NUOVE STRATEGIE TERAPEUTICHE PER LA MALATTIA DI ALZHEIMER

MEETING DELLE NEUROSCIENZE TOSCANE

Società dei Neurologi, Neurochirurghi e Neuroradiologi Ospedalieri

SIN SOCIETÀ ITALIANA DI NEUROLOGIA

Gemma Lombardi

UNIVERSITÀ DEGLI STUDI FIRENZE

7 aprile 2017

MEETING DELLE NEUROSCIENZE TOSCANE

Società dei Neurologi,
Neurochirurghi e
Neuroradiologi Ospedalieri

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

- Update immunoterapia (β)
- Nuove strategie terapeutiche
- Prevenzione

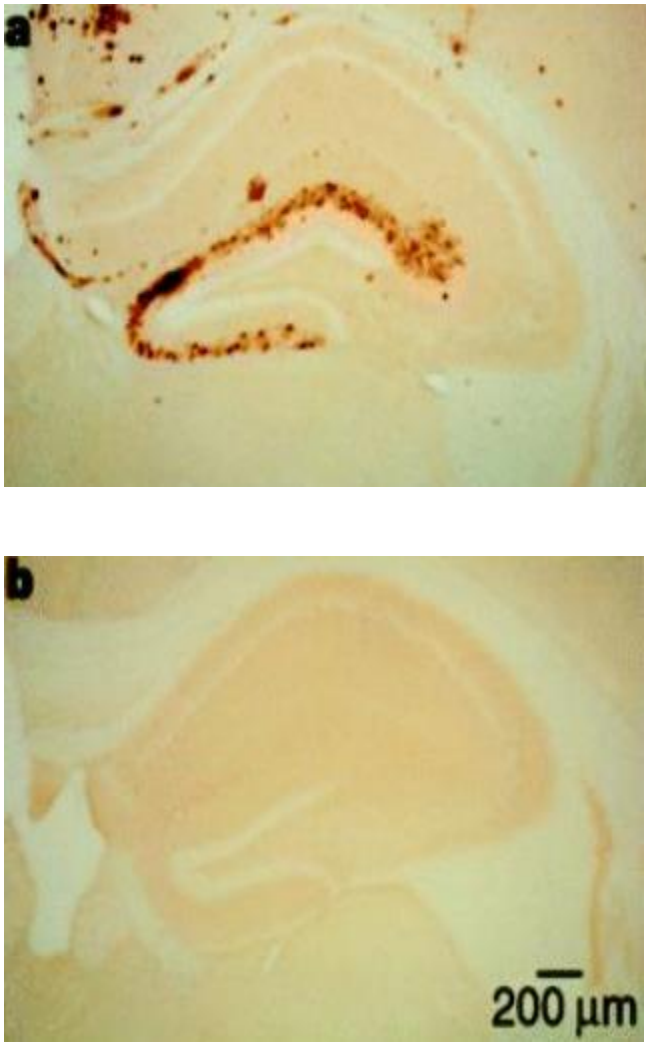
LE ORIGINI DELL'IMMUNOTERAPIA

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

(APPVal717Ph)

IMMUNIZZAZIONE A 6 SETTIMANE: effetto preventivo sulla formazione di depositi di amiloide

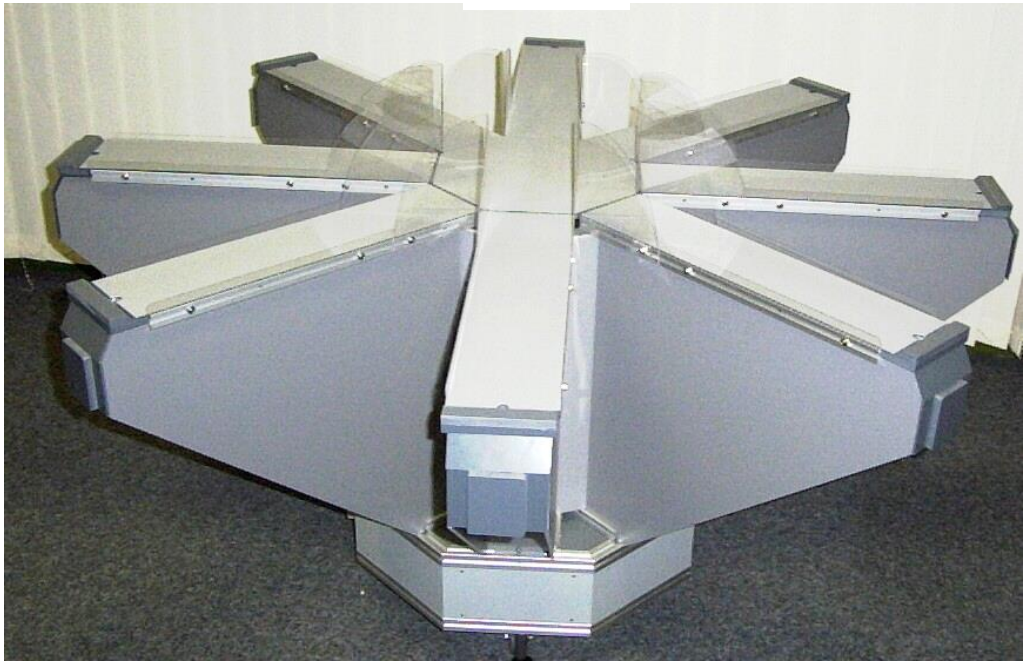
IMMUNIZZAZIONE A 11 MESI: effetto di riduzione marcata dei depositi di amiloide



(Schenk D et al, Nature, 1999)

LE ORIGINI DELL'IMMUNOTERAPIA

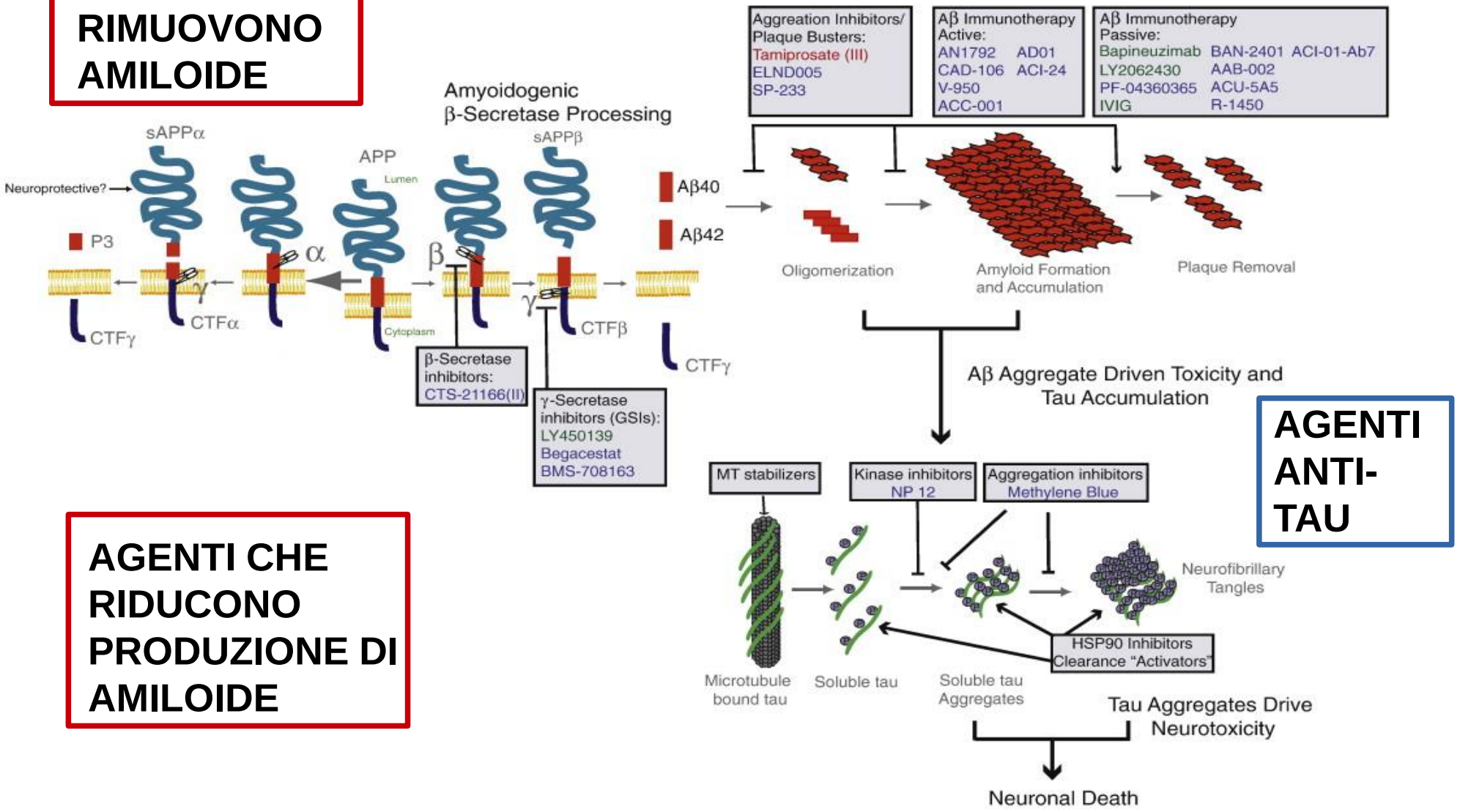
La vaccinazione attiva con amiloide previene il deficit cognitivo in modelli animali di Malattia di Alzheimer



(Morgan D et al, Nature, 2000)

AD: DISEASE MODIFYING STRATEGIES

AGENTI CHE RIMUOVONO AMILOIDE

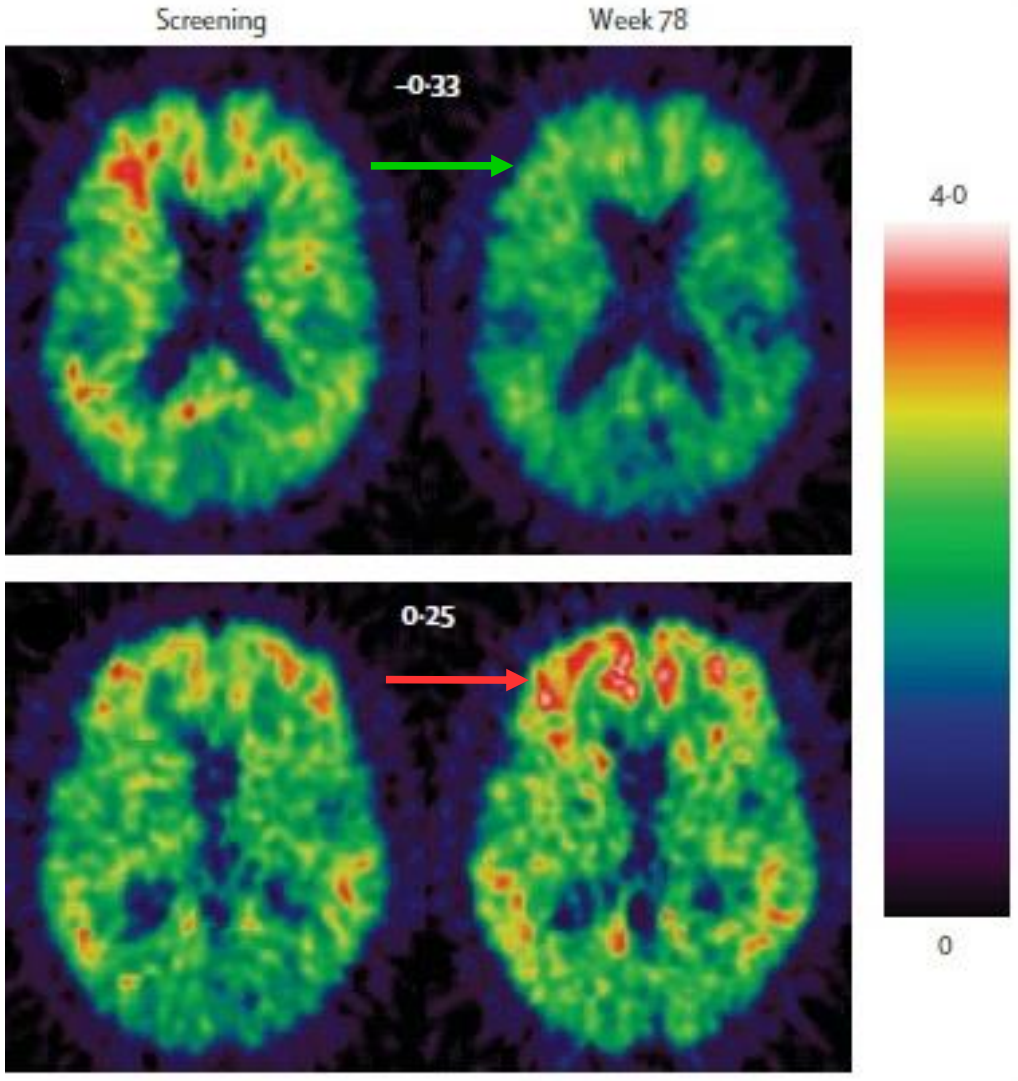


AGENTI ANTI-TAU

AGENTI CHE RIDUCONO PRODUZIONE DI AMILOIDE

EFFETTI DELL'IMMUNOTERAPIA PASSIVA

Bapineuzumab



Placebo

Imaging:

Effetto di riduzione del carico di amiloide visibile alla PET con PIB

(Rinne JO, 2010)

EFFETTI DELL'IMMUNOTERAPIA PASSIVA

ClinicalTrials.gov

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NO EFFICACIA CLINICA in AD lieve-moderata

- Bapineuzumab (Pfizer)-fase III
- Solanezumab (Lilly)-fase III

NO EFFICACIA CLINICA in AD lieve

- Solanezumab (Lilly)- fase III (amy+)
- EXPEDITION 3

IN CORSO DI VALUTAZIONE in podromal AD (MCI due to AD): fase III (amy+)

- Solanezumab (Lilly)
- Gantenerumab (Roche)
- Crenezumab (Roche) e ADUCANUMAB (Biogen)

MOTIVI DEL FALLIMENTO ?

- ✓ Fase avanzata di malattia
- ✓ Selezione scorretta
- ✓ Preclinical model: topo-uomo
- ✓ Cascata amiloide
- ✓ Passaggio della BEE
- ✓ Dosaggio/sicurezza
- ✓ Target del farmaco

ANTICORPI ANTIAMILOIDE: sono tutti uguali? NO

	Manufacturer	Epitope	Origin	Isotype	Target	Possible mechanism of action	Outcomes in latest stage trial
Solanezumab (NCT0760005, NCT01900665)	Eli Lilly	Mid-domain	Humanised	IgG1	Soluble, monomeric, non-fibrillar Aβ	Sequestration of soluble monomeric Aβ	Negative clinical outcomes in two phase 3 trials in mild-to-moderate Alzheimer's disease; possible slowing of cognitive decline in mild disease
Bapineuzumab (NCT00575055, NCT00574132)	Pfizer/Johnson & Johnson	N-terminus	Humanised	IgG1	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in two phase 3 trials despite significant decrease in amyloid PET and phosphorylated tau concentrations in cerebrospinal fluid
Crenezumab (NCT 01397378, NCT01723826, NCT01998891)	Roche/ Genentech	Mid-domain	Humanised	IgG4	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in phase 2 trials in mild-to-moderate Alzheimer's disease; possible cognitive slowing in mild disease in patients given high doses

(Scheltens P, Lancet, 2016)

ANTICORPI ANTIAMILOIDE: sono tutti uguali? NO

	Manufacturer	Epitope	Origin	Isotype	Target	Possible mechanism of action	Outcomes in latest stage trial
BAN2401 (NCT01767311)	Eisai/Biogen	N-terminus	Humanised	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	No phase 2 trials yet completed
Gantenerumab (NCT01224106, NCT02051608)	Roche/ Genentech	N-terminus and mid-domain	Human (phage display library and affinity maturation)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Negative clinical outcomes in phase 3 trial for prodromal Alzheimer's disease
Aducanumab (NCT02484547, NCT02477800)	Biogen/ Neurimmune	N-terminus	Human (RTM)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Dose-dependent decrease in amyloid PET and cognitive decline in early Alzheimer's disease (mild cognitive impairment and mild disease) in interim analysis of phase 1b trial

Tossicità

(Scheltens P, Lancet, 2016)

ADUCANUMAB: studio di fase 1b

Studio randomizzato, controllato, in doppio cieco Aducanumab (a dosi diverse)/placebo in soggetti prodromal o mild AD (MMSE>20) e Aβ PET+ (durata 12 mesi)

valutare sicurezza e tollerabilità

+

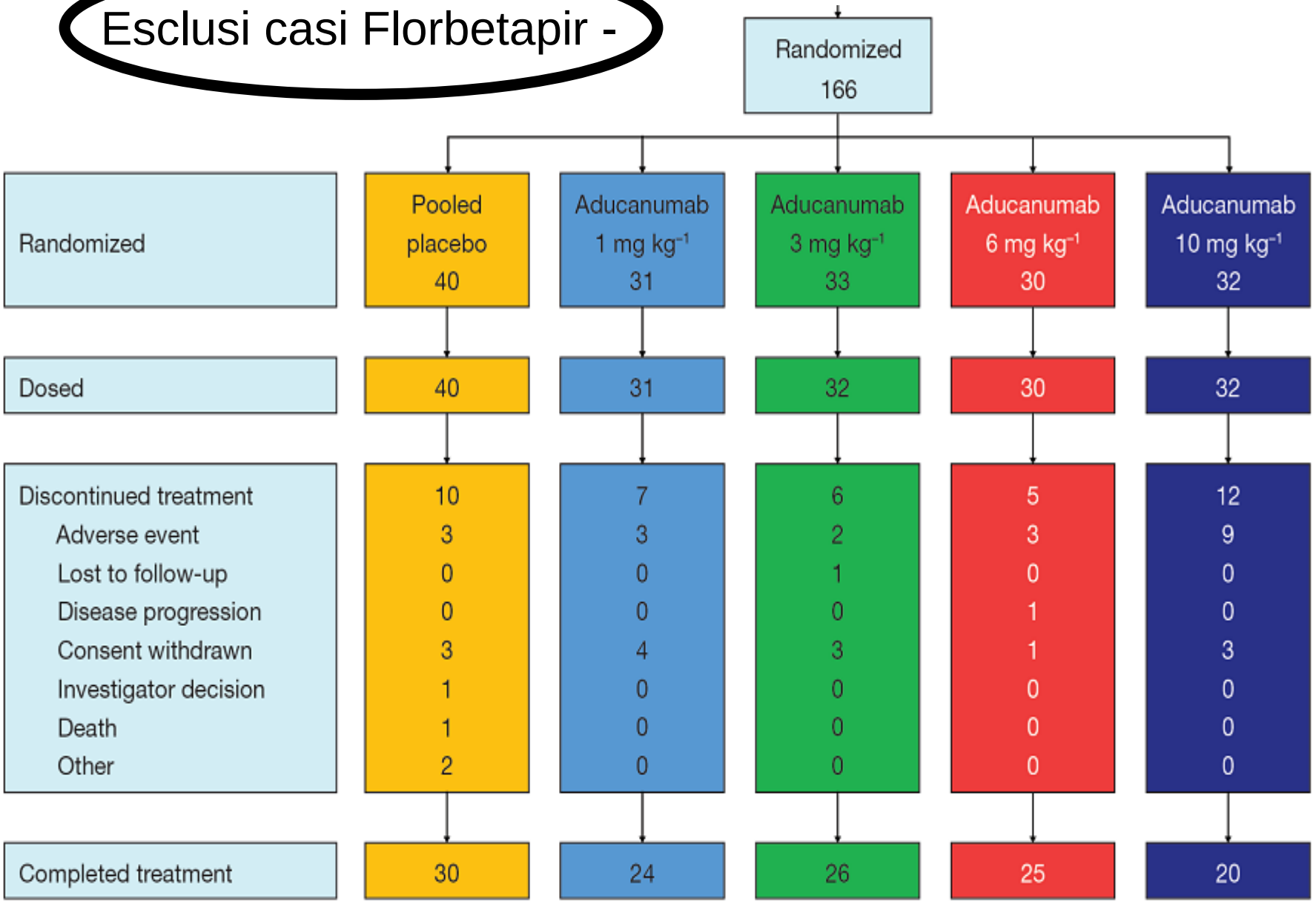
"exploratory clinical endpoints"

(Sevigny J, 2016)

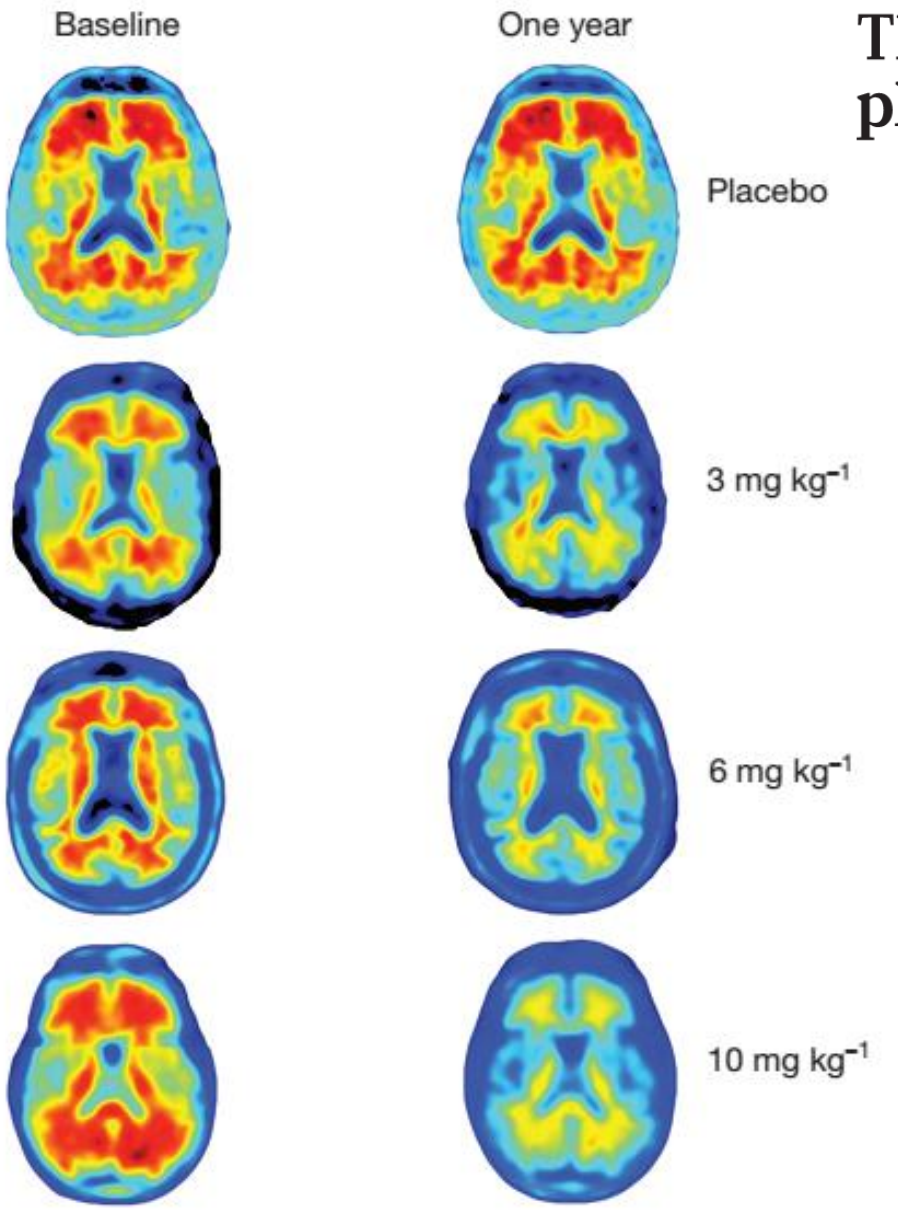
nature

ADUCANUMAB

Esclusi casi Florbetapir -



ADUCANUMAB



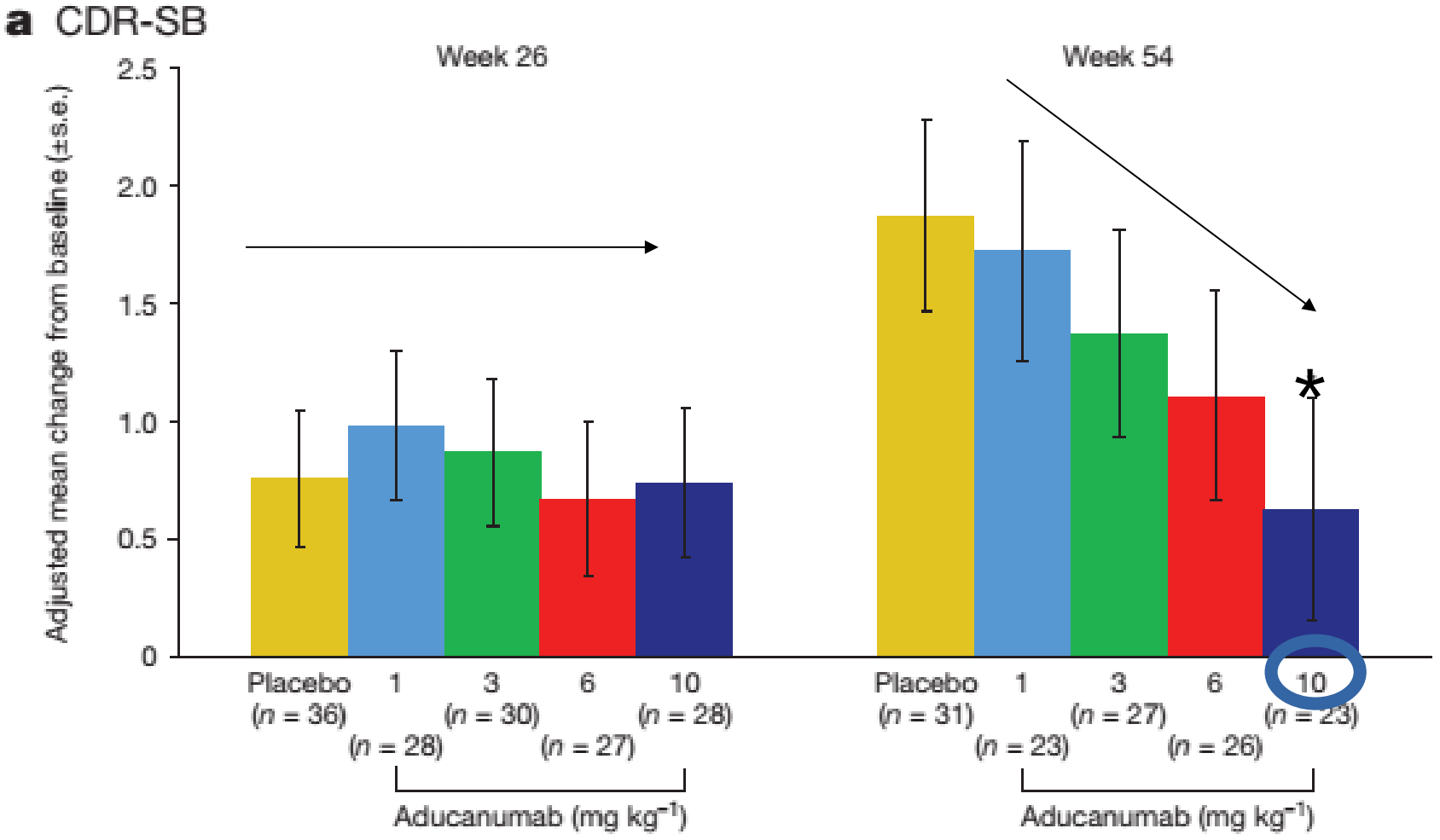
The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Effetti sull'imaging (PET con Florbetapir): ADUCANUMAB riduce il carico di amiloide alla PET in modo dose e tempo dipendente ($p<0,001$) (non influenzato da apo E)

(Sevigny J, Nature, 2016)

ADUCANUMAB

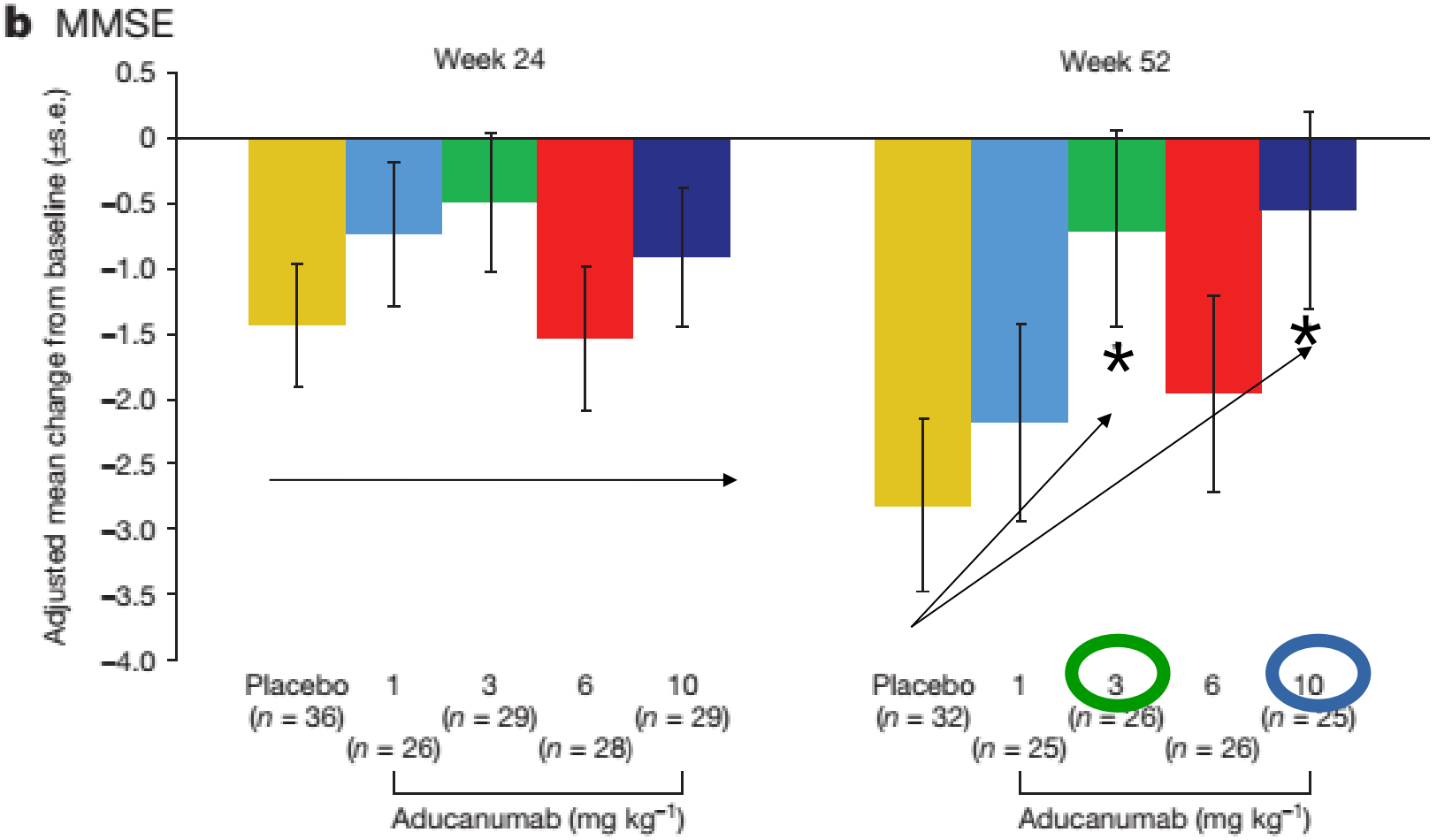
CDR-SOB: a 1 anno rallentamento nella progressione clinica nel gruppo Aducanumab 10 mg/Kg vs placebo (p<0,05, non corretto per c.m.)



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

ADUCANUMAB

MMSE: a 1 anno rallentamento nella progressione clinica nel gruppo Aducanumab 3 e 10 mg/Kg vs placebo (p<0,05, non corretto per c.m)



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

ADUCANUMAB: ARIA

ARIA: amyloid-related imaging abnormalities

- ARIA-E: vasogenic-edema: dose dip , apoE
- ARIA-H: ARIA haemorrhages or superficial siderosis

		Aducanumab			
	Placebo	1 mg kg^{-1}	3 mg kg^{-1}	6 mg kg^{-1}	10 mg kg^{-1}
ARIA-E, n (%)	0	1 (3)	2 (6)	11 (37)	13 (41)
By ApoE ε4					
ApoE ε4 carrier	0	1 (5)	1 (5)	9 (43)	11 (55)
ApoE ε4 non-carrier	0	0	1 (9)	2 (22)	2 (17)
Isolated ARIA-H, n (%)	2 (5)	2 (6)	3 (9)	0	2 (6)
ApoE ε4 carrier	2 (8)	1 (5)	2 (10)	0	2 (10)
ApoE ε4 non-carrier	0	1 (8)	1 (9)	0	0

20%

The amyloid hypothesis of Alzheimer's disease at 25 years

Dennis J Selkoe[1,†] & John Hardy[2,*,†]

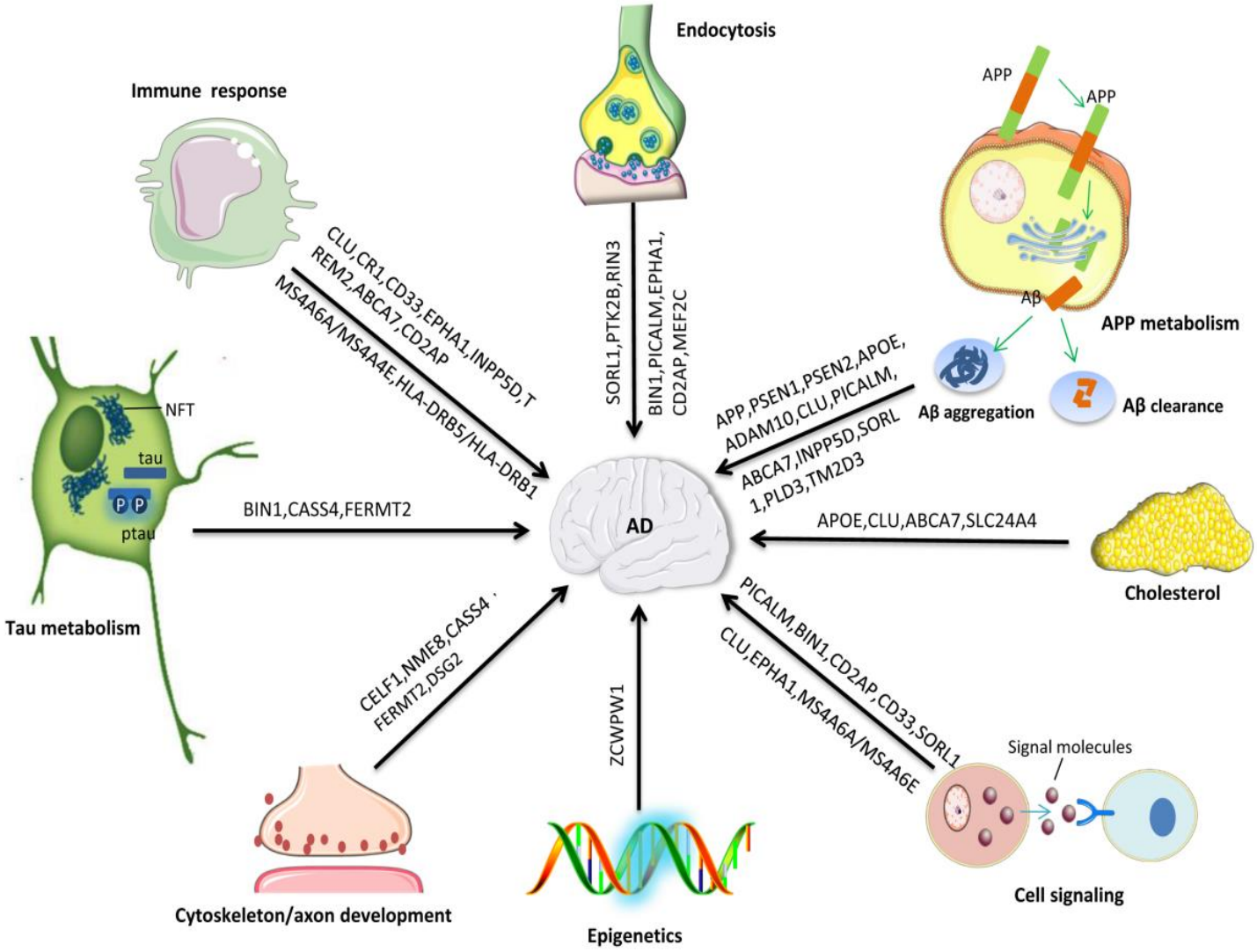
NON SOLO AMILOIDE

Pending issues

What are the toxic species of Aβ and tau?
What is the connection between Aβ and tangle pathology? Is it direct and cell autonomous or does it involve non-neuronal cells?
What is the mechanism of pathology spread and does understanding this spread provide therapeutic opportunities?
What is the function of APP and does Aβ have a function?
GWA studies have identified cholesterol metabolism, the innate immune system, and endosomal vesicle recycling as important pathogenic processes in AD: how do these relate to each other?

(Selkoe D e Hardy J, EMBO, 2016)

Revisione patogenesi AD: nuove strategie terapeutiche per l'AD



Update on Alzheimer's Disease Therapy and Prevention Strategies

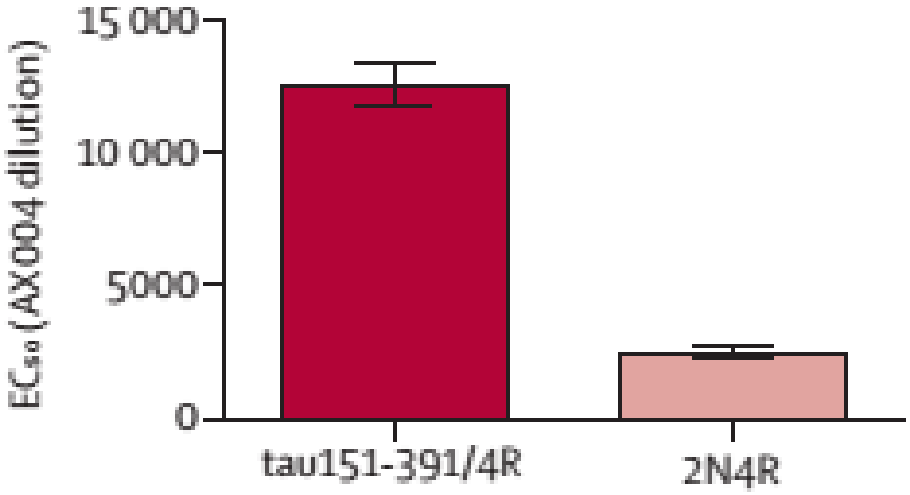
ClinicalTrials.gov

(Graham WV et al) Annu. Rev. Med. 2017. 68:413–30

Target type	Name	Therapy type	Status	Company
Tau aggregation inhibitor	Rember TM	Small molecule	Discontinued	TauRx Therapeutics Ltd.
Tau aggregation inhibitor	TRx0237 (LMTX)	Small molecule	Phase III (Gauthier S, 2016)	TauRx Therapeutics Ltd.
p-Tau clearance	AADvac-1	Immunotherapy (active)	Phase I Phase II	Axon Neuroscience SE (Novak P, 2017)
p-Tau clearance	ACI-35	Immunotherapy (active)	Phase I	AC Immune SA, Janssen Pharmaceutica
Microglial activation inhibitor	Alzhemed™	Small molecule	Discontinued	Neurochem, Inc.
Microglial activation inhibitor	Azeliragon	Small molecule	Phase III	Pfizer, Inc., TransTech Pharma, Inc., vTv Therapeutics
Microglial activation inhibitor	Ibuprofen	Small molecule	Discontinued	
Microglial activation inhibitor	Flurizan™	Small molecule	Discontinued	Myriad Genetics, Inc.

Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 1 trial

IMMUNOBLOT:
Anticorpi (prodotti alla 24 settimana dopo 6 dosi) riconoscono le forme patologiche di tau (linea 1 e 2)

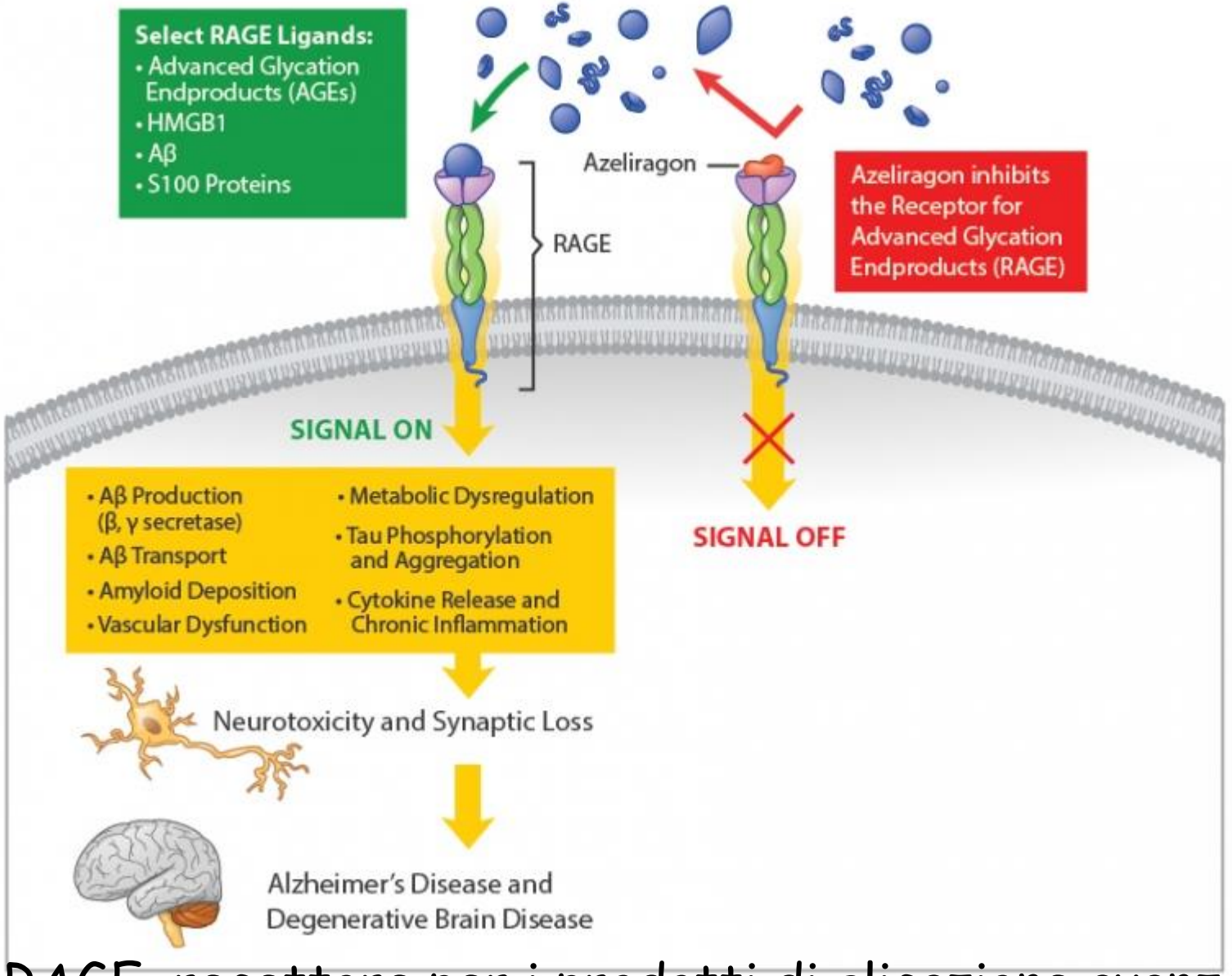


Anticorpi con affinità > per troncata di tau rispetto alla forma tau fisiologica "2N4R"

NO meningoencefalite,
NO edema vasogenico

(NovaK P, Lancet Neurol, 2017)

AZELIRAGON: RAGE INHIBITOR



RAGE, recettore per i prodotti di glicazione avanzata

AZELIRAGON (x os, fase III in AD lieve)

- Inibisce l'afflusso di Aβ40 e Aβ42 circolanti verso il cervello e inibisce la beta-secretasi
- Inibisce l'attivazione della microglia

A multimodal RAGE-specific inhibitor reduces amyloid β–mediated brain disorder in a mouse model of Alzheimer disease

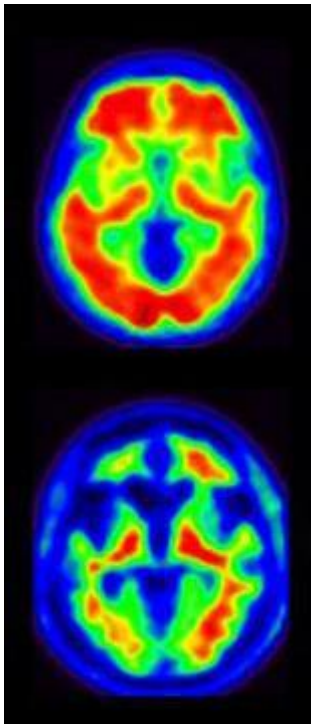
(Deane R, 2012)

PREVENZIONE

- Su soggetti sani anziani → Fattori di rischio modificabili
- Su soggetti mutati

DIAN TU
Dominantly Inherited Alzheimer Network Trials Unit

- Su anziani sani a > rischio (amyloid PET+) (Studio A4)
- Su MCI



A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Finnish Geriatric Intervention Study per prevenire il disturbo cognitivo e la disabilità

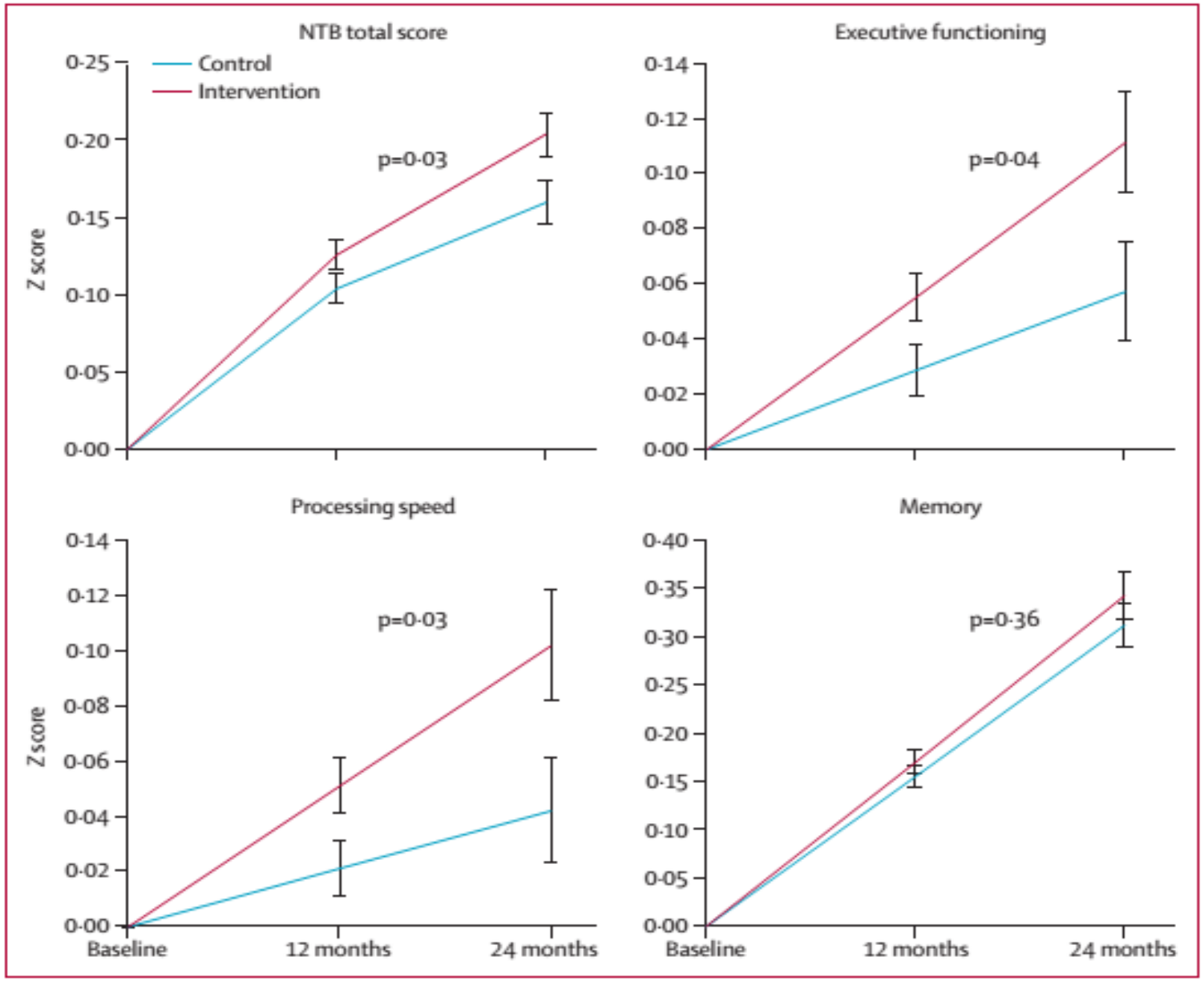
Intervento multimodale in soggetti a rischio per demenza
n. 1200, età 60-77
Durata 2 anni

- Fattori di rischio vascolari
- Dieta
- Esercizio fisico
- Training cognitivo

(Ngandu T, Lancet 2015)

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

(Ngandu T, Lancet 2015)



OR 1,3 nei non trattati

PREVENZIONE IN MCI

(Petersen RC, 2005)

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

769 aMCI:
Vit E (2000 UI) o
Donepezil 10 mg o
placebo
3 anni di follow-up

No differenze in percentuale di conversione a AD

(Cooper C, 2013)

A systematic review of treatments for Mild Cognitive Impairment

MCI: 41 studi
Isolate evidenze positive per:

- Intervento neuropsicologico di gruppo>6 mesi
- **Piribedil** (dopaminoagonista)>3 mesi
- Donepezil >48 settimane (1/9 studi)

Non evidenza replicata di intervento efficace

PREVENZIONE in MCI

Games for Olders Active Life

Consorzio di Bioingegneria e Informatica Medica
CBIM
Università degli Studi Firenze
Fondazione Don Carlo Gnocchi Onlus
Gutenberg
ECM Standard n. 409
Regione Toscana
FAS Fondo Aree Sottoutilizzate 2007-2013

Progetto finanziato dal Bando Fas Salute della Regione Toscana

http://goaltoscana.cbim.it/
progetto.goal@dongnocchi.it

CONCLUSIONI

- É necessario aspettare i risultati degli studi di fase III per poter affermare che Aducanumab ha una efficacia clinica
- L'amiloide non è l'unico target terapeutico e probabilmente un approccio multitarget potrebbe essere la strategia giusta
- In assenza di una terapia efficace la prevenzione riveste un ruolo di primaria importanza

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