Aula Congressi
Ospedale S. Anna
Cona - Ferrara

26 OTTOBRE 2012

Presidente:
Prof. Giovanni Zuliani

Co-Presidente:
Dr. Amedeo Zurlo

Segreteria scientifica:
Dr. G. Guerra, Dr. F. Bonetti

CONVEGNO NAZIONALE

LE DEMENZE NELL'ANZIANO: DALLA DIAGNOSI ALLA TERAPIA

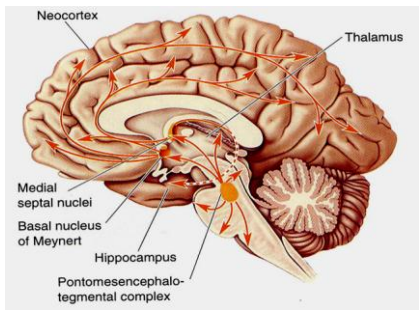# Prospettive future nella terapia della demenza di Alzheimer

Annachiara Cagnin
Dipartimento di Neuroscienze
Padova

Figure: Drug development in Alzheimer's disease

Mangialasche, Lancet Neurol 2010
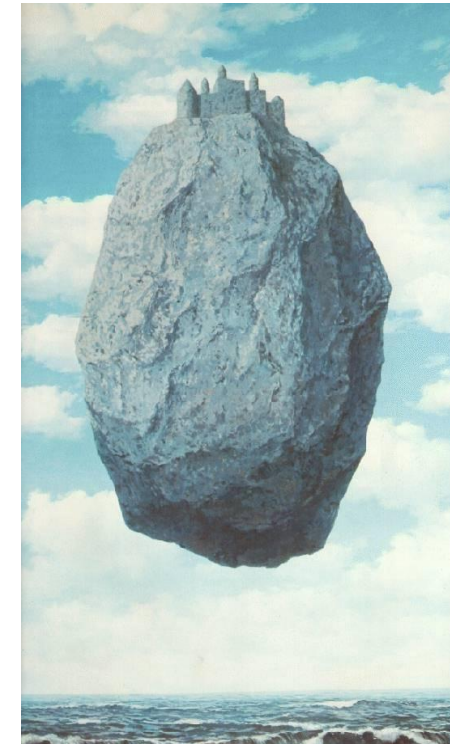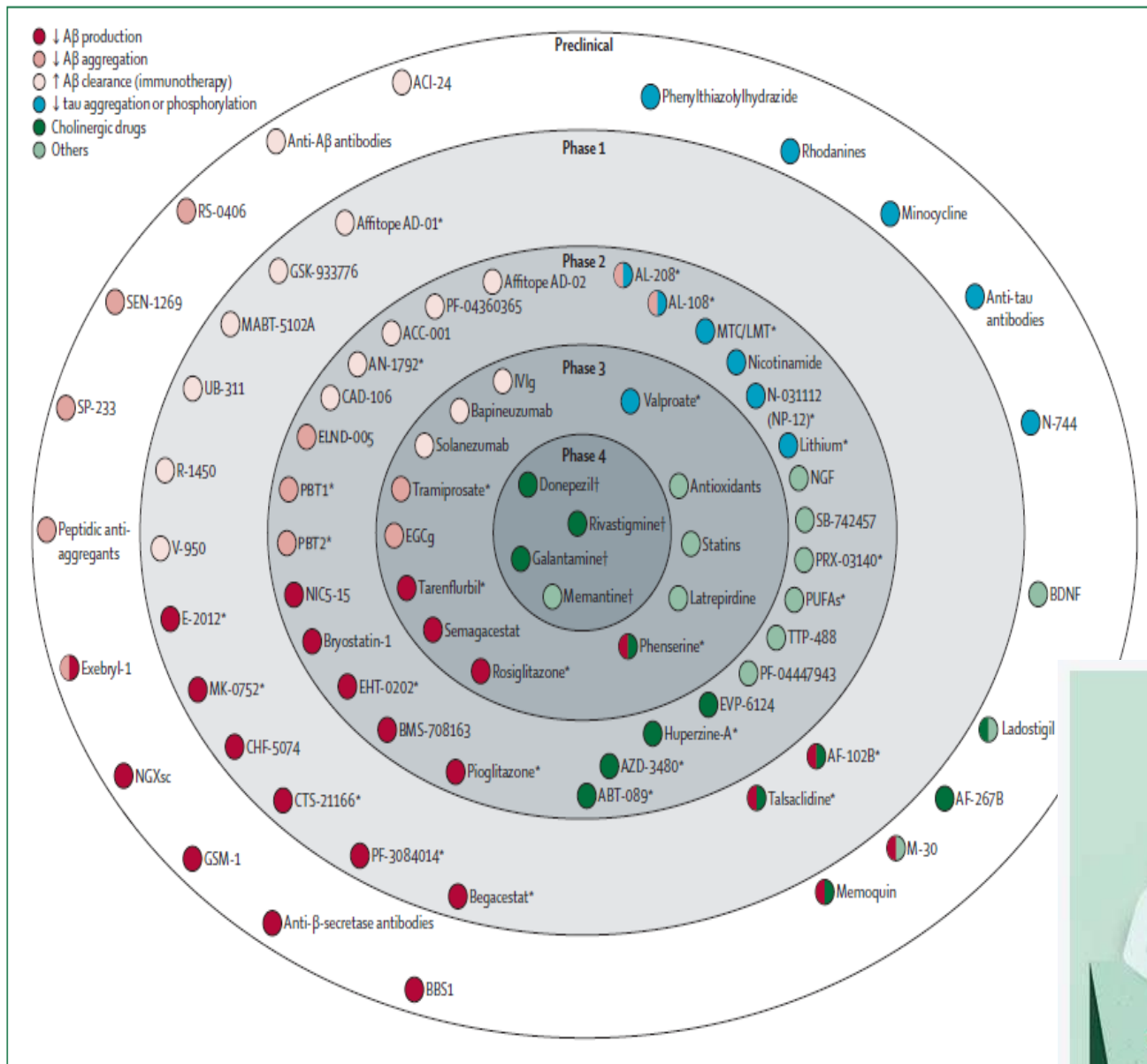
ILLUSTRATIONS BY GRACIA LAM

Targeting Aβ and tau

Aβ Vaccine
2000

Cholinergic hypothesis
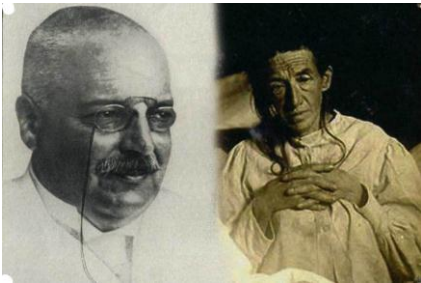1982

AchE inhibitors
1993

1906

1984
Aβ
sequence

1987
APP

1992
Amyloid-cascade
hypothesis

1986
tau

Biomarkers
Preclinical mouse models >100

BIOMARKERS NOVELTY

Clinical Symptoms
- Functional Impairment
- Cognitive Impairment

Clinical Diagnosis
- Dementia
- MCI
- Preclinical

Biomarkers
- sMRI
- FDG PET
- CSF Tau
- Amyloid PET/CSF Aβ
- fMRI neuronal network dysfunction

Pathological Changes
- Tau
- Aβ

-30   -20   -10   onset

Estimated Years from symptom onset

STAGES

DRUGS

Stage 1
Aβ Plaque Pathology

Biomarkers (one or both)
Postive Amyloid PET scan
Low CSF Aβ42

Anti-Amyloid

Stage 2
Neurodegeneration
NFT Pathology

Stage 1 Biomarker plus one of
the following:
CSF tau or p-tau
sMRI brain atrophy
FDG-PET
fMRI

Anti-tau

Stage 3
Biomakers +
Subtle Cognitive
Decline → MCI → AD

Neuroprotection

Amyloid based therapy

PRODUCTION

CLEARANCE

AGGREGATION

Aβ synthesis inhibitors

oligomerization inhibitors

degraded

Aβ 37-38
Aβ 40
Aβ 42

APP
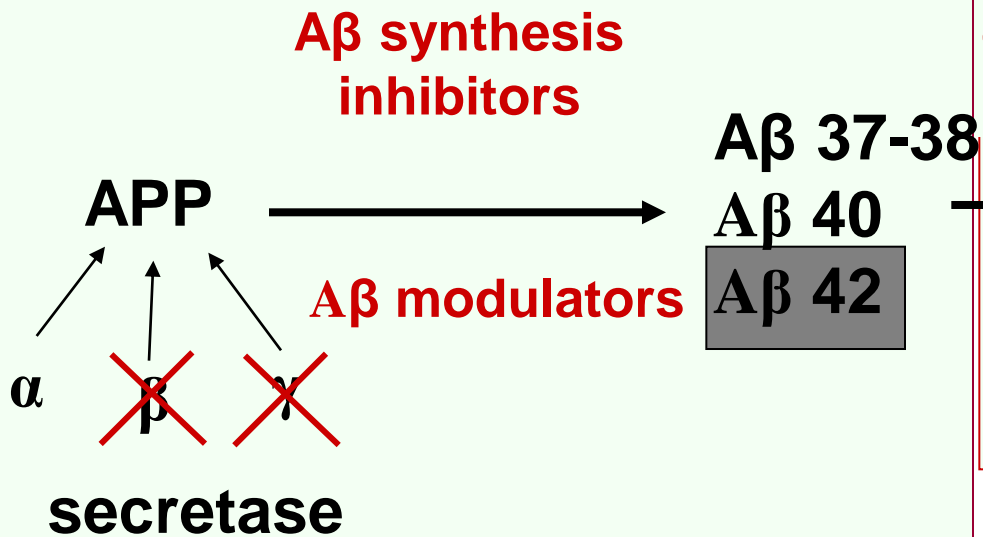
Aβ modulators

Aβ42 oligomers

Immunotherapy

α   β   γ

amyloid plaques

secretase
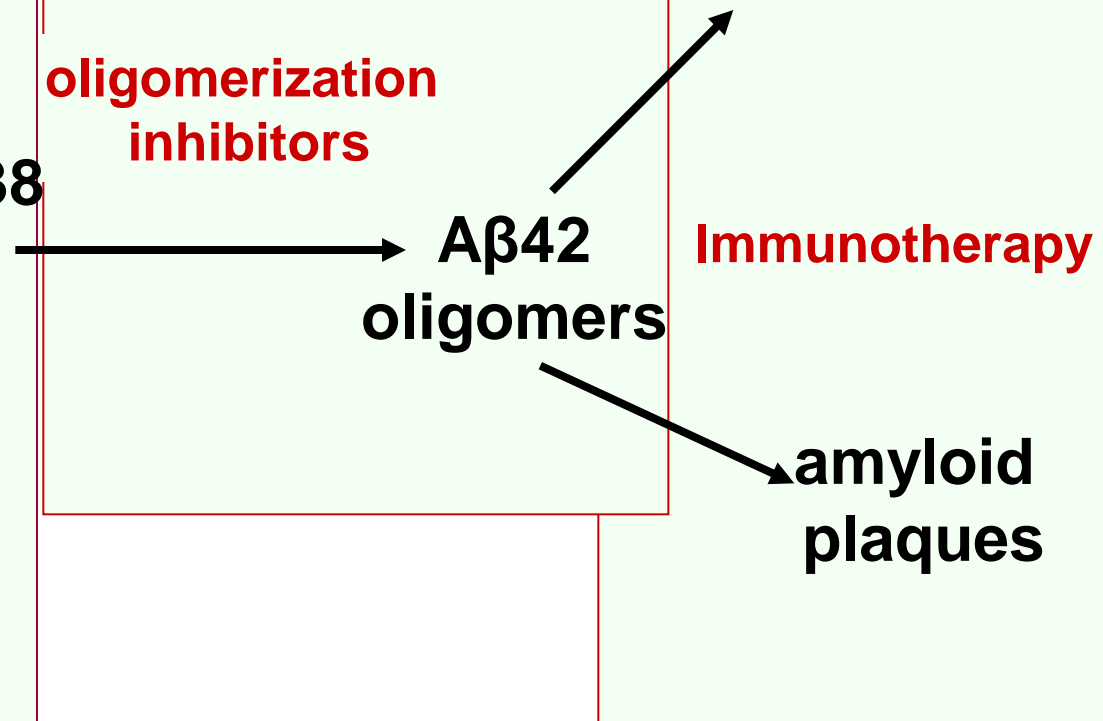
Effect of Tarenflurbil on Cognitive Decline and Activities of Daily Living in Patients With Mild Alzheimer Disease: A Randomized Controlled Trial

Robert C. Green; Lon S. Schneider; David A. Amato; et al.

SHOT ON GOAL THAT MISSED

Study: Randomized, double blind; phase III; 18 months
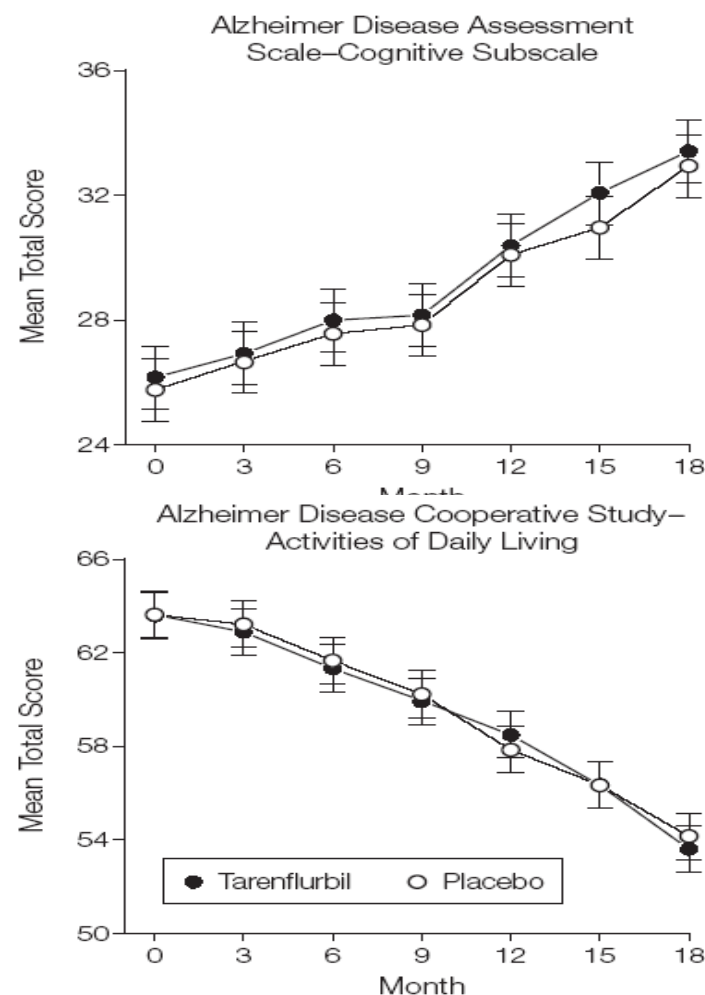
Drug: 800 mg bid R-flurbiprofen

Patients: MILD AD (MMSE 20-26)

Outcomes
I: ADAS-Cog
II: ADAS-ADL, CDR-sb, MMSE, NPI

Safety: no sides effects

Alzheimer Disease Assessment Scale–Cognitive Subscale

Alzheimer Disease Cooperative Study– Activities of Daily Living

● Tarenflurbil   ○ Placebo

Semagacestat
Identity trial

Lilly Halts Development of Semagacestat for Alzheimer's Disease Based on Preliminary Results of Phase III Clinical Trials

Decision does not affect other Lilly Alzheimer's compounds in development

Peggioramento outcome cognitivo
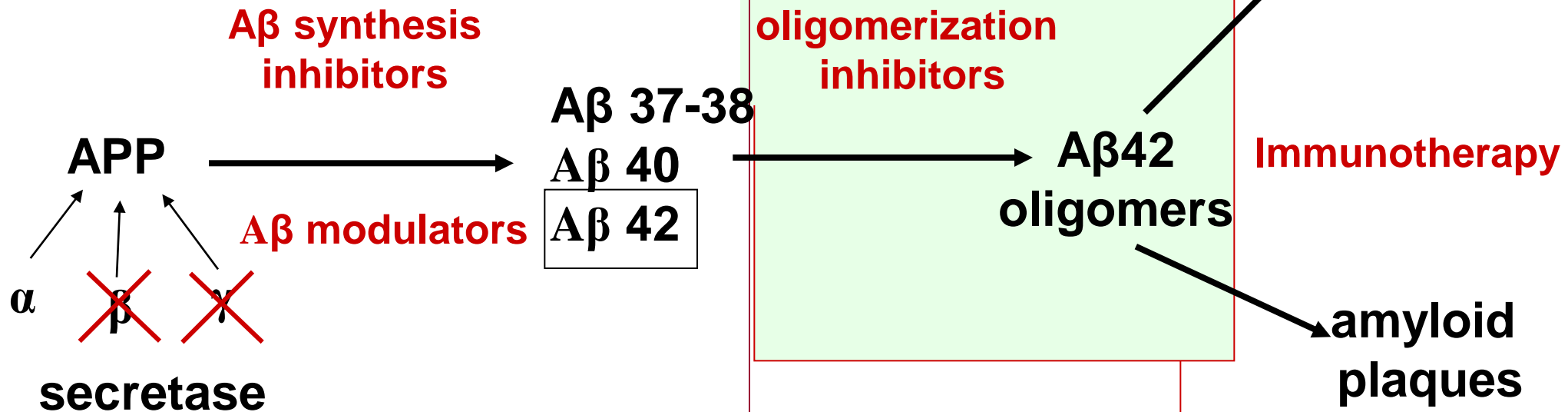
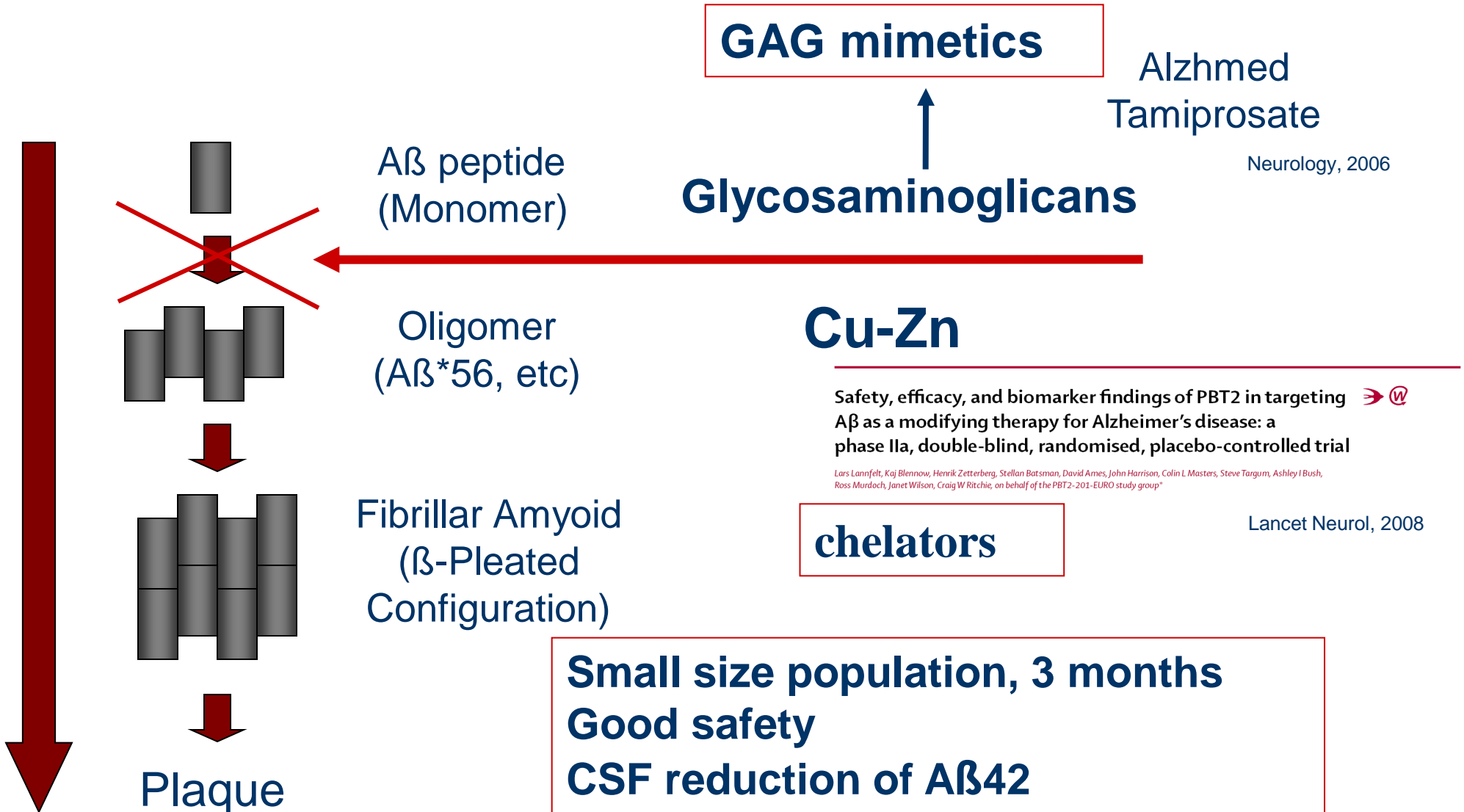**Aumento tumori cutanei**

Agosto 2010

Amyloid based therapy

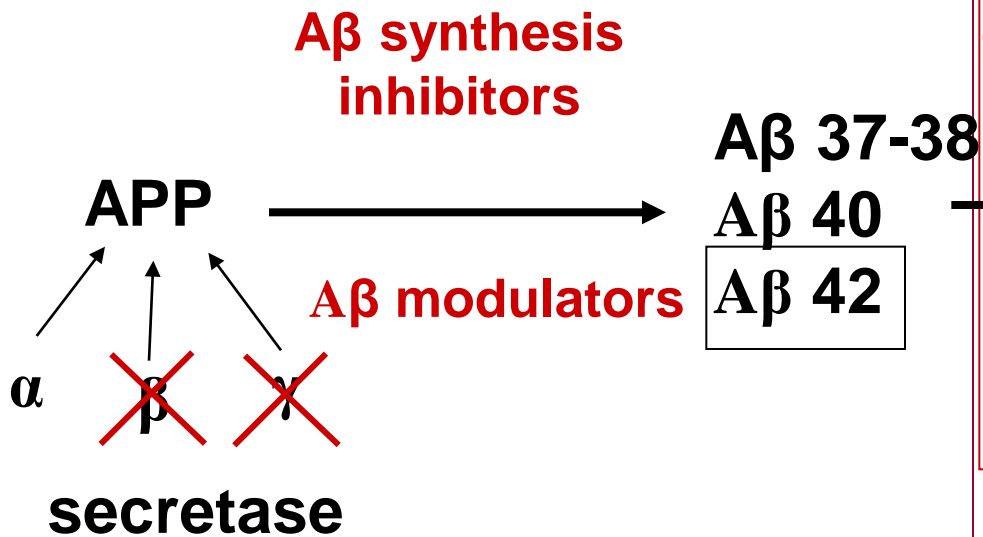**PRODUCTION**

CLEARANCE

AGGREGATION

degraded

Aβ synthesis inhibitors

oligomerization inhibitors

Aβ 37-38

Aβ 40

APP

Aβ modulators   Aβ 42

Aβ42 oligomers

Immunotherapy

α   β   γ

secretase

amyloid plaques

Aß oligomers inhibitors

GAG mimetics

Alzhmed
Tamiprosate

Aß peptide
(Monomer)

Glycosaminoglicans

Oligomer
(Aß*56, etc)

Cu-Zn

Safety, efficacy, and biomarker findings of PBT2 in targeting
Aβ as a modifying therapy for Alzheimer's disease: a
phase IIa, double-blind, randomised, placebo-controlled trial

Lars Lannfelt, Kaj Blennow, Henrik Zetterberg, Stellan Batsman, David Ames, John Harrison, Colin L Masters, Steve Targum, Ashley I Bush, Ross Murdoch, Janet Wilson, Craig W Ritchie, on behalf of the PBT2-201-EURO study group*

Fibrillar Amyoid
(ß-Pleated
Configuration)

chelators

Small size population, 3 months
Good safety
CSF reduction of Aß42

Plaque

Amyloid based therapy

PRODUCTION

CLEARANCE

AGGREGATION

Aβ synthesis inhibitors

oligomerization inhibitors

degraded

APP ⟶ Aβ 37-38
Aβ 40
Aβ 42 ⟶ Aβ42 oligomers

Aβ modulators

Immunotherapy

α β γ
secretase

amyloid plaques

Mechanisms of Aβ immunomodulation

Legend:
- Aβ monomer
- Aβ oligomer
- Antibody
- IgM
- Microglia

Blood vessel
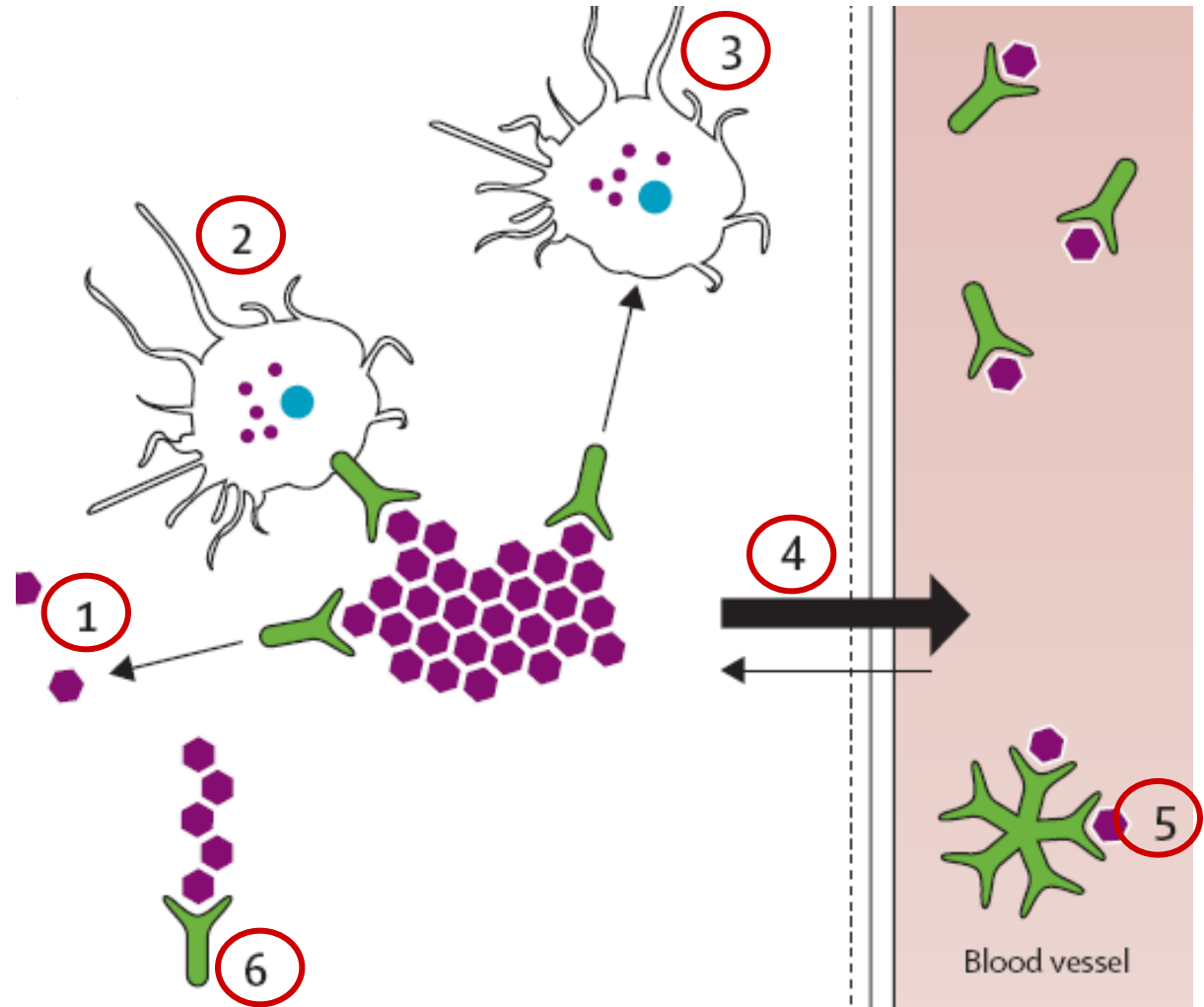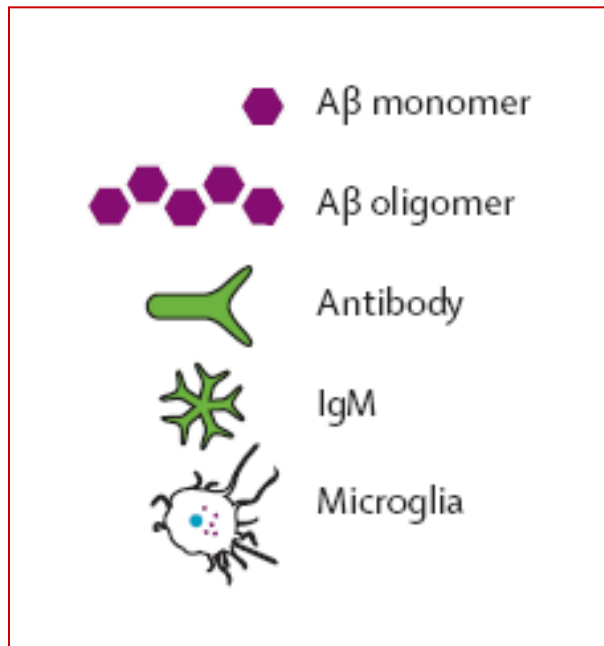
Active immunotherapy

Trial AN1792
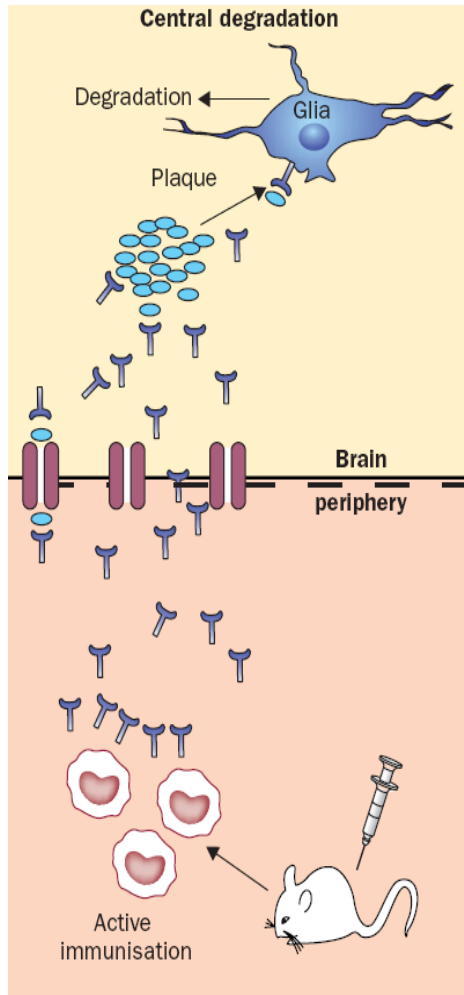
300 AD vaccinated with Aβ42 + adjuvant
19.7% good humoral immune response

1 year follow up:

CSF: reduced tau level

Neuropathology:
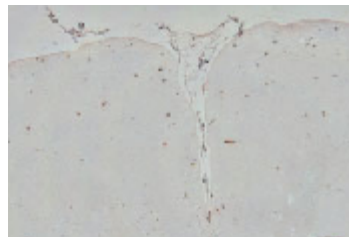
AD immunized

AD placebo

Negative clinical outcomes
Aseptic meningoencephalitis 6%

Gilman, Neurology 2005
Fox, Neurology 2005
Nicoll, Nature Med 2003

Long-term effects of Aβ$_{42}$ immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial

➢ No improved survival time or time to severe dementia (progression)

➢ Aß plaques are necessary to initiate but not maintain progressive degeneration

➢ Immunization could fail to reduce Aß oligomers

2° LINE Active immunotherapy

Safety, tolerability, and antibody response of active Aβ immunotherapy with CAD106 in patients with Alzheimer's disease: randomised, double-blind, placebo-controlled, first-in-human study

The first second line active immunization Abeta1-6 plus carrier

Passive immunotherapy
Humanized monoclonal antibodies

BAPINEUZUMAB (Johnson&Johnson/Pfizer)
N-terminal directed monoclonal antibody binding to soluble and aggregated Aβ

SOLANEZUMAB (Ely Lilly): targeting monomeric Aβ

Human Intravenous Immunoglobulins

Periphery degradation

Plaque

Degradation

Passive immunisation
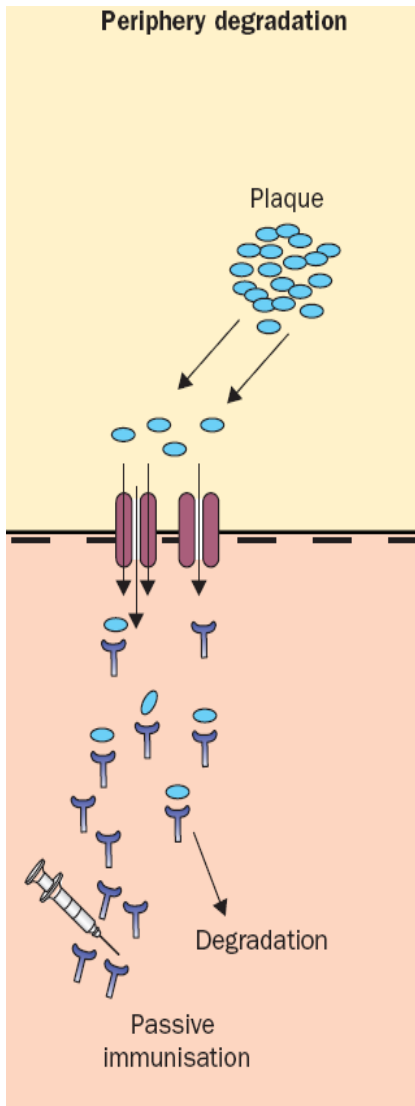
Salloway et al Neurology 2009
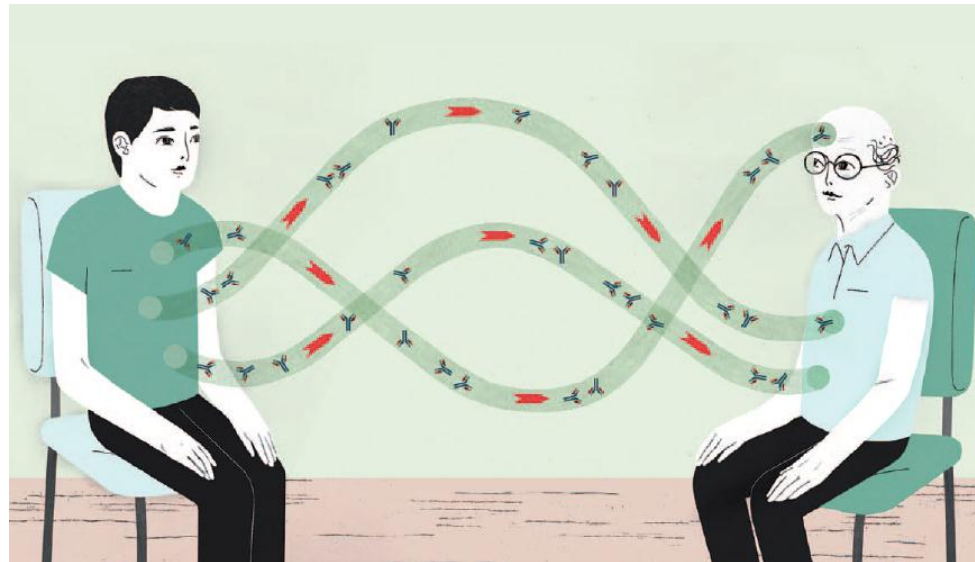
¹¹C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

Lancet Neurol 2010; 9: 363–72

11C-PIB-PET

CSF analysis
Bapineuzumab vs placebo

Δ P-tau: 0.03
Δ T-tau: 0.09
No diff. Abeta

Blennow, Archives Neurol 2012

−0.33
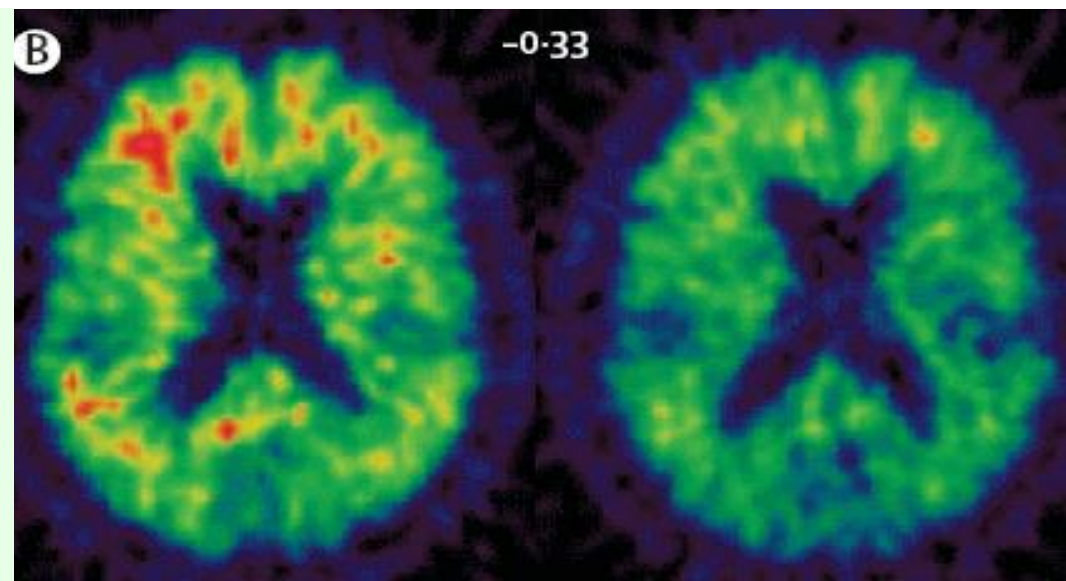
BASELINE   Week 78

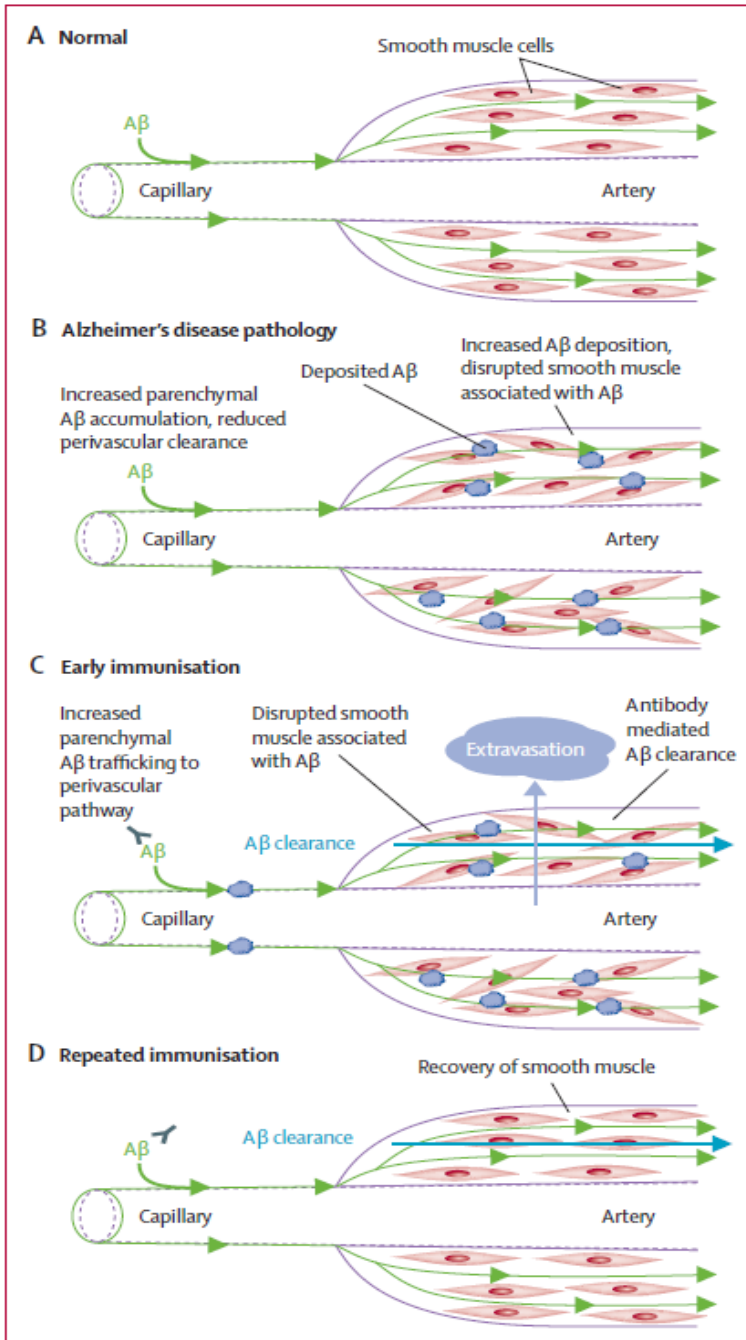BAPINEUZUMAB TREATED PATIENT

ARIA
Amyloid Related Imagin
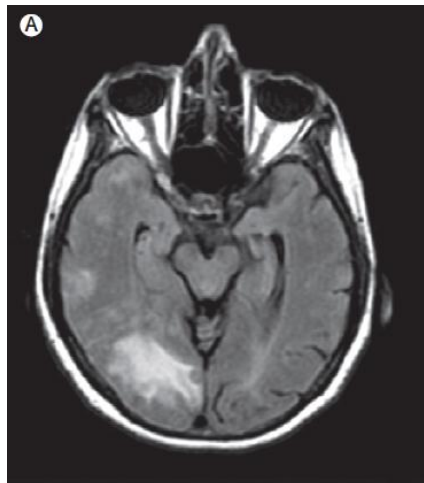
ARIA-E   **ARIA-H**

Lancet Neurol, 2012

Bapineuzumab

- Press release in August 2012

- Two phase III trials failed to show cognitive benefit

- *Too small doses (APOE4 patients)?*
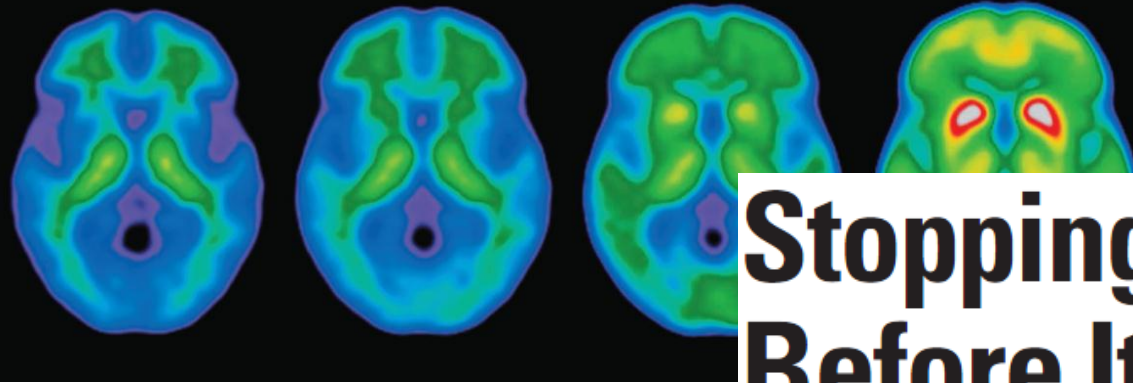
- *Too late intervention?*

Solanezumab
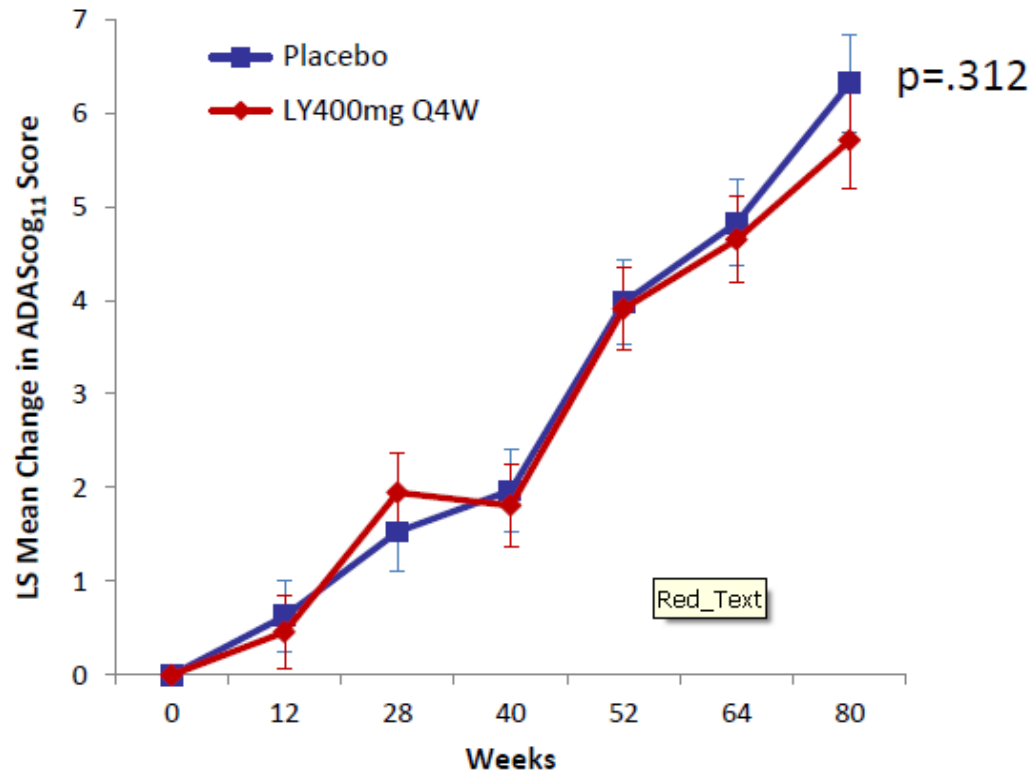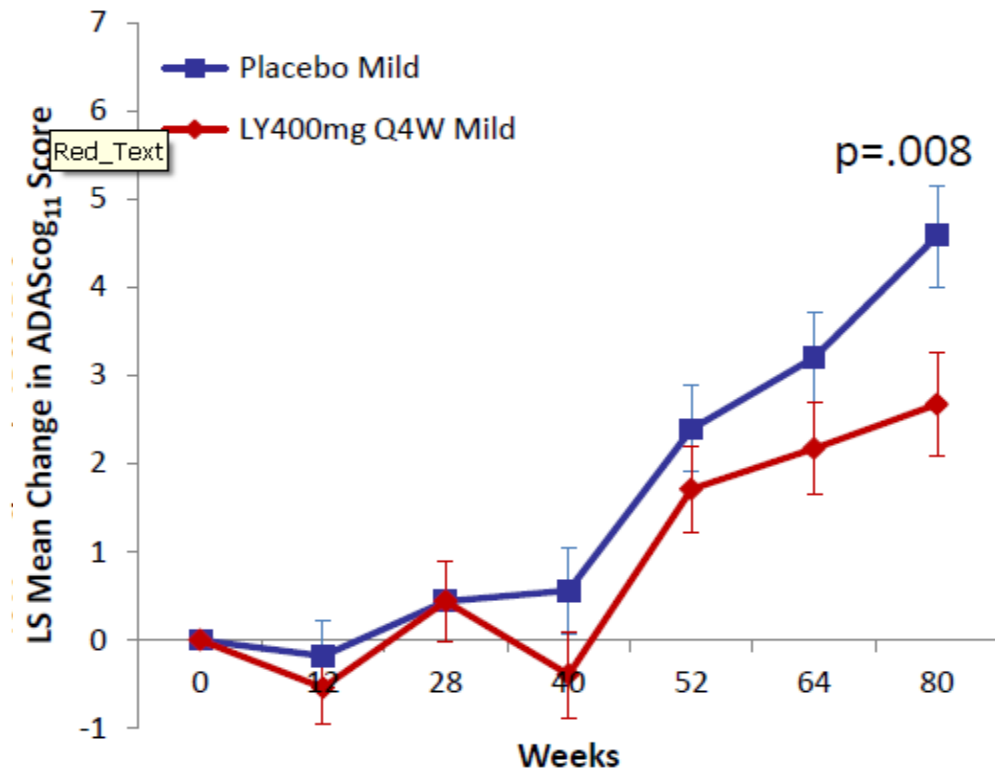
Stopping Alzheimer's Before It Starts

Alzheimer's drugs take a new tack
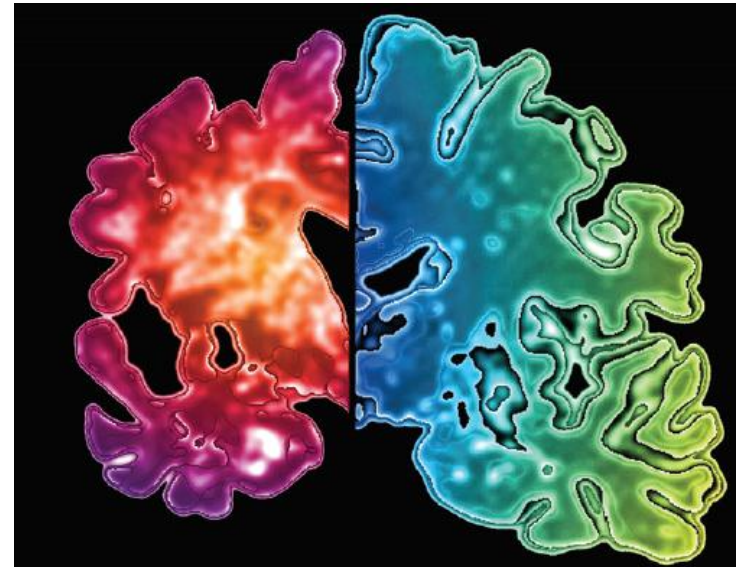
Prevention Trials

| Trial	Participants	Treatment	Outcome Measures
API: Alzheimer's Prevention Initiative	300 members of Colombian families, including 100 carriers of a mutated *PSEN1* gene	Crenezumab (Genentech)	Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy
DIAN: Dominantly Inherited Alzheimer Network	240 members of families with early-onset Alzheimer's; 60 have a mutation in one of three genes	Three anti-amyloid therapies to be determined	An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects
A4: Anti-Amyloid Treatment of Asymptomatic Alzheimer's	1500 healthy seniors, including 500 with amyloid-positive brain scans	One anti-amyloid therapy to be determined	Primary: Cognitive Secondary: Biomarkers

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease
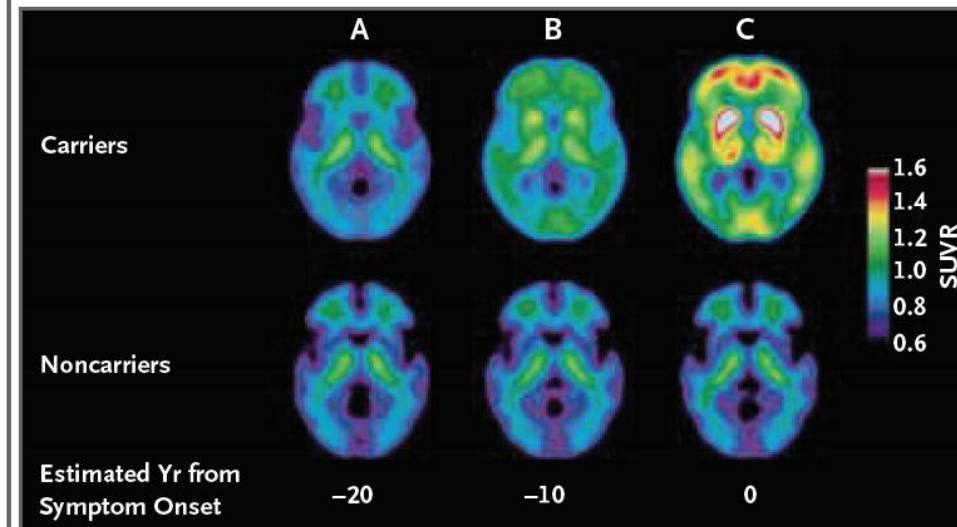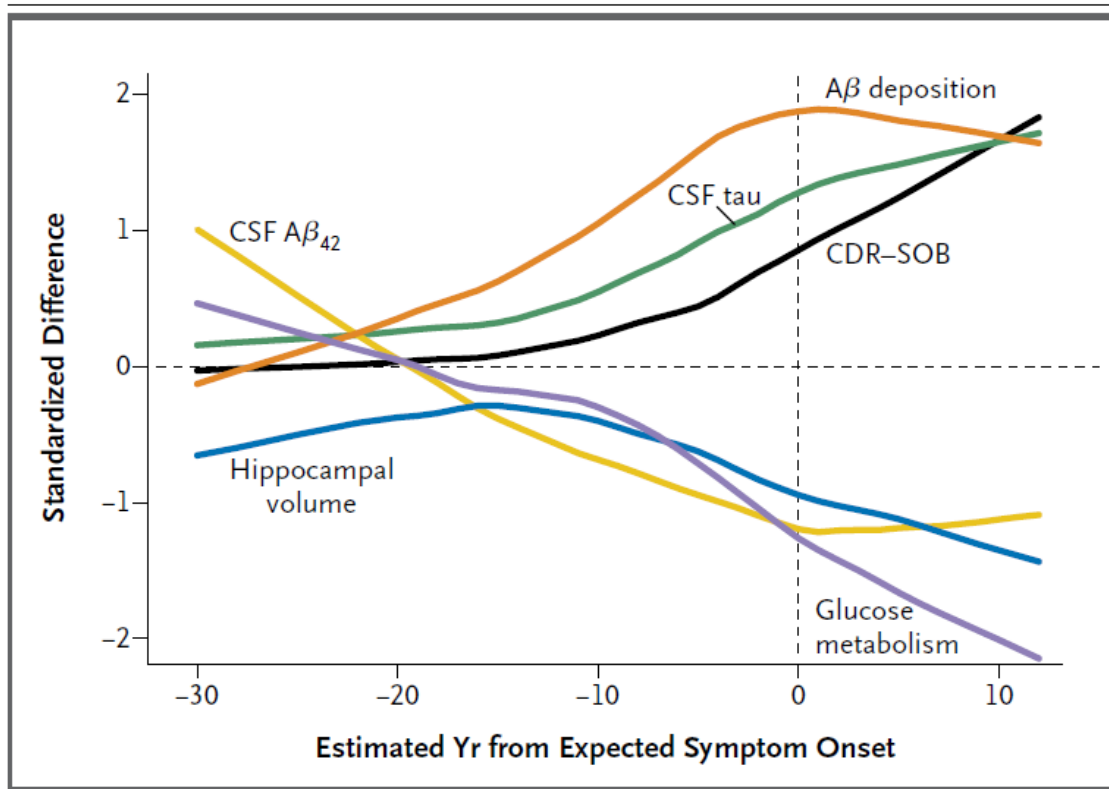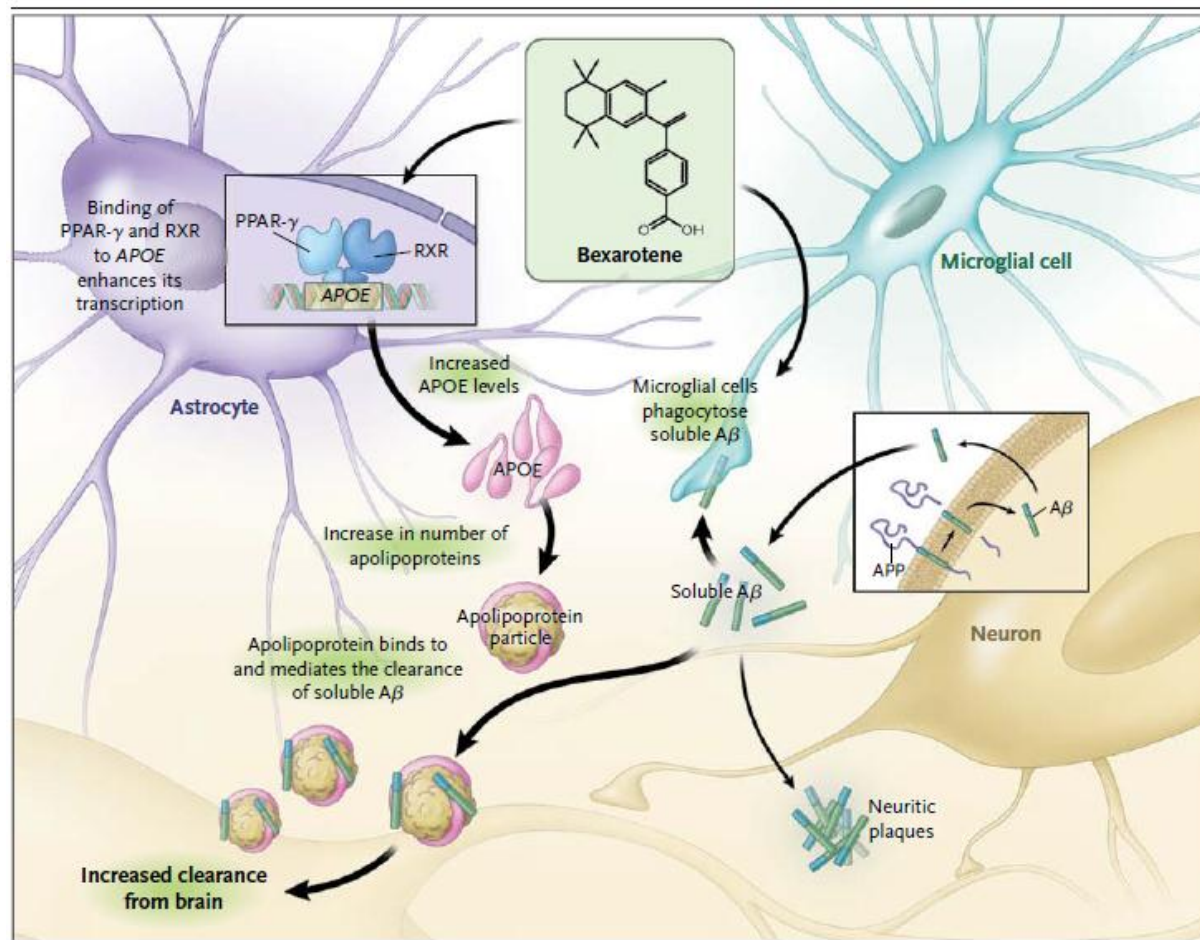

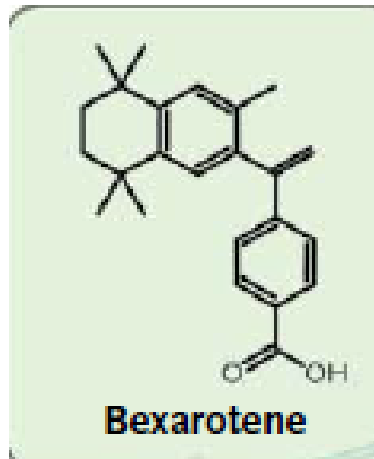Bateman et al, 2012

ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models

Bexarotene

Anti NH skin lymphoma

↓50% amyloid

72 h

Reversal cognitive & funct. deficits

APOE dependent function

Cramer et al, 2012

Aβ oligomer

TAU protein
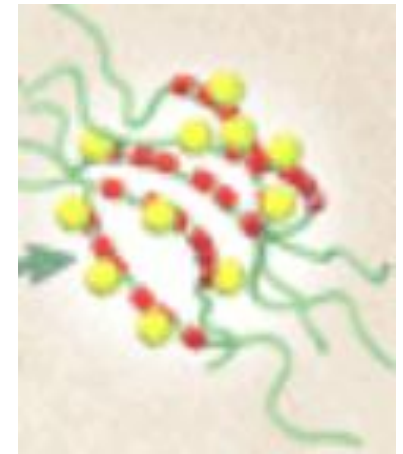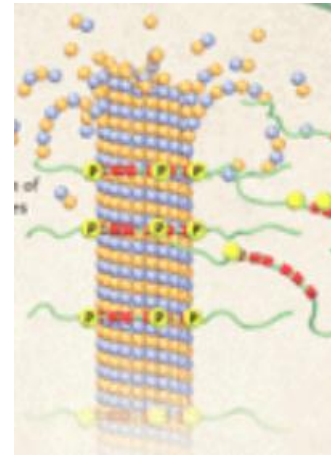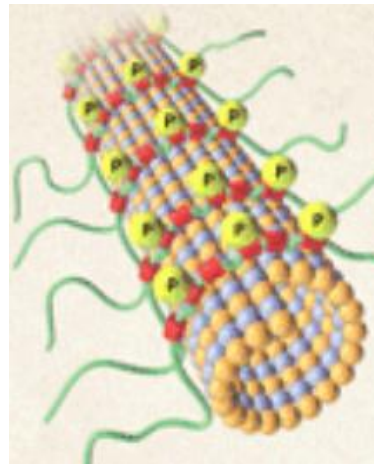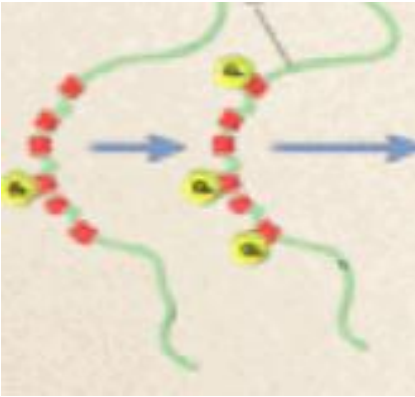
Hyperphosphorilation

Microtubule destabilization

Tangles formation

Kinase inhibitors
GSK3, Cdk5
Phosphatases

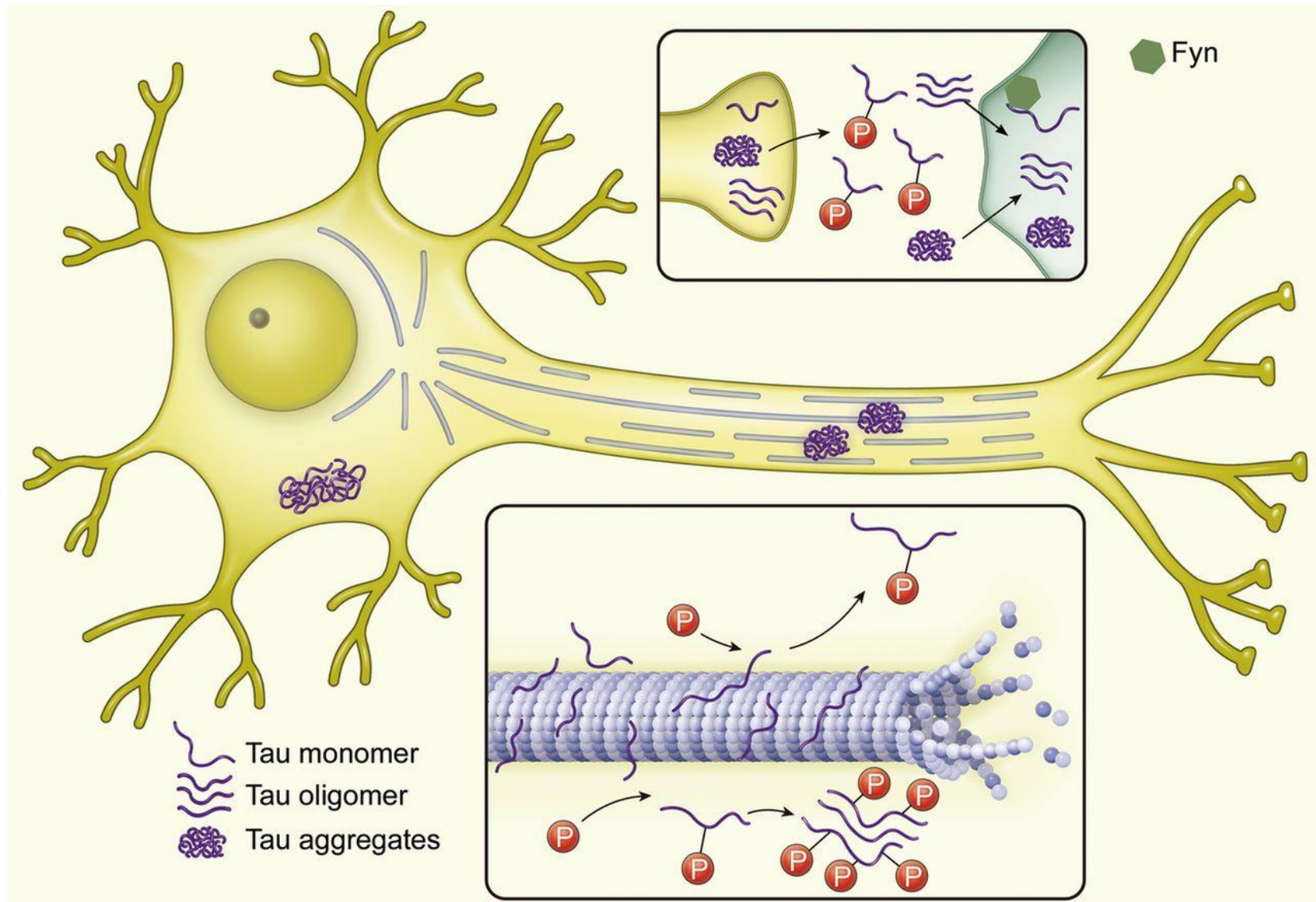**Microtubule stabilizers**

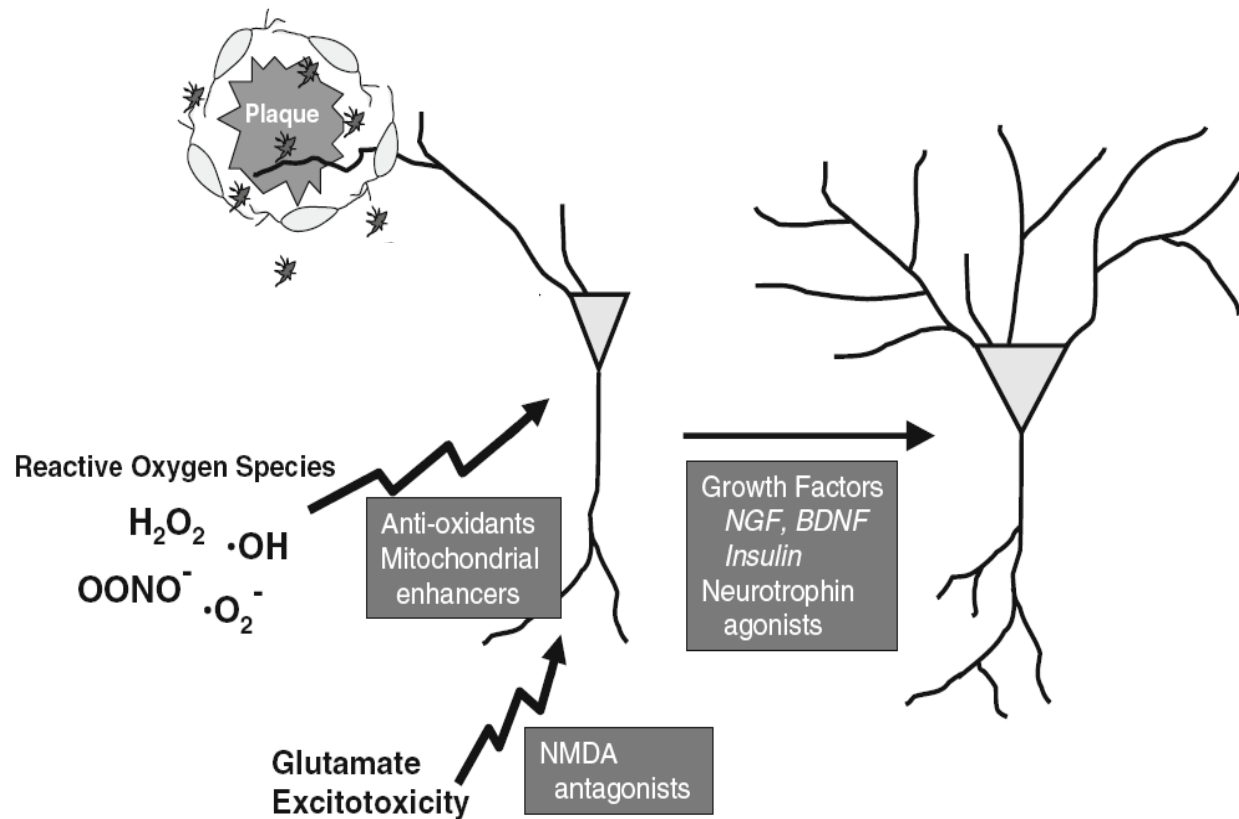**Fibril inhibitors**
Tau immunization

Methylthioninum chloride (methylene blu)

Fyn

Tau monomer

Tau oligomer

Tau aggregates

Neuroprotection

Plaque

Reactive Oxygen Species

H_2O_2 $\cdot OH$

$OONO^-$ $\cdot O_2^-$

Anti-oxidants
Mitochondrial
enhancers

Glutamate
Excitotoxicity

NMDA
antagonists

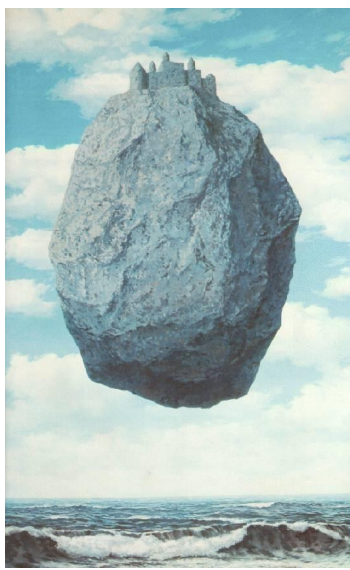Growth Factors
NGF, BDNF
Insulin
Neurotrophin
agonists

- Antioxidants
- Methylene blu (III)
- PPAr agonist
- Dimebon (III)
- Resveratrol
- Neurotrophic factors

Souvenaid
Nutricia/Danone

- Specific nutrient combination

- Improve synaptic function

- 6 mths controlled study = benefit on memory

- Extension 12 mths = maintenance effect

Scheltens et al, JAD 2012

Summary

1) *Amyloid: the right target at the wrong time ?*
   Primary prevention or early presymptomatic phase

2) The era of anti-tau treatments /multiple drugs with individualized targets is starting

3) Imaging and biomarker studies assist in confirming whether a therapy is hitting the target

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

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*

Design: randomized vs placebo
20 mg X 3 /day
6 months- (12months)

AD pts: n. 183
mild- moderate (MMSE10-24)

Endpoint: ADAS-Cog

Results: 70% stabilization or improvement
good safety and tolerability (increased depression)

Lancet, 2008