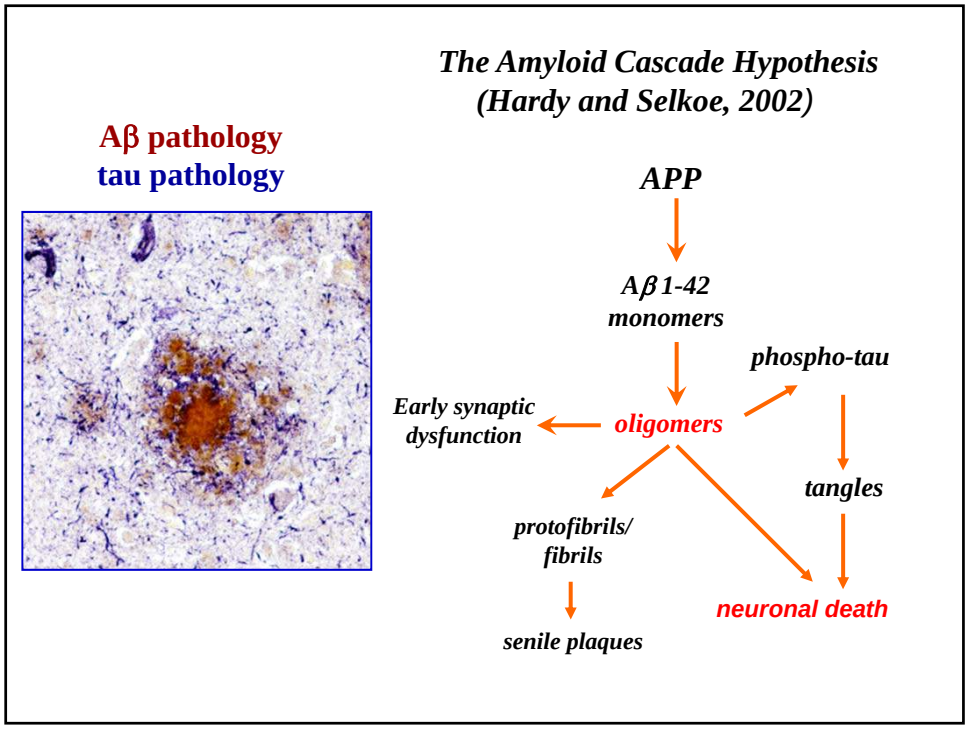
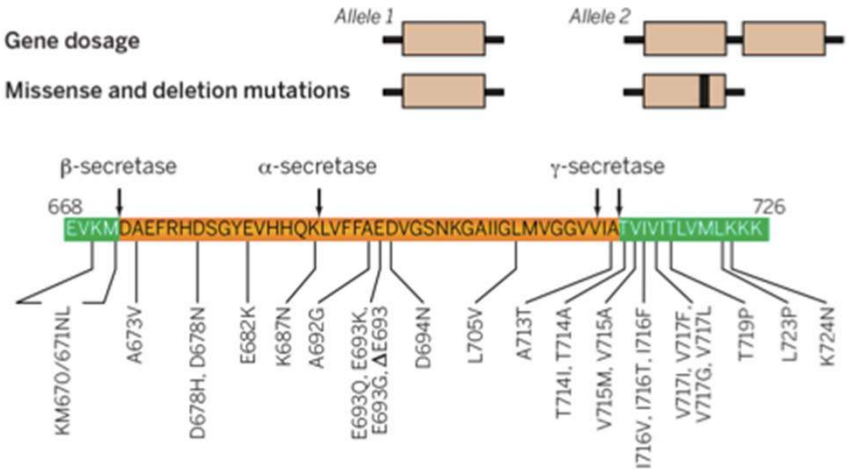

XXXVI
CONGRESSO NAZIONALE
SIFO
IL FARMACISTA PER
Scelte
Interventi
Futuro
Outcome
Catania,
Centro Congressuale Fieristico
Culturale "Le Ciminiere"
22-25 OTTOBRE 2015

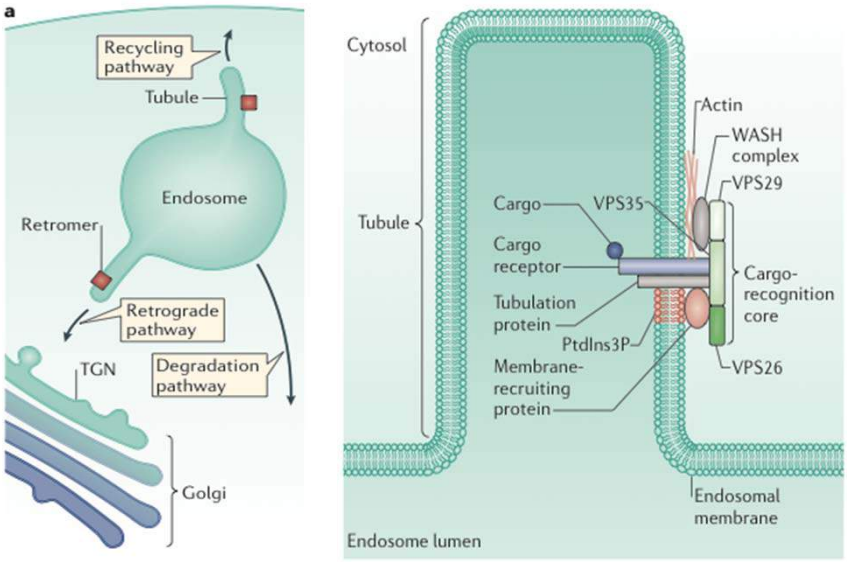

Aβ pathology
tau pathology
The Amyloid Cascade Hypothesis
(Hardy and Selkoe, 2002)
APP
Aβ 1-42
monomers
phospho-tau
Early synaptic
dysfunction
oligomers
tangles
protofibrils/
fibrils
neuronal death
senile plaques



Goedert, Science, 349, 2015

Retromers in Alzheimer's disease

(Small and Petsko, Nat. Rev. Neurosci. 16, 2015)



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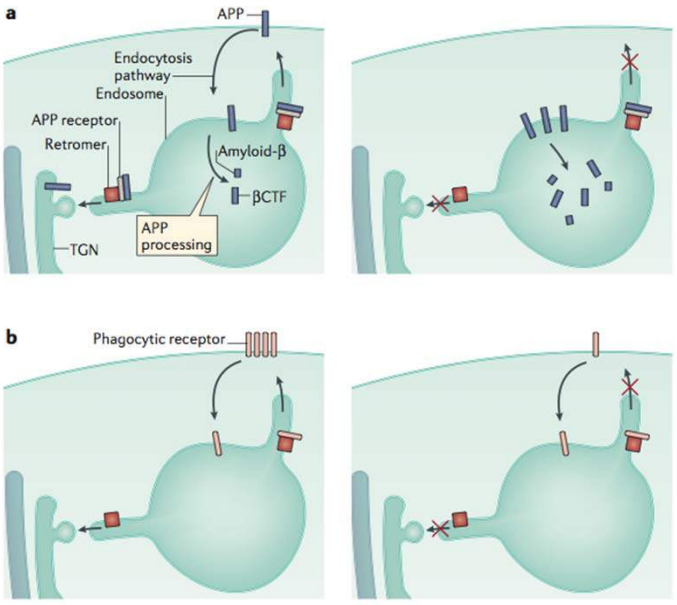
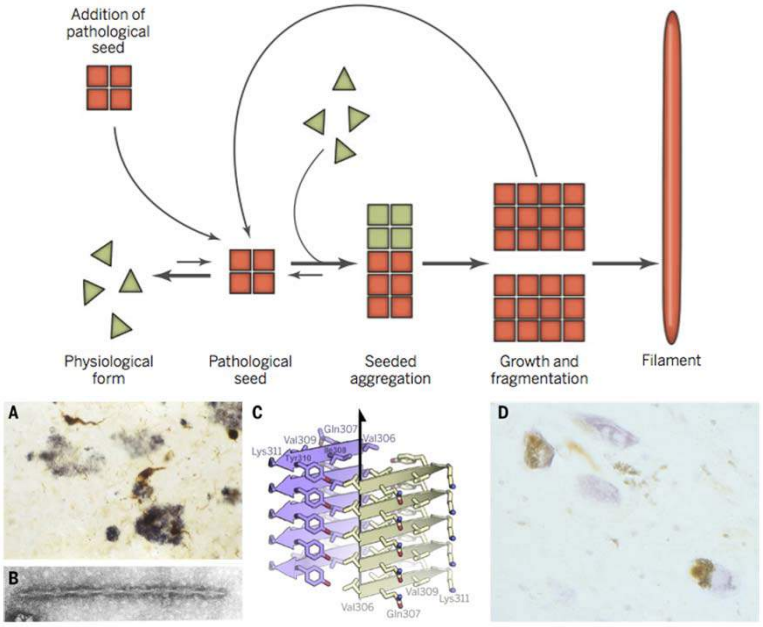
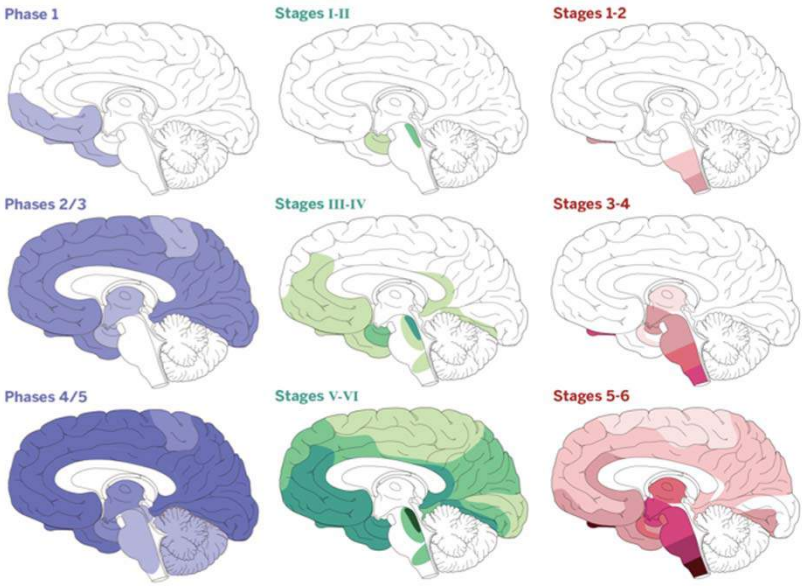


The prion hypothesis: mechanism of seeding and template in neurodegenerative disorders (Goedert et al., Science, 349, 2015)

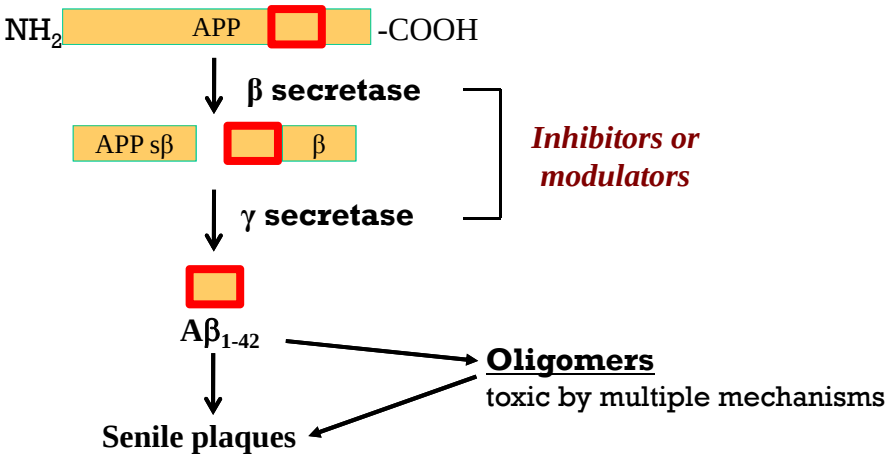


Amyloid plaques *Tangles* *Lewy bodies*



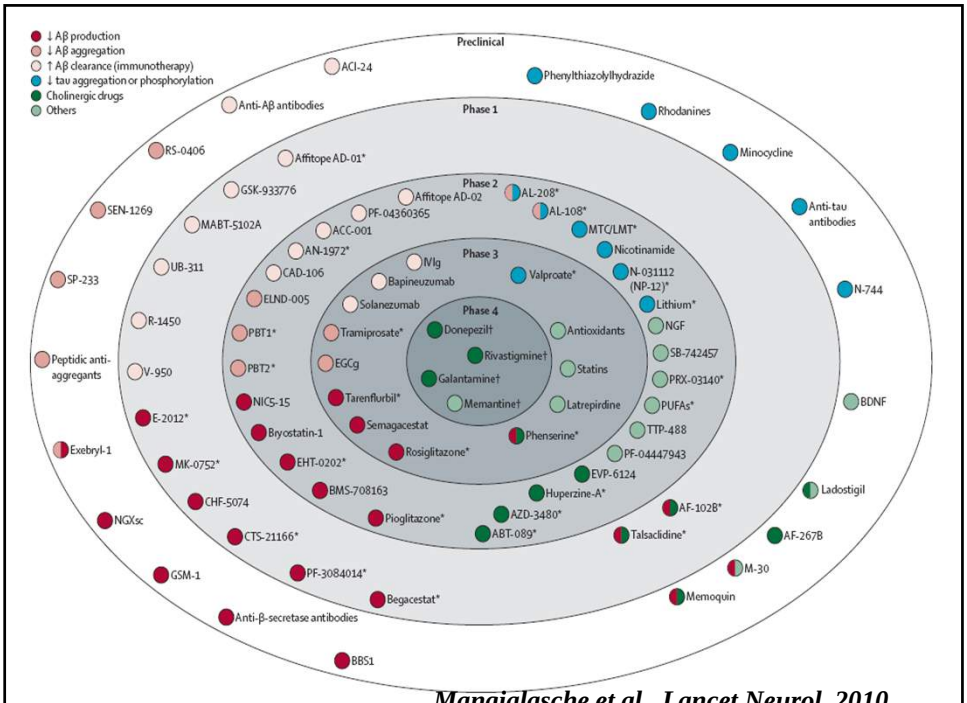
Reducing the formation of β-amyloid peptide: a strategy for the design of disease-modifying drugs in Alzheimer's Disease

Amyloid Precursor Protein



Inhibitors or modulators

From Sisodia & St George-Hyslop, 2002



Mangialasche et al., Lancet Neurol, 2010

ORIGINAL ARTICLE

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

Table 2. Estimated Mean Change from Baseline for the Coprimary and Secondary Outcomes, According to a Mixed-Model Repeated-Measures Analysis.*

Outcome	Placebo	Semagacestat, 100 mg	Semagacestat, 140 mg	P Values	
				Semagacestat, 100 mg, vs. Placebo	Semagacestat, 140 mg, vs. Placebo
ADAS-cog score				0.15	0.07
No. of participants with results	486	483	497		
Mean change in score (95% CI)	6.4 (5.48 to 7.40)	7.5 (6.44 to 8.53)	7.8 (6.72 to 8.85)		
ADCS–ADL†				0.14	<0.001
No. of participants with results	480	481	490		
Mean change in score (95% CI)	−9.0 (−10.37 to −7.67)	−10.5 (−11.94 to −9.07)	−12.6 (−14.1 to −11.2)		
CDR-SB‡				0.06	<0.01
No. of participants with results	485	480	494		
Mean change in score (95% CI)	2.4 (2.06 to 2.67)	2.8 (2.47 to 3.13)	3.1 (2.73 to 3.41)		
NPI§				0.28	0.05
No. of participants with results	473	463	472		
Mean change in score (95% CI)	1.9 (0.69 to 3.12)	2.9 (1.58 to 4.21)	3.7 (2.36 to 5.08)		
MMSE				0.23	0.03
No. of participants with results	400	328	303		
Mean change in score (95% CI)	−3.4 (−3.95 to −2.86)	−3.9 (−4.51 to −3.30)	−4.3 (−4.99 to −3.68)		

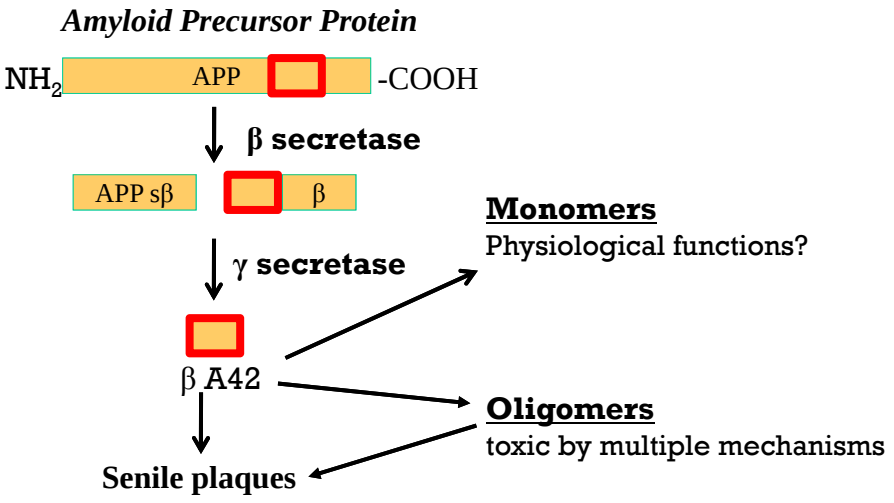
Doody et al., N. Engl. J. Med. 2013

Table 2 Ongoing and terminated passive immunotherapy clinical programs in Alzheimer's disease

Name	Company	Phase	Trial population	Binding domain	Target
Solanezumab	Eli Lilly and Company	3	Prodromal and mild AD	$A\beta_{16-23}$	Soluble Aβ
Gantenerumab	Roche	2/3	Prodromal and mild AD	Combined Aβ N-terminal and mid domain, conformational	Aggregated Aβ
BAN2401	Eisai/ BioArctic Neuroscience/Eisai	2b	MCI due to AD or mild AD	N-terminal, conformational	Soluble Aβ protofibrils
Crenezumab	Genentech/Roche	2	Prodromal and mild/moderate AD	Aβ 12-23	Soluble oligomeric/ fibrillar Aβ and plaque
Bapineuzumab	Elan/ Pfizer Inc./ Johnson & Johnson	Intravenous and subcutaneous programs terminated	Mild/moderate AD	$A\beta_{1-5}$	Soluble and aggregated Aβ
BIIB037	Biogen Idec/ Neuroimmune Therapeutics	1	MCI due to AD or mild AD	Conformational Aβ	Fibrillar Aβ
AAB003	Elan/Pfizer Inc./ Janssen	1	Mild/moderate AD	$A\beta_{1-6}$	Soluble and aggregated Aβ
SAR228810	Sanofi	1	Mild/moderate AD	Not published	Soluble oligomeric/ protofibrillar Aβ
ABP102	Abiogen Pharma	1	AD	Catalytic antibody cleaving Aβ	Aggregated Aβ
Ponezumab[a]	Pfizer Inc.	1	Mild/moderate AD	$A\beta_{33-40}$	Soluble and aggregated Aβ

Lannfelt et al., Alzh. Res. Ther. 2014

Amyloid hypothesis of Alzheimer's disease: loss or gain of function?



From Sisodia & St George-Hyslop, 2002

A.Copani, M.L. Giuffrida, F.M. Tomasello, F. Caraci, S. Chiechio

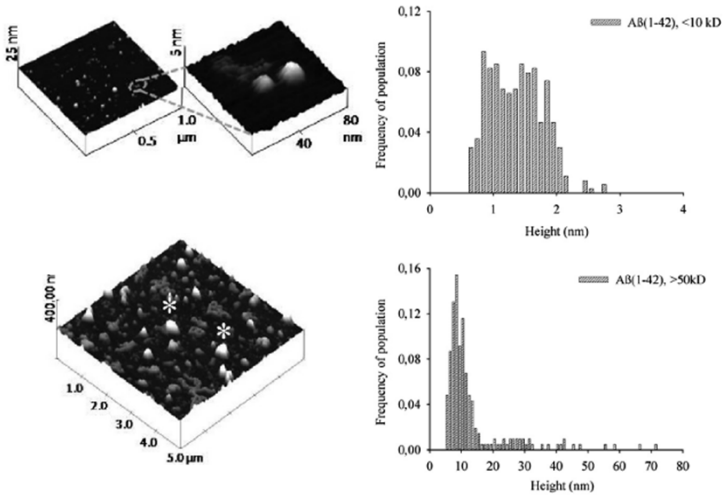
S. Sorbi, B. Nacmias,

R. Vigneri, G. Pandini

E. Rizzarelli, G. Pappalardo, F. Attanasio

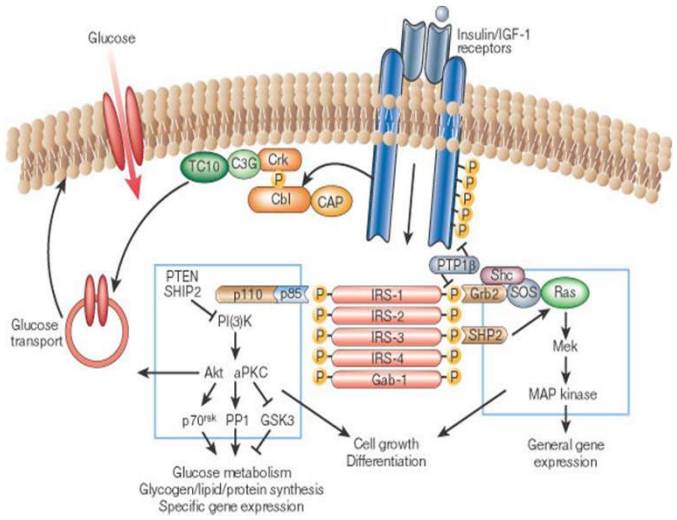
Monomers of β-amyloid are neuroprotective (Giuffrida et al., J. Neurosci, 29, 10582, 2009)

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)

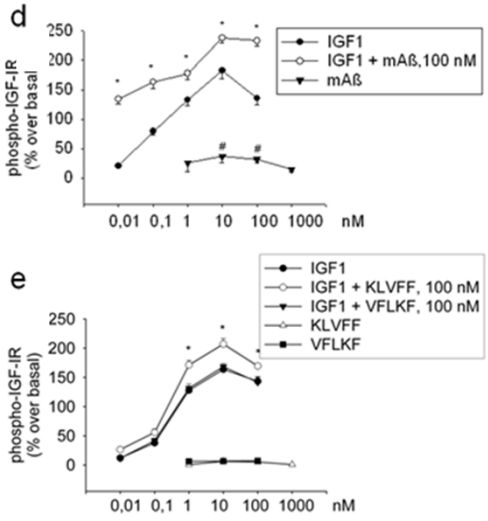


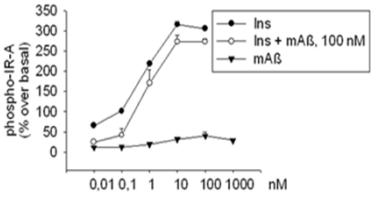
The Insulin Receptor Family

Insulin		IGF-I/IGF-II			?
IR-A	IR-B	IR-A	type-1 IGF	"hybrid" IR/IGFR	IRR

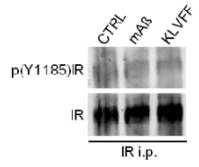


Monomeric β-amyloid acts as a positive allosteric modulator of type-I IGF receptors immune captured from transfected 3T3 cells



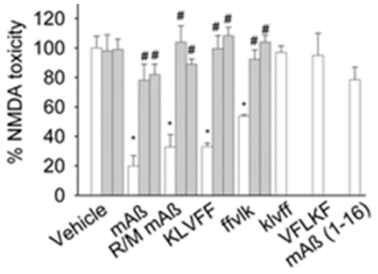


No effect on insulin receptor

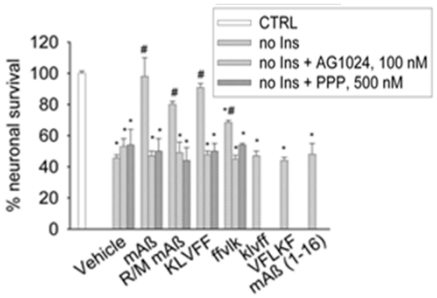


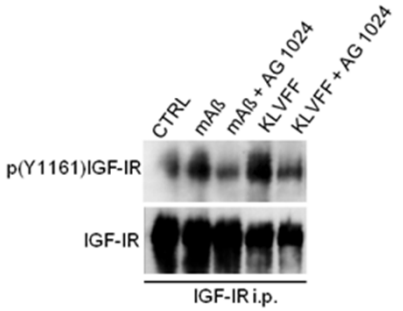
DAEF**R**HDSG**Y**EV**H**HQKLVFFA
EDVGSNKGAIIGLMVGGVVIA

Neuroprotection by β-amyloid monomers is mediated by type-I IGF receptors



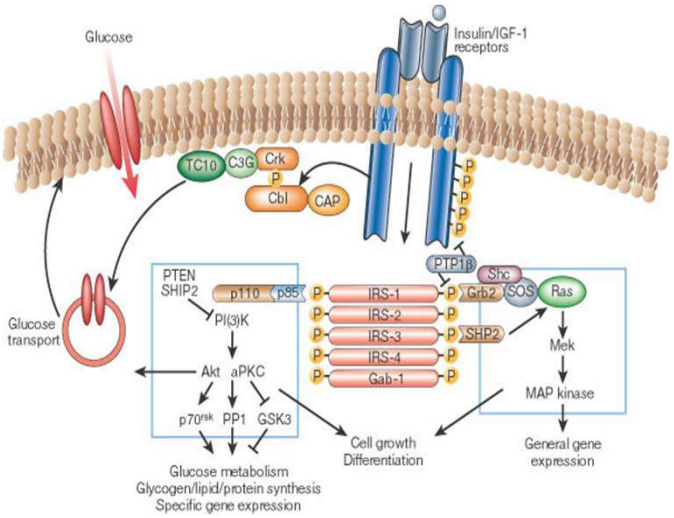
DAEF**R**HDSG**Y**EV**H**HQKLVFFA
EDVGSNKGAIIGLMVGGVVIA



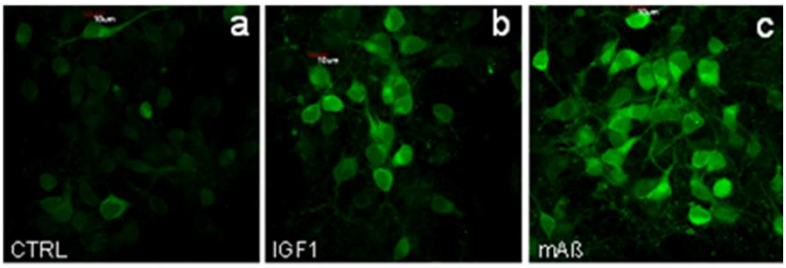


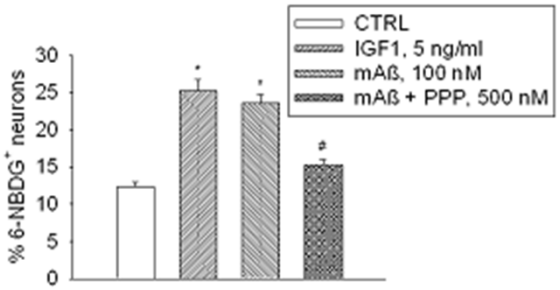
Does amyloid monomer stimulate glucose uptake in neurons?

Insulin		IGF-I/IGF-II			?
IR-A	IR-B	IR-A	type-1 IGF	"hybrid" IR/IGFR	IRR

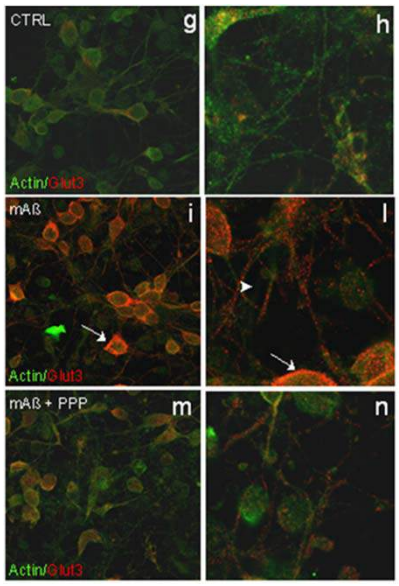


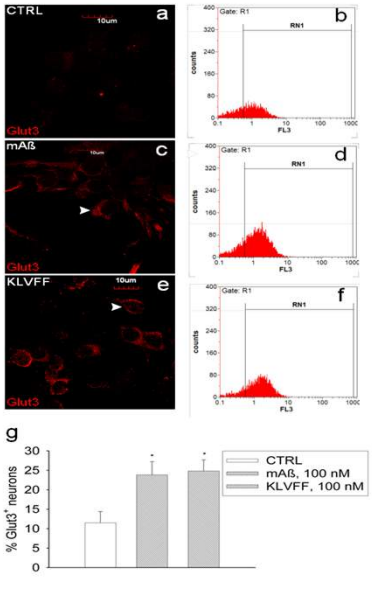
Monomeric β-amyloid stmulates glucose uptake in neurons



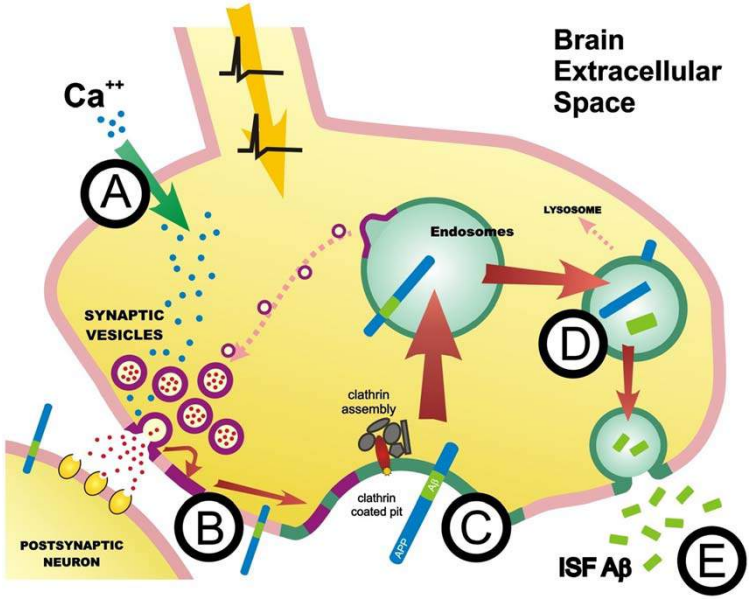


Monomeric β-amyloid stimulates translocation of the neuropil Glut3 glucose transporter in neurons





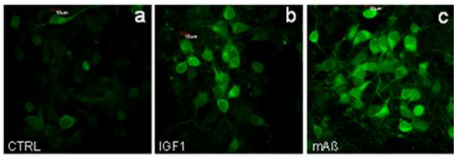
Model of Synaptic-Dependent Release of Aβ

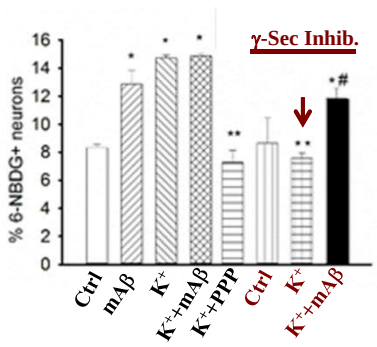


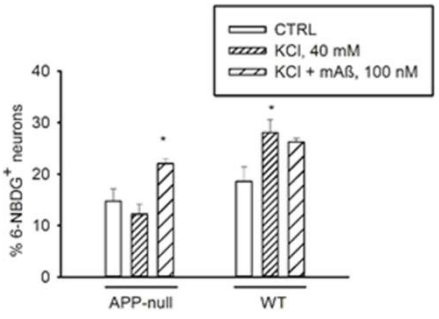
Cirrito et al., Neuron 2008

Endogenous production of β-amyloid monomers is required for activity-dependent glucose uptake in neurons

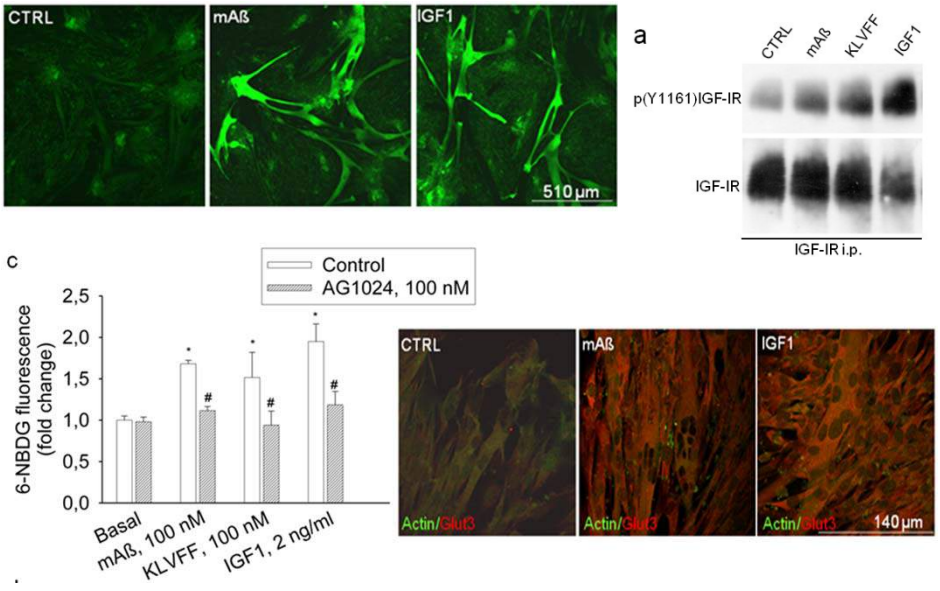
Condition	$A\beta_{1-42}$ release (pmol/L)
Control	3.593 ± 0.569
γ-Sec Inh, 100 nM	0.257 ± 0.068*
KCl, 40 mM	14.033 ± 1.486**
γ-Sec Inh + KCl	4.237 ± 0.917#

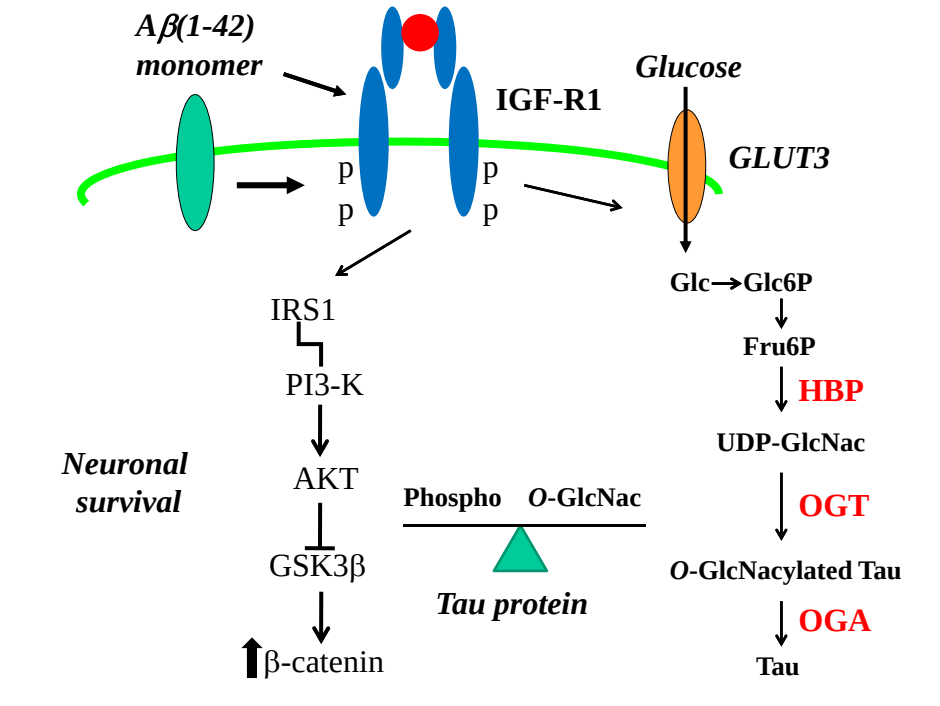




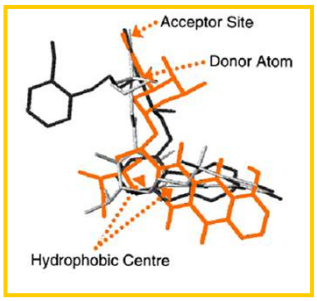


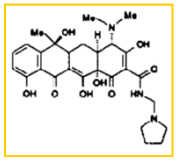
Monomeric β-amyloid stimulates Glut3 translocation and glucose uptake in differentiated skeletal muscle cells



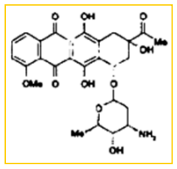


Inhibitors of Aß aggregation

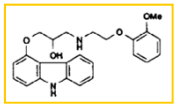




Daunomycin



Rolitetracycline

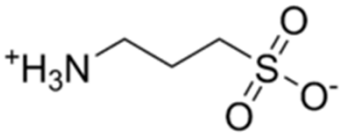


Carvedilol

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 Caltagirone[1], Luigi Ferrannini[2], Niccolò Marchionni[3], Giuseppe Nappi[4], Giovanni Scapagnini[5] and Marco Trabucchi[6]

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

Endogenous production of β-amyloid monomers is required for activity-dependent glucose uptake in neurons

Condition	$A\beta_{1-42}$ release (pmol/L)
Control	3.593 ± 0.569
γ-Sec Inh, 100 nM	0.257 ± 0.068*
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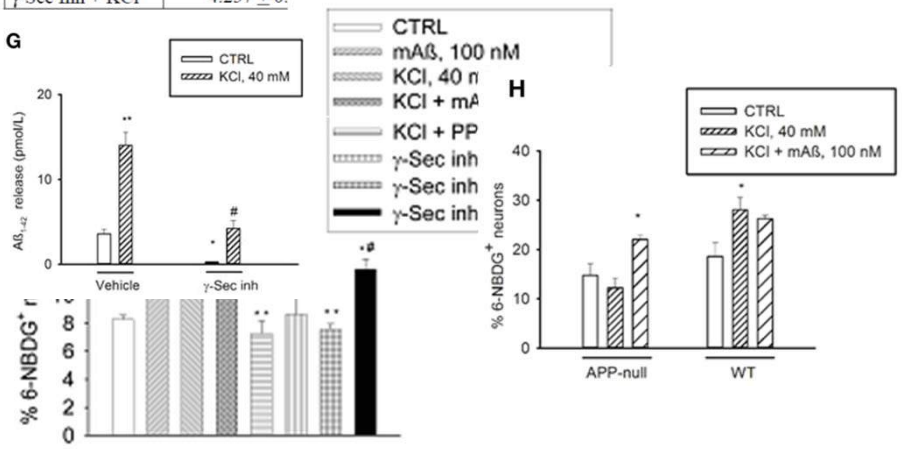
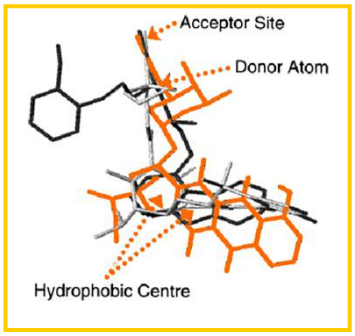
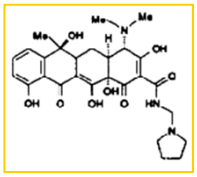


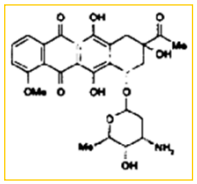
Inhibitors of Aß aggregation



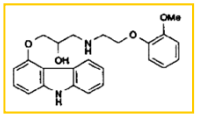
Congo red derivatives, Rifampicin, Tetracyclines, Antracyclines, Inositols, β-Sheet breaking peptides
Zinc and Cupper chelators
Inhibitors of pathological chaperones
(ApoE4, α1-antichymotrypsin, C1q factor, glycosaminoglycans)



Daunomycin

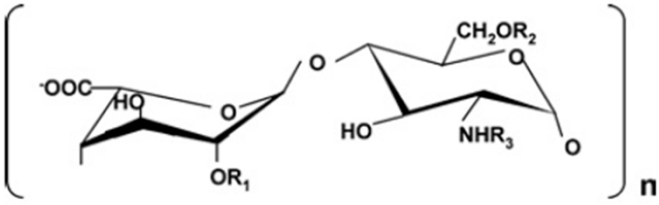


Rolitetracycline



Carvedilol

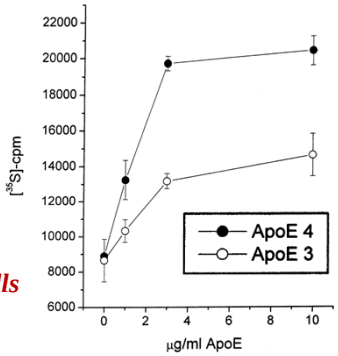
Glycosaminoglycans accelerate amyloid aggregation



R_1 =SO_3^-/H R_2 =SO_3^-/H R_3 =SO_3^-/H/$COCH_3$

$$G = y_0 + aP_S + bP_B + cP_{MR} + c'(P_{MR})^2$$

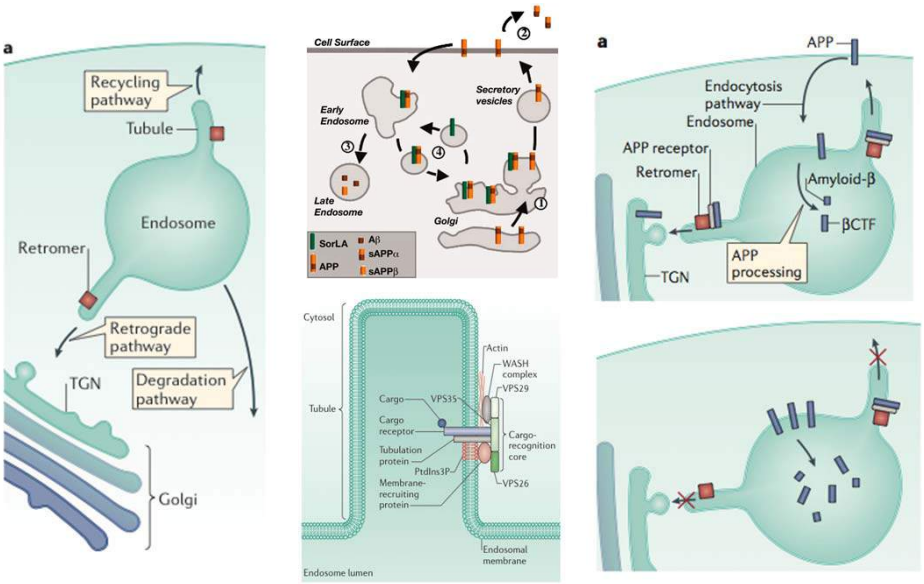
1. ***Number of sulfate groups***
2. ***Amyloid protein: GAG ratio***
3. ***Molarity of solutes***



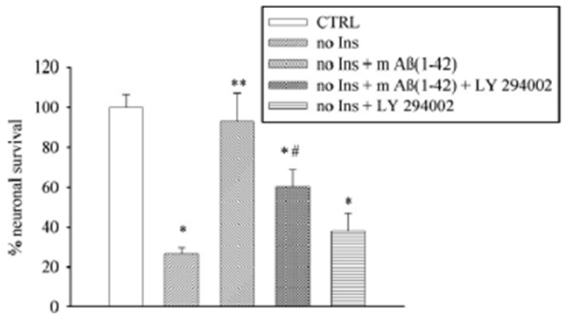
ApoE4 enhances sulfatation of GAGs in neural cells (Bonay and Avila, BBA 2001)

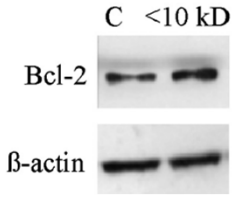
Retromers in Alzheimer's disease

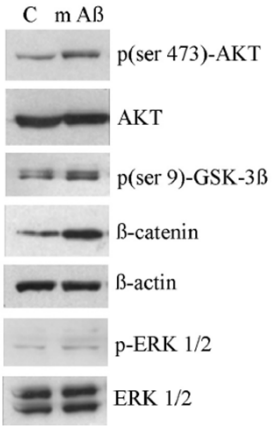
(Small and Petsko, Nat. Rev. Neurosci. 16, 2015)



β-Amyloid monomers protect cultured neurons against death by trophic deprivation by activating the PtdIns-3-K pathway





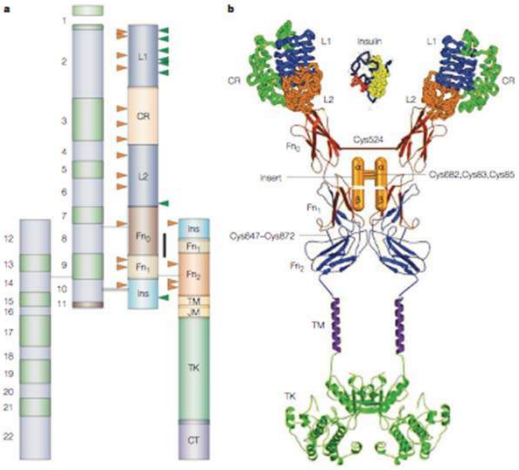


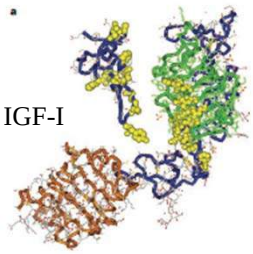
PtdIns-3-K → p-Akt → p-GSK3β → β-catenin

T

LY294002

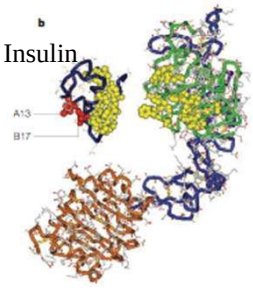
Ligand binding sites at insulin receptor and type-I IGF receptor
(De Meyts and Whittaker, Nat Rev Drug Disc, 2002)





IGF-I

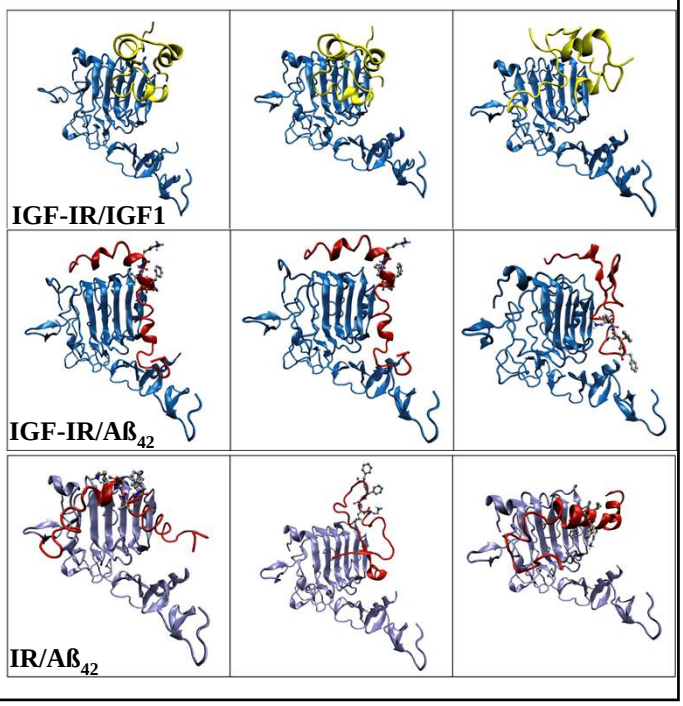
Type-I IGFR



Insulin

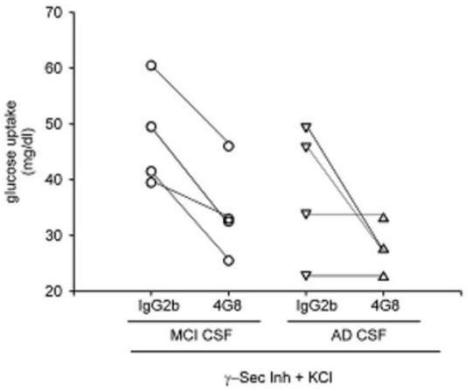
IR

Docking simulation of monomeric Aβ on type-I IGF-R or insulin receptor (IR)



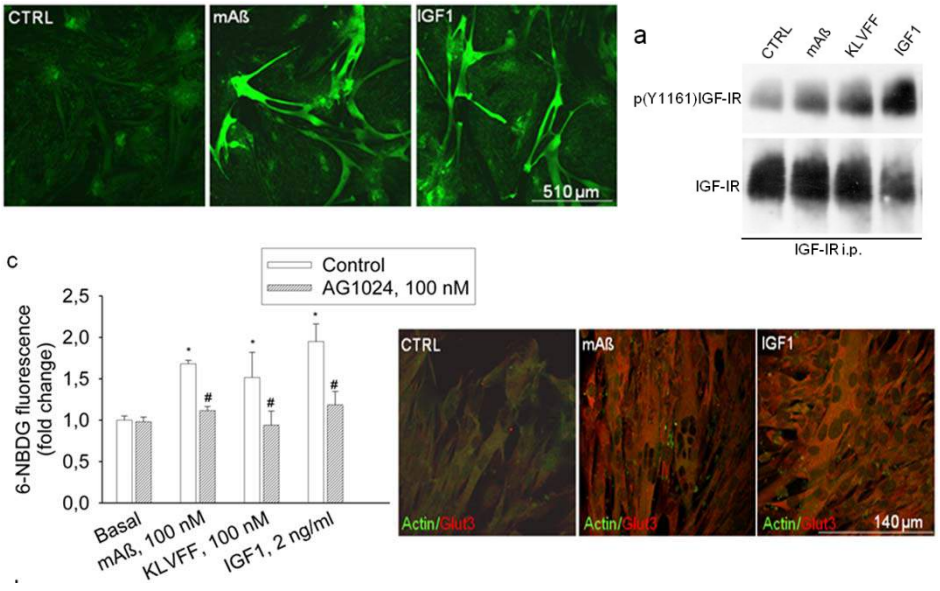
Dr. A. Pietropaolo
Univ. Of Catanzaro

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

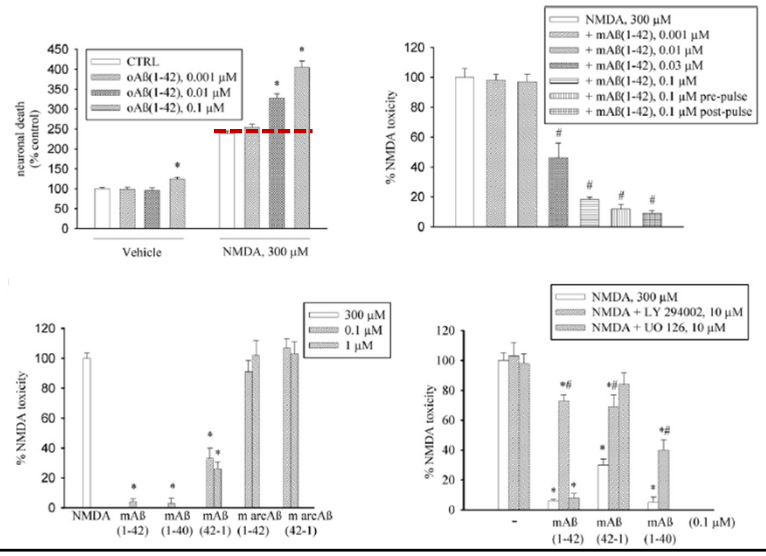


Clinical diagnosis	Gender	Age	CSF Aß 1-42 (pg/ml)	CSF glucose (mM)
MCI	M	66	1,200	4.4
	F	51	1,280	4.38
	F	57	1,076	3.5
	M	51	815	3.8
AD	F	72	290	4.33
	M	70	391	2.88
	M	61	390	3.94
	F	55	463	4.6

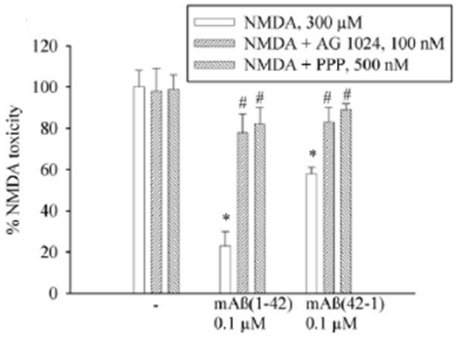
Monomeric β-amyloid stimulates Glut3 translocation and glucose uptake in differentiated skeletal muscle cells

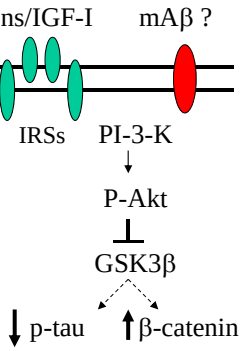


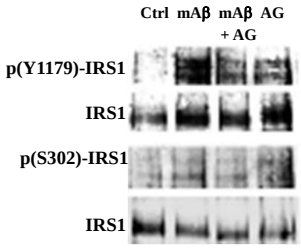
β-Amyloid monomers, but not those carrying the E22G mutation, protect neurons against NMDA toxicity via PtdIns-3-K activation



Neuroprotection by the β-amyloid monomer involves the activation of a member of the insulin receptor family



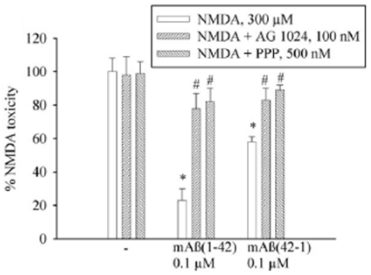


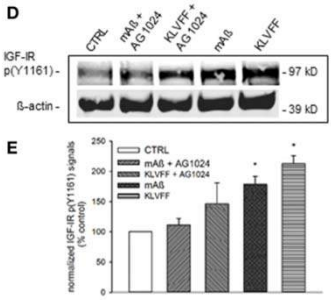


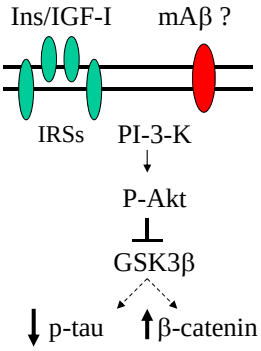
PPP = selective inhibitor of type-I IGF receptor

AG1014 = duql inhibitor of IR qnd IGF-R1

Neuroprotection by the β-amyloid monomer involves the activation of a member of the insulin receptor family

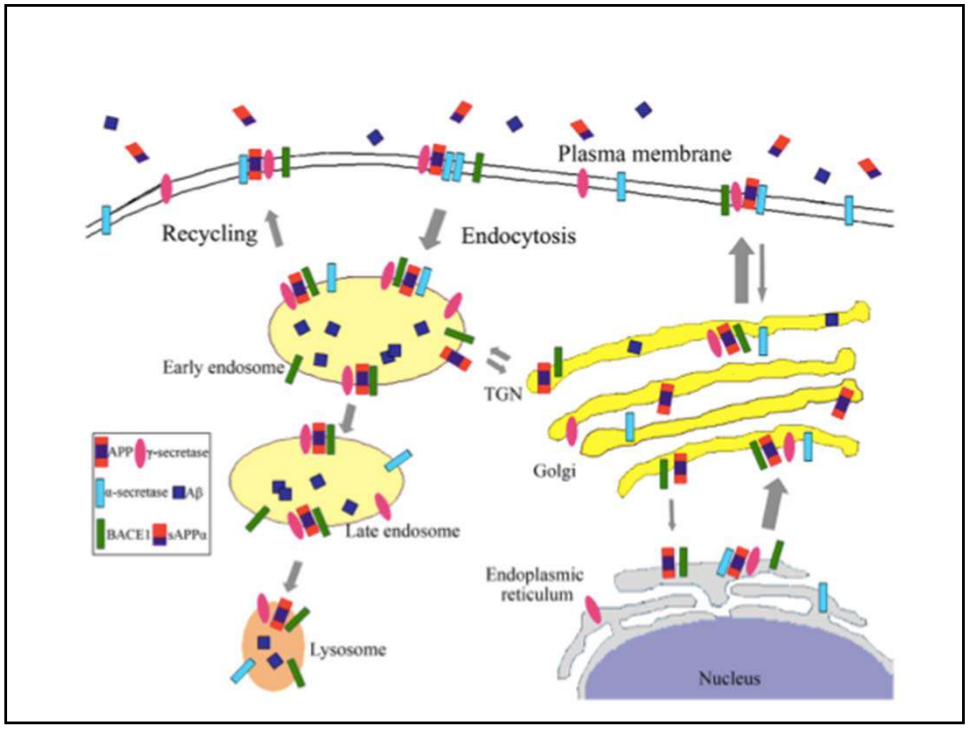




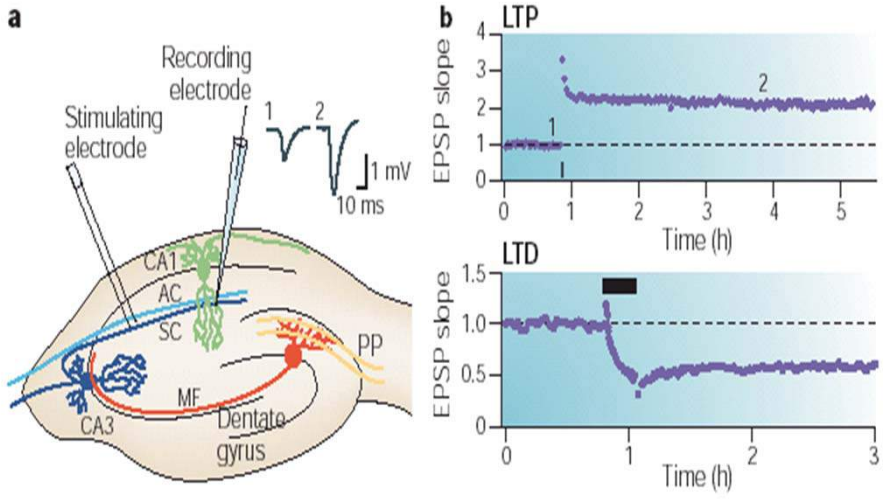


PPP = type-I IGF receptor inhibitor

AG1014 = IR/IGF-R1 inhibitor



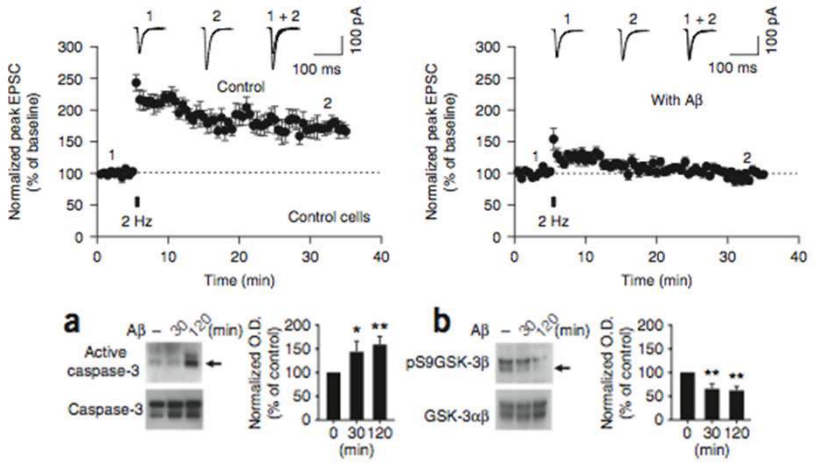
Long-term potentiation (LTP) of excitatory synaptic transmission: the substrate for associative learning



Collingridge et al., Nat Rev Neurosci 2005

Oligomers of $A\beta_{1-42}$ disrupt LTP in the hippocampus by inhibiting the PtdIns-3-K/Akt/GSK3β pathway

(Cho and Collingridge's lab, Nat. Neurosci., 2012)



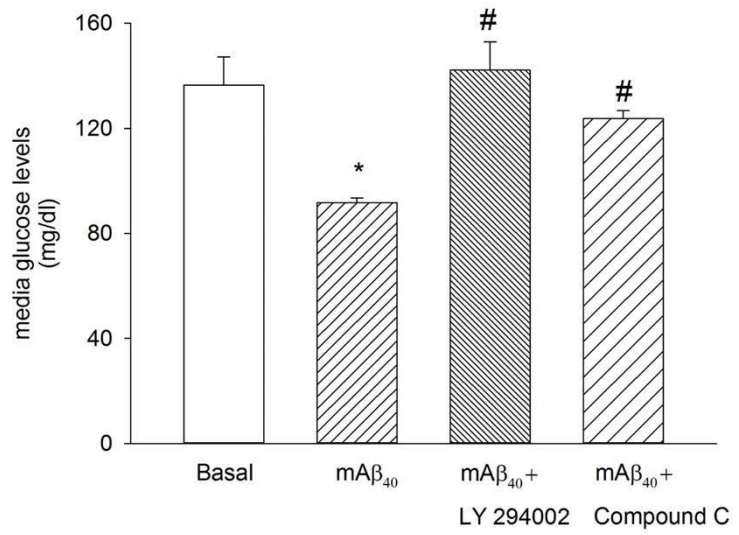
Aβ olig. → ↑Caspase-3 ⊣ Akt1 ⇢ ↑GSK3β → ↑p-Tau

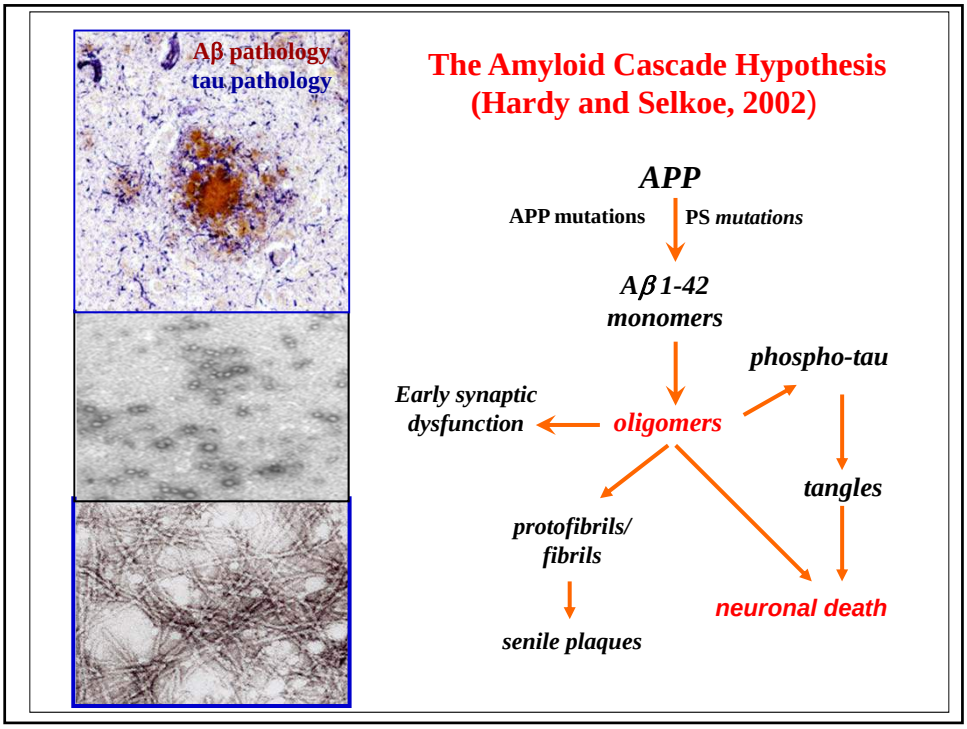
Starting points

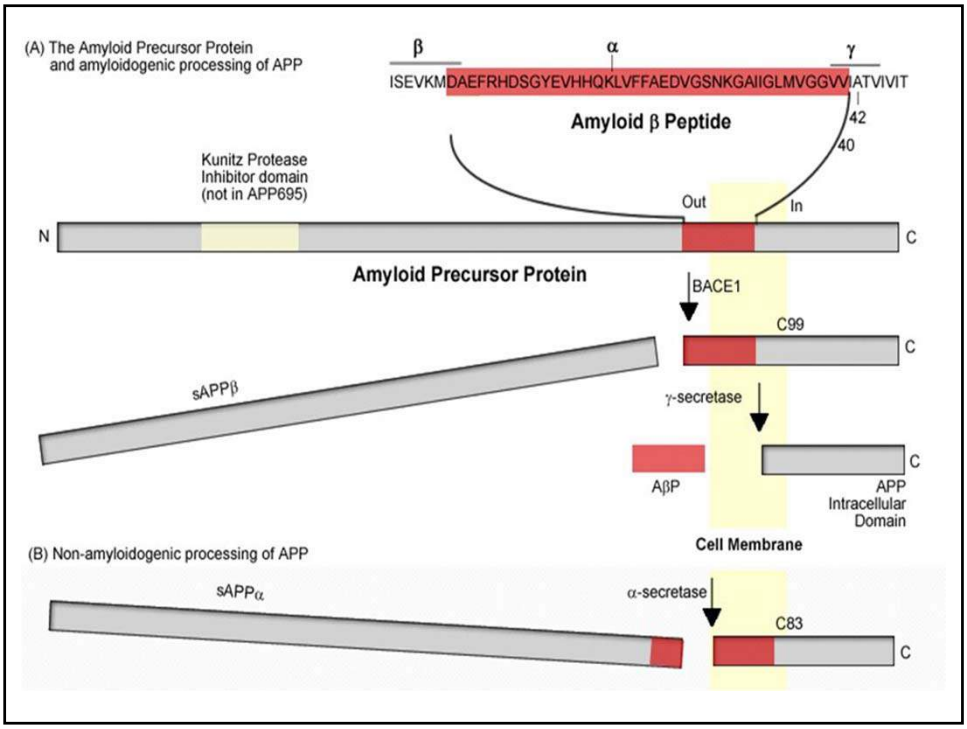
Reduced CSF β-amyloid levels in AD: loss of function hypothesis?

Early reduction in brain glucose uptake in AD

Monomeric $A\beta_{1-40}$ (100 nM) enhances glucose uptake in cultured neurons via the activation of PtdIns-3-K and AMP kinase




Aβ pathology
tau pathology
The Amyloid Cascade Hypothesis
(Hardy and Selkoe, 2002)
APP
APP mutations
PS mutations
Aβ 1-42
monomers
phospho-tau
Early synaptic
dysfunction
oligomers
tangles
protofibrils/
fibrils
neuronal death
senile plaques


(A) The Amyloid Precursor Protein
and amyloidogenic processing of APP
β
α
γ
ISEVKMDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVIVIT
Amyloid β Peptide
42
40
Kunitz Protease
Inhibitor domain
(not in APP695)
Out
In
N
C
Amyloid Precursor Protein
BACE1
C99
C
sAPPβ
γ-secretase
AβP
C
APP
Intracellular
Domain
Cell Membrane
(B) Non-amyloidogenic processing of APP
sAPPα
α-secretase
C83
C

β-*Secretase Inhibitors*

General pitfalls:
Neureguline-1
Blood-brain barrier

PPAR-γ activators (Pioglitazone, Rosiglitazone)

↓ ***BACE-1 and APP expression***

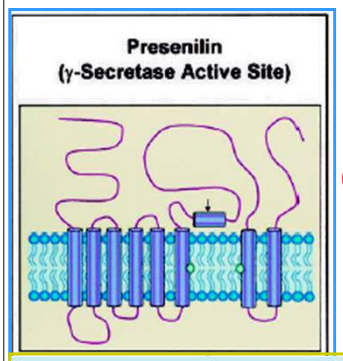
↑ ***APP degradation***

↓ ***Insulin levels***

Phase 3 RCTs Rosiglitazione: no effect

CTS21166 (oral) on going

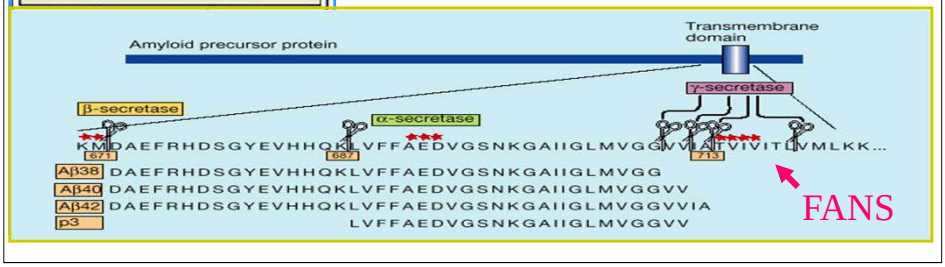
γ-Secretase inhibitors in AD



•***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.

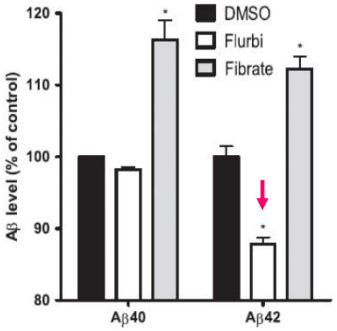


Selective Amyloid Lowering Agents (SALAs)

R-Flurbiprofen, Ibuprofen, Sulindac, Indomethacin

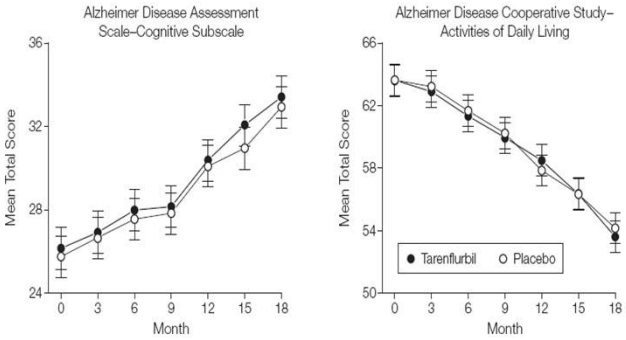
Selective Amyloid Raising Agents (SARAs)

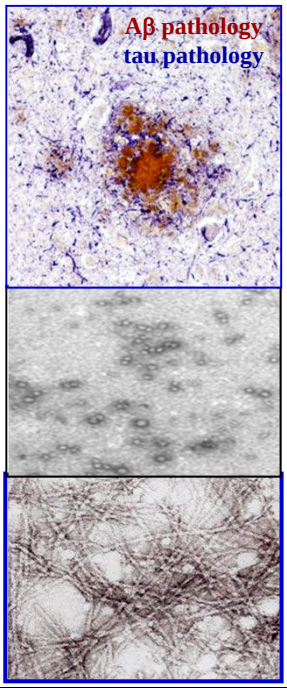
Fenofibrate, Celecoxib



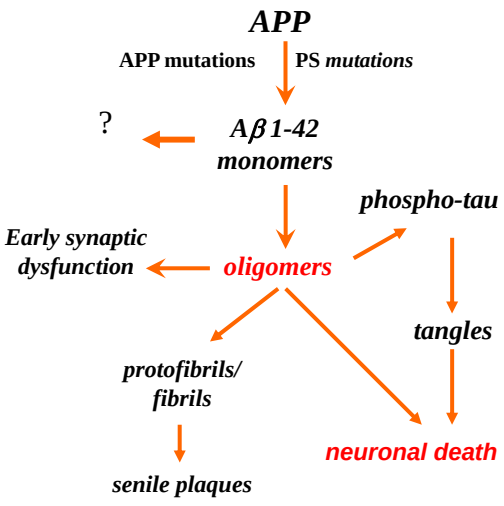
Tarenflurbil for AD "a shot on goal that missed"

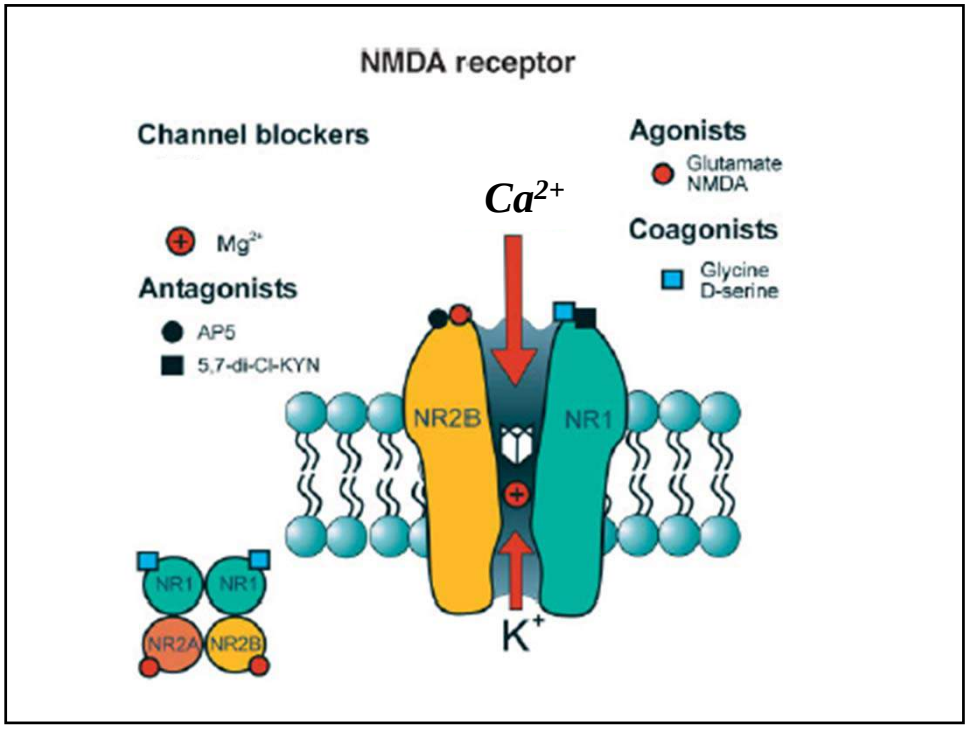
Green et al., JAMA 302, 2009

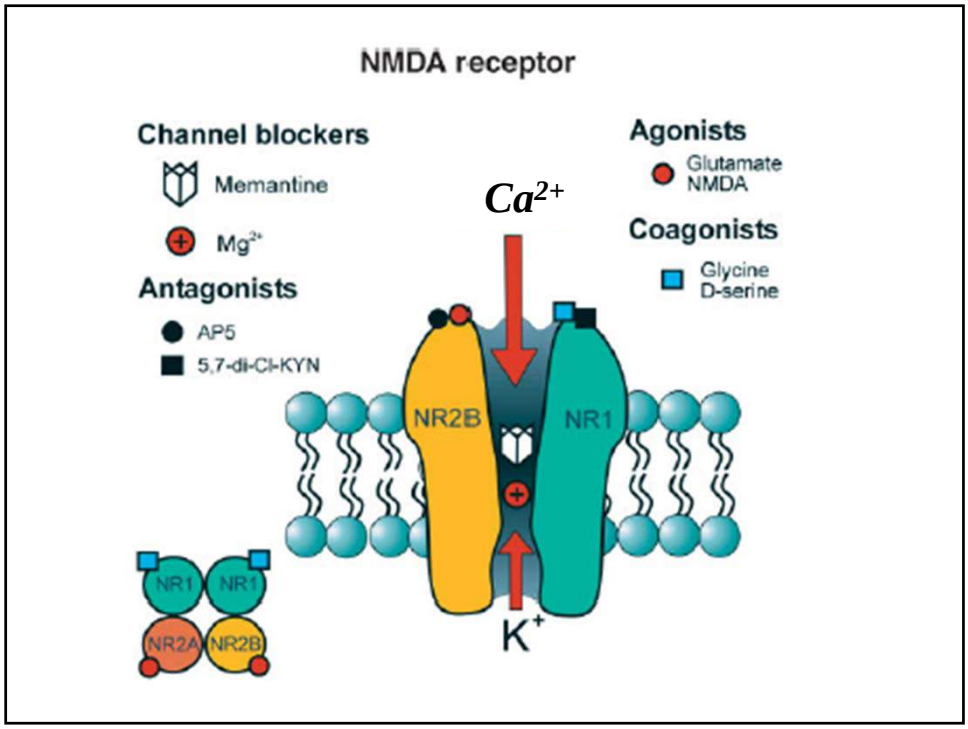




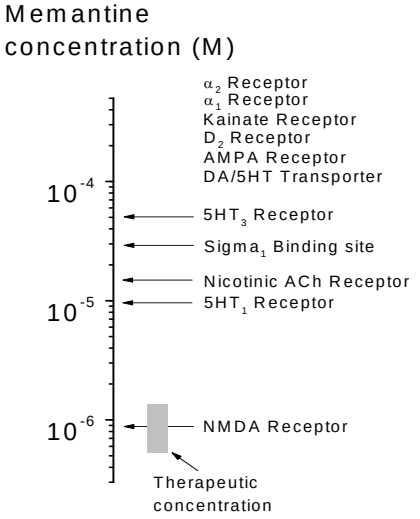
The Amyloid Cascade Hypothesis (Hardy and Selkoe, 2002)

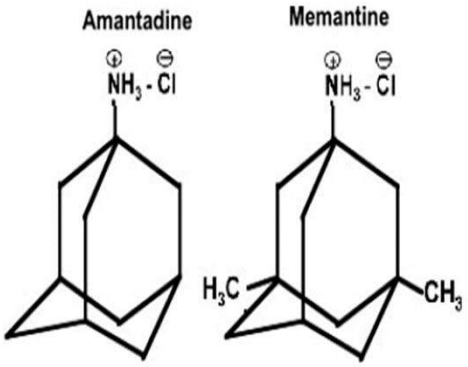



NMDA receptor
Channel blockers
Mg2+
Antagonists
AP5
5,7-di-Cl-KYN
Agonists
Glutamate
NMDA
Coagonists
Glycine
D-serine
Ca2+
NR2B
NR1
K+
NR1
NR1
NR2A
NR2B

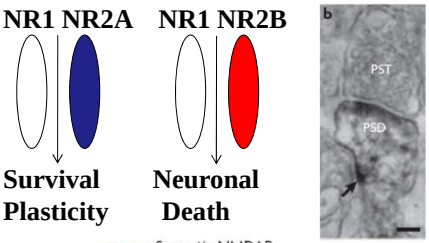

NMDA receptor
Channel blockers
Memantine
Mg2+
Antagonists
AP5
5,7-di-Cl-KYN
Agonists
Glutamate
NMDA
Coagonists
Glycine
D-serine
Ca2+
NR2B
NR1
K+
NR1
NR1
NR2A
NR2B

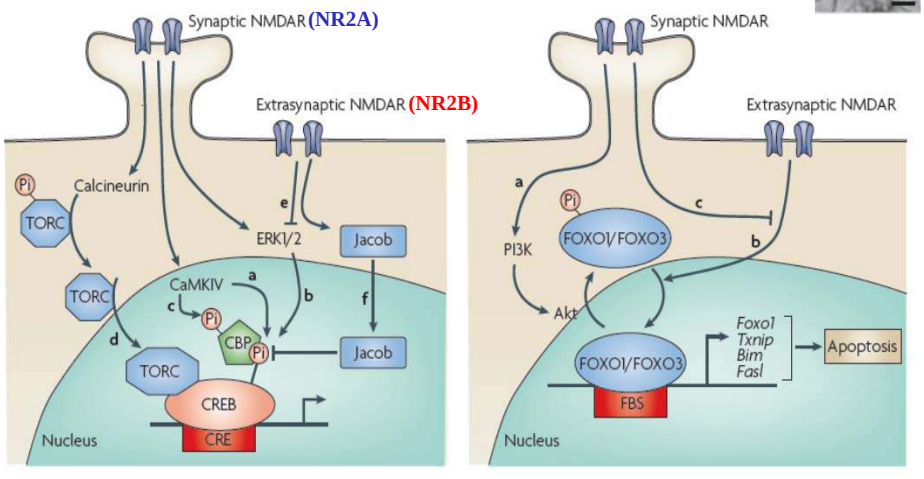
Memantine: NMDA receptor antagonist



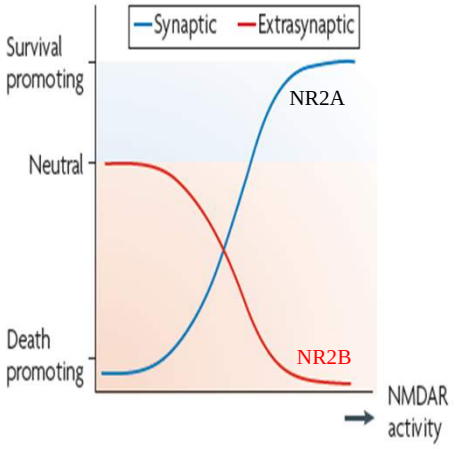


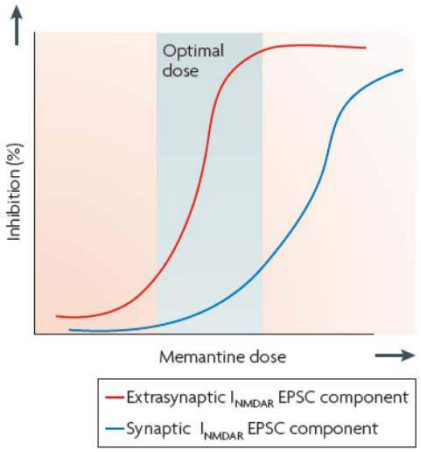
Dual role for synaptic (NR2A) and extrasynaptic (NR2B) NMDA-R in neuronal viability
(Hardingham and Bading, Nat. Rev. Neurosci., 2010)



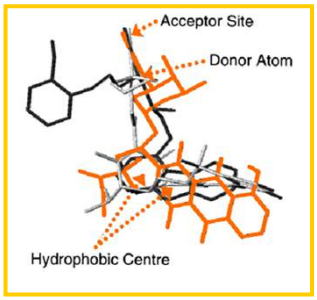


Memantine preferentially inhibits extrasynaptic "neurotoxic" NMDA receptors



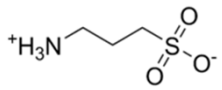


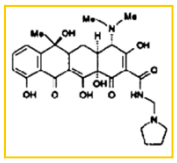
Inhibitors of Aß fibrillization



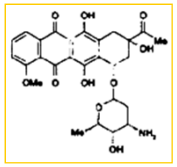
3-Amino-1-propansulphonate (Tramiprosate – Alzhemed)

Curcumine; PIB; Metal chelators

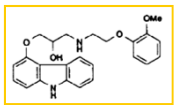




Daunomycin



Rolitetracycline



Carvedilol

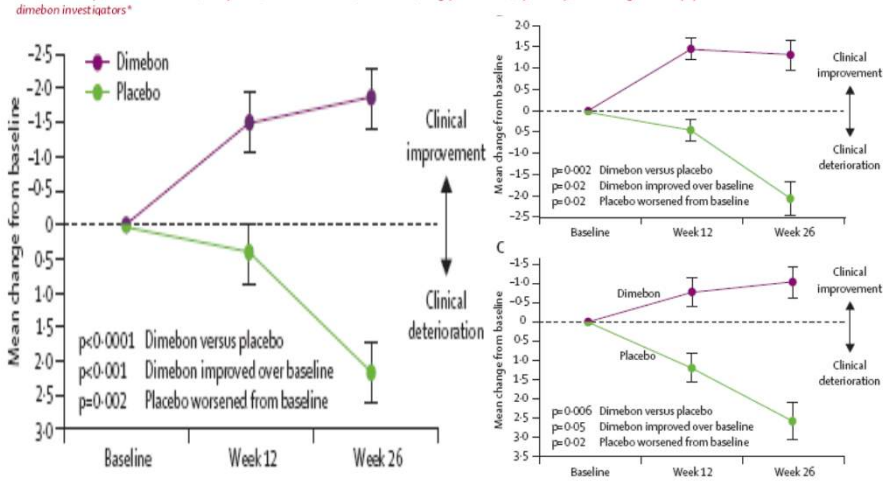
Inhibitors of tau aggregation

Methylthioninium chloride (Rember; TauRx) phase II; 7.8 in ADAS-cog

Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study

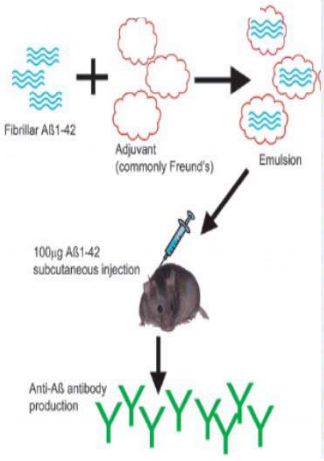
Lancet 2008; 372: 207–15

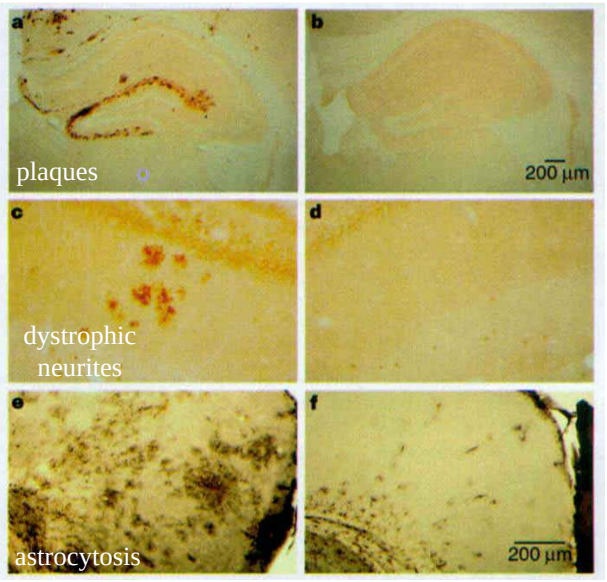
Rachelle S Doody, Svetlana I Gavrilova, Mary Sano, Ronald G Thomas, Paul S Aisen, Sergey O Bachurin, Lynn Seely, David Hung, on behalf of the dimebon investigators*



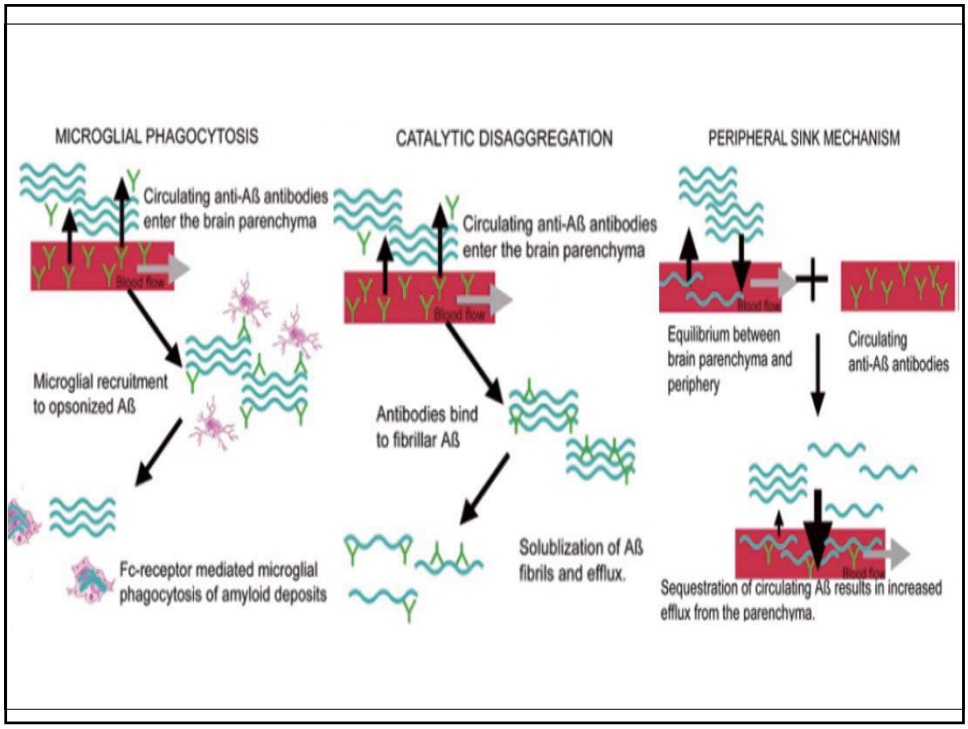
PDAPP mice ***Aß42-immunized***

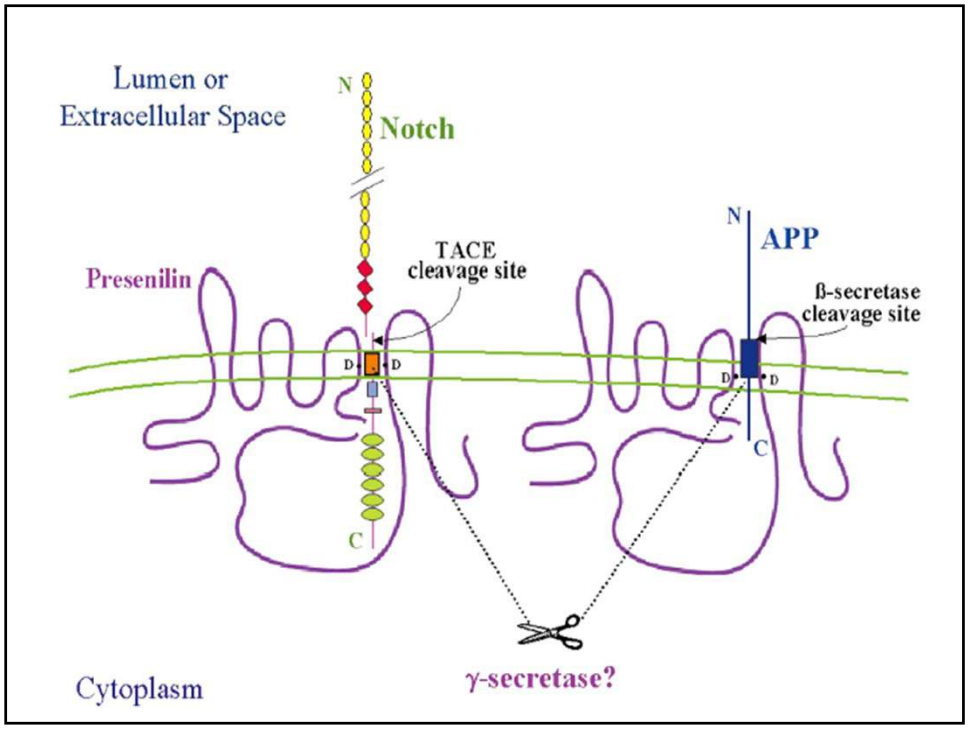
Vaccine in AD: Active immunization



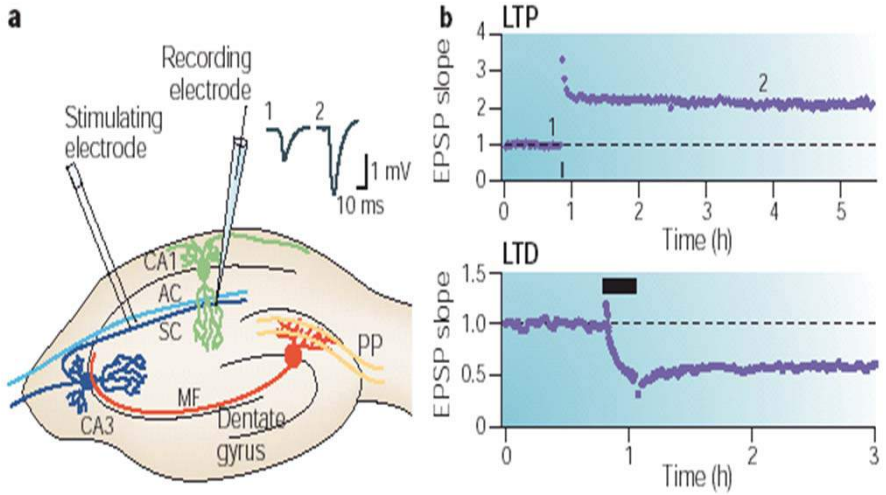


Schenk et al., Nature 400: 173, 1999


MICROGLIAL PHAGOCYTOSIS
Circulating anti-Aß antibodies enter the brain parenchyma
Microglial recruitment to opsonized Aß
Fc-receptor mediated microglial phagocytosis of amyloid deposits
CATALYTIC DISAGGREGATION
Circulating anti-Aß antibodies enter the brain parenchyma
Antibodies bind to fibrillar Aß
Solublization of Aß fibrils and efflux.
PERIPHERAL SINK MECHANISM
Equilibrium between brain parenchyma and periphery
Circulating anti-Aß antibodies
Sequestration of circulating Aß results in increased efflux from the parenchyma.

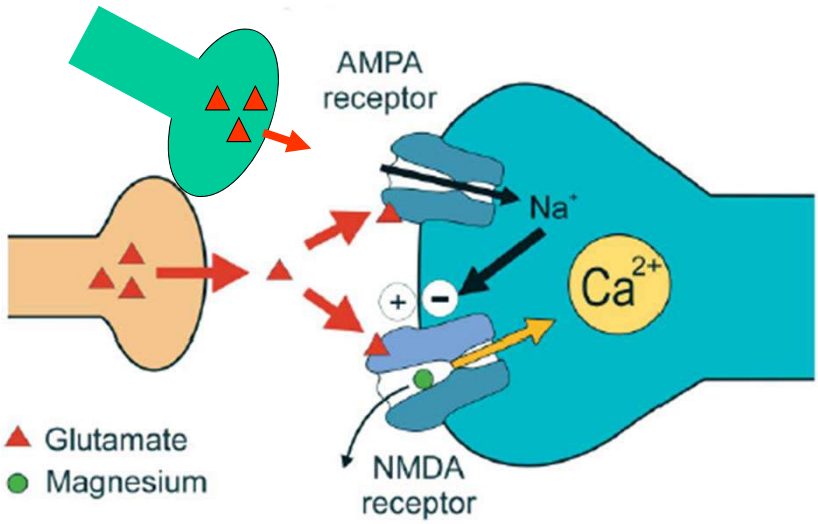

Lumen or Extracellular Space
N
Notch
TACE cleavage site
Presenilin
N
APP
ß-secretase cleavage site
D
D
D
D
C
C
Cytoplasm
γ-secretase?

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



Collingridge et al., Nat Rev Neurosci 2005

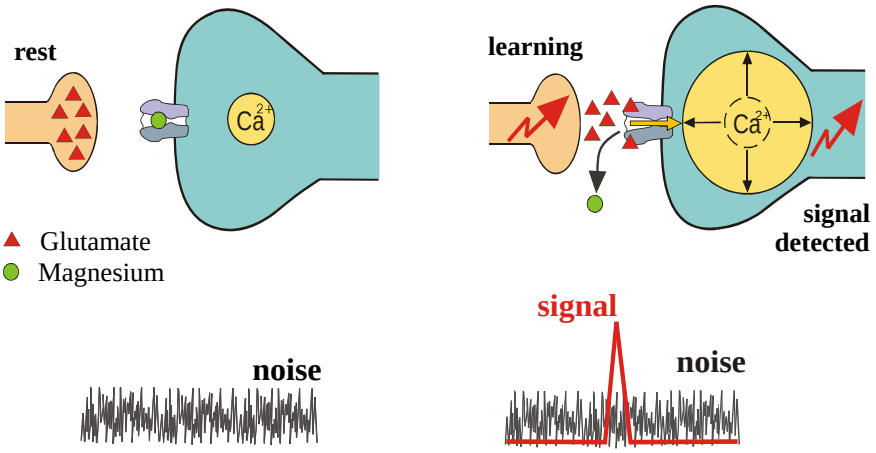
2. L'attivazione dei recettori NMDA dipende dalla presenza di uno stimolo di rinforzo con carattere di associatività e cooperatività



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



An increased basal level of glutamate induces "noise" at the glutamatergic synapse preventing LTP.

Normal conditions

Alzheimer

Ca^{2+} level

Depolarization

- Increased noise to signal inhibits LTP
- Increased intracellular Ca2+ levels can induce neuronal cell dead

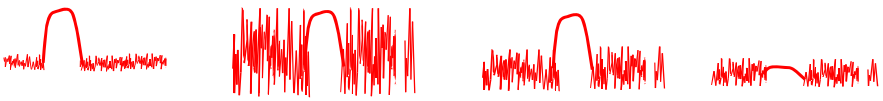
An increased basal level of glutamate induce "noise" at the glutamatergic synapse.

Normal conditions

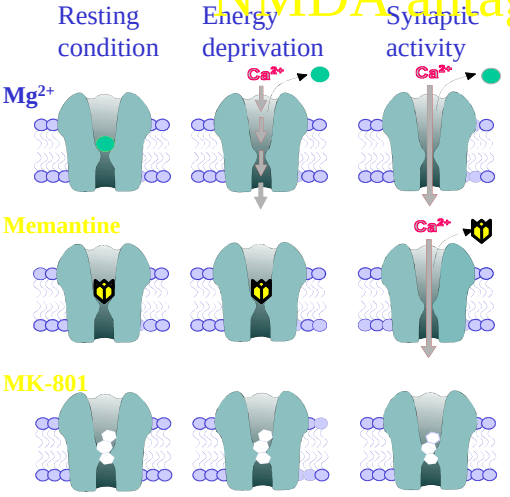
Alzheimer

Alzheimer + memantine

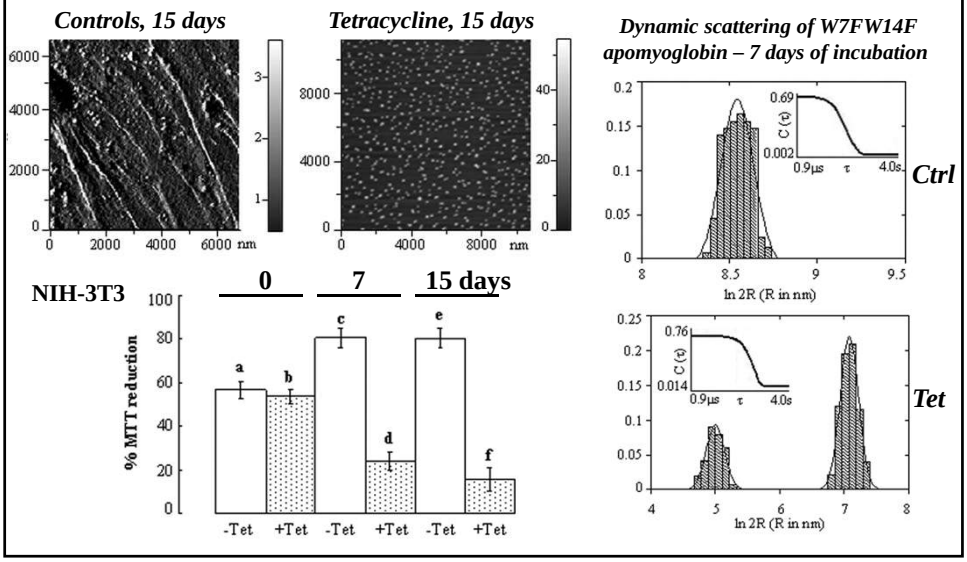
Alzheimer + MK-801



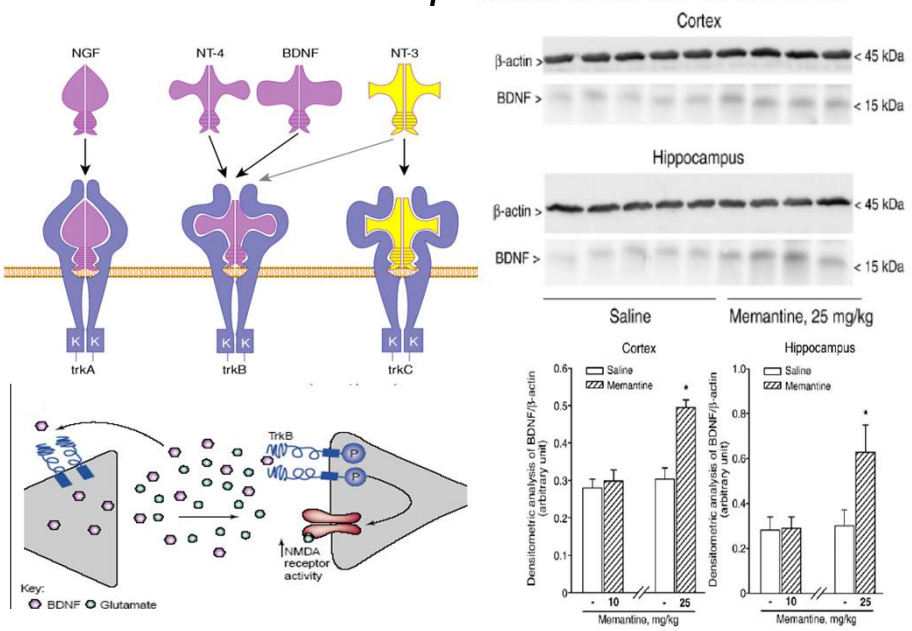
Differentiation from other NMDA antagonists



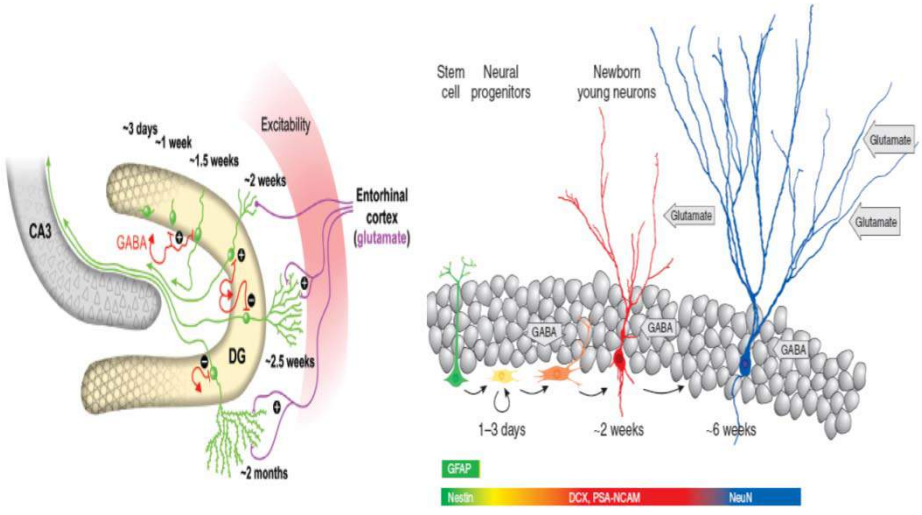
Tetracycline inhibits fibril extension and keeps the amyloid protein in a prefibrillar cytotoxic state (Malmo et al., FASEB J. 2005)



Memantine enhances the formation of BDNF in the CNS

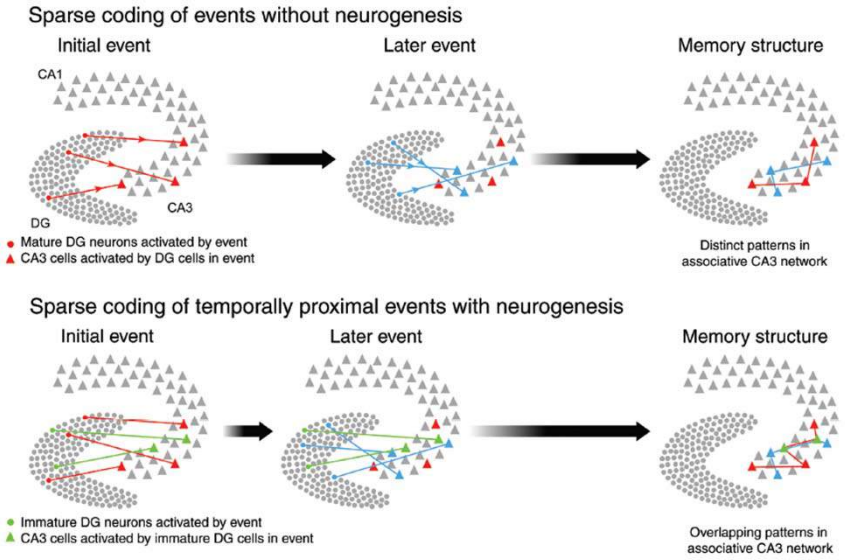


Adult neurogenesis in the dentate gyrus

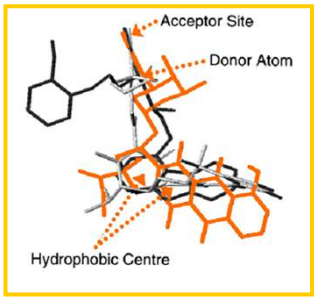


Neurogenesis and the encoding of time in new memories

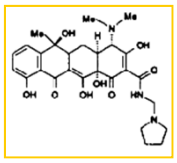
Aimone et al., Nat. Neurosci., 2006



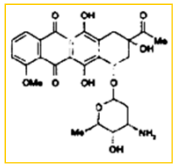
Inhibitors of Aß aggregation



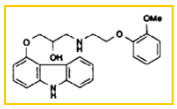
Congo red derivatives, Rifampicin,
β-Sheet breaking peptides
Inhibitors of pathological chaperones
(ApoE4, α1-antichymotrypsin, C1q factor)
Zinc and Cupper chelators



Daunomycin



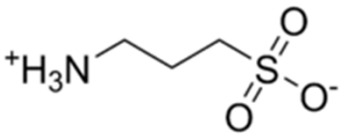
Rolitetracycline

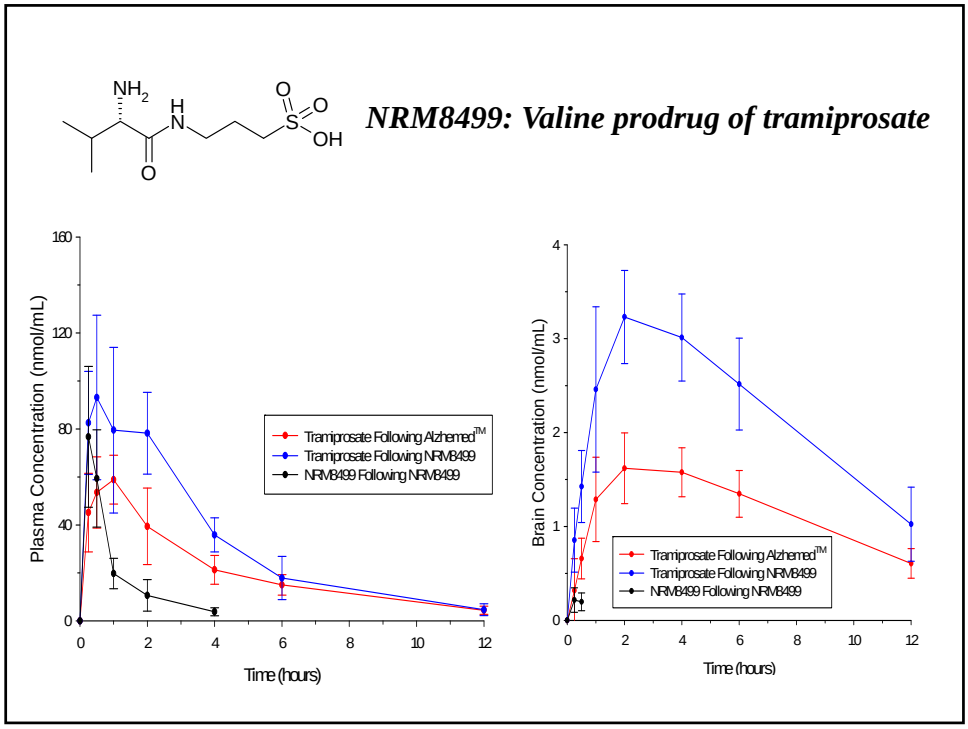


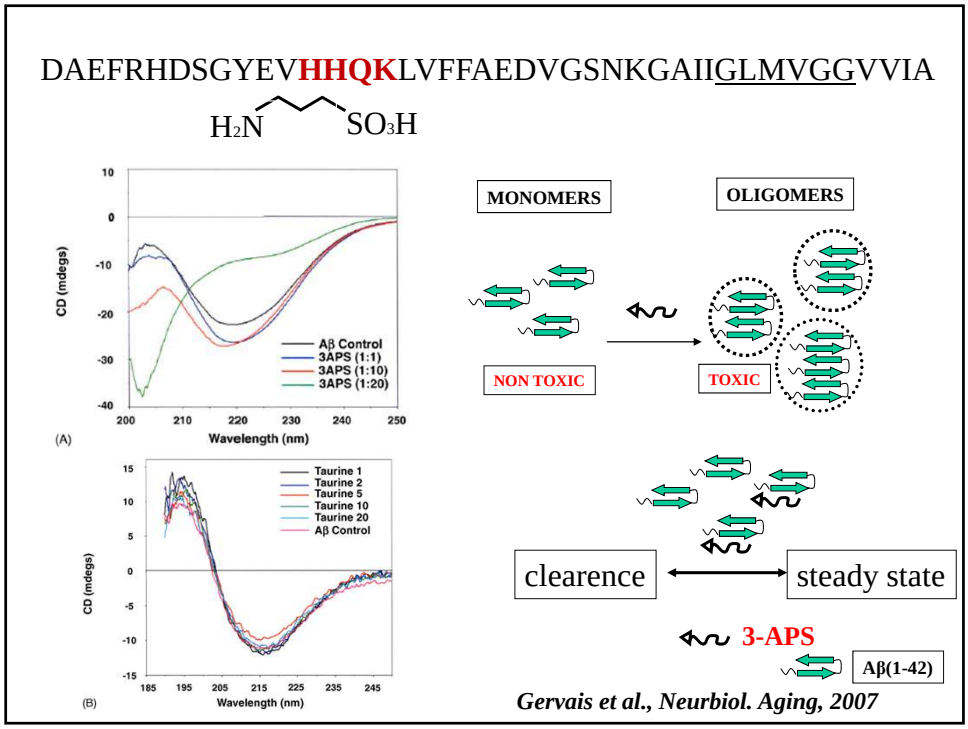
Carvedilol

Inhibitors of glycosaminoglycans

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

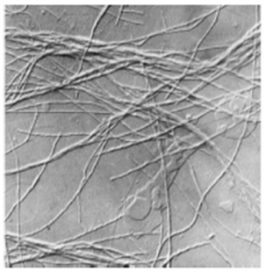



NRM8499: Valine prodrug of tramiprosate
Plasma Concentration (nmol/mL)
Time (hours)
Tramiprosate Following Alzhemed™
Tramiprosate Following NRM8499
NRM8499 Following NRM8499
Brain Concentration (nmol/mL)
Time (hours)
Tramiprosate Following Alzhemed™
Tramiprosate Following NRM8499
NRM8499 Following NRM8499

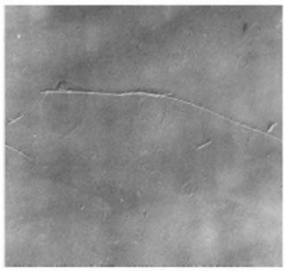

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA
H2N
SO3H
CD (mdegs)
Wavelength (nm)
Aβ Control
3APS (1:1)
3APS (1:10)
3APS (1:20)
(A)
Taurine 1
Taurine 2
Taurine 5
Taurine 10
Taurine 20
Aβ Control
CD (mdegs)
Wavelength (nm)
(B)
MONOMERS
OLIGOMERS
NON TOXIC
TOXIC
clearence
steady state
3-APS
Aβ(1-42)
Gervais et al., Neurbiol. Aging, 2007

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

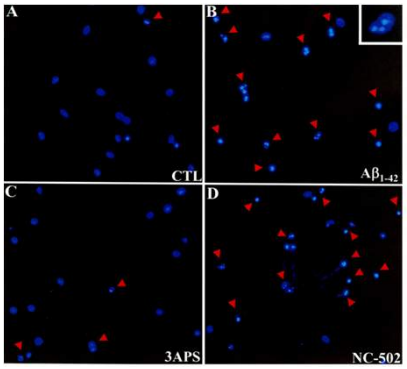
24 hrs

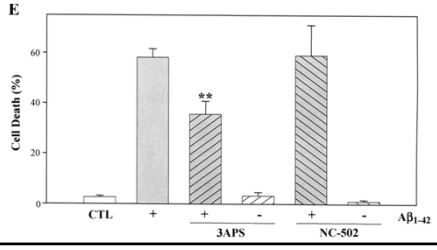


Amyloid Aß



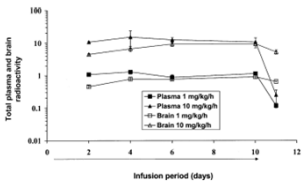
Amyloid Aß + homotaurine

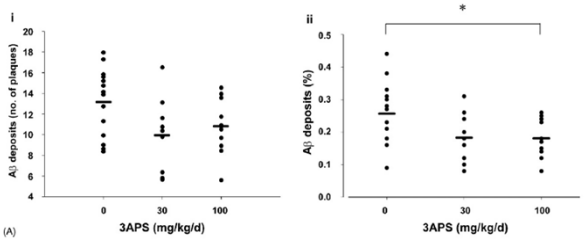




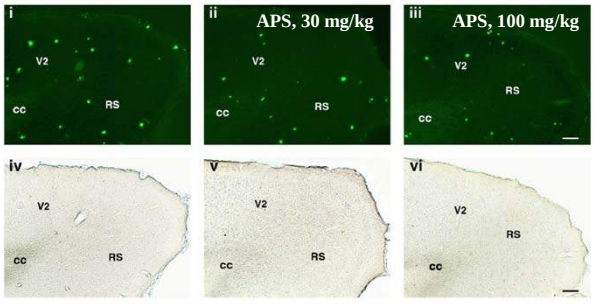
Targeting soluble Aβ peptide with tramiprosate for the treatment of brain amyloidosis

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

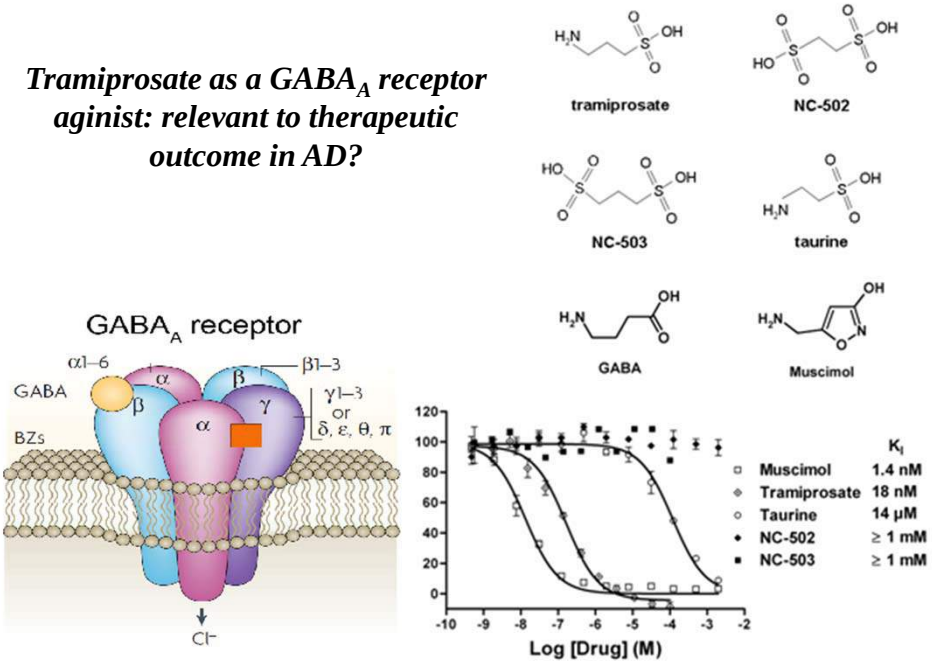




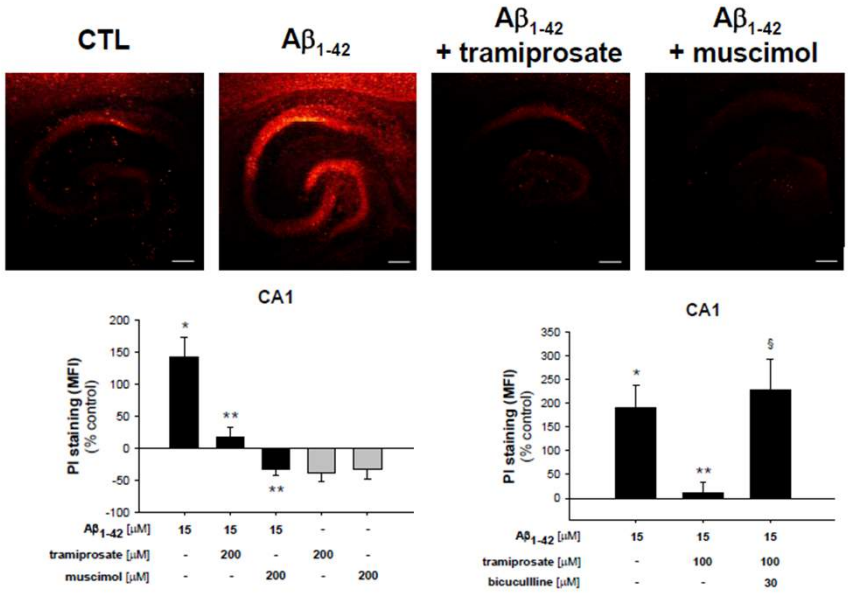
TgCRND8 mice (9 weeks) treated for 8 weeks with tramiprosate (APS)



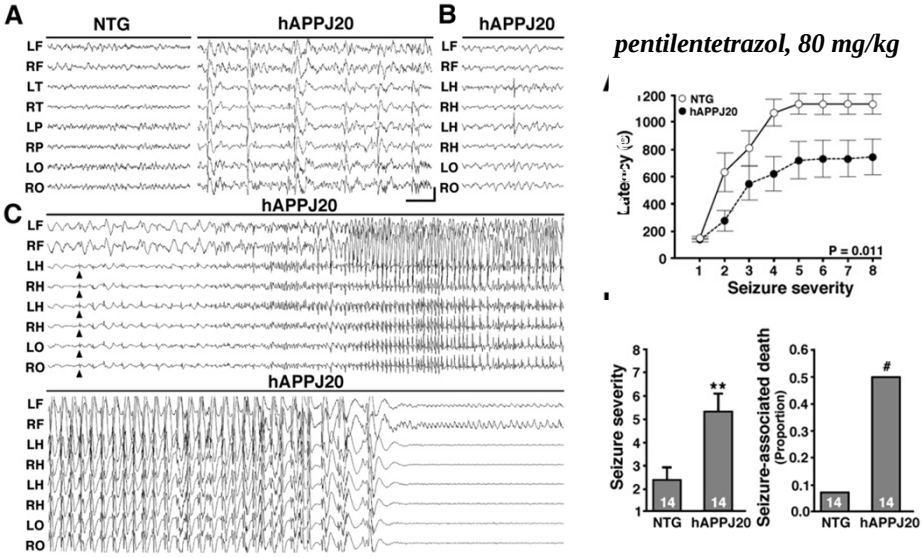
Tramiprosate as a $GABA_A$ receptor aginist: relevant to therapeutic outcome in AD?



$GABA_A$ receptor-dependent neuroprotection by tramiprosate against Aβ-mediated toxicity (Martin et al., Neurochem Inc. 2013)

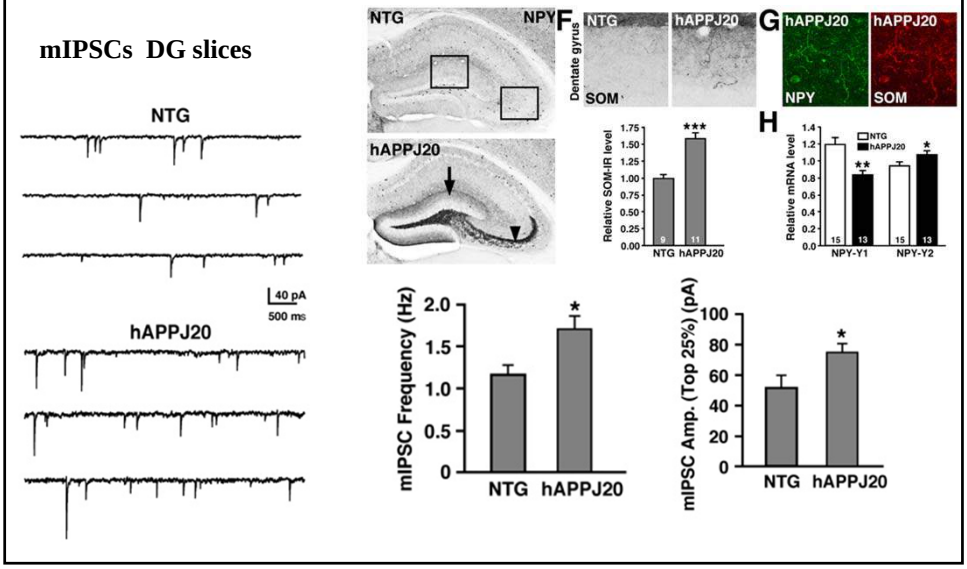


Enhanced excitation and seizure-prone phenotype in AD mice (Palop et al., Neuron 55, 2007)

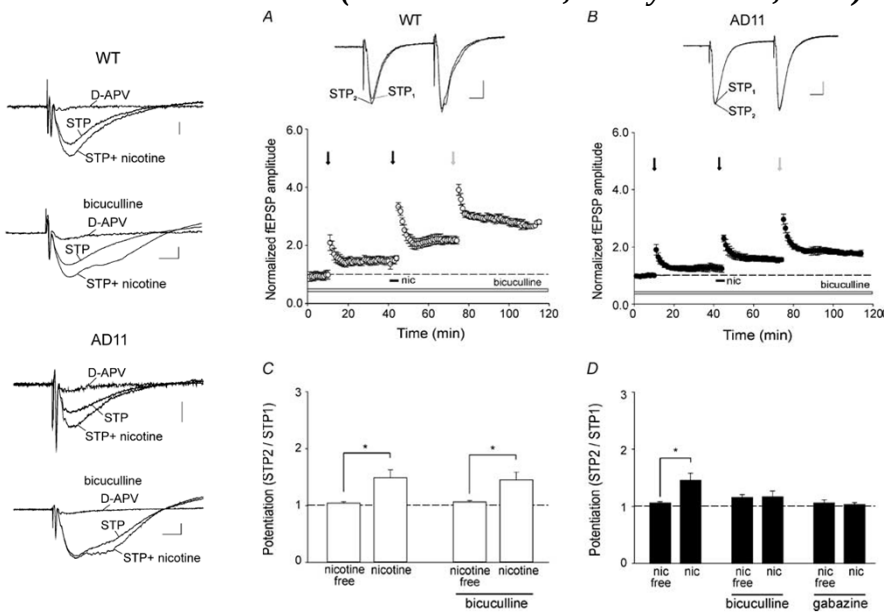


Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in AD mutant mice
(Palop et al., Neuron, 55, 2007)

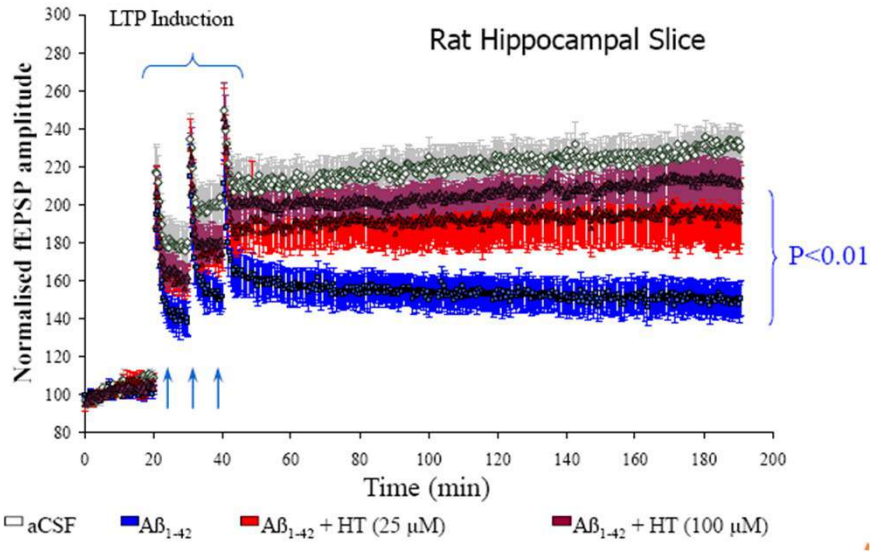
mIPSCs DG slices



Nicotine boosting of synaptic plasticity requires GABAergic neurons in anti-NGF "AD" mice (Rosato-Siri et a., 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***

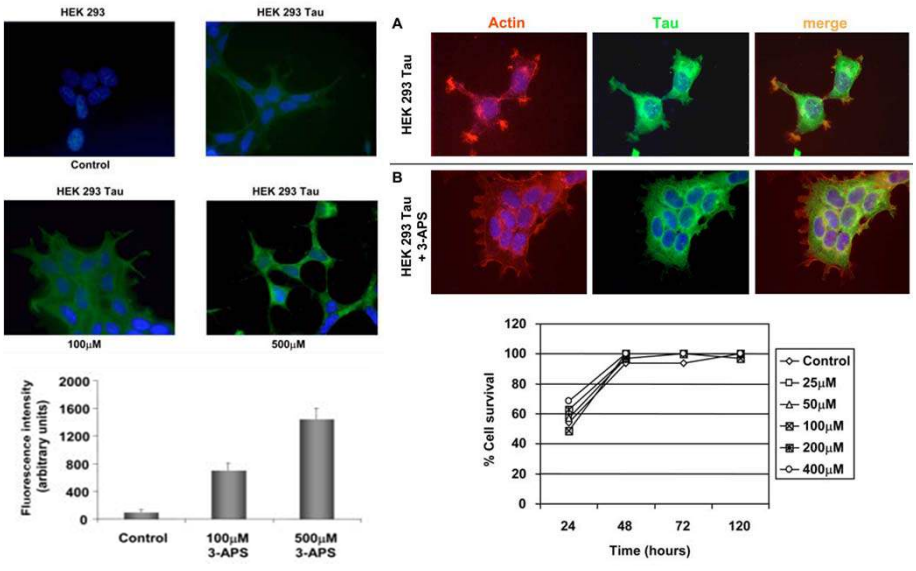
2. ***Agonist activity at $GABA_A$ receptors: implications for neuroprotection and cognition-enhancing effect in AD***

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

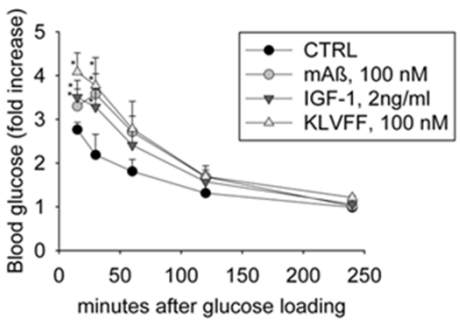
4. ***Main question: any interference with the physiological activity of Aβ monomers?***

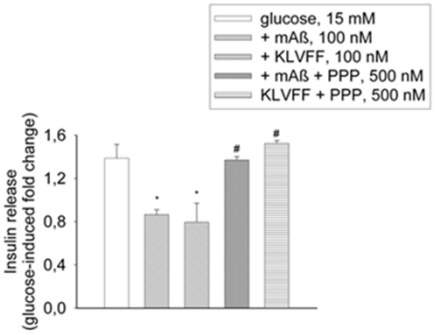
Tramiprosate enhances tau aggregation reducing tau binding to β-actin without affecting neuronal survival

(Santa-Maria et al., Mol. Neurodeg. 2007)



Monomeric β-amyloid mimics the action of IGF-1 in suppressing insulin secretion



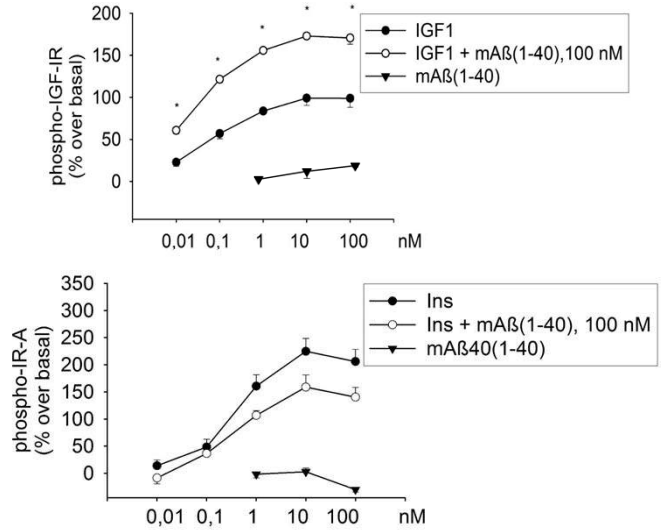


InsE1 insulinoma cells

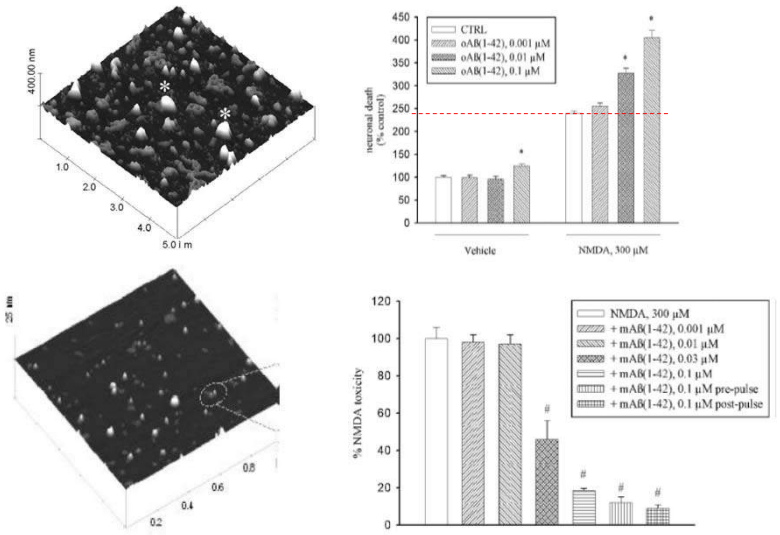
Glucose consumption and type-I IGFR phosphorylation in hippocampal slices from wt and AD mice incubated with IGF-I and β-amyloid monomer

	TgCRND8		**Non-Tg**	
	p(Y1161)IGF-IR levels (% of basal)	glucose consumption (µmol)/hr	p(Y1161)IGF-IR levels (% of basal)	glucose consumption (µmol)/hr
Basal	100	0.2 ±0.02	100	0.35 ± 0.01
IGF1, 1 nM	88.5 ± 5.35	0.2 ± 0.018	153.467 ± 14.91*	0.35 ± 0.02
mAß, 100 nM	147.767 ± 4.68*	0.34 ± 0.014#	74.543 ± 12.25	0.35 ± 0.015

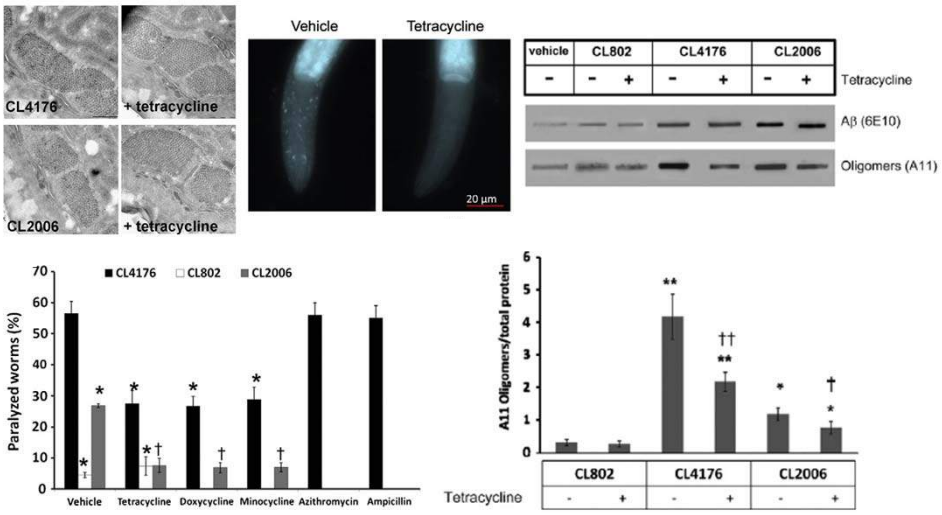
Aβ (1-40) acts as a PAM at immunocaptured type-I IGF receptors with no agonist activity



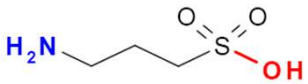
Monomers of β-amyloid protect neurons against excitotoxic death (Giuffrida et al., J. Neurosci, 2009)



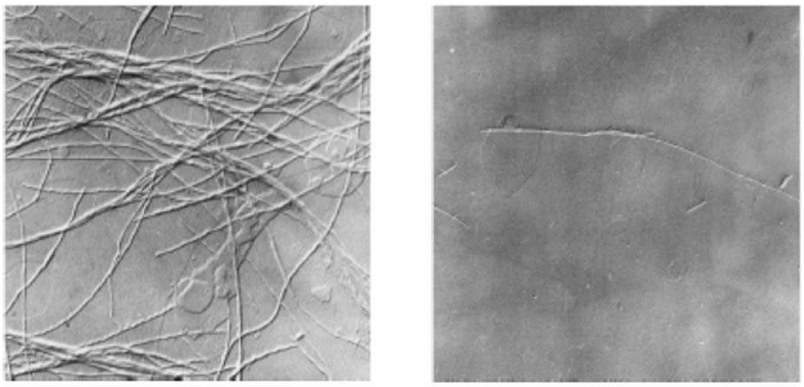
Tetracyclines protect C. elegans against human amyloid toxicity by targeting oligomers (Diomede et al., Neurobiol. Dis. 40, 2010)



Glycosaminoglycan inhibitors:



3-Aminopropansulphonate (3-APS, homotaurine, tramiprosate)



Amyloid Aß

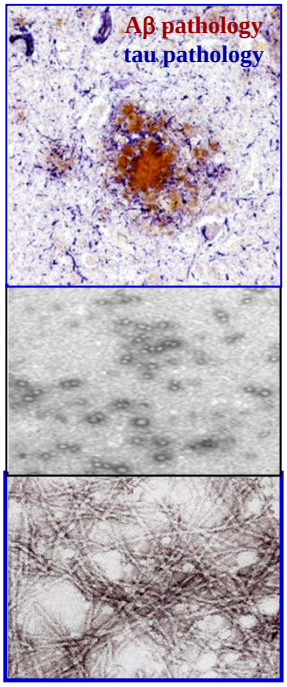
Amyloid Aß + homotaurine

24-hour incubation

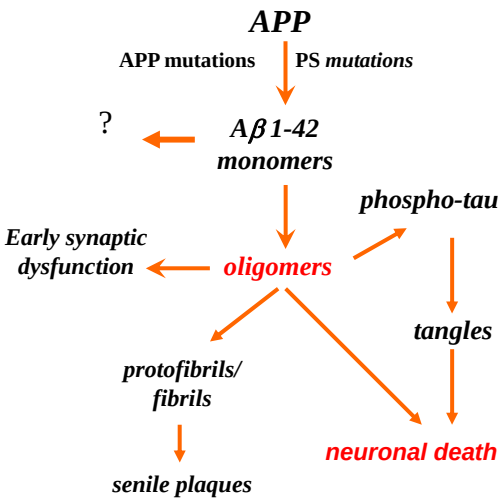
Starting points

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

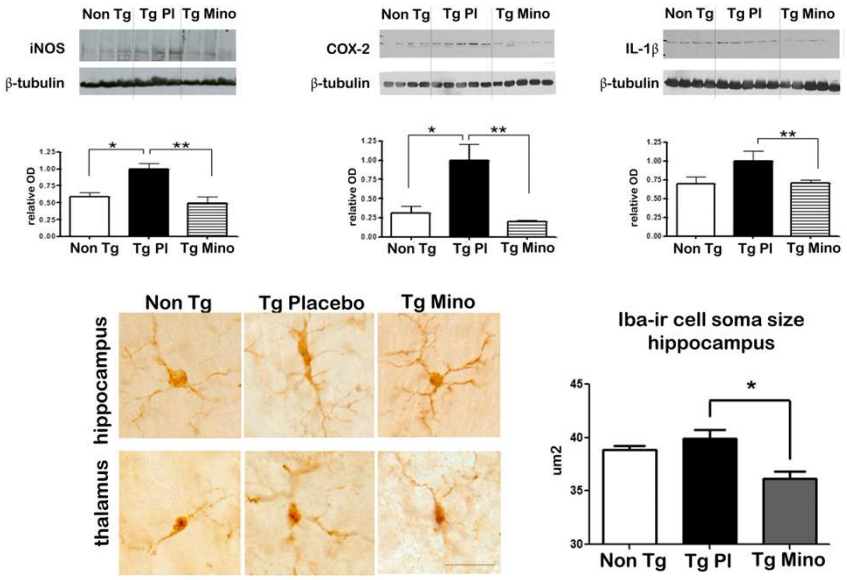
Early reduction in brain glucose uptake in AD



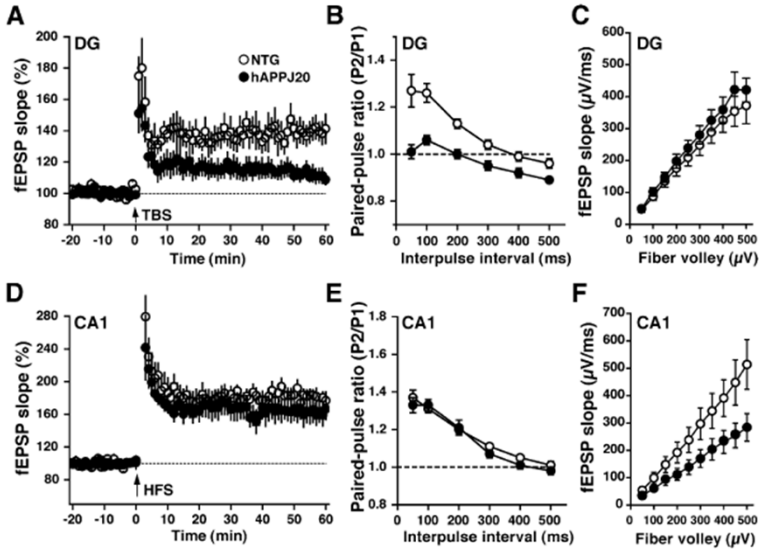
The Amyloid Cascade Hypothesis (Hardy and Selkoe, 2002)



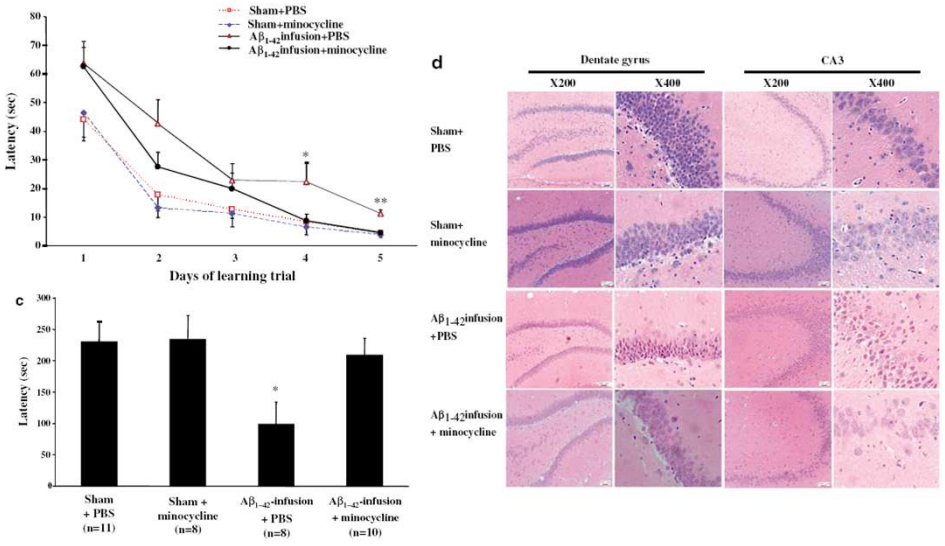
Minocycline inhibits early pre-plaque neuroinflammation in AD mice (McGill-Thy1-APP) ***(Ferretti et al., J. Neuroinflammation, 9, 2012)***

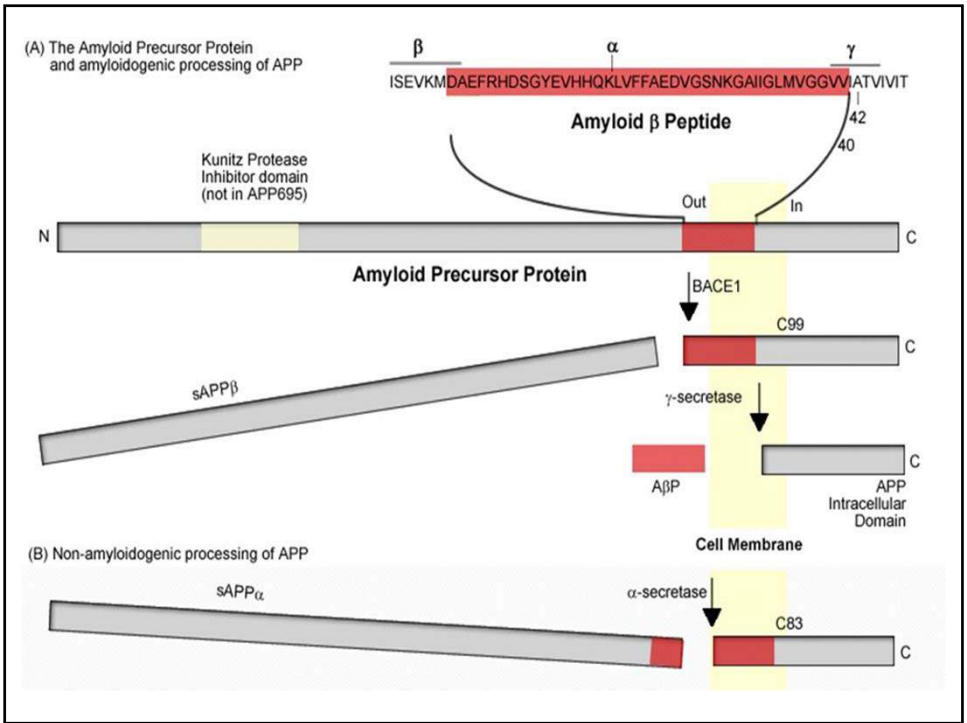


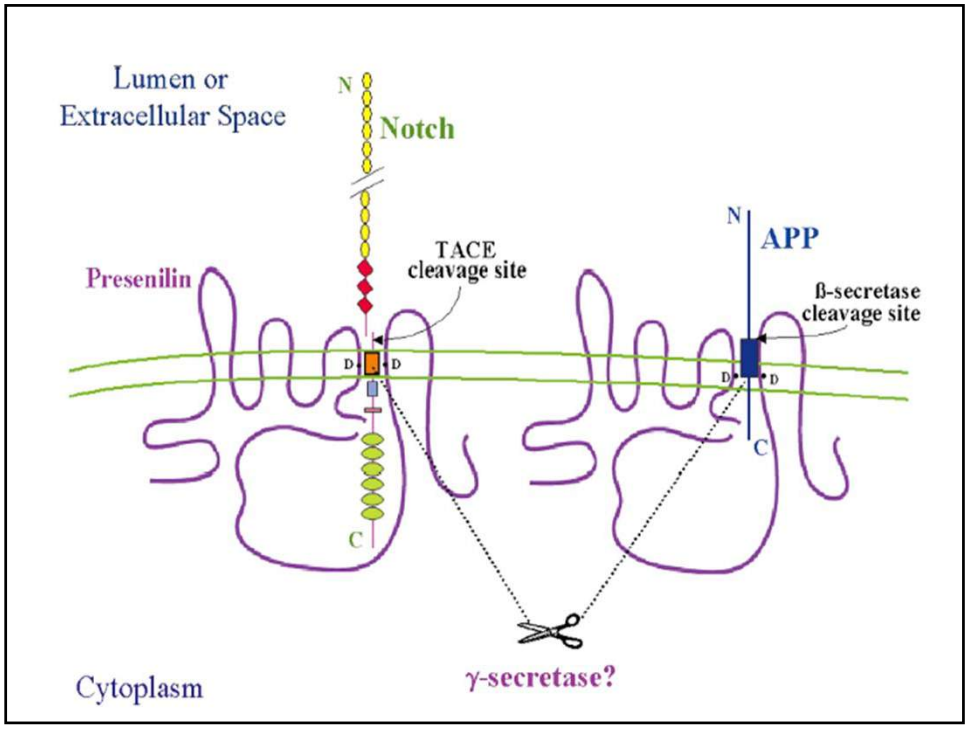
Abnormal activity-dependent synaptic plasticity in AD mutant mice (Palop et al., Neuron 55, 2007)



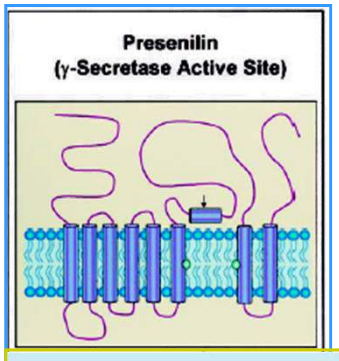
Minocycline attenuates neuronal death and improves cognitive impairment in Tg2576 AD mice ***(Choi et al., Neuropsychopharm. 32, 2007)***







γ-Secretase inhibitors in AD



•***Pros***

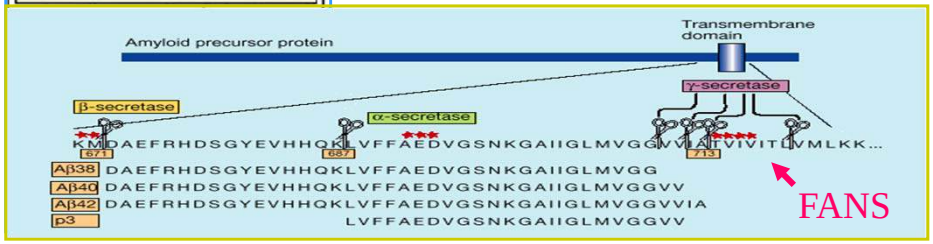
Improve cognitive deficits in AD mice

LY450139 and MK-0572 ↓ serum Aβ levels in AD

Cons

Notch-related effects [GI, blood cells, Neurodegeneration]

"Rebound" effect.

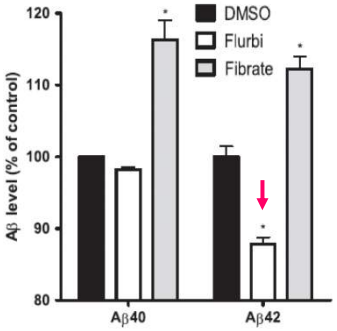


Selective Amyloid Lowering Agents (SALAs)

R-Flurbiprofen, Ibuprofen, Sulindac, Indomethacin

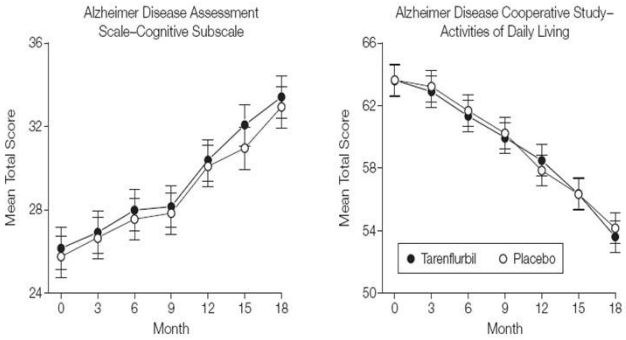
Selective Amyloid Raising Agents (SARAs)

Fenofibrate, Celecoxib

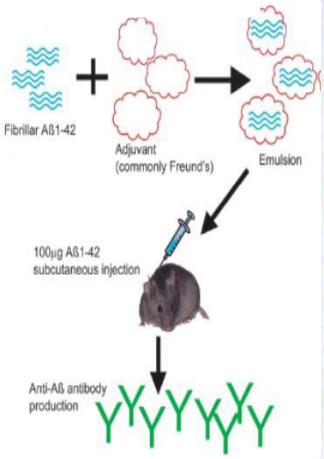


Tarenflurbil for AD "a shot on goal that missed"

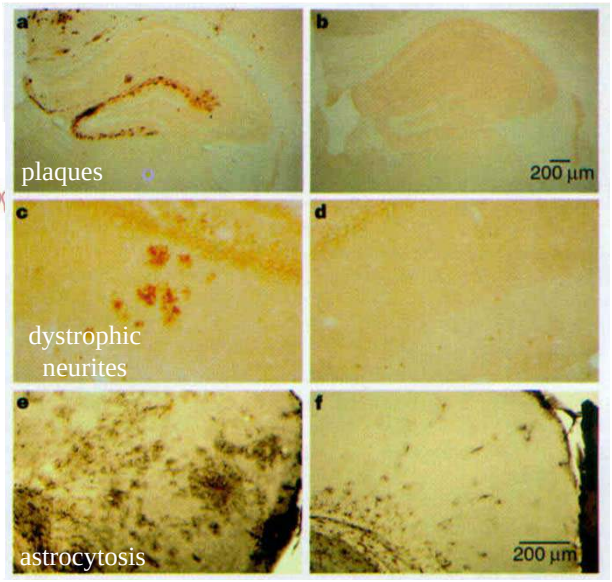
Green et al., JAMA 302, 2009



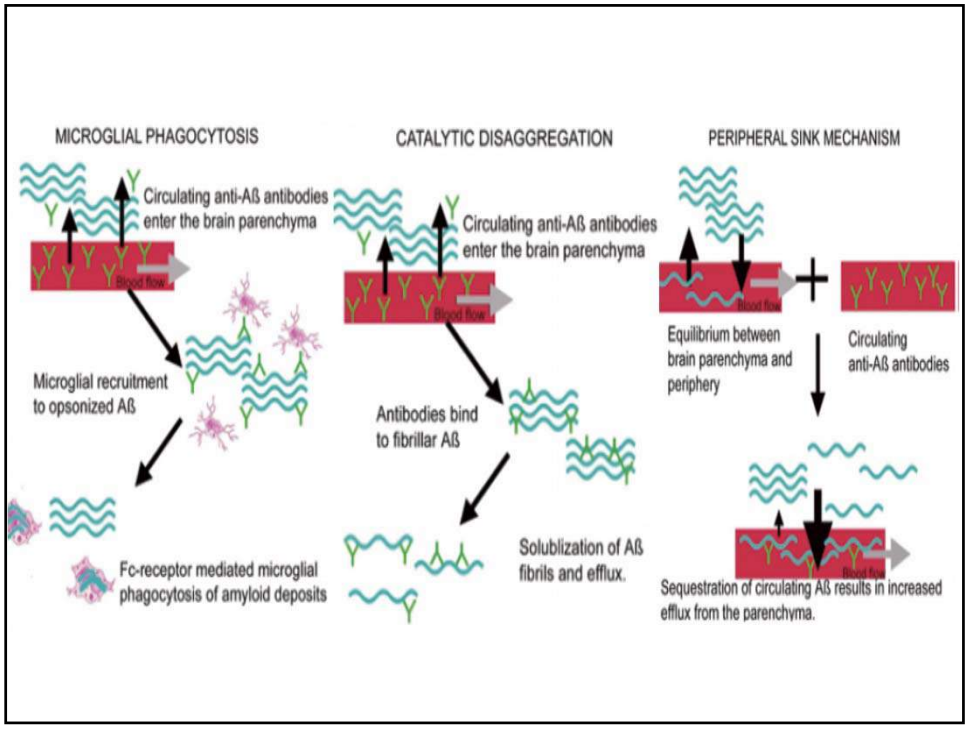
Vaccine in AD: Active immunization



PDAPP mice ***Aß42-immunized***



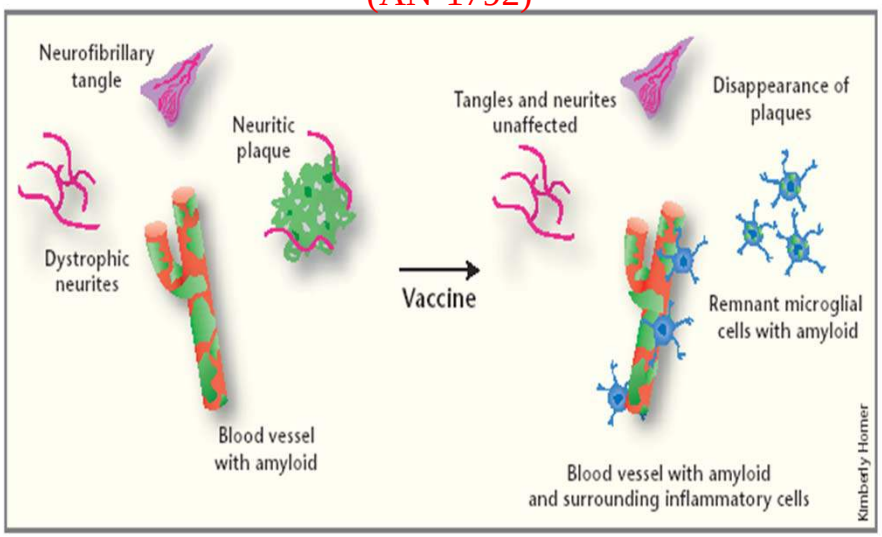
Schenk et al., Nature 400: 173, 1999



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 (Aß1-11/PADRE/MDC/CCL22)

Passive Immunization

1) Catalytic IgM
2) Deglycosylated antibodies
3) F(ab')2 fragments
4) BAPINEUZUMAB (AAB-001; Elan) phase III in ApoE4 non carriers
5) SOLANEZUMAB (LY2062430; Eli Lilly; phase II)

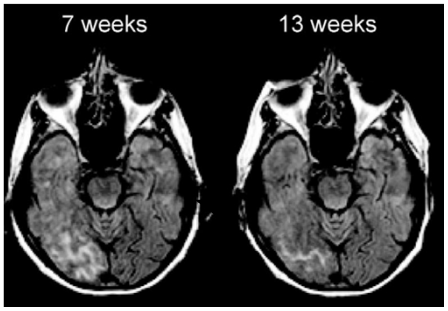
APOE ϵ4 and bapineuzumab

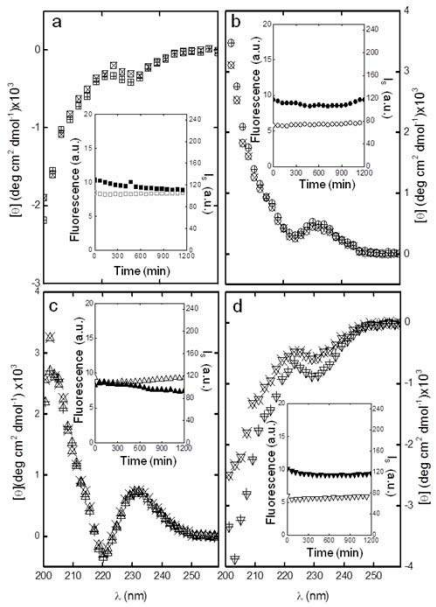
Infusing pharmacogenomics into Alzheimer disease therapeutics

Dan Kaufer, MD
Sam Gandy, MD, PhD

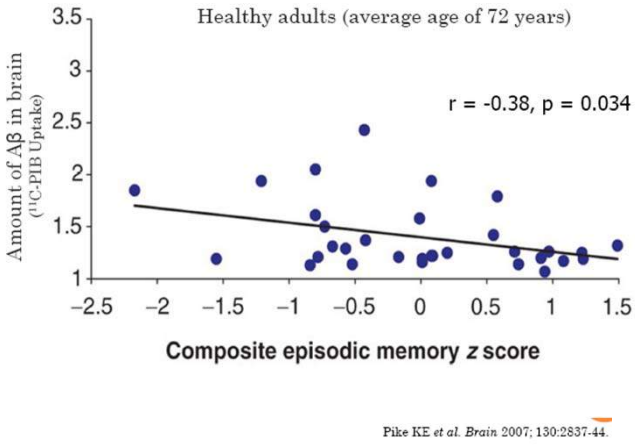
Neurology® 2009;73:2052–2053

Vasogenic edema in 12/124 (10%) associated with ***APOE 4 carrier status (10/12 or 33% of all APOE ε4 carriers***
Dose-dependent and reversible on MRI after discontinuation.

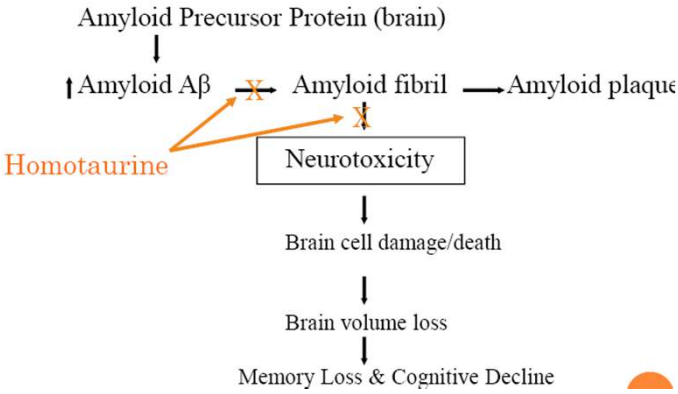


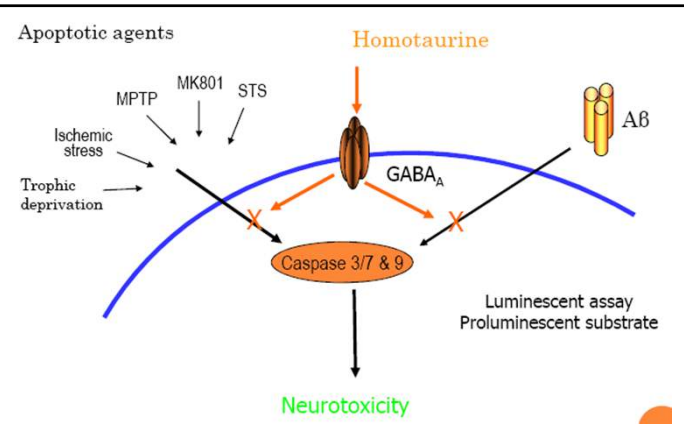


Healthy Adults with Lower Aß Brain Levels Scored Better on Memory Test

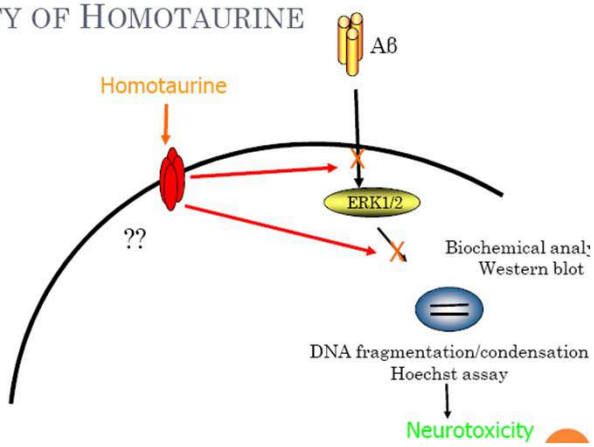


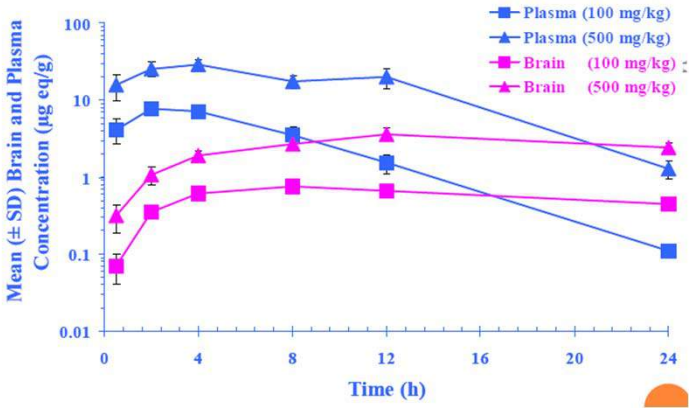
Pike KE *et al. Brain* 2007; 130:2837-44.


Amyloid Precursor Protein (brain)
Amyloid Aβ
Amyloid fibril
Amyloid plaque
Homotaurine
Neurotoxicity
Brain cell damage/death
Brain volume loss
Memory Loss & Cognitive Decline

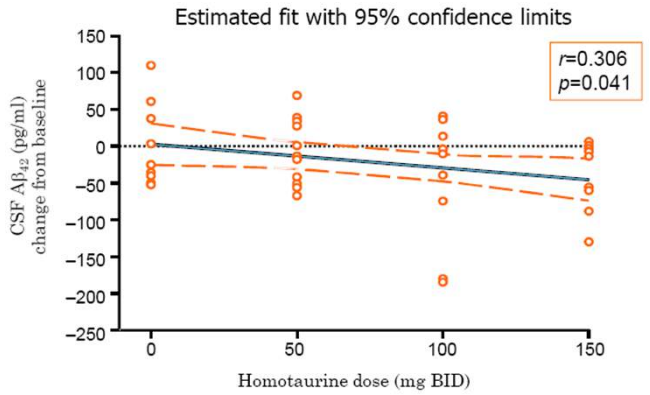

Apoptotic agents
Homotaurine
MPTP
MK801
STS
Ischemic stress
Trophic deprivation
Aβ
GABA$_A$
Caspase 3/7 & 9
Luminescent assay
Proluminescent substrate
Neurotoxicity

GABA-Independent Neuroprotective Activity of Homotaurine

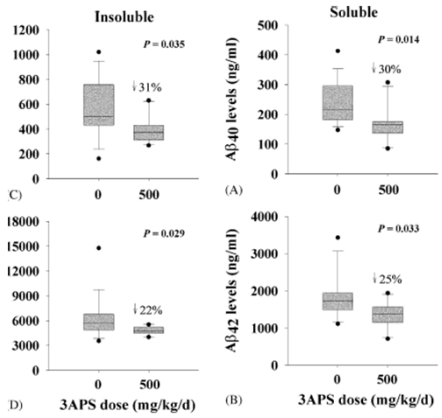


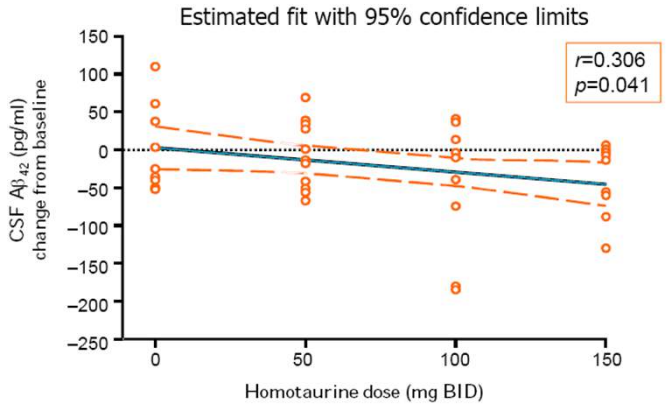


Phase II: Dose-Dependent Decrease of $A\beta_{42}$ Cerebrospinal (CSF) Levels in AD Patients

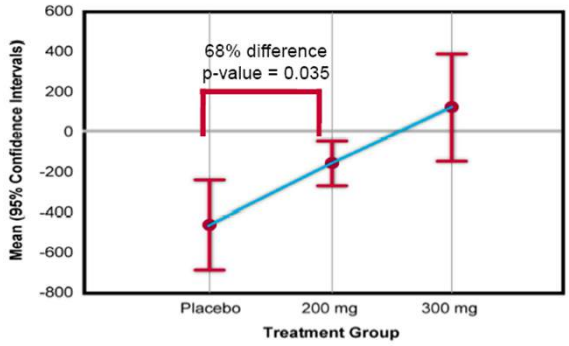


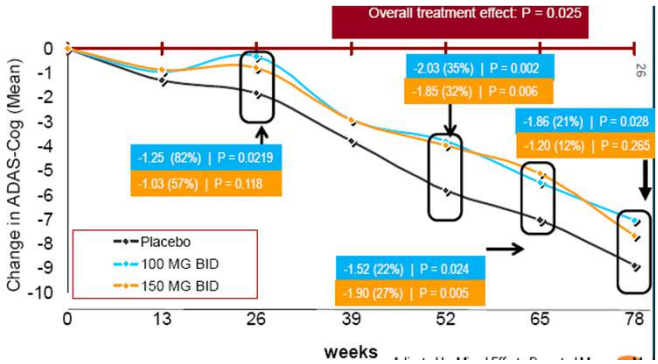
Targeting soluble Aβ peptide with tramiprosate for the treatment of brain amyloidosis (Gervais et al., Neurobiol. Aging 28. 2007)





- **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**


600
400
200
0
-200
-400
-600
-800
Mean (95% Confidence Intervals)
68% difference
p-value = 0.035
Placebo
200 mg
300 mg
Treatment Group


Overall treatment effect: P = 0.025
Change in ADAS-Cog (Mean)
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-2.03 (35%) | P = 0.002
-1.85 (32%) | P = 0.006
-1.86 (21%) | P = 0.028
-1.20 (12%) | P = 0.265
-1.25 (82%) | P = 0.0219
-1.03 (57%) | P = 0.118
Placebo
100 MG BID
150 MG BID
-1.52 (22%) | P = 0.024
-1.90 (27%) | P = 0.005
0
13
26
39
52
65
78
weeks

Aging Clinical and Experimental Research

REVIEW ARTICLE

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

Carlo Caltagirone[1], Luigi Ferrannini[2], Niccolò Marchionni[3], Giuseppe Nappi[4], Giovanni Scapagnini[5] and Marco Trabucchi[6]

[1]Chair of Neurology, University of Roma Tor Vergata, and Scientific Director, IRCSS Santa Lucia Foundation, Rome, [2]Department of Mental Health and Addictions - ASL 3 Genoa, and President of the Italian Psychiatry Association, [3]Division of Geriatric Cardiology and Medicine, University of Florence, Azienda Ospedaliero-Universitaria Careggi, Florence, [4]Scientific Director, IRCCS "C. Mondino National Neurological Institute", Pavia, and Chair of Neurology, University "La Sapienza", Rome, [5]Department of Health Sciences, Faculty of Medicine and Surgery, University of Molise, Campobasso, [6]Geriatric 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 Cummings (26)

Strategy	Target
Aβ production	α-secretase activation
	β-secretase inhibition
	γ-secretase inhibition
	γ-secretase modulation
	APP modulation
Aβ degradation	Neprilysin activation
	Insulin-degrading enzyme activation
	ApoE
Aβ removal	Vaccination
	Passive immunization
	General immune system modulation
	Microglial activation
	Receptor-mediated removal from CNS to periphery
	Prevent entry from periphery to CNS
	Modulation of Aβ balance between CNS and periphery
Preventing Aβ toxicity	Aggregation inhibition by binding Aβ
	Oligomerization inhibition through metal protein attenuation
	Prevent formation of pyroglutaminyl Aβ
Tau	Tau aggregation inhibition
	Prevent tau hyperphosphorylation
	Facilitate tau phosphatase
	Microtubule stabilization
	Increase tau clearance
Neuroprotection	Neuronal growth factor
	Anti-apoptotic agents
	Mitochondrial improvement
	Anti-imflammation
	BBB integrity
	Neuronal metabolism

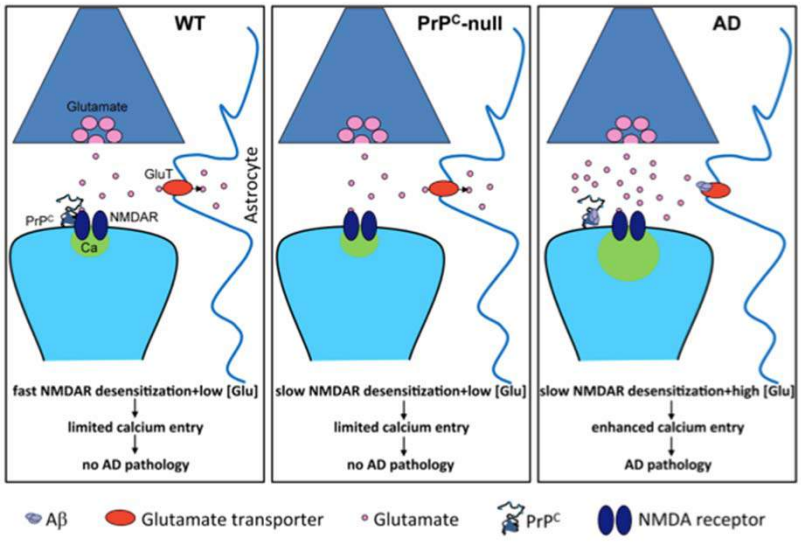
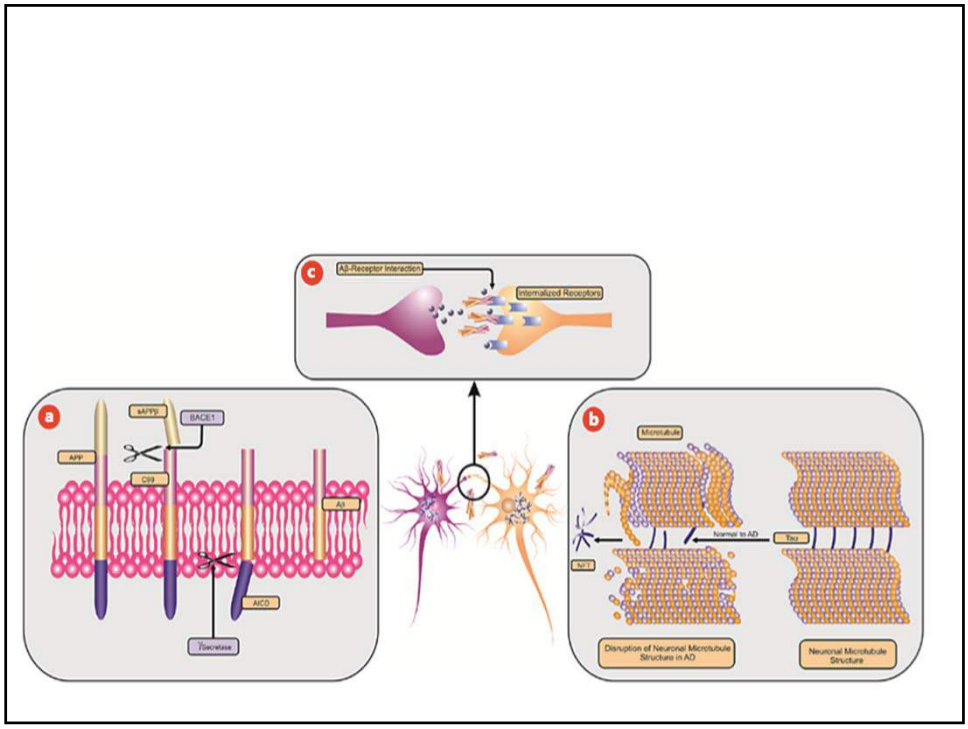


Table 1. Some of amyloid-based transgenic animal models of AD

Transgenic line	Promoter	Memory deficits	Neurological characteristic	Ref.
PDAPP	PDGF β	+	Aβ deposits, neuritic plaques, synaptic loss, astrocytosis and microgliosis	104
BRI-Aβ42	MoPrp	–	Aβ plaques in the cerebellum, extracellular Aβ plaques in the hippocampus	96
Arc Aβ	MoPrP	+	Aβ deposits in cortex and hippocampus, Aβ plaques, cerebral amyloid angiopathy present	97
TgAPParc	Thy1.2	+	High APParc levels, amyloid deposition in subiculum and thalamus	107
5XFAD	Thy1	+	$A\beta_{42}$ accumulation, amyloid deposition and gliosis, synapse degeneration, increased p25 levels, neuron loss	108
Tg-SwDI/B	Thy1.2	+	Plaques in hippocampus and cortex, Aβ deposits throughout forebrain	109
Tet-$APP_{Swe/Ind}$	Tetracycline responsive (pTetSplice)	NA	High MMo/huAPP overexpiration, doxycycline inhibits APP expression and reduces Aβ production	110
APPSWE	Hamster PrP	+	Aβ plaques, oxidative lipid and glycoxidative damage	111
PDGF-APP_{SwInd}	PDGF β	+	Aβ and $A\beta_{42}$ in neocortical and hippocampus, high levels of $A\beta_{1-42}$ resulted in Aβ plaques	112
McGill-R-Thy1-APP	Thy1.2	+	Intraneuronal Aβ accumulation, extracellular Aβ deposits, thioflavine S-positive amyloid plaques, glial activation	113

NA = Not assessed.


c
Aβ-Receptor Interaction
Internalized Receptors
a
sAPPβ
BACE1
APP
C99
Aβ
AICD
γ-secretase
b
Microtubule
Normal in AD
Tau
NFT
Disruption of Neuronal Microtubule Structure in AD
Neuronal Microtubule Structure

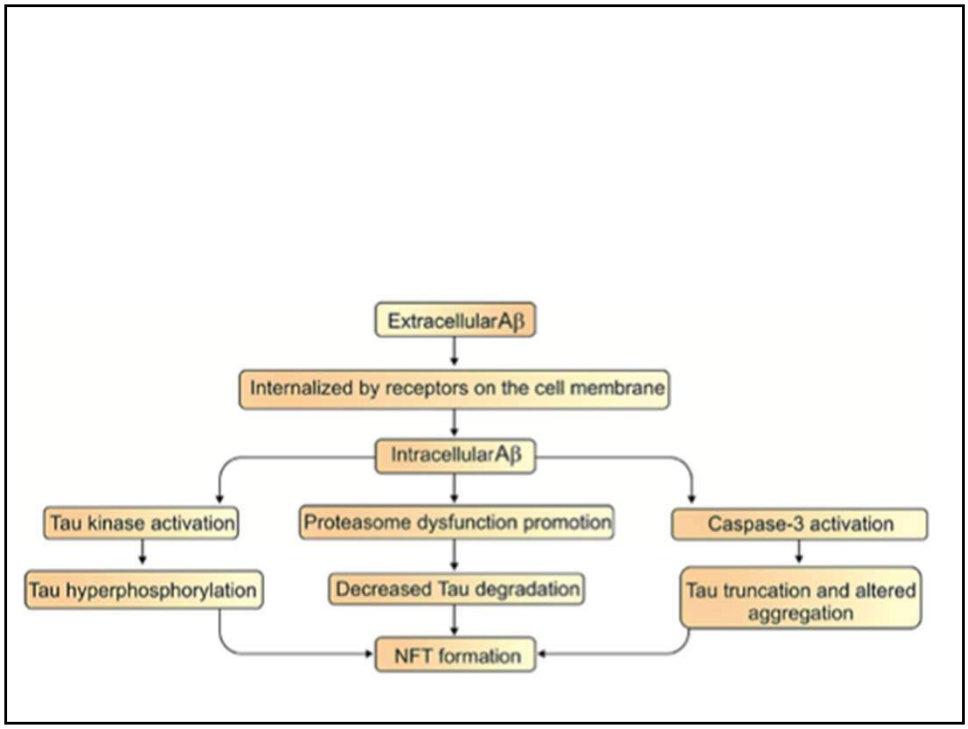

ExtracellularAβ
Internalized by receptors on the cell membrane
IntracellularAβ
Tau kinase activation
Proteasome dysfunction promotion
Caspase-3 activation
Tau hyperphosphorylation
Decreased Tau degradation
Tau truncation and altered aggregation
NFT formation

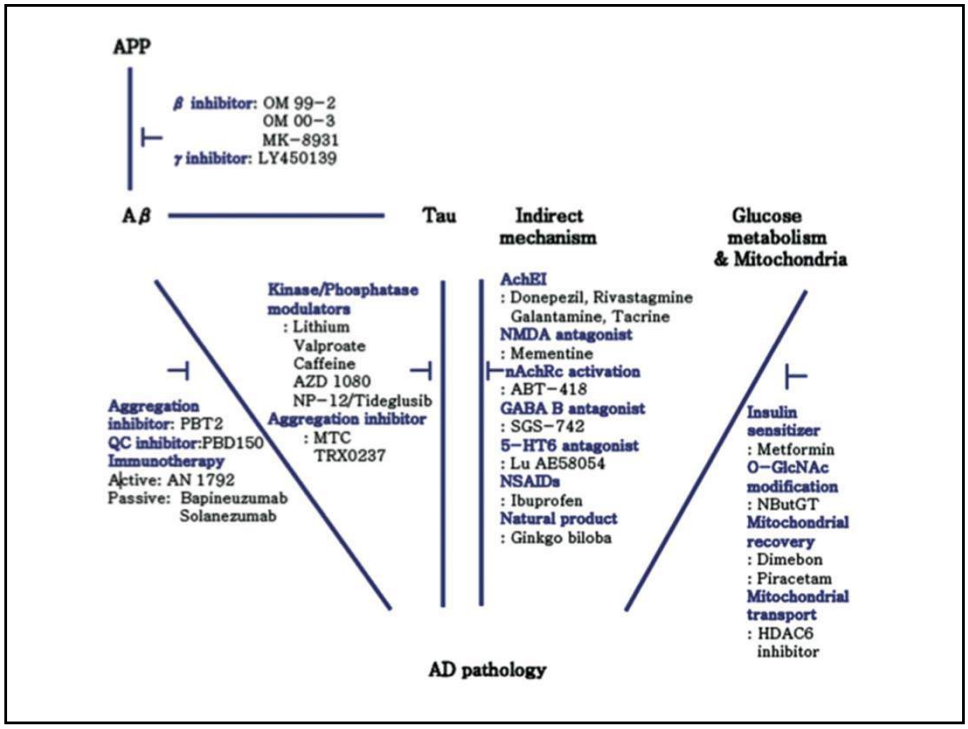
Table 1. Principal secondary prevention trials of monoclonal antibodies targeting β-amyloid for the treatment of AD.

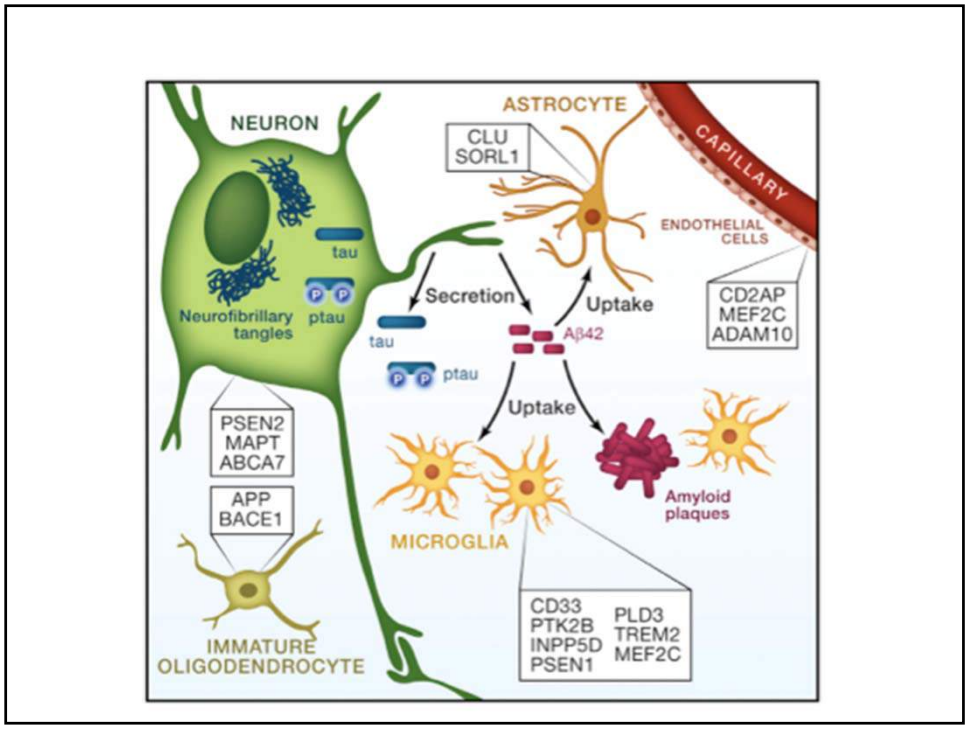
Trial Compound Company Collaborators ClinicalTrials.gov Identifier	Binding characteristics	Estimated or completed enrollment	Characteristics	Status	Ref.
Anti-amyloid treatment in Asymptomatic AD (A4) Solanezumab (Eli Lilly) (LY2062430) NCT02008357	Humanized monoclonal IgG1 anti-$A\beta_{1-42}$ antibody ($A\beta_{13-28}$), binding soluble Aβ	1000 older individuals at-risk for progression to AD (2014 – 2018)	400 mg i.v. administered once every 4 weeks for 168 weeks	Phase III trial (currently recruiting)	[46]
Dominantly inherited Alzheimer Network-trials unit (DIAN-TU) Solanezumab (Eli Lilly) (LY2062430) Gantenerumab (Hoffmann-La Roche) (RO4909832) Washington University School of Medicine Alzheimer's Association National Institute on Aging Avid Radiopharmaceuticals NCT01760005	Humanized monoclonal IgG1 anti-$A\beta_{1-42}$ antibody ($A\beta_{13-28}$), binding soluble Aβ Fully human monoclonal IgG1 antibody against $A\beta_{1-42}$ ($A\beta_{1-10}$ and $A\beta_{19-26}$), not binding soluble Aβ	210 subjects with autosomal dominant AD mutations (2012 – 2016)	Solanezumab: 400 mg i.v. every 4 weeks for 2 years Gantenerumab: 225 mg s.c. every 4 weeks for 2 years	Phase II/III trial (currently recruiting)	[48]
Alzheimer's prevention initiative Crenezumab (Genentech) (MABT5102A) Banner Alzheimer's Institute NCT01998841	Humanized monoclonal IgG4 antibody against $A\beta_{1-42}$ ($A\beta_{12-23}$)	300 individuals with autosomal dominant AD-causing genetic mutations (2013 – 2020)	Crenezumab s.c. injections every 2 weeks for 260 weeks	Phase II trial (currently recruiting)	[53]

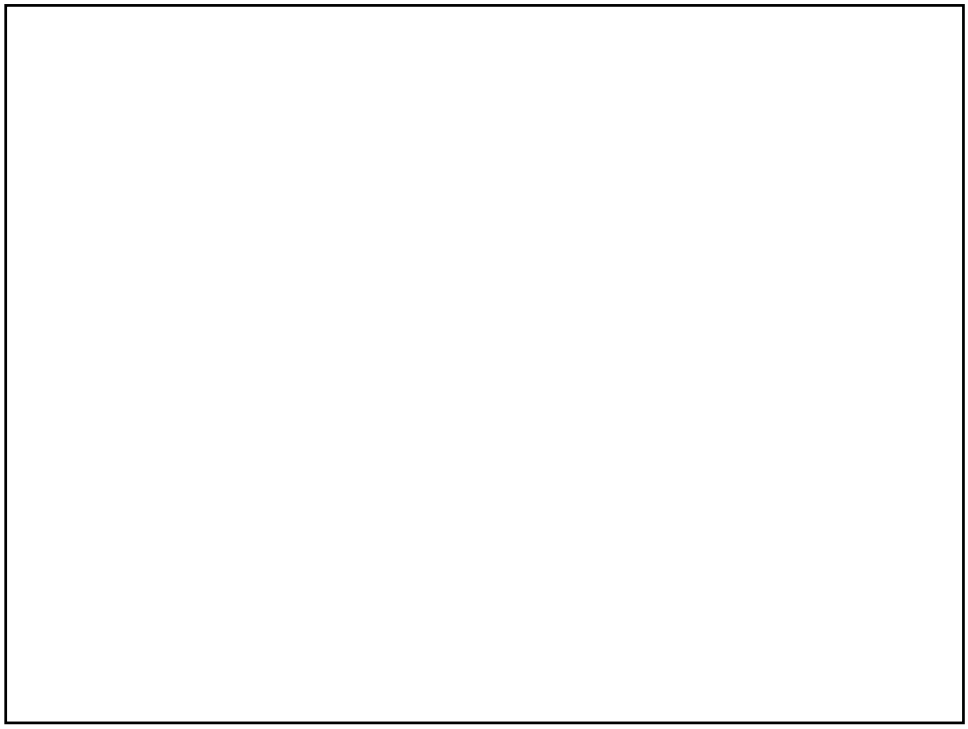
Table 1 Overview of monoclonal antibodies that have been or are being tested for the treatment of Alzheimer's disease

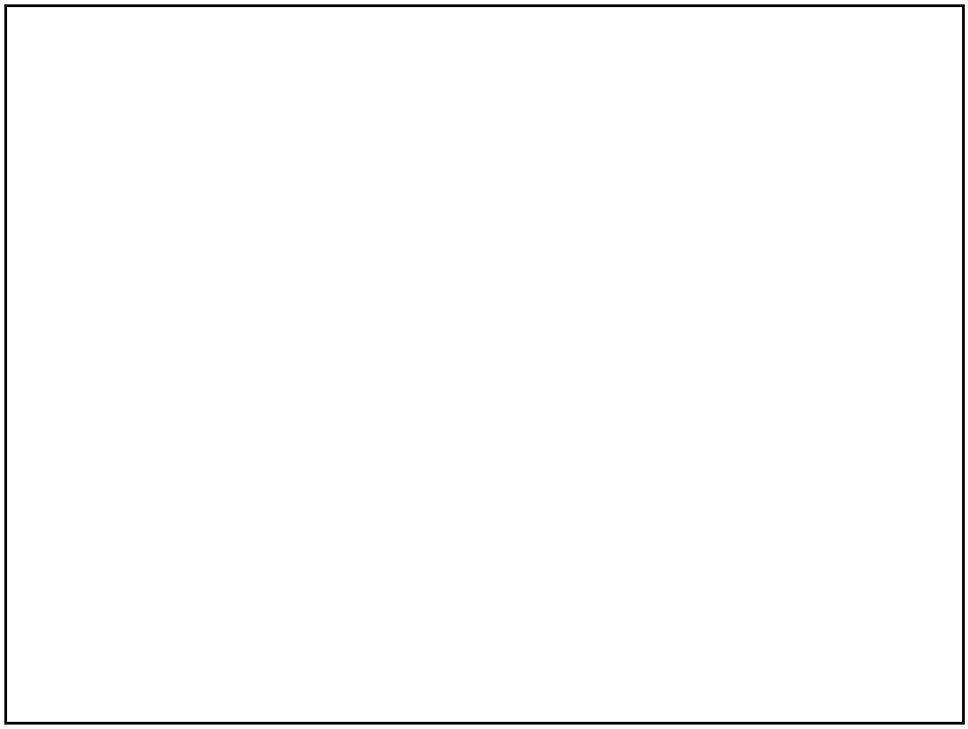
Compound	Company	Epitope	Trial results	References
Bapineuzumab, humanized 3D6	Janssen/Pfizer	Amino terminus	Phase 3 trials did not meet cognitive and functional endpoints	[22,23]
Solanezumab, humanized m266	Eli Lilly	Central (amino acids 16 to 24), accessible only on soluble amyloid-β	Phase 3 trials did not meet functional endpoint; did meet cognitive endpoint in pooled analyses in mild AD	[24,25]
Gantenerumab, full human	Hoffmann-La Roche	Amino terminus and central portions of amyloid-β	Phase 2a trial showed reduction in brain amyloid β on PET	[26,27]
Crenezumab, humanized IgG4	Genentech	Conformational epitopes, including oligomeric and protofibrillar forms	Phase 1 trial showed compound was safe and well-tolerated	[28,29]
BAN2401, humanized mAb158	Eisai Inc.	Binds large-size amyloid-β protofibrils (>100 kDa)	Phase 1 trial showed compound was safe and well-tolerated	[9,30]
GSK 933776, humanized IgG1	GlaxoSmithKline	Amino terminus	Phase 1 trial showed compound was safe and well-tolerated	[9,31]
AAB-003, Fc-engineered bapineuzumab	Janssen/Pfizer	Amino terminus	Phase 1 trial ongoing	[9,32]
SAR228810, humanized 13C3	Sanofi	Protofibrils, and low molecular weight amyloid-β	Phase 1 trial ongoing	[9,33]
BIIB037/BART, full human IgG1	Biogen Idec	Insoluble fibrillar human amyloid-β	Phase 1 trial ongoing	[9,34]

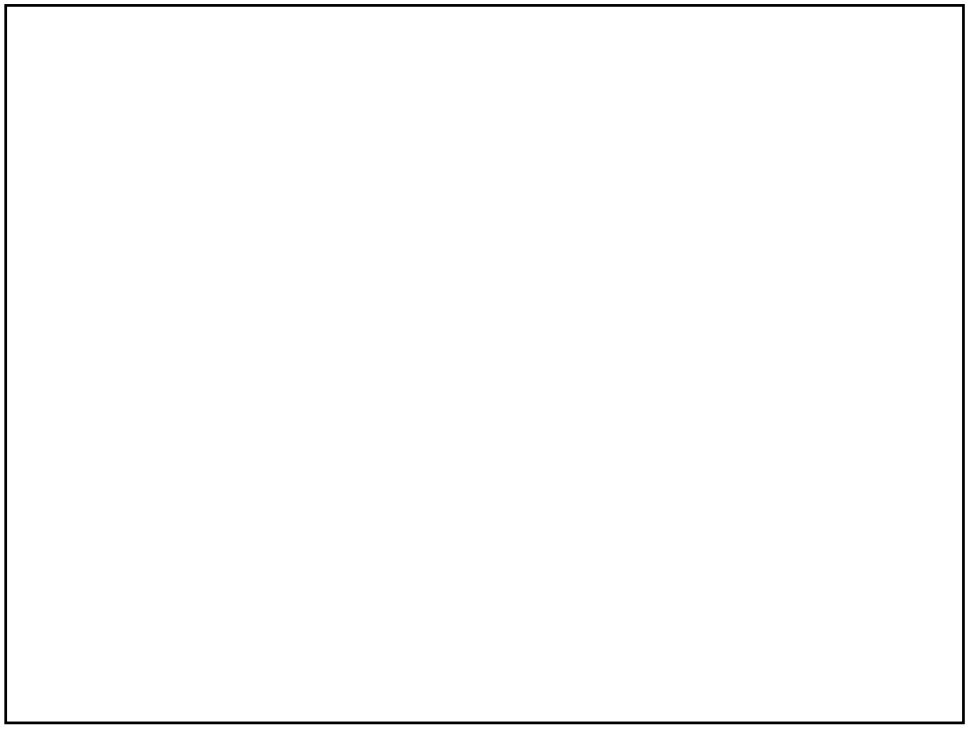
Adapted from Moreth and colleagues [9]. AD, Alzheimer's disease; Ig, immunoglobulin; mAb, monoclonal antobody; PET, positron emission tomography.

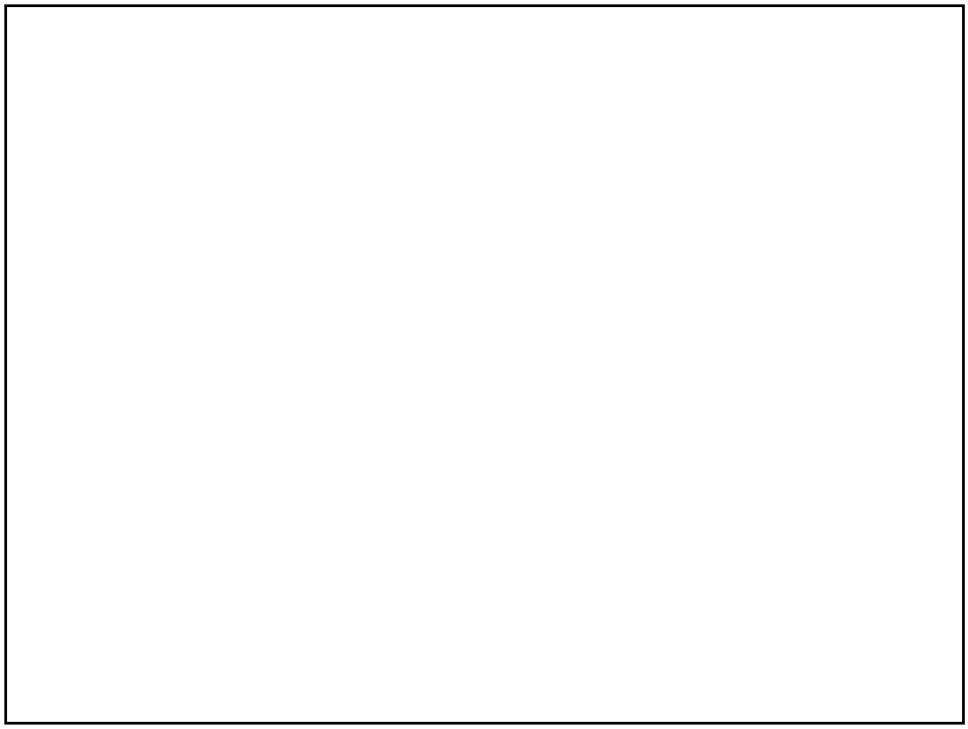

APP
β inhibitor: OM 99-2
OM 00-3
MK-8931
γ inhibitor: LY450139
Aβ
Tau
Indirect mechanism
Glucose metabolism & Mitochondria
Aggregation inhibitor: PBT2
QC inhibitor:PBD150
Immunotherapy
Active: AN 1792
Passive: Bapineuzumab
Solanezumab
Kinase/Phosphatase modulators
: Lithium
Valproate
Caffeine
AZD 1080
NP-12/Tideglusib
Aggregation inhibitor
: MTC
TRX0237
AchEI
: Donepezil, Rivastagmine
Galantamine, Tacrine
NMDA antagonist
: Mementine
nAchRc activation
: ABT-418
GABA B antagonist
: SGS-742
5-HT6 antagonist
: Lu AE58054
NSAIDs
: Ibuprofen
Natural product
: Ginkgo biloba
Insulin sensitizer
: Metformin
O-GlcNAc modification
: NButGT
Mitochondrial recovery
: Dimebon
: Piracetam
Mitochondrial transport
: HDAC6 inhibitor
AD pathology

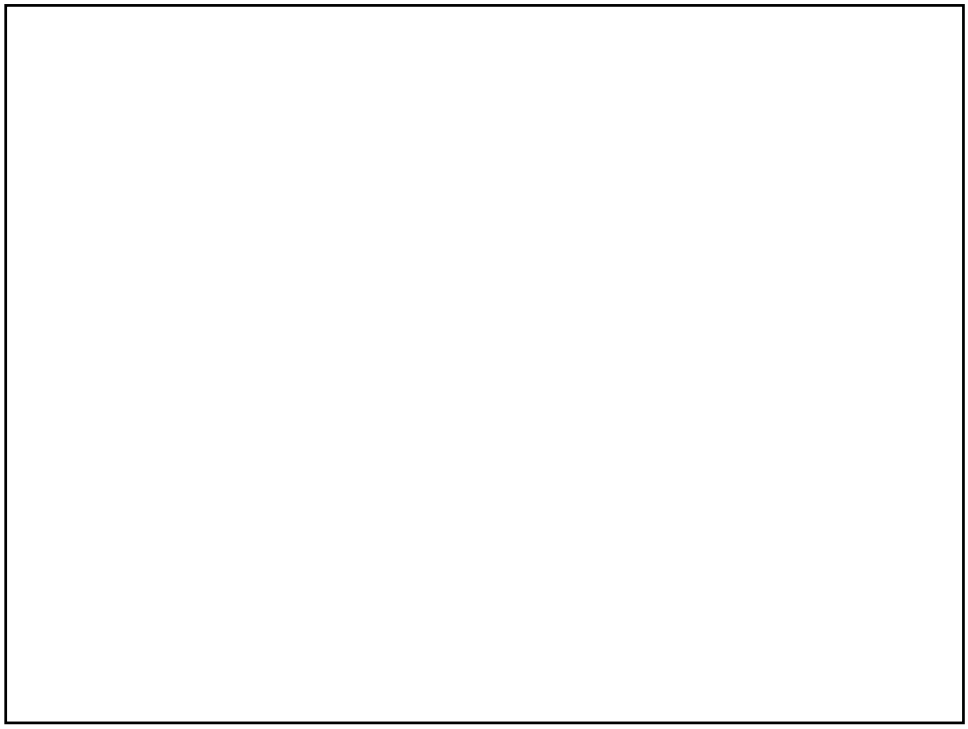

NEURON
ASTROCYTE
CAPILLARY
CLU
SORL1
ENDOTHELIAL CELLS
CD2AP
MEF2C
ADAM10
tau
Neurofibrillary tangles
ptau
Secretion
Uptake
tau
Aβ42
ptau
Uptake
PSEN2
MAPT
ABCA7
APP
BACE1
MICROGLIA
Amyloid plaques
IMMATURE OLIGODENDROCYTE
CD33
PTK2B
INPP5D
PSEN1
PLD3
TREM2
MEF2C

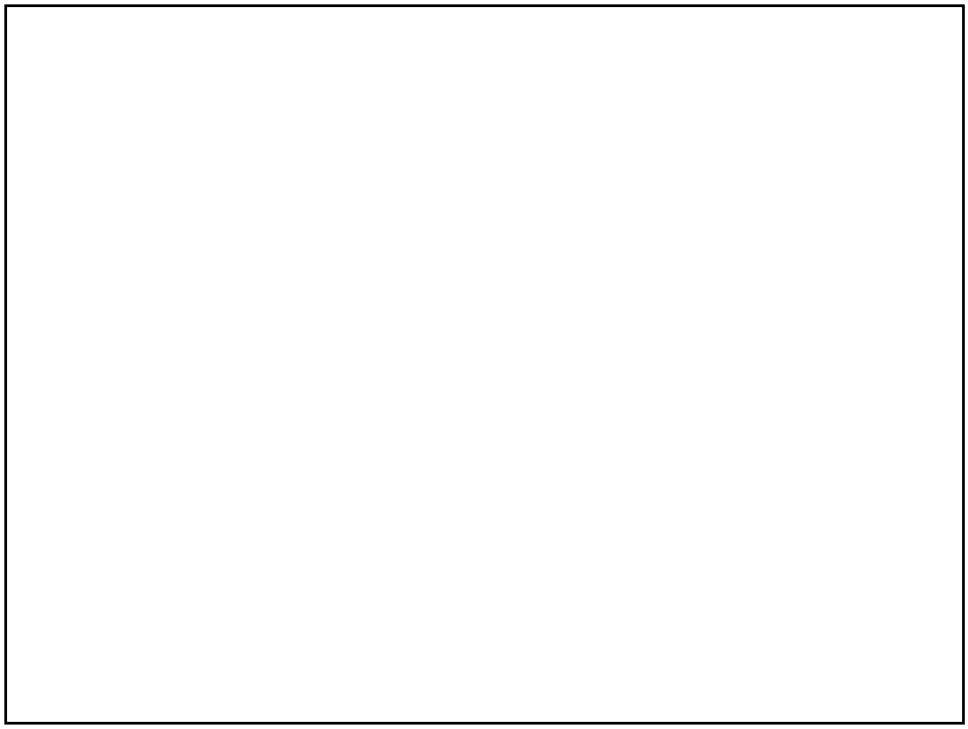


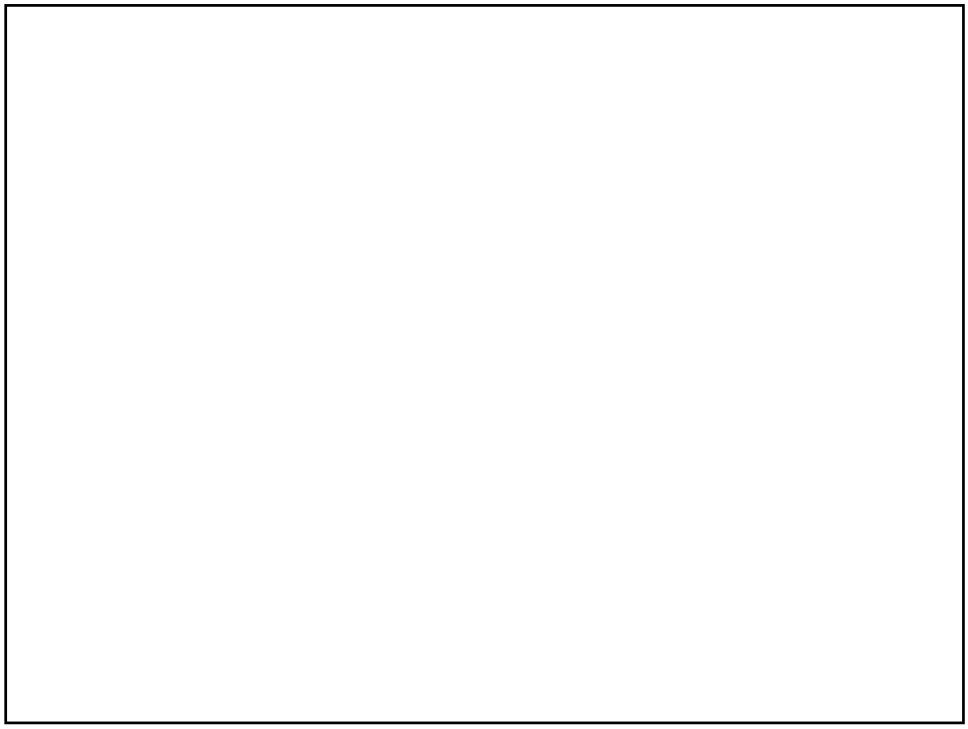


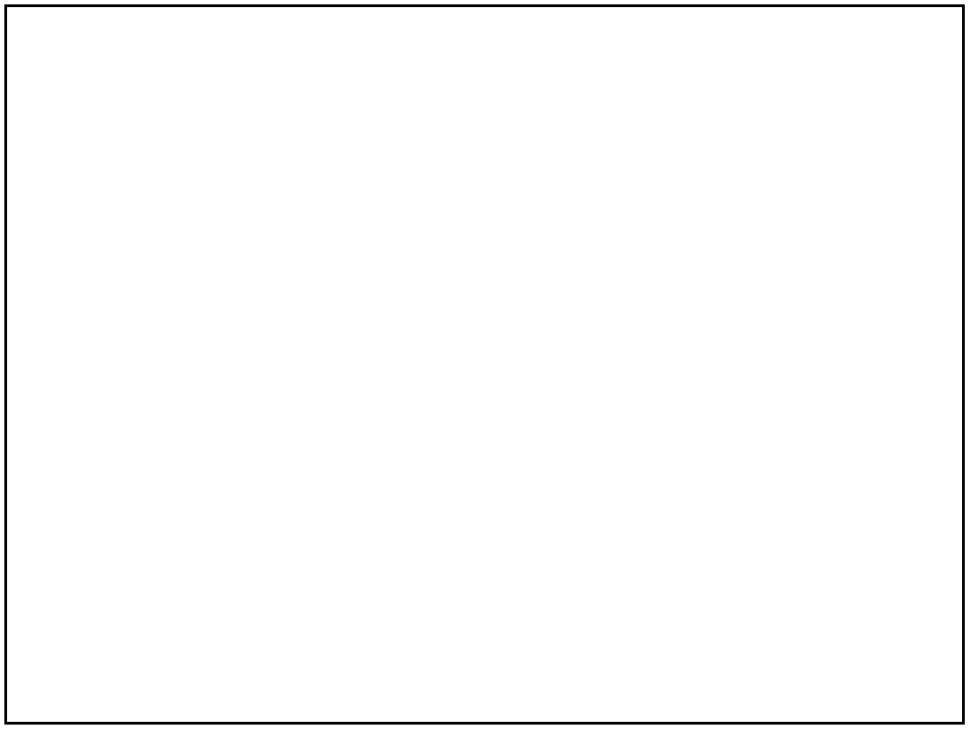













XXXVI
CONGRESSO NAZIONALE
SIFO
IL FARMACISTA PER
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Futuro
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Catania,
Centro Congressuale Fieristico
Culturale "Le Ciminiere"
22-25 OTTOBRE 2015