Combined bilateral stimulation lead to improvement in attention, concentration, alertness, drive, and spontaneity	Freund et al. (2009)
	Rats N = 10	Unilateral, 200 μ A, 50 Hz and 0.5 ms pulse width, duration of 100 min		In adult, but not aged rats, NGF levels were significantly increased	Hotta et al. (2009)
Anterior thalamic nucleus	Rats N = 4	Bilateral, 2.5 V, 130 Hz and 90 μ s pulse width, duration 1 h		High-frequency stimulation of the ANT restores corticosterone-suppressed hippocampal neurogenesis	Toda et al. (2008)
	Rats N = 12	Bilateral, 500 μ A, 130 Hz and 90 μ s pulse width, acute stimulation	Contextual fear conditioning, spatial alternating test	High frequency stimulation of 500 μ A disrupted the acquisition of contextual fear conditioning and impaired spatial memory	Hamani et al. (2010)
	Rats N = 17	Bilateral, 2.5 V, 130 Hz and 90 μ s pulse width, duration 1 h	Non-matching-to-Sample and delayed non-matching-to-sample	ANT stimulation administered to corticosterone-treated rats one month prior to testing improved performance on a delayed non-matching to sample task and increased hippocampal neurogenesis	Hamani et al. (2011)
Hippocampus	Human (epileptic patients) N = 12	Bilateral, 4–6 mA, single pulse, 1 ms pulse width	Computerized recognition test	Bilateral stimulation was associated with a pronounced decrease in memory scores	Lacruz et al. (2010a,b)

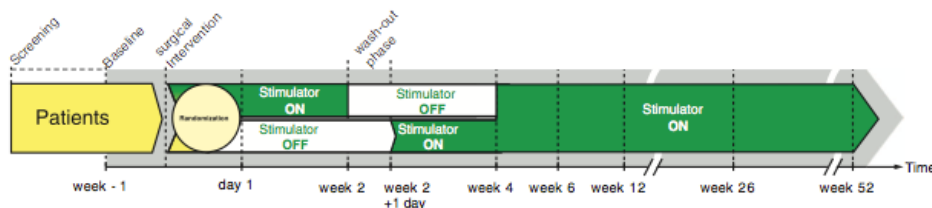
DBS in AD

Structure	Subject	Type of stimulation	Memory task	Effect	Reference
Fornix	Human (morbid obesity patient) N = 1	Bilateral, 3–5 V, 130 Hz and 60 μ s pulse width, continuous for 3 weeks	Neuropsychological tests, e.g. verbal learning test, WAIS attention index, spatial associative learning, etc.	Significant improvements on the California Verbal Learning Test and Spatial Associative Learning Test	Hamani et al. (2008)
	Human (AD patients) N = 6	Bilateral, 3.0–3.5 V, 130 Hz, and 90 μ s pulse width, continuous for 12 months	ADAS-cog, MMSE	Possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients	Laxton et al. (2010)
	Human (AD patient) N = 1	Bilateral, 2.5 V, 130 Hz and 210 ms pulse width, continuous for 12 month	ADAS-cog, MMSE, Free and Cued Selective Reminding Test	Cognitive scores worsened after 6 months but returned to baseline after 12 months of chronic DBS	Fontaine et al. (2013)
	Rats (model of experimental dementia) N = 10	Bilateral, 100 and 200 μ A, 10 and 100 Hz, 100 μ s pulse width, acute stimulation	OLT	Memory enhancement in high current densities (frequency-independent)	Heschem et al. (2013)
Entorhinal cortex	Mice N = 25	Bilateral, 50 μ A, 130 Hz and 90 μ s pulse width, for 1 h during surgery	Morris water maze	Water-maze memory was facilitated 6 weeks after stimulation due to hippocampus-dependent neurogenesis	Stone et al. (2011)
	Human (epilepsy patients) N = 7	Bilateral, 0.5 to 1.5 mA, 50–130 Hz and 300–450 μ s pulse width, cycle of 5 s on and 5 s off	Virtual memory task	Memory enhancement and theta-phase resetting	Suthana et al. (2012)

ORIGINAL ARTICLE

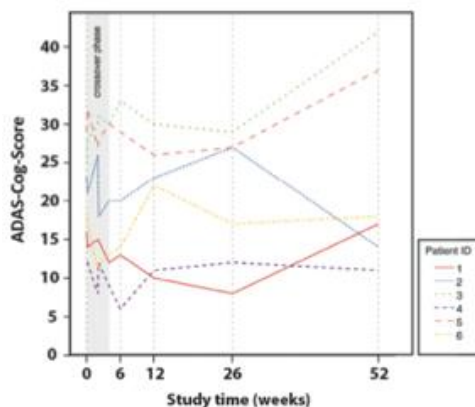
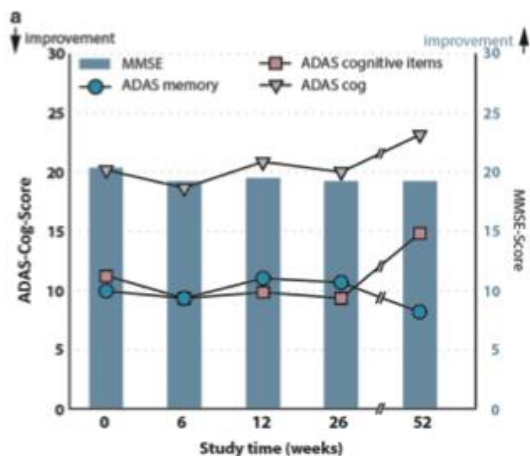
Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia

J Kuhn^{1,17}, K Hardenacke^{1,17}, D Lenartz², T Gruendler^{1,3,4}, M Ullsperger^{4,5}, C Bartsch¹, JK Mai⁶, K Zilles^{7,8}, A Bauer^{7,9}, A Matusch⁷, R-J Schulz¹⁰, M Noreik¹⁰, CP Bührle², D Maintz¹¹, C Woopen¹², P Häussermann¹³, M Hellmich¹⁴, J Klosterkötter¹, J Wiltfang¹⁵, M Maarouf¹⁶, H-J Freund^{6,18} and V Sturm^{2,18}



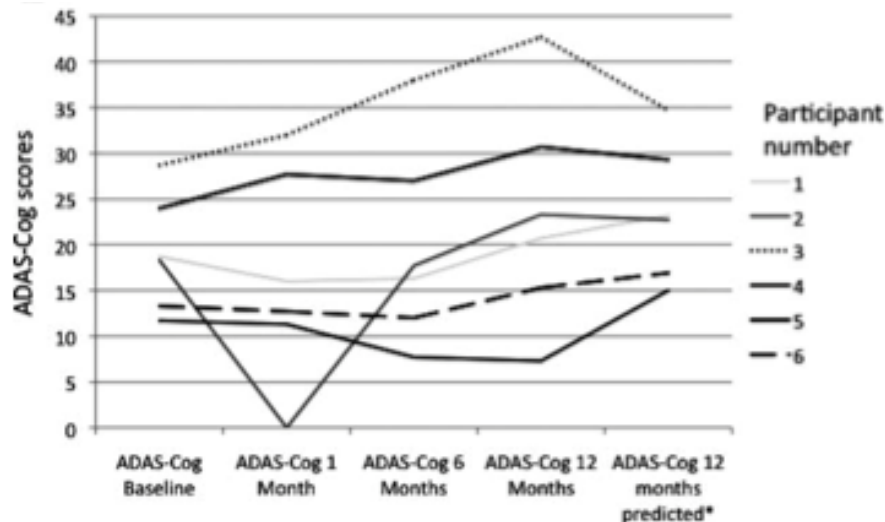
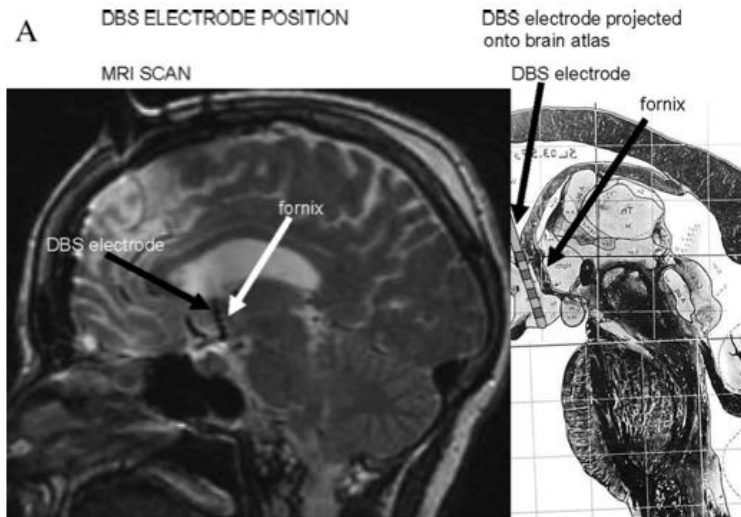
2014 Kuhn et al.

- 6 pazienti affetti da AD impiantati con elettrodi nel NBM
- una fase di 4 settimane in doppio cieco e con sham, seguita da 11 mesi di stimolazione continua a 20 Hz
- sulla base della valutazione delle scale cognitive (ADAS-cog) e degli esami strumentali (EEG, FDG-PET), 4 dei 6 pazienti sono stati definiti responder, in quanto stabili o migliorati nei 12 mesi successivi alla stimolazione
- effetti collaterali: non viene segnalata la comparsa



A Phase I Trial of Deep Brain Stimulation of Memory Circuits in Alzheimer's Disease

Adrian W. Laxton, MD,¹ David F. Tang-Wai, MDCM, FRCPC,^{2,5} Mary Pat McAndrews, PhD,³
Dominik Zumsteg, MD,⁴ Richard Wennberg, MD, FRCPC,⁵ Ron Keren, MD, FRCPC,²
John Wherrett, MD, FRCPC,^{2,5} Gary Naglie, MD, FRCPC,² Clement Hamani, MD, PhD,²
Gwenn S. Smith, PhD,⁶ and Andres M. Lozano, MD, PhD, FRCSC¹



2010 Laxton et al.

- 6 pazienti affetti da AD impiantati con elettrodi nell'area del fornice/ipotalamo
- stimolo elettrico di 3-3.5 V, 130 Hz e 90 mcs di durata per un periodo di 12 mesi
- la valutazione delle scale cognitive (MMSE e ADAS-cog) ha evidenziato un beneficio clinico della terapia, soprattutto nei pazienti con una forma lieve, mentre le analisi dei dati PET con FDG hanno evidenziato un immediato miglioramento del metabolismo temporale e parietale, mantenuto per i 12 mesi di stimolazione
- effetti collaterali: prevalentemente autonomici e cardiovascolari esclusivamente con una stimolazione superiore ai 7 V.

DBS in AD

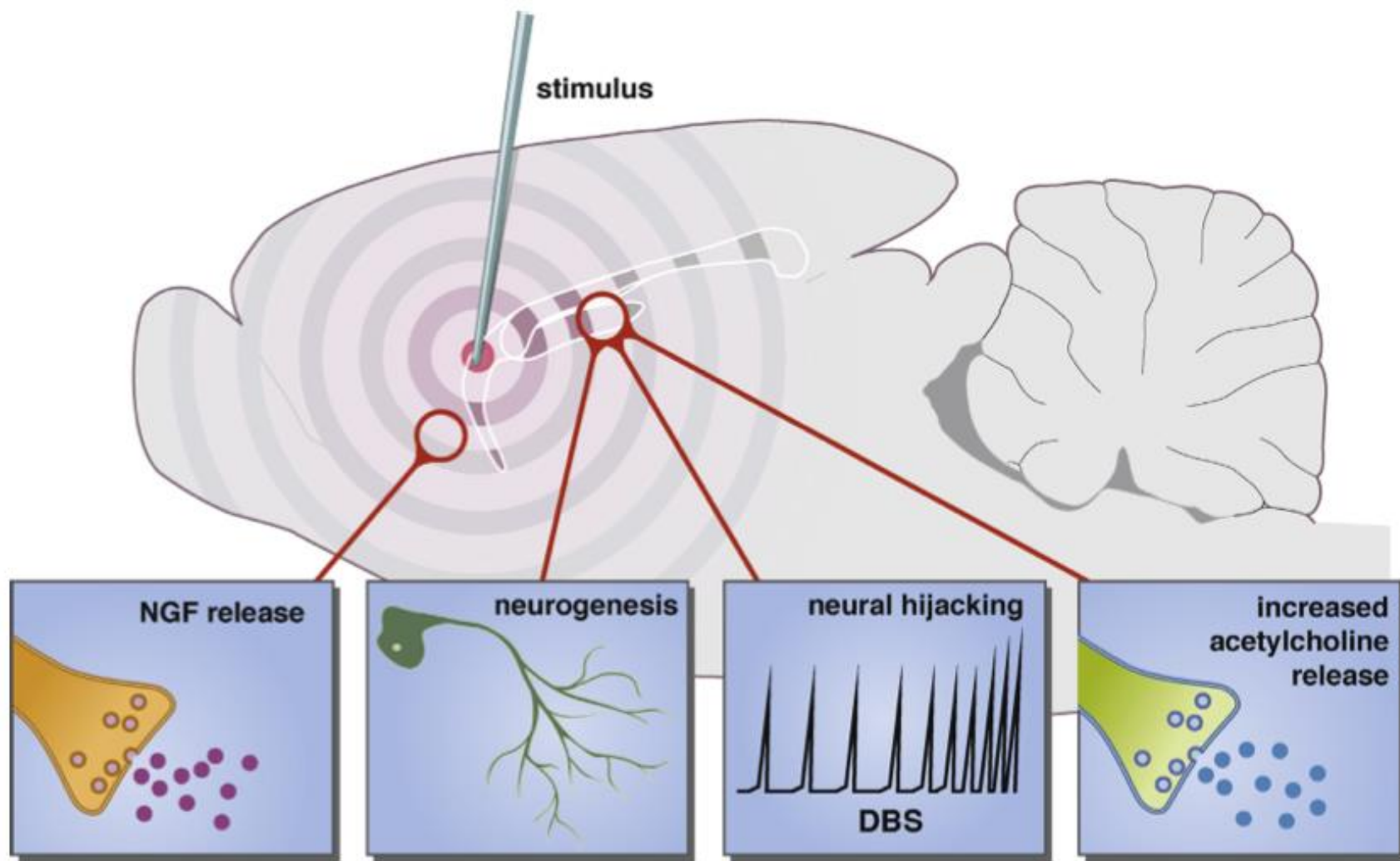
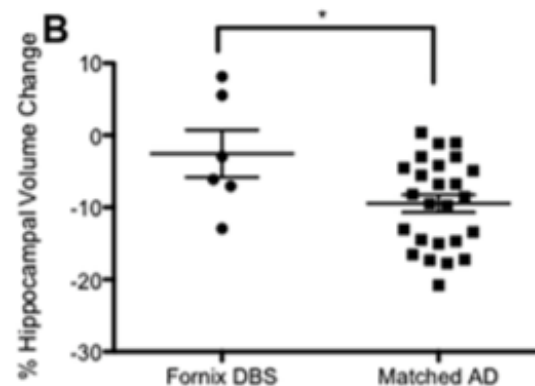
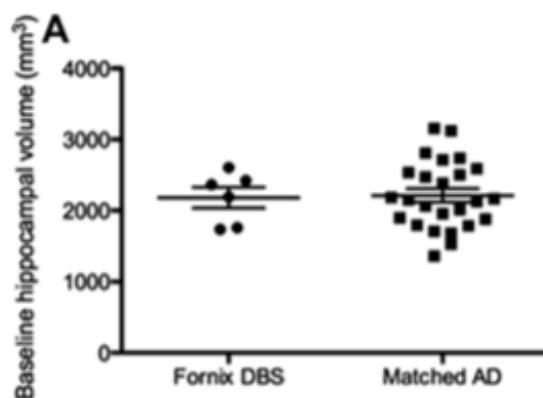
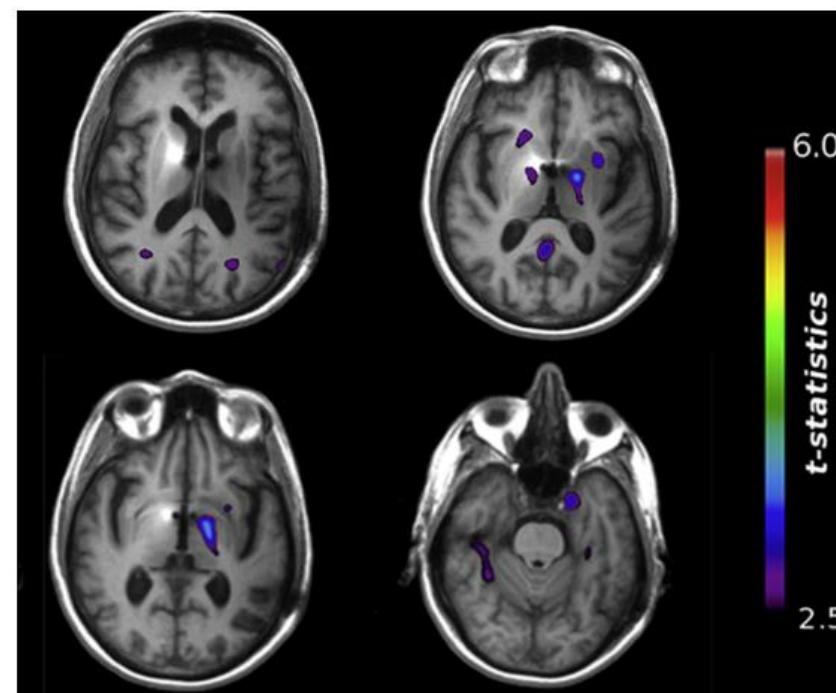
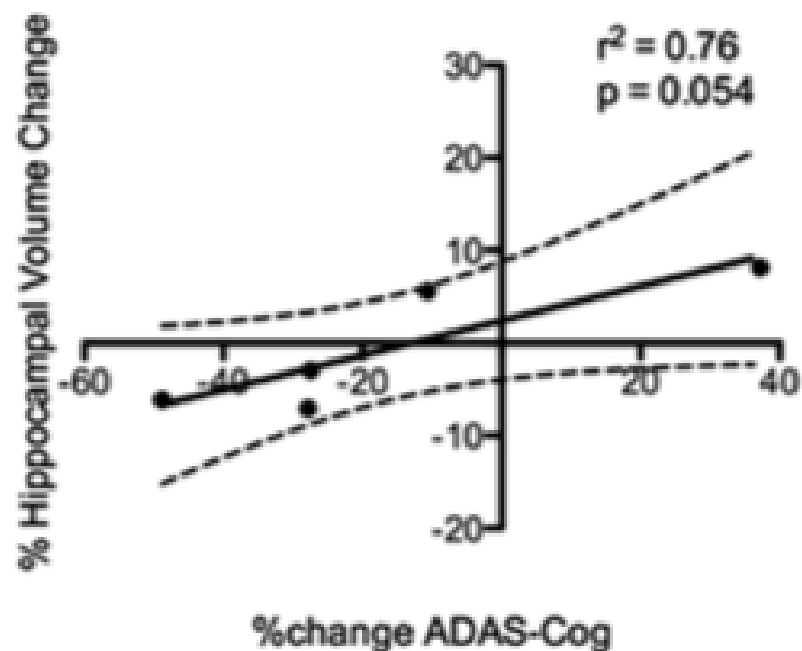


Fig. 2. Schematic representation of the potential mechanisms involved in enhancing memory functions by deep brain stimulation. Stimulation of a target area within the memory circuit (e.g. fornix) can provoke NGF release in the NBM, hippocampal-dependent neurogenesis, neural hijacking by resetting theta activity and increased acetylcholine release within the hippocampal region.

Deep Brain Stimulation Influences Brain Structure in Alzheimer's Disease

Tejas Sankar^{a,1}, M. Mallar Chakravarty^{b,1}, Agustin Bescos^c, Monica Lara^d, Toshiki Obuchi^e, Adrian W. Laxton^f, Mary Pat McAndrews^g, David F. Tang-Wai^{h,i}, Clifford I. Workman^j, Gwenn S. Smith^j, Andres M. Lozano^{k,*}



Bilateral Fornix Deep Brain Stimulation for Alzheimer Disease: Surgical Safety in the ADvance Trial

Francisco A. Ponce, MD; Wael Asaad, MD, PhD; Kelly D. Foote, MD; William S. Anderson, MD, PhD; Rees Cosgrove, MD, FRCSC; Gordon H. Baltuch, MD, PhD; Kara D. Beasley, DO, MBE; Donald E. Reymers, Esther S. Oh, Steven D. Targum, Gwenn Smith, Constantine G. lyketsos, Andres M. Lozano, MD

CLINICAL NEUROSURGERY

VOLUME 62 | NUMBER 1 | AUGUST 2015 | 207

INTRODUCTION: This report describes the stereotactic technique, hospitalization, and 90-day perioperative safety in patients who underwent bilateral deep brain stimulation (DBS) of the fornix for the treatment of mild probable Alzheimer disease.

METHODS: The ADvance Trial is a multicenter, 12-month, double-blind, randomized, controlled, feasibility study being conducted to evaluate the safety, efficacy, and tolerability of DBS of the fornix in patients with mild probable Alzheimer disease. Intraoperative and perioperative data were collected prospectively. All patients underwent postoperative magnetic resonance imaging (MRI). Stereotactic analyses were performed in a blinded fashion by a single surgeon. Adverse events (AEs) were reported to an independent clinical events committee and adjudicated to determine relationship between the AE and the study procedure.

RESULTS: Between June 1, 2012 and April 30, 2014, 42 patients with mild probable Alzheimer disease were treated with bilateral fornix DBS (mean age 68.2 ± 7.8 [range 48.0-79.7], 19 male and 23 female). The mean planned target coordinates were $x = 5.2 \pm 1.0$ mm (range 3.0-7.9), $y = 9.6 \pm 0.9$ mm (range 8.0-11.6), $z = -7.5 \pm 1.2$ mm (range -5.4 to 10.0), and the mean postoperative stereotactic radial error on MRI was 1.5 ± 1.0 mm (range 0.2-4.0). Mean length of hospitalization was 1.4 ± 0.8 days. Twenty-six (61.9%) patients experienced 64 AEs related to the study procedure, of which 7 were serious AEs experienced by 5 patients (11.9%). Four (9.5%) patients required return to surgery: 2 for explantation because of infection, 1 for lead repositioning, and 1 for chronic subdural hematoma. No patients experienced neurological deficits as a result of the study and no mortalities were reported.

CONCLUSION: Accurate targeting of DBS to the fornix without direct injury to it is feasible across surgeons and centers. At 90 days after surgery, bilateral fornix DBS was well tolerated by patients with mild probable Alzheimer disease.

A Phase II Study of Fornix Deep Brain Stimulation in Mild Alzheimer's Disease

Andres M. Lozano^a, Lisa Fosdick^b, M. Mallar Chakravarty^c, Jeannie-Marie Leoutsakos^d, Cynthia Munro^d, Esther Oh^{d,e}, Kristen E. Drake^b, Christopher H. Lyman^d, Paul B. Rosenberg^d, William S. Anderson^f, David F. Tang-Wai^{a,g}, Jo Cara Pendergrass^h, Stephen Sallowayⁱ, Wael F. Asaad^j, Francisco A. Ponce^k, Anna Burke^l, Marwan Sabbagh^m, David A. Wolkaⁿ, Gordon Baltuch^o, Michael S. Okun^p, Kelly D. Foote^p, Mary Pat McAndrews^a, Peter Giacobbe^a, Steven D. Targum^b, Constantine G. Lyketsos^{d,*†} and Gwenn S. Smith^{d,†}

Methods: We evaluated active “on” versus sham “off” bilateral DBS directed at the fornix—a major fiber bundle in the brain’s memory circuit—in a randomized, double-blind trial (ClinicalTrials.gov NCT01608061) in 42 patients with mild AD. We measured cognitive function and cerebral glucose metabolism up to 12 months post-implantation.

Results: Surgery and electrical stimulation were safe and well tolerated. There were no significant differences in the primary cognitive outcomes (ADAS-Cog 13, CDR-SB) in the “on” versus “off” stimulation group at 12 months for the whole cohort. Patients receiving stimulation showed increased metabolism at 6 months but this was not significant at 12 months. On *post-hoc* analysis, there was a significant interaction between age and treatment outcome: in contrast to patients <65 years old ($n = 12$) whose results trended toward being worse with DBS ON versus OFF, in patients ≥ 65 ($n = 30$) DBS-f ON treatment was associated with a trend toward both benefit on clinical outcomes and a greater increase in cerebral glucose metabolism.

Conclusion: DBS for AD was safe and associated with increased cerebral glucose metabolism. There were no differences in cognitive outcomes for participants as a whole, but participants aged ≥ 65 years may have derived benefit while there was possible worsening in patients below age 65 years with stimulation.

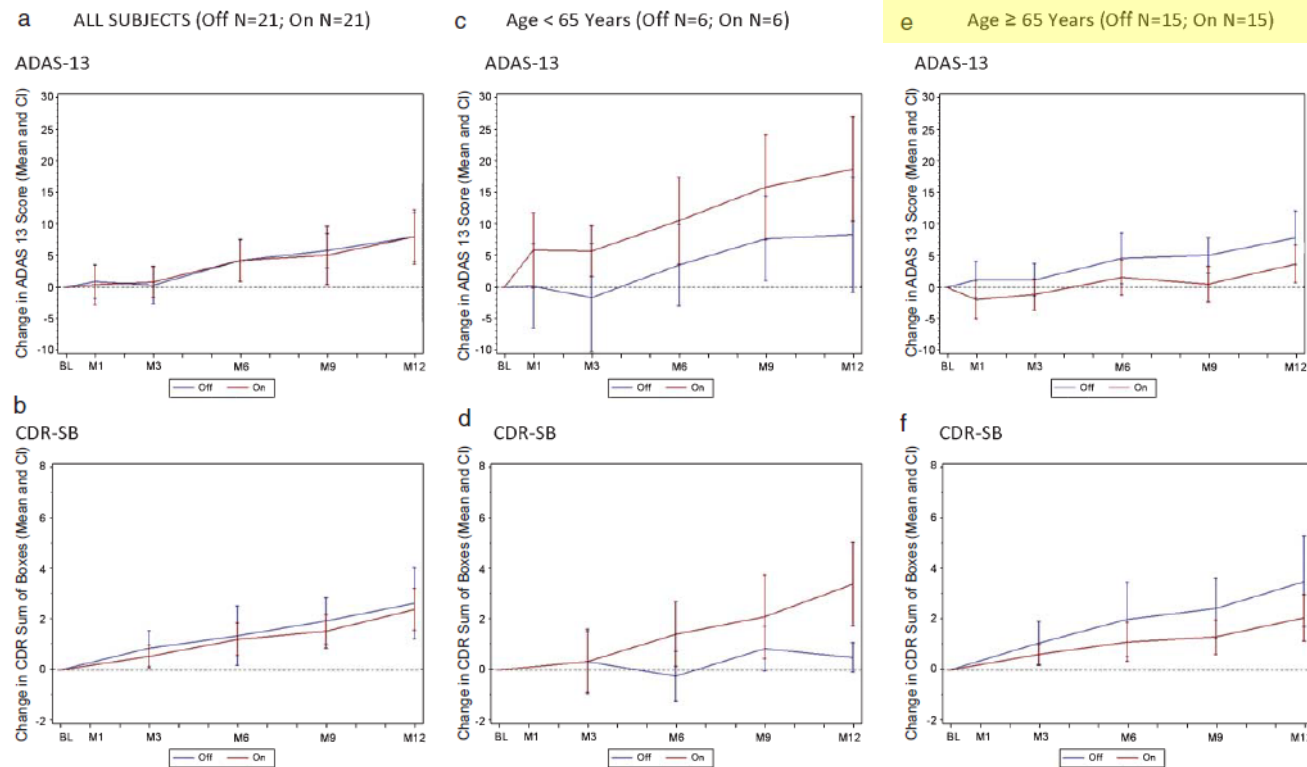
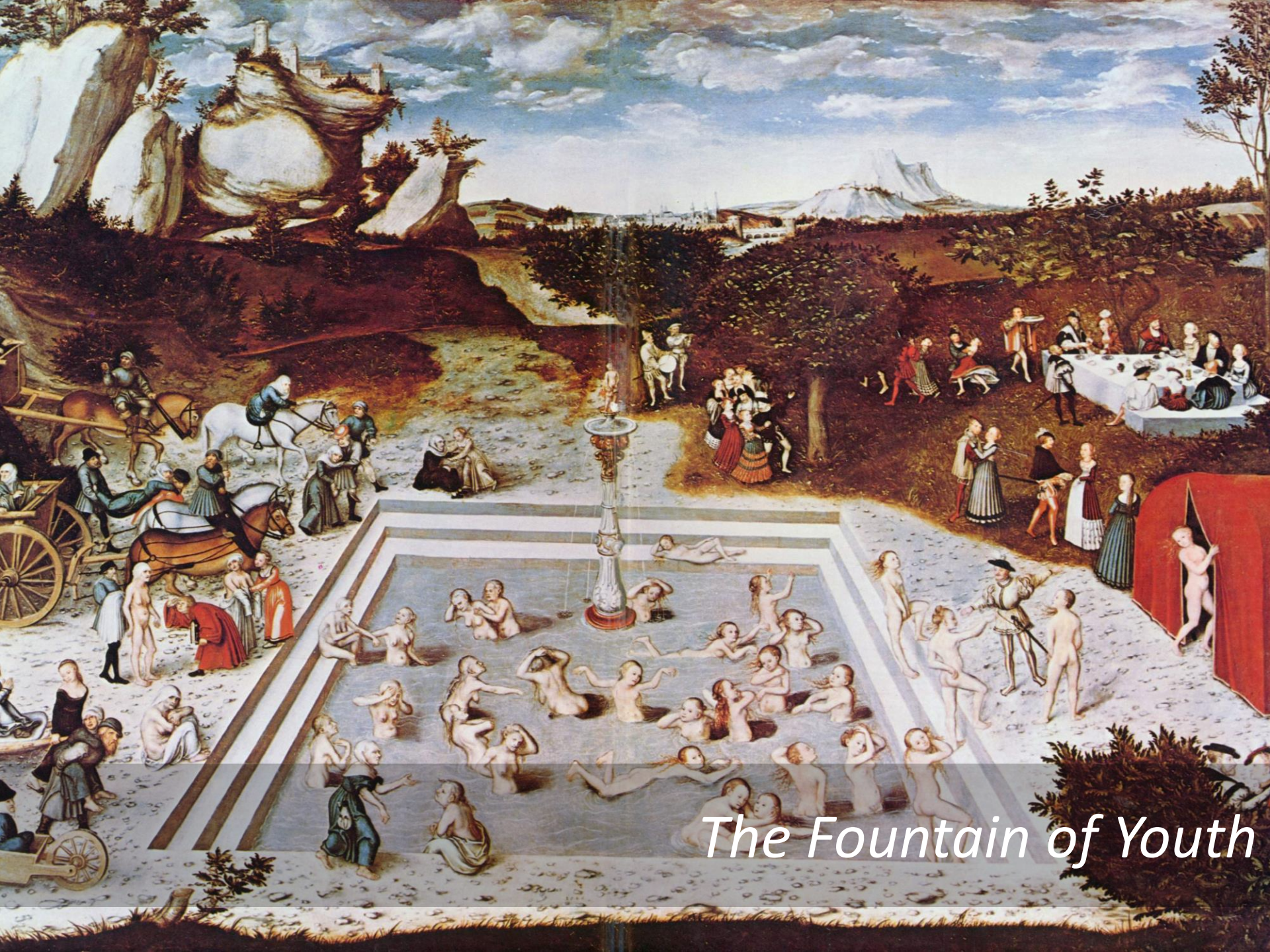


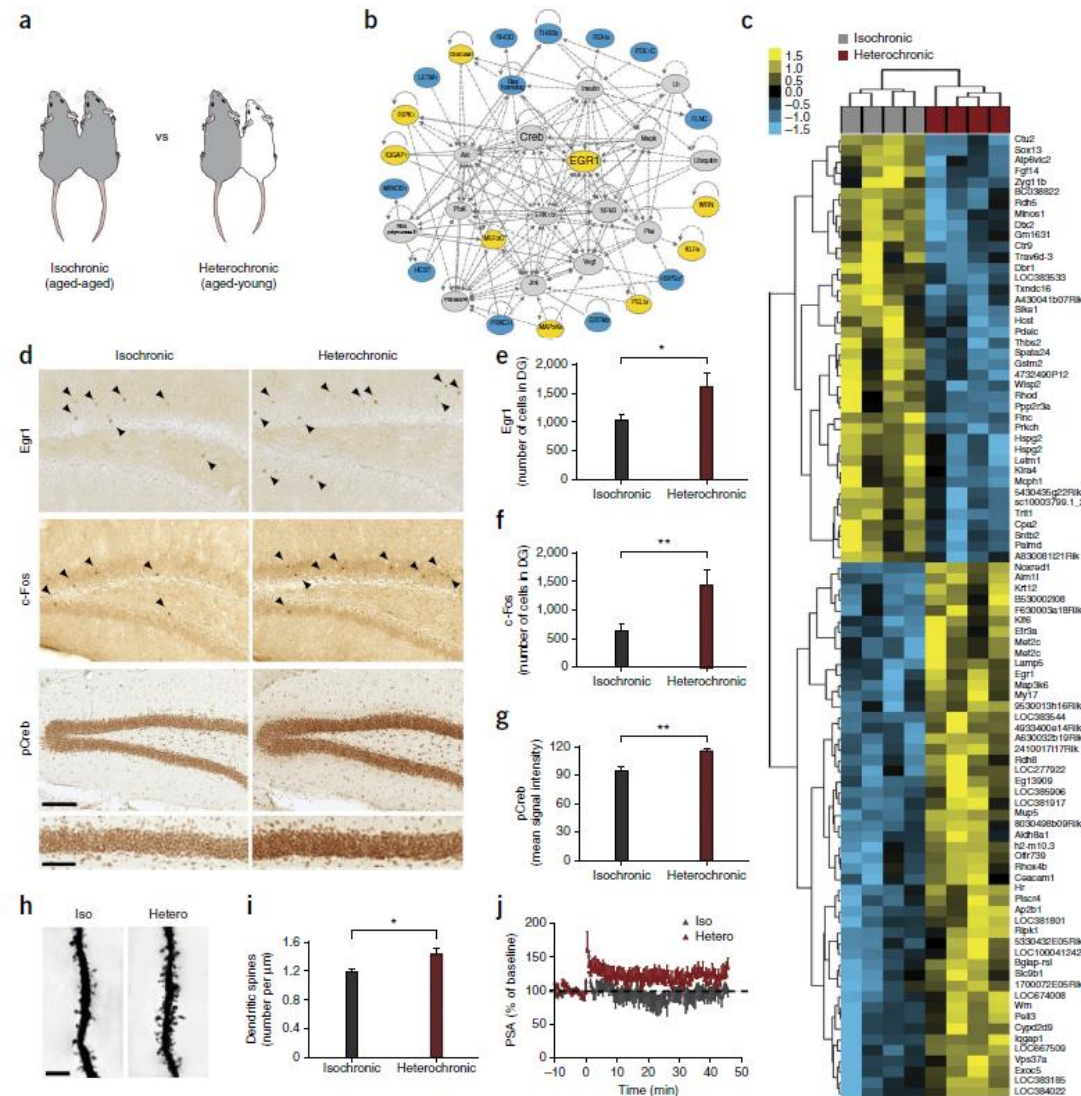
Fig. 1. Change in ADAS-Cog 13 and CDR by treatment groups (all subjects) and effect of patient age on clinical outcome. A decreased score (down on the y axis) indicates improvement while an increased score (up on the y axis) indicates worsening. a) Change in ADAS-Cog 13 over 12 months by treatment group in all subjects ($n = 42$). b) Change in CDR-SB over 12 months by treatment group in all subjects ($n = 42$). c) Change in ADAS-Cog 13 over 12 months by treatment group in patients <65 ($n = 12$). d) Change in CDR-SB over 12 months by treatment group in patients <65 ($n = 12$). e) Change in ADAS-Cog 13 over 12 months by treatment group in patients ≥ 65 ($n = 30$). f) Change in CDR-SB over 12 months by treatment group in patients ≥ 65 ($n = 30$). Values shown on graphs are mean $\pm$ standard error.



The Fountain of Youth

Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice

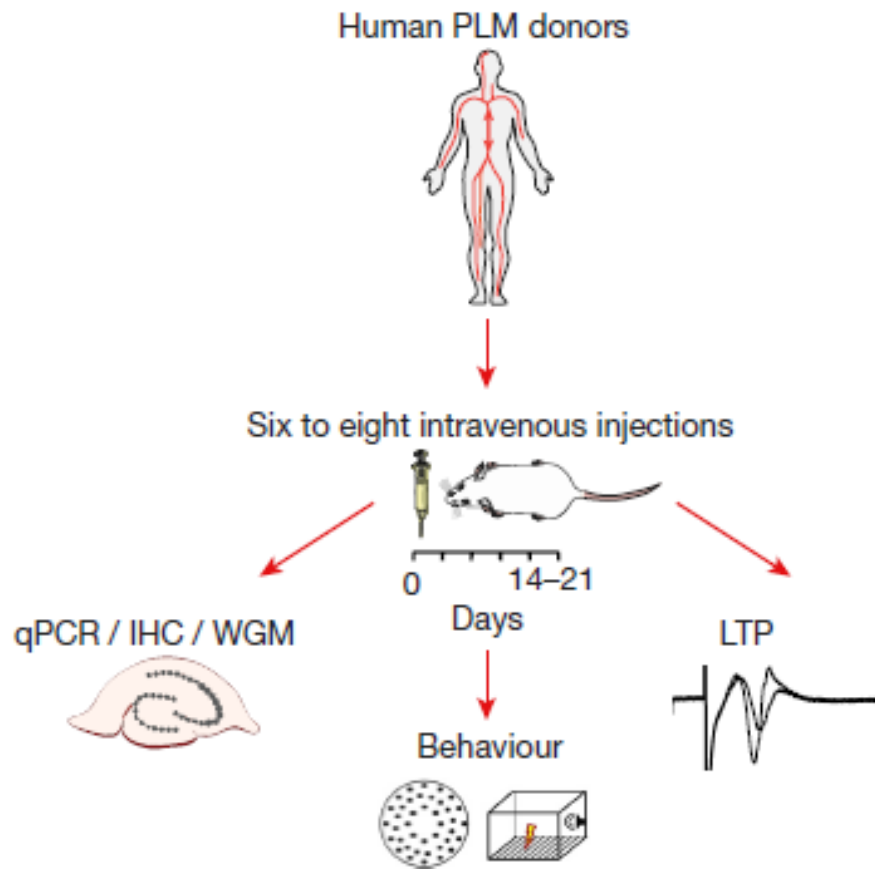
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- Exposure of an aged animal to young blood can counteract and **reverse pre-existing effects of brain aging** at the molecular, structural, functional and cognitive level.
- Genome-wide microarray analysis of heterochronic parabionts identified **synaptic plasticity-related transcriptional changes** in the hippocampus of aged mice.
- Dendritic spine density of mature neurons increased and **synaptic plasticity improved in the hippocampus** of aged heterochronic parabionts.
- At the cognitive level, systemic administration of young blood plasma into aged mice **improved age-related cognitive impairments** in both contextual fear conditioning and spatial learning and memory.
- Our data indicate that **exposure of aged mice to young blood late in life is capable of rejuvenating synaptic plasticity and improving cognitive function.**

Human umbilical cord plasma proteins revitalize hippocampal function in aged mice

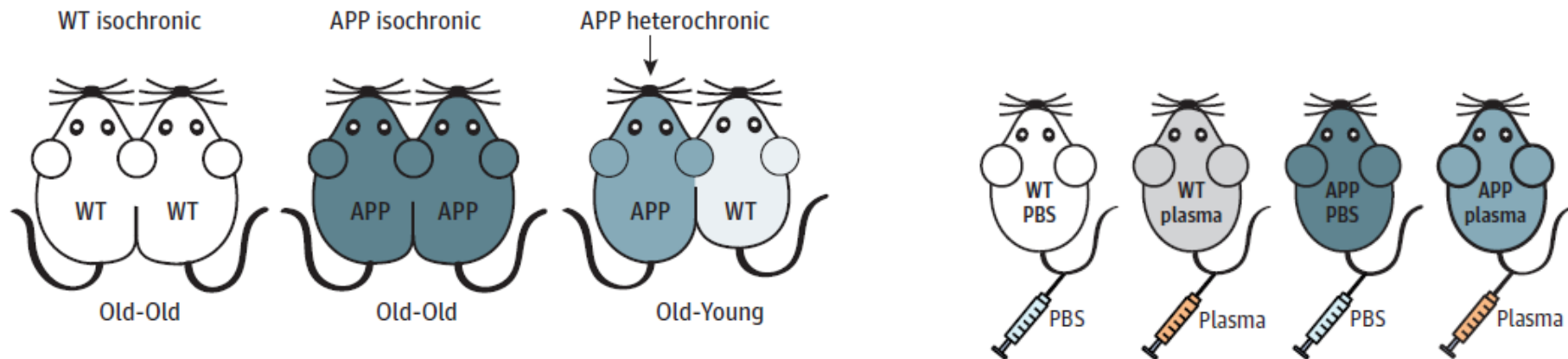
Joseph M. Castellano^{1,2}, Kira I. Mosher^{1,2,3}, Rachelle J. Abbey^{1,2,4}, Alisha A. McBride^{1,2,4}, Michelle L. James^{1,5}, Daniela Berdnik^{1,2,4}, Jadon C. Shen^{1,2,4}, Bende Zou⁶, Xinmin S. Xie^{6,7}, Martha Tingle⁷, Izumi V. Hinkson^{1,2,4}, Martin S. Angst⁷ & Tony Wyss-Coray^{1,2,3,4}



- **Tissue inhibitor of metalloproteinases 2 (TIMP2)**, a blood-borne factor enriched in human cord plasma, young mouse plasma, and young mouse hippocampi, appears in the brain after systemic administration and **increases synaptic plasticity and hippocampal dependent cognition** in aged mice.
- Our findings reveal that human cord plasma contains plasticity-enhancing proteins of high translational value for targeting ageing- or disease-associated hippocampal dysfunction.

Preclinical Assessment of Young Blood Plasma for Alzheimer Disease

Jinte Middeldorp, PhD; Benoit Lehallier, PhD; Saul A. Villeda, PhD; Suzanne S. M. Miedema, MSc; Emily Evans; Eva Czirr, PhD; Hui Zhang, PhD; Jian Luo, MD, PhD; Trisha Stan, PhD; Kira I. Mosher, PhD; Eliezer Masliah, MD, PhD; Tony Wyss-Coray, PhD



RESULTS:

- Aged mutant amyloid precursor protein mice with established disease showed a near complete restoration in levels of synaptic and neuronal proteins after exposure to young blood in parabiosis (synaptophysin $P = .02$; calbindin $P = .02$) or following intravenous plasma administration (synaptophysin $P < .001$; calbindin $P = .14$).
- Young plasma administration was associated with improved working memory ($P = .01$) and associative memory ($P = .02$) in amyloid precursor protein mice.
- Factors in young blood have the potential to ameliorate disease in a model of AD.

SNAP

Tau treatments also for:

- FTLD
- PSP
- CBD

Other pathogenic proteins

- TDP-43
- FUS
- Synuclein

Stage 0
No biomarker
abnormalities

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

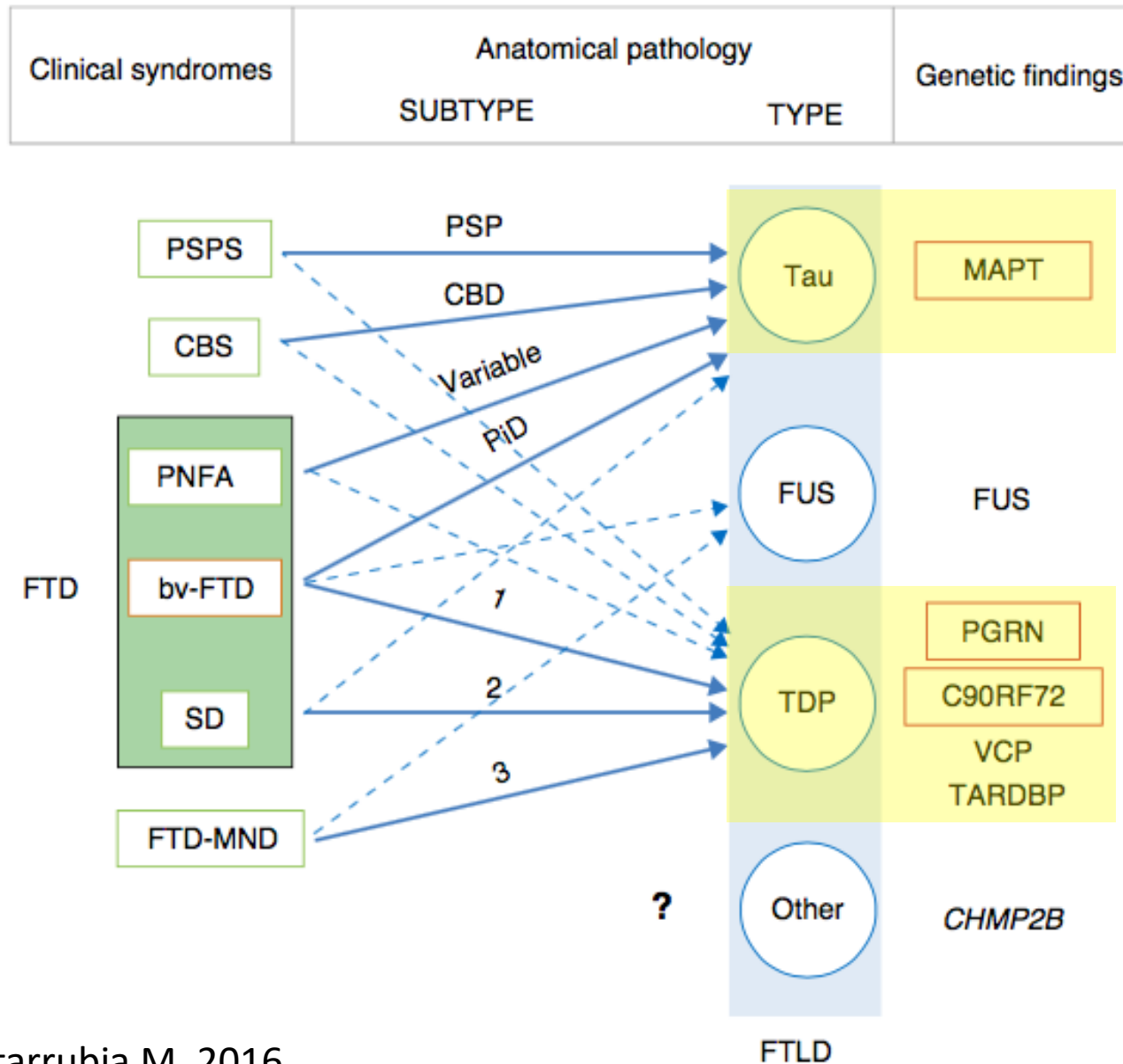
Stage 2
Amyloidosis + Neurodegeneration
-Neuronal dysfunction on FDG-PET/fMRI
-High CSF tau/p-tau
-Cortical thinning/Hippocampal atrophy on sMRI

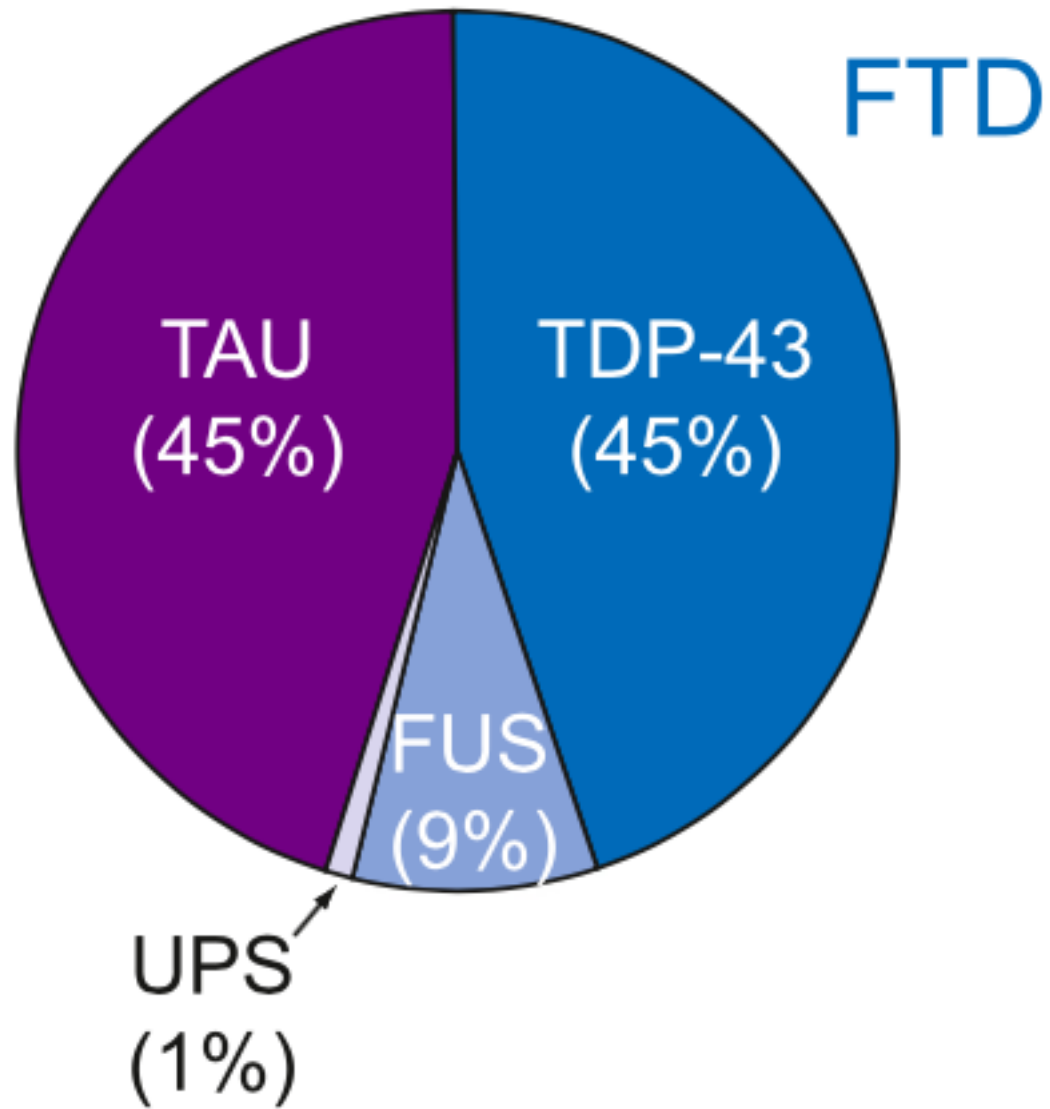
Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
-Evidence of subtle change from baseline level of cognition
-Poor performance on more challenging cognitive tests
-Does not yet meet criteria for MCI

MCI → Dementia
due to AD

SNAP
**Suspected non-Alzheimer
pathology**
- Neurodegeneration
markers without evident
amyloidosis

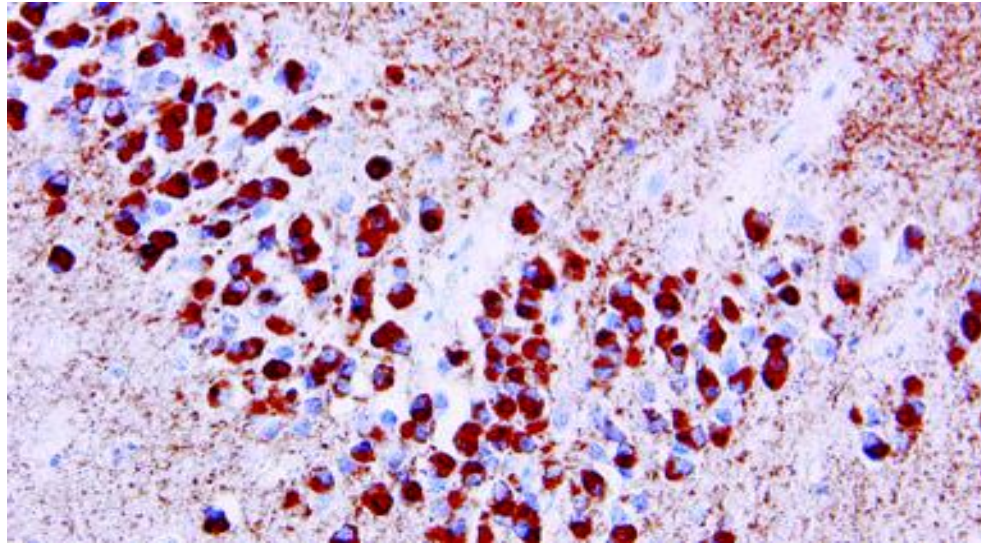
FTLD is a heterogeneous disease





FTLD-Tau

Approximately **45%** of FTLD cases: a tau protein pathology



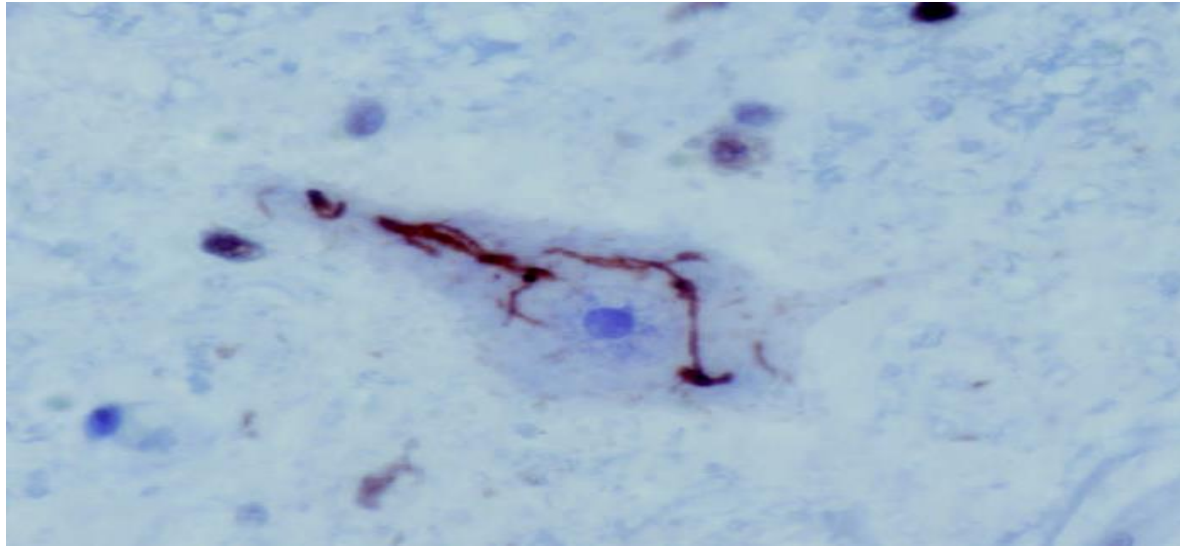
No biomarkers available to predict ongoing tau deposition

But Tau pathology predicted (100% concordance with clinical phenotype) in:

- . **PSP**
- . carriers of *MAPT* mutations

FTLD-TDP43

Approximately 45–50% of FTLD: TDP-43 pathology



No biomarkers available to predict ongoing TDP deposition

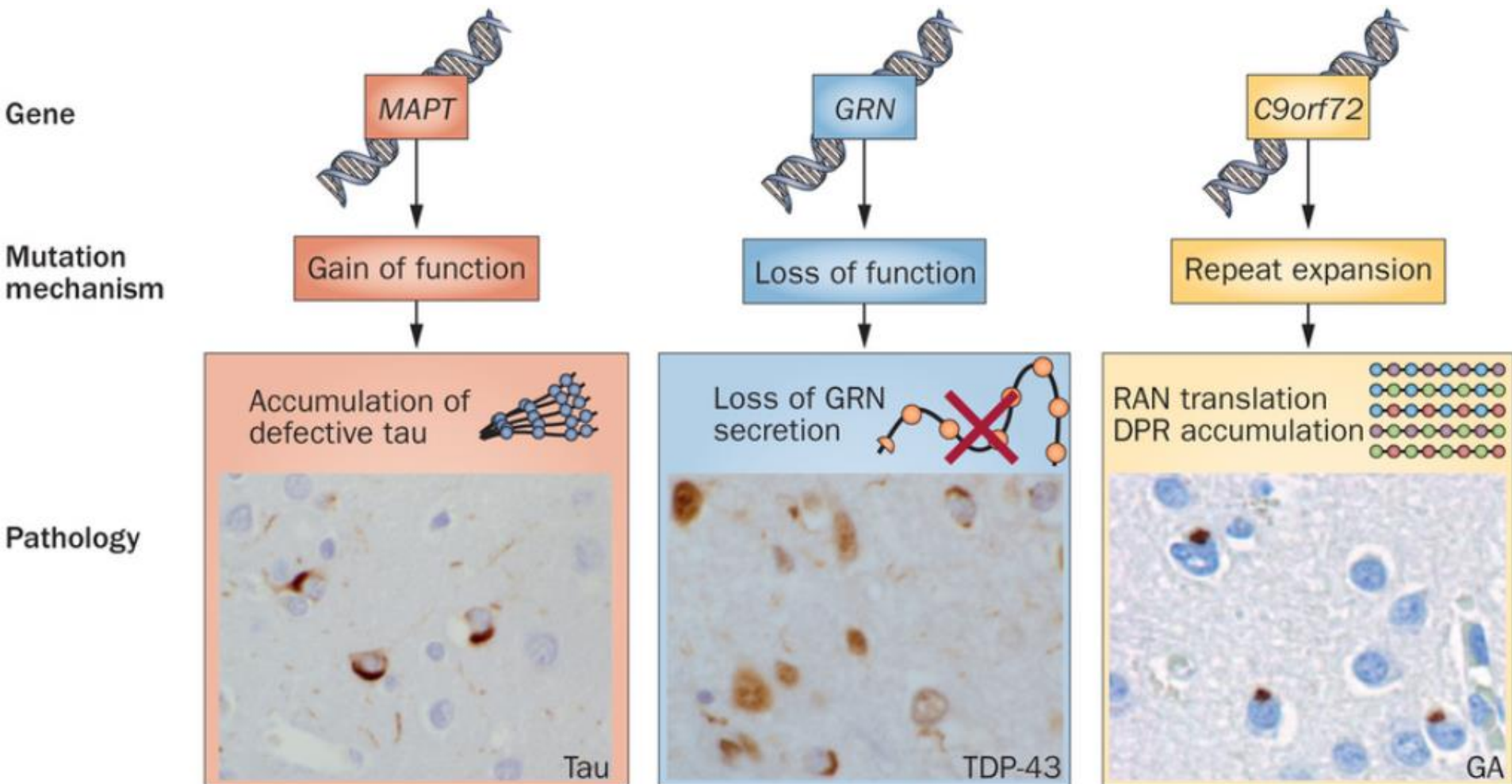
TDP-43 pathology predicted in mutation carriers of:

- . GRN
- . C9ORF72
- . VCP-1

Targets and investigational therapies in FTD and related disorders

Target	Agent	Mechanism(s)	Status	Limitations	Reference/NCT*
Tau	Lithium	GSK inhibitor	Phase 2 CBD/PSP completed	Toxicity	NCT00703677
	NP12 (tideglusib)	GSK inhibitor	Phase 2 AD, PSP	Toxicity	NCT01350362, NCT01049399
	Riluzole	Na channel blocker	Phase 2 PSP completed	Not efficacious	[18]
	Co-Q10	Improve mitochondrial function	Phase 2 in PSP completed, Phase 3 underway	Mechanism	[19,20] NCT00382824
	Rasagiline	MAO inhibitor	Phase 3 underway, PSP	Mechanism	NCT01187888
	Davunetide	Microtubule stabilizer	Phase 2/3 underway in PSP	Specificity	NCT01110720, NCT01056965
	Methylene blue	Inhibits aggregation	Completed phase 2 in AD	Mechanism	NCT00515333
	Epothilones	Microtubule stabilizer	Preclinical	Toxicity	[21]
	Anti-tau mAb or vaccines	Block transmission, increase clearance	Preclinical	Safety	[22–24]
	Hsp90 inhibitors	Increased clearance	Preclinical	N/A	[25]
	Chloroquine	Enhance autophagy	Preclinical	N/A	[25]
	RNA binding drugs, antisense oligonucleotides	Alter tau exon 10 splicing to decrease 4R, decrease tau mRNA	Preclinical	BBB permeability, feasibility	[26]
PGRN	Chloroquine	Increase secretion/vacuolar alkalization	Preclinical, clinical trial planned	Toxicity, BBB penetration	[27]
	Amiodarone	Increase secretion/vacuolar alkalization	Preclinical	Toxicity, mechanism	[27]
	SAHA	Increase PGRN expression (HDAC inhibitor)	Preclinical	Toxicity, BBB penetration	[28]
	Resveratrol	Increase PGRN expression	Preclinical	N/A	[28]

Abbreviations: BBB, blood-brain barrier; MAO, monoamine oxidase; HDAC, histone deacetylase



Progranulin: an attractive target

- Possibility to **measure** and monitor plasma and CSF levels as **biomarker**
- **Haploinsufficiency**: can PGRN levels be restored or the expression of the normal allele increased?

PGRN	Chloroquine	Increase secretion/vacuolar alkalization	Preclinical, clinical trial planned
	Amiodarone	Increase secretion/vacuolar alkalization	Preclinical
	SAHA	Increase PGRN expression (HDAC inhibitor)	Preclinical
	Resveratrol	Increase PGRN expression	Preclinical

Targeted manipulation of the sortilin–progranulin axis rescues progranulin haploinsufficiency

Wing C. Lee¹, Sandra Almeida², Mercedes Prudencio¹, Thomas R. Caulfield¹, Yong-Jie Zhang¹, William M. Tay¹, Peter O. Bauer¹, Jeannie Chew¹, Hiroki Sasaguri¹, Karen R. Jansen-West¹, Tania F. Gendron¹, Caroline T. Stetler¹, NiCole Finch¹, Ian R. Mackenzie³, Rosa Rademakers¹, Fen-Biao Gao² and Leonard Petrucelli^{1,*}

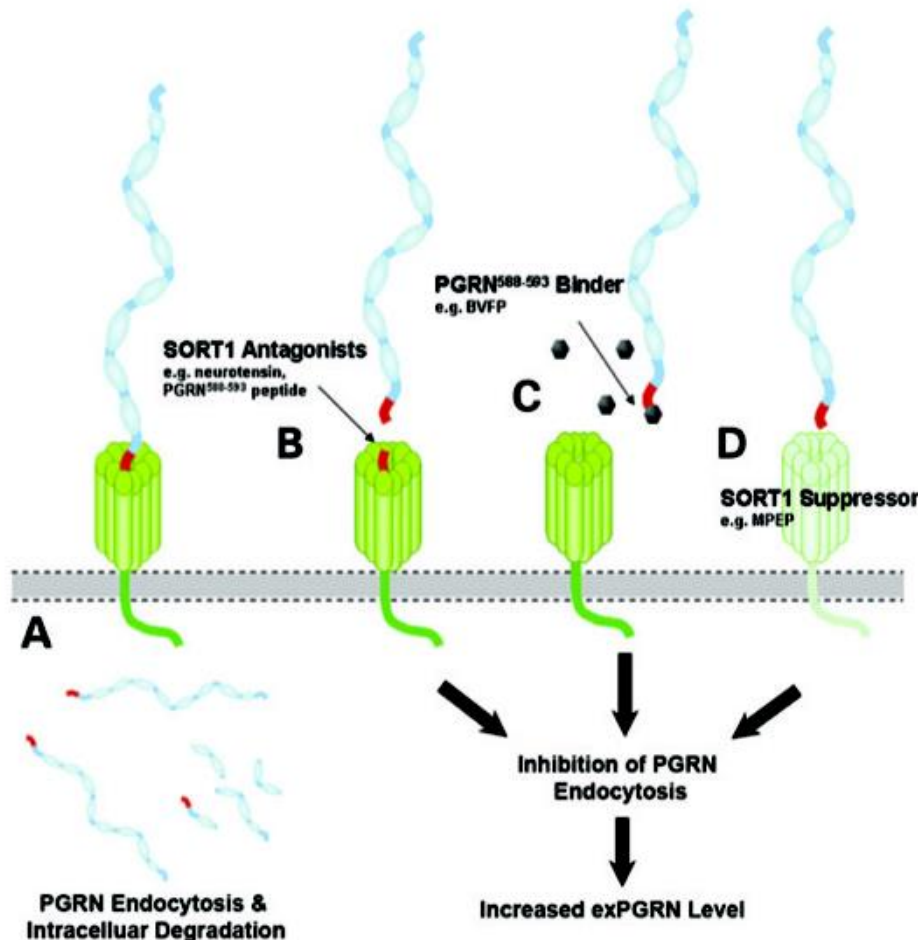
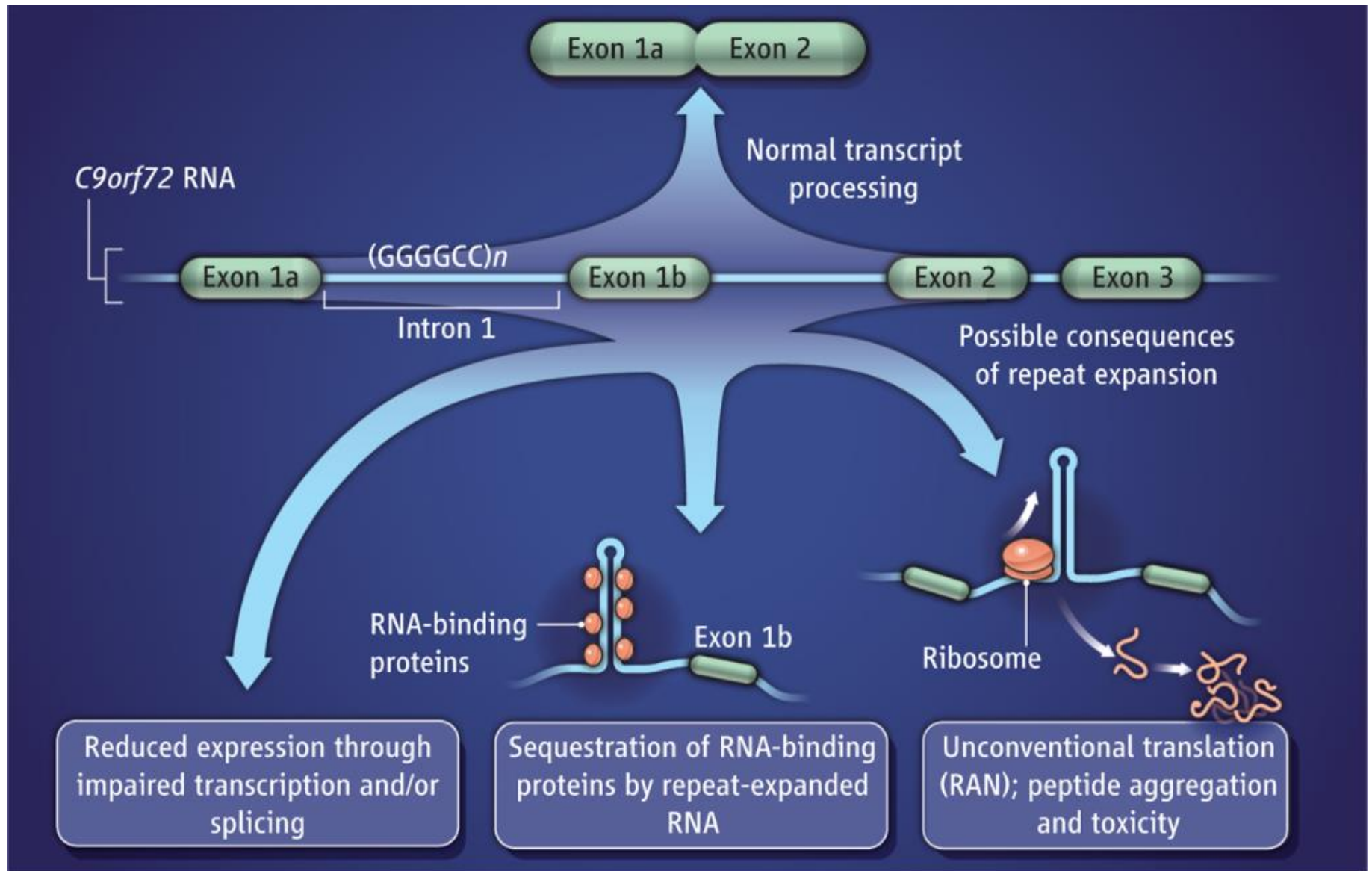
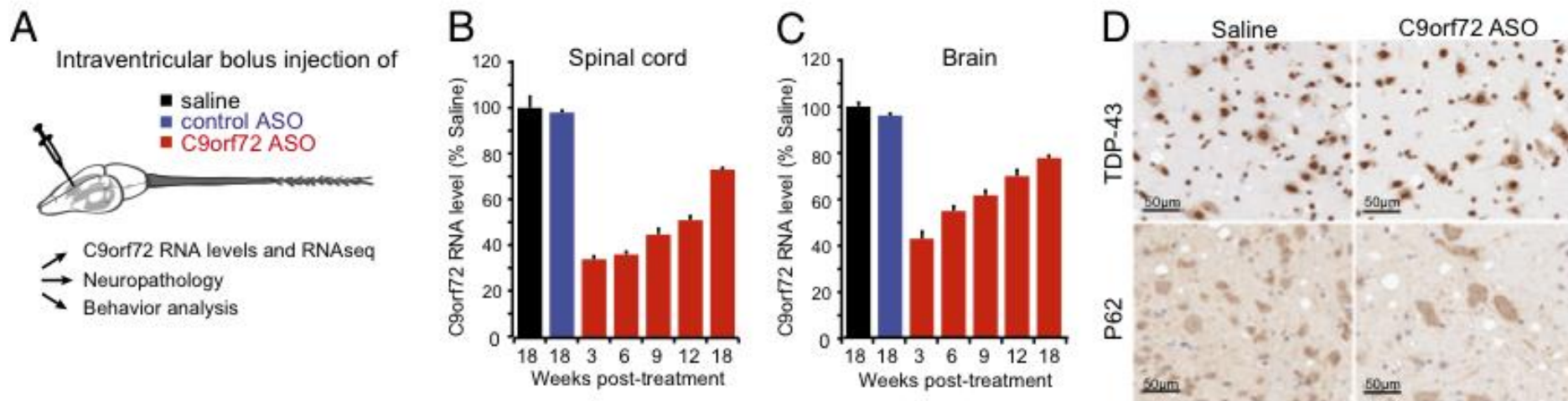


Figure 6. Schematic diagram summarizing the strategies applied to inhibit SORT1-mediated endocytosis in the current study. (A) Under normal conditions, extracellular PGRN interacts with the β -propeller tunnel structure of SORT1 using its C-terminal end binding motif as shown in red color. SORT1 facilitates endocytosis of exPGRN and directs it to the endolysosomal pathway for degradation. (B) High-affinity SORT1 ligands such as NTS or the PGRN_(588–593) peptide competitively limits the access of exPGRN to SORT1-binding sites, thereby inhibiting PGRN endocytosis. (C) To improve target specificity, we have also identified a small-molecule binder, BVFP, targeting the PGRN_(588–593) motif that is essential for PGRN–SORT1 interaction. We demonstrated that pretreatment of BVFP to rPGRN significantly reduced the amount of rPGRN captured by SORT1 *in vitro* and inhibited SORT1-mediated rPGRN endocytosis. (D) Suppressors of SORT1 expression, such as MPEP, reduce SORT1-mediated endocytosis, thereby increasing extracellular PGRN levels. The above-mentioned strategies, used alone or in combination with others, are potential avenues for discovery of SORT1-dependent PGRN enhancers for the treatment of FTD-GRN.

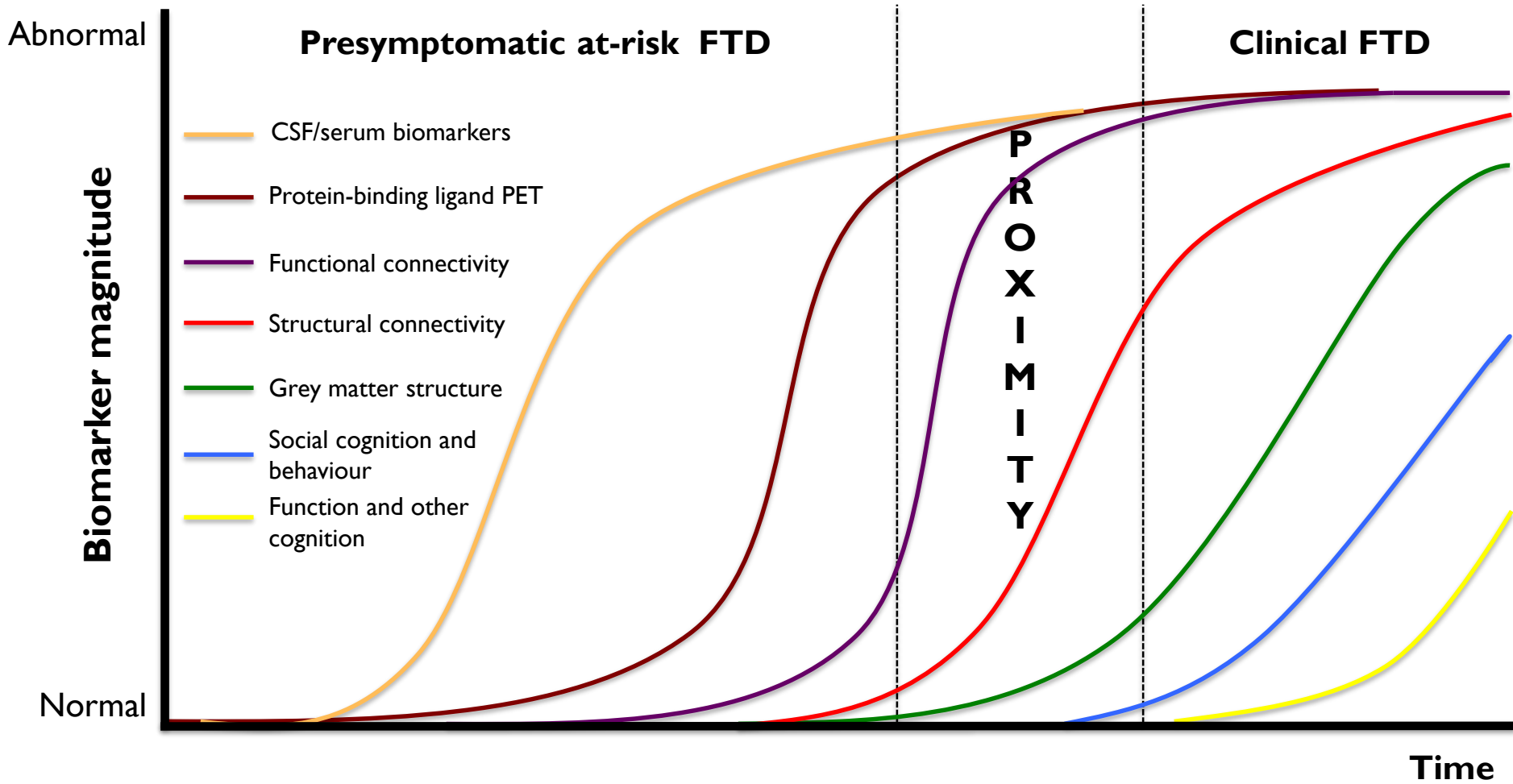


Targeted degradation of sense and antisense *C9orf72* RNA foci as therapy for ALS and frontotemporal degeneration

Clotilde Lagier-Tourenne^{a,b,1}, Michael Baughn^{a,1}, Frank Rigo^c, Shuying Sun^{b,d}, Patrick Liu^d, Hai-Ri Li^d, Jie Jiang^{b,d}, Andrew T. Watt^c, Seung Chun^c, Melanie Katz^c, Jinsong Qiu^d, Ying Sun^{a,b,d}, Shuo-Chien Ling^{a,b,d}, Qiang Zhu^{b,d}, Magdalini Polymenidou^{b,d,2}, Kevin Drenner^{a,b}, Jonathan W. Artates^{b,d}, Melissa McAlonis-Downes^{b,d}, Sebastian Markmiller^d, Kasey R. Hutt^d, Donald P. Pizzo^e, Janet Cady^f, Matthew B. Harms^f, Robert H. Baloh^g, Scott R. Vandenberg^e, Gene W. Yeo^d, Xiang-Dong Fu^d, C. Frank Bennett^c, Don W. Cleveland^{a,b,d,3}, and John Ravits^{a,3}



- Role of pathologic proteins **unknown**
- Additional **basic knowledge** on pathways in which these proteins are involved needed
- **Causal** relationship between **gene** defects and **proteins** remains to be fully elucidated
- Targeting **one** protein **only** could not result in clinical benefit
- Outcome measures



Are there concerns on inappropriately labeling individuals with «*preclinical Alzheimer's disease*» people who might never progress to manifest dementia in spite of biomarker evidence of amyloid deposition?

In other fields, terms as «*precancerous lesions*» or «*prediabetes*» did not raise any ire...

Apprehension over **preclinical AD** terminology reflects the stigma of the clinical syndrome of AD

The Future

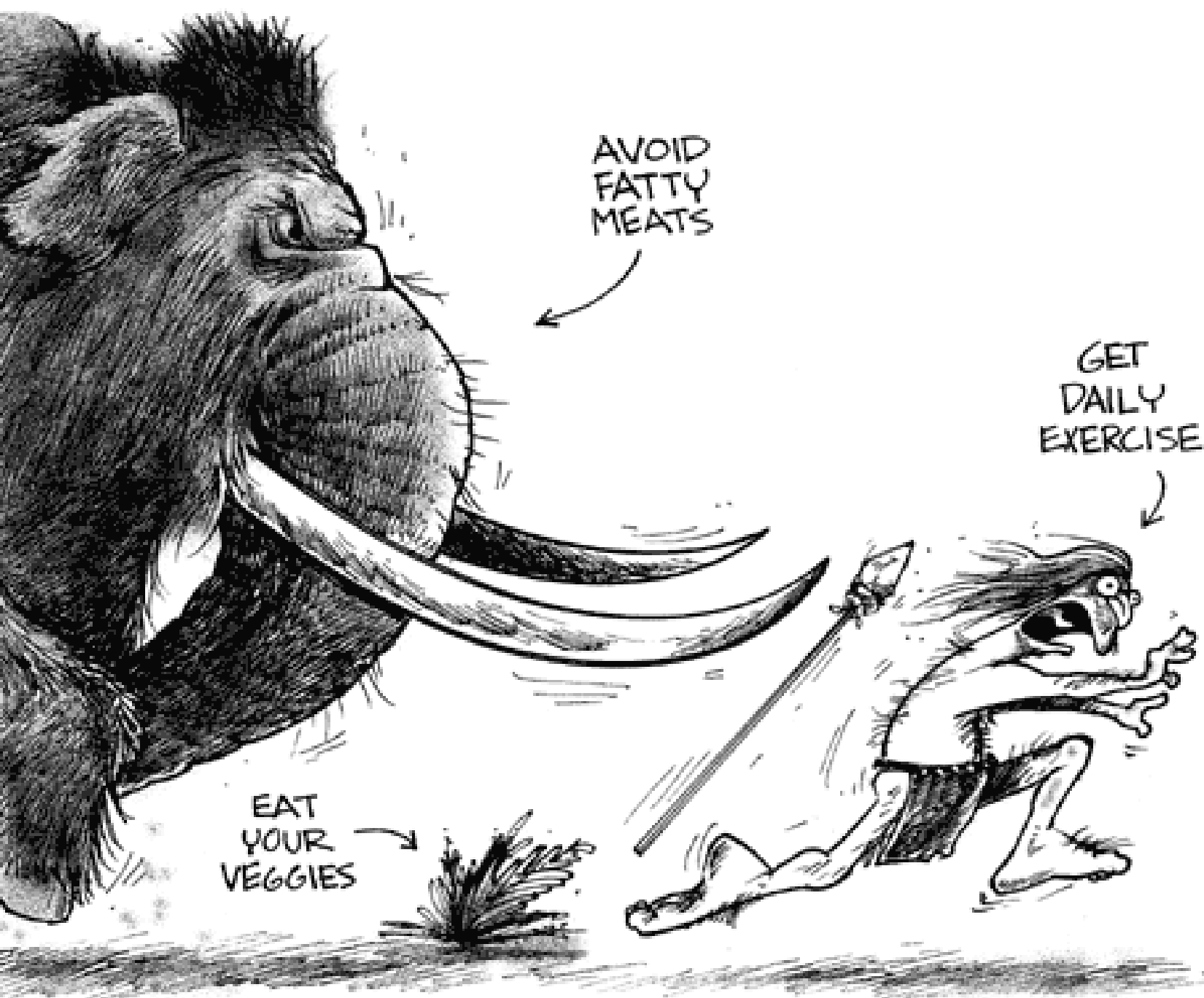
NEXT EXIT



Biohacking

Neural implants, merging the human brain with AI

The logo for Kernel, featuring the word "kernel" in a lowercase, sans-serif font. The letter "e" is stylized with a grey circular shape behind it.



AVOID
FATTY
MEATS

GET
DAILY
EXERCISE

EAT
YOUR
VEGGIES

Cox &
Forkum
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SINdem4Juniors

6th Winter Seminar on Dementia and
Neurodegenerative Disorders



January 17-19, 2018

Bressanone, Italy
Dolomiti – Sud Tirol

Save the date!

January 17th - Contamination Session

January 18-19th - Scientific Session

Deadline for abstract submission
and moderators call:

November 19th

Call for Abstracts

Call for Young Moderators

Submission is restricted to investigators under 40 years of age.
SINdem4Juniors and SINdem will publish abstracts as a
supplement of JAD..



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Contamination Session

January 17th

Microbiota and Neurodegenerative Disorders: a Gut Feeling

Sylvie Claeysen (Montpellier - France)

Chronobiology: Implications for Health and Disease

Christian Cajochen (Basel - Switzerland)

The Brain's Fountain of Youth: Young Blood Transfusions to Reverse Ageing

Joseph Castellano (New York - USA)

Alzheimer's in the Wild: Natural Models of Disease

January 18th

Broca and Wernicke Are Dead: the New Neurobiology of Language

Pascale Tremblay (Quebec - Canada)

From Trauma to Tau: Traumatic Brain Injury and Neurodegeneration

Steve Gentleman (London - UK)

Debate: Epigenetics in Neurodegeneration: Contributor or Bystander?

Alfredo Ramirez (Köln - Germany)

Bart Rutten (Maastricht - Germany)

January 19th

Dishing out Mini-Brains: Current Progress and Future Prospects in Brain Organoids

Alessio Di Fonzo (Milan - Italy)

Data Integration in the Era of "Omics": Current and Future Challenges

Albin Sandelin (Copenhagen - Denmark)

Discussion: Emerging Targets in Neurodegeneration: Dementia

Ferdinando Nicoletti (Rome - Italy)

Movement Disorders

Alice Chen-Plotkin (Philadelphia - USA)

Amyotrophic Lateral Sclerosis

Elamin Marwa (Brighton - UK)

SINdem4Juniors

Lifestyle for Ageing Prevention

January 19th

Physical Activity and Plasticity in Parkinson's Disease

Alice Nieuwboer (Leuven - Belgium)

Diet Style

Cherubino Di Lorenzo (Latina - Italy)

Medical Food

Arrigo F.G. Cicero (Bologna - Italy)

Fast Mimicking Diet

Wanda Rizza (Rome - Italy)

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