The Amyloid Cascade Hypothesis
(Hardy and Selkoe, 2002)

Aβ pathology
tau pathology

APP
Aβ 1-42 monomers
phospho-tau

oligomers
tangles
protofibrils/fibrils
senile plaques
neuronal death

Early synaptic dysfunction
Gene dosage
Missense and deletion mutations

β-secretase  α-secretase  γ-secretase

668 SVKMDAEPRHDGYEVHHQKLVDFAEDVGSNKGVAIIGLMLVGGQYVIVITLVMLKKK 726


Retromers in Alzheimer’s disease
**Retromers in Alzheimer’s disease**

The prion hypothesis: mechanism of seeding and template in neurodegenerative disorders *(Goedert et al., Science, 349, 2015)*
Reducing the formation of $\beta$-amyloid peptide: a strategy for the design of disease-modifying drugs in Alzheimer's Disease

**Amyloid Precursor Protein**

\[
\text{NH}_2 \quad \text{APP} \quad -\text{COOH}
\]

$\beta$-secretase

\[
\text{APP s} \beta \quad \beta
\]

$\gamma$-secretase

\[
\text{A} \beta_{1-42}
\]

Oligomers toxic by multiple mechanisms

Senile plaques

Inhibitors or modulators

From Sisodia & St George-Hyslop, 2002
Amyloid hypothesis of Alzheimer’s disease: loss or gain of function?

**Amyloid Precursor Protein**

\[ \text{NH}_2 \xrightarrow{\beta \text{ secretase}} \text{APP} \xrightarrow{\gamma \text{ secretase}} \beta_{42} \]

*Monomers*

Physiological functions?

*Oligomers*

toxic by multiple mechanisms

From Sisodia & St George-Hyslop, 2002
Monomers of β-amyloid are neuroprotective
(Giuffrida et al., J. Neurosci, 29, 10582, 2009)

Peptides dissolved in TFA, HFIP, suspended in DMSO, diluted in DMEM/F12, overnight at cold T, isolated by filtration (cut-off 10, 30, 50 kDa)
### The Insulin Receptor Family

<table>
<thead>
<tr>
<th>Insulin</th>
<th>IGF-I/IGF-II</th>
<th>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR-A</td>
<td>IR-A</td>
<td>IR-B</td>
</tr>
<tr>
<td>IR-A</td>
<td>type-1 IGF</td>
<td>“hybrid” IR/IGFR</td>
</tr>
<tr>
<td>IR-A</td>
<td></td>
<td>IRR</td>
</tr>
</tbody>
</table>

**Table:**

| Monomeric β-amyloid acts as a positive allosteric modulator of type-I IGF receptors immune captured from transfected 3T3 cells |

**Figure:**

- Diagram showing interactions between insulin and IGF receptors.
- Graphs illustrating the effect of monomeric β-amyloid on insulin and IGF receptors.

**EDVGSNKGAIIGLMVGGVIA**

**DAEFRHDSGYEVHHQKLVFFA**

**No effect on insulin receptor**
Neuroprotection by β-amyloid monomers is mediated by type-I IGF receptors

Does amyloid monomer stimulate glucose uptake in neurons?

<table>
<thead>
<tr>
<th>Insulin</th>
<th>IGF-I/IGF-II</th>
<th>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR-A</td>
<td>IR-A type-1 IGF “hybrid” IR/IGFR</td>
<td>IRR</td>
</tr>
<tr>
<td>IR-B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Monomeric β-amyloid stimulates glucose uptake in neurons

Monomeric β-amyloid stimulates translocation of the neuropil Glut3 glucose transporter in neurons
Endogenous production of β-amyloid monomers is required for activity-dependent glucose uptake in neurons

<table>
<thead>
<tr>
<th>Condition</th>
<th>Aβ1-42 release (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.593 ± 0.569</td>
</tr>
<tr>
<td>γ-Sec Inh, 100 nM</td>
<td>0.257 ± 0.068</td>
</tr>
<tr>
<td>KCl, 40 mM</td>
<td>14.033 ± 1.486**</td>
</tr>
<tr>
<td>γ-Sec Inh + KCl</td>
<td>4.237 ± 0.917**</td>
</tr>
</tbody>
</table>

Cirrito et al., Neuron 2008
Monomeric β-amyloid stimulates Glut3 translocation and glucose uptake in differentiated skeletal muscle cells
**Inhibitors of Aβ aggregation**

- Daunomycin
- Rolitetracycline
- Carvedilol

**Congo red derivatives, Rifampicin, β-Sheet breaking peptides**

**Inhibitors of pathological chaperones**
(ApoE4, α1-antichymotrypsin, C1q factor)

**Zinc and Cupper chelators**

**Inhibitors of glycosaminoglycans**

- 3-Amino-1-propansulphonate
  *(Tramiprosate; Homotaurine)*

---

**Aging Clinical and Experimental Research**

**REVIEW ARTICLE**

**The potential protective effect of tramiprosate (homotaurine) against Alzheimer’s disease: a review**

Carlo Caltagirone¹, Luigi Ferrannini², Niccolò Marchionni³, Giuseppe Nappi⁴, Giovanni Scapagnini⁵ and Marco Trabucchi⁶

¹Chair of Neurology, University of Roma Tor Vergata, and Scientific Director, IRCSS Santa Lucia Foundation, Rome; ²Department of Mental Health and Addictions - ASL 3 Genoa, and President of the Italian Psychiatry Association; ³Division of Geriatric Cardiology and Medicine, University of Florence, Azienda Ospedaliero-Universitaria Careggi, Florence; ⁴Scientific Director, IRCCS “C. Mondino National Neurological Institute”, Pavia, and Chair of Neurology, University “La Sapienza”, Rome; ⁵Department of Health Sciences, Faculty of Medicine and Surgery, University of Molise, Campobasso; ⁶Geriatric Research Group, Brescia, Italy
Endogenous production of β-amyloid monomers is required for activity-dependent glucose uptake in neurons

<table>
<thead>
<tr>
<th>Condition</th>
<th>Aβ42 release (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.50 ± 0.569</td>
</tr>
<tr>
<td>γ-Sec Inh, 100 nM</td>
<td>0.257 ± 0.068</td>
</tr>
<tr>
<td>KCl, 40 mM</td>
<td>14.03 ± 1.48</td>
</tr>
<tr>
<td>γ-Sec Inh + KCl</td>
<td>4.237 ± 0</td>
</tr>
</tbody>
</table>

**Inhibitors of Aβ aggregation**

- Congo red derivatives, Rifampicin, Tetracyclines, Antracyclines, Inositols, β-Sheet breaking peptides
- Zinc and Copper chelators
- Inhibitors of pathological chaperones
  (ApoE4, α1-antichymotrypsin, C1q factor, glycosaminoglycans)

**Daunomycin**

**Rolitetracycline**

**Carvedilol**
**Glycosaminoglycans accelerate amyloid aggregation**

1. Number of sulfate groups
2. Amyloid protein: GAG ratio
3. Molarity of solutes

ApoE4 enhances sulfatation of GAGs in neural cells (Bonay and Avila, BBA 2001)

**Retromers in Alzheimer’s disease**  
**β-Amyloid monomers protect cultured neurons against death by trophic deprivation by activating the PtdIns-3-K pathway**

![Graph showing the effect of β-Amyloid monomers on neuronal survival](image)

- **CTRL**
- **no Ins**
- **no Ins + m Ab(1-42)**
- **no Ins + m Ab(1-42) + LY 294002**
- **no Ins + LY 294002**

**Graph legend:**
- Bcl-2: C <10 kD
- β-actin
- PtdIns-3-K ➔ p-Akt ➔ p-GSK3β ➔ β-catenin
- LY294002

---

**Ligand binding sites at insulin receptor and type-I IGF receptor**

(De Meyts and Whittaker, Nat Rev Drug Disc, 2002)

![Diagram showing ligand binding sites at insulin receptor and type-I IGF receptor](image)
Docking simulation of monomeric Aβ on type-I IGF-R or insulin receptor (IR)

IGF-IR/IGF1

IGF-IR/Aβ42

IR/Aβ42

Dr. A. Pietropaolo
Univ. Of Catanzaro

Native CSF human β-amyloid supports glucose uptake in cultured neurons

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Gender</th>
<th>Age</th>
<th>CSF Aβ42 (pg/ml)</th>
<th>CSF glucose (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>M</td>
<td>66</td>
<td>1,200</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>51</td>
<td>1,280</td>
<td>4.38</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>57</td>
<td>1,076</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>51</td>
<td>815</td>
<td>3.8</td>
</tr>
<tr>
<td>AD</td>
<td>F</td>
<td>72</td>
<td>290</td>
<td>4.33</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>70</td>
<td>391</td>
<td>2.88</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>61</td>
<td>590</td>
<td>3.94</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>55</td>
<td>463</td>
<td>4.6</td>
</tr>
</tbody>
</table>
Monomeric β-amyloid stimulates Glut3 translocation and glucose uptake in differentiated skeletal muscle cells

β-Amyloid monomers, but not those carrying the E22G mutation, protect neurons against NMDA toxicity via PtdIns-3-K activation
Neuroprotection by the β-amyloid monomer involves the activation of a member of the insulin receptor family

PPP = selective inhibitor of type-I IGF receptor
AG1014 = dual inhibitor of IR and IGF-R1

PPP = type-I IGF receptor inhibitor
AG1014 = IR/IGF-R1 inhibitor
Long-term potentiation (LTP) of excitatory synaptic transmission: the substrate for associative learning

Collingridge et al., Nat Rev Neurosci 2005
Oligomers of Aβ_{1-42} disrupt LTP in the hippocampus by inhibiting the PtdIns-3-K/Akt/GSK3β pathway
(Cho and Collingridge’s lab, Nat. Neurosci., 2012)

Aβ olig. → ↑Caspase-3 →↓ Akt1 →↑ GSK3β →↑ p-Tau
**Starting points**

*Reduced CSF β-amyloid levels in AD: loss of function hypothesis?*

*Early reduction in brain glucose uptake in AD*

**Monomeric Aβ_{1-40} (100 nM) enhances glucose uptake in cultured neurons via the activation of PtdIns-3-K and AMP kinase**
The Amyloid Cascade Hypothesis
(Hardy and Selkoe, 2002)

**APP**
- APP mutations
- PS mutations
- $A\beta$ 1-42 monomers
  - Early synaptic dysfunction
  - oligomers
    - phospho-tau
    - tangles
  - protofibrils/fibrils
  - senile plaques
  - neuronal death

(A) The Amyloid Precursor Protein and amyloidogenic processing of APP.
(B) Non-amyloidogenic processing of APP.
**β-Secretase Inhibitors**

**General pitfalls:**
- Neureguline-1
- Blood-brain barrier

**PPAR-γ activators (Pioglitazone, Rosiglitazone)**

- \( \downarrow \text{BACE-1 and APP expression} \)
- \( \uparrow \text{APP degradation} \)
- \( \downarrow \text{Insulin levels} \)

**Phase 3 RCTs Rosiglitazione: no effect**

CTS21166 (oral) on going

---

**γ-Secretase inhibitors in AD**

**Pros**
- Improve cognitive deficits in AD mice
- LY450139 and MK-0572 ↓ serum Aβ levels in AD (Semagacestat)

**Cons**
- Notch-related effects [GI, blood cells, Neurodegeneration]
- “Rebound” effect.
Tarenflurbil for AD “a shot on goal that missed”

Green et al., JAMA 302, 2009

The Amyloid Cascade Hypothesis
(Hardy and Selkoe, 2002)

APP
- APP mutations
- PS mutations

? → Aβ1-42 monomers → phospho-tau

Early synaptic dysfunction → oligomers → tangles → neuronal death

Aβ pathology
tau pathology

protofibrils/fibrils

senile plaques
NMDA receptor

Channel blockers
- Mg
- Memantine

Agonists
- Glutamate
- NMDA

Coagonists
- Glycine
- D-serine

Ca²⁺

Antagonists
- AP5
- 5,7-dihydroxykynurenic acid (5,7-dioxykynurenic acid, 5,7-DMOA)

NR2B NR1

K⁺
Memantine: NMDA receptor antagonist

Memantine concentration (M)

- $\alpha_2$ Receptor
- $\alpha_1$ Receptor
- Kainate Receptor
- D$_2$ Receptor
- AMPA Receptor
- DA/5HT Transporter
- 5HT$_3$ Receptor
- Sigma Binding site
- Nicotinic ACh Receptor
- 5HT$_1$ Receptor

- NMDA Receptor

Therapeutic concentration

Dual role for synaptic (NR2A) and extrasynaptic (NR2B) NMDA-R in neuronal viability (Hardingham and Bading, Nat. Rev. Neurosci., 2010)

Survival Plasticity

Neuronal Death

Synaptic NMDAR(NR2A)

Extrasynaptic NMDAR(NR2B)

Synaptic NMDAR

Extrasynaptic NMDAR

Calcineurin

TCOR

CaMKIV

CREB

Nucleus

ERK2

CRE

Jacob

FOXO1/FOXO3

Alk

Apoptosis

Foxo7

TRAP

Bim

Fadd

Nucleus
Memantine preferentially inhibits extrasynaptic “neurotoxic” NMDA receptors

Inhibitors of Aβ fibrillization
- 3-Amino-1-propansulphonate (Tramiprosate – Alzhemed)
- Curcumine; PIB; Metal chelators
- Daunomycin
- Rolitetracycline
- Carvedilol

Inhibitors of tau aggregation
- Methylthioninium chloride (Rember; TauRx) phase II; 7.8 in ADAS-cog
Vaccine in AD: Active immunization

PDAPP mice  Aβ42-immunized

plaque

dystrophic neurites

astrocytosis

Schenk et al., Nature 400: 173, 1999
Lumen or Extracellular Space

Notch

Presenilin

TACE cleavage site

Cytoplasm

γ-secretase?

β-secretase cleavage site

APP

03/11/2015
Induction of long-term potentiation/long-term depression at the Schaffer collateral/CA3 synapse

Collingridge et al., Nat Rev Neurosci 2005

2. L’attivazione dei recettori NMDA dipende dalla presenza di uno stimolo di rinforzo con carattere di associatività e cooperatività
**Improvement of learning and memory by memantine**

1. **Improvement of signal-to-noise**
2. **Production of BDNF**
3. **Increased neurogenesis**
4. **Reduced synaptic inhibition**

---

**The signal-to-noise hypothesis of learning**

![Diagram showing the signal-to-noise hypothesis of learning.](image)

- Rest: Glutamate (△), Magnesium (●)
- Learning: Signal detected, Increased Glutamate, Reduced Magnesium

---

- Signal
- Noise
An increased basal level of glutamate induces “noise” at the glutamatergic synapse preventing LTP.

- Increased noise to signal inhibits LTP
- Increased intracellular Ca2+ levels can induce neuronal cell death
Differentiation from other NMDA antagonists

- Resting condition
- Energy deprivation
- Synaptic activity

- **Mg**$^{2+}$
  - Physiological Mg$^{2+}$ block

- **Memantine**
  - Moderate-affinity antagonist

- **MK-801**
  - High-affinity antagonists

Tetracycline inhibits fibril extension and keeps the amyloid protein in a prefibrillar cytotoxic state (Malmo et al., FASEB J. 2005)

Controls, 15 days

Tetracycline, 15 days

Dynamic scattering of W7FW14F apomyoglobin – 7 days of incubation

NIH-3T3

- 0
- 7
- 15 days
Memantine enhances the formation of BDNF in the CNS

Adult neurogenesis in the dentate gyrus
Neurogenesis and the encoding of time in new memories
Aimone et al., Nat. Neurosci., 2006

Inhibitors of Aβ aggregation

Congo red derivatives, Rifampicin, 
β-Sheet breaking peptides
Inhibitors of pathological chaperones
(ApoE4, α1-antichymotrypsin, C1q factor)
Zinc and Copper chelators

Inhibitors of glycosaminoglycans
3-Amino-1-propansulphonate
(Tramiprosate; Homotaurine)
**NRM8499: Valine prodrug of tramiprosate**

![Chemical structure of NRM8499]

**Graphs showing plasma and brain concentration over time**

**DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA**

**H2N SO3H**

**MONOMERS**

**OLIGOMERS**

**Non toxic**

**Toxic**

**3-APS**

*Gervais et al., Neurbiol. Aging, 2007*
**Protective activity of tramiprosate against Aβ-induced apoptosis in cultured neurons** (Gervais et al., Neurobiol. Aging, 2007)

24 hrs

Amyloid Aβ

Amyloid Aβ + homotaurine

---

**Targeting soluble Aβ peptide with tramiprosate for the treatment of brain amyloidosis**

(Gervais et al., Neurobiol. Aging 28. 2007)

TgCRND8 mice (9 weeks) treated for 8 weeks with tramiprosate (APS)
Tramiprosate as a GABA_A receptor agonist: relevant to therapeutic outcome in AD?

GABA_A receptor-dependent neuroprotection by tramiprosate against Aβ-mediated toxicity (Martin et al., Neurochem Inc. 2013)
Enhanced excitation and seizure-prone phenotype in AD mice
(Palop et al., Neuron 55, 2007)

Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in AD mutant mice
(Palop et al., Neuron, 55, 2007)
Nicotine boosting of synaptic plasticity requires GABAergic neurons in anti-NGF "AD" mice (Rosato-Siri et al., J. Physiol. 576, 2006)

Homotaurine (HT) prevents Aβ-induced inhibition of LTP, a physiological substrate of associative learning
Rationale for the use of tramiprosate in AD

1. GAG inhibitor that reduces the formation of toxic oligomers lowering brain levels of insoluble aggregates. Expected greater efficacy in the presence of pathological chaperons

2. Agonist activity at GABA_A receptors: implications for neuroprotection and cognition-enhancing effect in AD

3. Linear kinetics and good brain penetration (further improved with the valine prodrug)

4. Main question: any interference with the physiological activity of Aβ monomers?

Tramiprosate enhances tau aggregation reducing tau binding to β-actin without affecting neuronal survival (Santa-Maria et al., Mol. Neurodeg. 2007)
Monomeric \( \beta \)-amyloid mimics the action of IGF-1 in suppressing insulin secretion

Glucose consumption and type-I IGFR phosphorylation in hippocampal slices from wt and AD mice incubated with IGF-I and \( \beta \)-amyloid monomer

<table>
<thead>
<tr>
<th>TgCRND8</th>
<th>glucose consumption (( \mu )mol/hr)</th>
<th>Non-Tg</th>
<th>glucose consumption (( \mu )mol/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>100</td>
<td>100</td>
<td>0.35 ± 0.01</td>
</tr>
<tr>
<td>IGF-I, 1 nM</td>
<td>88.5 ± 5.35</td>
<td>153.467 ± 14.91</td>
<td>0.35 ± 0.02</td>
</tr>
<tr>
<td>mAB, 100 nM</td>
<td>147.767 ± 4.68</td>
<td>74.543 ± 12.25</td>
<td>0.35 ± 0.015</td>
</tr>
</tbody>
</table>
**Aβ (1-40) acts as a PAM at immunocaptured type-I IGF receptors with no agonist activity**

Monomers of β-amyloid protect neurons against excitotoxic death (Giuffrida et al., J. Neurosci, 2009)
Tetracyclines protect *C. elegans* against human amyloid toxicity by targeting oligomers (Diomede et al., *Neurobiol. Dis.* 40, 2010)

Glycosaminoglycan inhibitors:

3-Aminopropan sulphonate (3-APS, homotaurine, tramiprosate)

*H₂N* \[\begin{array}{c}
\text{S}\text{O} \text{S} \\
\text{O} \text{H}
\end{array}\]

Amyloid Aβ  
Amyloid Aβ + *homotaurine*

24-hour incubation
Starting points

Reduced CSF β-amyloid levels in AD: loss of function hypothesis?

Early reduction in brain glucose uptake in AD

The Amyloid Cascade Hypothesis
(Hardy and Selkoe, 2002)
Minocycline inhibits early pre-plaque neuroinflammation in AD mice (McGill-Thyl-APP) (Ferretti et al., J. Neuroinflammation, 9, 2012)

Abnormal activity-dependent synaptic plasticity in AD mutant mice (Palop et al., Neuron 55, 2007)
Minocycline attenuates neuronal death and improves cognitive impairment in Tg2576 AD mice (Choi et al., Neuropsychopharm. 32, 2007)
**γ-Secretase inhibitors in AD**

*Pros*
- Improve cognitive deficits in AD mice

LY450139 and MK-0572 ↓ serum Aβ levels in AD

*Cons*
- Notch-related effects [GI, blood cells, Neurodegeneration]
- “Rebound” effect.
**Selective Amyloid Lowering Agents (SALAs)**
- R-Flurbiprofen, Ibuprofen, Sulindac, Indomethacin

**Selective Amyloid Raising Agents (SARAs)**
- Fenofibrate, Celecoxib

Tarenflurbil for AD “a shot on goal that missed”

Green et al., JAMA 302, 2009

---

**Vaccine in AD:**
**Active immunization**

PDAPP mice  
Aβ42-immunized

- plaques
- dystrophic neurites
- astrocytosis

Schenk et al., Nature 400: 173, 1999
Elan/Wyett active vaccination: phase II trial (n = 360)
Trial suspended for aseptic encephalitis (6%) (AN-1792)
Potential Avenues

Active immunization
1) Th2-preferential adjuvant (e.g. alumen vs QS21)
2) Th2-directed epitope (Aβ1-11/PADRE/MDC/CCL22)

Passive Immunization
1) Catalytic IgM
2) Deglycosylated antibodies
3) F(\text{ab}’)2 fragments
4) BAPINEZUMAB (AAB-001; Elan) phase III in ApoE4 non carriers
5) SOLANEZUMAB (LY2062430; Eli Lilly; phase II)

\textit{APOE \epsilon 4} and bapineuzumab
Infusing pharmacogenomics into Alzheimer disease therapeutics

Vasogenic edema in \textit{12/124 (10%)} associated with \textit{APOE 4 carrier status (10/12 or 33% of all APOE \epsilon 4 carriers)}
\textit{Dose-dependent and reversible} on MRI after discontinuation.
Healthy Adults with Lower Aβ Brain Levels Scored Better on Memory Test

Healthy adults (average age of 72 years)

\[ r = -0.38, \ p = 0.034 \]

Pike KE et al. Brain 2007; 130:2397-44.
GABA-INDEPENDENT NEUROPROTECTIVE ACTIVITY OF HOMOTAUrine

Homotaurine

E834G

Biochemical anal.
Western blot

DNA fragmentation/condensation
Hoechst assay

Neurotoxicity

Mean (± SD) Brain and Plasma Concentration (µg eq/g)

Time (h)
Targeting soluble Aβ peptide with tramiprosate for the treatment of brain amyloidosis (Gervais et al., Neurobiol. Aging 28. 2007)
Phase II: Tramiprosate reduces CSF Aβ42 levels in patients with mild-to-moderate AD

Aisen et al., Neurology 2006

ORTH AMERICAN PHASE III STUDY DESIGN FOR TRAMIPROSATE (ALPHASE STUDY)…..

RULED INCONCLUSIVE BY FDA in 2008

- 1,052 mild to moderate AD patients were given either placebo or homotaurine for 18 months
- Homotaurine/placebo administered as add-on to AChE inhibitors ± memantine
- Cognitive function was tested using the standard, validated ADAS-cog test every 3 months
- Brain Volume (hippocampus) was measured at baseline and after 18 months of treatment in a subset of patients
Results from the vMRI subgroup of the ALPHASE Study (adjusted by mixed effects model)


Data presented at the GerontoNet Symposium

Post-hoc analysis of ALPHASE study: Tramiporate reduces cognitive decline in ApoE4 + AD patients.
The potential protective effect of tramiprosate (homotaurine) against Alzheimer’s disease: a review

Carlo Caltagirone¹, Luigi Ferrannini², Niccolò Marchionni³, Giuseppe Nappi⁴, Giovanni Scapagnini⁵ and Marco Trabucchi⁶

¹Chair of Neurology, University of Roma Tor Vergata, and Scientific Director, IRCCS Santa Lucia Foundation, Rome, ²Department of Mental Health and Addictions - ASL 3 Genoa, and President of the Italian Psychiatry Association, ³Division of Geriatric Cardiology and Medicine, University of Florence, Azienda Ospedaliero-Universitaria Careggi, Florence, ⁴Scientific Director, IRCCS “C. Mondino National Neurological Institute”, Pavia, and Chair of Neurology, University “La Sapienza”, Rome, ⁵Department of Health Sciences, Faculty of Medicine and Surgery, University of Molise, Campobasso, ⁶Geriatric Research Group, Brescia, Italy

| Table 1. Diverse strategies for Alzheimer’s disease therapeutic target. This table was modified from the box table by Grill and Curren(|
Table 1. Some of amyloid-based transgenic animal models of AD

<table>
<thead>
<tr>
<th>Transgenic line</th>
<th>Promoter</th>
<th>Memory deficits</th>
<th>Neurological characteristic</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDAPP</td>
<td>PDGFβ</td>
<td>+</td>
<td>Aβ deposits, neuritic plaques, synaptic loss, astrocytosis and microgliosis</td>
<td>104</td>
</tr>
<tr>
<td>BRI-Aβ42</td>
<td>MoPrp</td>
<td>−</td>
<td>Aβ plaques in the cerebellum, extracellular Aβ plaques in the hippocampus</td>
<td>96</td>
</tr>
<tr>
<td>Arc Aβ</td>
<td>MoPrP</td>
<td>+</td>
<td>Aβ deposits in cortex and hippocampus, Aβ plaques, cerebral amyloid angiopathy present</td>
<td>97</td>
</tr>
<tr>
<td>TgAPPscrc</td>
<td>Thy1.2</td>
<td>+</td>
<td>High APPscrc levels, amyloid deposition in subiculum and thalamus</td>
<td>107</td>
</tr>
<tr>
<td>SXXFAD</td>
<td>Thy1</td>
<td>+</td>
<td>Aβ oligodendrocyte accumulation, amyloid deposition and gliosis, synaptic degeneration,</td>
<td>108</td>
</tr>
<tr>
<td>Tg-SwDI/B</td>
<td>Thy1.2</td>
<td>+</td>
<td>Plaques in hippocampus and cortex, Aβ deposits throughout forebrain</td>
<td>109</td>
</tr>
<tr>
<td>Tet-APP&lt;sub&gt;trans&lt;/sub&gt;</td>
<td>Tetacycline responsive (pTetSplice)</td>
<td>NA</td>
<td>High MM/670 APP overexpression, doxycycline inhibits APP expression and reduces Aβ production</td>
<td>110</td>
</tr>
<tr>
<td>APPSWE</td>
<td>Hamster PrP</td>
<td>+</td>
<td>Aβ plaques, oxidative lipid and glycosidase damage</td>
<td>111</td>
</tr>
<tr>
<td>PDGF-APP&lt;sub&gt;trans&lt;/sub&gt;</td>
<td>PDGFβ</td>
<td>+</td>
<td>Aβ and Aβ oligodendrocyte accumulation in neocortical and hippocampus, high levels of Aβ oligodendrocyte, resulted in Aβ plaques</td>
<td>112</td>
</tr>
<tr>
<td>McGill-R-</td>
<td>Thy1.2</td>
<td>+</td>
<td>Intraneuronal Aβ accumulation, extracellular Aβ deposition, thioflavine S-positive amyloid plaques, glial activation</td>
<td>113</td>
</tr>
</tbody>
</table>

NA = Not assessed.
### Table 1. Principal secondary prevention trials of monoclonal antibodies targeting β-amyloid for the treatment of AD.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Compound</th>
<th>Company</th>
<th>Collaborators</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Binding characteristics</th>
<th>Estimated or completed enrollment</th>
<th>Characteristics</th>
<th>Status</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-amyloid treatment in Asymptomatic AD (A4)</td>
<td>Solanum tuberosum (BS ULO)</td>
<td>(I/2006430)</td>
<td>NCT02089037</td>
<td>Humanized monoclonal IgG1 anti-Aβ, aβ antibody</td>
<td>1200 older individuals at risk for progression to AD (2014 – 2018)</td>
<td>400 mg iv, administered once every 4 weeks for 108 weeks</td>
<td>Phase III trial (currently recruiting)</td>
<td>(44)</td>
</tr>
<tr>
<td></td>
<td>Dominantly inherited Alzheimer Network trials unit (DIAN-TU)</td>
<td>Solanum tuberosum (BS ULO)</td>
<td>(I/2006430)</td>
<td>NCT02089037</td>
<td>Humanized monoclonal IgG1 anti-Aβ, aβ antibody</td>
<td>Fully human monoclonal IgG1 antibody against Aβ, Aβ, not binding stable Aβ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gantenemab (Hoffmann-La Roche)</td>
<td></td>
<td>(IG200299)</td>
<td>NCT04093832</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Washington University School of Medicine Alzheimer’s Association National Institute on Aging and AxovantSciences</td>
<td></td>
<td></td>
<td>NCT01760006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alzheimer’s prevention initiative</td>
<td>Cerezyme (Genentech)</td>
<td></td>
<td>NCT04773326</td>
<td>Humanized monoclonal IgG4 antibody against Aβ, aβ, Aβ</td>
<td>210 subjects with autosomal dominant AD mutations (2012 – 2016)</td>
<td>Solanezumab: 400 mg q 4 weeks; every 4 weeks for 2 years</td>
<td>225 mg sc, every 4 weeks for 2 years</td>
<td>Phase II trial (currently recruiting)</td>
</tr>
<tr>
<td></td>
<td>Gantenemab (Hoffmann-La Roche)</td>
<td></td>
<td>(IG200299)</td>
<td>NCT04093832</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Table 1 Overview of monoclonal antibodies that have been or are being tested for the treatment of Alzheimer’s disease

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Epitope</th>
<th>Trial results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavneumab, humanized 3D6</td>
<td>Janssen/Pfizer</td>
<td>Amino terminus</td>
<td>Phase 3 trials did not meet cognitive and functional endpoints</td>
<td>(22,23)</td>
</tr>
<tr>
<td>Solaneumab, humanized mAB66</td>
<td>Eli Lilly</td>
<td>Central (amino acids 16 to 24), accessible only on soluble amyloid β</td>
<td>Phase 3 trials did not meet functional endpoints; did not meet cognitive endpoint in pooled analyses in mild AD</td>
<td>(24,25)</td>
</tr>
<tr>
<td>Gantenemab, full human</td>
<td>Hoffmann-La Roche</td>
<td>Amino terminus and central portions of amyloid β</td>
<td>Phase 1 trial showed decreased reduction in brain amyloid β on PET</td>
<td>(26,27)</td>
</tr>
<tr>
<td>Cerezymeumab, humanized IgG4</td>
<td>Genentech</td>
<td>Conformational epitopes, including oligomers and protofibrillar forms</td>
<td>Phase 1 trial showed compound was safe and well-tolerated</td>
<td>(28,29)</td>
</tr>
<tr>
<td>BAN2401, humanized mAB158</td>
<td>Elsi Inc.</td>
<td>Specific antibodies to Aβ (170–178)</td>
<td>Phase 1 trial showed compound was safe and well-tolerated</td>
<td>(30)</td>
</tr>
<tr>
<td>GS 9337/76, humanized IgG1</td>
<td>Biogen/IdeC</td>
<td>Amino terminus</td>
<td>Phase 1 trial showed compound was safe and well-tolerated</td>
<td>(31)</td>
</tr>
<tr>
<td>AAB-001, fc-engineered Bavneumab</td>
<td>Janssen/Pfizer</td>
<td>Amino terminus</td>
<td>Phase 1 trial ongoing</td>
<td>(32)</td>
</tr>
<tr>
<td>SAR22810, humanized 13C3</td>
<td>Sanofi</td>
<td>Probiotics and low molecular weight amyloid β</td>
<td>Phase 1 trial ongoing</td>
<td>(33)</td>
</tr>
<tr>
<td>IB0037/BAMT, full human IgG1</td>
<td>Biogen/IdeC</td>
<td>Insoluble fibrilar human amyloid β</td>
<td>Phase 1 trial ongoing</td>
<td>(34)</td>
</tr>
</tbody>
</table>

Adapted from Moreh and colleagues (5), AD, Alzheimer’s disease; Ig, immunoglobulin; mAb, monoclonal antibody; PET, positron emission tomography.
AD pathology

APP
- \# inhibitor: OM 99-2
- OM 00-3
- MX-8931
- \gamma\text{-}inhibitor: LY450139

A\beta

\text{AchE}:
- Donepezil
- Rivastigmine
- Galantamine
- Tacrine

NMDA antagonist:
- Memantine

Activation:
- A\beta

Aggregation inhibitors:
- PBT2
- QC inhibitor: FBD150
- Immunotherapy
- Active: AN 1792
- Passive: Bapineunuab, Solanezumab

\text{Agg.} \\

\text{AchE} modulators:
- Lithium
- Valproate
- Caffeine
- AZD 1080
- NP-12/7/deglubisib

Aggregation inhibitor:
- MTC
- TX00237

Tau

Indirect mechanism

Glucose metabolism & Mitochondria

Insulin sensitizers:
- Metformin
- O-GlcNAc modification
- N6AT6

	ext{Mitochondrial recovery}:
- Dimebon
- Piracetam

Mitochondrial transport:
- HDAC6

inhibitor