CLINICAL TRIALS: OVERVIEW, CURRENT TRIALS AND PIPELINE

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Brief History of AD Therapeutics

- 1906: Dr. Alois Alzheimer describes AD
- 1906-1970's: General assumption that this is an untreatable degenerative disease
- Late 1970's Cholinergic hypothesis suggests treatment possibilities
- 1985: First positive treatment study
- 1993: Tacrine is approved; 3 other similar drugs follow
- 2003: Memantine is approved, representing a second therapeutic class for AD

AD Therapeutics

Therapeutic target development

- Cholinergic hypothesis
- NMDA antagonism
- Oxidative stress
- Inflammation
- Amyloid hypothesis
- Tau, kinase inhibition
- Neurotrophins
- Mitochondrial stabilization

Trial methodology

- Access to subjects
- Operationalized diagnosis/subject selection
- Outcome measures
- Biomarkers
- Analytic methods
- Regulatory guidance

Standard therapy of AD in 2009

- Cholinesterase inhibitor
- Add memantine at moderate stage (MMSE≤14)

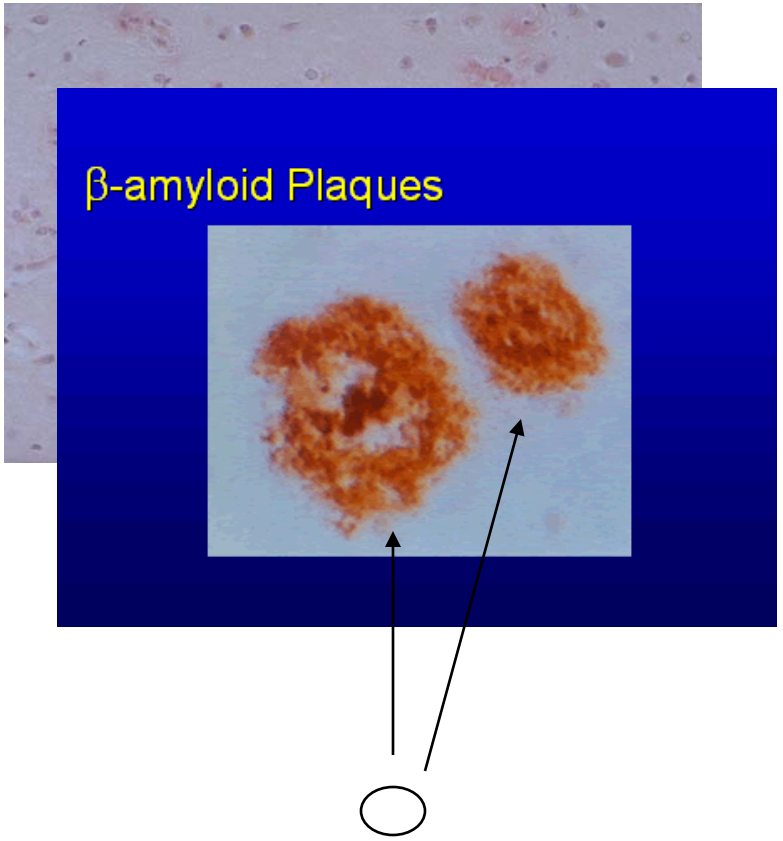
- No established treatment for MCI (vitamin E ineffective, cholinesterase inhibitors minimally effective, possibly risky)

AD Therapeutics: Current Outlook

- 1999-present: growing consensus that specific molecular cause of AD may be Aβ (amyloid beta peptide)
- Optimism that disease-modifying, possibly disease-halting treatment can be developed, targeting Aβ
- Other targets: tau and tangles, mitochondrial function, transport, cell survival, vascular factors …

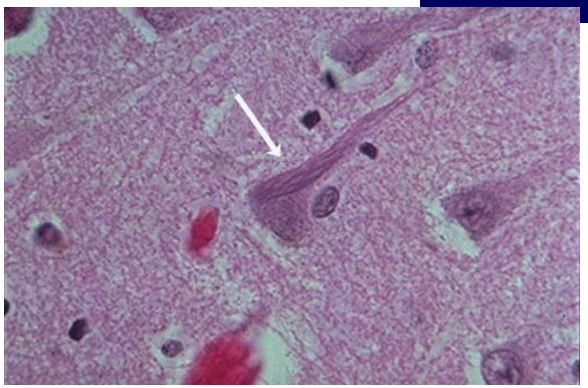
Hallmarks of AD

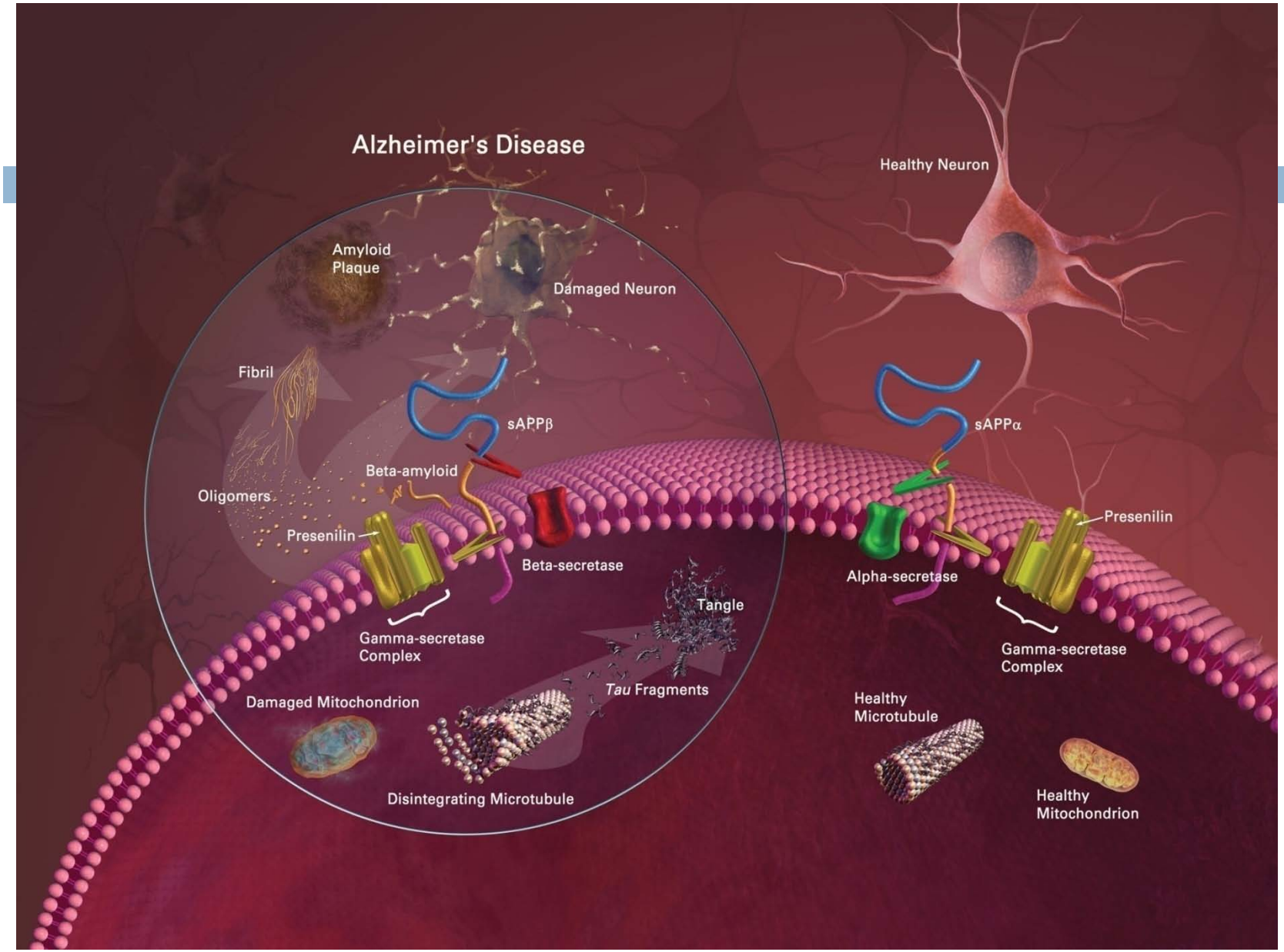
- Amyloid plaque (Aβ)
  - **Clumps of toxic material in the brain tissue**



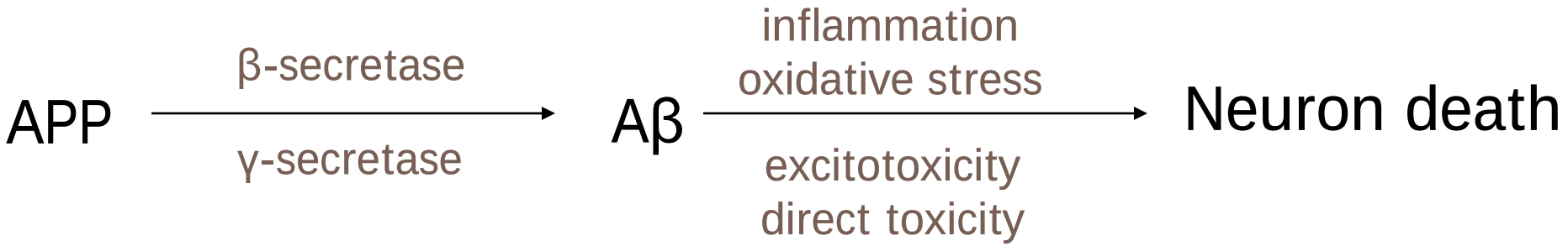
Hallmarks of AD

- Neurofibrillary tangles: hyperphophorylated tau
  - Deposits within the cells of the brain

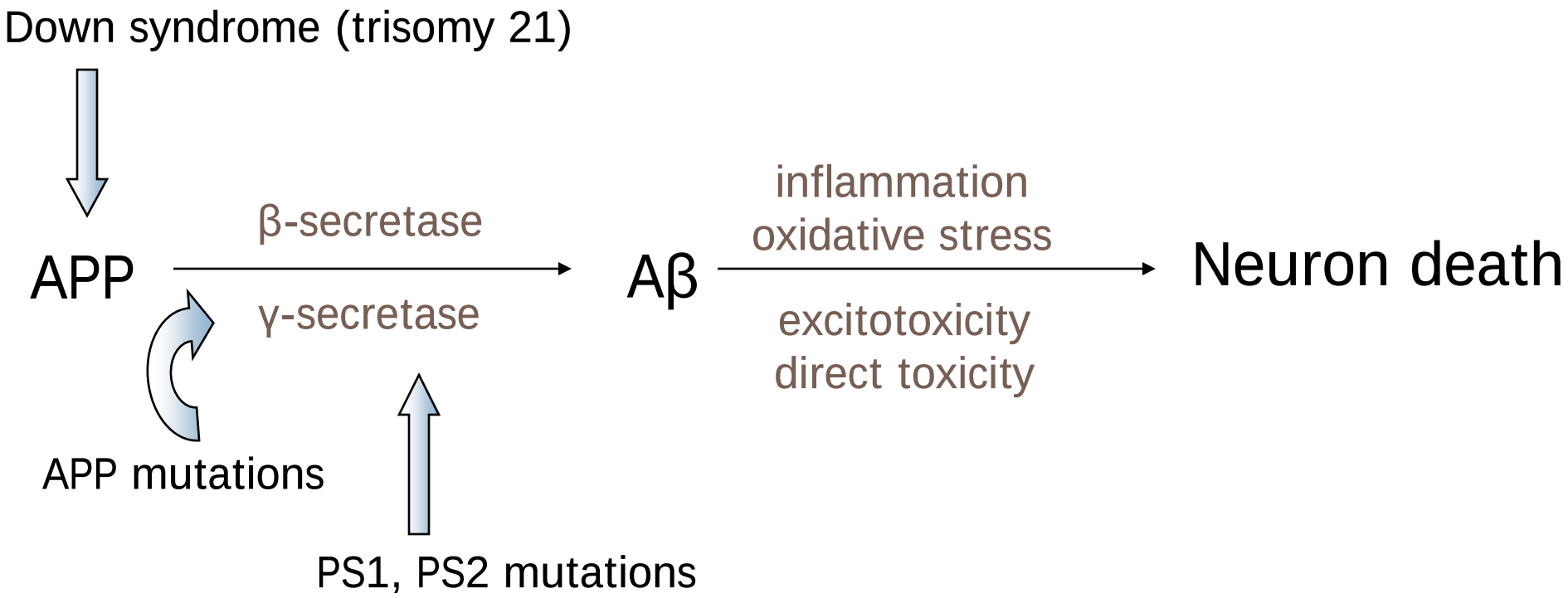



Alzheimer's Disease
Amyloid Plaque
Damaged Neuron
Fibril
sAPPβ
Beta-amyloid
Oligomers
Presenilin
Beta-secretase
Gamma-secretase Complex
Tangle
Tau Fragments
Damaged Mitochondrion
Disintegrating Microtubule
Healthy Neuron
sAPPα
Presenilin
Alpha-secretase
Gamma-secretase Complex
Healthy Microtubule
Healthy Mitochondrion

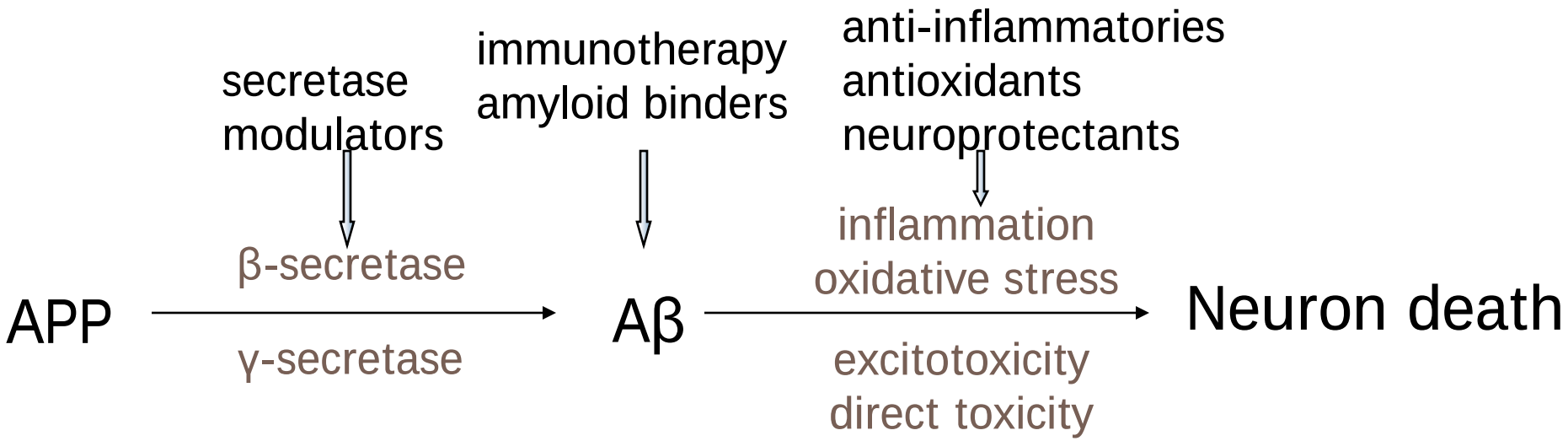
Pivotal pathway in AD pathophysiology



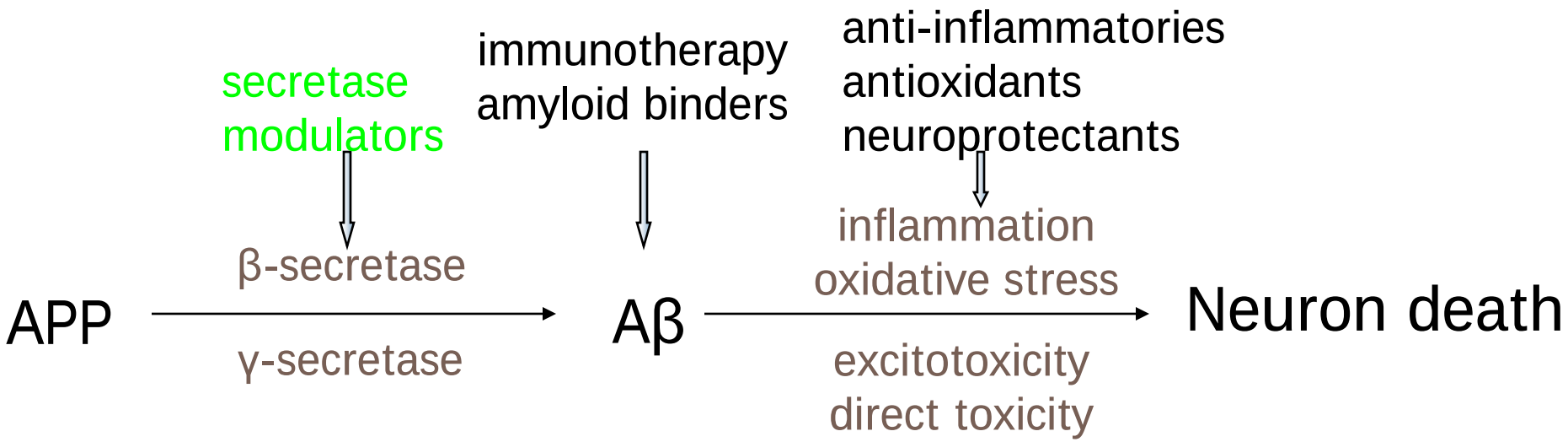
Genetic causes of AD



Disease-Modifying Strategies



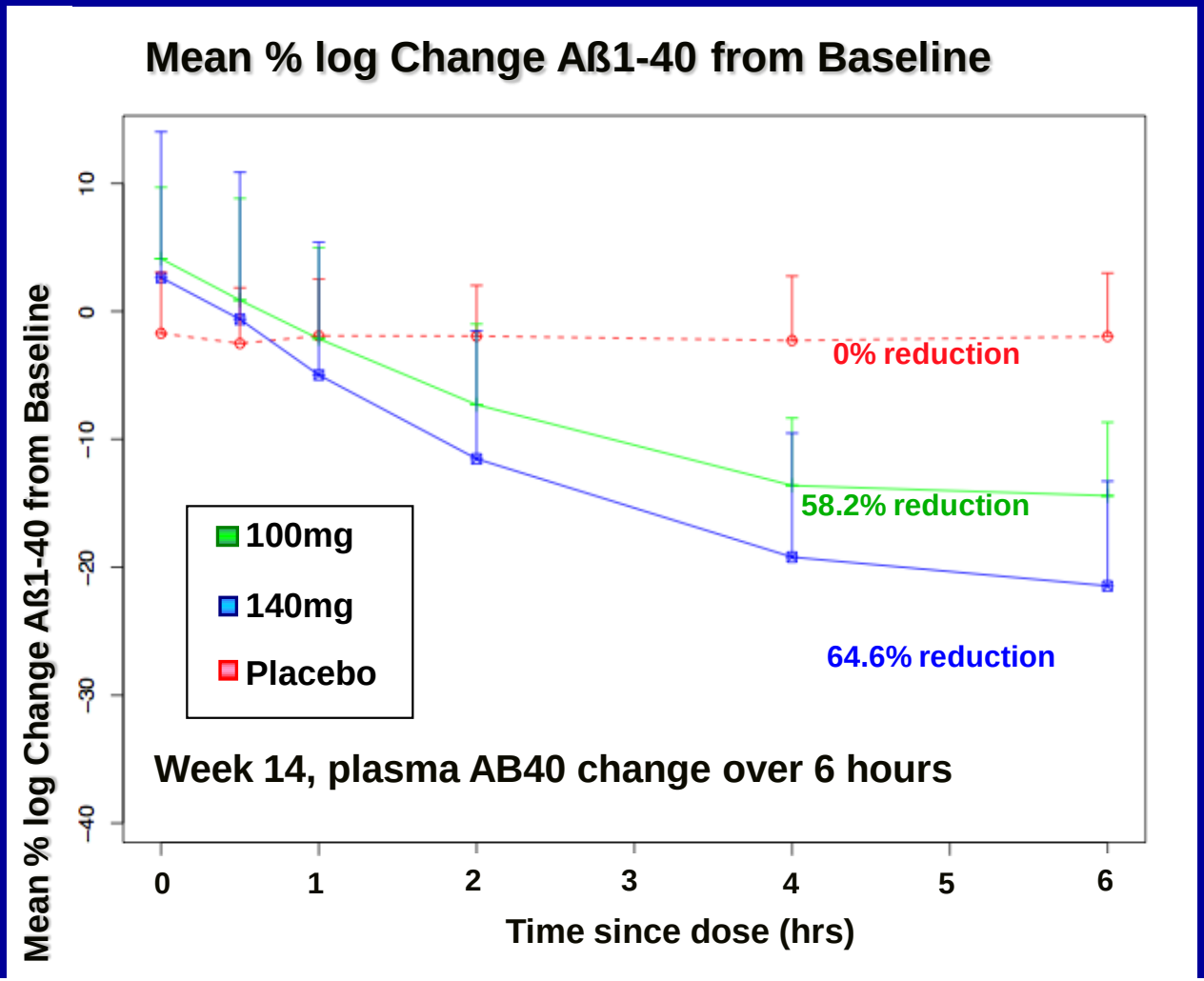
Disease-Modifying Strategies



Secretase Modulators

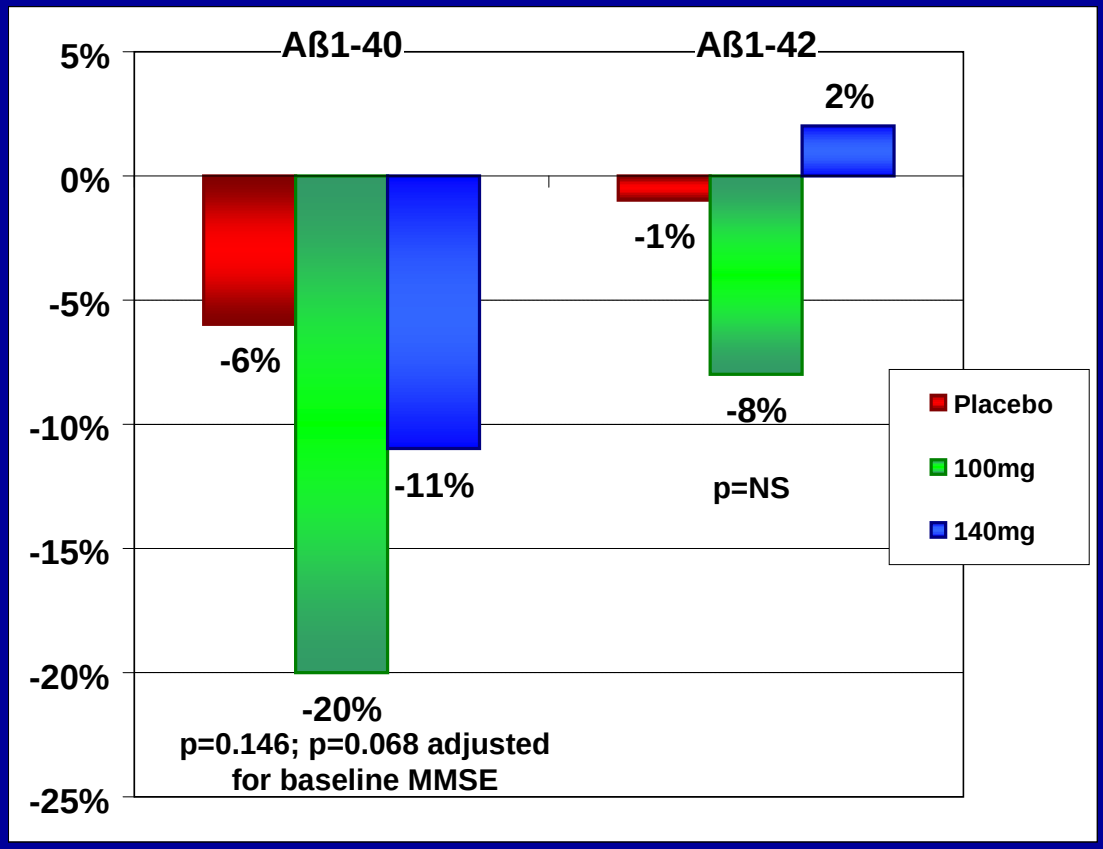
- β-secretase inhibitors
  - #1 strategy; enzyme structure known; knock-out mice viable
  - disappointingly slow to develop drug
  - candidates emerging (in vitro and in vivo activity); two have entered clinical trials
- γ-secretase inhibitor
  - toxicity related to other substrates (eg, Notch)
  - treatment with non-specific inhibitors may nonetheless be feasible (eg, Lilly)
  - inhibitors/modulators specific to APP emerging
- NSAID γ-secretase modulators (eg tarenflurbil)
- GSK-3β inhibitors (eg, lithium)
- α-secretase activators (eg, PKC activators: bryostatin)

Plasma Concentrations Aß1-40



Fleisher AS, Raman R, Siemers ER, Sowell BB, Becerra LM, Clark CM, Farlow MR, Galvin JE, Peskind ER, Quinn JF, Sherzai D, Aisen PS, Thal LJ. **Phase II Trial with a Gamma-Secretase Inhibitor** in Mild-to-Moderate Alzheimer's Disease. Alzheimer's Disease Prevention meeting, Washington DC, June 11, 2007.

Reductions in CSF Aß



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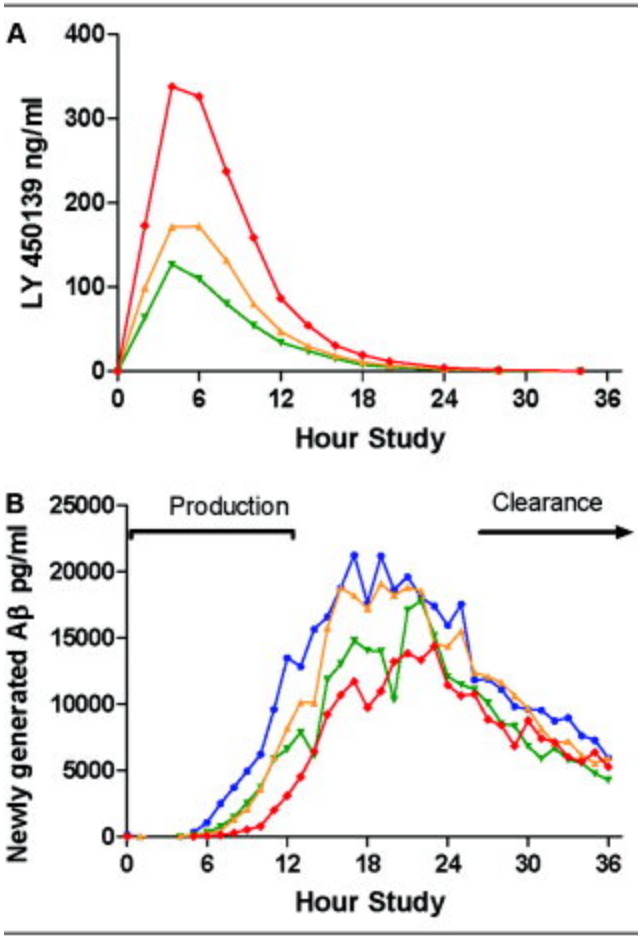
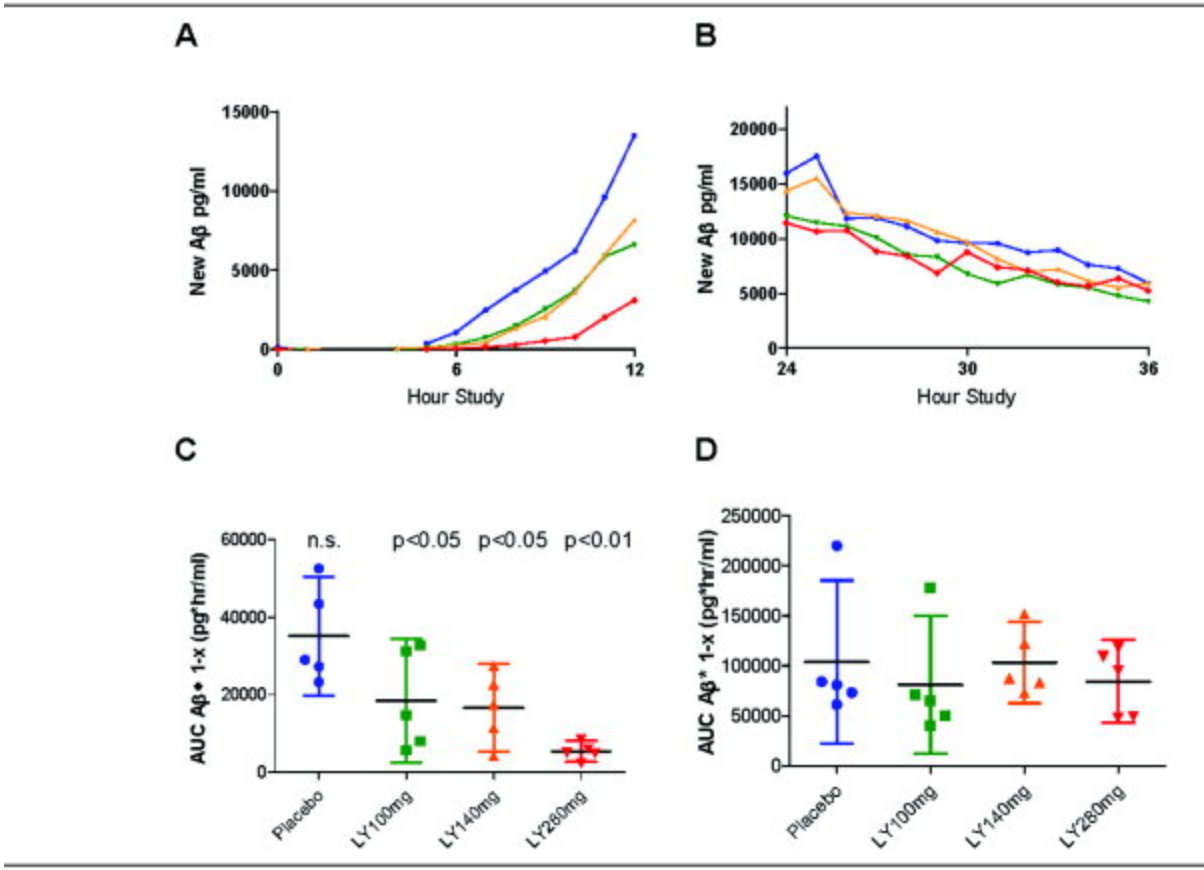
Bateman et al, Annals Neurol. March, 2009



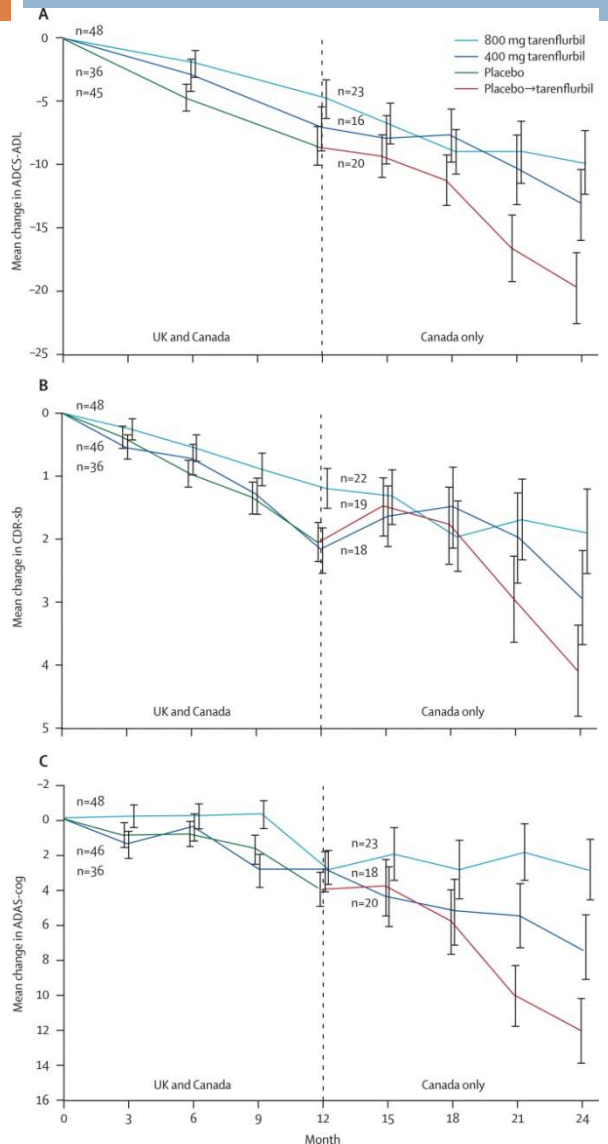


tarenflurbil (Flurizan)

- Enantiomer of NSAID, free of COX inhibition
- Like certain NSAIDs (ibuprofen, sulindac), R-flurbiprofen modulates γ-secretase activity, reducing Aβ production in vitro and in vivo
- In absence of COX activity, high doses can be administered

Efficacy and safety of tarenflurbil in mild to moderate Alzheimer's disease: a randomised phase II trial

Gordon K Wilcock, Sandra E Black*, Suzanne B Hendrix, Kenton H Zavitz, Edward A Swabb, Mark A Laughlin, on behalf of the Tarenflurbil Phase II Study investigators†*



Summary

Background The amyloid-β peptide $A\beta_{42}$ has been implicated in the pathogenesis of Alzheimer's disease (AD). We aimed to test the effects of tarenflurbil, a selective $A\beta_{42}$-lowering agent (SALA), on cognition and function in patients with mild to moderate AD.

Methods 210 patients living in the community who had a mini-mental state examination (MMSE) score of 15–26 were randomly assigned to receive tarenflurbil twice per day (400 mg [n=69] or 800 mg [n=70]) or placebo (n=71) for 12 months in a phase II, multicentre, double-blind study. Primary efficacy outcomes were the AD assessment scale cognitive subscale (ADAS-cog), the Alzheimer's Disease Cooperative Study activities of daily living scale (ADCS-ADL), and the clinical dementia rating sum of boxes (CDR-sb). In a 12-month extended treatment phase, patients who had received tarenflurbil continued to receive the same dose, and patients who had received placebo were randomly assigned to tarenflurbil at 800 mg or 400 mg twice per day. Primary efficacy analyses were done by intention to treat. This trial is registered with Health Canada (084527) and the Medicines and Healthcare products Regulatory Agency in the UK (20365/0001/A 69316).

Findings A prespecified interaction analysis revealed that patients with mild AD (baseline MMSE 20–26) and moderate AD (baseline MMSE 15–19) responded differently to tarenflurbil in the ADAS-cog and the ADCS-ADL ($p \leq 0 \cdot 10$); therefore, these groups were analysed separately. Patients with mild AD in the 800 mg tarenflurbil group had lower rates of decline than did those in the placebo group in activities of daily living (ADCS-ADL difference in slope 3·98 [95% CI 0·33 to 7·62] points per year, effect size [reduction from placebo decline rate] 46·4%, Cohen's d 0·45; p=0·033) and global function (CDR-sb difference –0·80 [–1·57 to –0·03] points per year, effect size 35·7%, Cohen's d 0·42; p=0·042); slowing of cognitive decline did not differ significantly (ADAS-cog difference –1·36 [–4·07 to 1·36] points per year, effect size 33·7%, Cohen's d 0·20; p=0·327). In patients with moderate AD, 800 mg tarenflurbil twice per day had no significant effects on ADCS-ADL and ADAS-cog and had a negative effect on CDR-sb (–52%, Cohen's d –1·08; p=0·003). The most common adverse events were diarrhoea (in seven, nine, and five patients in the 800 mg, 400 mg, and placebo groups, respectively), nausea (in seven, seven, and four patients), and dizziness (in five, nine, and four patients). Patients with mild AD who were in the 800 mg tarenflurbil group for 24 months had lower rates of decline for all three primary outcomes than did patients who were in the placebo group for months 0–12 and a tarenflurbil group for months 12–24 (all p<0·001), and had better outcomes than did patients who were in the placebo group for months 0–12 and the 800 mg tarenflurbil group for months 12–24 (all p<0·05).

Interpretation 800 mg tarenflurbil twice per day was well tolerated for up to 24 months of treatment, with evidence of a dose-related effect on measures of daily activities and global function in patients with mild AD.

Tarenflurbil Phase III

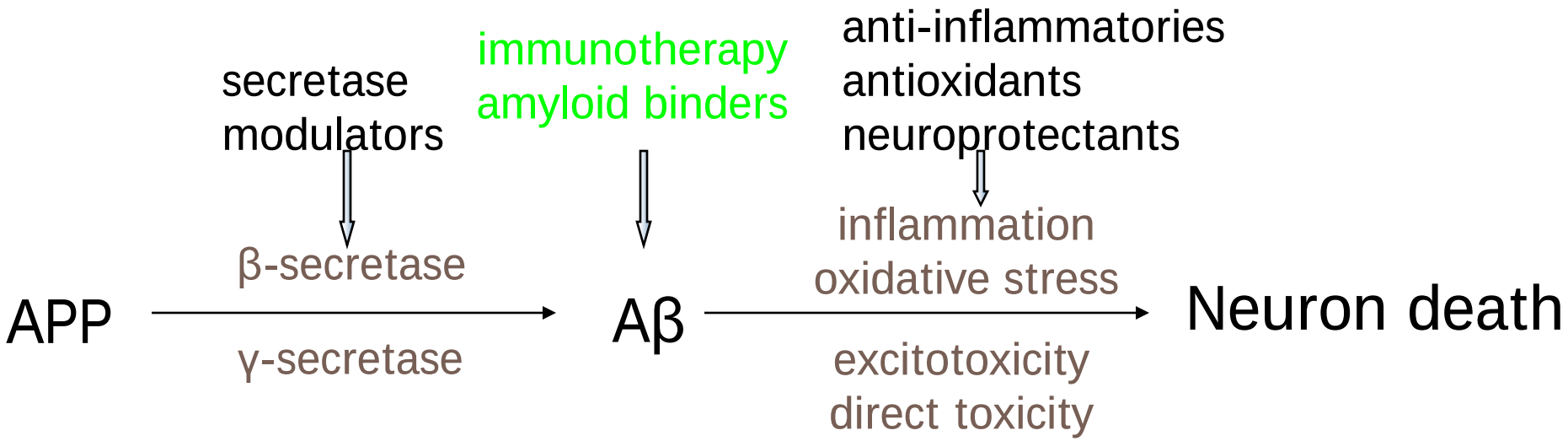
- 1700 mild AD subjects, 18 months

- Absolutely negative

Secretase inhibitors: pipeline

- Selective gamma secretase inhibitors: greater efficacy with safety
- Beta secretase inhibitors: entering phase II

Disease-Modifying Strategies



Amyloid-binding agents

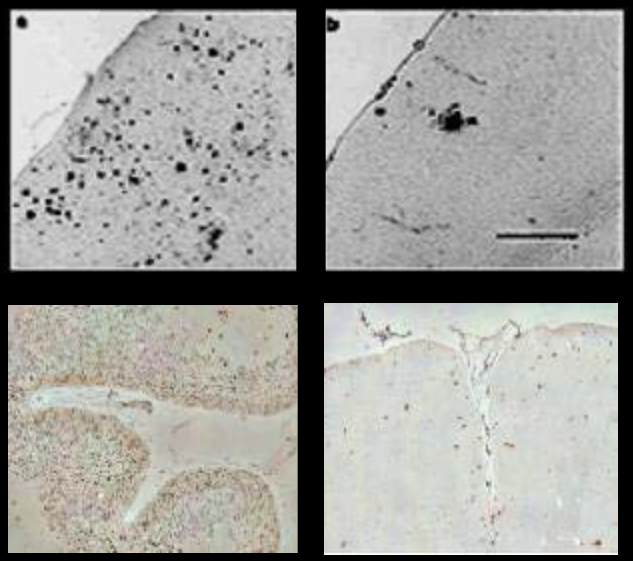
- Active vaccine
- Passive immunotherapy (Elan-Wyeth III)
- IGIV
- Non-immunologic agents
  - CNS-penetrating anti-aggregation agents (eg, GAG-mimetic tramiprosate)
  - ELND005 (AZD-103, scyllo-cyclohexanehexol) now in Phase II

Active immunotherapy

- Remarkable results in APP transgenic mice
- Vaccine (AN1792) Phase II
  - Halted early because of encephalitis in 6%
  - Trend toward cognitive benefit in antibody responders
  - Surprisingly, antibody responders show *increased atrophy rate by MRI*
  - Autopsies show striking plaque clearance in most subjects
- Vaccine results provide support to concept of immunotherapy

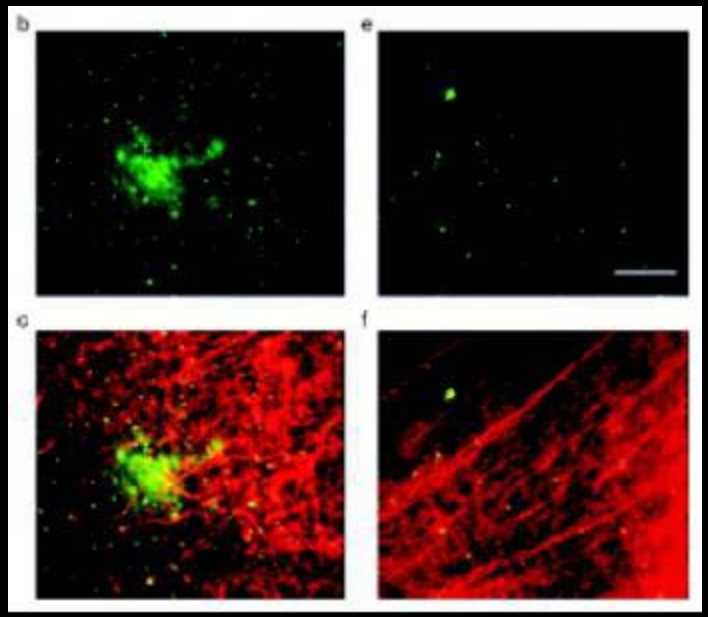
Immunotherapy Targeting β-Amyloid Alters Alzheimer Neuropathology

ACTIVE VACCINATION



Top : Schenk, et al, Nature, 1999
Bottom: Nicoll, et al, Nature Medicine, 2003

PASSIVE IMMUNIZATION



Lombardo, et al, J Neuroscience, 2003

Slide prepared by Norm Relkin

Active immunotherapy

- New active vaccines in Phase I, II testing
  - Short peptide fragment, eg Aβ amino acids 1-7 or 1-4, can induce a humoral immune response without a cellular immune response (Elan-Wyeth, Merck, Novartis)
  - Plaque clearance without risk of encephalitis?

Passive immunotherapy

- Humanized monoclonal anti-amyloid antibodies under development by a number of companies
- Expected to reduce brain amyloid (shown in transgenic mice) without risk of encephalitis (no T cell immune response)
- Concerns: focal edema,microhemorrrhages
- Issues: sequestration v. phagocytosis, N-terminus v. mid-sequence, oligomers?, deglycosylation, natural (IgIV) v. monoclonal
- Elan/Wyeth, Lilly, Roche, Pfizer, Genentech …

Phase II study of Gammagard IVIG for Alzheimer's Disease

The initial 6 month double blind, placebo-controlled phase was completed in July 2007. An 18 month extension study in progress.

- Analysis of the 6 month results:
  - Gammagard IVIg-treated AD patients had superior outcomes on tests of cognition, behavior and global assessment of change.
  - PET results indicate improvements in brain metabolism in the IVIg-treated group versus decline in placebo.
  - Results exceeded pre-set criteria for proceeding with a pivotal Phase III study.

<u>An 18 month Phase III trial (ADCS, Baxter) has started</u>

Immunotherapy pipeline

- Active amylopid vaccines: ACC-001, CAD106, Merck
- Passive approaches: bapineuzumab, solaneuzumab, Pfizer c-terminus, Genentech conformational antibodies

- And also: DNA amyloid vaccines, tau vaccines

Anti-aggregation rx: tramiprosate

- Phase II: reduction in CSF Abeta
- Phase III: negative
- Now marketed as a nutriceutical!

Other amyloid reduction strategies

- DHA (ADCS, Martek)
- RAGE inhibitor (ADCS, TTP, Pfizer)

Other amyloid-reducing strategies: DHA

- long chain omega-3 fatty acid
- major component of neuronal membrane phospholipids
- reduced in AD
- DHA supplementation reduces amyloid accumulation in Tg2576 mice

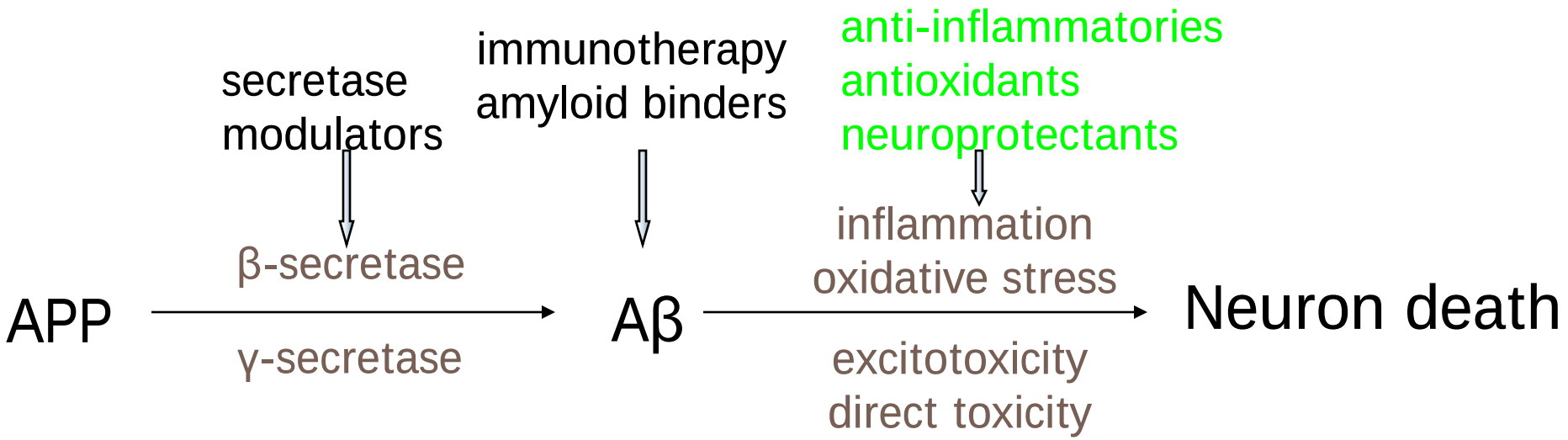
ADCS trial nearly done, results at ICAD

Other amyloid-reducing strategies: RAGE inhibitors

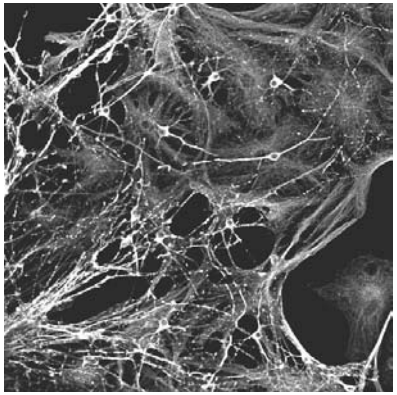
- RAGE=receptor for advanced glycation end-products
- Involved in Aβ transport and toxicity
- RAGE inhibitors reduce amyloid accumulation and improve cognition in transgenic mice
- A RAGE inhibitor is now in Phase II trial for diabetes

A Phase II trial of a RAGE inhibitor in AD is now under way (ADCS, Pfizer)

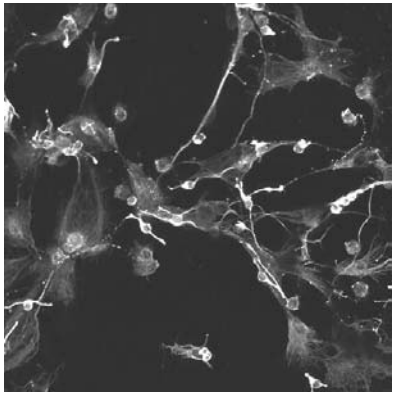
Disease-Modifying Strategies



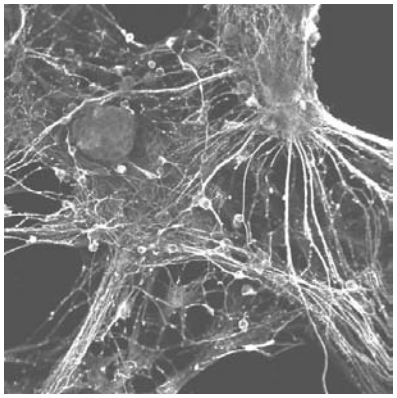
NAP (AL-108) protects the neuronal microtubular network



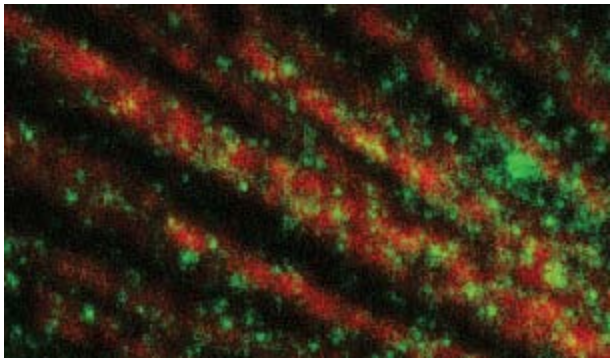
Control



Microtubule toxicity



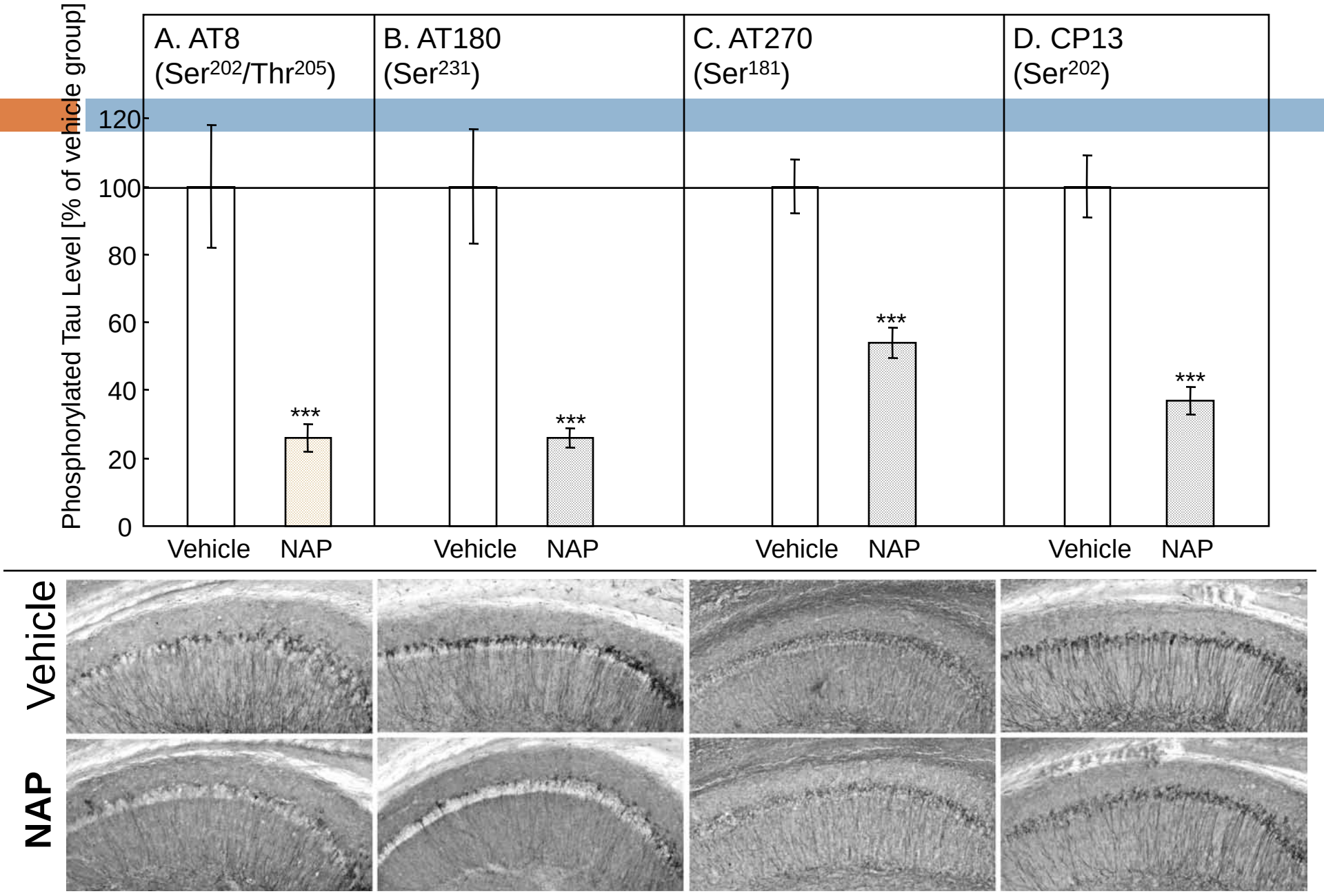
Microtubule toxicity + AL-108



Microtubule decoration with anti-NAP antibodies

J Biol Chem. 2004 Jul 2;279(27):28531-8. Neuron Glia Biology, 2005

NAP reduced pTau level in crude brain homogenate



NAP: current status

- Phase I, II studies conducted by Allon Therapeutics (very encouraging)
- IV NAP under development for post-CABG cognitive impairment
- NIMH-funded study of intranasal NAP for cognitive impairment in schizophrenia
- FTLD study at UCSF
- AD: Allon seeking partner

NGF Gene Delivery for AD

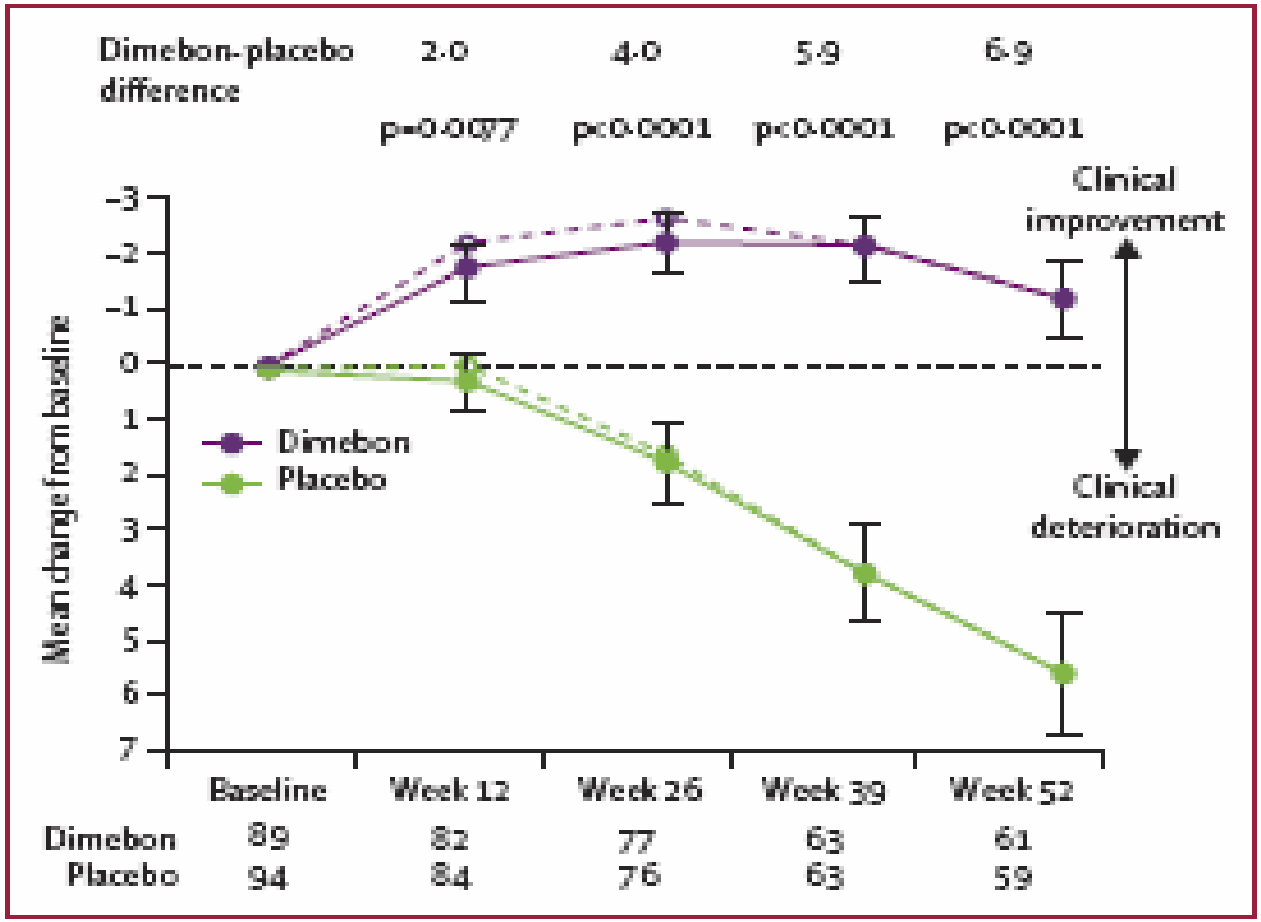
- Mark Tuszynski, UCSD: encouraging work in primates
- Phase I: UCSD (ex vivo, in vivo), Rush (in vivo), sponsored by Ceregene
- Phase II: NIA has funded a randomized, sham-surgery controlled, multicenter trial of NGF gene delivery in AD; start-up under way

Other neuroprotection studies, pipeline

- Lithium, valproic acid
- Other GSK-3 inhibitors
- Anti-inflammatory drugs

- Resveratrol (ADCS trial next year)

12 month Dimebon trial



Doody et al, Lancet, 2008

AD Trial Design Issues

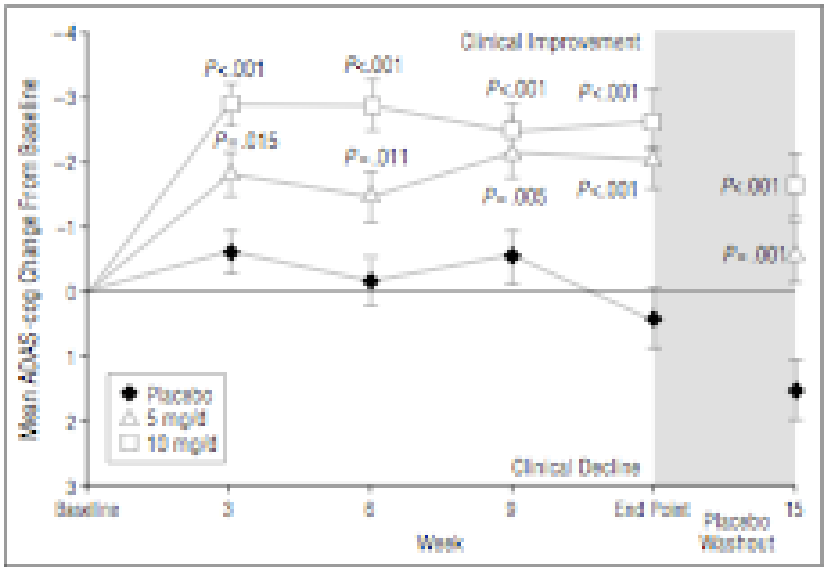
FDA Guidelines for AD Trials

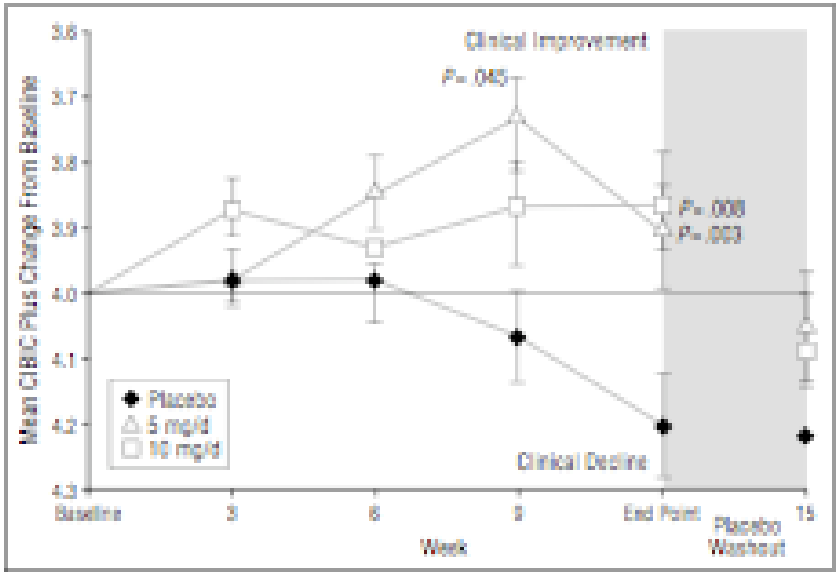
- Co-Primary outcome measures
- Memory/cognition test, plus global or functional measure

- ADAS-cog has worked well for cognitive enhancers in mild-moderate AD
- CIBIC-plus (CGIC) has worked well as a global
- CDR-SB, ADCS-ADL, DAD reasonable co-primaries for long trials

ADAScog change, CIBIC+ for assessment of cognitive enhancement

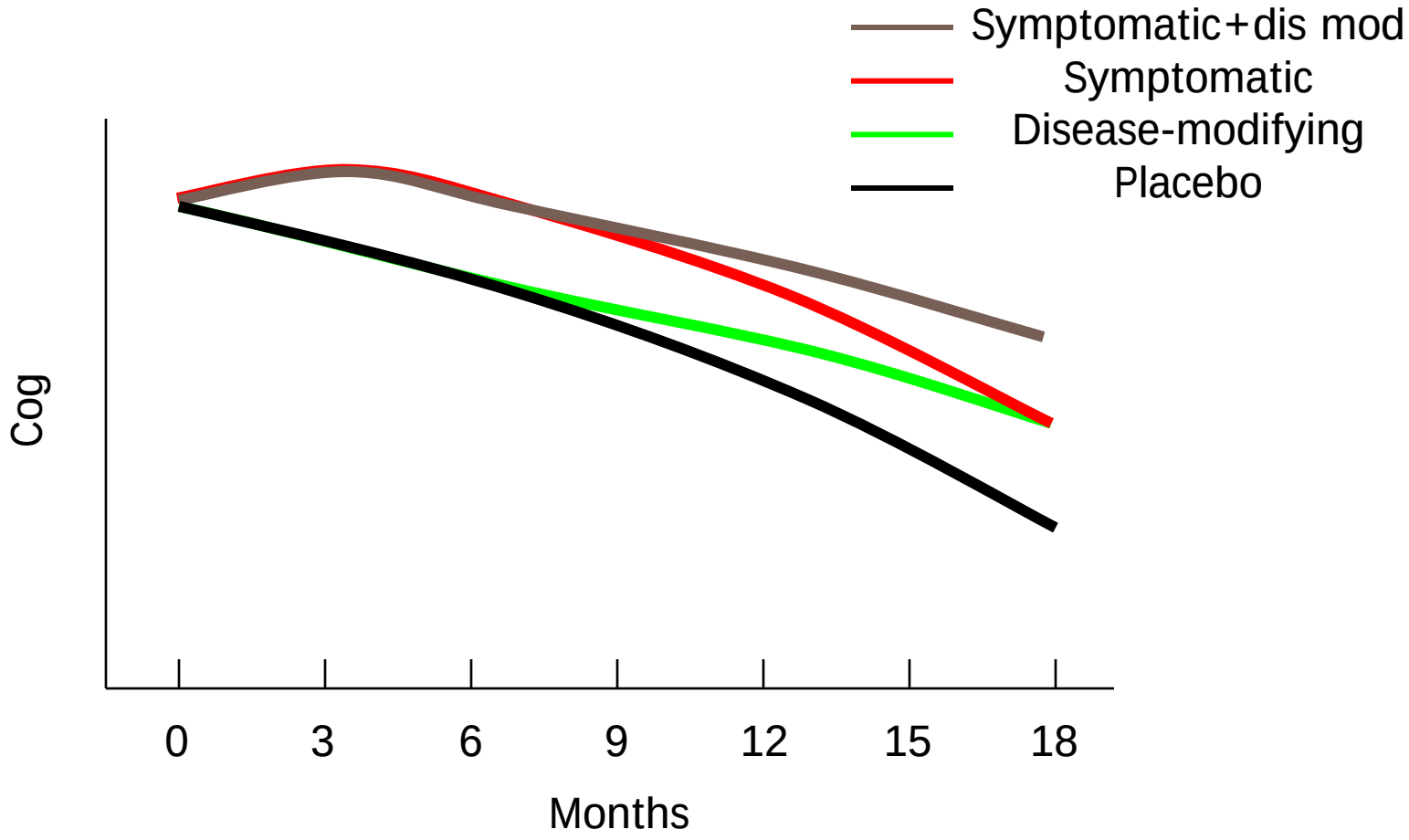
12 Week Phase II Donepezil Trial





Rogers et al, Arch Neurol, 1998

Cognitive Decline in AD Treatment Trials



Disease-Modifying Drug Development: Phase II problem

- No short-term benefit expected, rather change in slope of decline
- Placebo groups in mild AD studies don't decline in 6 months; placebo decline minimal in 12 months
- To see effect on slope, need hundreds or thousands of subjects followed for at least 18 months

- Cannot see proof of efficacy in Phase II-type trial (in contrast to currently approved drugs)

Phase II

- Aim for hints of clinical efficacy (tarenflurbil, bapineuzumab)
- Focus on biomarkers (tramiprosate, IgIV, semagacestat and Lilly monoclonal antibody)
- Or both
- Or neither: skip Phase II

Has the Amyloid Hypothesis Been Damaged?

- Tramiprosate
- Flurizan
- Holmes et al (Lancet paper on end-stage dementia despite amyloid plaque removel)

- Not really?

- We must recognize that in the absence of an efficacy signal in Phase II, a Phase III trial of a disease-modifying treatment is high risk (10-20% chance of success?)

- Nonetheless, the potential gains may justify this risk

Moving forward

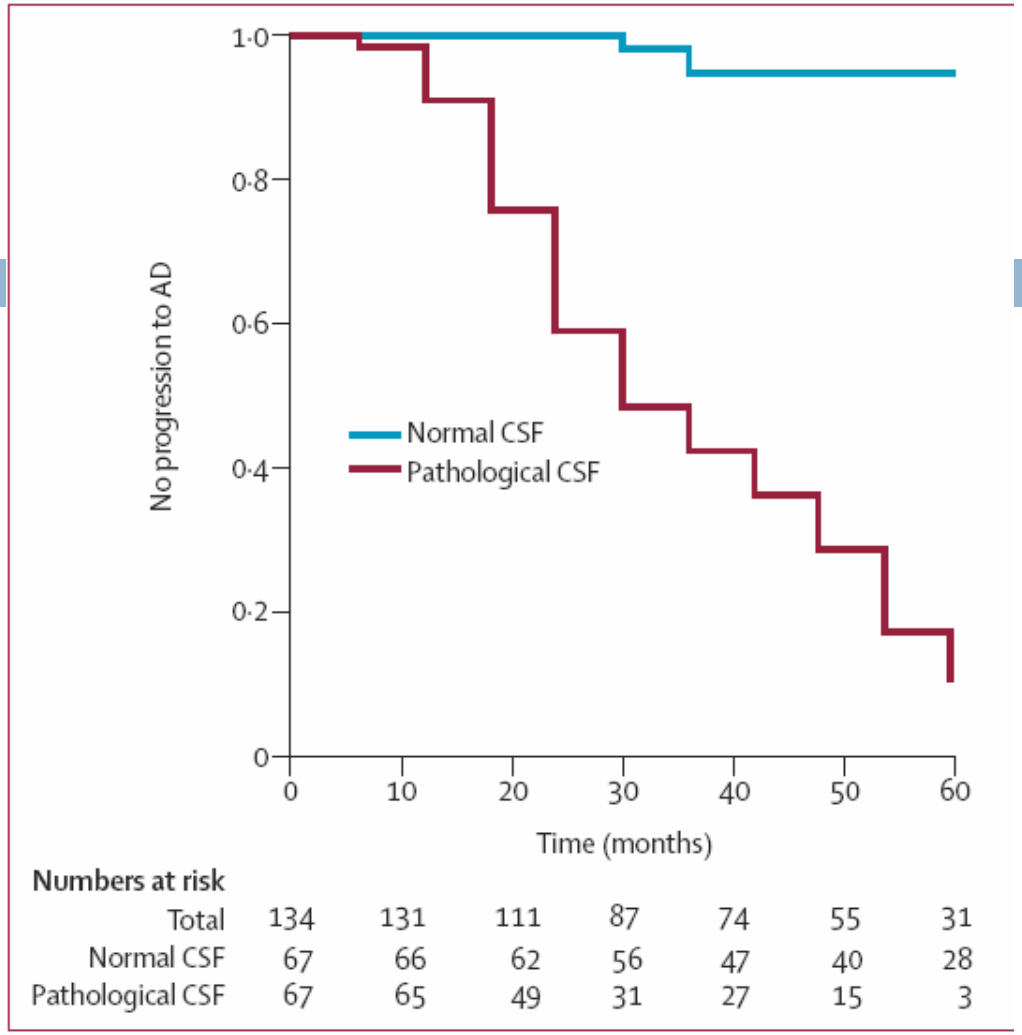
- Biomarkers
- Improvements to measures
- Recruitment and training of sites, PIs, coordinators, raters
- Recruitment/retention of participants

- Aiming for earlier intervention in the neurobiological cascade

Biochemical markers

ADNI baseline CSF samples – general statistics

	AD (n=100)			CONTROL (n=114)			MCI (n=196)		
	Mean±SD	95% CI	Median	Mean±SD	95% CI	Median	Mean±SD	95% CI	Median
Tau	121.6±57.6	110.2 - 133.0	110.5	69.7±30.4	64.0 - 75.3	61.0	103.5±60.8	95.0 - 112.1	87.0
$A\beta_{1-42}$	143.5±41.0	135.4 - 151.6	137.5	205.6±55.1	195.4 - 215.8	217.0	163.2±54.8	155.4 - 170.9	145.5
P-Tau $_{181P}$	41.7±20.0	37.7 - 45.7	36.0	24.9±14.6	22.2 - 27.6	20.0	35.8±18.2	33.3 - 38.4	32.0
$Tau/A\beta_{1-42}$	0.92±0.48	0.82 - 1.0	0.86	0.39±0.27	0.34 - 0.43	0.31	0.75±0.61	0.67 - 0.84	0.63
$P\text{-}Tau_{181P}/A\beta_{1-42}$	0.32±0.19	0.28 - 0.36	0.29	0.14±0.13	0.12 - 0.17	0.10	0.26±0.18	0.24 - 0.29	0.24



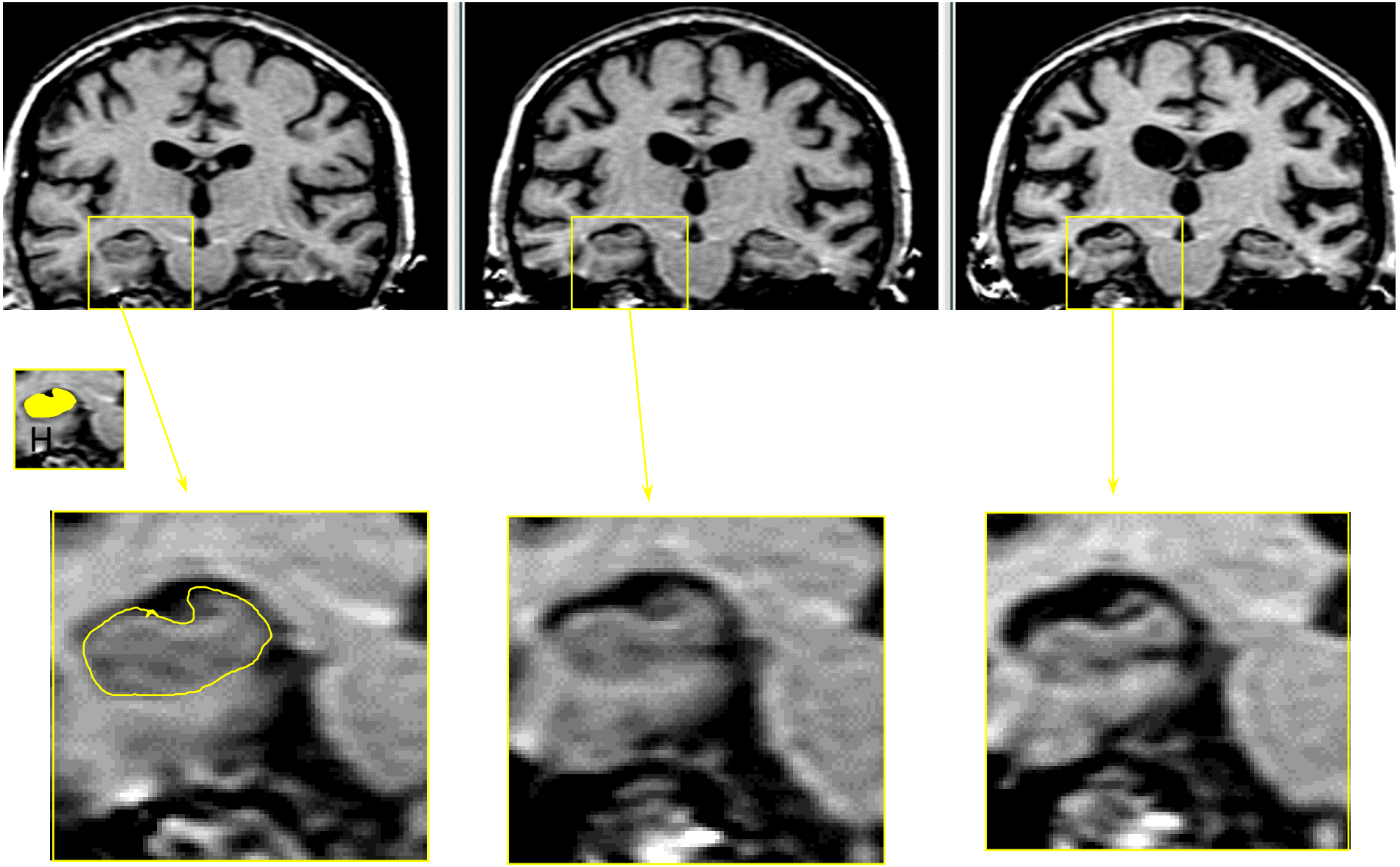
Numbers at risk

Total	134	131	111	87	74	55	31
Normal CSF	67	66	62	56	47	40	28
Pathological CSF	67	65	49	31	27	15	3

***Figure 2*: Kaplan-Meier estimates of the rate of progression to Alzheimer's disease in patients with MCI who have either normal CSF or pathological CSF at baseline**

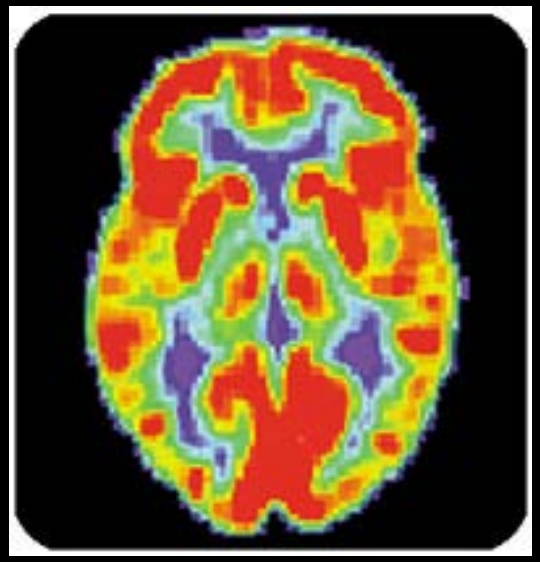
Numbers at risk are the number of patients with MCI at each time point who had not developed any type of dementia and for whom clinical follow-up was still ongoing. Cut-off values for pathological CSF were >350 ng/L for T-tau and <530 ng/L for Aβ42. The incidence of Alzheimer's disease in patients with MCI who had pathological CSF (n=67) was 27% per year compared with 1% per year in patients with normal CSF (n=67).

Neuroimaging markers

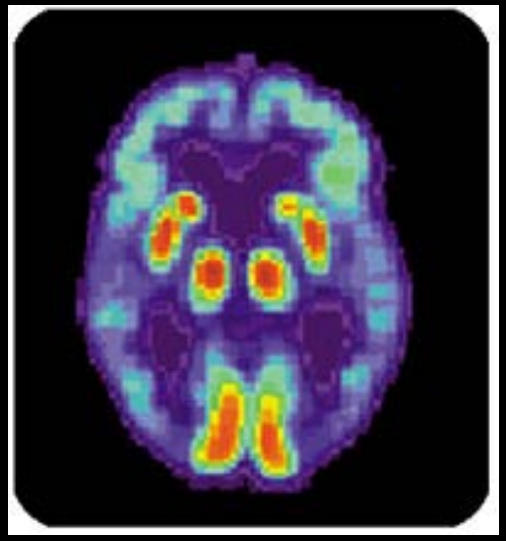


Serial coronal MRI of an individual with initially mild AD

PET Scan of
Normal Brain



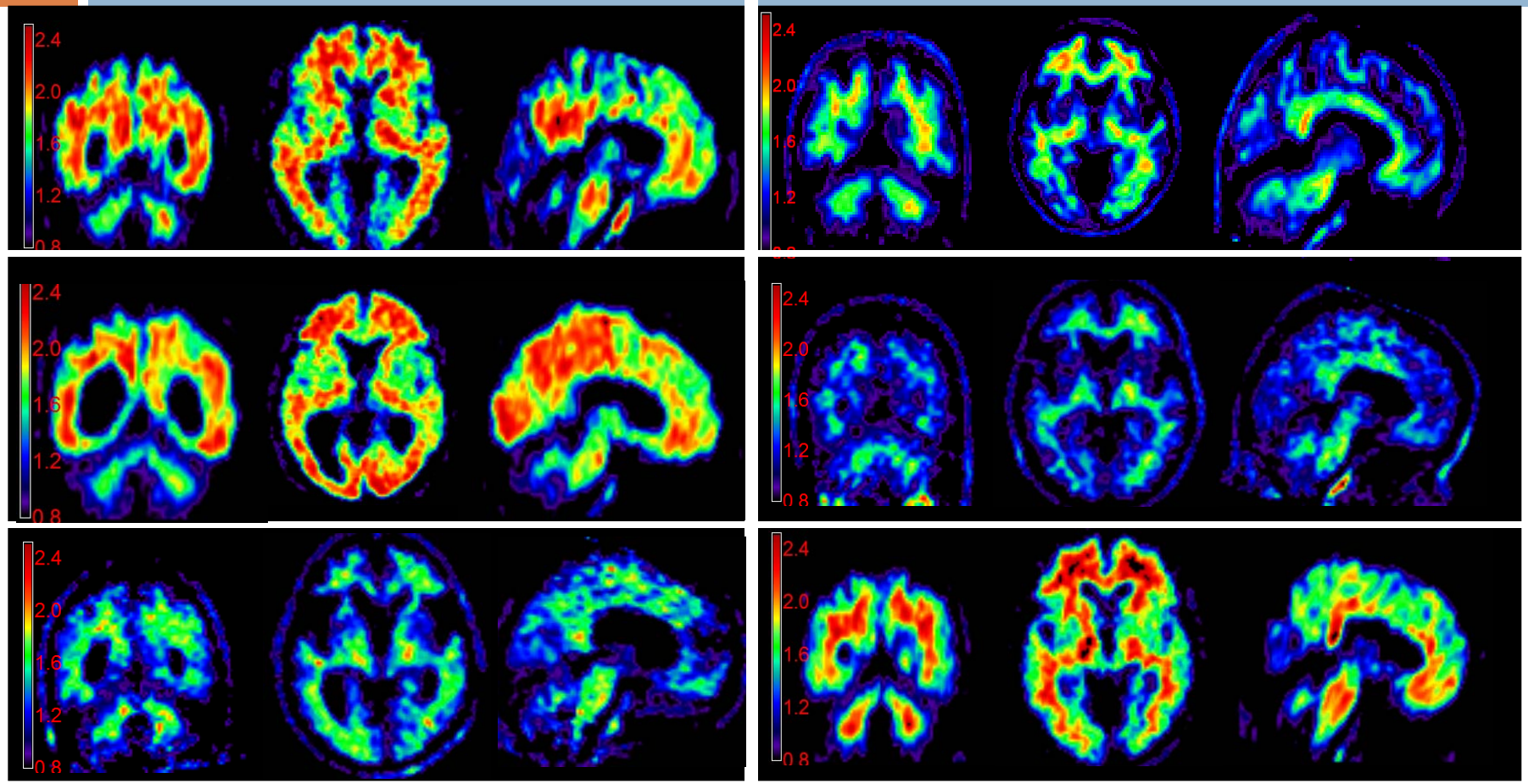
PET Scan of Alzheimer's
Disease Brain



Typical Imaging Results with ^{18}F-AV-45

Alzheimer's Patients

Healthy Elderly Controls



One "AD" with control-like amyloid levels had symptoms suggestive of Parkinson's

Some healthy controls had AD-like levels of amyloid

Future: A Surrogate Marker

- Pathology begins years/decades before dementia
- Disease-modifying treatment likely most effective early
- Impossible to use clinical outcomes in an early prevention trial (too long to wait)

Possible surrogates

- CSF Abeta42 (or tau, p-tau)
- Amyloid neuroimaging
- Brain volume loss
- Neuropsych measures

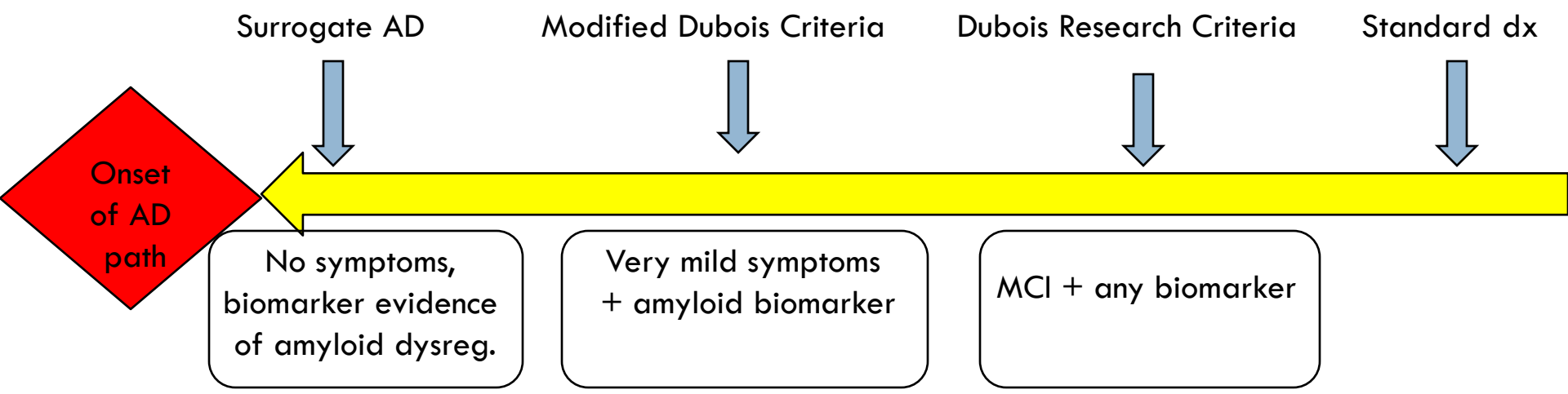
What we need to do to establish an AD surrogate marker

- Strengthen link in mild AD
  - Continue to build evidence linking potential surrogate to AD diagnosis and progression
  - Show that in mild AD or MCI, with more than one agent, drug impact on clinical measures is associated with drug impact on potential surrogate
  - Establish link between potential surrogate in asymptomatic individuals and later clinical disease
- Strategize with regulators

Summary of trial design issues

- Disease-modifying therapy likely to be modestly beneficial in mild AD
- We are reaching consensus on development/regulatory pathways targeting milder disease (even asymptomatic)
- Ultimately, we will screen/diagnosis AD neurobiology using biomarkers (eg amyloid imaging)
- Very early treatment will maximize benefits

AD diagnosis marching leftward



Early AD Trial Issues

- Diagnosis
  - Extending diagnosis to pre-dementia stages
- Outcomes
  - Traditional outcomes will work in pre-dementia stage
  - Surrogates needed for asymptomatic stage
- Trial design: selection, duration, stratification, covariates
- Analysis plan

	Mild AD Trial	Early AD Trial	Very Early AD Trial
Cognitive Status	Mild dementia	Mild cognitive impairment	Cognitively normal
Clinical Dementia Rating global score	0.5-1	0.5	0
MMSE range	16-26	25-30	28-30
Biomarker for subject selection	none	Amyloid imaging and/or CSF abeta42	Amyloid imaging and/or CSF abeta42
Biomarker for subject stratification	None or APOE genotype	APOE genotype	APOE genotype
Primary cognitive outcome measure	ADAScog11	ADAScog12 (includes delayed recall)	Sensitive memory and/or exec. function measure
Primary global/functional outcome measure	CDR-SB	CDR-SB	none
Analysis covariates	Baseline cognition and regional brain volume	Baseline cognition and regional brain volume	Regional brain volume
Biomarker outcome	Regional brain atrophy	Regional brain atrophy	Regional brain atrophy and/or amyloid measure (as surrogate endpoint)
Duration of treatment	18 months	24 months	24-36 months
Primary analysis	Change score or slope of co-primaries: ADAScog11, CDR-SB	Change score or slope of co-primaries: ADAScog12, CDR-SB	Regional brain atrophy rate and cognitive decline

Acknowledgments

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