Alzheimer's Disease: from Pathology to Therapeutics

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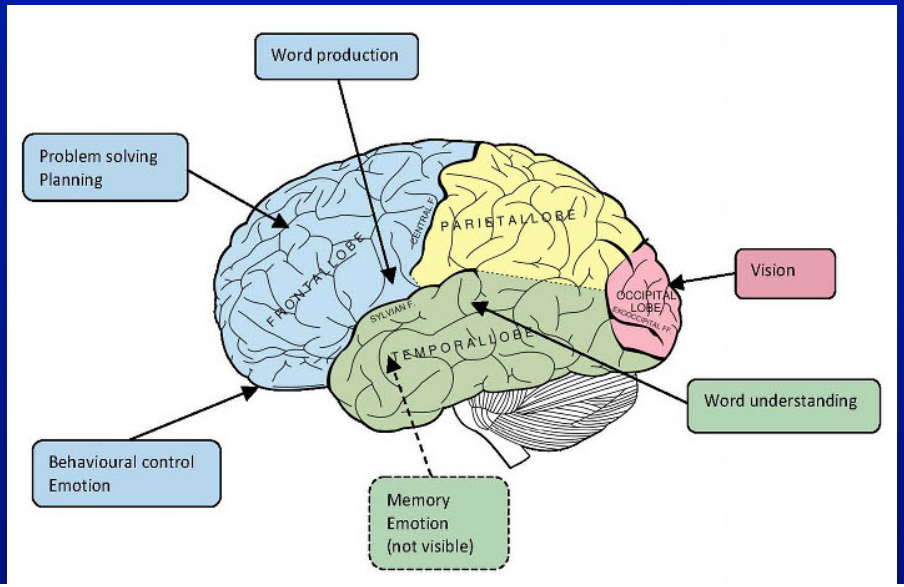
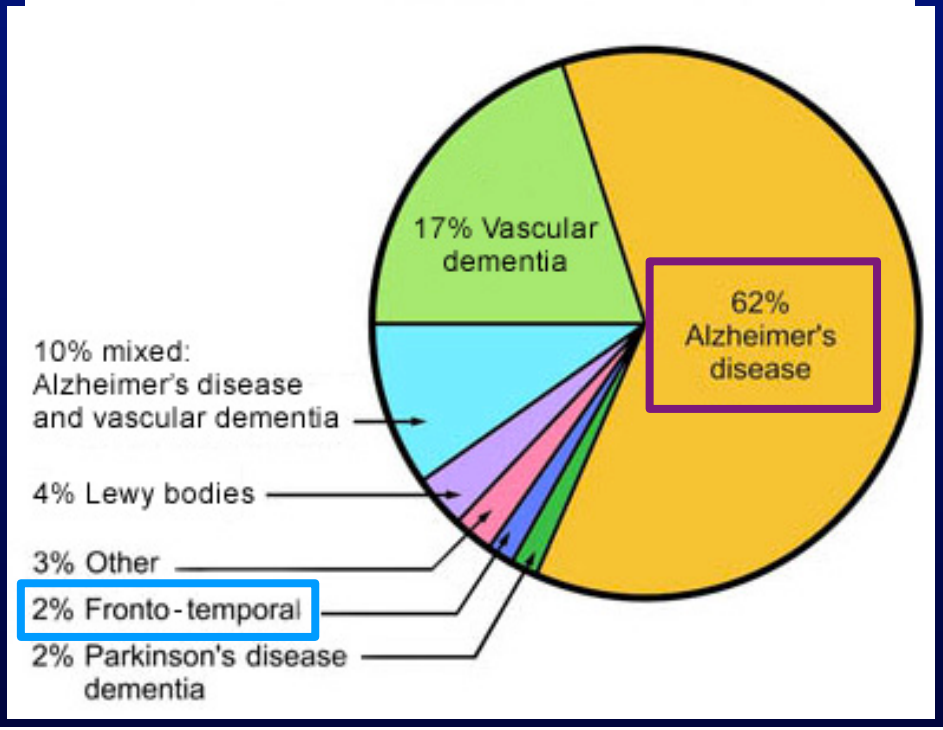
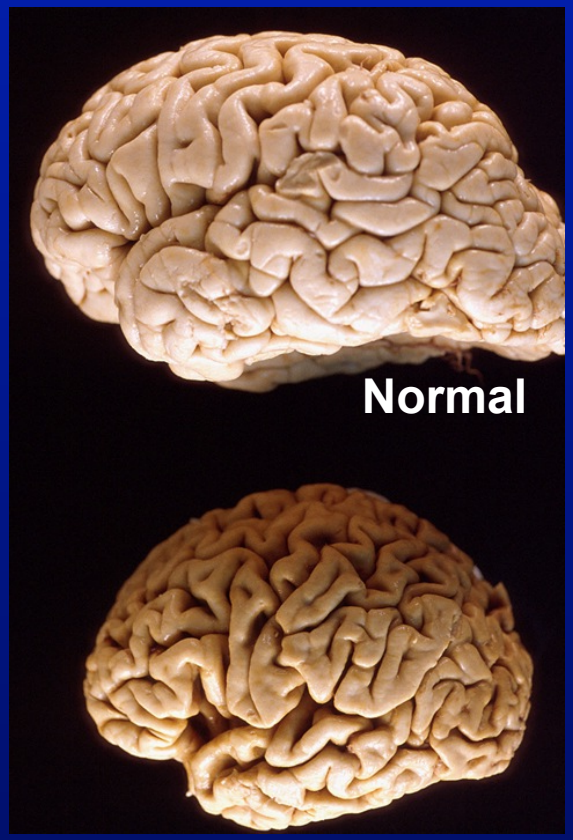
Basic demographics on dementia and Alzheimer disease

- Total number of demented in Japan: 4.39 million; 36 million WW (~60% caused by Alzheimer disease; AD)
- 3.8 Million “Mild cognitive impairment” individuals (=early stage of dementia) in Japan
- Costs for medical and social care for the demented people, amounting to 10K billion JPY/y (>600 billion USD worldwide)
- To reduce the rate of increase in newly demented patients (triple by 2050), there is a compelling need for treatment or prevention of dementia or AD!

Different types of dementia



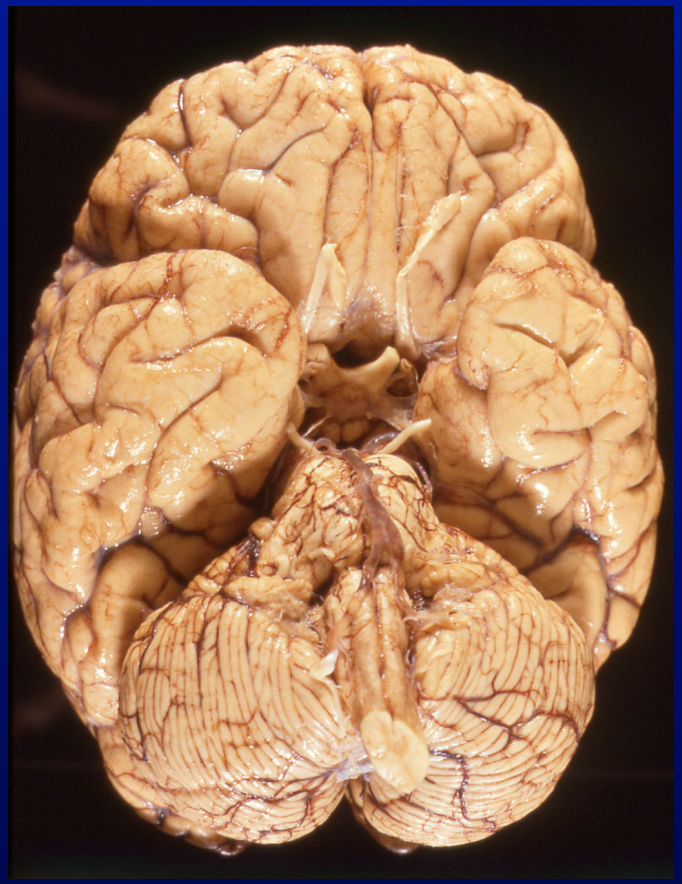




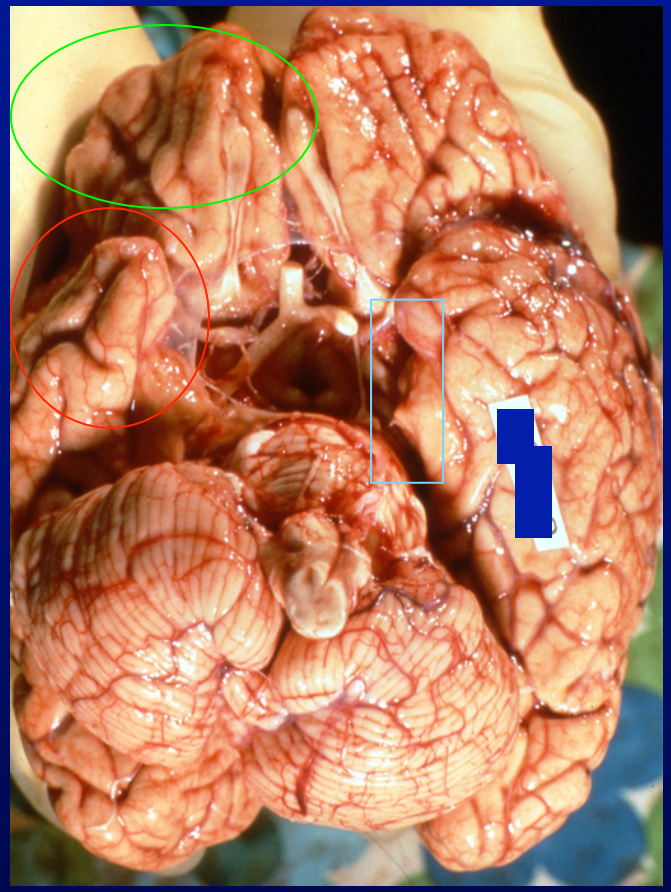
Alzheimer (AD)

Fronto-temporal (FTLD)

What is happening in AD brains?

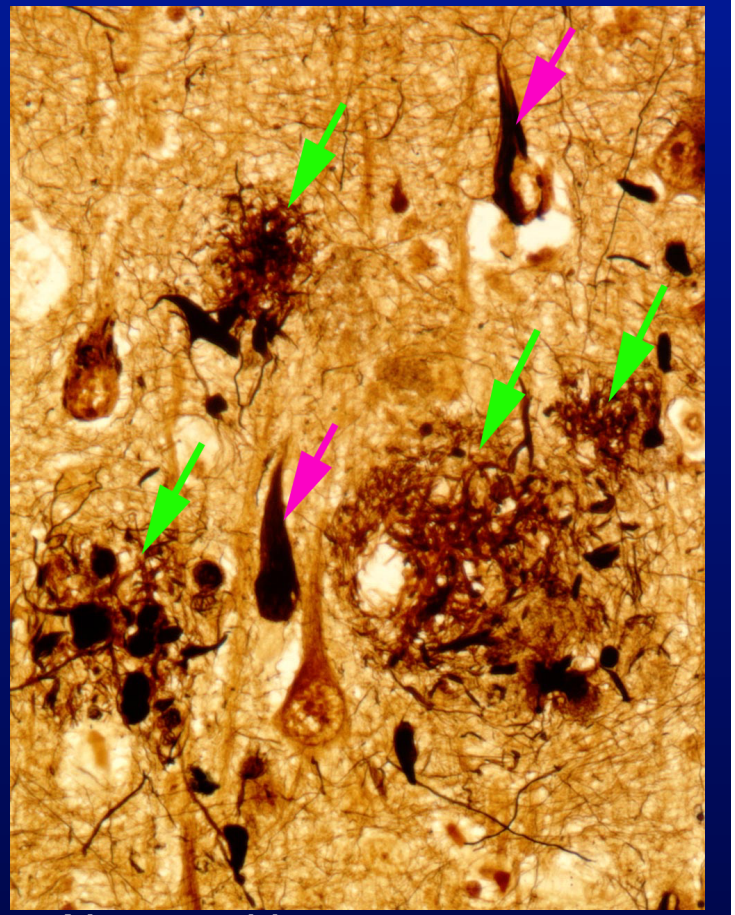


Normal brain



AD brain
cerebrocortical atrophy

AD hippocampus

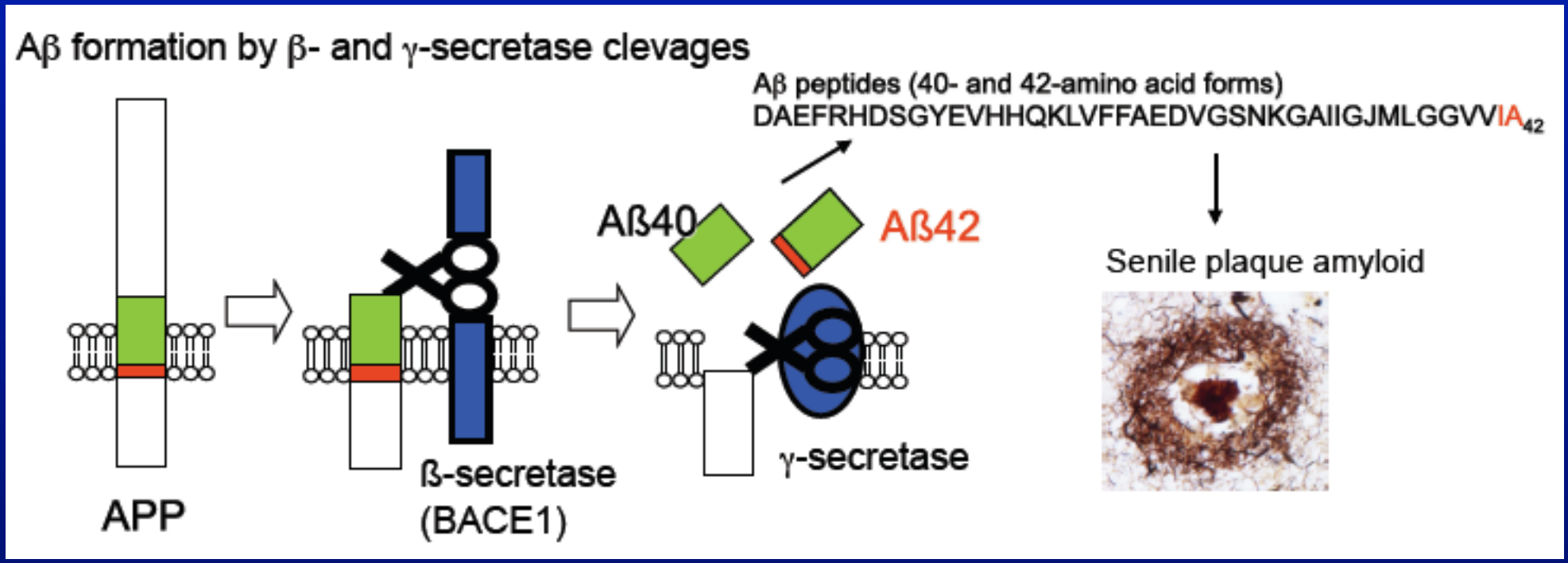


Neuronal loss
Neurofibrillary changes (tau)
Senile plaques (β amyloid)

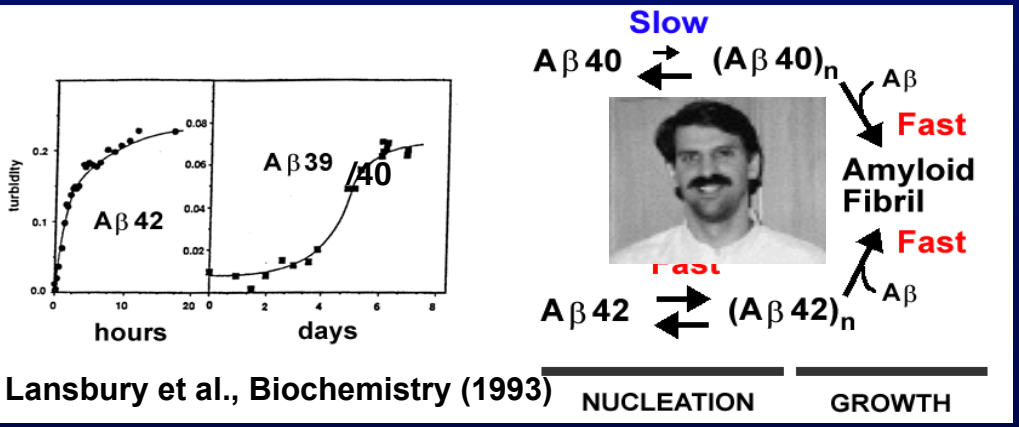
Evidence supporting the β-amyloid hypothesis

(i.e. the concept that Aβ is related to the pathogenesis of AD)

1. Specificity to AD and related conditions
2. Chronology: Aβ deposition as the earliest pathological change in AD pathology
3. Genetic evidence: mutations in genes linked to familial AD altogether lead to enhanced accumulation of Aβ

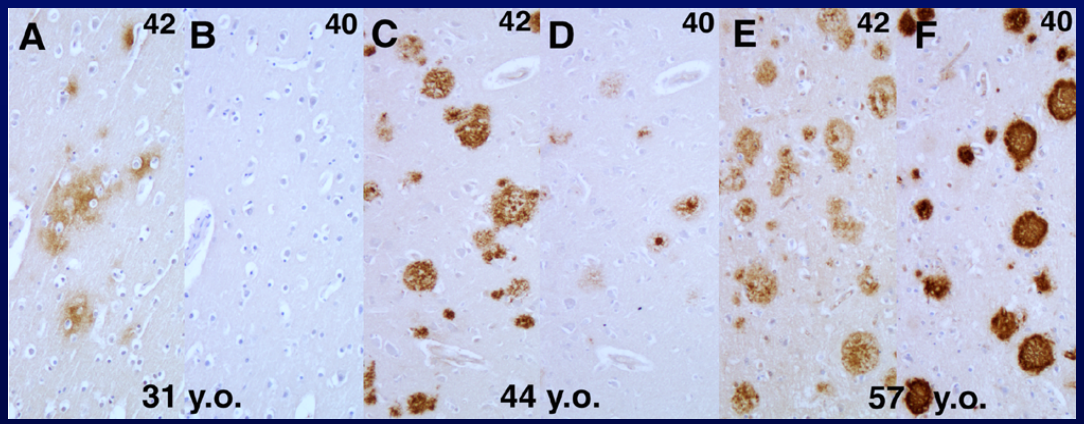


Aß42 aggregates faster than Aß40 to form amyloid fibrils



Lansbury et al., Biochemistry (1993)

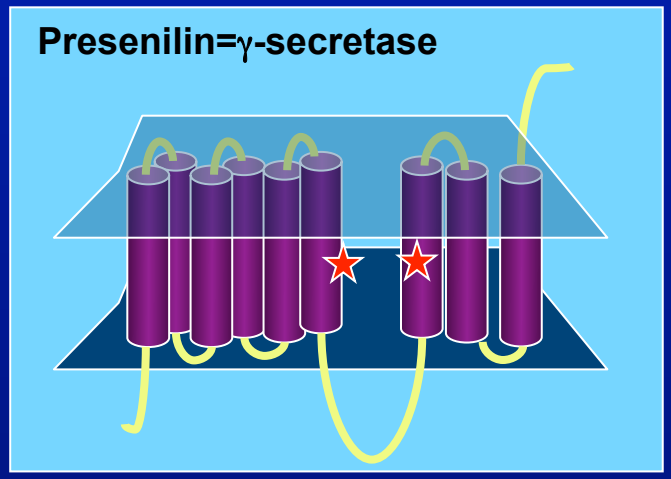
Aß42 precedes Aß40 in the progression of AD pathology in Down syndrome



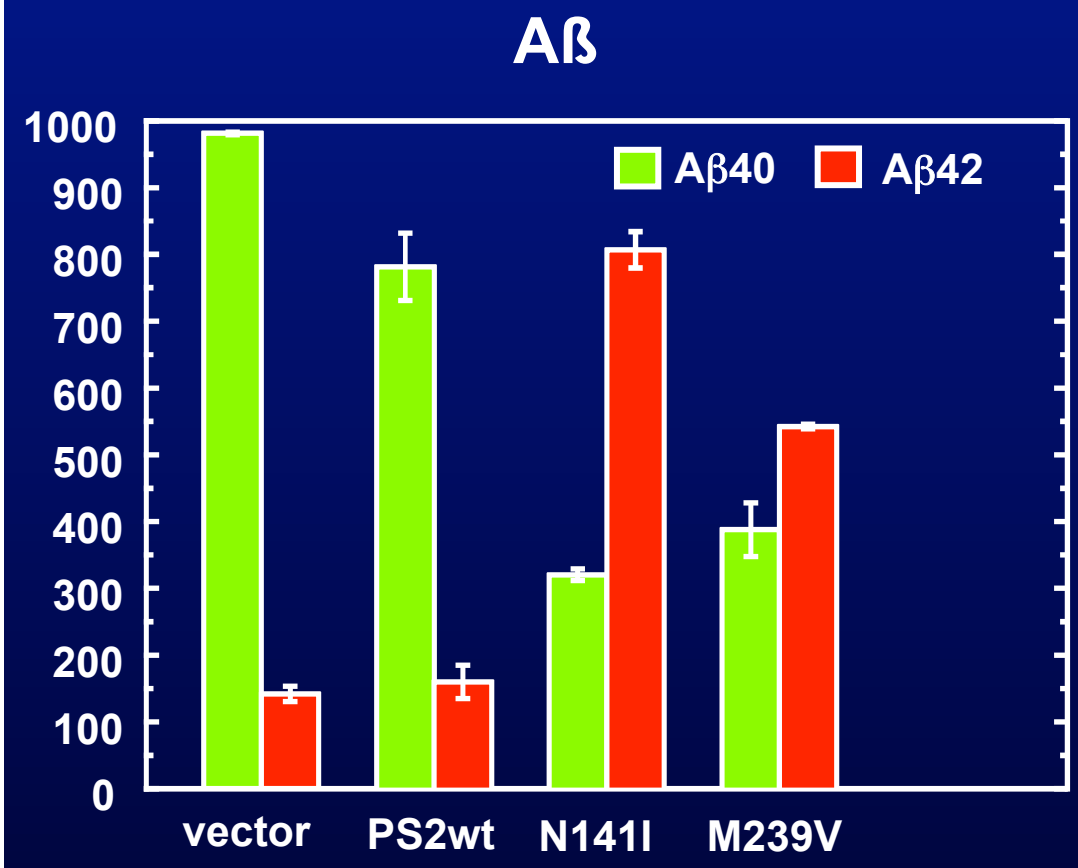
Iwatsubo, Asami, Suzuki et al. Neuron (1994)

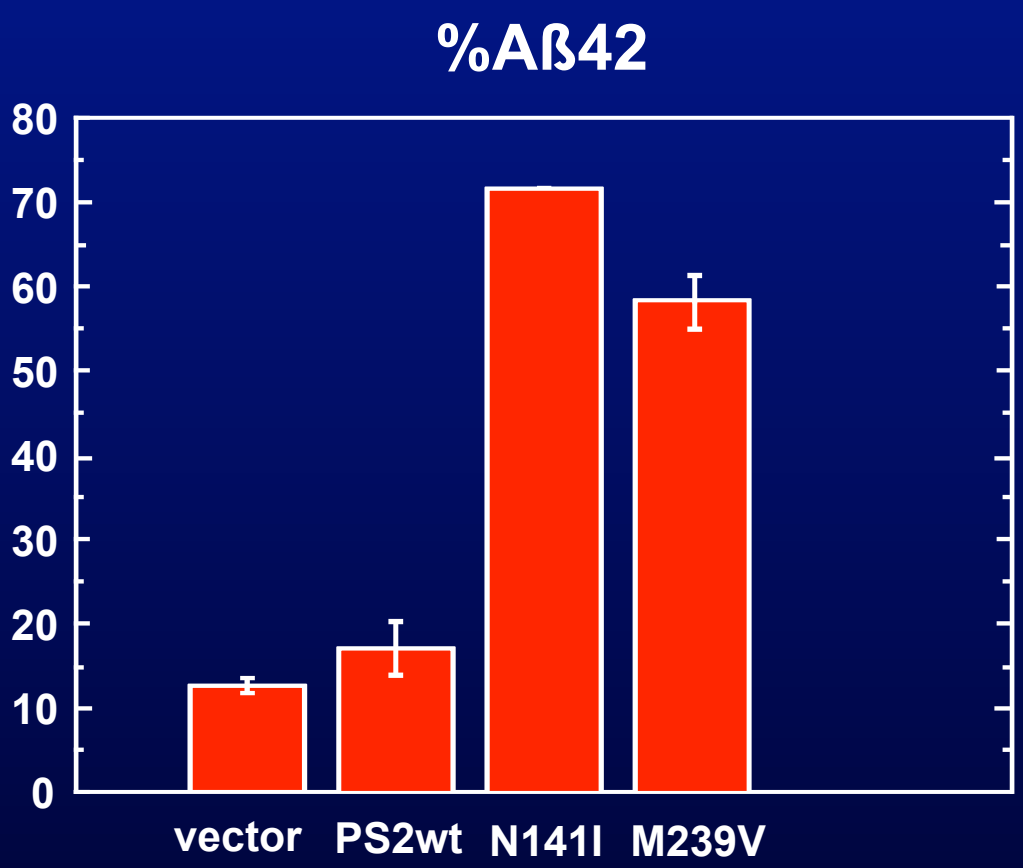
Mutations in familial AD gene (presenilins) increase production of Aß42

Tomita et al., *Proc Natl Acad Sci USA* (1997)

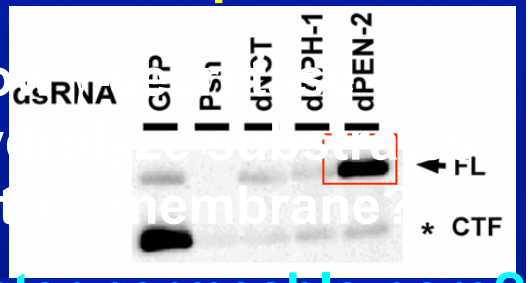


Aβ42: pathogenic protein causing AD evidenced by genetics!





Structure-funcdion relationship of γ-secretase—A set of complex membrane proteins: PS, APH-1, NCT, PEN-2, form γ-secretase



Ho
hy
wi
membrane?

Water permeable pore?

Introduction of RNAi into AD researc

PEN-2

APH-1/ NCT

initial subcomplex

PS

Stable, inactive complex

active γ-secretase

letters to nature

The role of presenilin cofactors in the γ-secretase complex

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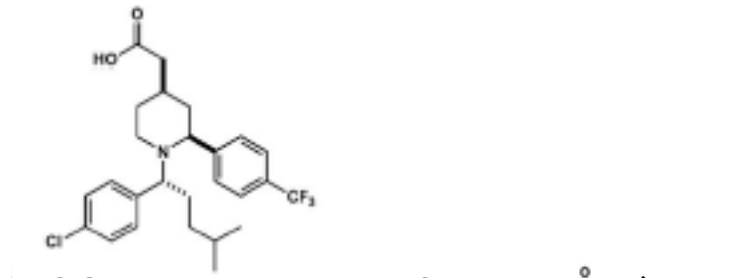
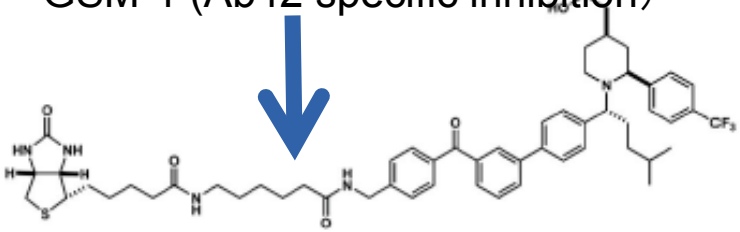
NATURE | 16 MARCH 2003 | doi:10.1038/nature01506 | www.nature.com/nature
advance online publication (AOP)

(Takasugi et al. *Nature* 2003)

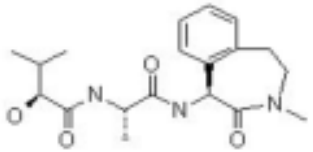
Identification of target of γ-secretase modifier drugs and mechanism of action (EMBO Journal, 2011)

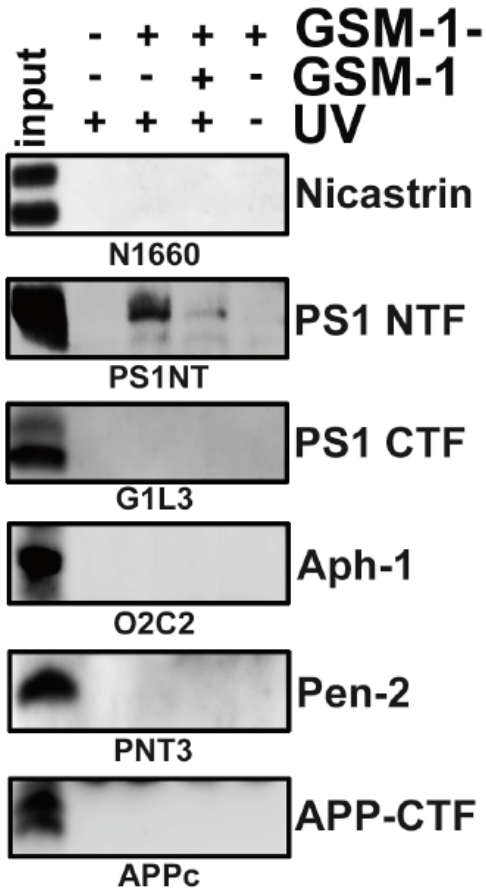


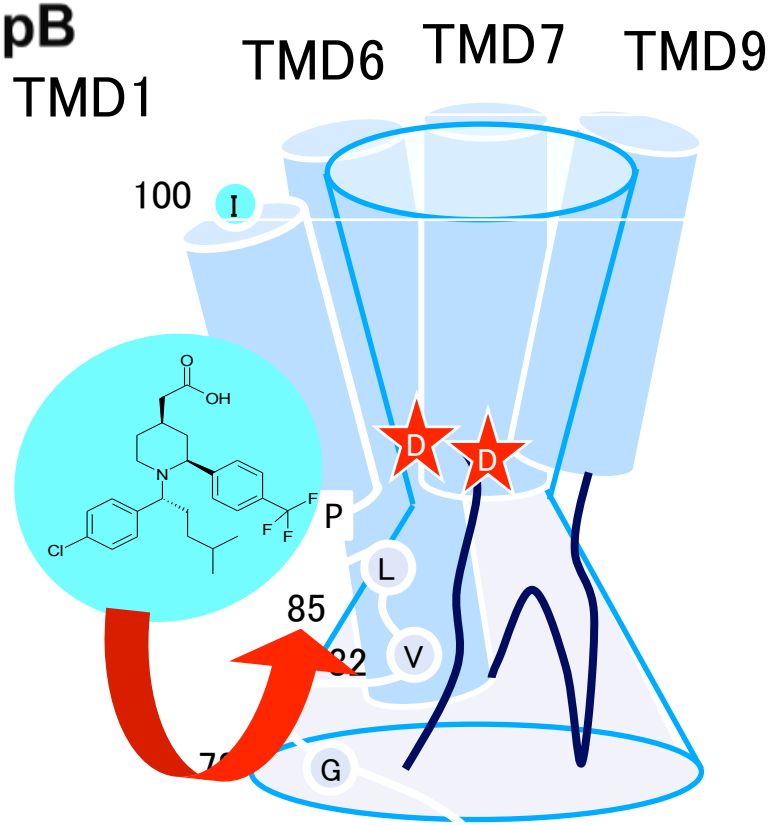
GSM-1 (Ab42 specific inhibition)



GSM-1-BpB





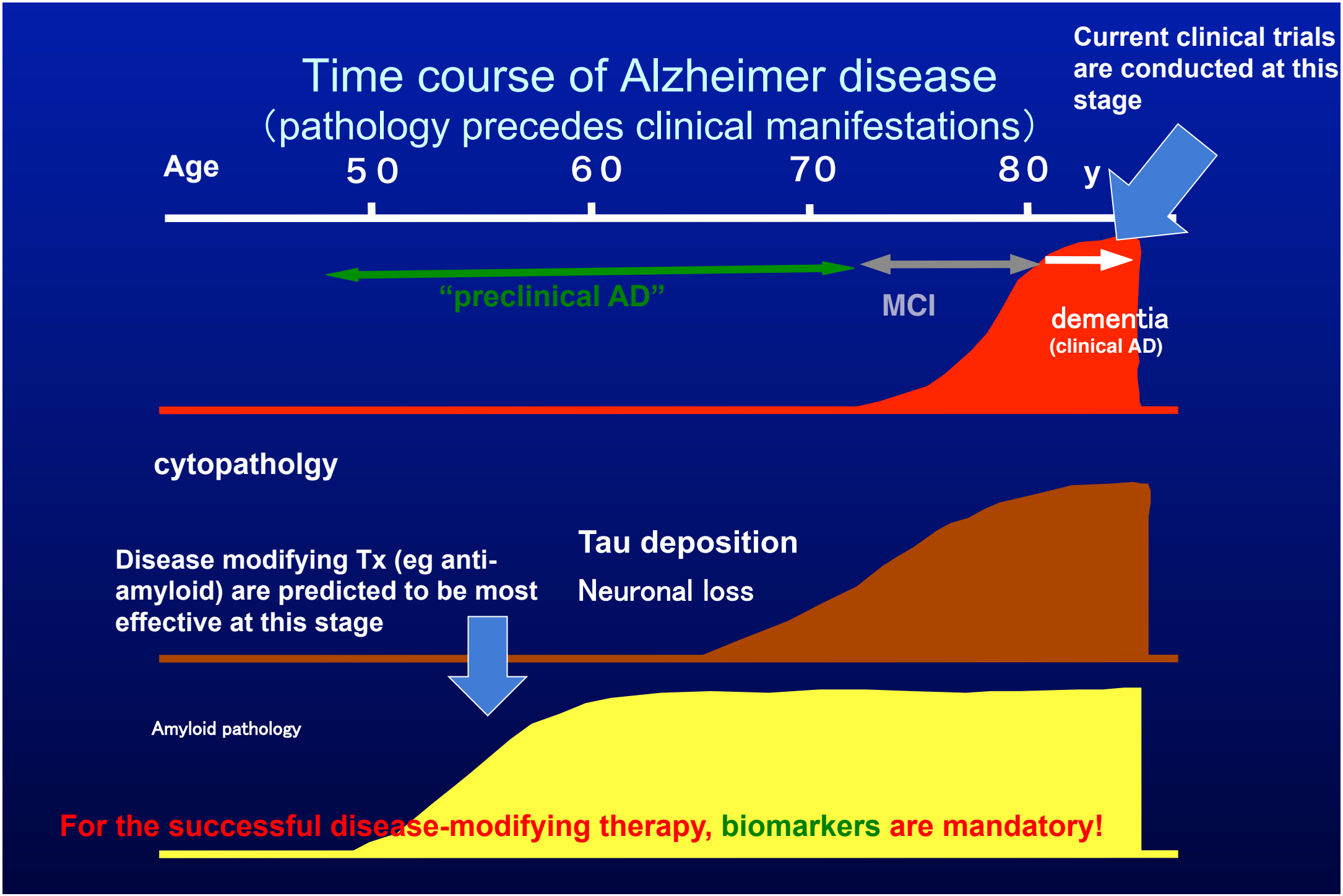


γ-secretase inhibitor "Semagacestat" Failure in Phase III clinical trial with no cognitive effects (2011)

The EMBO Journal (2011), 1–10 | © 2011 European Molecular Biology Organization | All Rights Reserved 0261-4189/11
www.embojournal.org

Phenylpiperidine-type γ-secretase modulators target the transmembrane domain 1 of presenilin 1

THE EMBO JOURNAL


Time course of Alzheimer disease
(pathology precedes clinical manifestations)
Current clinical trials are conducted at this stage
Age
50
60
70
80
y
"preclinical AD"
MCI
dementia
(clinical AD)
cytopatholgy
Tau deposition
Neuronal loss
Disease modifying Tx (eg anti-amyloid) are predicted to be most effective at this stage
Amyloid pathology
For the successful disease-modifying therapy, biomarkers are mandatory!

AD Neuroimaging initiative Worldwide

Dr. Takeshi Iwatsubo

J-ADNI

Dr. Michael Weiner

US ADNI

S-ADNI

EU ADNI

Dr. Giovanni Frisoni

Korean-ADNI (Dr. Seol-Heui Han, Konkuk Univ)

AIBL (Au-ADNI)

Dr. Chris Rowe

1) Develop improved methods, which will lead to uniform standards for acquiring longitudinal, multi-site MRI and PET data on patients with AD, MCI, and elderly controls.
2) Acquire a generally accessible data repository, which describes longitudinal changes in brain structure and metabolism. In parallel, acquire clinical, cognitive and biomarker data for validation of imaging surrogates.
3) Determine those methods, which provide maximum power to determine treatment effects in clinical trials.

Japanese ADNI: a longitudinal observational study for imaging/fluid biomarkers that predict/surrogate clinical progression

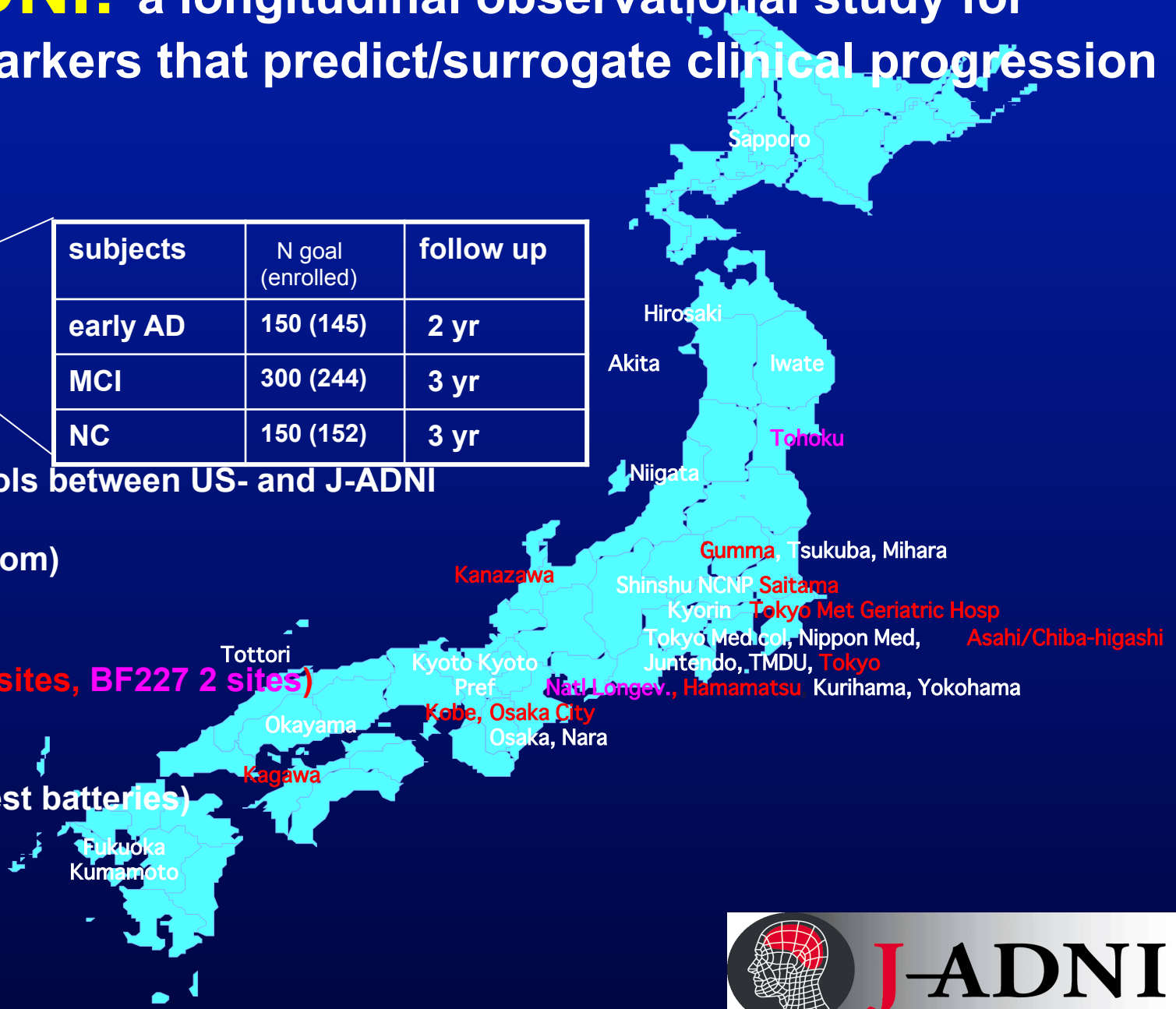
- 7-year study (since 2007)
- 38 clinical sites
- 600 subjects

545 cases enrolled
~3600 visits completed

subjects	N goal (enrolled)	follow up
early AD	150 (145)	2 yr
MCI	300 (244)	3 yr
NC	150 (152)	3 yr

Highly compatible protocols between US- and J-ADNI

- 1.5T MRI
(3D MPRAGE, ADNI phantom)
- PET
  ---FDG ~67%
  ---amyloid ~42% (PIB 16 sites, BF227 2 sites)
- Blood + apoE (100%)
- CSF ~40%
- Clinical (14 compatible test batteries)



J-ADNI
Alzheimer's Disease Neuroimaging Initiative

J-ADNI2 launching on Oct 2013

- Consists of two observational studies:(1)Preclinical AD (n=150) screened by amyloid PET, 3-y follow up (2) early (n=100) /late MCI (n=100) studies using protocols compatible to ADNI2
- 41 clinical sites, completely covered by amyloid PET (^{11}C-PiB, florbetapir or flutemetamol) at ~30 PET centers nationwide
- 3T MRI (including resting fMRI, ASL, DTI)
- CSF examination at baseline, 12M and 36M in all cases
- ~4M USD eq./y for FY2013 from NEDO and MHLW + private funding from pharma company consortium
- Towards successful clinical trials of DMTs in prodromal AD, and “preemptive medicine” in preclinical AD

Application of J-ADNI experience to investigator-initiated clinical trials: early & exploratory clinical trial center for AD/CNS drugs at U. Tokyo

東大病院 The University of Tokyo Hospital

J-ADNI Alzheimer's Disease Neuroimaging Initiative

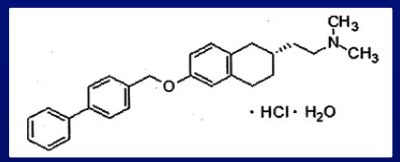
Early clinical application of AD disease modification!

Identification and evaluation of AD drug seeds

Unit for early/explolatory clinical development of AD/ CNS drugs

Support and execution of AD clinical trials

TAK-070 (BACE1 inhibitor)
1st in human & POC trials



Licensed to U Tokyo
June 1 2012

Clinical Research Ctr

- clinical trial unit
- Site network unit
- UT adm unit
- pharmacy

1st-in-human trials

- Phase I trial Unit
- nursing
- Lab medicine

Clinical Departments

- Dementia Board
  POC studies and P2/3 trials
- Memory Clinic
  - Neurology
  - Psychiatry
  - Geriatrics
  - Neurosurgery
- Internal med
- diabetology
- Radiology (MRI, PET)
- Anesthesiology

Summary and future directions towards AD disease modification

- ADNI studies are establishing markers for very early diagnosis and evaluation of rate of progression that are applicable to clinical trials of disease modifying Tx of AD
- Investigator initiated AD clinical trials are being initiated in the early/exploratory Ctr at U Tokyo
- Long-term observational study for preclinical AD being started as a part of J-ADNI2, in parallel with the preclinical AD intervention studies in US (DIAN, API, A4).
- Like lowering cholesterol at healthy stage and preventing from atherosclerosis and vascular events, we aim at very early AD therapies by lowering Aβ or other causative factors from the preclinical AD stage!