SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

OMOTAURINA (TRAMIPROSATO) nella malattia di Alzheimer

Relatore:
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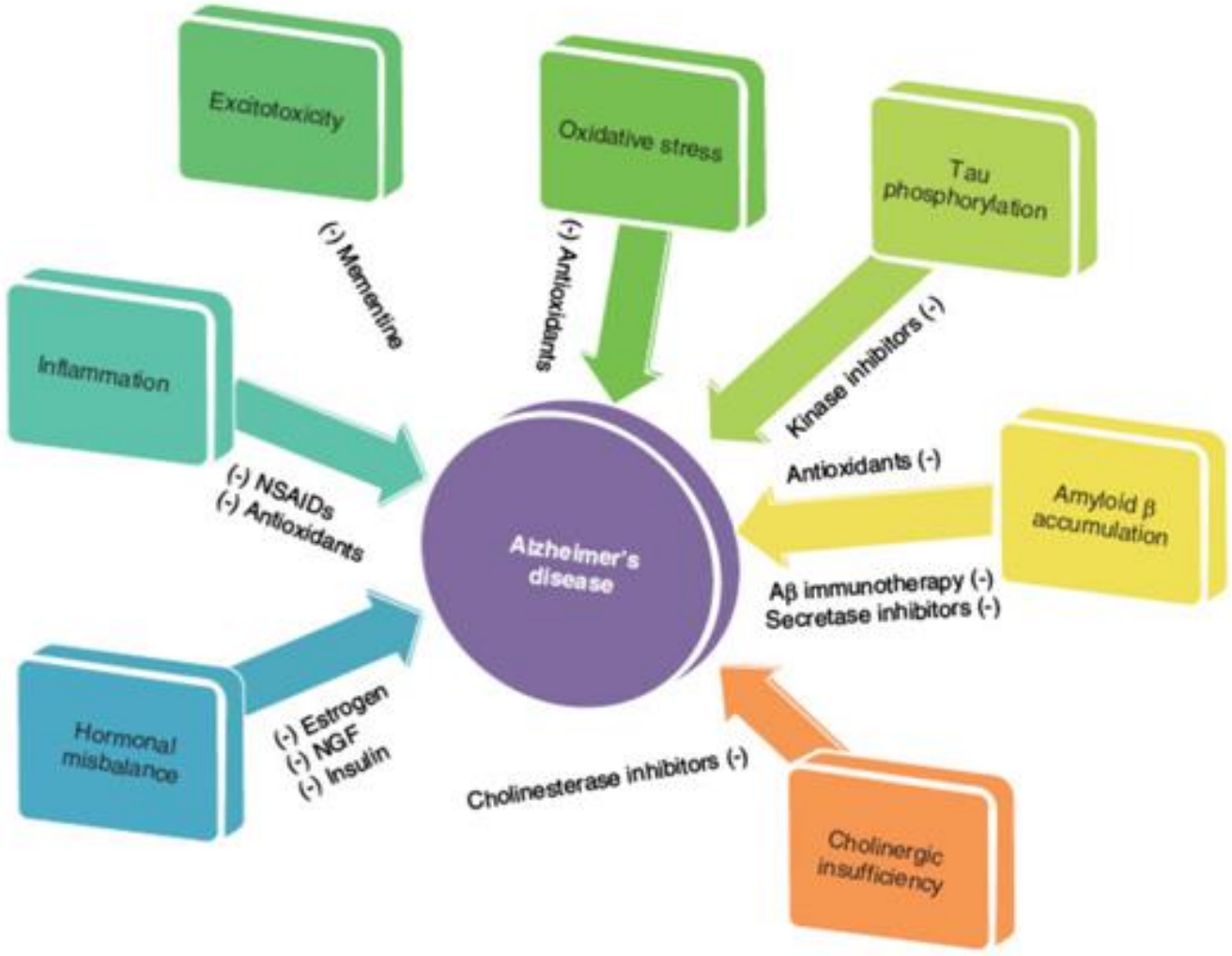
U.O. GERIATRIA AOU FE

Cona (FE) - 24 ottobre 2014

CALMAN’S GAP

Elementi della cascata patogenetica: chi è il protagonista ?

Fig. 1 Pharmacotherapeutic targets in Alzheimer's disease



LETTER

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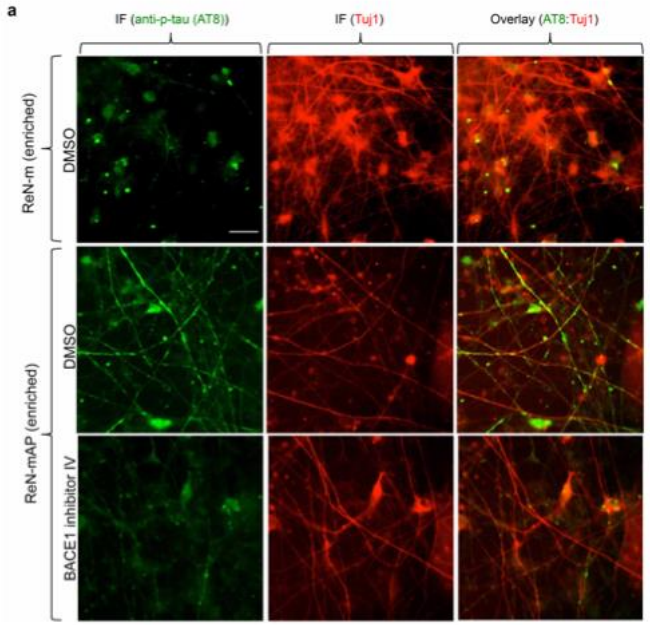
doi:10.1038/nature13800

A three-dimensional human neural cell culture model of Alzheimer's disease

Se Hoon Choi[1]*, Young Hye Kim[1,2]*, Matthias Hebisch[1,3], Christopher Sliwinski[1], Seungkyu Lee[4], Carla D'Avanzo[1], Hechao Chen[1], Basavaraj Hooli[1], Caroline Asselin[1], Julien Muffat[5], Justin B. Klee[1], Can Zhang[1], Brian J. Wainger[4], Michael Peitz[3], Dora M. Kovacs[1], Clifford J. Woolf[4], Steven L. Wagner[6], Rudolph E. Tanzi[1] & Doo Yeon Kim[1]

RESEARCH LETTER



Extended Data Figure 7 | Increased p-tau levels in FAD ReN cells. **a**, Immunofluorescence of AT8 p-tau and Tuj1 in the enriched ReN-mAP and control ReN-m cells after 9 weeks of 3D differentiation. BACE1 inhibitor IV treatment for 3 weeks dramatically reduced AT8 p-tau staining (green, AT8 p-tau; red (pseudo-coloured), Tuj1; scale bar, 25 μm). **b**, Western blot of total and p-tau levels in control (enriched ReN-m) and FAD ReN (enriched ReN-mAP) cells. The cells were 3D differentiated for 9 weeks. Three weeks of BACE1 inhibitor treatments significantly decreased p-tau levels without changing total tau levels. HSP70 heat shock protein levels are shown to demonstrate equal loading of each sample.

Questo è il primo modello in vitro che ha permesso di stabilire un nesso causale tra l'accumulo della proteina beta-amiloide e la patologia legata a tau nelle cellule nervose umane, supportando quindi l'ipotesi della cascata dell'amiloide come meccanismo patogenetico per la Malattia di Alzheimer. Il modello, una volta perfezionato, potrebbe essere utilizzato per valutare l'efficacia di farmaci anti-amiloide e anti-tau, in modo più rapido e meno costoso rispetto alla sperimentazione animale.

TABLE 1. Outcomes of Phase 3 Clinical Trials of Amyloidocentric Drugs

Drug Name and Proposed Mechanism of Action	Phase 2 Results	Phase 3 Results
Tramiprosate, Aβ aggregation inhibitor.	58 mild–moderate AD patients randomized to 4 groups: placebo, 50, 100, 150mg/kg tramiprosate b.i.d. for 3 months. Drug mediated a significant lowering of Aβ42 in CSF samples.[21]	1,052 mild–moderate AD patients randomized to 3 groups: placebo, 100, 150mg/kg b.i.d. for 78 weeks. No significant effects on primary outcome measures on ADAS-cog and CDR-SB.[25]
Tarenflurbil, γ-secretase modulator.	210 mild–moderate AD patients randomized to placebo, 400, 800mg b.i.d. tarenflurbil for 12 months. Some evidence of an improvement ADCS-ADL at the 800mg b.i.d. dose.[46]	1,684 mild AD patients randomized to placebo, 800mg b.i.d. tarenflurbil for 18 months. No significant effects on primary outcome measures on ADAS-cog and ADCS-ADL.[47]
Semagacestat, γ-secretase inhibitor.	51 mild–moderate AD patients randomized to placebo, 100, 140mg o.d. semagacestat following dose escalation for a total duration of 18 weeks. Significant reduction in plasma Aβ40 peptide.[77]	2,600 mild–moderate AD patients randomized to placebo, 100, 140mg semagacestat o.d. for 76 weeks in 2 trials (ClinicalTrials.gov identifiers NCT00594568, NTC00762411). Trials were halted after interim analysis showed increased incidence of skin cancer and worsening of cognition and activities of daily living.[78]
Bapineuzumab, humanized monoclonal antibody directed at amino acids 1–5 of Aβ peptide. Amyloid plaque clearance mediated by microglial activation.	234 mild–moderate AD patients, randomized to placebo, 0.15, 0.5, 1.0, or 2.0mg/kg bapineuzumab i.v. infusions every 13 weeks for 78 weeks. Some evidence of an improvement in cognitive and functional endpoints in study completers and *APOE4* noncarriers.[106]	4,500 mild–moderate AD patients randomized to placebo and 0.5mg/kg i.v. every 13 weeks for 18 months in *APOE4* carriers, and randomized to placebo, 0.5, 1.0mg/kg i.v. every 13 weeks for 18 months in *APOE4* noncarriers in 4 trials (ClinicalTrials.gov identifiers lNCT00575055, NCT00574132, NCT00676143, NCT00667810). Trials were halted after completion of 2 trials demonstrated a failure to meet primary outcome measures on ADAS-cog and activities of daily living.[109]
Solanezumab, humanized monoclonal antibody directed at amino acids 16–24 of Aβ peptide. Amyloid plaque clearance mediated via peripheral sink mechanism.	52 mild–moderate AD patients were randomized to placebo, 100mg every 4 weeks, 100mg weekly, 400mg every 4 weeks, 400mg weekly i.v. solanezumab for 12 weeks. There was a significant dose-dependent increase in Aβ42 peptide in CSF.[132]	2,000 mild–moderate AD patients randomized to placebo and 400mg solanezumab monthly i.v. for 18 months (ClinicalTrials.gov identifiers NCT00905372, NCT00904683). Trials failed to meet their primary outcome measures on ADAS-cog and ADCS-ADL. A secondary analysis of mild AD patients pooled from both trials showed a significant effect on cognition.[115]
Gammagard, intravenous immunoglobulin.	55 mild–moderate AD patients randomized to placebo, 0.2, 0.5, 0.8g/kg/4 weeks, or 0.1, 0.25, 0.4g/kg/2 weeks for 24 weeks. There was no increase in Aβ40 peptide in plasma at any dose.[129]	Trial data currently unpublished. 390 mild–moderate AD patients randomized to 0.2g/kg/2 weeks and 0.4g/kg/2 weeks vs placebo for 18 months (ClinicalTrials.gov Identifier NCT00818662). Gammagard failed to reach its coprimary outcomes of ADAS-cog and ADCS-ADL.

AD = Alzheimer disease; ADAS-cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; b.i.d. = twice daily; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebrospinal fluid; i.v. = intravenous; o.d. = once per day.

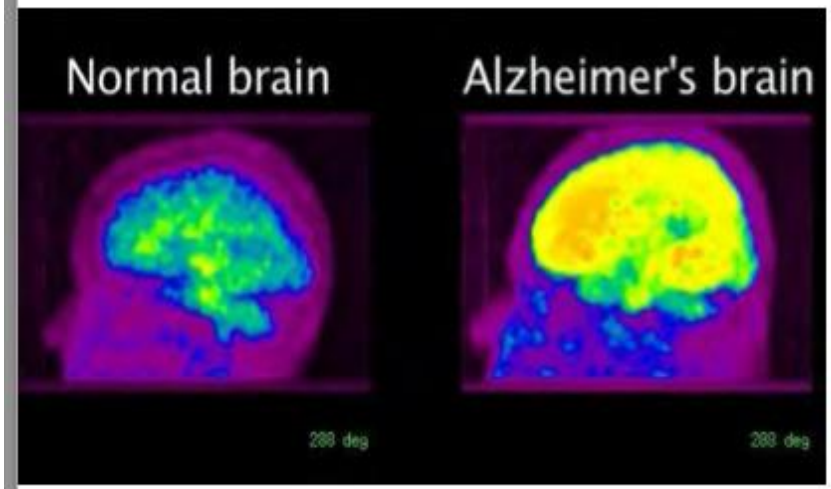
The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Antiamyloid Therapy for Alzheimer's Disease — Are We on the Right Road?

Eric Karran, Ph.D., and John Hardy, Ph.D.

N Engl J Med 2014; 370:377-378 | January 23, 2014 | DOI: 10.1056/NEJMe1313943


Normal brain
Alzheimer's brain
288 deg
288 deg

Nuove strategie farmacologiche disease modifying

- Il processo fisiopatologico dell'AD comincia in realtà molti anni prima della diagnosi clinica di deficit cognitivo, indicando la possibilità di un continuum nella progressione della patologia.

- Questo determina un'opportunità per approcci preventivi e molecole in grado di modificare il percorso e il decorso della malattia.

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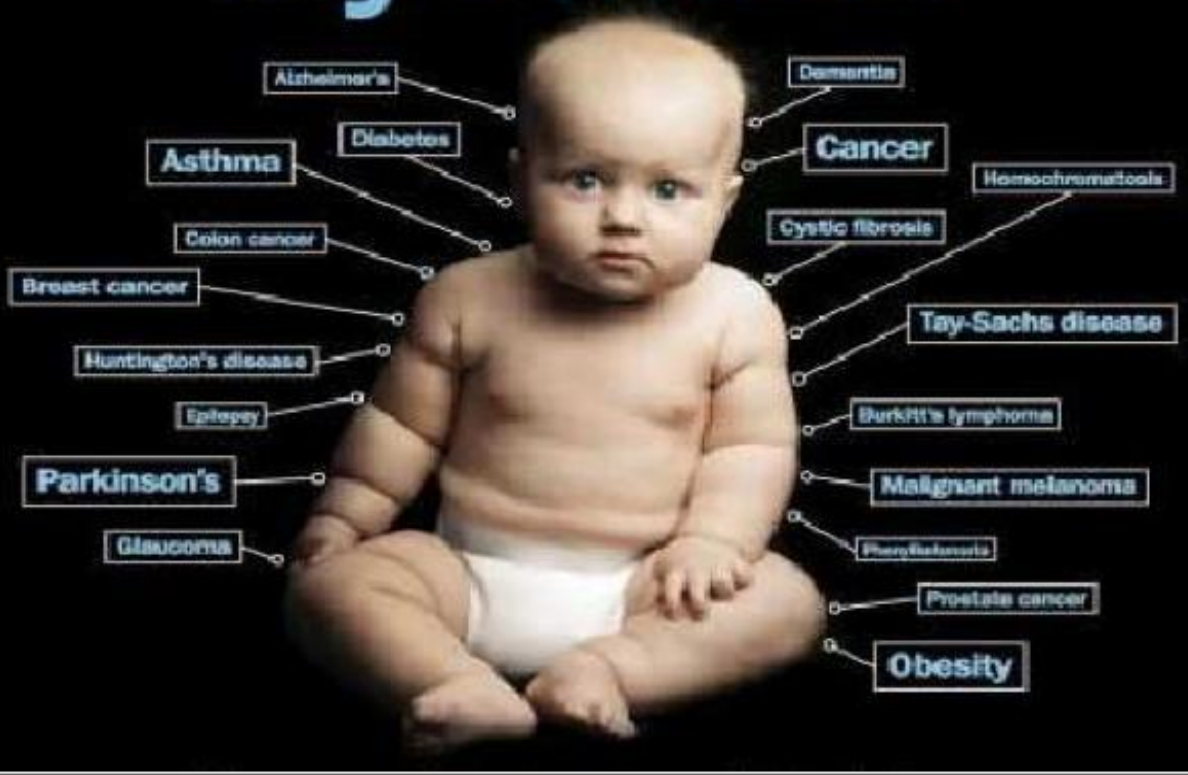
TIME

Want to Know My Future?

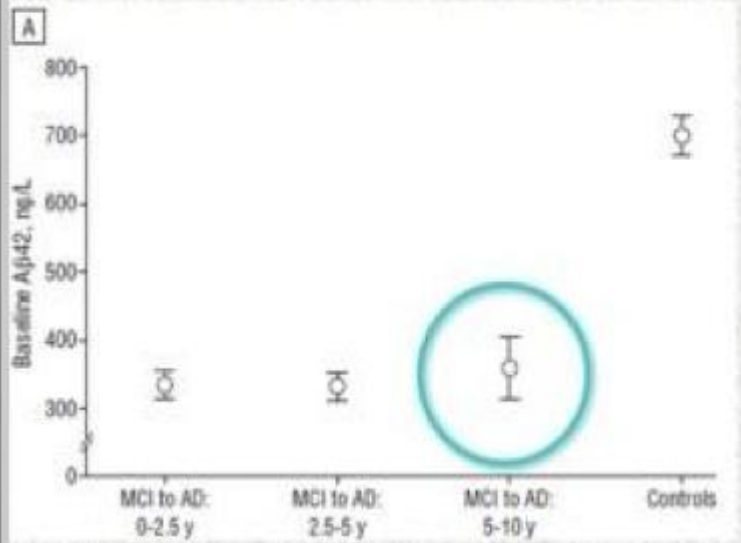


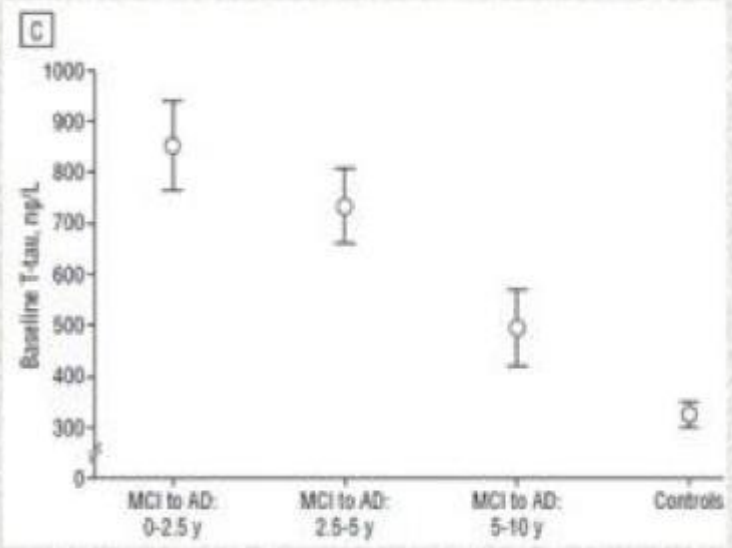
ORIGINAL ARTICLE

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

FARMACI ANTI-AMILOIDE
meccanismi

- F. che diminuiscono la produzione di beta amiloide (inibitori beta e gamma secretasi).
- F. che prevengono l'aggregazione di beta amiloide (TRAMIPROSATO).
- F. che promuovono la clearance di beta amiloide (immunoterapia attiva-vaccini-e immunoterapia passiva-anticorpi monoclonali-).

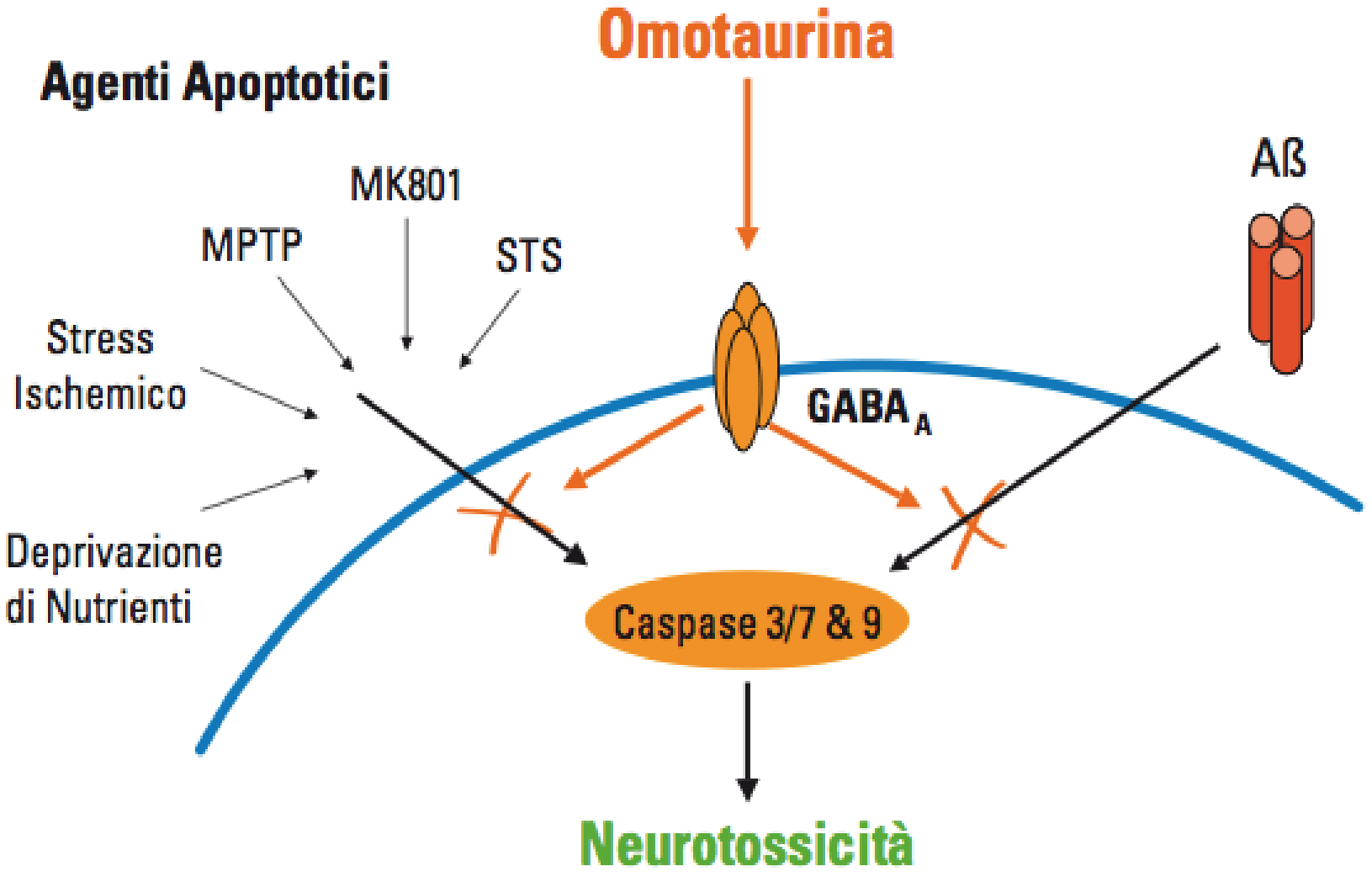
DALLE ALGHE ALL'IPPOCAMPO: TRAMIPROSATO (OMOTAURINA)

1: Struttura chimica del tramiprosato (omotaurina) e della taurina

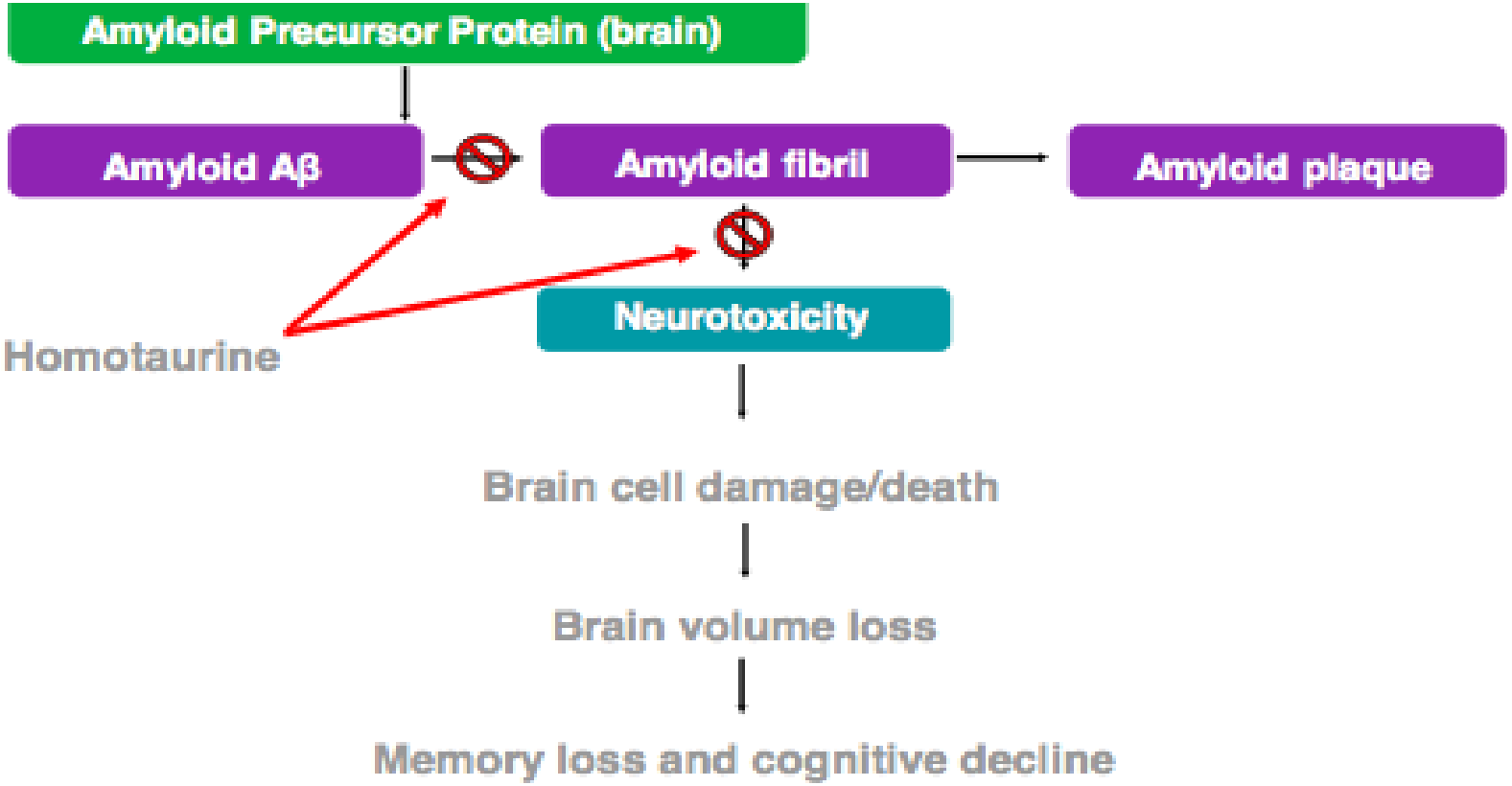
acido 3-amino-1-propansulfonico
(3-APS o Tramiprosato)

acido 2-aminoetansulfonico
(3-AES o Taurina)

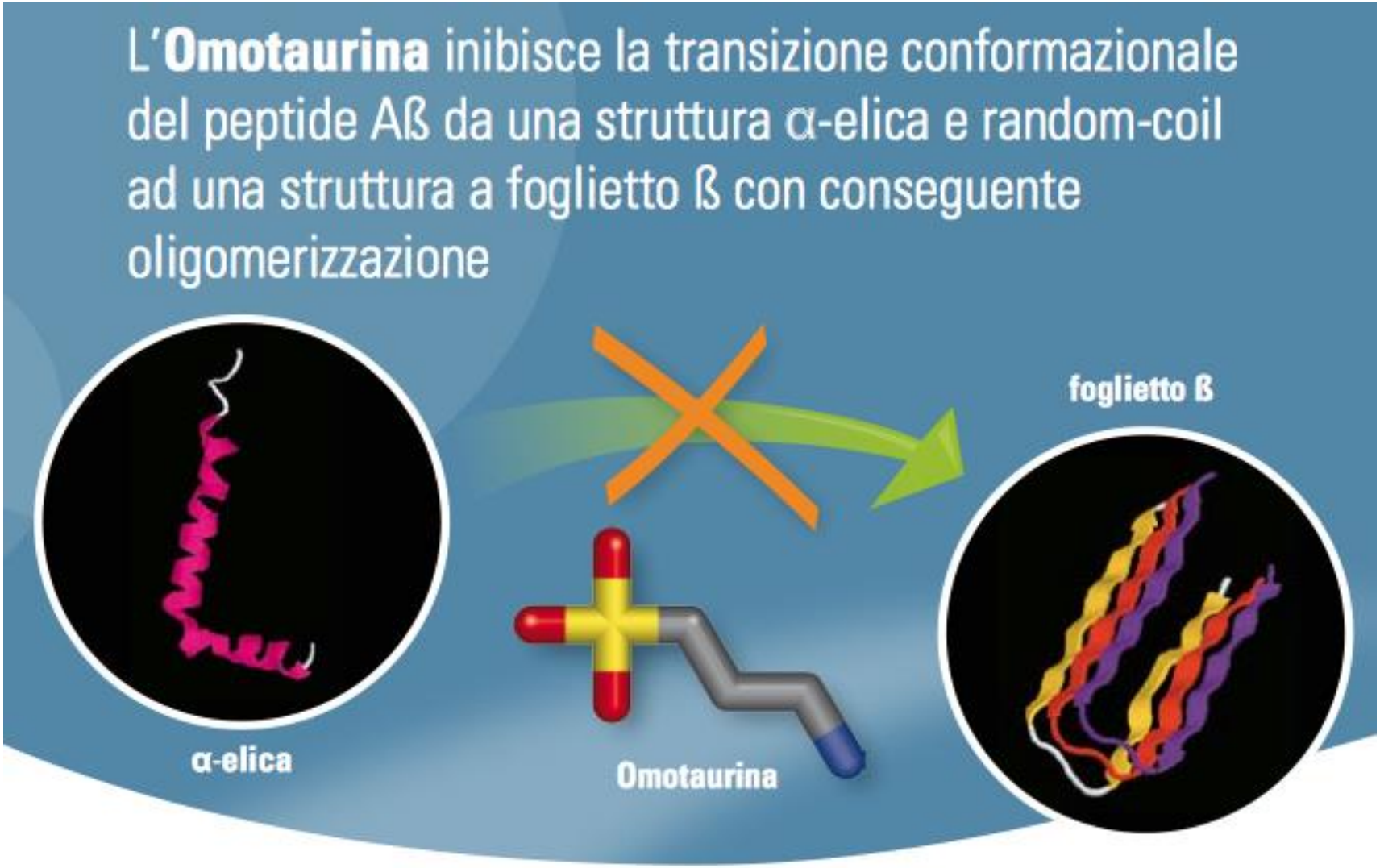
Effetto Neuroprotettivo GABA-Dipendente dell'Omotaurina

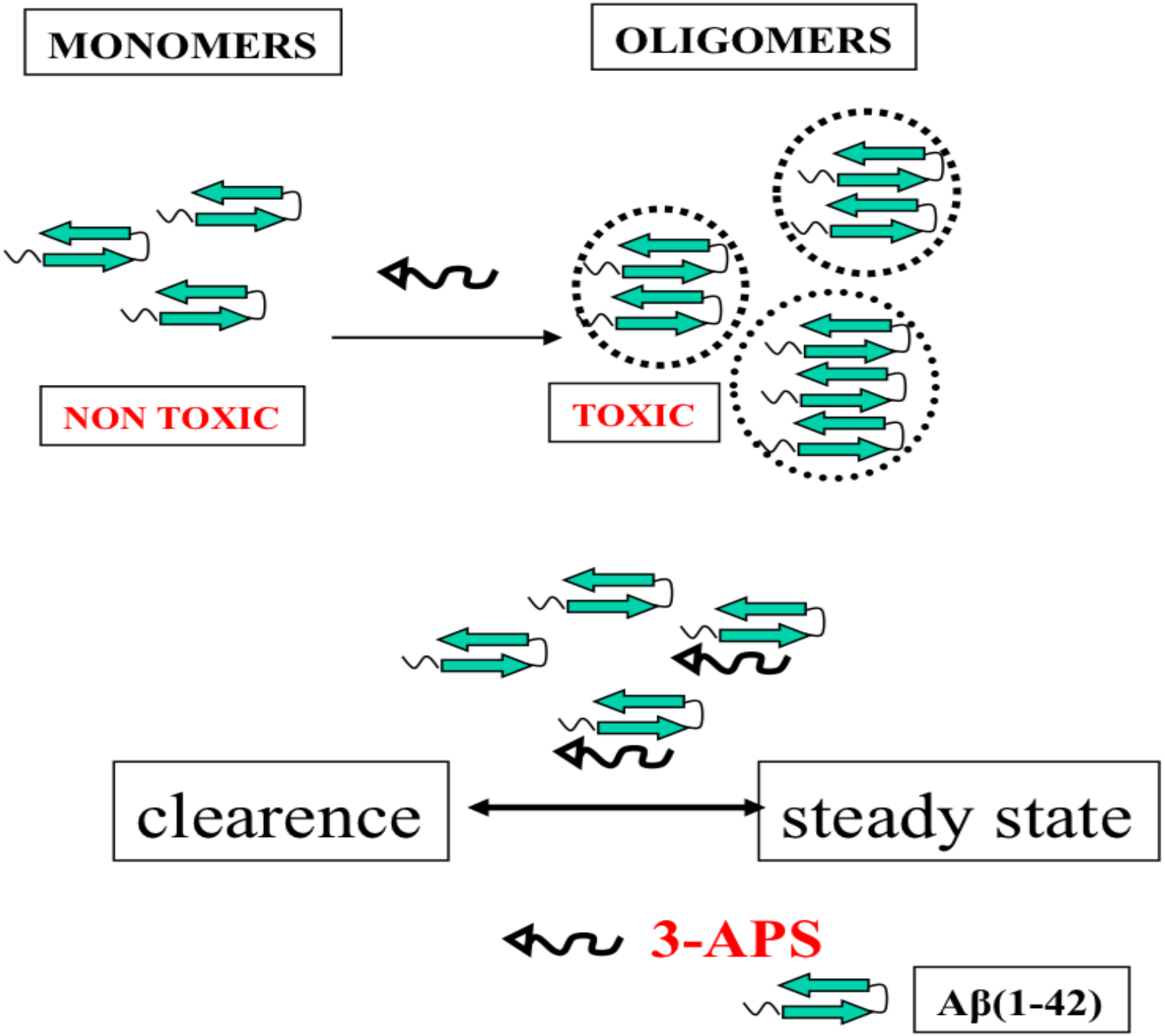


MECCANISMO D'AZIONE:
riduce l'aggregazione di A beta.



MECCANISMO D'AZIONE:
riduce l'aggregazione di A beta.





Gervais et al., Neurbiol. Aging, 2007

CHE COSA DETERMINA LA NEUROTOSSICITA' di A beta?

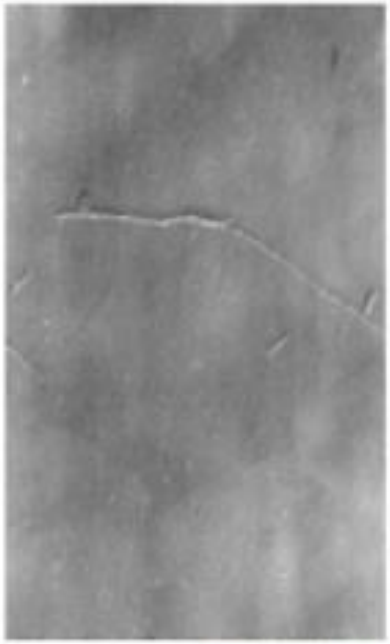
- La " corretta piegatura" (beta sheets) di A beta.

- Lo stato di aggregazione di A beta.

- Questi sembrano gli elementi piuttosto che la concentrazione in senso assoluto di A beta.

Homotaurine Inhibits Formation of Toxic Amyloid Fibrils *in vitro*

Amyloid Aß



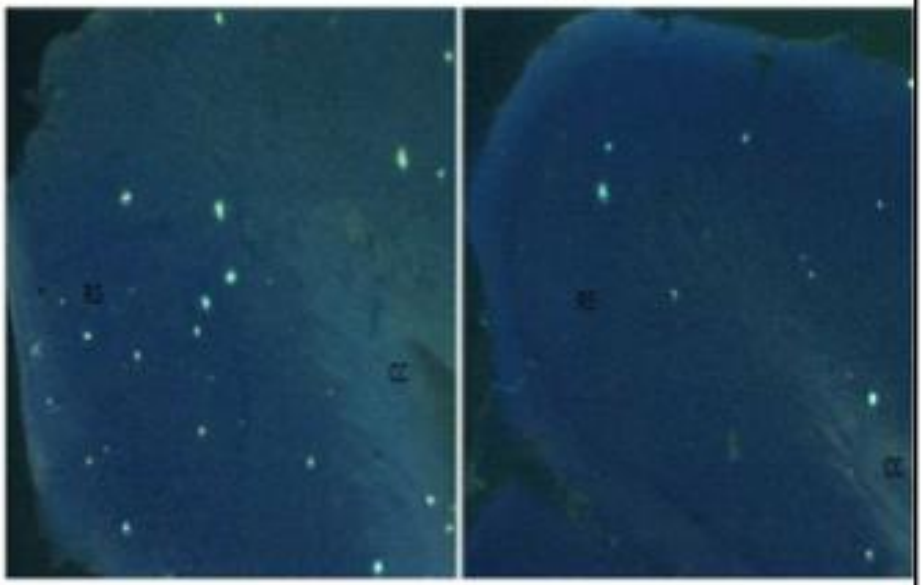
Amyloid Aß + homotaurine

24-hour incubation

Homotaurine Reduces Amyloid Deposition in hAPP Transgenic Mouse Brain

Control (untreated)

Homotaurine (100 mg/kg/day)
(8 weeks of treatment)



NEUROLOGY

A Phase II study targeting amyloid-ß with 3APS in mild-to-moderate Alzheimer disease

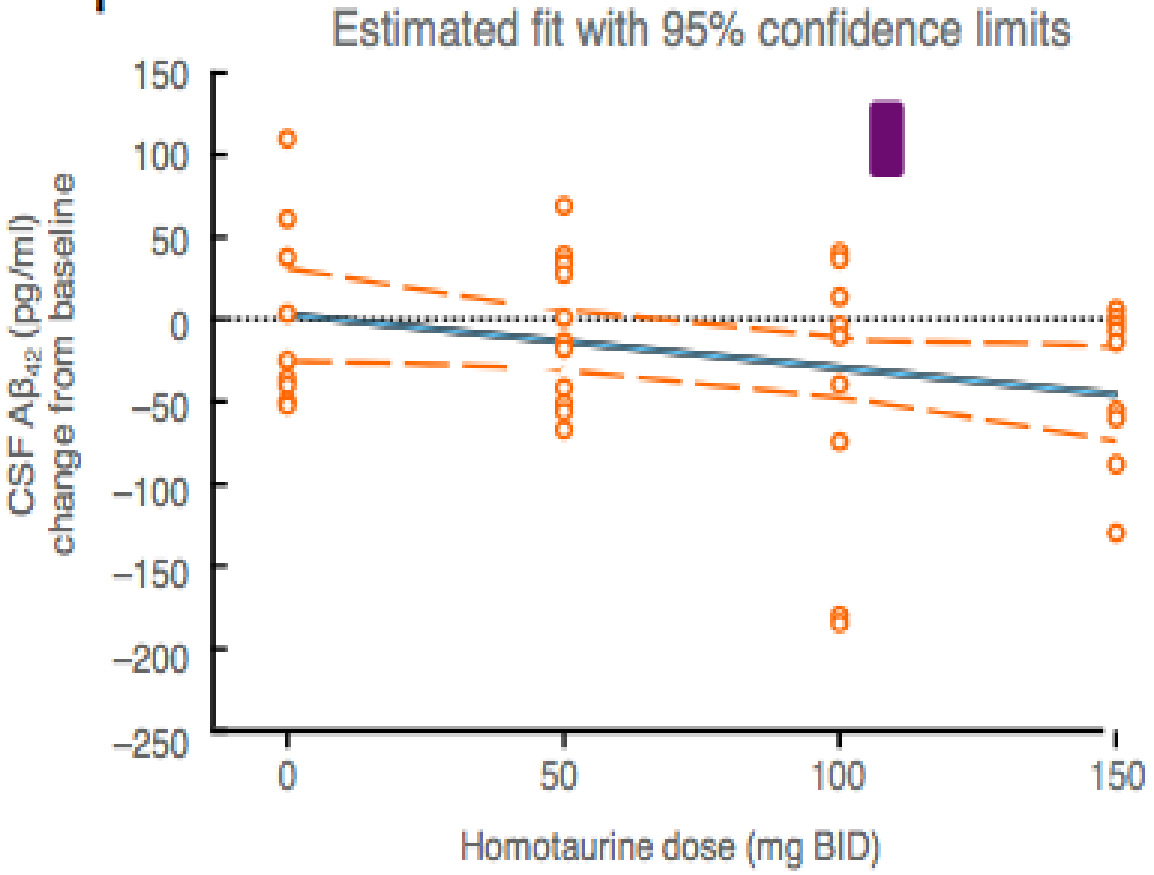
P. S. Aisen, D. Saumier, R. Briand, J. Laurin, F. Gervais, P. Tremblay and D. Garceau

Neurology 2006;67;1757-1763; originally published online Nov 2, 2006;
DOI: 10.1212/01.wnl.0000244346.08950.64

TRIAL FASE 2

- Studio randomizzato,in doppio cieco, controllato con placebo.
- 58 pazienti con AD lievo-moderato (MMSE tra 13-25).
- Placebo.
- Tramiprosato 50,100,150 mg x2 per tre mesi.

Phase II: Dose-dependent Decrease $A\beta_{42}$ Cerebrospinal Levels in AD Patients



Aisen PS et. al. Neurology 2008; 67(10): 1757-63.

TRIAL FASE 3 ALPHASE

- STUDIO RANDOMIZZATO, IN DOPPIO CIECO, CONTROLLATO CONTRO PLACEBO,
  con disegni a bracci paralleli,
  condotto in 67 centri negli USA ed in CANADA.

- 1052 pazienti con età sopra 50 anni, MMSE tra 16-26 inclusi.

- Tutti i pazienti erano trattati con inibitori delle colinesterasi e/o memantina per un minimo di 4 mesi prima della visita screening.

TRIAL FASE 3 ALPHASE

- Pazienti randomizzati per ricevere per 18 mesi:
- TRAMIPROSATO 100 MG X2/DIE
- TRAMIPROSATO 150 MG X2/DIE
- PLACEBO
- Endpoint primari: ADAS-Cog e Clinical Dementia Rating Scale Sum of Boxes.
- Lo studio era impostato per rilevare una riduzione del 25% del peggioramento clinico.

TRIAL FASE 3 ALPHASE

- Il potenziale effetto disease modifying

  era valutato attraverso misure di volumetria ippocampale alla MRI in un sottogruppo di pazienti (312) attraverso scansioni basali e finali.

TRIAL FASE 3 ALPHASE

- I modelli di analisi pianificati sono stati influenzati da un'alta varianza tra pazienti e confusi da un effetto sito (site effect).

- L'analisi post-hoc ha mostrato:
- trend di un effetto positivo sulle funzioni cognitive.
- trend di ridotta perdita di volume dell'ippocampo.

- Purtroppo la caratteristica dello studio di fase 2 (la riduzione di A beta 42 nel liquor), non è stata disponibile nello studio Alphase.

The Journal of Nutrition, Health & Aging©
Volume 13, Number 9, 2009

DOMAIN-SPECIFIC COGNITIVE EFFECTS OF TRAMIPROSATE IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE: ADAS-COG SUBSCALE RESULTS FROM THE ALPHASE STUDY

D. SAUMIER[1], A. DUONG[2,5], D. HAINE[2], D. GARCEAU[3], J. SAMPALIS[2,4]

Conclusion: This exploratory analysis suggests that tramiprosate may have some benefit on memory, language and praxis skills in mild to moderate AD individuals. Future clinical studies of tramiprosate should include specialized neuropsychological tests to validate its effects within these cognitive domains.

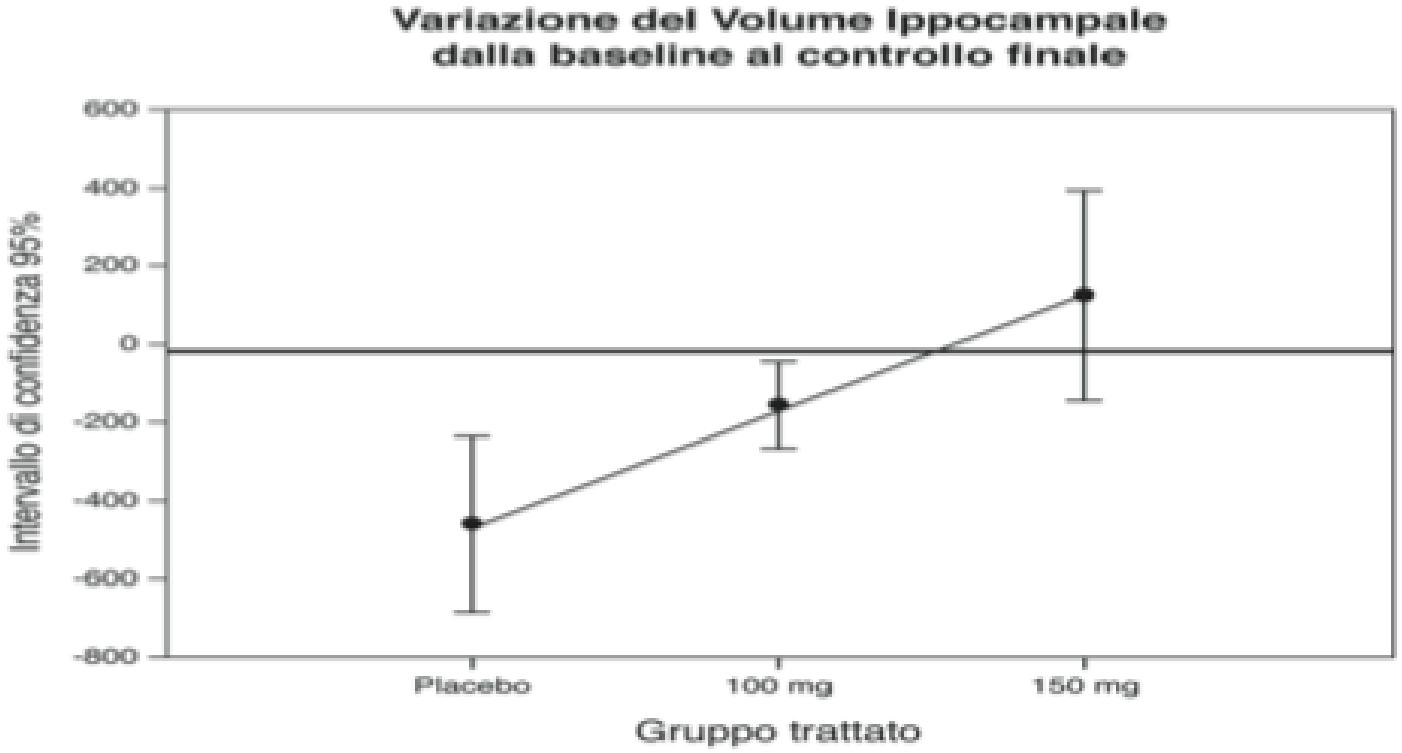
The Journal of Nutrition, Health & Aging©
Volume 13, Number 6, 2009

EFFECT OF TRAMIPROSATE IN PATIENTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE: EXPLORATORY ANALYSES OF THE MRI SUB-GROUP OF THE ALPHASE STUDY

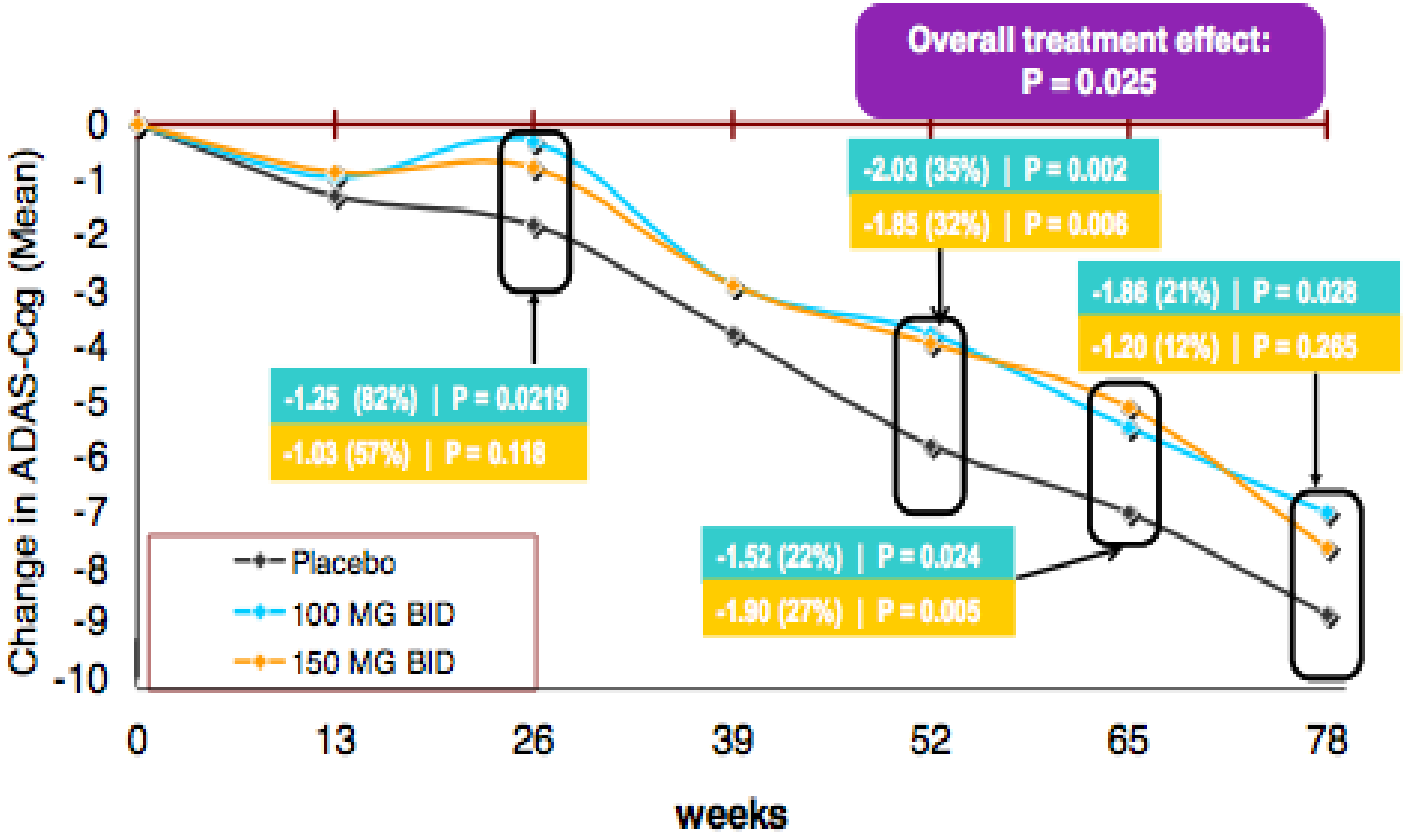
S. GAUTHIER[1], P.S. AISEN[2], S.H. FERRIS[3], D. SAUMIER[4,9], A. DUONG[4], D. HAINE[5], D. GARCEAU[6], J. SUHY[7], J. OH[7], W. LAU[7], J. SAMPALIS[8] FOR THE ALPHASE GROUP

Conclusion: Exploratory analysis of the vMRI subgroup suggests that tramiprosate slows hippocampal atrophy, and reveals some evidence of a beneficial effect on cognition. The clinical validity of the vMRI biomarker is discussed.

Cambiamento nel volume dell'ippocampo (HV) = (Volume alla settimana 78). Le unità sono in mm^3. L'atrofia è da intendersi indicata da un cambiamento medio < 0.



Homotaurine Reduces Cognitive Decline Significantly in AD Patients - ApoE4+



Adjusted by Mixed Effects Repeated Measures Model

Arch Med Sci 2011; 7, 1: 102-111
DOI: 10.5114/aoms.2011.20612

Tramiprosate in mild-to-moderate Alzheimer's disease – a randomized, double-blind, placebo-controlled, multi-centre study (the Alphase Study)

Paul S. Aisen[1], Serge Gauthier[2], Steven H. Ferris[3,4], Daniel Saumier[5], Denis Haine[6], Denis Garceau[7], Anh Duong[6], Joyce Suhy[8], Joonmi Oh[8], Wan C. Lau[8], John Sampalis[6,9] for the Alphase group

Conclusions: The primary planned analyses did not show a significant treatment effect, but were confounded by unexplained variance. Post-hoc analyses showed a significant treatment-related reduction in HV loss. However, there was only a trend towards slowing of decline on the ADAS-cog and no slowing of decline on the CDR-SB. These results must be interpreted in consideration of the limitations of clinical and disease-modification outcome measures and their relationship, the heterogeneity of the disease and the impact of confounding demographic and clinical variables.

Tramiprosate (Alzhemed) for Alzheimer's disease (Protocol)

Malouf R, Collins H

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

Clinical and Brain Structural Correlates of Homotaurine Treatment in MCI and AD: Preliminary One-year Follow-up Evidence

Gianfranco Spalletta, MD, PhD

IRCCS Fondazione Santa Lucia,
Laboratorio di Neuropsichiatria,
Dipartimento di Neurologia Clinica e Comportamentale,
via Ardeatina, 306, Roma

Studio longitudinale osservazionale

Prevista l'inclusione di 40 pazienti con MCI + 40 pazienti con AD

-Follow-ups a 0-6-12-24 mesi
-Esordio di malattia (prima diagnosi)
-Pazienti non trattati farmacologicamente con AChEI o psicofarmaci
-MCI amnesico e AD neurodegenerativo puro

Conclusioni

- Omotaurina 100 mg/die in soggetti con MCI amnesico alla prima diagnosi:
  - Potrebbe avere un effetto selettivo su memoria (verbale-episodica?) a breve termine;
  - Potrebbe stabilizzare o, addirittura, migliorare la progressione della sintomatologia apatica;
  - Stabilizza la progressione dell'atrofia a livello ippocampale con maggiore effetto sull'ippocampo sinistro;
  - Potrebbe avere un effetto sulla volumetria dell'accumbens, spiegando così l'effetto su apatia.

Futuri studi in doppio cieco dovrebbero confermare tali dati e focalizzarsi sui meccanismi legati a tali effetti.

Conclusioni sul ruolo del TRAMIPROSATO 1

Modelli statistici predittivi hanno mostrato:

- Trend a favore di effetti benefici cognitivi.
- Trend verso una minore riduzione del volume dell'ippocampo.
- Riduzione del deterioramento cognitivo nella sottopopolazione APOE4+.

Conclusioni sul ruolo del TRAMIPROSATO 2

- Buon profilo di sicurezza e tollerabilità.
- Commercializzato come integratore alimentare e nutraceutico.
- Possibile impiego in prevenzione secondaria a lungo termine.

Alzheimer facebook italia