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9.01 Introduction to Neuroscience
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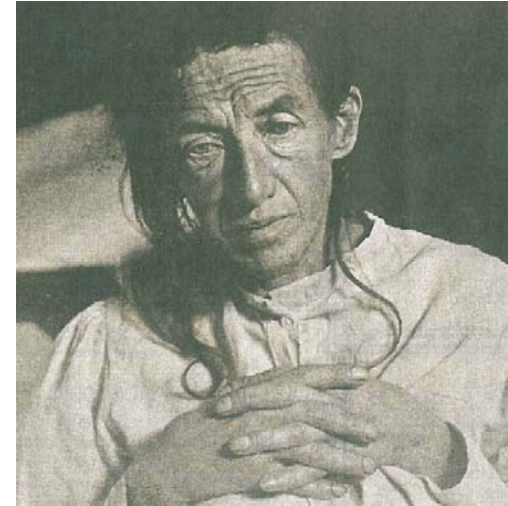
Age-dependent neurodegenerative disorder with cortical dementia - Alzheimer's disease

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100 years of Alzheimer's disease



Dr. Alois Alzheimer



Auguste Deter

“Alzheimer: What is your name?”

Auguste D: Auguste

Alzheimer: Last name?

Auguste D: Auguste

Alzheimer: What is your husband's name?

Auguste D: Auguste I think

Alzheimer: How long have you been here?

Auguste D: 3 weeks (it was her 2nd day in the hospital)”

(Translated from A Alzheimer, 1906)

Alzheimer's disease

Affect 4.5 million people in US (10% over the age of 65 and 45-50% over the age of 85); probably 20-30 million people world wide. The number is expected to triple over the next few decades.

Symptoms: loss of recent memory, forgetfulness (mild cognitive impairment, MCI), transient periods of confusion, restlessness, word finding difficulty, spatial disorientation, progressive deterioration of memory and other cognitive functions, dementia. From MCI to marked dementia may take several years.

Pathology: severely atrophied cerebral hemispheres and dilated ventricles; loss of neurons in selected brain regions; neurofibrillary tangles; amyloid plaques

Lecture Outline

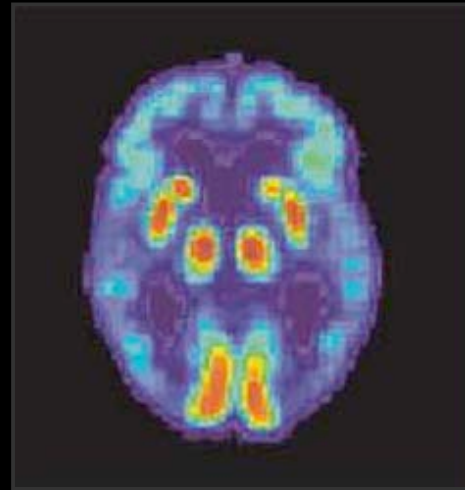
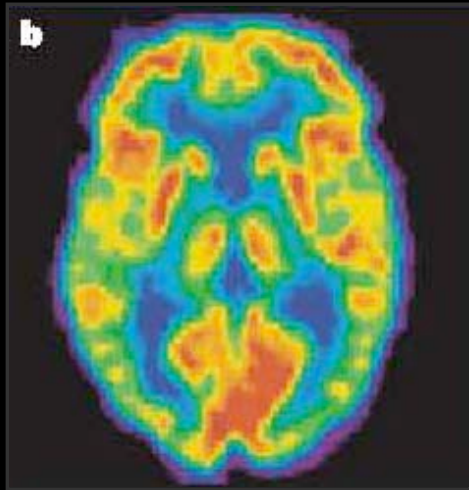
- Pathological features of AD
- Pathogenesis of AD
 - β -amyloid and learning impairment
 - The relationship of tau and AD
 - Cdk5 and AD
- Diagnosis of AD
- Therapeutic intervention of AD

Alzheimer's disease – Brain Atrophy

Autopsy Brain



MRI Scan



Normal brain

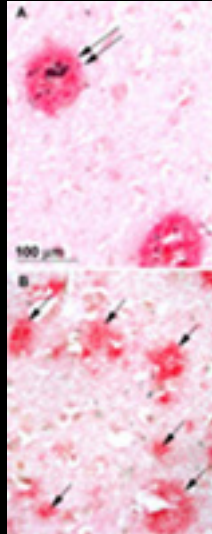
Alzheimer's brain

(Adapted from
M. Mattson, 2004)

Courtesy of Mark P. Mattson. Used with permission.

Amyloid plaques and neurofibrillary tangles (NFT)

Amyloid plaques



APP

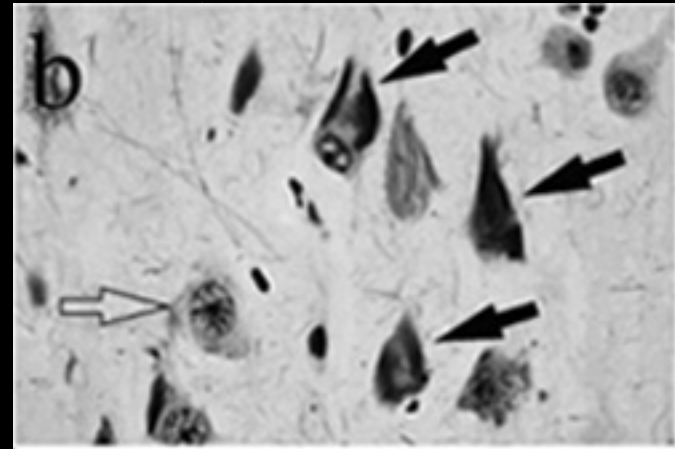


A β



Plaques

Neurofibrillary tangles (NFT)



Tau



P-Tau



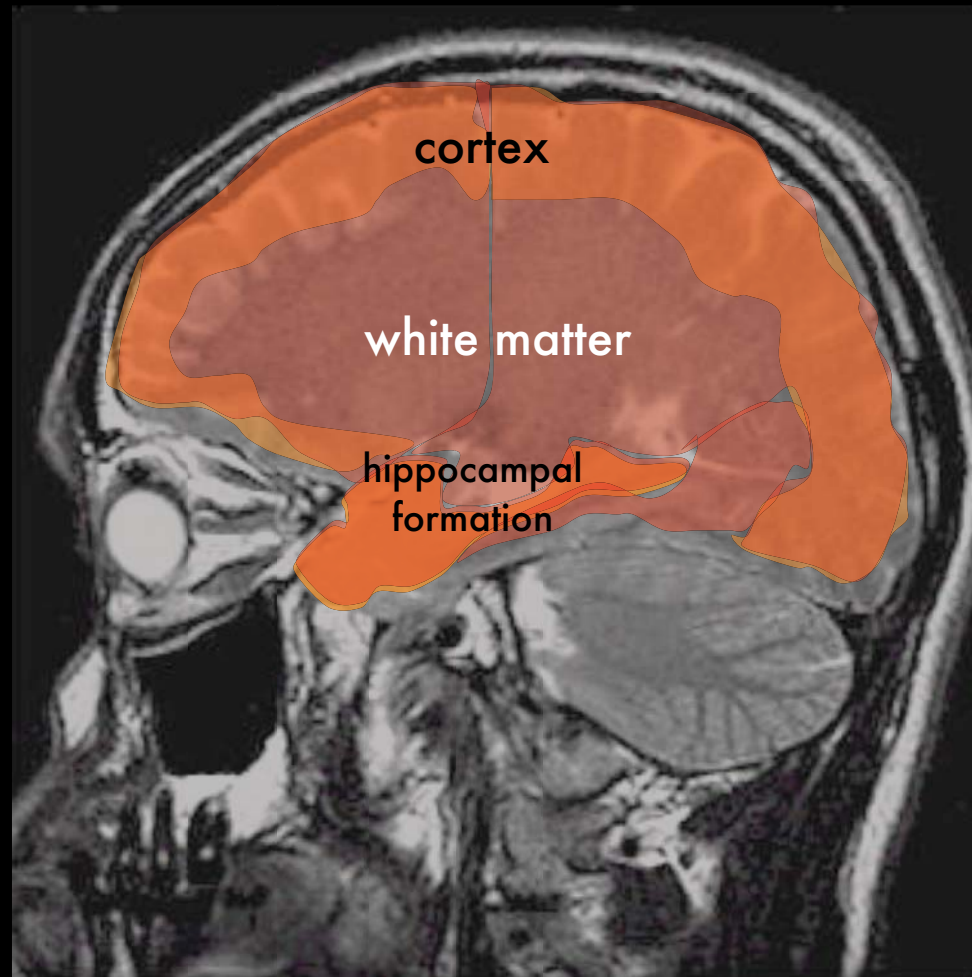
Tangles

Images courtesy of Elsevier,
Inc., <http://www.sciencedirect.com>. Used with permission
Left: Price, J. L., et al. *Neurobiology of Aging* 30
, no. 7 (July 2009): 1026-1036.
Right: Gorrie, C. A. *Accident Analysis & Prevention*
39, no. 6 (2007): 1114-1120.

Brain areas initially affected by AD pathology

NFT pathology

Brain atrophy

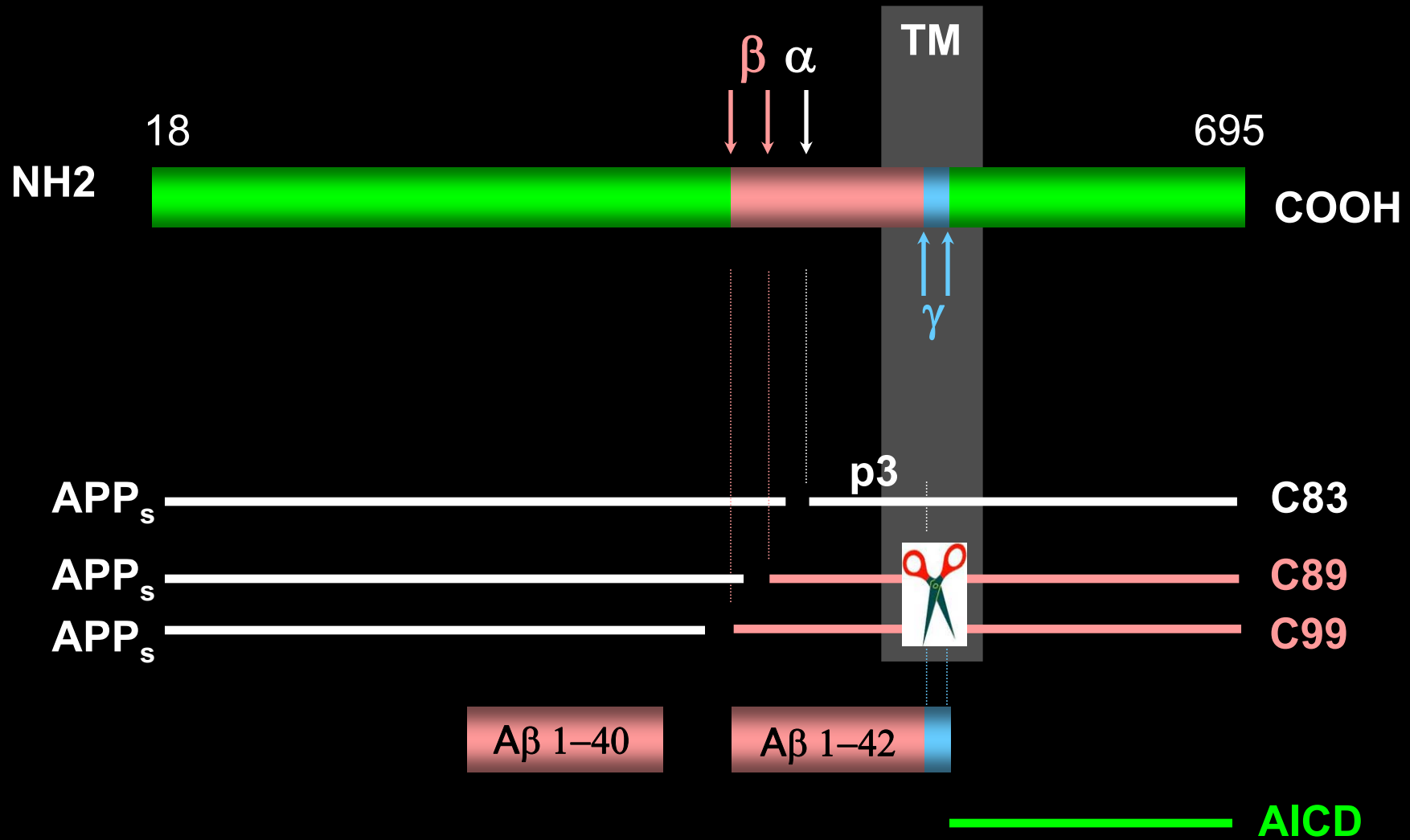


Mutations in APP, PS1 and PS2 cause familial Alzheimer's disease (FAD)

Image removed due to copyright restrictions. See Figure 1 in Probst, L. et al. " β Secretase (BACE1) Activity Assay Kit: A FRET Based Assay Designed for BACE1 Inhibitor Screening." <http://www.sigmaaldrich.com/life-science/cell-biology/learning-center/bace1-assay-kit.html>.

(Sigmaaldrich.com) :

β amyloid precursor protein (APP)



Genetics of familial Alzheimer's disease

Missense mutations in APP

- found in about 2 dozens of families
- mutations are usually around α -, β - or γ -secretase sites. These mutations lead to alterations of APP processing and increased $A\beta$ production.
- trisomy 21 in Down's syndrome leads to the premature occurrence of AD neuropathology during middle adult years and overproduction of $A\beta_{40}$ and $A\beta_{42}$.

Missense mutations in the presenilins: the most common cause of autosomal dominant familial AD

- chrom14, PS1, missense mutations usually lead to early onset AD (40s-50s)
>75 different mutations found
- chrom1, PS2, early onset, 3 different mutations identified
- PS mutations cause increase in $A\beta_{42}/A\beta_{40}$ ratio

Risk factors for Alzheimer's disease

The ApoE4 allele is a major genetic risk factor for late-onset AD

- chrom19
- one E4 allele increases the likelihood of developing AD by 2-5 fold
- two E4 alleles increase the likelihood of developing AD by >5 fold
- however, there are also individuals with both E4 alleles without developing AD
- mechanism unknown, likely enhances the deposition or decreases the clearance of Ab peptides.

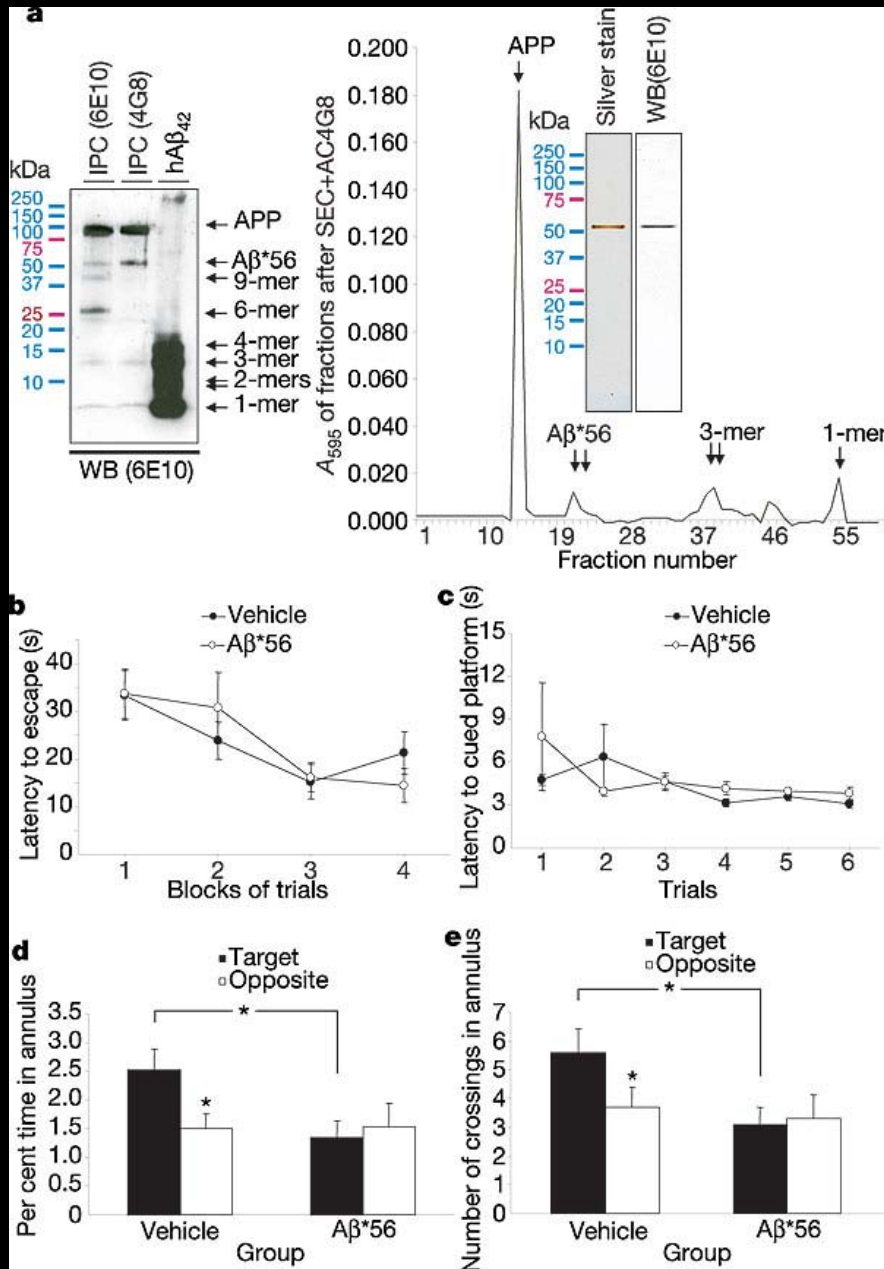
Other genetic alternations predisposing to AD

- chrom12, risk factor for late onset, alteration in or near a2-macroglobulin
- chrom10q, late onset
- others, likely to be more

Learning impairment in APP_{FAD} mouse models

- **PDAPP (London mutation) mice exhibit age-related deficits in learning a series of spatial locations (Chen et al, 2000)**
- **Tg2576 (Swedish mutation) mice exhibit age-related impairment in spatial reference memory (Westerman et al, 2002; Lesne et al, 2006)**
- **AbetaE22G (Arctic mutation) mice display deficits in water maze tasks (Cheng et al, 2007)**
- **In many of the APP_{FAD} models, learning impairment is detected prior to the manifestation of plaque pathology (Lesne et al., 2006)**

The amyloid species that impairs learning



- In middle-aged Tg2576 (Swedish mutation) mice extracellular accumulation of a 56 kDa soluble Abeta assembly (A β *56) correlates with memory deficits (Lesne et al, 2006)

- Introduction of purified A β *56 into young rats impairs spatial memory (Lesne et al, 2006)

Courtesy of Karen H. Ashe. Used with permission.

A β in synaptic function

- Secreted oligomers of A β potently inhibit hippocampal LTP in anesthetized rats (Walsh et al, 2002)
- Neuronal activity can modulate formation and secretion of A β and A β can decrease AMPA and NMDA-dependent currents (Kamenetz et al, 2003)
- Oligomers of A β can induce reversible synapse loss by modulating an NMDAR signaling pathway (Shankar et al., 2007)
- APP_{FAD} mice have spontaneous nonconvulsive seizure activity in cortical and hippocampal networks, increased GABAergic sprouting, enhanced synaptic inhibition, and synaptic plasticity deficits in the dentate gyrus (Palop et al, 2007)

Neurofibrillary tangles (NFT)

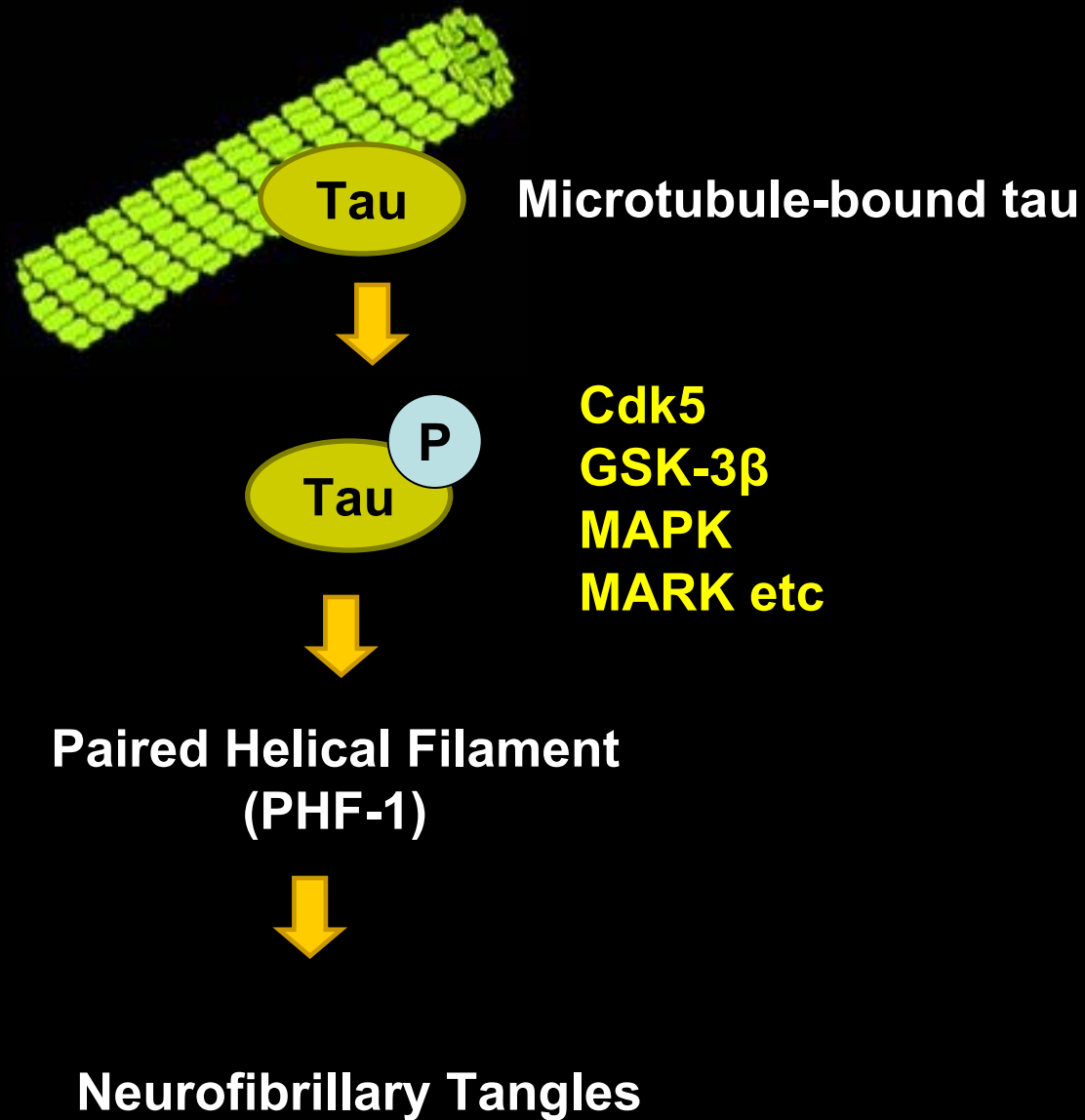
Non-membrane bound masses of fibers known as paired helical filaments (PHF) in the cell bodies of select neurons

PHF is made primarily, if not solely of the microtubule associated protein tau, in the hyperphosphorylated state

In general, the neurofibrillary pathology and neuronal loss associate closely in affected brain regions

Neurofibrillary pathology is also present in other neurodegenerative disorders including Down's syndrome, fronto-temporal dementia, Parkinson's disease, and progressive supranuclear palsy.

Alzheimer's Disease and Tau



Tau Phosphorylation and Tau Kinases

Image removed due to copyright restrictions.

Figure 4 (table) in Morishima-Kawashima et al. "Proline-directed and Non-proline-directed Phosphorylation of PHF-tau." *J.Biol.Chem.* 270, no. 2 (1995): 823.

Adopted and Modified from Morishima-Kawashima et al *J.Biol.Chem.*270:823.

How phosphorylation leads to dysfunction of tau?

- **Phosphorylation on tau results in loss of binding affinity of tau to microtubules (PNAS 83, 4913).**
- **Phosphorylation can affect tau conformation (Synapse 27, 208) which eventually leads to aggregation of tau.**
- **Phosphorylation of Thr231 affects the activity of Pin1, which changes tau structures and precludes phosphatases from dephosphorylating tau (Nature 399, 784).**
- **Phosphorylation on tau may facilitate the aggregation of tau although there is evidence that phosphorylation is not necessary for aggregation in vitro (Biochemistry 38, 3549).**

Frontal temporal dementia Parkinsonism-chrom17 (FTDP-17) tau

Six different mutations found in FTDP-17 families including 3 missense mutations: G272V, P301L and R406W

Three other mutations are found in the 5' splice site of exon 10. The splice site mutations destabilize a potential stem-loop structure which is probably involved in regulating the alternative splicing of exon 10. This causes more frequent usage of the 5' splice site, increase in exon 10+ mRNA and increase in proportion of tau containing 4 microtubule binding repeats.

Diagram removed due to copyright restrictions.

Tau P301L Tg mice

- Human P301L tau containing 4 MT binding repeats is expressed under the mouse prion promoter
- After 6 1/2 months, transgenic animals develop motor and behavioral deficits and die after 12 months
- Age-dependent development of NFT in the diencephalon, brainstem, cerebellar nuclei and spinal cord which is associated with neuronal loss
- Pre-tangle tau in the cortex, hippocampus and basal ganglia
- The pathology is reminiscent of progressive supranuclear palsy (PSP)

**Dyes that
cause spectral
shift upon
binding to
 β -sheet
structure**

Silver stains

Image removed due to copyright restrictions.

Figure 2 in Lewis, J. et al. "Neurofibrillary Tangles, Amyotrophy and Progressive Motor Disturbance in Mice Expressing Mutant (P301L) Tau Protein." *Nature Genetics* 25 (2000): 402-405. doi:10.1038/78078.

**Phospho-tau
antibody
staining**

Congo Red: *a-c*

Gallyas Ag: *e*

AT8: *i*

Bielschowsky Ag: *f*

AT180: *j*

Thioflavin-S: *d*

Bodian Ag: *g* Ubiquitin: *h*

CP13: *k*

Neurodegeneration and reversible memory loss in an inducible mutant Tau transgenic mouse

Images removed due to copyright restrictions.

SantaCruz, K., et al. *Science* 309, no. 5733 (2005): 476-481.

doi:10.1126/science.1113694. Fig. 1E: Photo showing gross forebrain atrophy, with preservation of hindbrain structures, in a tau transgenic mouse compared with a nontransgenic littermate. Fig 3D: Graph of longitudinal memory test results.

Tau and neurodegeneration

Loss of function hypothesis:

Loss of physiological tau function, e.g. in microtubule stabilization

Gain of function hypothesis:

Tau aggregations are neurotoxic and can hamper cellular functions such as axonal transport

Link between A β and tau: A β induces tau pathology

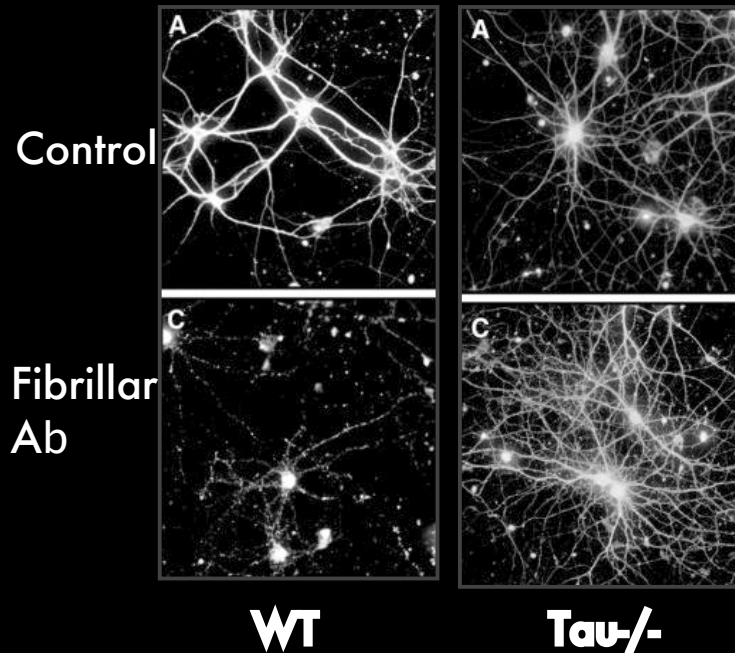
- Gotz et al (2003): Injection of A β fibrils in P301L mice results in increased neurofibrillary tangles
- Lewis et al (2003): Crossing of Tg2576 APP mice with P301L mice results in increased neurofibrillary tangles, especially in the hippocampus and cortex

Images removed due to copyright restrictions.

Fig 2C and D in Lewis, J. et al. "Enhanced Neurofibrillary Degeneration in Transgenic Mice Expressing Mutant Tau and APP." *Science* 293, no. 5534 (2001): 1487 - 1491. doi: 10.1126/science.1058189.

Link between A β and tau: Reduction of tau is beneficial against A β -induced pathology

**Tau is essential for β -amyloid
Induced neurotoxicity
(Rapoport et al., PNAS 2002)**

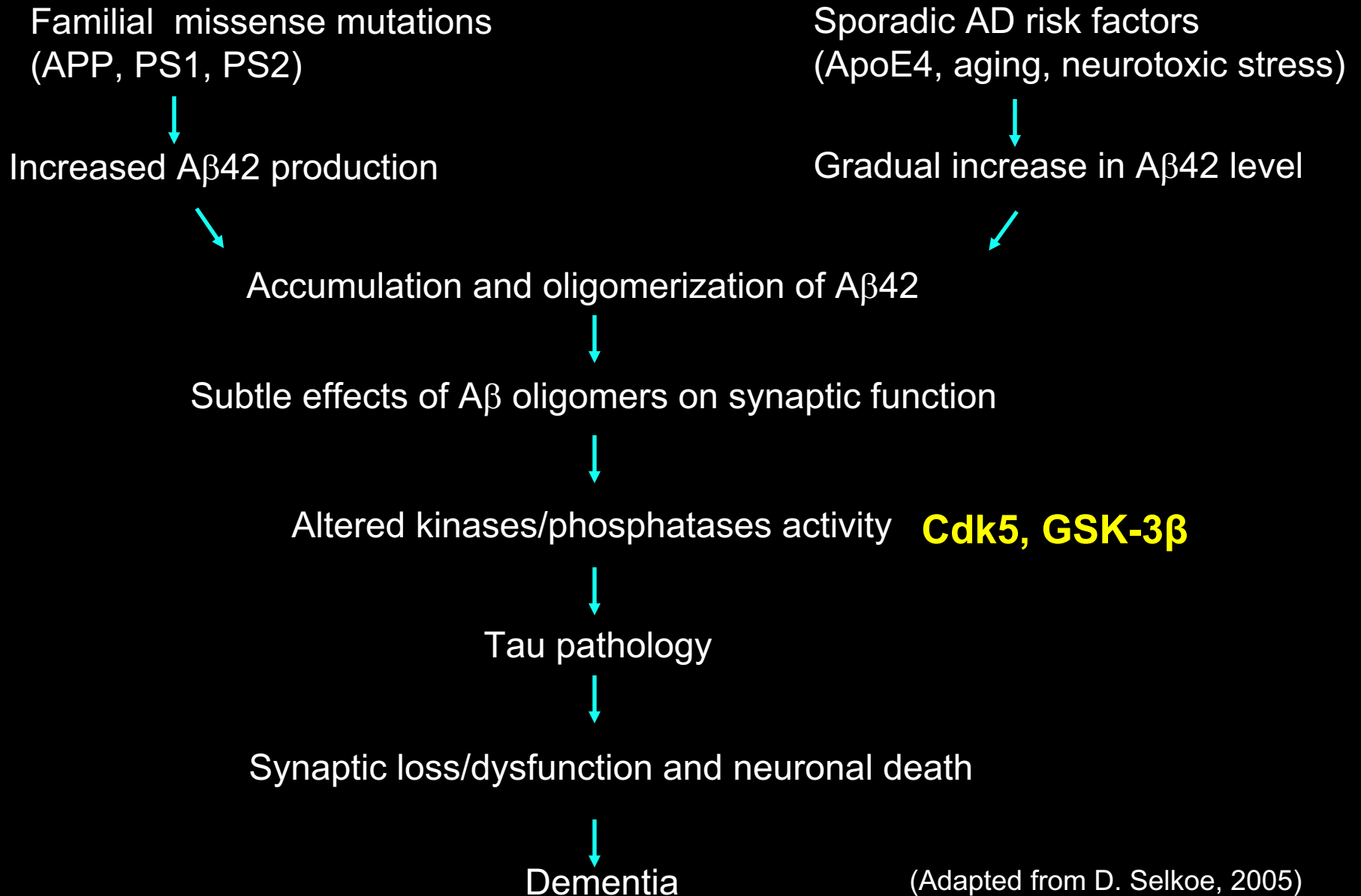


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Figures 1C and 2E in Roberson, E. D., et al. "Reducing Endogenous Tau Ameliorates Amyloid β -Induced Deficits in an Alzheimer's Disease Mouse Model." *Science* 316. no. 5825 (2007): 750-754. doi:10.1126/science.1141736.

Courtesy of National Academy of Sciences, U. S. A.
Used with permission. Source: Rapoport, M. et al. "Tau is Essential to β -Amyloid-Induced Neurotoxicity." *PNAS* 99, no. 9 (2002): 6364-6369. Copyright © 2002 National Academy of Sciences, U.S.A.

The Amyloid Hypothesis



(Adapted from D. Selkoe, 2005)

Molecular Diagnosis of AD in patients

- **Extensive neuropathological damage occurs prior to clinical diagnosis**
- **The AD hallmarks plaques and tangles cannot be detected in vivo**
- **No reliable biomarker available for plaques and tangles**
- **Early detection methods for AD will aid AD treatment and AD research**
- **MRI and PET scan are possible alternatives**

Molecular Diagnosis of AD in patients

**Functional MRI of explicit recognition memory
(Novel scene > Repeat scene contrast)**

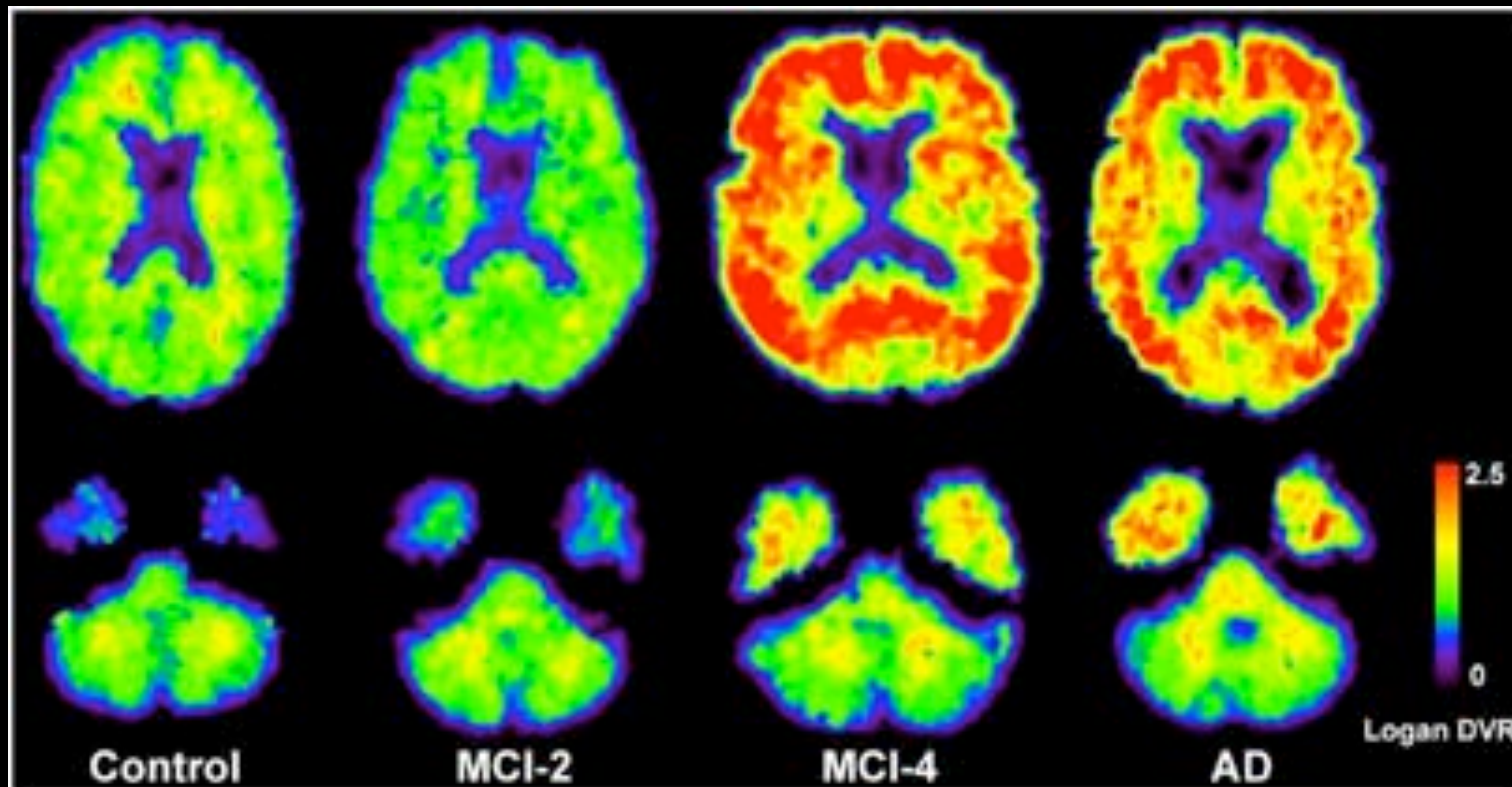
Image removed due to copyright restrictions.

Fig. 2 in Golby, A., et al. *Brain* 128, no. 4 (2005): 773-787.

Golby et al, 2005

Molecular Diagnosis of AD in patients

Pittsburg Compound B (PIB): congo red like properties
Amyloid-binding radiotracer for positron emission tomography



Courtesy of Dr. Julie C. Price. Used with permission.

Source: Price, J. C. et al. "Kinetic Modeling of Amyloid Binding in Humans Using PET Imaging and Pittsburgh Compound-B." *Journal of Cerebral Blood Flow & Metabolism* 25 (2005): 1528-1547.

Control-like
Mild cognitive
impairment

AD-like
Mild cognitive
impairment

Price et al, 2005

FDA-approved drugs for AD treatment

- **Memantine: NMDA receptor antagonist**
 - **Donepezil: acetylcholinesterase inhibitor**
 - **Galantamine: acetylcholinesterase inhibitor**
 - **Rivastigmine: butyrylcholinesterase/acetylcholinesterase inhibitor**
- **All of these drugs confer mild cognitive improvements and delay progression on the scale of a few months. For example, it is estimated that Galantamine confers a delay to full-time care by 3.0 months.**

Targeting amyloid--drugs under development

- A β vaccination
 - active immunization
 - passive immunization

- γ -secretase inhibitors

- β -secretase inhibitors

- Inhibitors of A β aggregation

Vaccination against A β as a therapeutic approach

Schenk et al from Elan Pharmaceuticals (1999):

In PDAPP mice, vaccination resulted in reduced plaque burden, neuritic dystrophy, and astrogliosis

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Fig. 2 a, b in Schenk, D., et al. "Immunization with Amyloid Beta Attenuates Alzheimer-Disease-Like Pathology in the PDAPP Mouse." *Nature* 400 (1999): 173-177.doi:10.1038/22124.

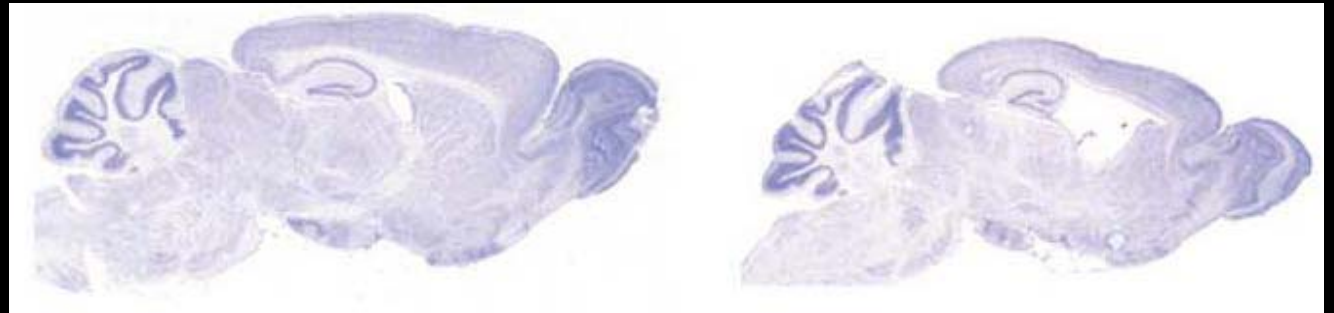
Janus et al (2000), Morgan et al (2000):

Protects against cognitive decline in APP transgenics

Human phase II trial of AN-1792 (Elan) stopped when 15 patients out of 300 developed meningoencephalitis after 1-2 rounds of a planned 6 rounds of vaccination. However, 21 responders were found to have significantly slower decline in Disability Assessment for Dementia test compared to placebo (p=0.015)

Targeting β - and γ - secretase with drug inhibitors

- γ - secretase:
 - Presenilin is the core catalytic component
 - Cleaves other potentially important substrates such as Notch and ErbB4
 - Presenilin knockouts have severe neurodegeneration (Saura et al, 2004)



Courtesy Elsevier, Inc., <http://www.sciencedirect.com>. Used with permission.
Source: Saura, C., et al. *Neuron* 42, no. 1 (2004): 23-26.

- β -secretase (BACE1):
 - Is the rate-limiting step in $A\beta$ generation
 - BACE1 knockouts do not display any gross abnormalities or nervous system defects (Roberds et al, 2001)
- BACE1 is an attractive target for AD therapy
- However, difficulty in designing small and lipophilic compound which can inhibit large catalytic cleft of BACE1

Other promising avenues:

Therapeutics:

Antioxidants

Anti-inflammation

GABA receptor antagonists

Nicotinic receptor modulators

GSK3 and Cdk5 inhibitors

Treatment and prevention:

Calorie restriction

Sirtuin activators

Cognitive enrichment

Chromatin remodeling