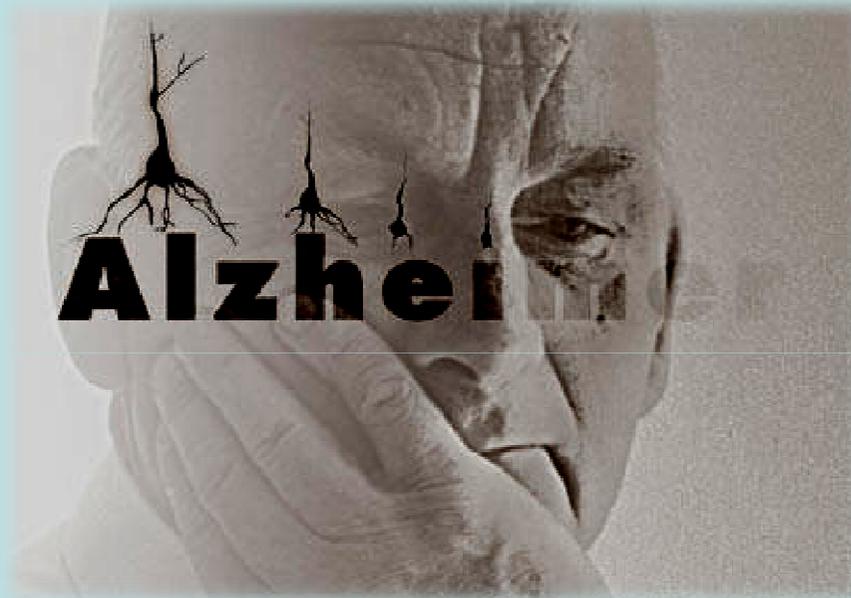


**Liceo Scientifico Cavalleri
Parabiago
“L’Alzheimer e la Famiglia”**

23 Novembre 2011



Biologia e patogenesi dell’Alzheimer

**Gianluigi Forloni
Dipartimento di Neuroscienze
Istituto di Ricerche Farmacologiche “Mario Negri”**

L'Istituto Mario Negri



www.marionegri.it

La storia

- 1960** Lascito di Mario Negri
- 1961** Creazione della Fondazione Mario Negri con DPR
- 1961- 62** Costruzione dell'edificio che ospiterà l'istituto Mario Negri a Milano
- 1963** Inizio dell'attività scientifica
- 1983** Apertura nuovi Laboratori a Bergamo
- 1986** Creazione dell'istituto "Mario Negri Sud" in S. Maria Imbaro (CH)
- 1987** Allargamento e nuove costruzioni nel Campus di Milano
- 1992** Apertura centro per le malattie rare Aldo e Cele Daccò a Ranica, Bergamo
- 2002** Apertura Centro per la ricerca sui trapianti a Ranica
- 2004-7** Realizzazione nuovo Istituto a Milano



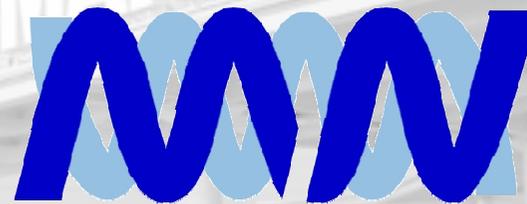
New Institute "Mario Negri" Milano



"Mario Negri" Institute in Bergamo



Center of Rare Diseases Cele Dacco'
Ranica (Bg)



MARIO NEGRI
ISTITUTO DI RICERCHE
FARMACOLOGICHE

Consortium "Mario Negri" South
S. Maria Imbaro (CH)



Transplant Research Center
Ranica (Bg)

IRFMN- il personale scientifico

	MILANO	BERGAMO	TOTAL
Staff Sc.	180	85	265
Post-Docs	126	59	185
altri	155	79	234
TOTAL	461	223	684

PRINCIPI GENERALI

- **INDIPENDENZA**

Nessuna risorsa finanziaria equivale a più del 5% del bilancio complessivo. Non ci sono fondi strutturali ne ne privati ne pubblici

- **RISORSE ECONOMICHE**

Partecipazione a bandi competitivi con agenzie nazionali e internazionali (40%)

Contratti con le industrie (30%)

Fondazioni (10%)

Donatori privati (20%)

- **BREVETTI**

E' dall'inizio dell'attività del Mario Negri che non brevettiamo, la nostra produzione scientifica è a disposizione della comunità

The image shows the exterior of the Mario Negri Institute for Pharmacological Research. The building is a modern, multi-story structure with a prominent entrance canopy supported by columns. Large white letters spelling "MARIO NEGRI" are mounted on the upper part of the building facade. Below this, smaller text reads "ISTITUTO DI RICERCA FARMACOLOGICHE". The foreground is a paved courtyard. Overlaid on the image is the title "IRFMN- le attività" in red and a list of activities in blue.

IRFMN- le attività

- **Ricerca**

- **Formazione**

- **Informazione**

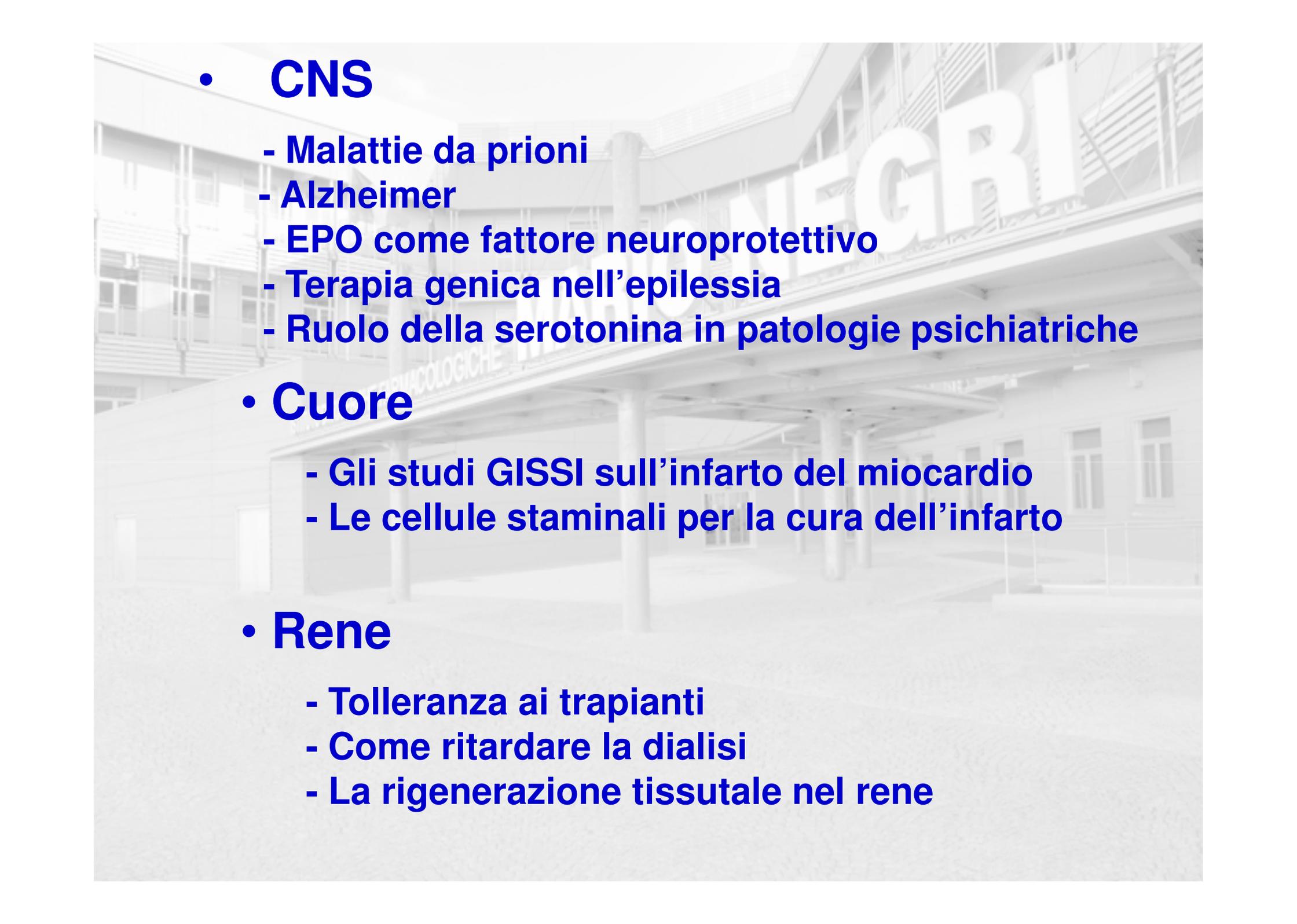
Dipartimenti

Milano

- Neuroscienze
- Oncologia
- Biochimica e farmacologia molecolare
- Ricerca cardiovascolare
- Salute e Ambiente
- Epidemiologia
- Salute pubblica

Bergamo

- Medicina molecolare
- Medicina Renale
- Bioingegneria



- **CNS**

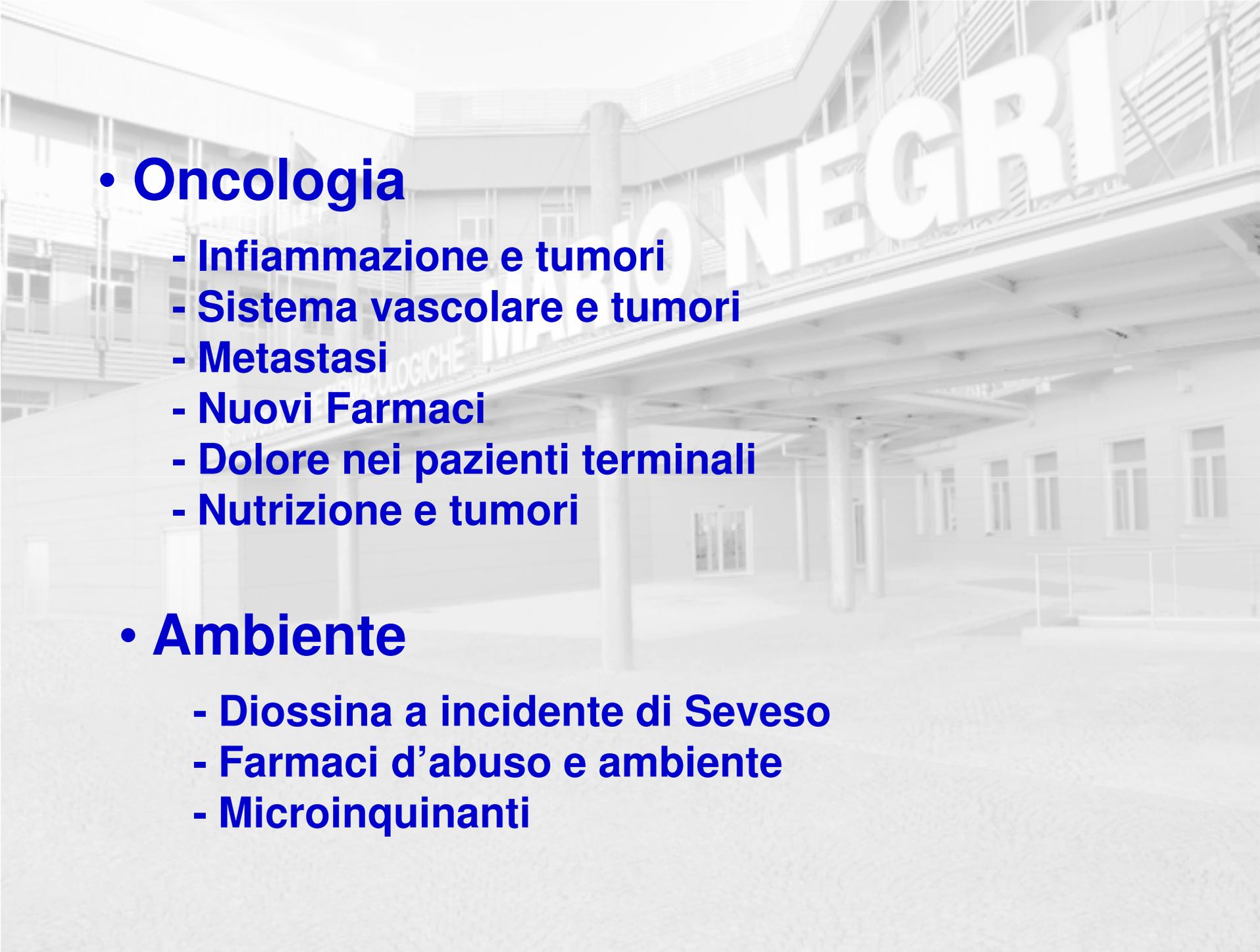
- Malattie da prioni
- Alzheimer
- EPO come fattore neuroprotettivo
- Terapia genica nell'epilessia
- Ruolo della serotonina in patologie psichiatriche

- **Cuore**

- Gli studi GISSI sull'infarto del miocardio
- Le cellule staminali per la cura dell'infarto

- **Rene**

- Tolleranza ai trapianti
- Come ritardare la dialisi
- La rigenerazione tissutale nel rene



• **Oncologia**

- **Infiammazione e tumori**
- **Sistema vascolare e tumori**
- **Metastasi**
- **Nuovi Farmaci**
- **Dolore nei pazienti terminali**
- **Nutrizione e tumori**

• **Ambiente**

- **Diossina a incidente di Seveso**
- **Farmaci d'abuso e ambiente**
- **Microinquinanti**

- 
- Più di 11.000 pubblicazioni su riviste con peer-review
 - circa 250 libri scientifici
 - Più di 47000 citazioni su riviste internazionali
 - Negli ultimi nove anni

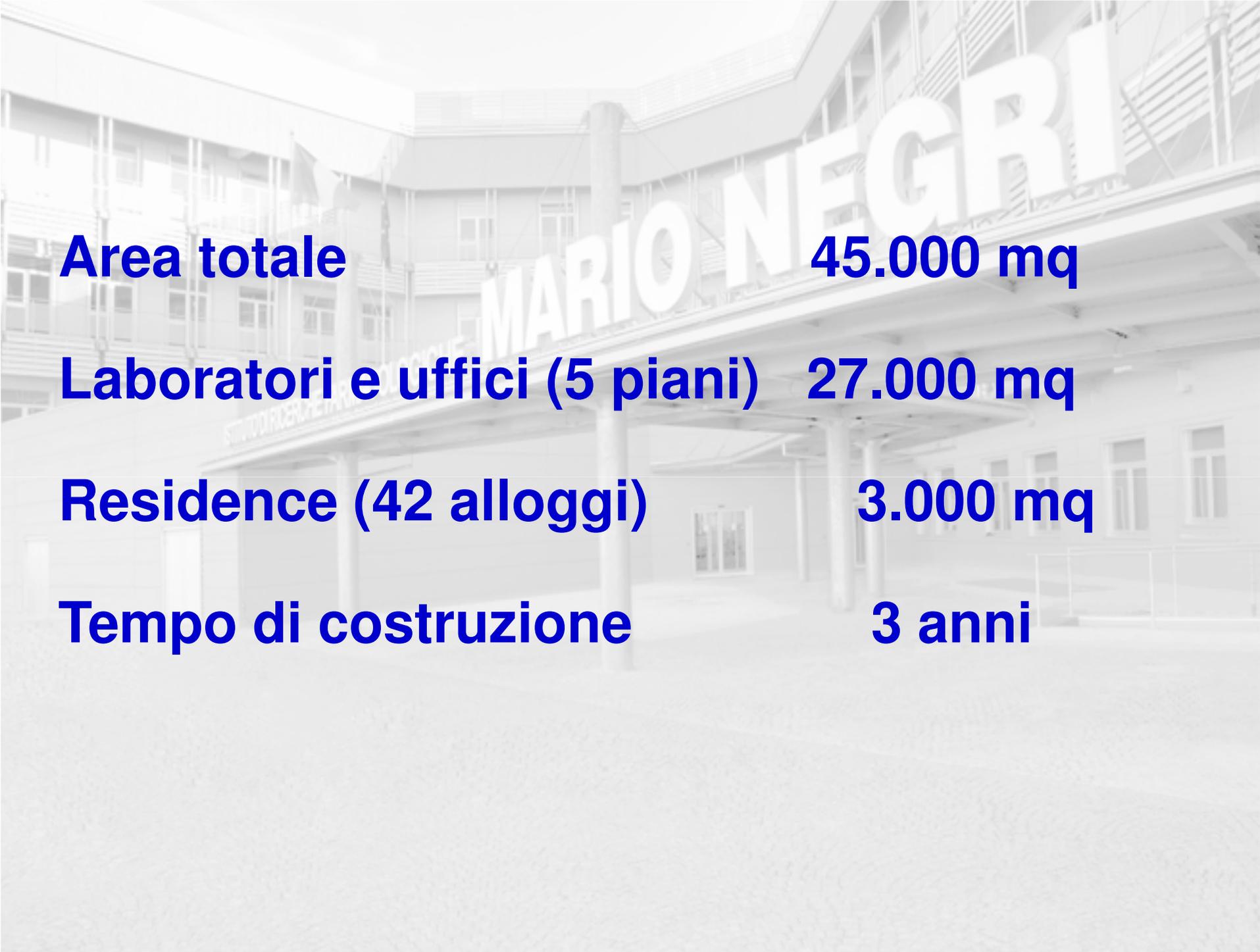
No. 1.751 articoli con IF > 3

No. 863 articoli con IF > 5

No. 298 articoli con IF > 10



**Il nuovo Istituto
a Milano**



Area totale 45.000 mq

Laboratori e uffici (5 piani) 27.000 mq

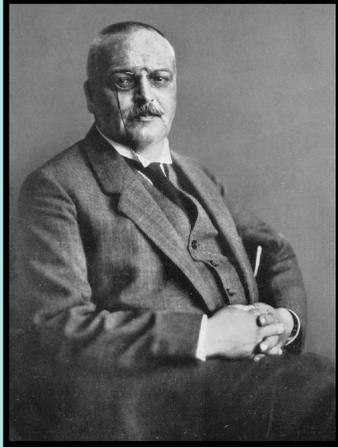
Residence (42 alloggi) 3.000 mq

Tempo di costruzione 3 anni

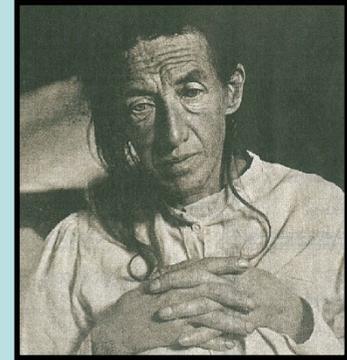
IL “NUOVO” MARIO NEGRI

- **RICERCA TRASLAZIONALE**
- **Analisi d'immagine e nuove tecnologie**
- **Farmacogenomica e proteomica**
- **Tumori e metastasi**
- **Malattie cardiovascolari**
- **Invecchiamento e neurodegenerazione**

Alois Alzheimer



Auguste D



Il primo caso di AD

Alzheimer's disease

Malattia neurodegenerativa caratterizzata da depositi cerebrali di β amiloide (placche) e da grovigli neurofibrillari (taupatia)

- Perdita delle sinapsi
- Perdita delle funzioni cognitive
- Morte delle cellule nervose

**Oltre 500 mila casi in Italia e
30 milioni nel mondo**

Studio delle malattie neurodegenerative

Prima età dell'oro (inizi XX sec)

- Uso del microscopio
- Procedure per fissare il tessuto (Nills; Bielchovsky)
- Pick (1906)
- Alzheimer (1907)
- Lewy (1912)

Seconda età dell'oro (fineXX e inizi XXI sec)

- Genetica molecolare
- Biologia molecolare
- Tecniche di immagine morfologiche e funzionali
- Marker biologici preclinici

MALATTIE NEURODEGENERATIVE

Perdita progressiva delle funzioni neuronali

Origine genetica (10-100%)

Vulnerabilità selettiva

**Meccanismo di neurotossicità comune
(radicali, EEA, Ca⁺⁺ ecc)**

**Le forme genetiche sono spesso associate ad una
acquisizione di funzione**

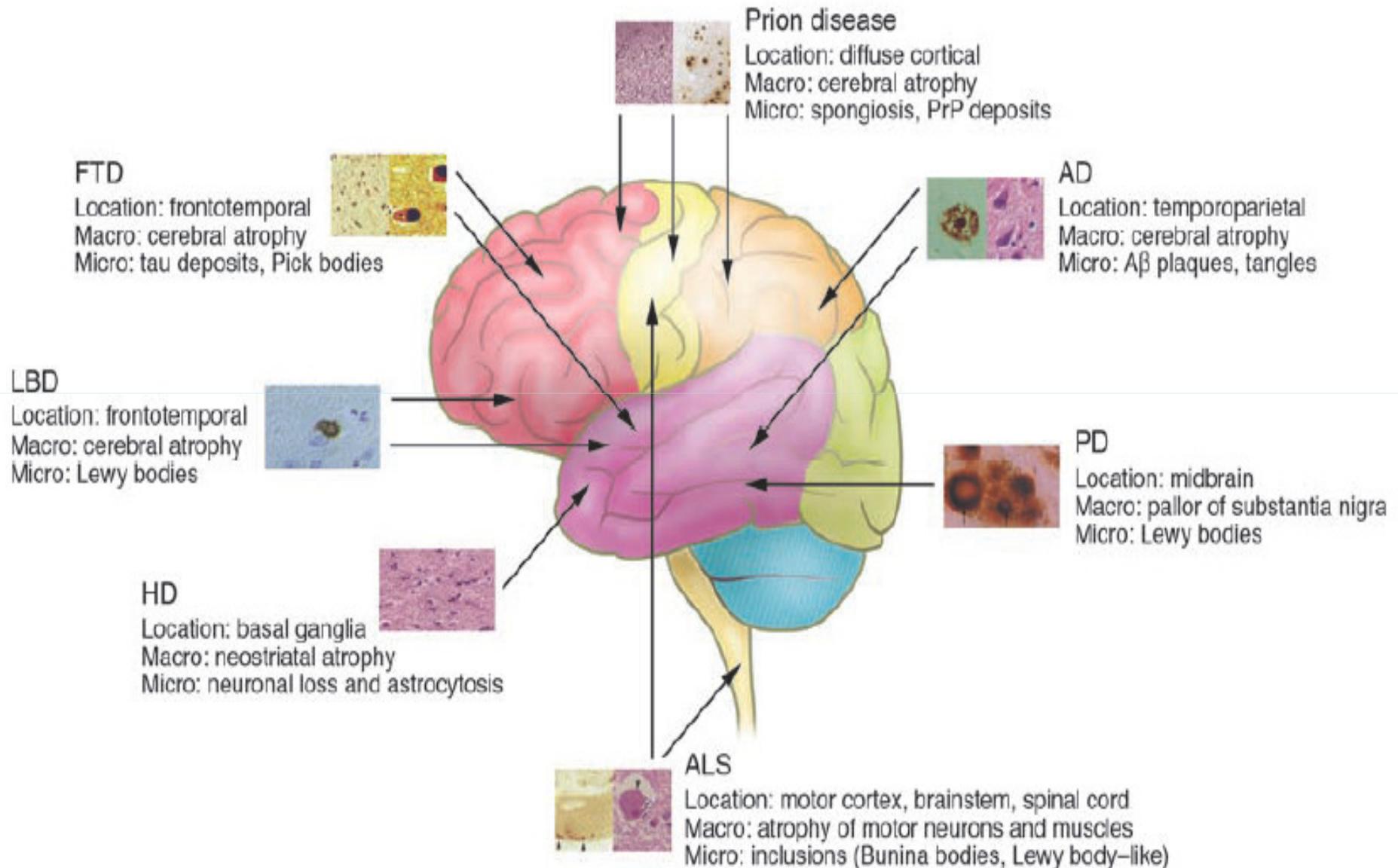
**La neuropatologia non distingue le forme di origine
genetica da quelle a eziologia ignota**

Aggregazione proteica ruolo causale comune

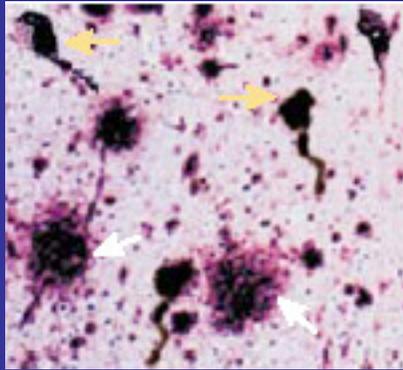
Patologia e caratteristiche biochimiche

<i>Malattia</i>	<i>Regione cerebrale coinvolta</i>	<i>Proteina degli aggregati</i>	<i>Localizzazione</i>
Alzheimer	ippocampo Cx cerebrale	β -amyloide tau	Extracellulare citoplasmatica
Parkinson	Sostanza nera	α -synuclein	Citoplasmatica
Huntington	Striato Cx Cerebrale	Huntingtin	Nucleare
SLA	Cx motoria brainstem	SOD1 Neurofilamenti	Citoplasmatica
TSE	Cervelletto cx, and talamo	Prion	Extracellulare

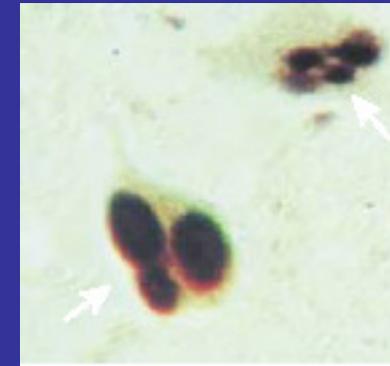
Neurodegenerative disorders



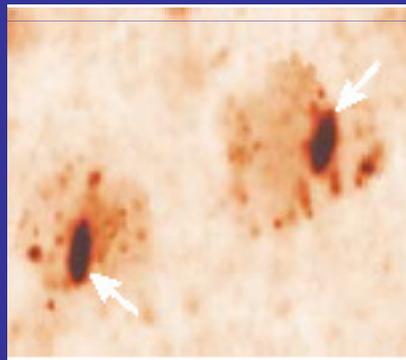
L'aggregazione proteica come tratto comune



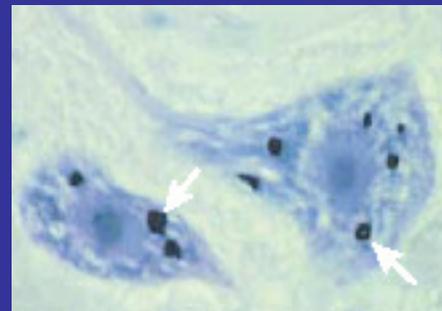
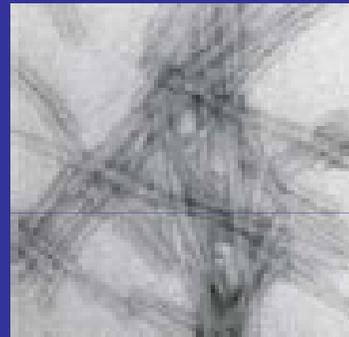
Placche e grovigli
Neurofibrillari in Alzheimer



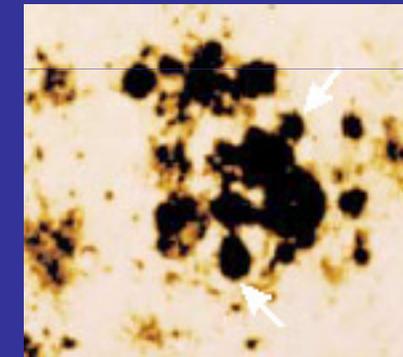
Corpi di Levi nel
Parkinson



Inclusioni intranucleari
di huntingtin



Aggregati nella SLE



Placche di amiloide

Cenni storici sulla demenza di Alzheimer

1906 Alzheimer descrive per la prima volta la malattia

1963-1966 Le demenze di tipo neurodegenerativo sono prevalenti rispetto a quelle di natura vascolare (arteriosclerosi)

1970-75 AD e Demenza senile vengono congiunti in un'unica entità nosografica AD *early* e *late onset*

1976 Davies & Maloney identificano un danno specifico del sistema colinergico corticale in AD

1984 Criteri NINCDS-ADRDA per definire *probable* and *possible* Alzheimer

1984 Estrazione purificazione e sequenziamento A β (Glenner)

1986 l'efficacia della tacrina (AChEI, Summers) 1993 FDA

1987 Clonaggio della proteina precursore dell'amiloide (APP)

1991 Prima mutazione APP associata all'Alzheimer

1992 Ipotesi cascata amiloide

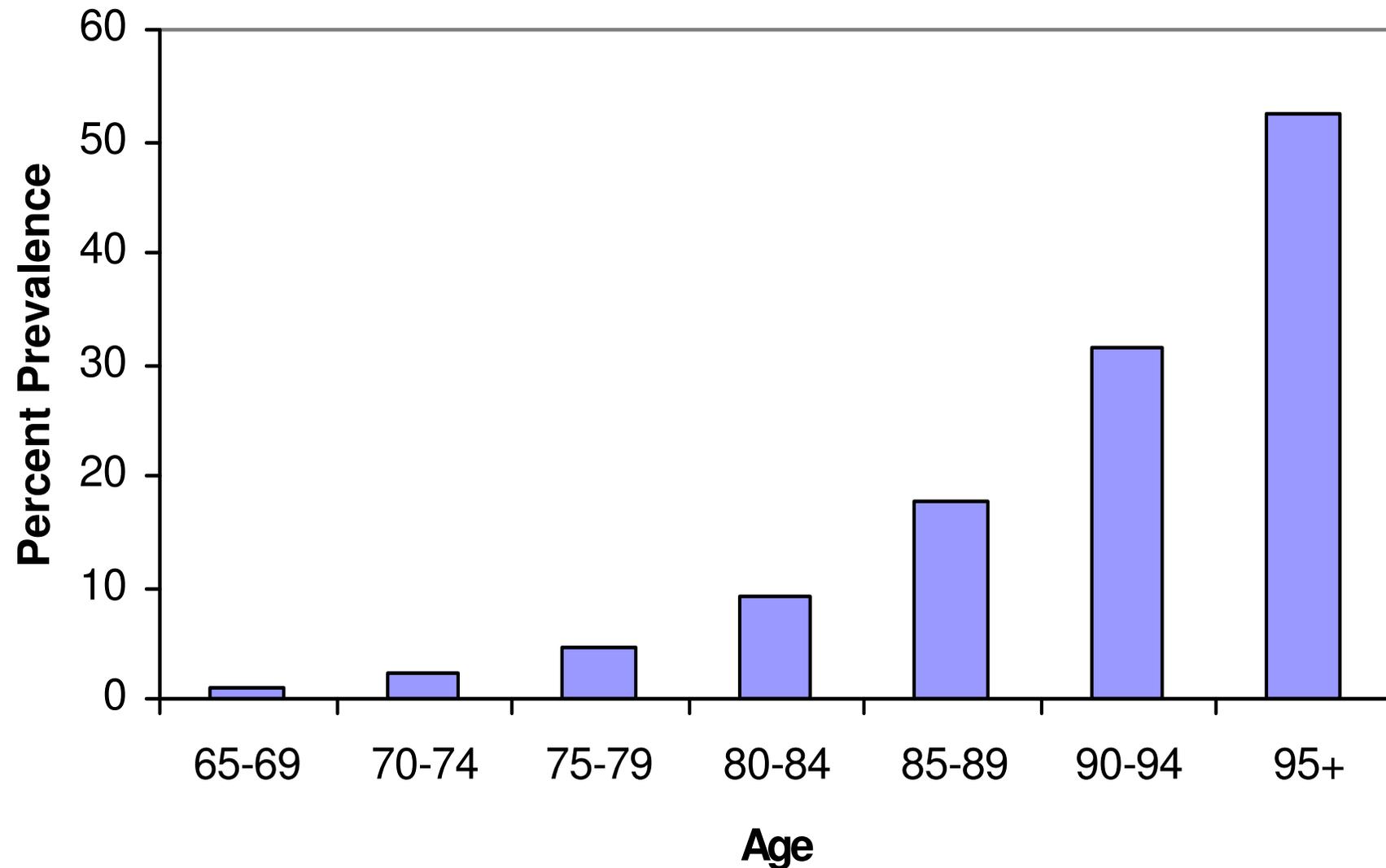
1993 ApoE ϵ 4 fattore di rischio in AD (Roses)

1995 Identificati 2 altri geni associati ad AD, PS1 e PS2

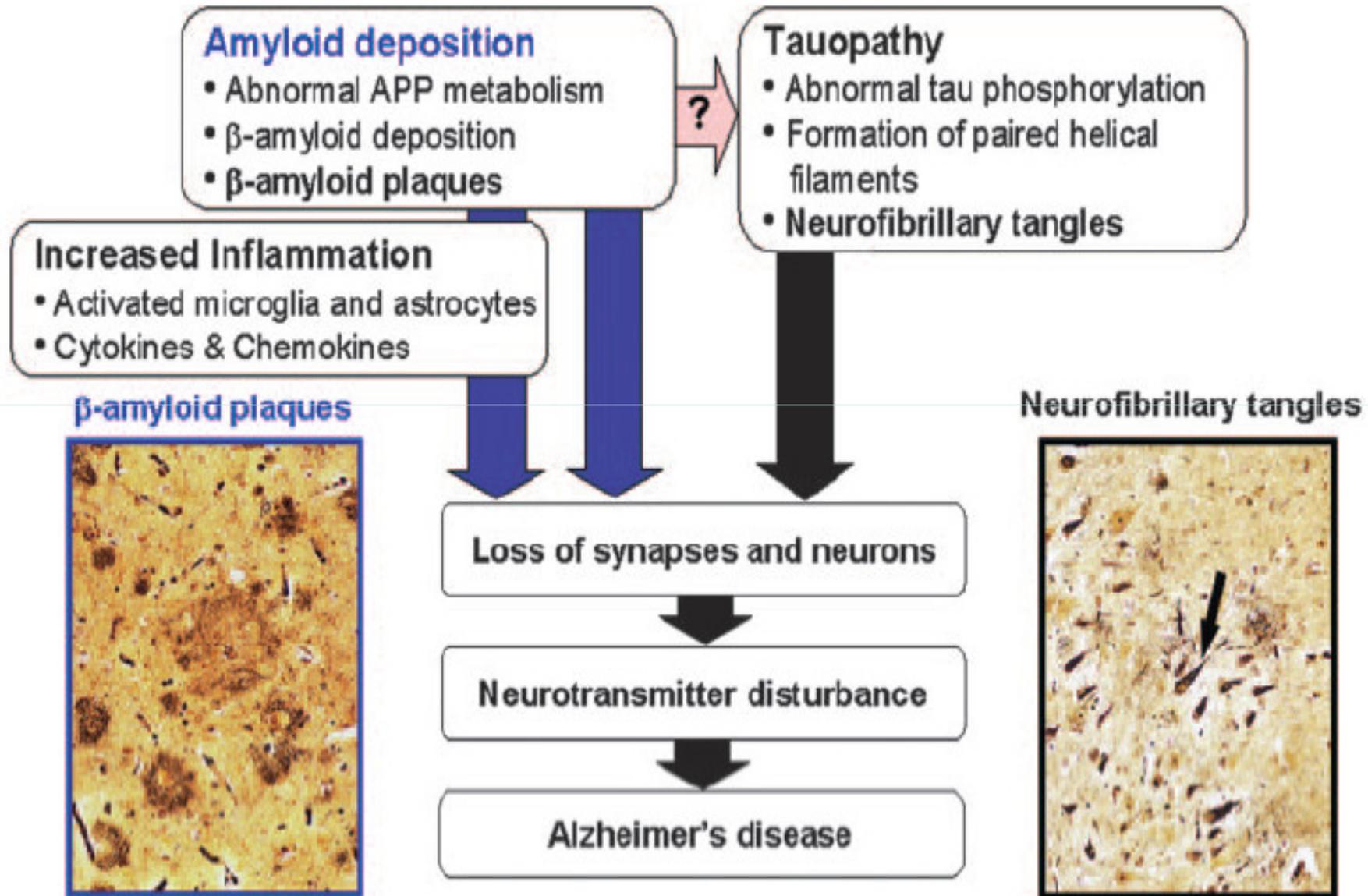
1999 Efficacia Memantina in Alzheimer 2003 FDA, 2004 EMEA

1999 Definizione MCI (Petersen)

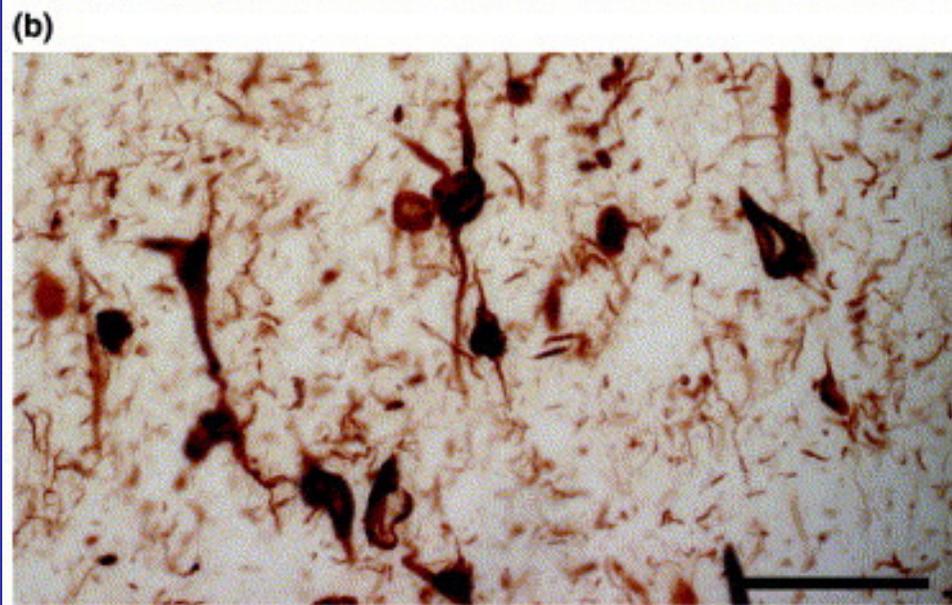
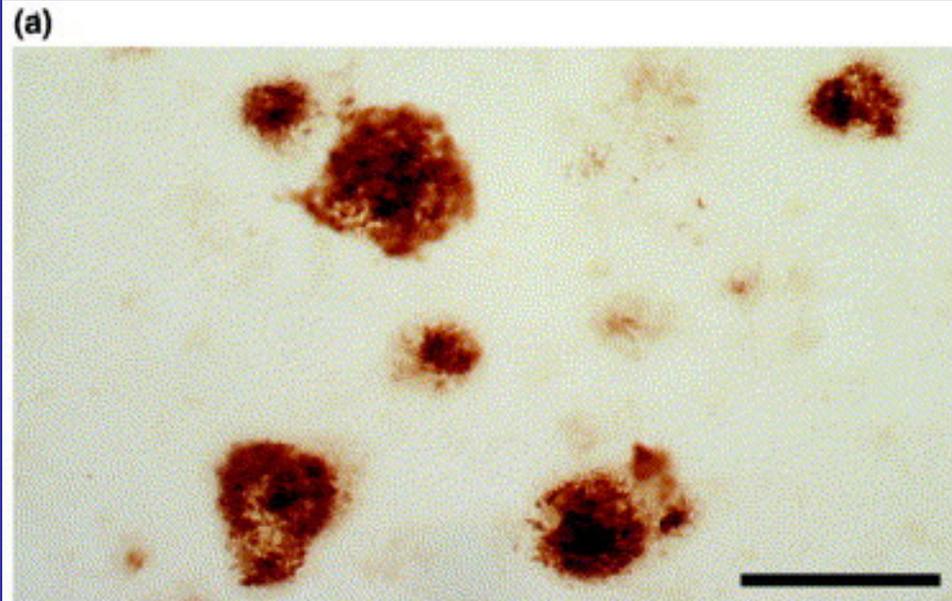
La prevalenza della malattia di Alzheimer è fortemente età dipendente



Neuropatologia della Malattia di Alzheimer



lesioni istologiche



TRENDS in Molecular Medicine

Placche
senili

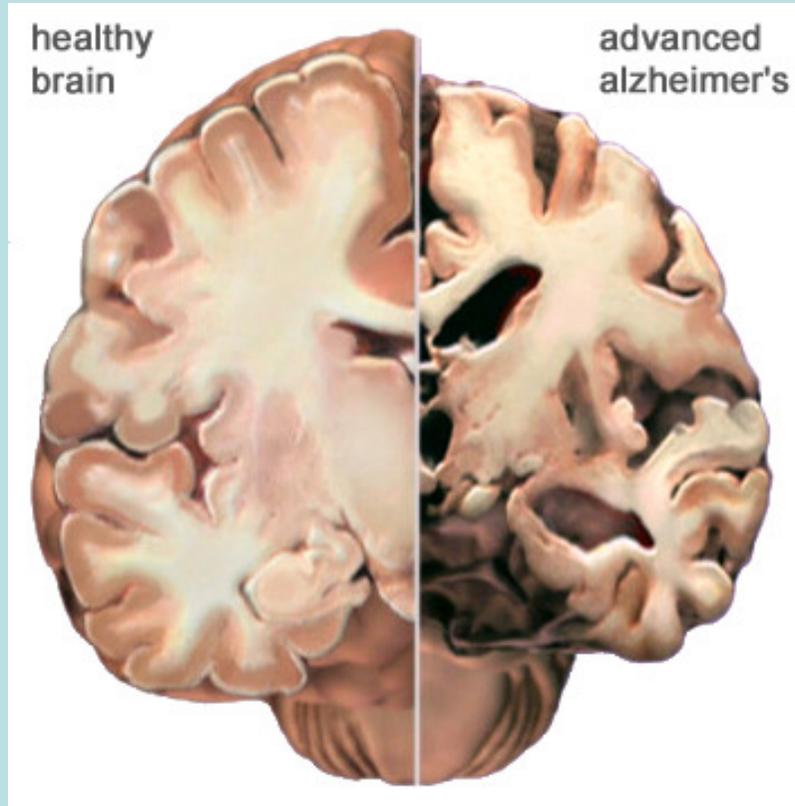
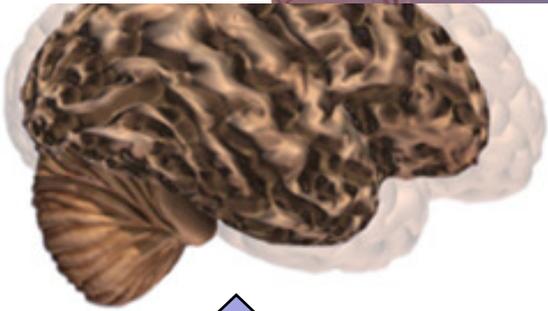
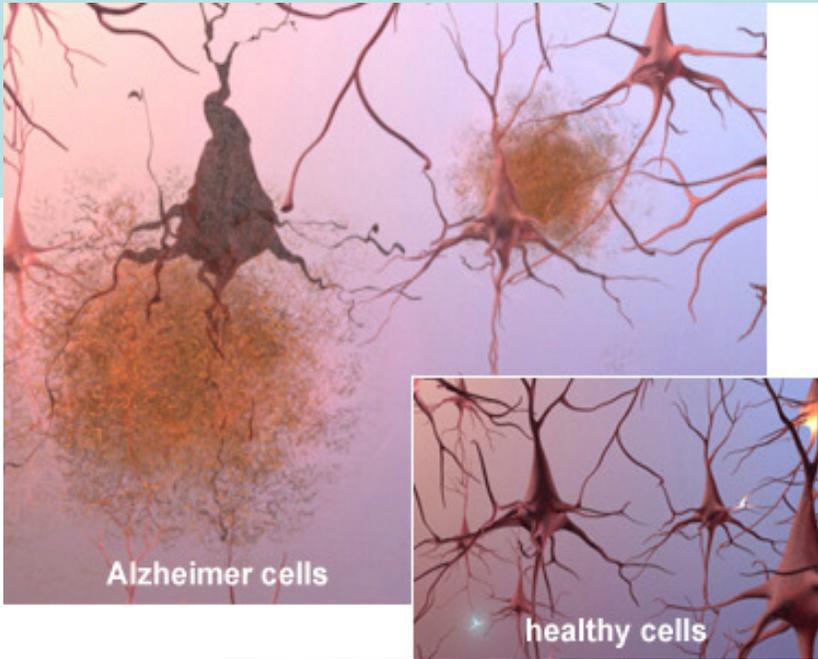
$A\beta_{1-40}$
 $A\beta_{1-42}$



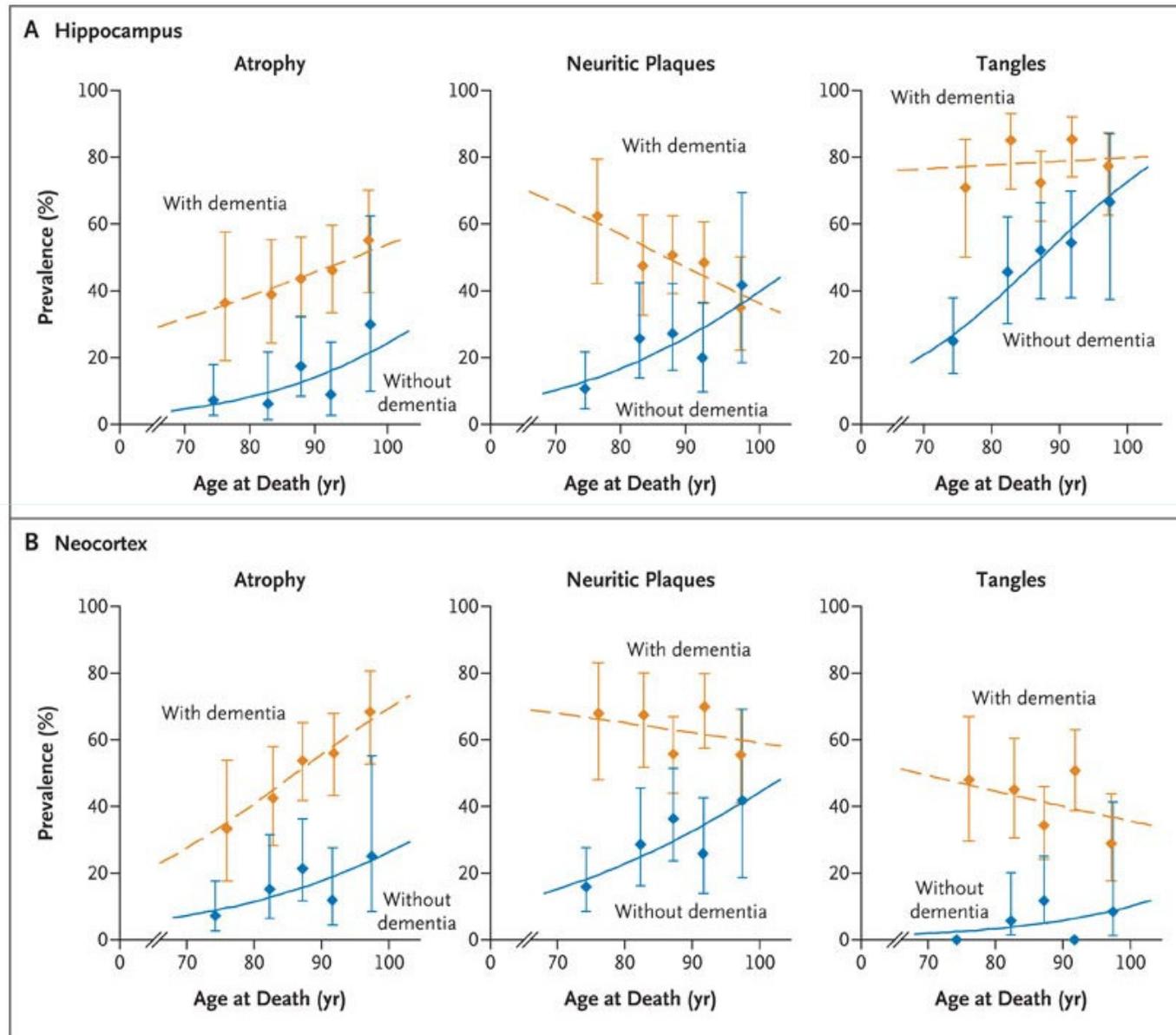
Grovigli
neurofibrillari



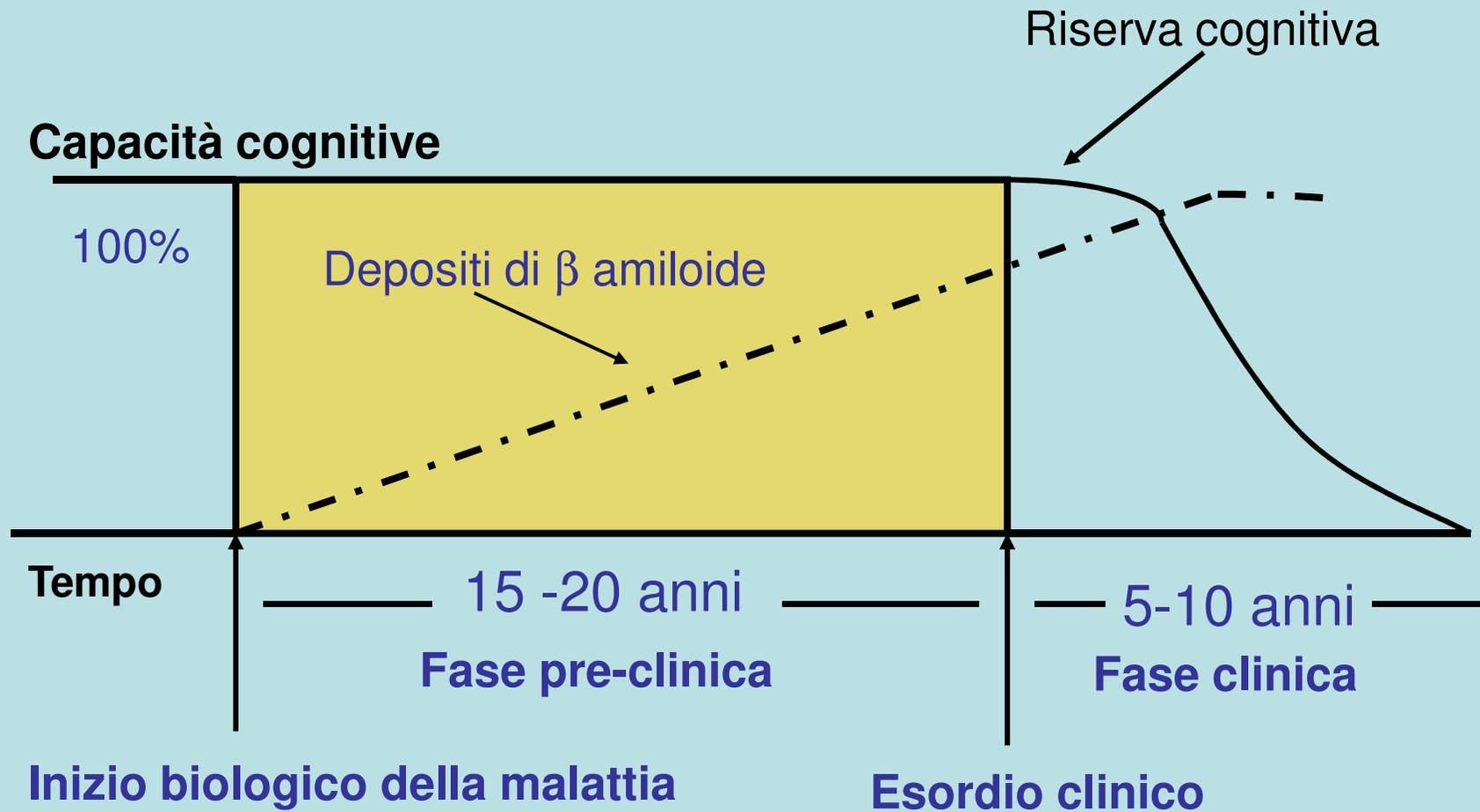
Tau iperfosforilata



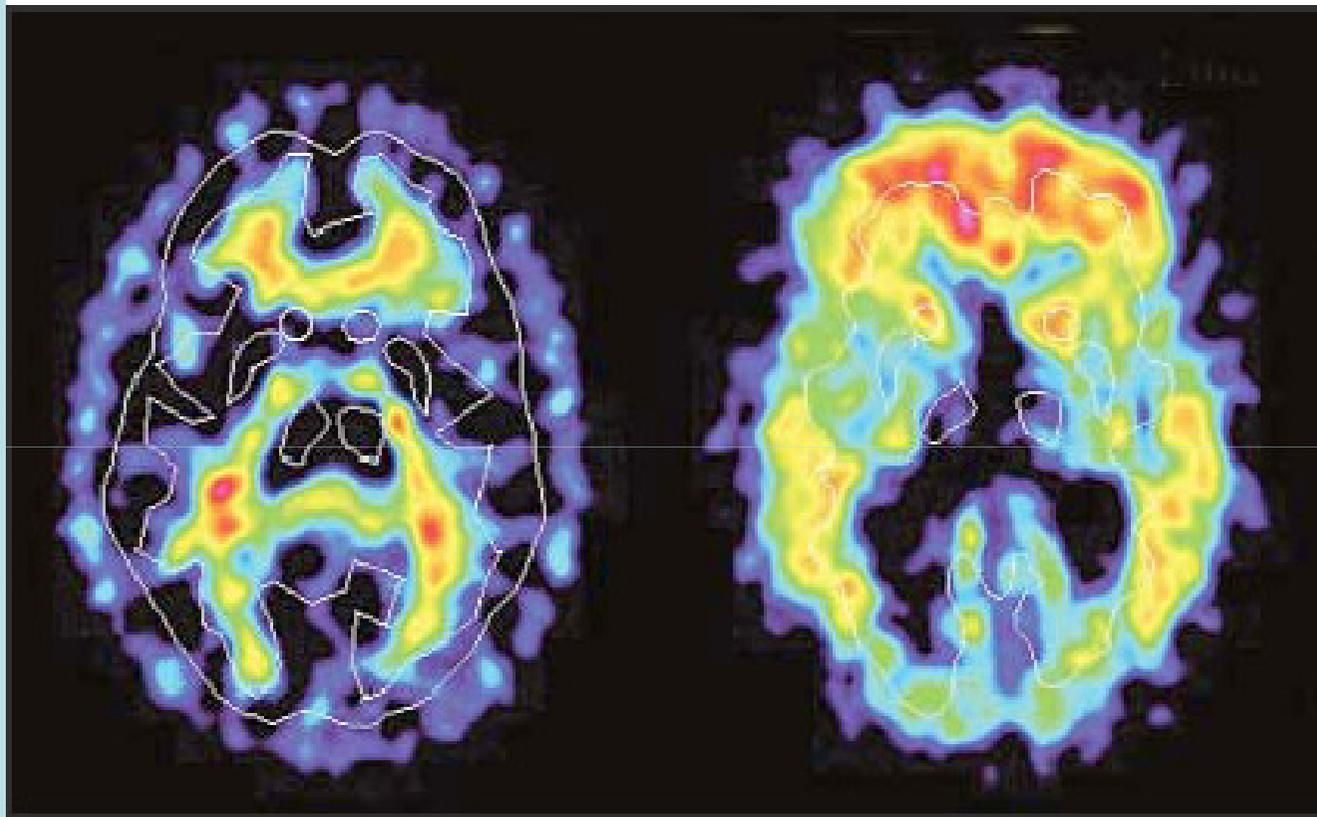
Prevalenza osservata delle lesioni patologiche caratteristiche della AD in funzione dell'età



Fase pre-clinica e clinica della Malattia di Alzheimer



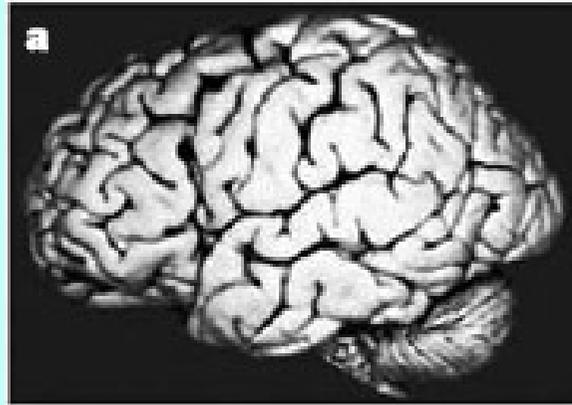
Analisi PET in soggetti AD



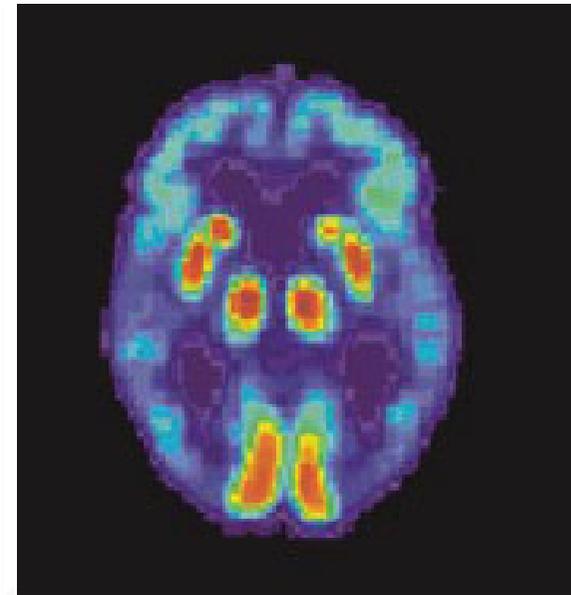
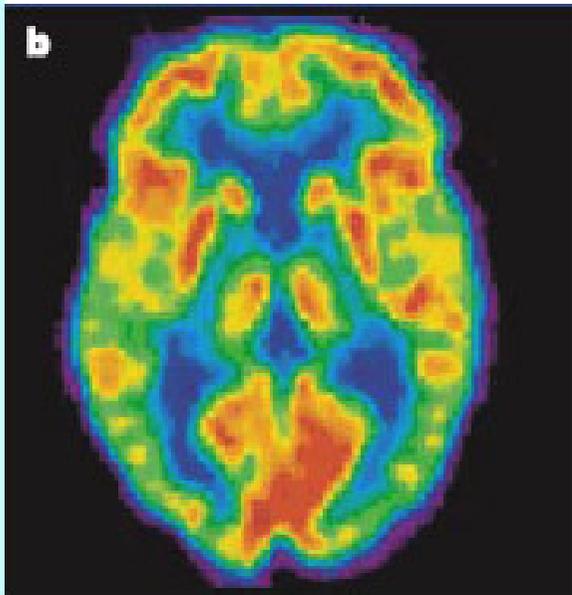
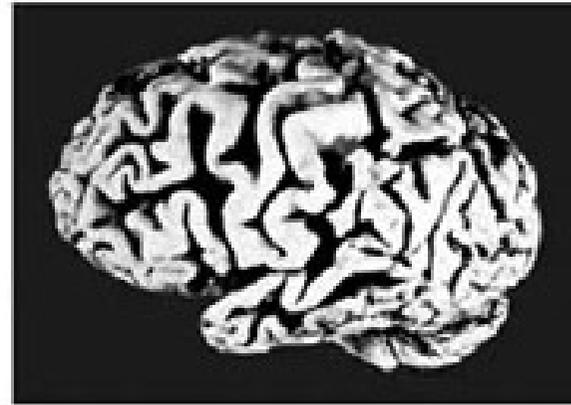
Controllo

AD

Normal brain



Alzheimer's brain



Normal brain

Alzheimer's brain

Pet scans (glucose utilization)

Componente genetica

Fattori di rischio /Fattori protettivi

ApoE ε4

ApoE ε2

Componente ambientale

Esercizio mentale
Esercizio fisico
Scolarità
Socialità

Markers biologici

Abitudini alimentari

Dieta mediterranea
Dieta ipocalorica



Profilo di rischio/protezione

Neuroinfiammazione

Markers metabolici

Componente specifica

β amiloide
pTau

Patogenesi dell'Alzheimer

Eventi antecedenti
ambiente genetica



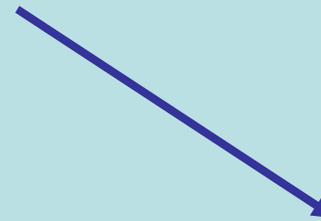
Produzione di $A\beta$, eliminazione aggregazione



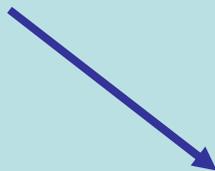
Stress ossidativo



Disfunzione sinaptica



Danno alla plasticità
e alla neurogenesi

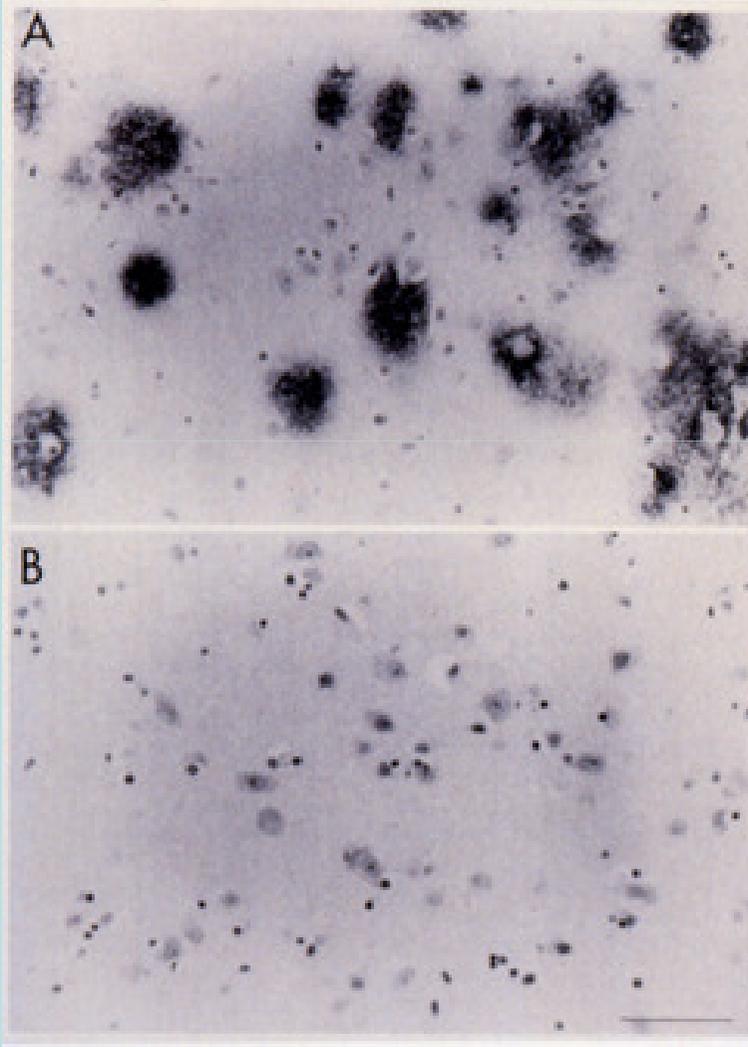


Formazione di NFT & apoptosi



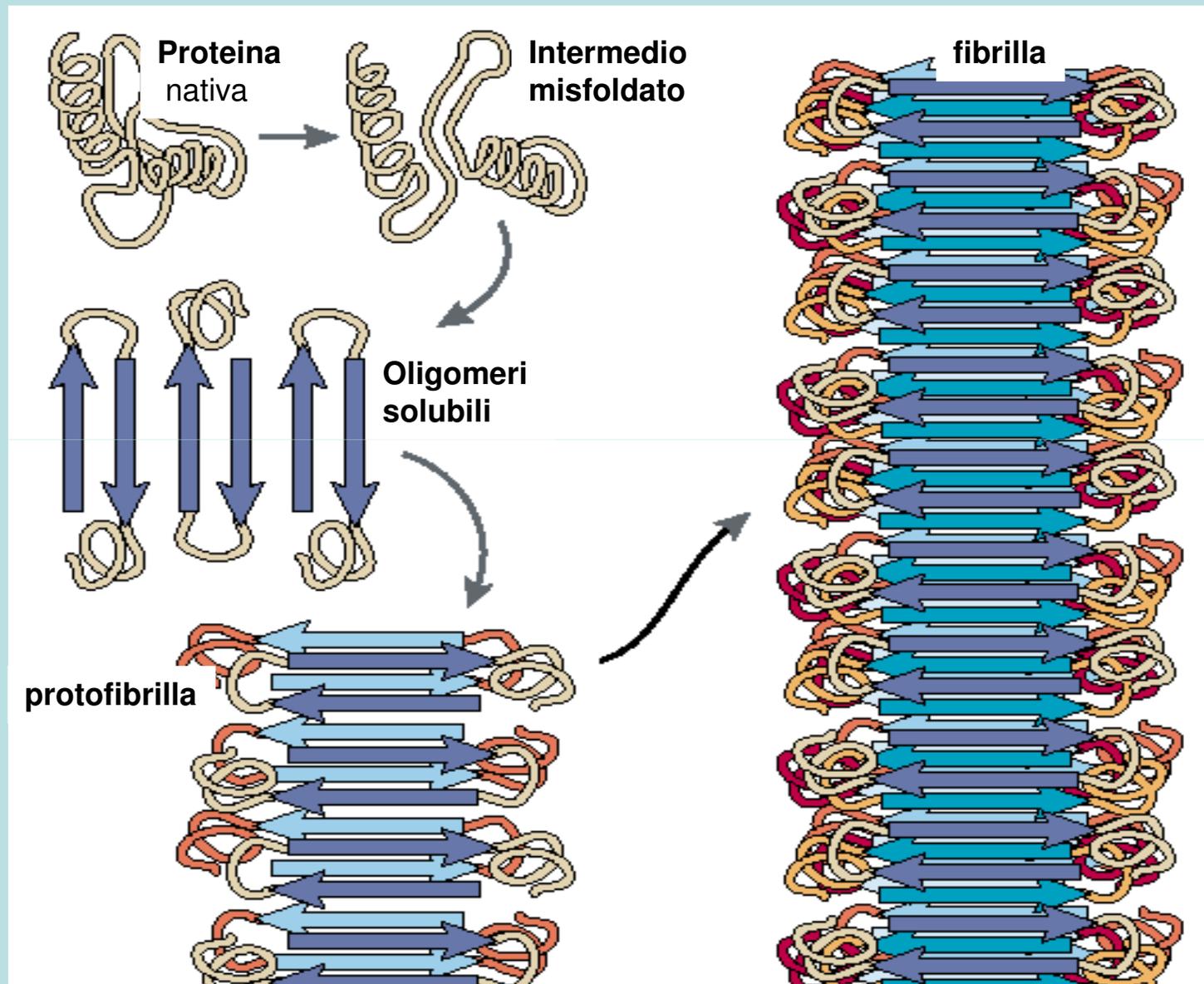
I depositi di β amiloide precedono le altre alterazioni

$A\beta_{42}$ deposition precedes other changes in PS-1 Alzheimer's disease



Lippa et al, Lancet 1998

Le diverse forme di proteina β amiloide

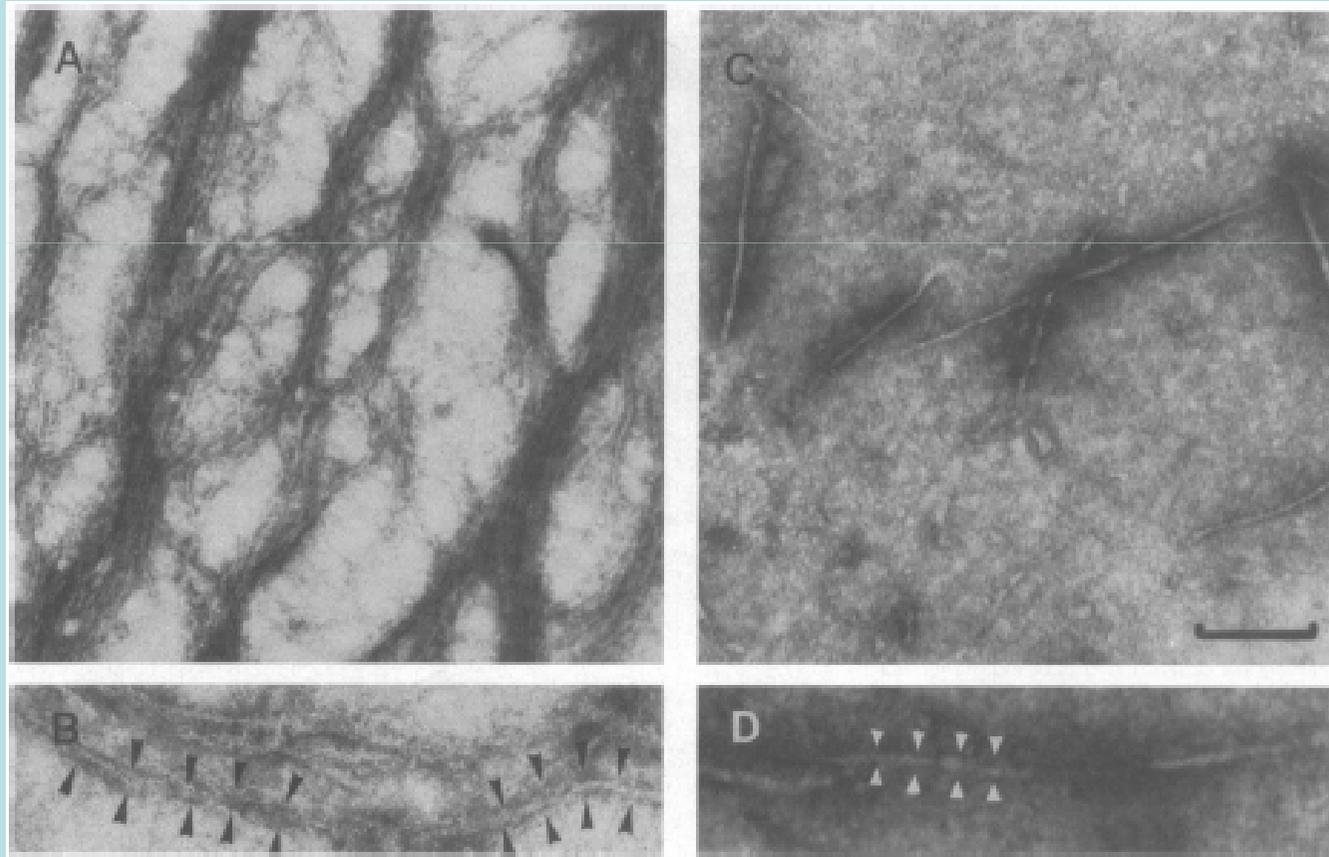


L'amidazione riduce la capacità di produrre fibrille del peptide β amiloide

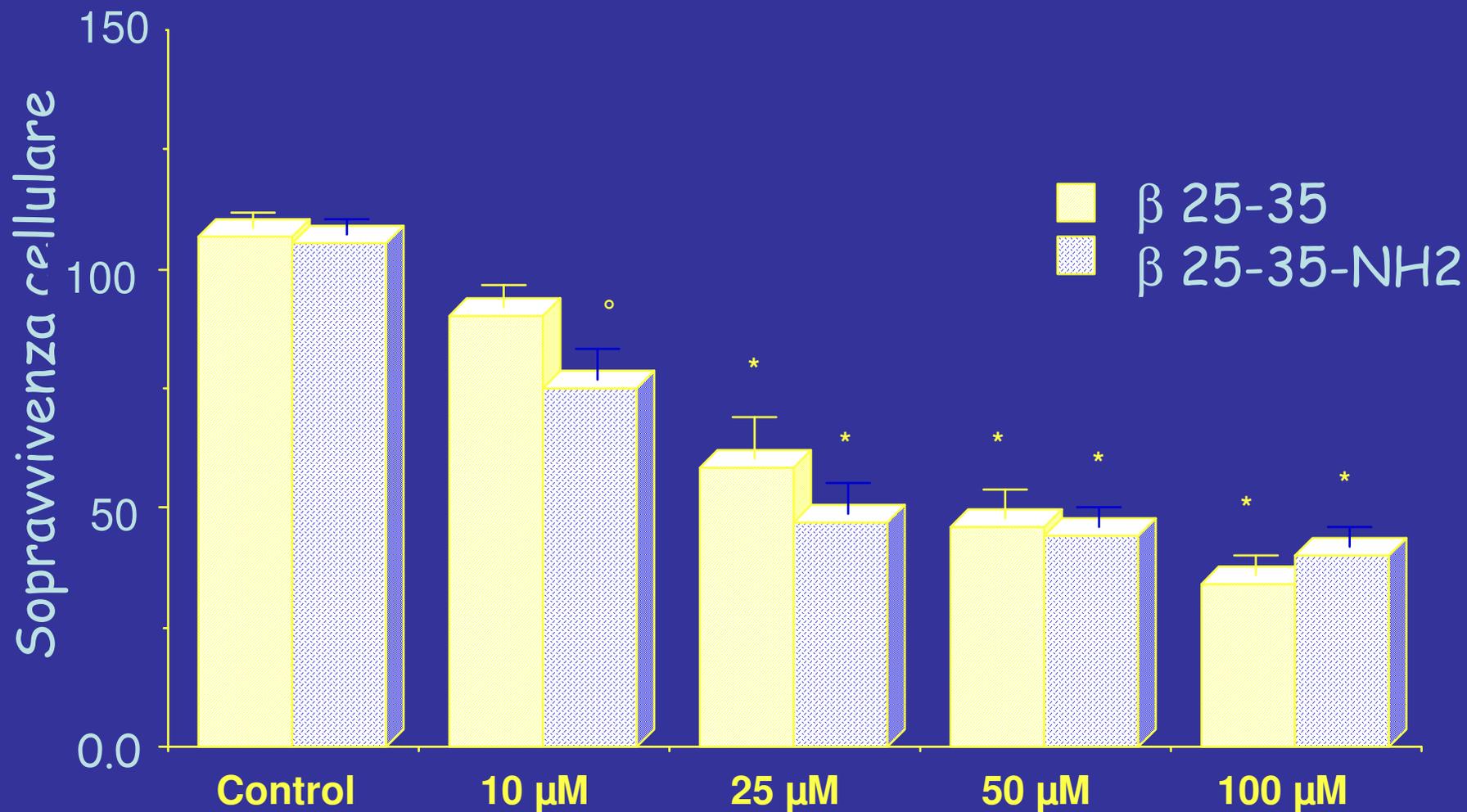
Forloni et al J. Neurochem. 1997

β 25-35

β 25-35-NH₂



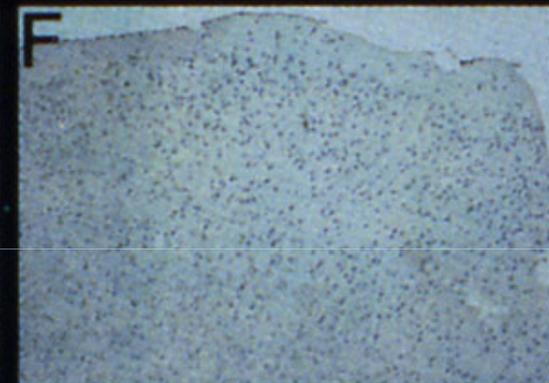
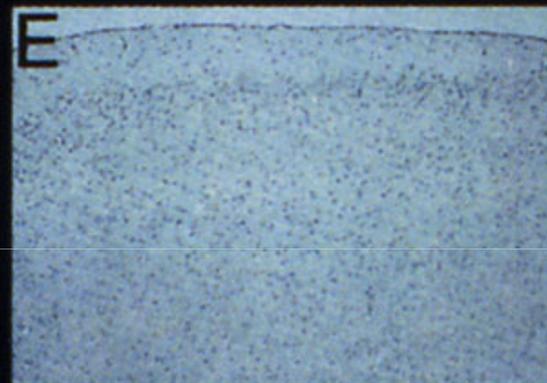
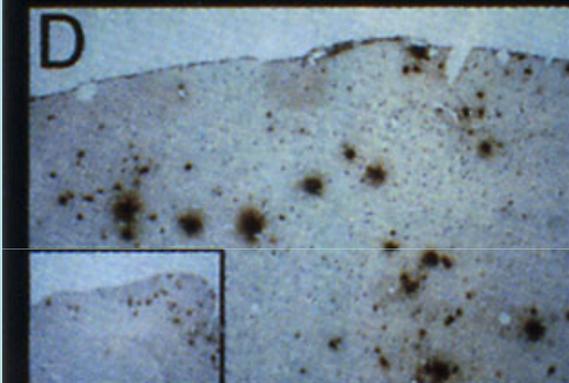
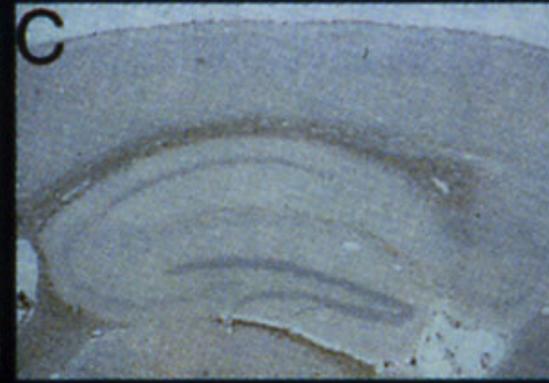
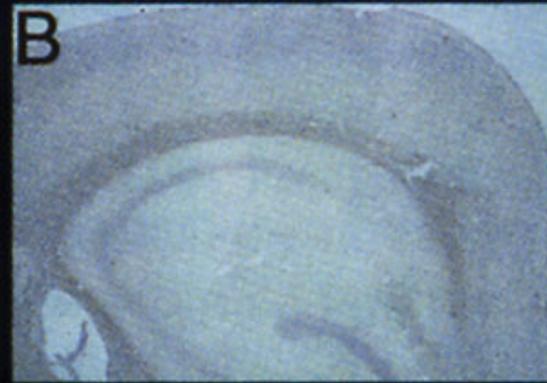
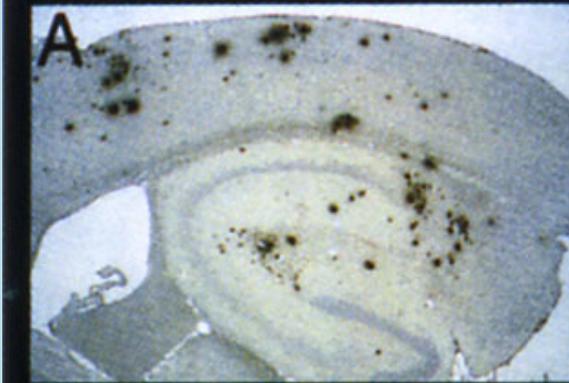
Anche con poche fibrille la β amiloide è tossica



APP swe X PS1-A246E

APP swe

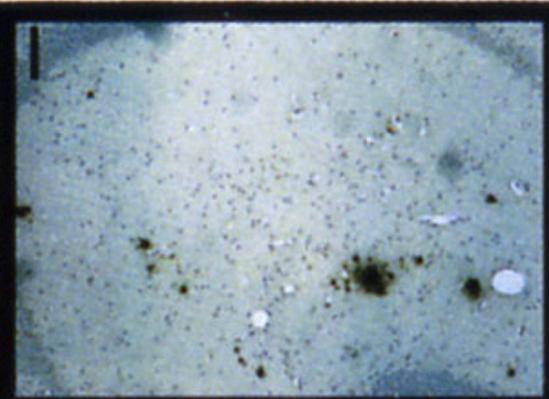
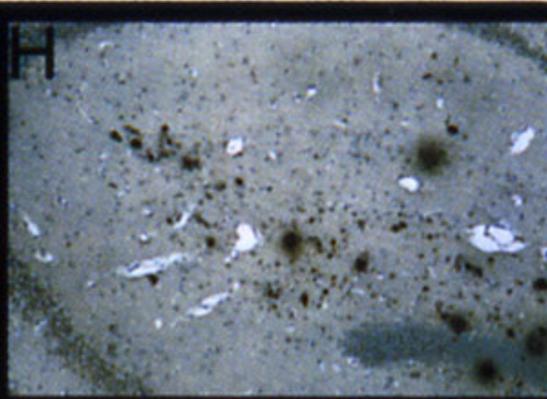
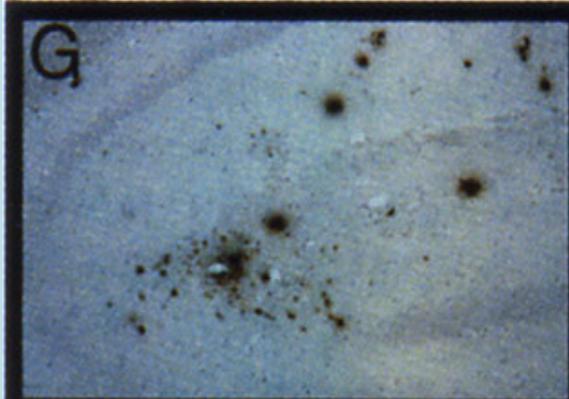
PS1 -A246E



mAb 10D5

mAb 6E10

mAb 4G8

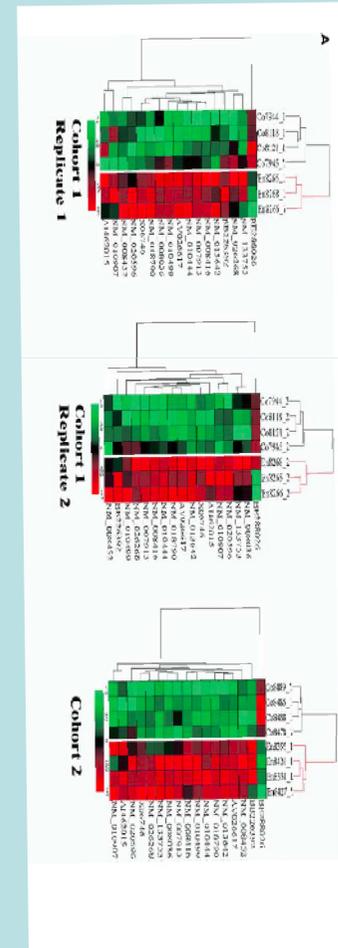
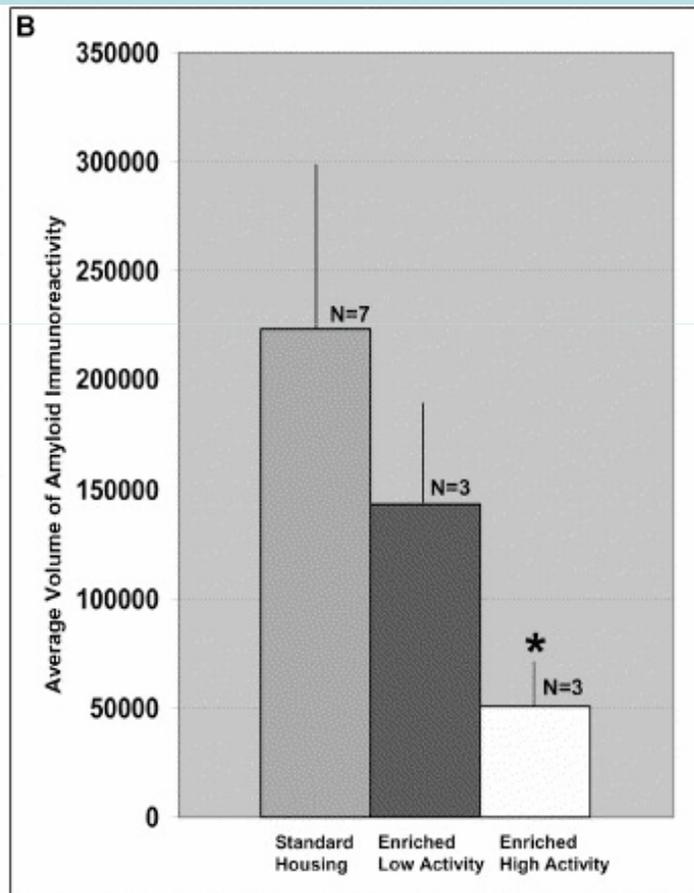


Environmental Enrichment Reduces A β Levels and Amyloid Deposition in Transgenic Mice

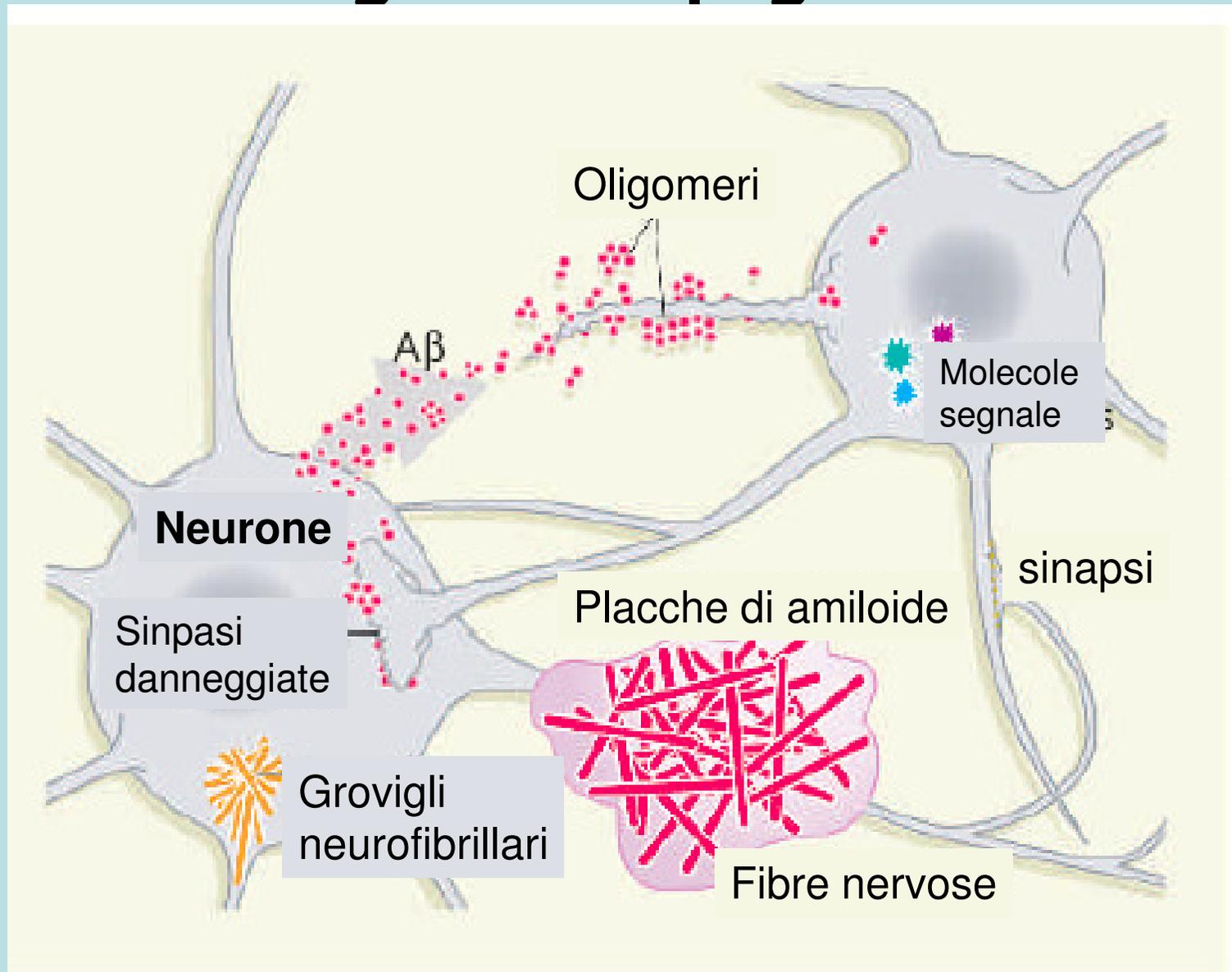
Orly Lazarov¹, John Robinson¹, Ya-Ping Tang², Ilana S. Hairston³, Zeljka Korade-Mirnic⁷, Virginia M.-Y. Lee⁴, Louis B. Hersh⁵, Robert M. Sapolsky³, Karoly Mirnic⁶, , and Sangram S. Sisodia¹,
Cell 120: 701-713, 2005

A

Enrichment	Enriched High activity	Enriched Low activity
% time running	44.3-62.4	<10.9
% time climbing	<0.5	<1
% time resting	<0.1	3.6-33.6



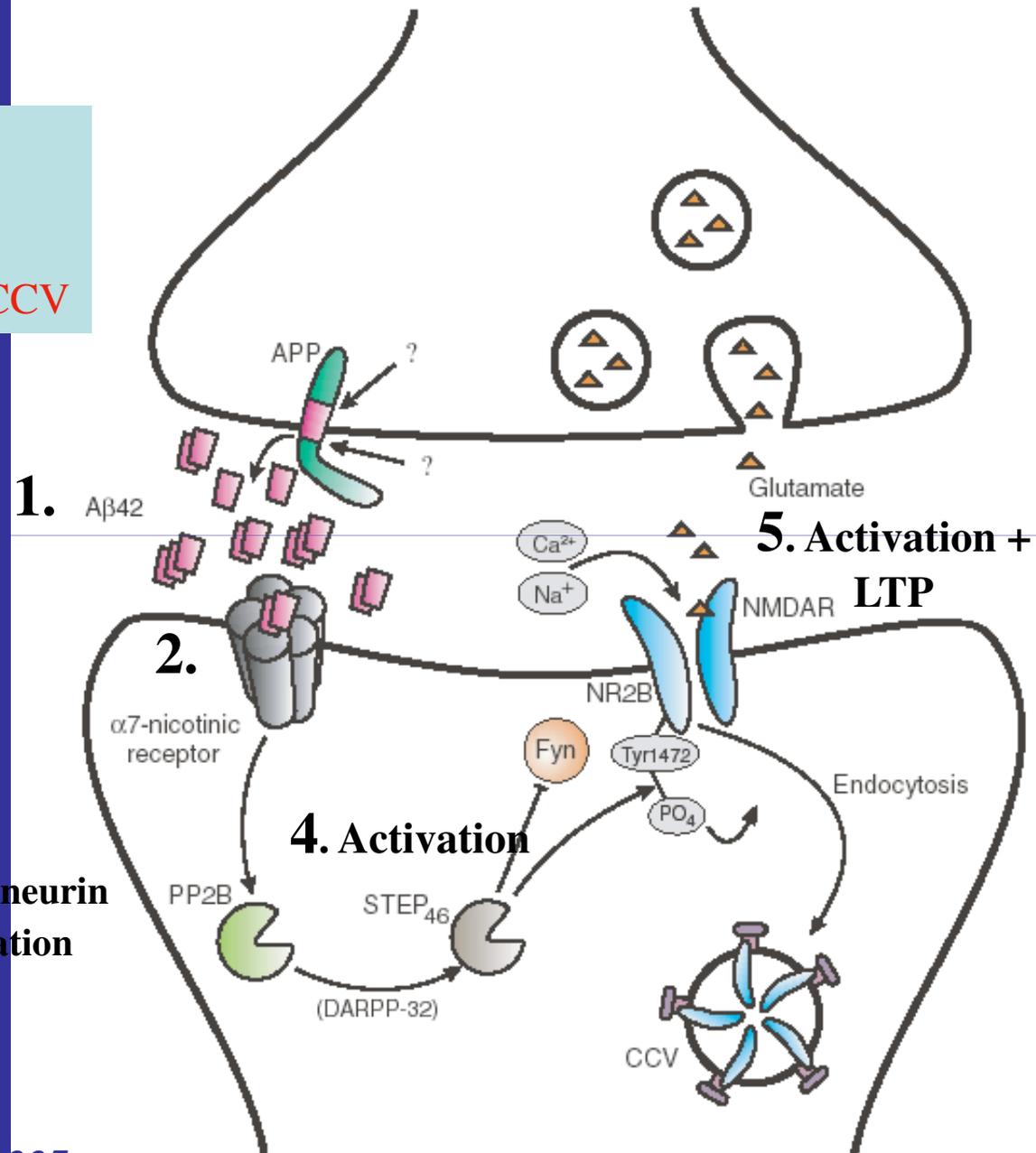
Un ago "dal" pagliaio



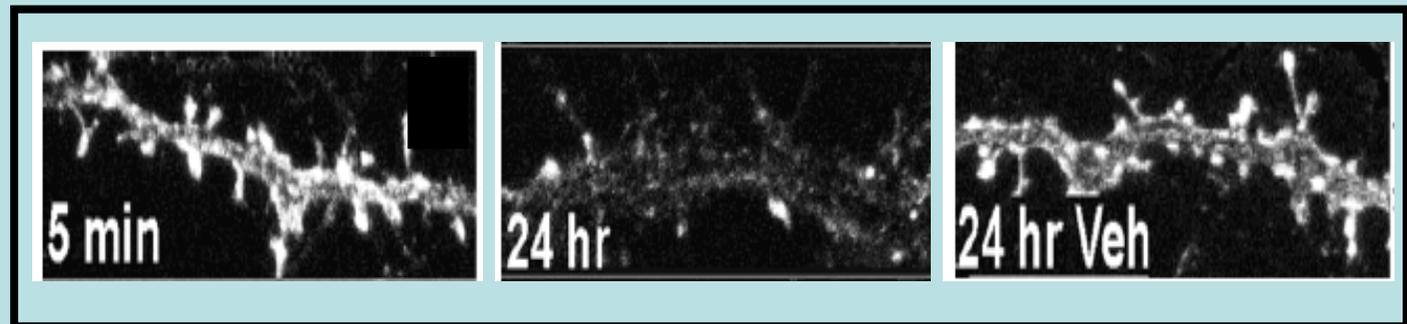
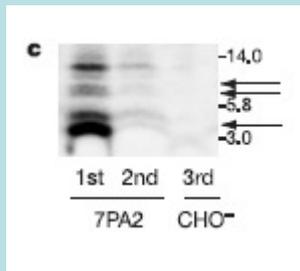
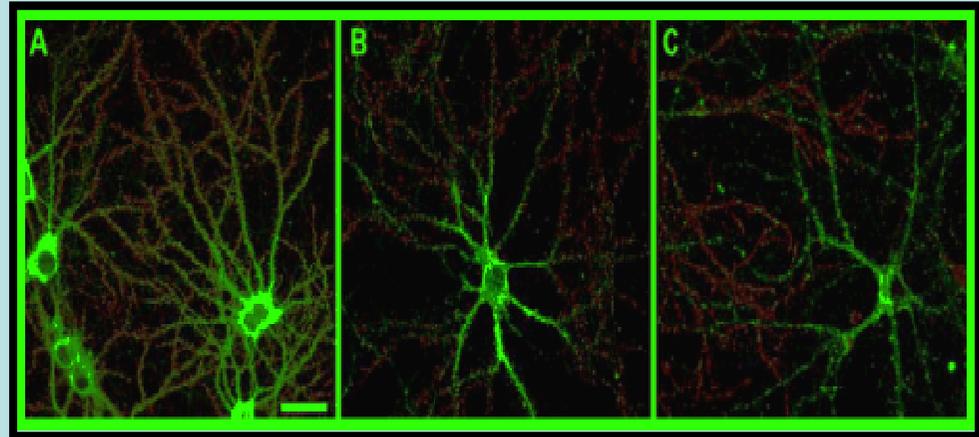
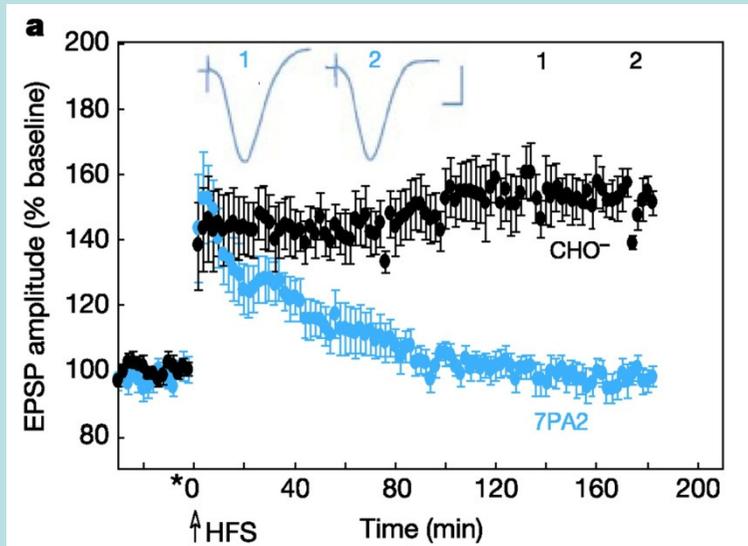
Lesnè et al, Nature, 2006

Effetto di Aβ42 sui recettori NMDA

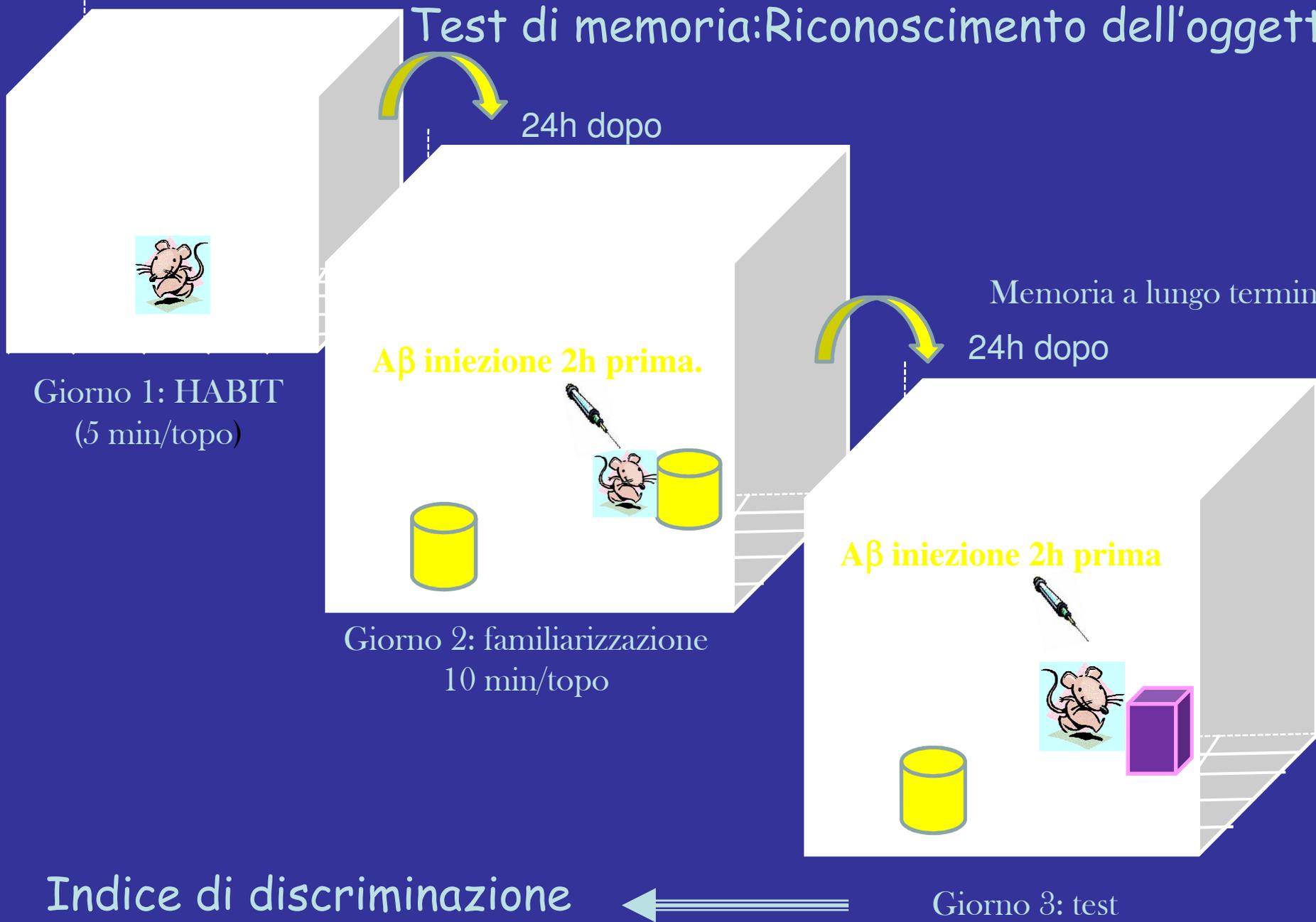
Regola binding NMDAr a PSD-95 e la proteina AP2.
De-P promuovendo
L'endocitosi di NMDAr in CCV



Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. *Nature*. 2002 Apr 4;416(6880):535-9. [Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ.](#)

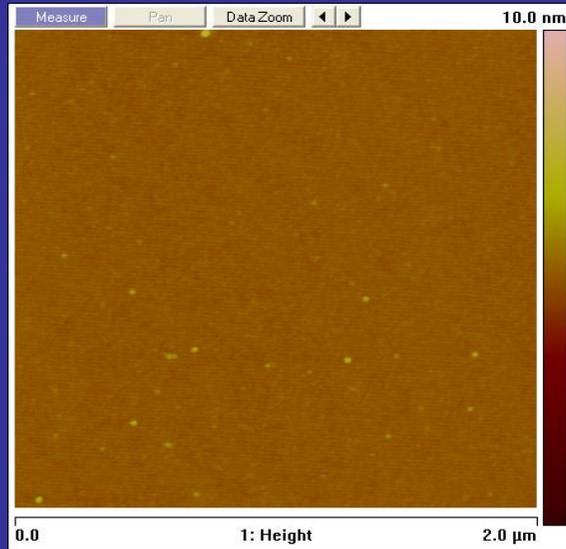


Test di memoria: Riconoscimento dell'oggetto

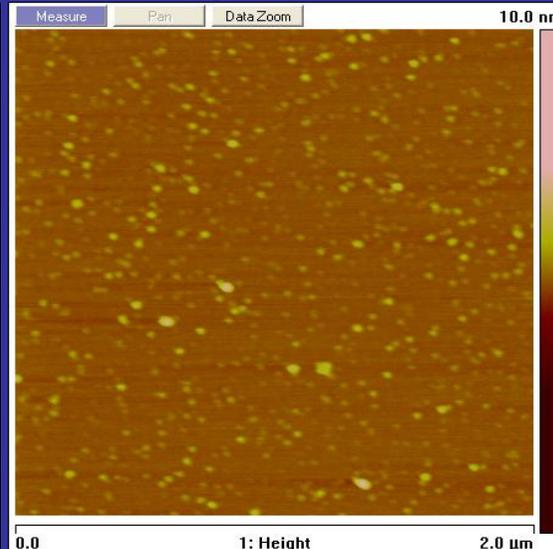


Caratterizzazione $A\beta_{1-42}$

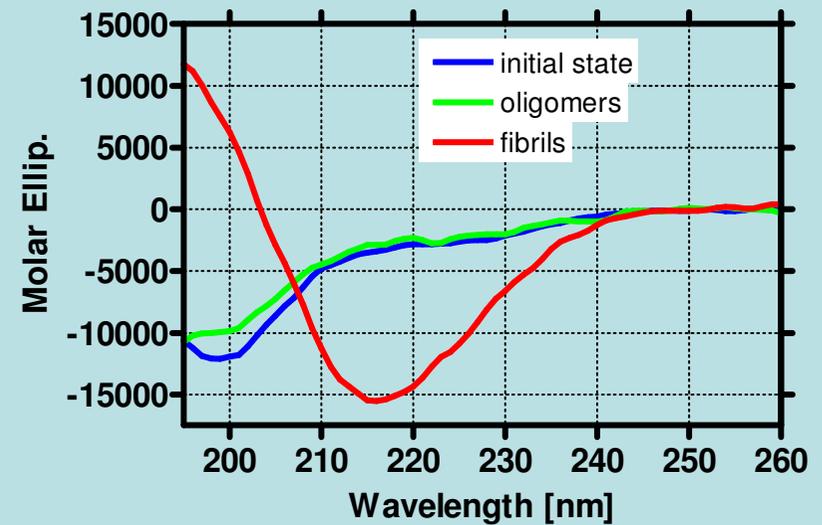
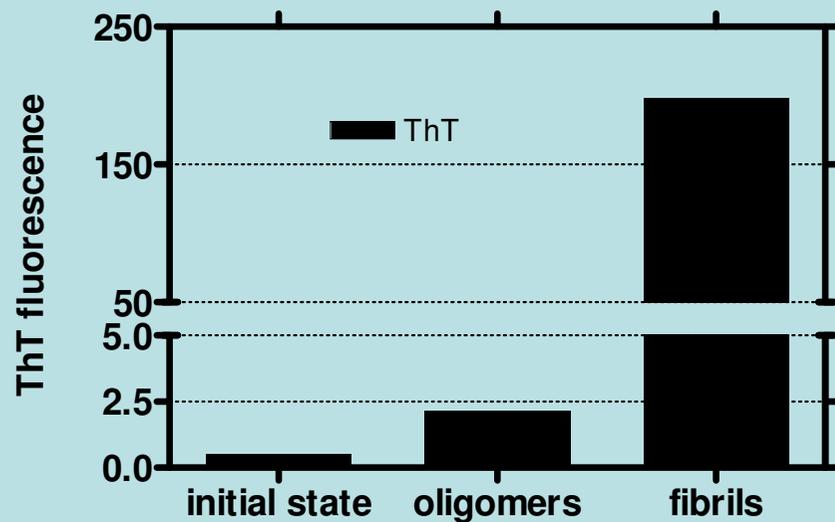
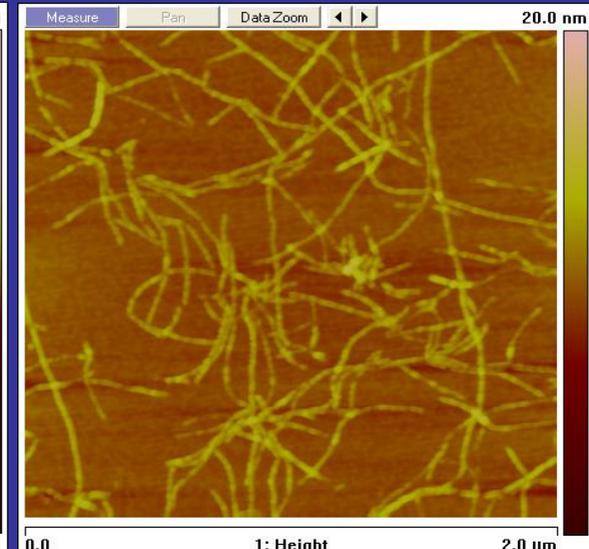
Stato iniziale



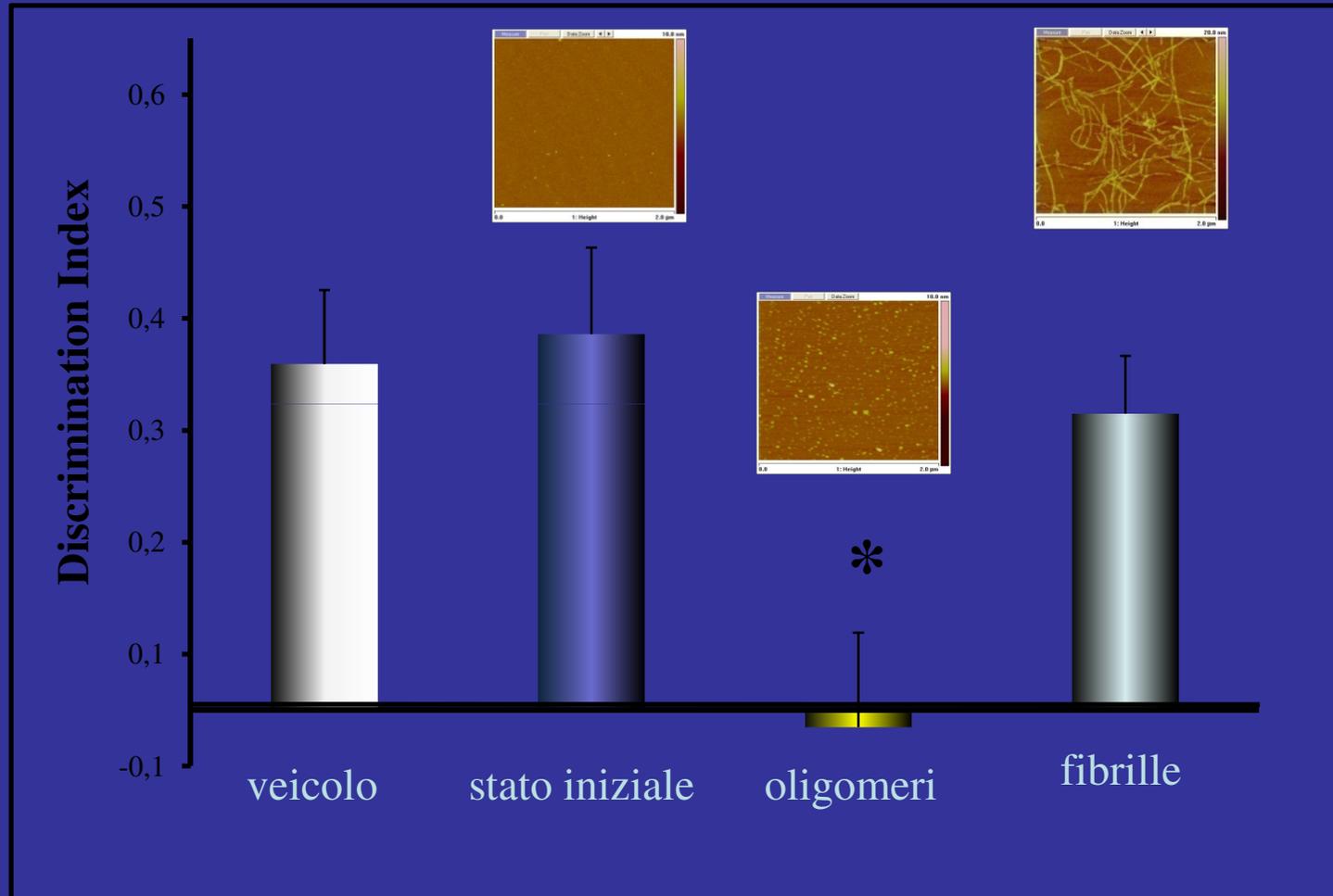
oligomeri



fibrille

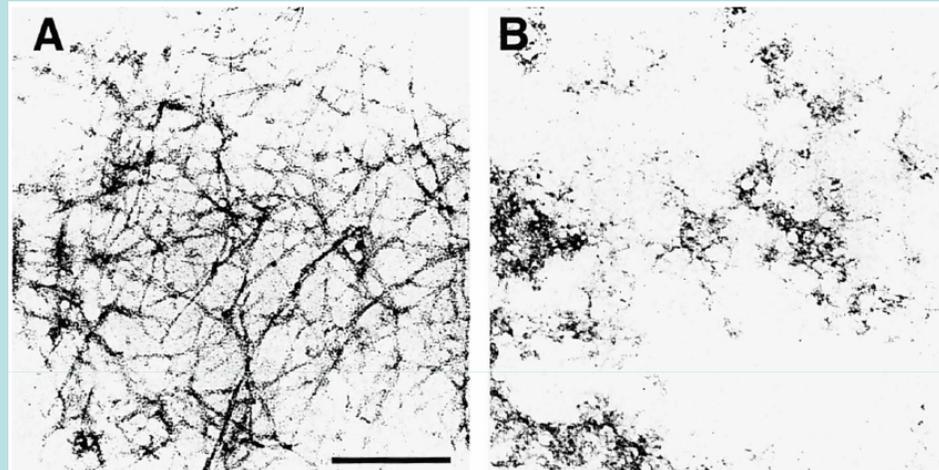


Nel nostro modello sperimentale gli oligomeri $A\beta_{1-42}$ producono un danno specifico alla memoria



Anti-amyloidogenic activity of tetracyclines:studies in vitro

Forloni et al 2001, FEBS letters

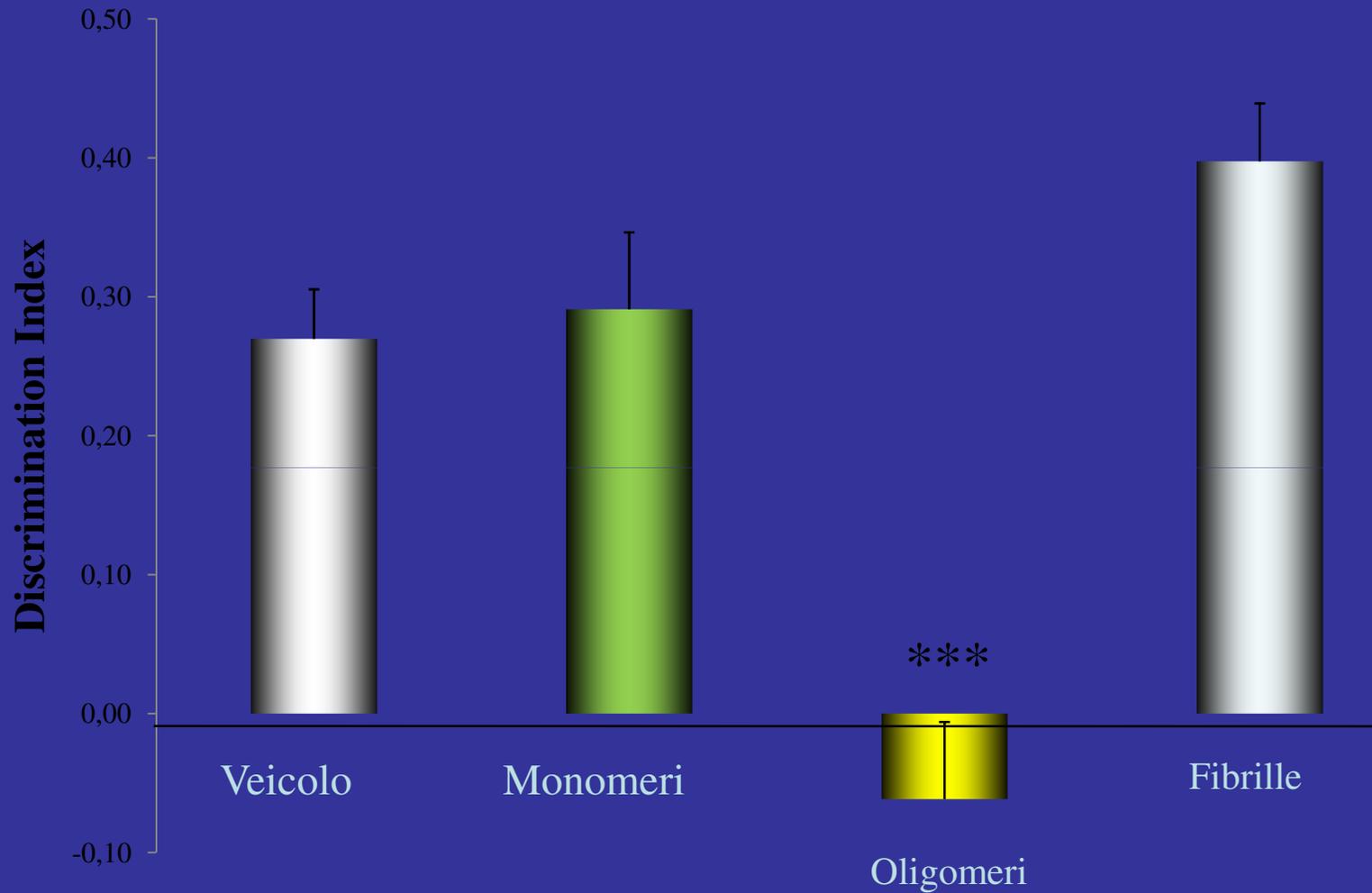


DOXYCYCLINE

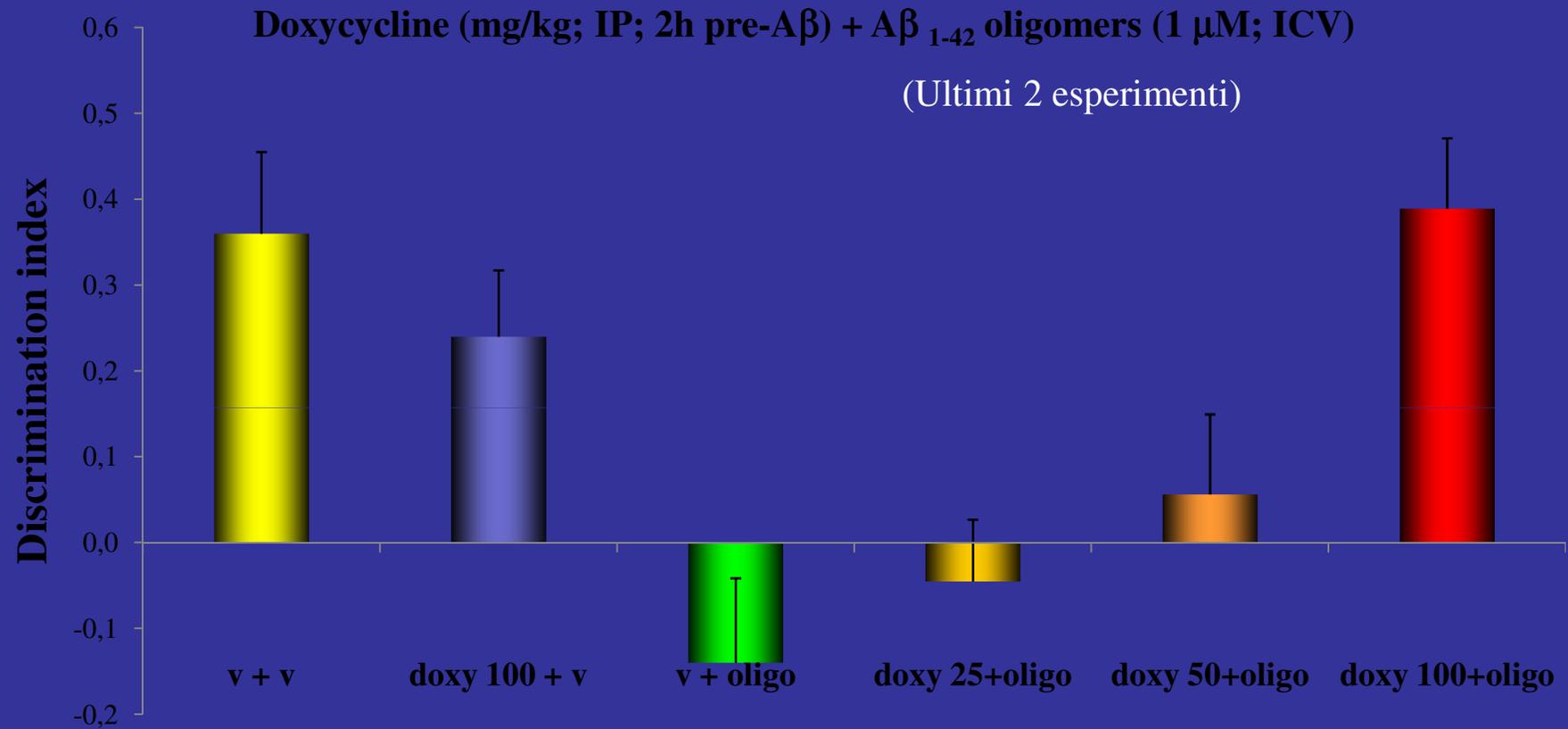
A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease

Loech et al 2006

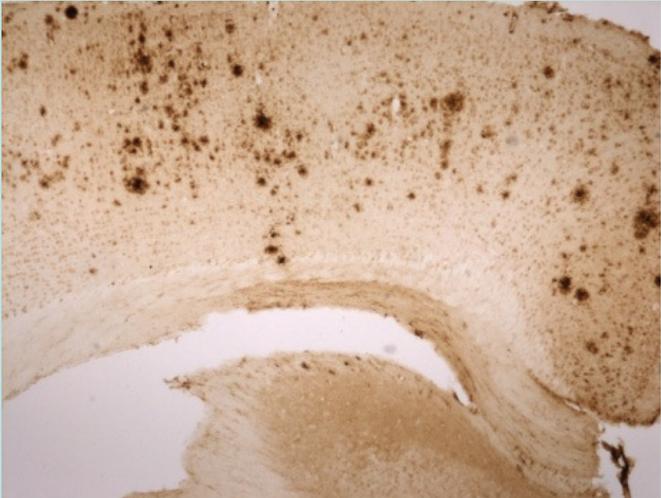
Nel nostro modello sperimentale anche gli oligomeri $A\beta_{1-40}$ producono un danno specifico alla memoria



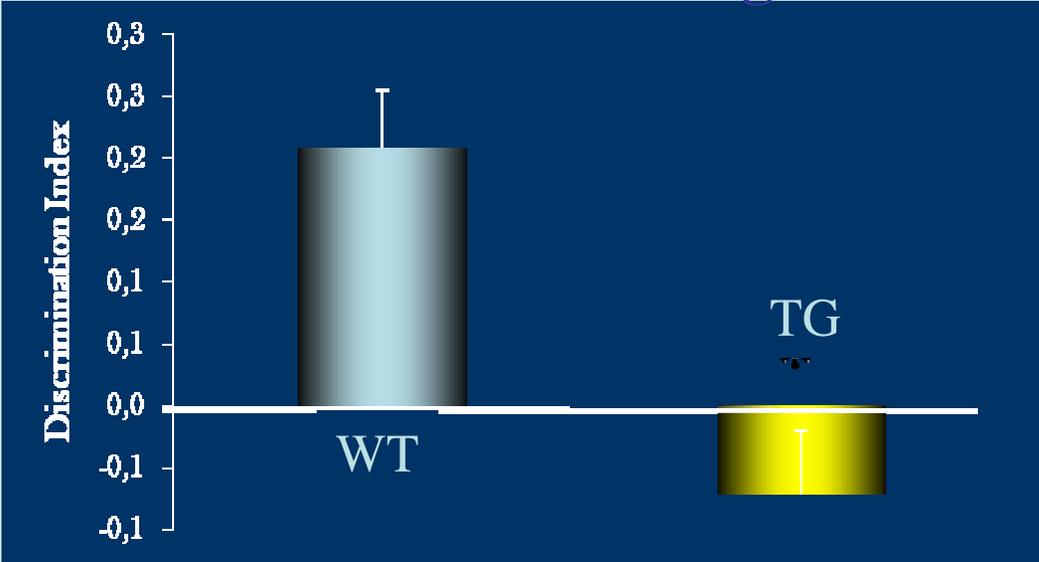
Treatment with doxycycline intraperitoneally



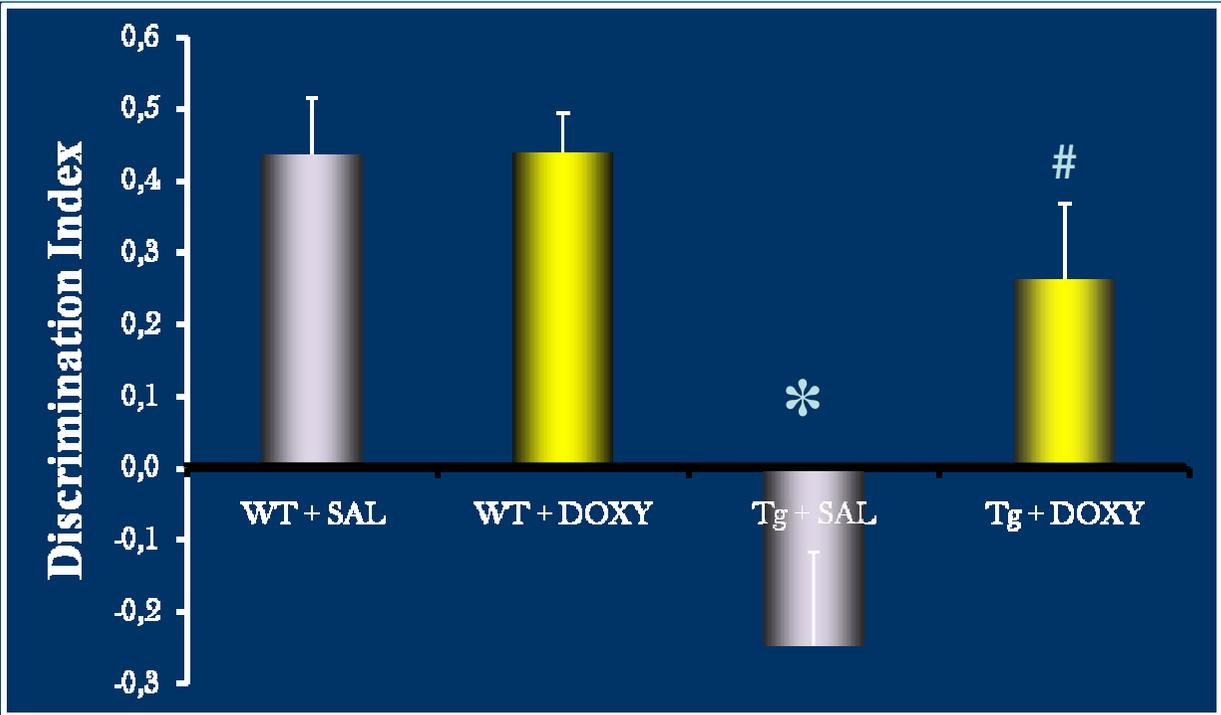
APP/PS1 tg mice



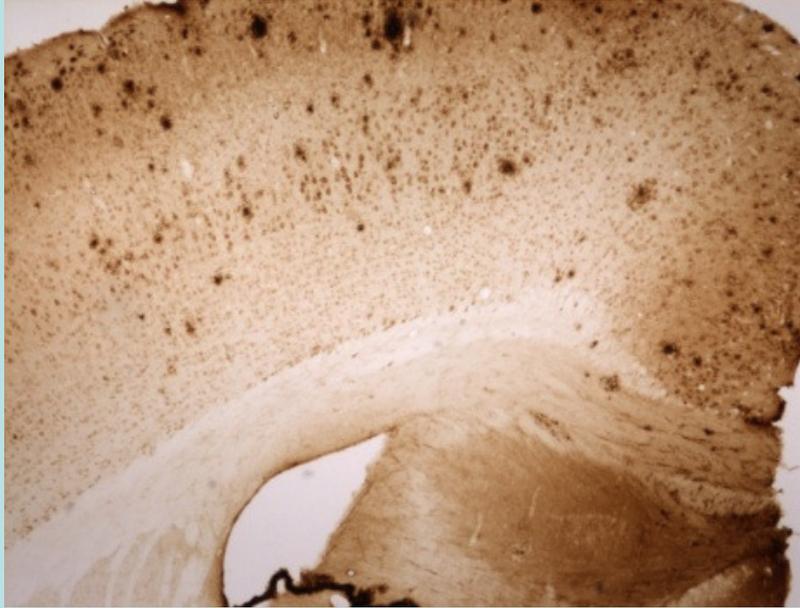
6E10 anti-Aβ antibody



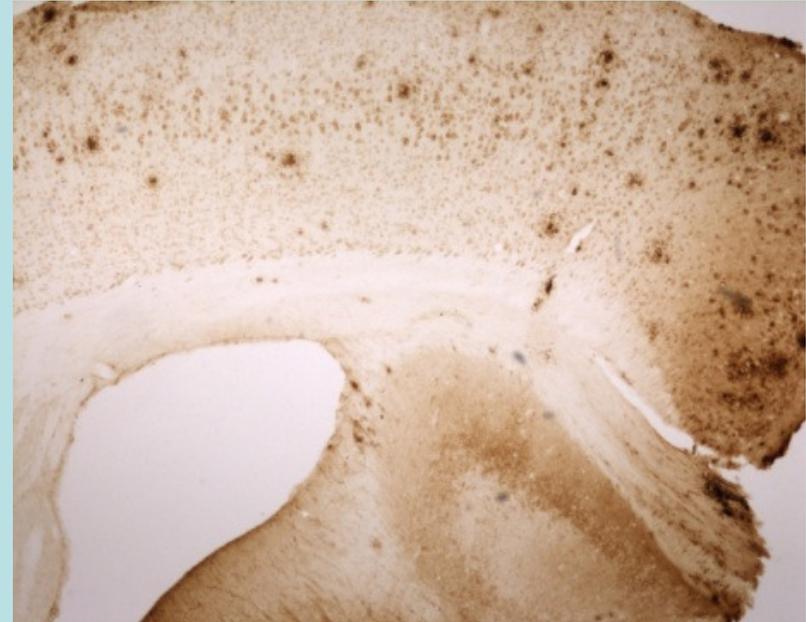
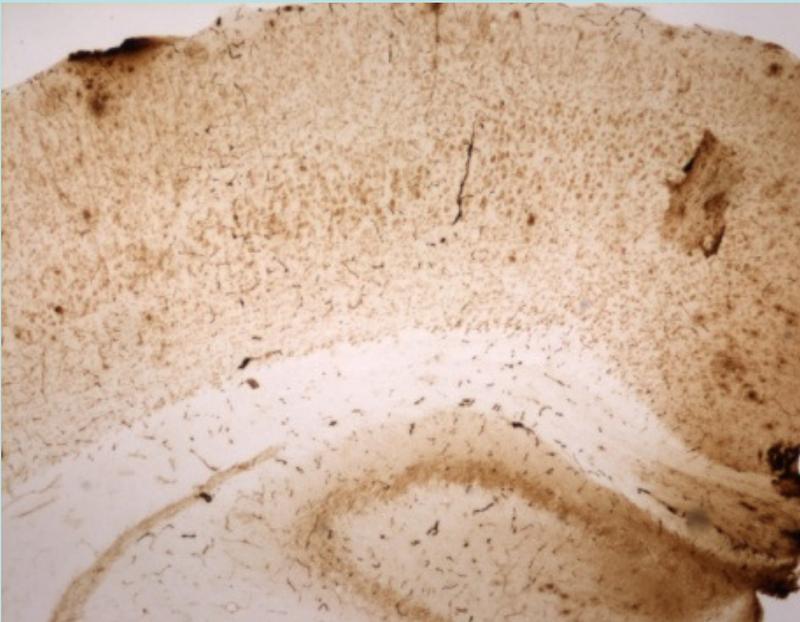
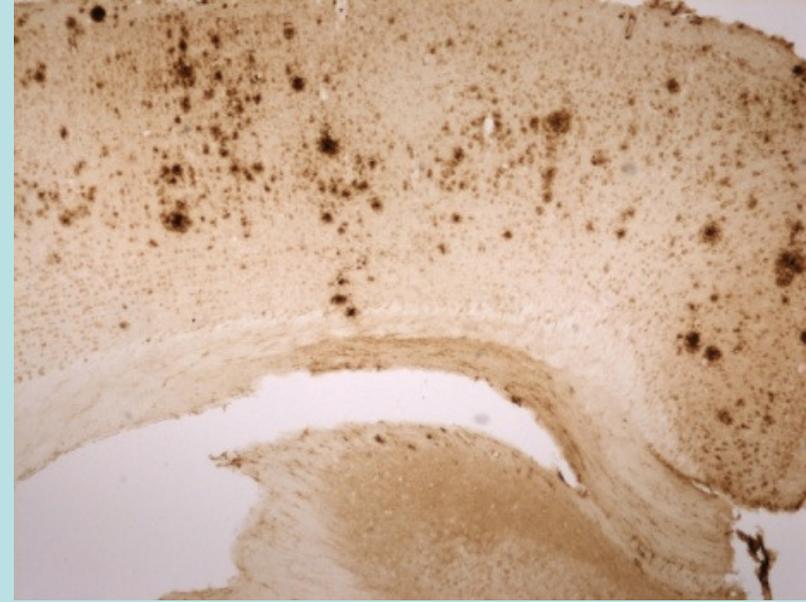
20 day-chronic treatment with DOXYCYCLINE(10mg/kg; IP)



APP/PS1tg + VEH

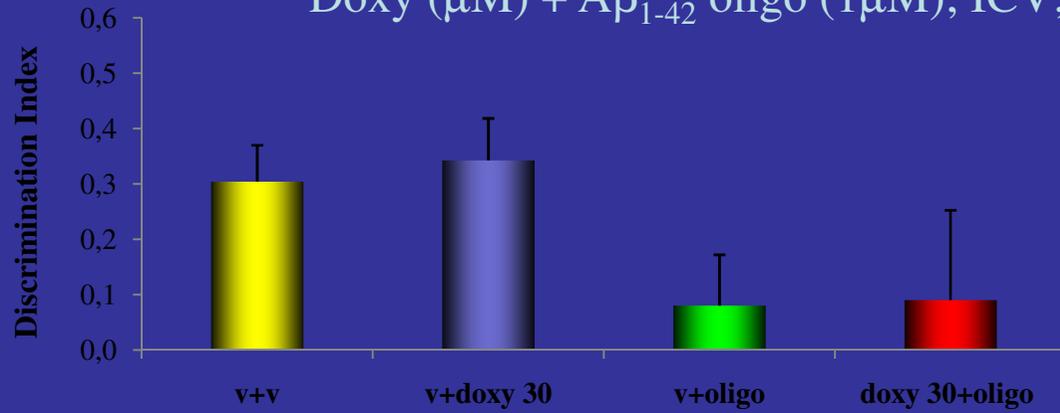


APP/PS1tg + DOXYCYCLINE

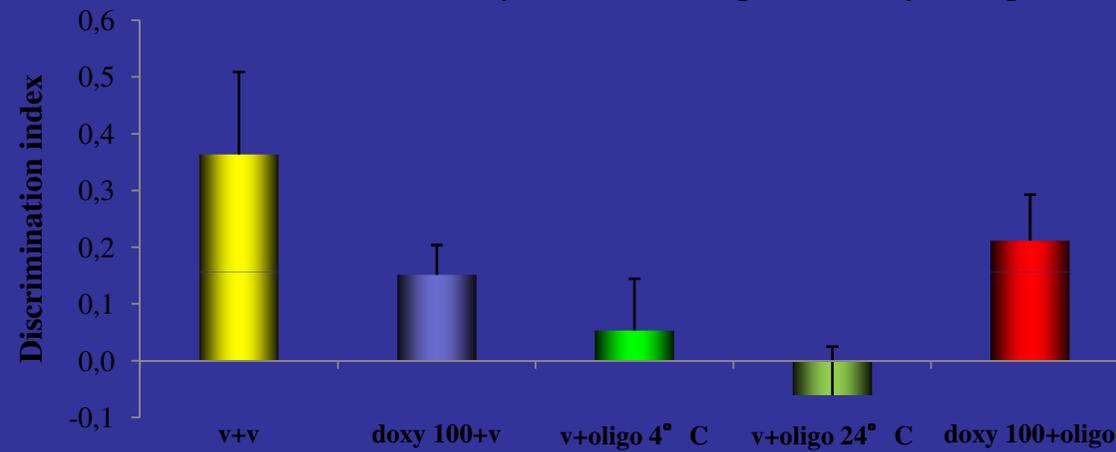


6E10 anti-Aβ antibody

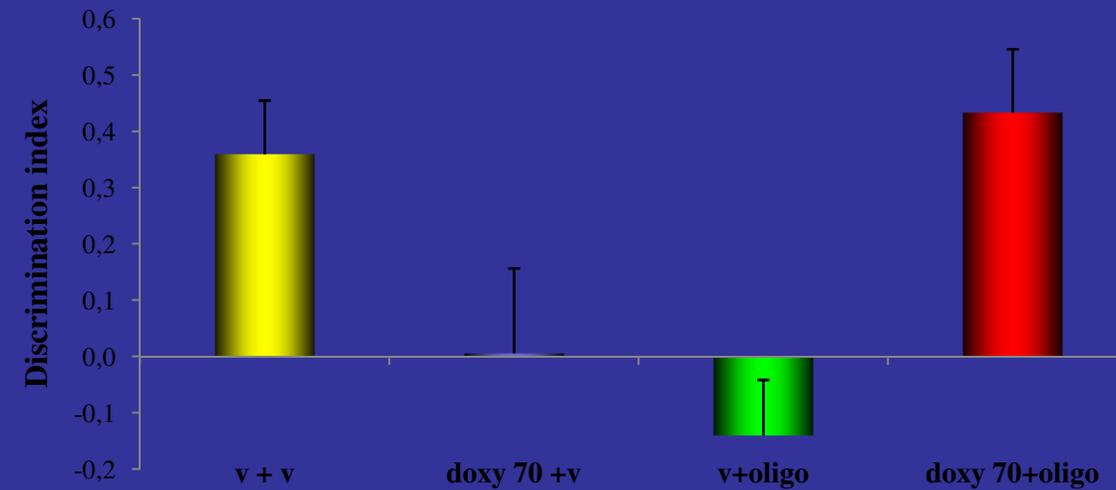
Doxy (μM) + $\text{A}\beta_{1-42}$ oligo ($1\mu\text{M}$); ICV; co-incub:1h;RT



DOXY 30 μM



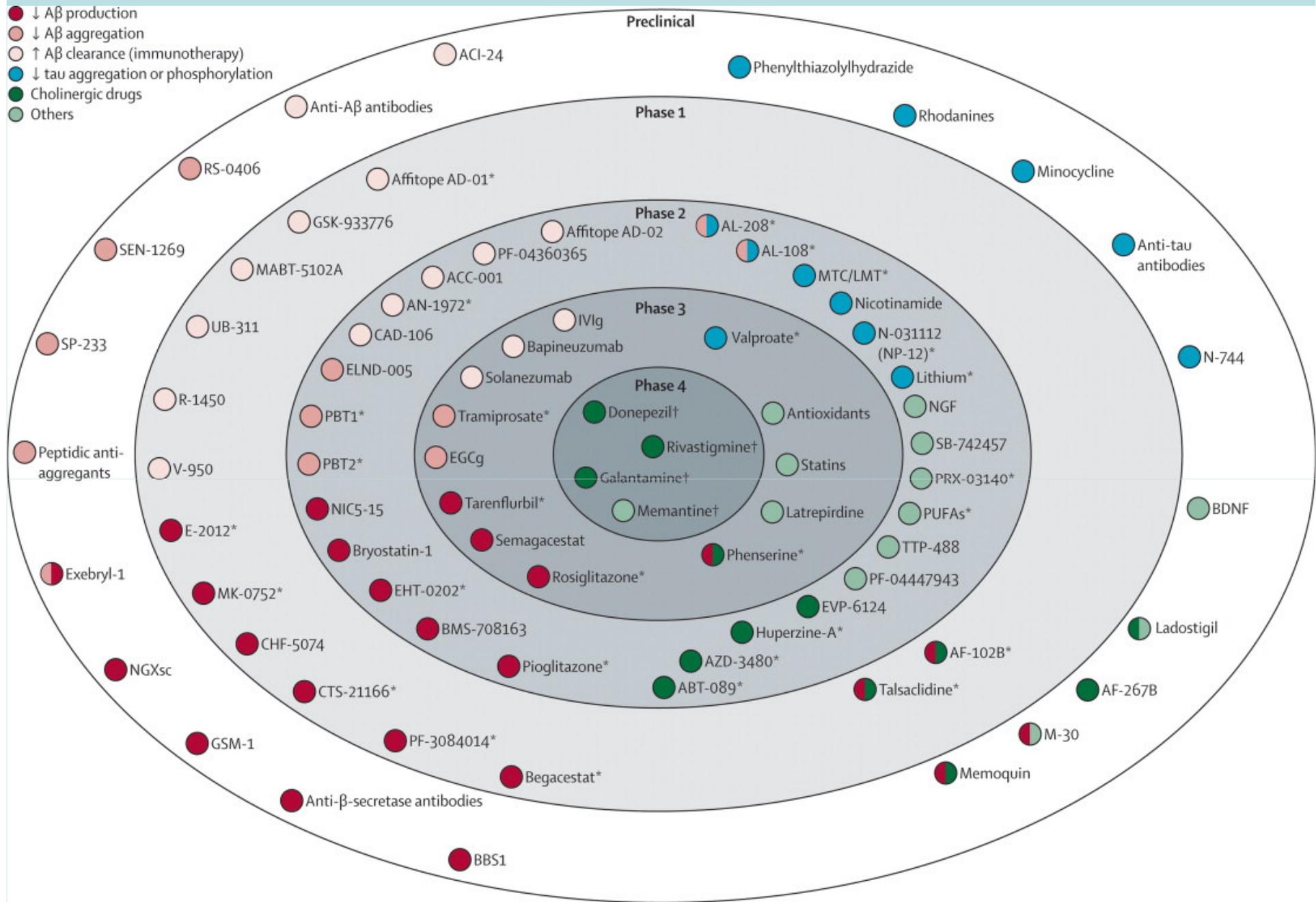
DOXY 100 μM



DOXY 70 μM



- ↓ Aβ production
- ↓ Aβ aggregation
- ↑ Aβ clearance (immunotherapy)
- ↓ tau aggregation or phosphorylation
- Cholinergic drugs
- Others



Farmaci approvati per il trattamento dell'Alzheimer

	<i>Disease stage</i>	<i>Symptomatic activity</i>	<i>Potential neuroprotective activity</i>
<i>AChEI improve cognition, behavior and functional and global clinical state</i>			
Donepezil	All stages	AChEI	↘ Aβ– Aβ toxicity ↗ Nicot Rec
Rivastigmine	Mild to moderate	AChEI and bChEI	↘ Aβ– Aβ toxicity ↗ Nicot Rec
Galantamine	Mild to moderate	AChEI and nicotinic receptors	↘ Aβ– Aβ toxicity ↗ Nicot Rec
Huperzine	Mild to moderate (China)	AChEI	↗ APPα Antioxidant, antiapopt Mit activator
<i>NMDA receptor antagonists: improve cognition behavior and functional state</i>			
Memantine	Moderate to severe also in combination with AChEI	Uncompetitive, voltage-dependent NMDA receptor antagonist	↘ Aβ toxicity and pTAU ↘ Inflammation by μglia ↗ Neurotrophic factor from astroglia

Alzheimer's Disease

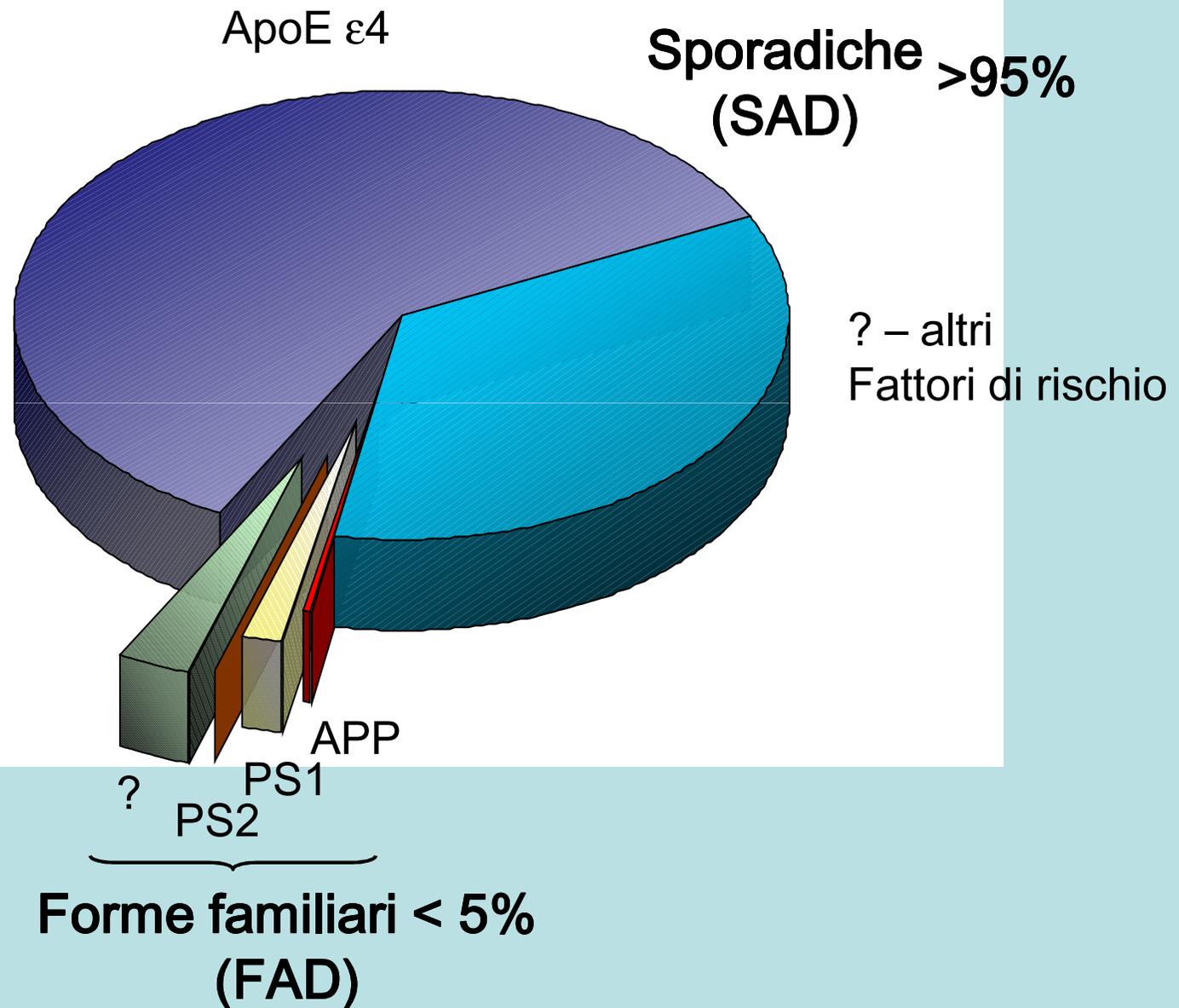
Possibili Terapie

A β Immunizzazione
Chelanti Cu⁺ and Fe²⁺
Inibitori BACE and γ secretasi
Antiossidanti e vitamina E
Fattori neurotrofici
Agenti che modulano i lipidi
Anti-amiloidogenici
Attivatori colinergici

Riduzione del rischio

Stimolazione cognitiva
Esercizio fisico
Restrizione calorica
Stimolazione sistema immunitario
Esposizione ad antinfiammatori
Esposizione alle statine

Distribuzione FAD-SAD



Studi genetici in AD

Estrazione DNA genomico

Reazione PCR

Analisi SSCP / DHPLC

Sequenziamento

STUDIO DI FUNZIONE

genealogia

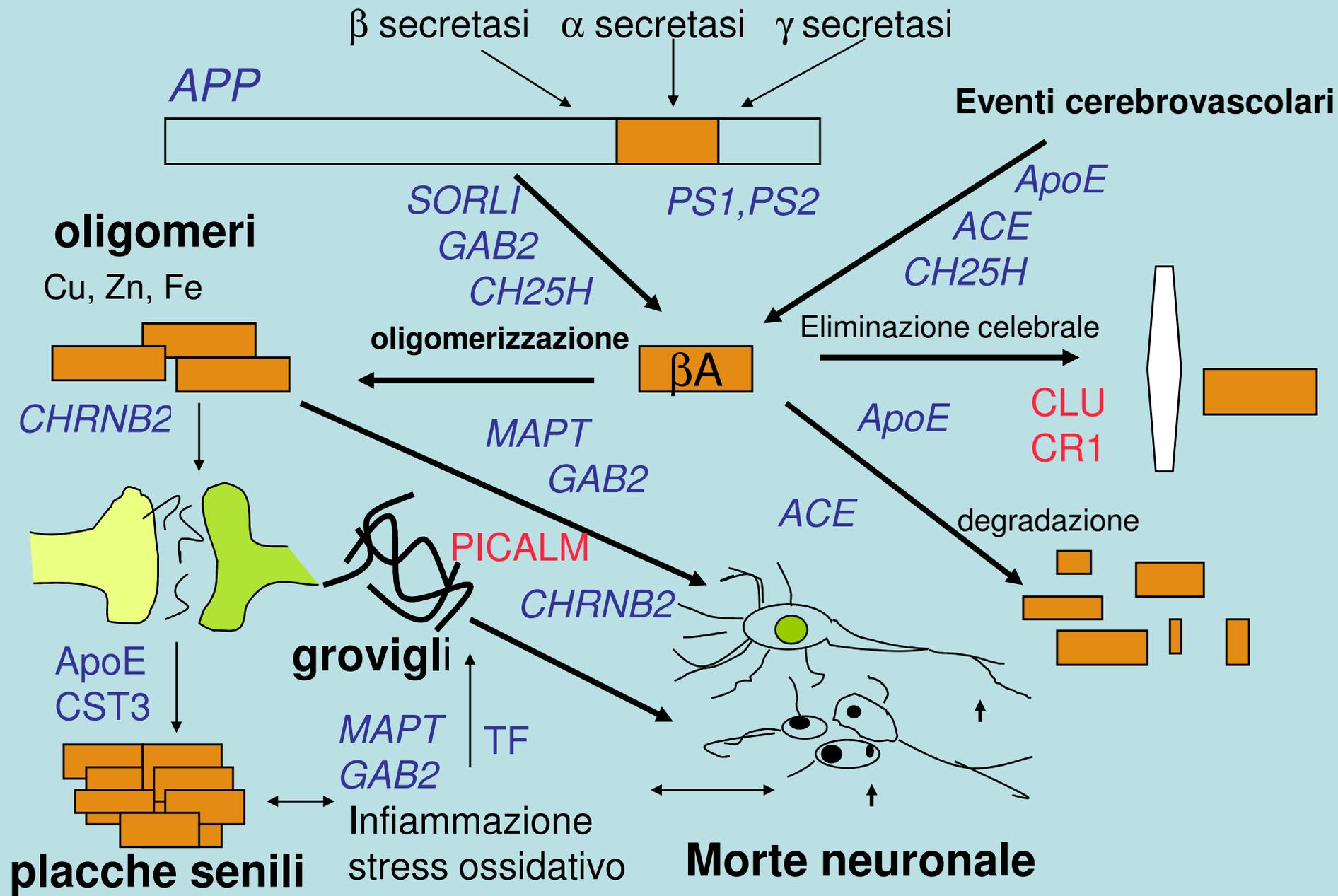
Trasfezione in cellule

Fibroblasti

Animali transgenici

Analisi proteomica

GENI e ALZHEIMER



Possibili funzioni a livello del sistema immunitario

Clusterin

CR1 (Complement receptor 1)

ABCA7 (ATP binding cassette transporter)

CD33

EPHA1

Funzione endocitotica a livello della membrana cellulare

PICALM

BIN1

CD33

CD2AP

MS4A6A

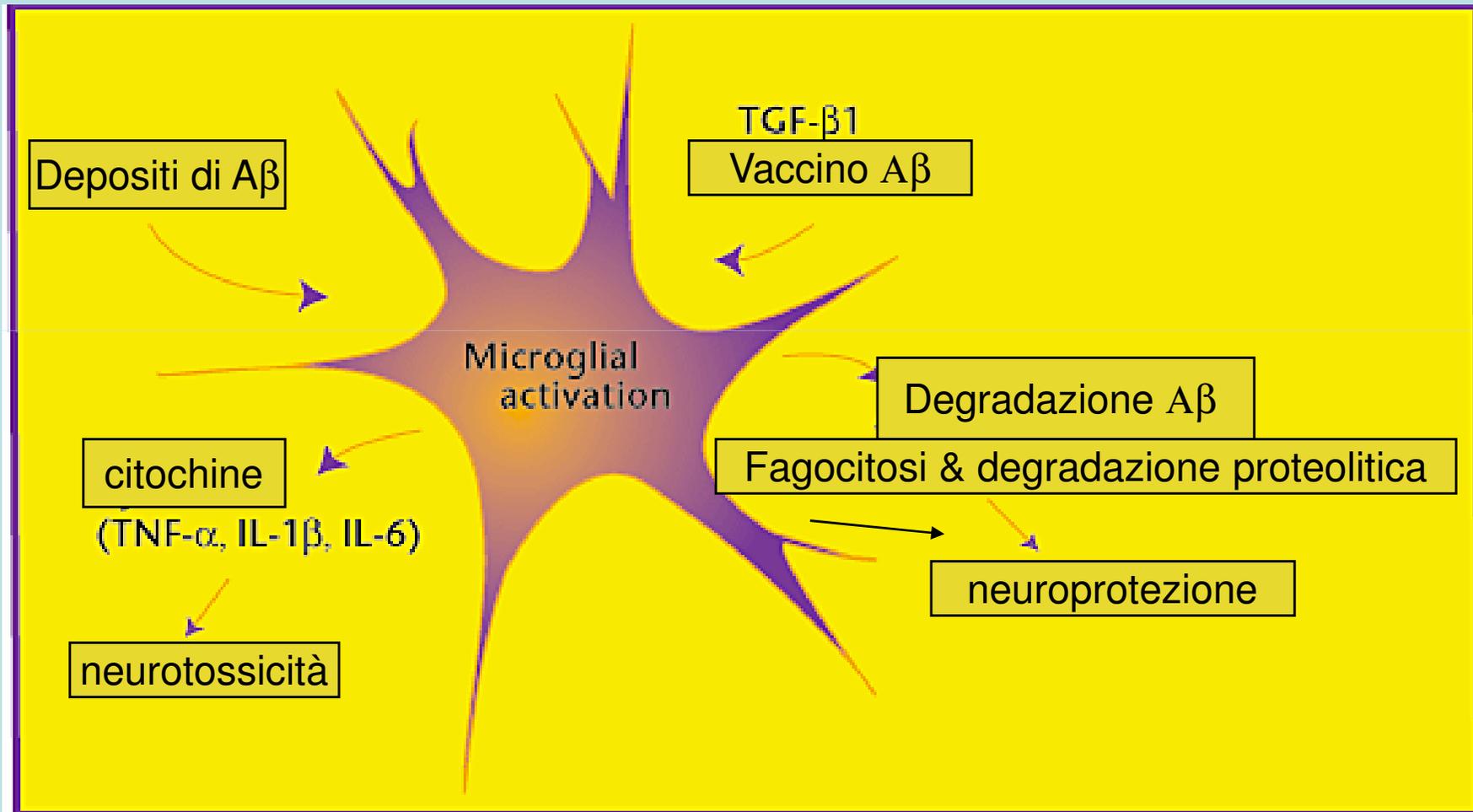
Metabolismo lipidico

ApoE

Clusterin (ApoJ)

ABCA7

Inflammation, a double-edged sword



Trattamento

Rischio relativo

NSAIDs	N°		AD	VD
Non esposti	210	2553	1.00	1.00
< 1 mese	88	2001	0.95	1.25
>1 a 23 mesi	93	2202	0.83	1.36
≥ 24 mesi	3	233	0.20	0:99
Aspirina orale				
Non esposti	252	4675	1.00	1.00
< 1 mese	7	285	0.76	-
>1 a 23 mesi	93	1017	1.30	2.99
≥ 24 mesi	42	1012	0.76	4.88

Bass et al NEJM, 2001

L'esposizione a farmaci antiinfiammatori riduce il rischio di sviluppare la malattia di Alzheimer, quando questa avviene almeno a due anni di distanza dalla diagnosi di malattia.

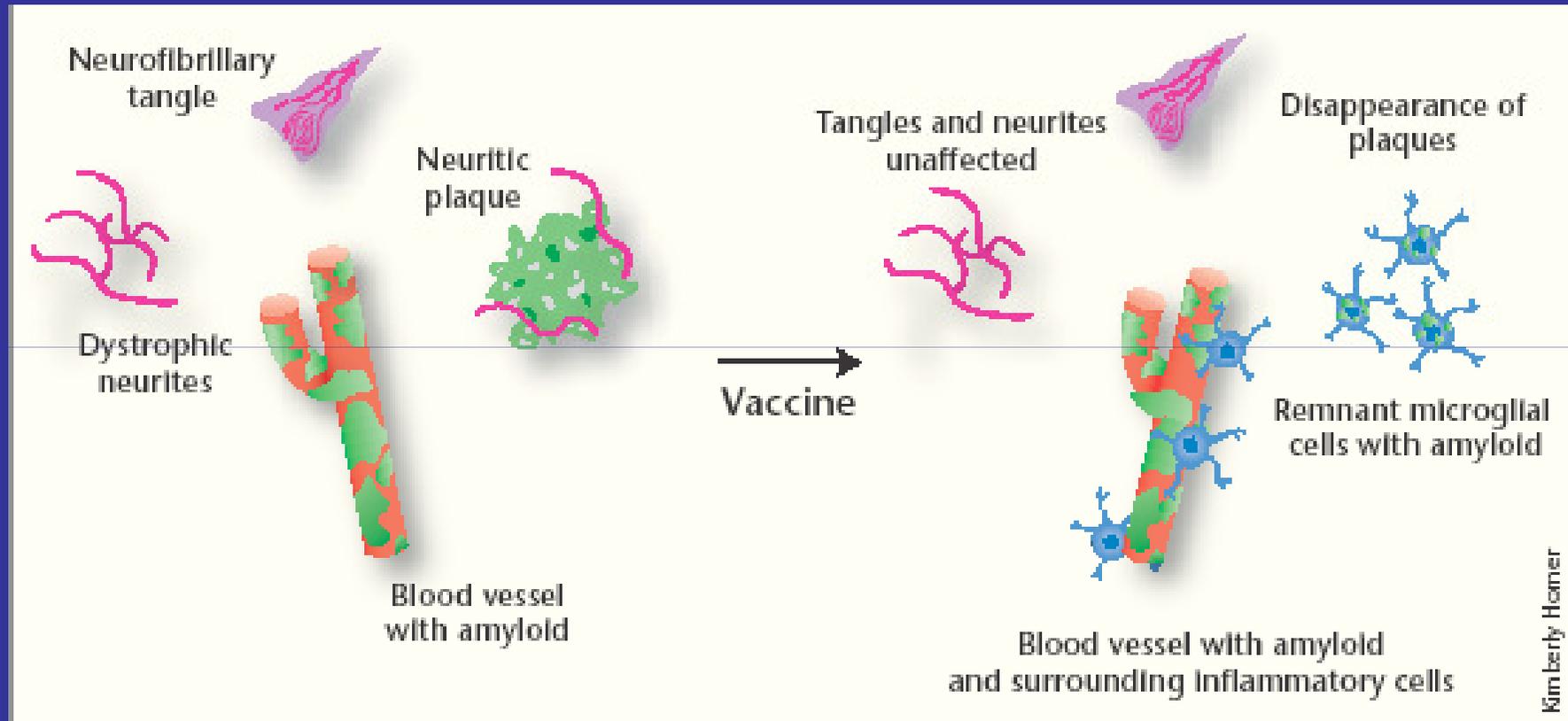
New England Journal of Medicine

Volume 345:1515-1521 November 22, 2001 Number 21

Nonsteroidal Antiinflammatory Drugs and the Risk of Alzheimer's Disease

Bas A. in 't Veld, M.D., Ph.D., Annemieke Ruitenber, M.D., Ph.D., Albert Hofman, M.D., Ph.D., Lenore J. Launer, Ph.D., Cornelia M. van Duijn, Ph.D., Theo Stijnen, Ph.D., Monique M.B. Breteler, M.D., Ph.D., and Bruno H.C. Stricker, M.B., Ph.D.

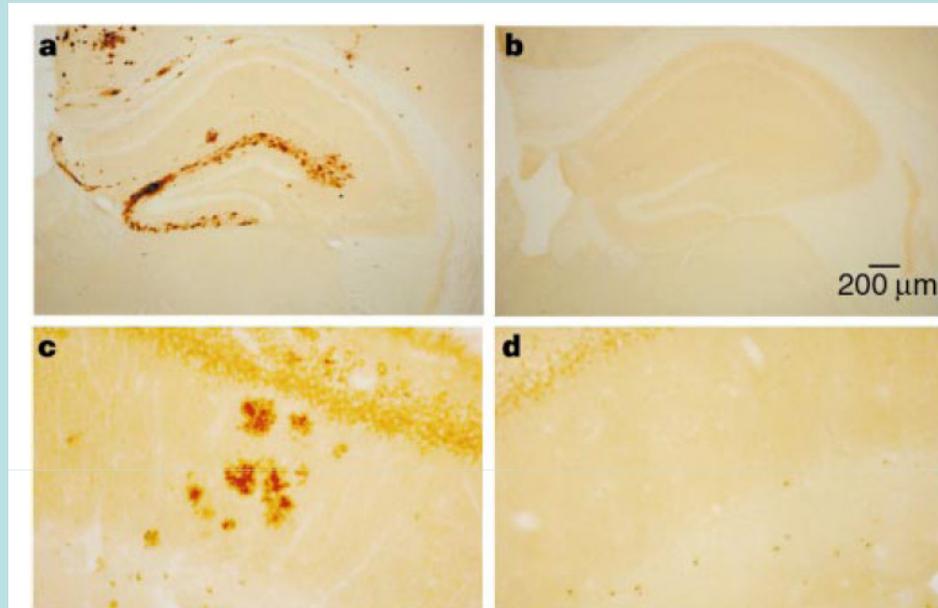
La vaccinazione una spada a doppio taglio



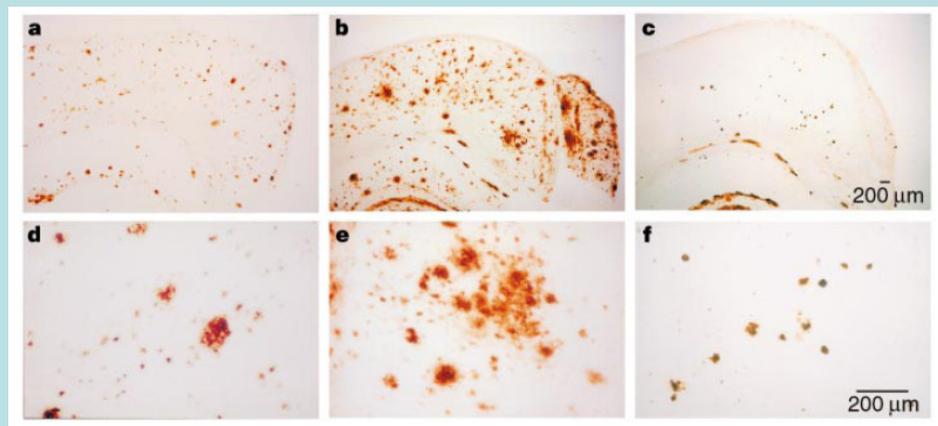
Nature Medicine 2003

Vaccinazione in topi tg

Reduction of **hippocampal** A β deposition in old PDAPPTg mice

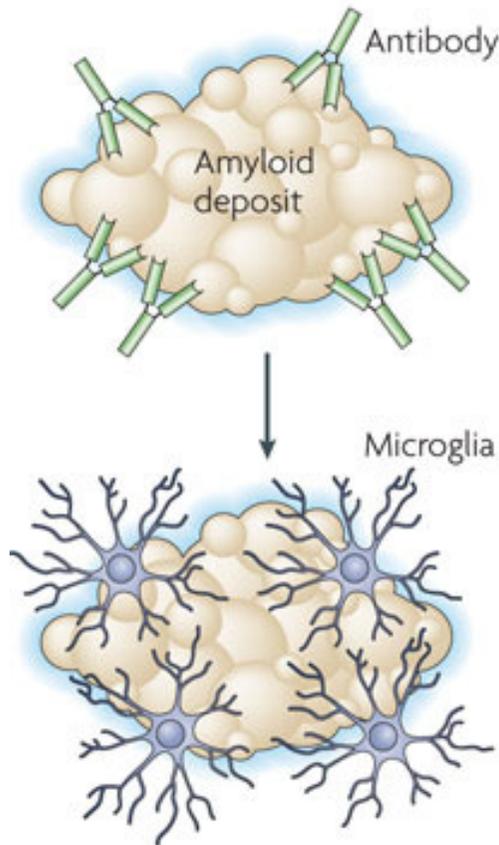


Reduction of **cortical** A β deposition in old PDAPPTg mice

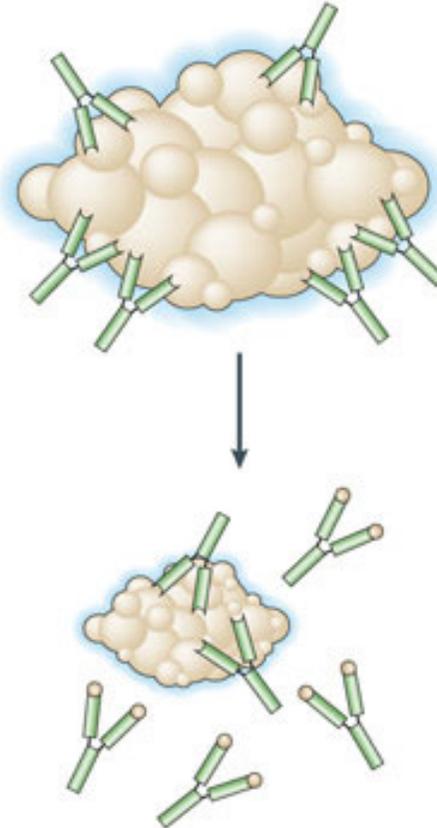


Possibili meccanismi dell'immunoterapia

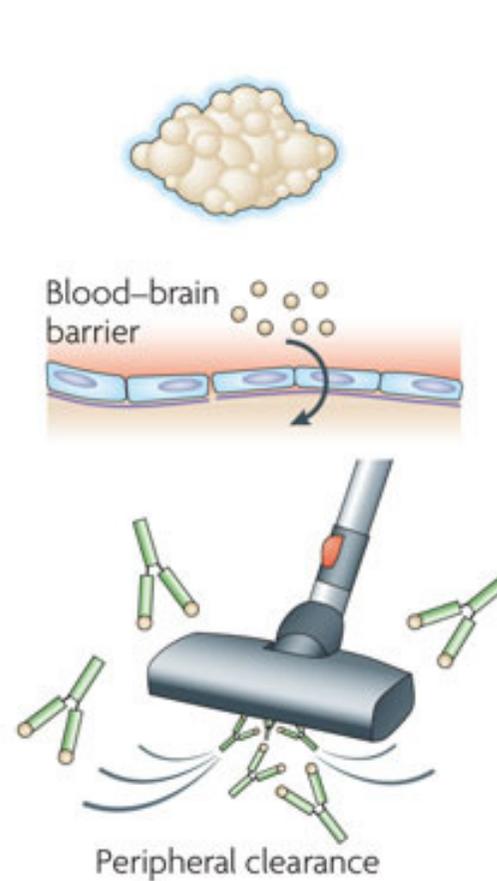
a Microglia mediated



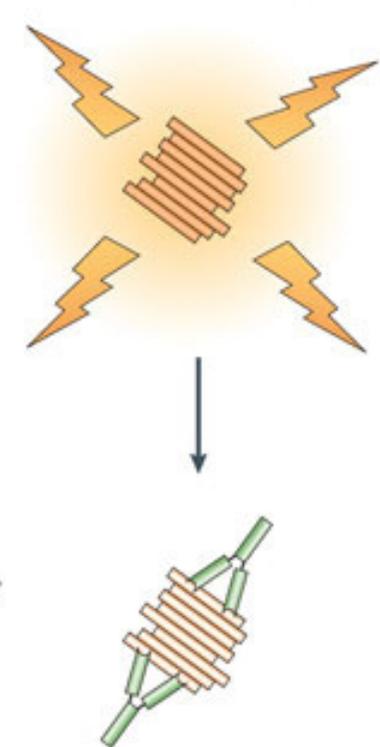
b Direct resolution



c Peripheral sink



d Blockade of toxic oligomers



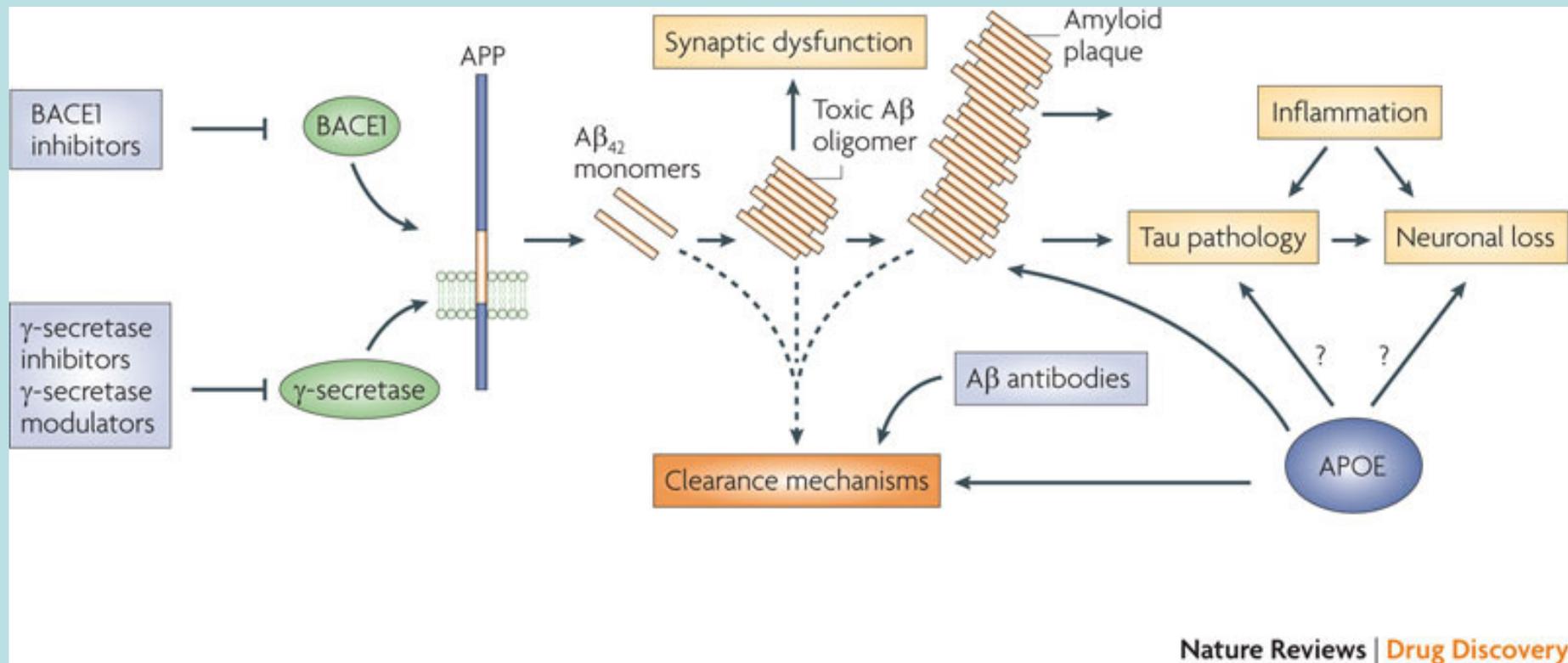
Anti-amyloid therapy

Name (initial sponsor)	Description	Proposed mechanism of action	Selected refs
Semagacestat (Eli Lilly and Company)	γ -secretase inhibitor	Reduces A β synthesis	20,108
Bapineuzumab (Elan and Wyeth)	Humanized monoclonal antibody to A β	Binds to A β deposits and reduces amyloid load primarily through microglial clearance	59,67
Solanezumab (Eli Lilly and Company)	Humanized monoclonal antibody to A β	Binds to soluble A β and reduces amyloid load via peripheral sink mechanism	61,65
Intravenous immunoglobulin G (Baxter)	Human immunoglobulin preparation containing endogenous polyclonal antibodies to A β	Primarily binds to soluble A β and reduces amyloid load via peripheral sink mechanism	54,66

A β , amyloid- β . *This table lists the four molecules that are currently in Phase III trials for Alzheimer's disease modification. In addition, dimebon (an antihistamine with neuroprotective properties¹⁰⁰ developed by Medivation and Pfizer, is currently in several Phase III trials to confirm the symptomatic benefits that were observed in Phase II trials⁹⁹.

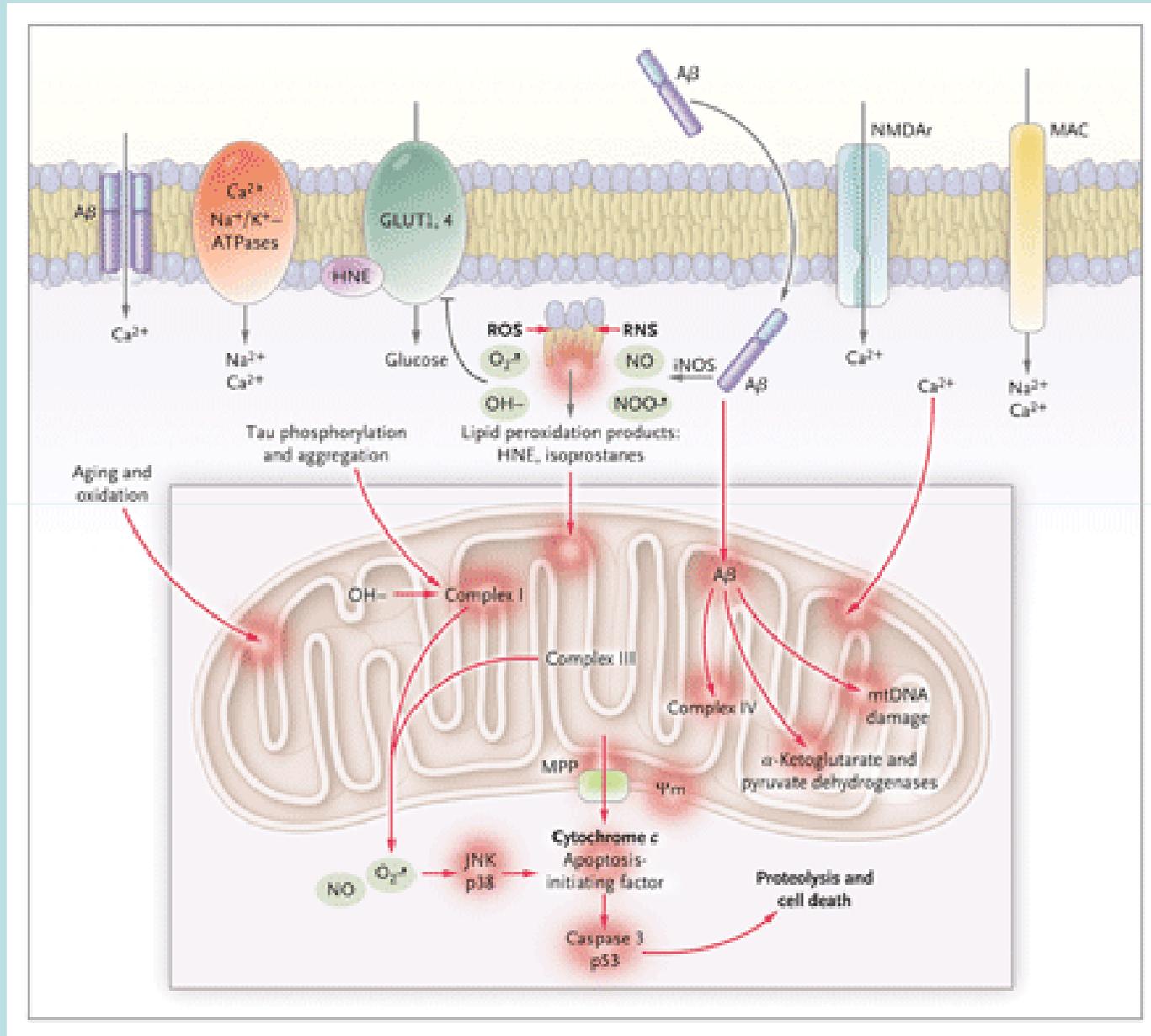
Citron, Nature Rev Drug Discov, 2010

Anti-amyloid intervention in AD



Citron, Nature Rev Drug Discov, 2010

Ruolo del mitocondrio nella patogenesi dell'Alzheimer

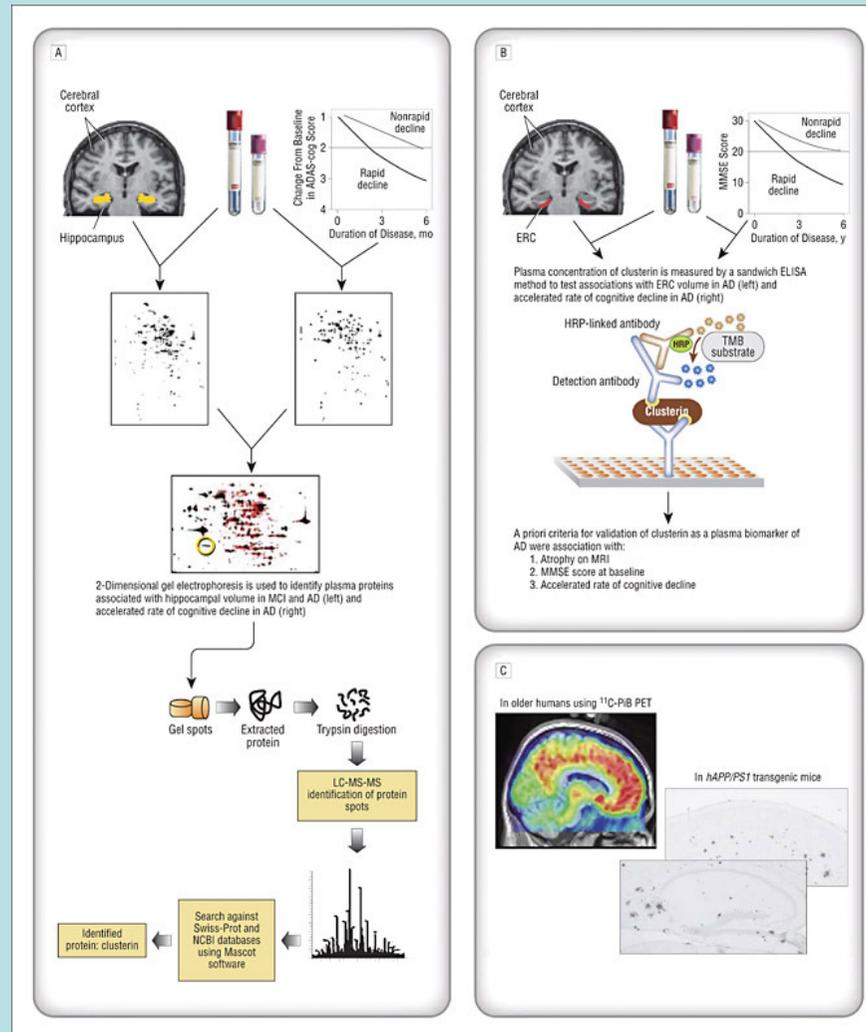


Conclusioni

- I progressi della neurobiologia consentono di sviluppare modelli di studio e ipotesi terapeutiche originali potenzialmente in grado di interferire con le cause prime della malattia
- I depositi di beta amiloide sono un target farmacologico acquisito, l'efficacia terapeutica di approcci che mirano all'eliminazione dei depositi è l'approccio più studiato con risultati ancora dubbi
- L'indagine genetica consente di migliorare gli strumenti terapeutici distinguendo tra le varie forme di malattia
- Gli strumenti diagnostici si stanno progressivamente affinando, non è illusorio pensare a markers preclinici di malattia grazie allo sviluppo delle tecnologie di immagine ma anche biochimiche.

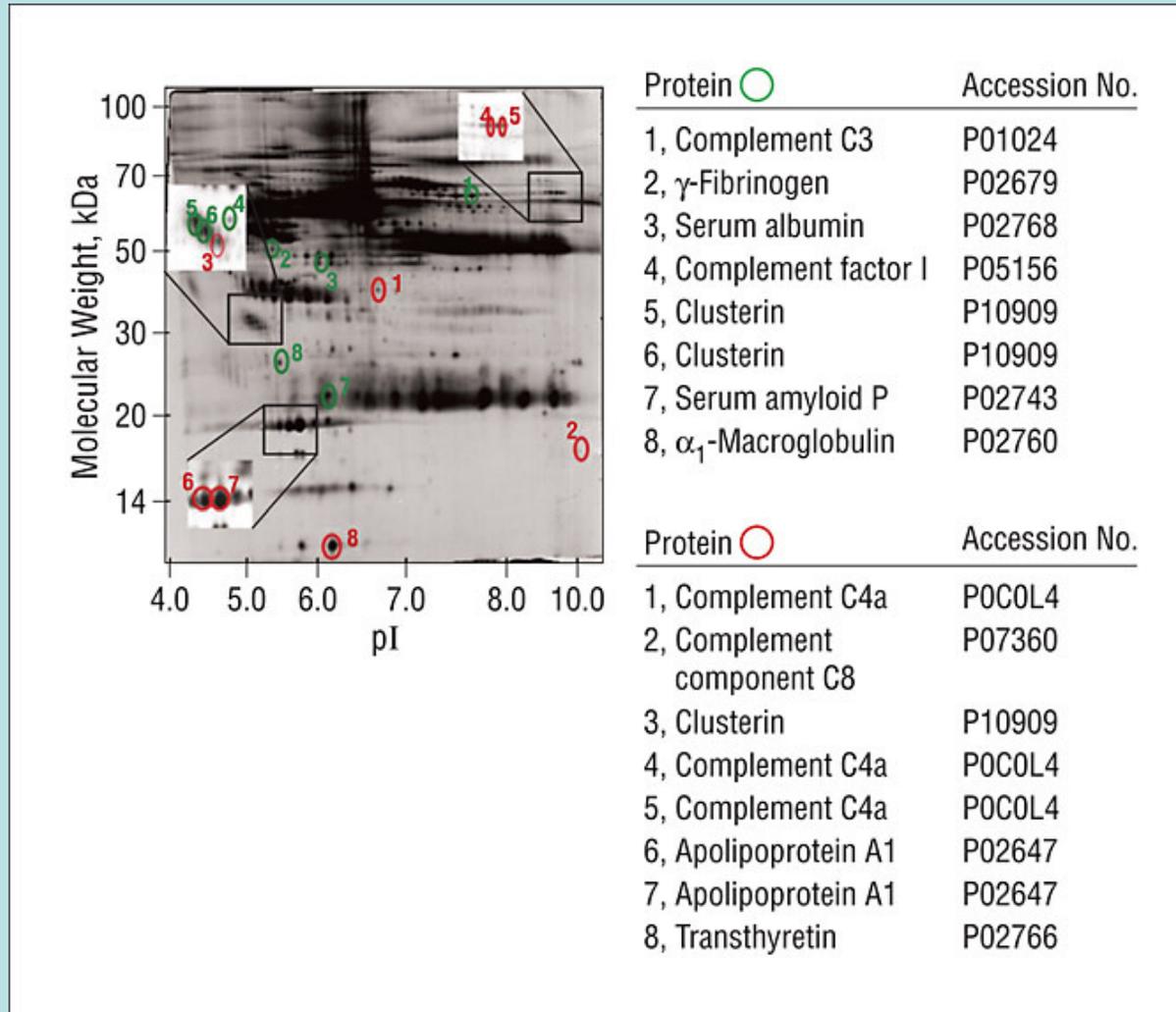
- **Uno stretto rapporto fra le varie discipline e un dialogo costante fra la ricerca e la clinica con il giusto livello di criticità è l'unica strategia che alla lunga potrà portare finalmente a risultati soddisfacenti per la prevenzione e la cura della malattia di Alzheimer**

Study design



Thambisetty, M. et al. Arch Gen Psychiatry 2010;67:739-748.

Gel-based proteomic discovery-phase studies



Thambisetty, M. et al. Arch Gen Psychiatry 2010;67:739-748.

Table 2. Associations of Baseline Characteristics With Plasma Clusterin Levels.

Table 2. Associations of Baseline Characteristics With Plasma Clusterin Levels^a

Characteristics	Difference in Plasma Clusterin Levels (95% CI), µg/mL	P Value
Age, per y	-0.15 (-0.37 to 0.07)	.18
Female sex, yes vs no	11.12 (8.00 to 14.23)	<.001
APOE ε4 allele present, yes vs no	0.57 (-2.94 to 4.09)	.75
Education, only primary, yes vs no	-0.72 (-4.28 to 2.83)	.69
Current smoking, yes vs no	-0.70 (-5.21 to 3.82)	.76
Coronary heart disease, yes vs no	-1.94 (-7.11 to 3.24)	.46
Diabetes, yes vs no	3.77 (-0.89 to 8.43)	.11
Hypertension, yes vs no	5.29 (1.43 to 9.15)	.01

Abbreviations: APOE, apolipoprotein E; CI, confidence interval.
^aLinear regression analyses were performed in the random subcohort (n=926) and are adjusted for age and sex, when applicable.

Schrijvers, E. M. C. et al. JAMA 2011;305:1322-1326



Table 3. Odds of Prevalent AD and Risk of Incident AD During Follow-up per SD Increase and per Quartile in Plasma Clusterin Levels.

	Plasma Clusterin Level, µg/mL					P for Trend
	Per SD Increase	Per Quartile of Distribution				
		47.2-99.5	99.6-115.4	115.5-132.4	132.5-198.0	
Odds of prevalent AD at baseline (n = 60)						
OR (95% CI)						
Adjusted for age and sex	1.49 (1.12-1.98)	1 [Reference]	0.98 (0.38-2.45)	1.73 (0.70-4.25)	2.32 (1.03-5.26)	.02
Adjusted for age, sex, and covariates ^a	1.63 (1.21-2.20)	1 [Reference]	0.99 (0.36-2.78)	2.17 (0.83-5.68)	2.99 (1.25-7.16)	.004
Risk of incident AD during total follow-up (n = 208)						
HR (95% CI)						
Adjusted for age and sex	0.98 (0.84-1.15)	1 [Reference]	1.07 (0.68-1.68)	1.07 (0.69-1.68)	0.90 (0.57-1.43)	.66
Adjusted for age, sex, and covariates ^a	1.00 (0.85-1.17)	1 [Reference]	1.07 (0.67-1.71)	1.12 (0.70-1.77)	0.92 (0.58-1.46)	.77
Risk of incident AD within 3 years (n = 76)						
HR (95% CI)						
Adjusted for age and sex	1.06 (0.82-1.37)	1 [Reference]	0.82 (0.39-1.71)	1.30 (0.66-2.55)	1.01 (0.48-2.11)	.68
Adjusted for age, sex, and covariates ^a	1.09 (0.84-1.42)	1 [Reference]	0.85 (0.39-1.85)	1.34 (0.65-2.74)	1.04 (0.49-2.24)	.65
Risk of incident AD after 3 years (n = 132)						
HR (95% CI)						
Adjusted for age and sex	0.97 (0.80-1.17)	1 [Reference]	1.24 (0.73-2.12)	0.97 (0.56-1.68)	0.91 (0.53-1.57)	.54
Adjusted for age, sex, and covariates ^a	0.99 (0.81-1.20)	1 [Reference]	1.23 (0.70-2.15)	1.00 (0.57-1.77)	0.96 (0.54-1.68)	.72

Abbreviations: AD, Alzheimer disease; CI, confidence interval; HR, hazard ratio; OR, odds ratio.
^aCovariates included education level, APOE ε4 (apolipoprotein E) status, diabetes, smoking, coronary heart disease, and hypertension.

Increased in plasma clusterin levels are associated with prevalent AD and are higher in more severe Cases of AD. However increased levels of clusterin do not precede development of AD and therefore Are not a potential early marker of subclinical disease

Schrijvers, E. M. C. et al. JAMA 2011;305:1322-1326

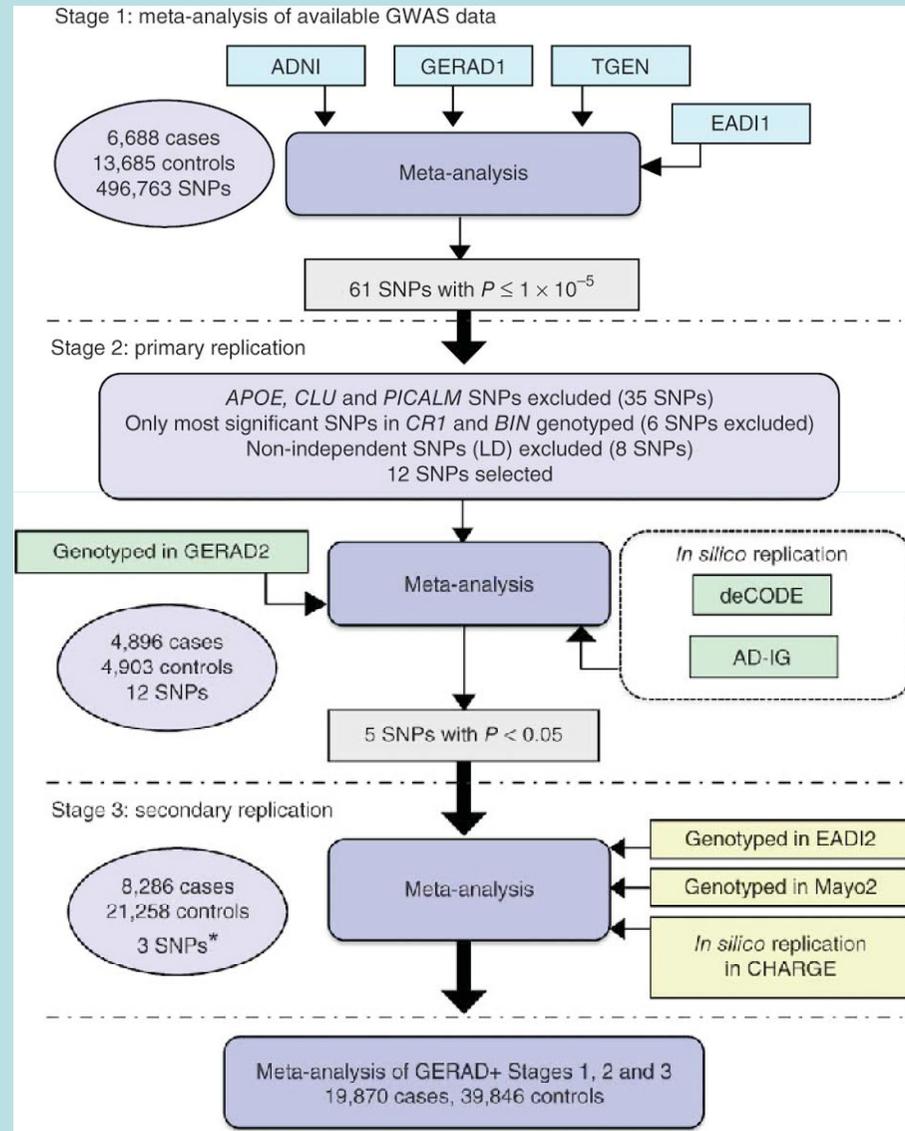


Nat Genet. 2011 May;43(5):429-435

- **Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease.**
- [Hollingworth P](#), [Harold D](#), [Sims R](#), [Gerrish A](#), [Lambert JC](#), [Carrasquillo MM](#), [Abraham R](#), [Hamshere ML](#), [Pahwa JS](#), [Moskvina V](#), [Dowzell K](#), [Jones N](#), [Stretton A](#), [Thomas C](#), [Richards A](#), [Ivanov D](#), [Widdowson C](#), [Chapman J](#), [Lovestone S](#), [Powell J](#), [Proitsi P](#), [Lupton MK](#), [Brayne C](#), [Rubinsztein DC](#), [Gill M](#), [Lawlor B](#), [Lynch A](#), [Brown KS](#), [Passmore PA](#), [Craig D](#), [McGuinness B](#), [Todd S](#), [Holmes C](#), [Mann D](#), [Smith AD](#), [Beaumont H](#), [Warden D](#), [Wilcock G](#), [Love S](#), [Kehoe PG](#), [Hooper NM](#), [Vardy ER](#), [Hardy J](#), [Mead S](#), [Fox NC](#), [Rossor M](#), [Collinge J](#), [Maier W](#), [Jessen F](#), [Rüther E](#), [Schürmann B](#), [Heun R](#), [Kölsch H](#), [van den Bussche H](#), [Heuser I](#), [Kornhuber J](#), [Wiltfang J](#), [Dichgans M](#), [Frölich L](#), [Hampel H](#), [Gallacher J](#), [Hüll M](#), [Rujescu D](#), [Giegling I](#), [Goate AM](#), [Kauwe JS](#), [Cruchaga C](#), [Nowotny P](#), [Morris JC](#), [Mayo K](#), [Sleegers K](#), [Bettens K](#), [Engelborghs S](#), [De Deyn PP](#), [Van Broeckhoven C](#), [Livingston G](#), [Bass NJ](#), [Gurling H](#), [McQuillin A](#), [Gwilliam R](#), [Deloukas P](#), [Al-Chalabi A](#), [Shaw CE](#), [Tsolaki M](#), [Singleton AB](#), [Guerreiro R](#), [Mühleisen TW](#), [Nöthen MM](#), [Moebus S](#), [Jöckel KH](#), [Klopp N](#), [Wichmann HE](#), [Pankratz VS](#), [Sando SB](#), [Aasly JO](#), [Barcikowska M](#), [Wszolek ZK](#), [Dickson DW](#), [Graff-Radford NR](#), [Petersen RC](#); the Alzheimer's Disease Neuroimaging Initiative, [van Duijn CM](#), [Breteler MM](#), [Ikram MA](#), [Destefano AL](#), [Fitzpatrick AL](#), [Lopez O](#), [Laurer LJ](#), [Seshadri S](#); CHARGE consortium, [Berr C](#), [Campion D](#), [Epelbaum J](#), [Dartigues JF](#), [Tzourio C](#), [Alpérovitch A](#), [Lathrop M](#); EADI1 consortium, [Feulner TM](#), [Friedrich P](#), [Riehle C](#), [Krawczak M](#), [Schreiber S](#), [Mayhaus M](#), [Nicolhaus S](#), [Wagenpfeil S](#), [Steinberg S](#), [Stefansson H](#), [Stefansson K](#), [Snædal J](#), [Björnsson S](#), [Jonsson PV](#), [Chouraki V](#), [Genier-Boley B](#), [Hiltunen M](#), [Soininen H](#), [Combarros O](#), [Zelenika D](#), [Delepine M](#), [Bullido MJ](#), [Pasquier F](#), [Mateo I](#), [Frank-Garcia A](#), [Porcellini E](#), [Hanon O](#), [Coto E](#), [Alvarez V](#), [Bosco P](#), [Siciliano G](#), [Mancuso M](#), [Panza F](#), [Solfrizzi V](#), [Nacmias B](#), [Sorbi S](#), [Bossù P](#), [Piccardi P](#), [Arosio B](#), [Annoni G](#), [Seripa D](#), [Pilotto A](#), [Scarpini E](#), [Galimberti D](#), [Brice A](#), [Hannequin D](#), [Licastro F](#), [Jones L](#), [Holmans PA](#), [Jonsson T](#), [Riemenschneider M](#), [Morgan K](#), [Younkin SG](#), [Owen MJ](#), [O'Donovan M](#), [Amouyel P](#), [Williams J](#).

Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease

[Paul Hollingworth](#) et al *Nature Genetics*



Common variants at *MS4A4/MS4A6E*, *CD2AP*, *CD33* and *EPHA1* are associated with late-onset Alzheimer's disease

