ADVANCES IN DEMENTIA

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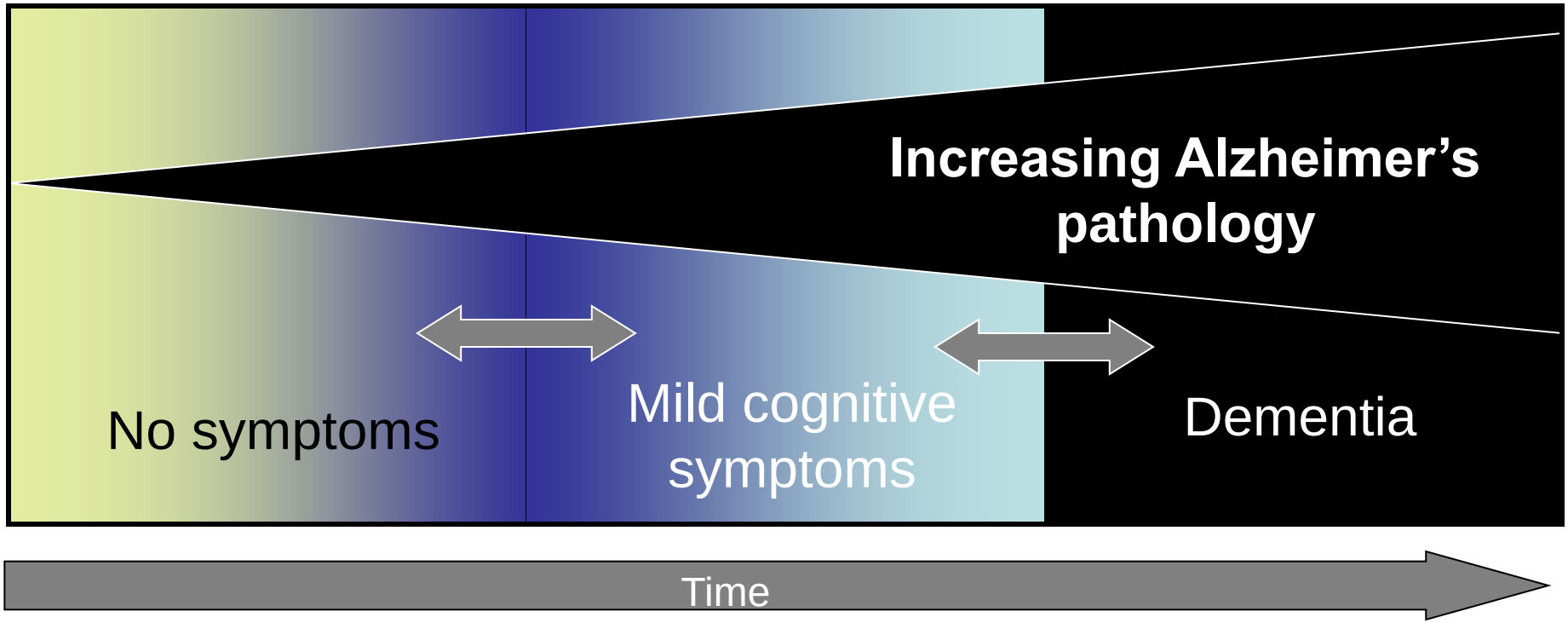
Conflicts of interest

- Clinical trial support from Lilly, Roche, TauRx, Lundbeck
- DSMB member for ADCS, ATRI, API, Eisai
- Scientific advisor for Alzheon, Boehringer-Ingelheim, Kalgene, Lilly, Lundbeck, Novartis, Schwabe, TauRx.

OUTLINE

- Earlier and more accurate diagnosis of AD
- Failure of new drugs at the dementia stage
- Having a second look at old drugs
- Prevention strategies are popular
- New treatment hypothesis: neuroinflammation
- Canadian efforts under way

STAGES OF ALZHEIMER'S DISEASE

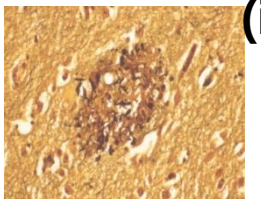


PATHOLOGIES ASSOCIATED WITH AD

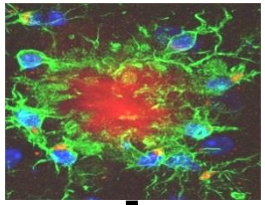
AGE

30
40
50
60
70
80
90
100

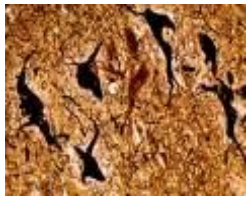
β-amyloid Deposition (plaques)



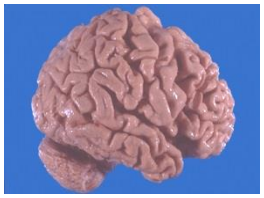
Microglial Activation (inflammation)



NFTs (tangles)



Neuronal Loss (atrophy)

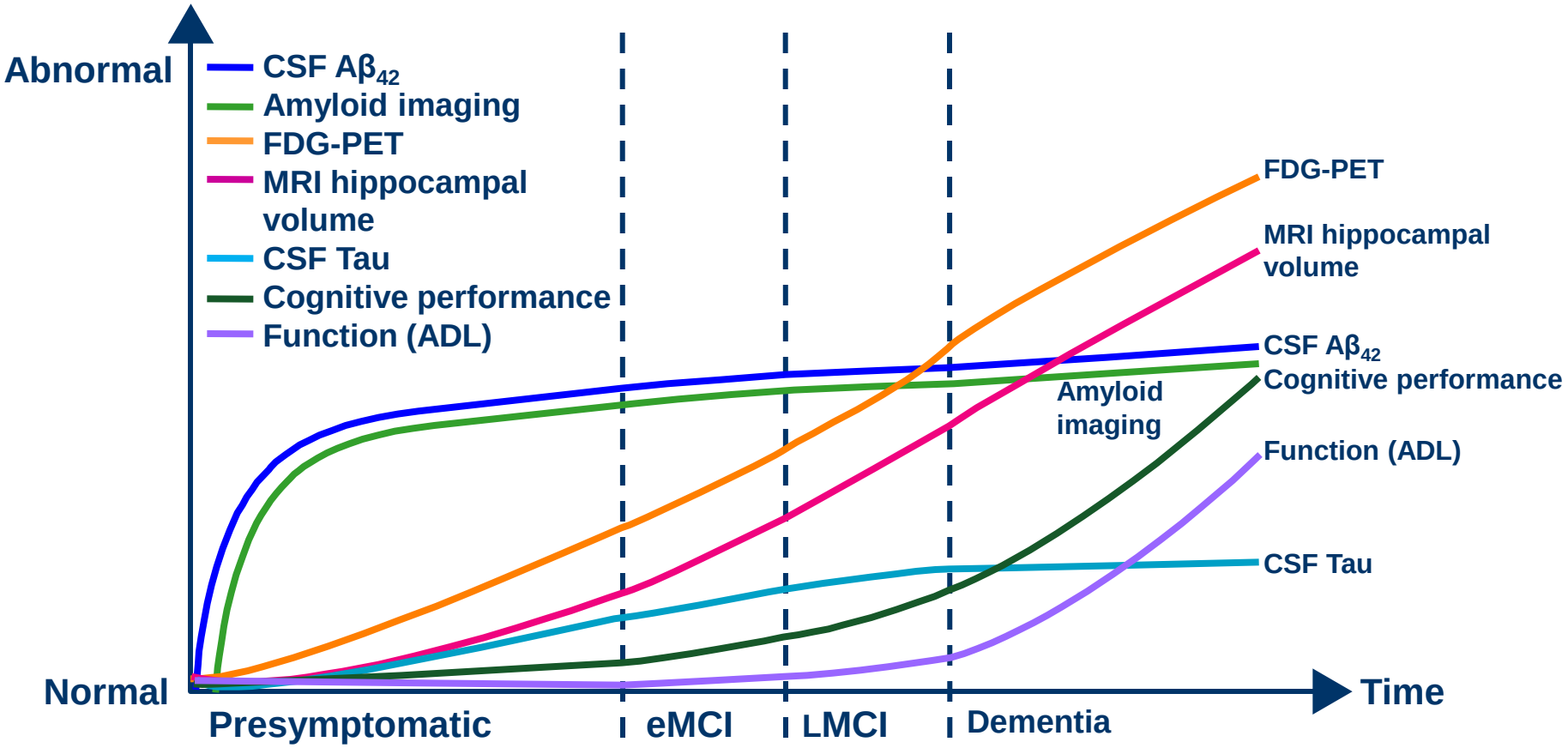


Symptoms

WHAT IS ALZHEIMER'S DISEASE? BIOMARKERS

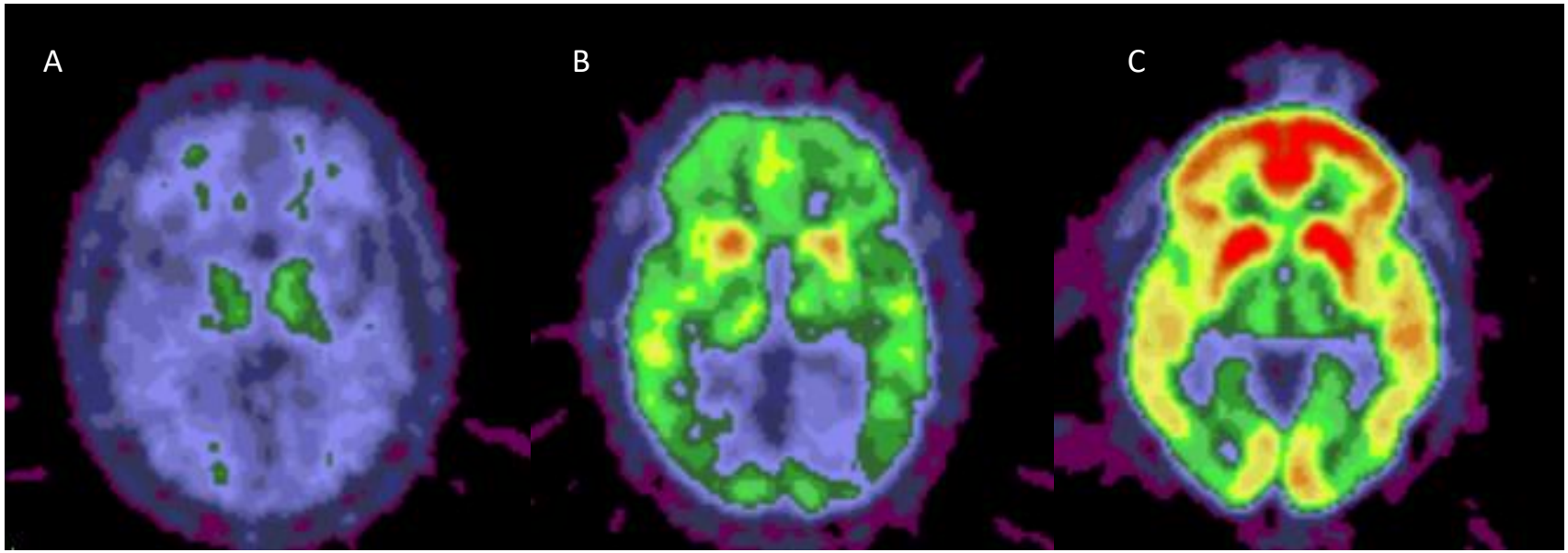
- *Pathophysiology markers* include amyloid deposition seen on PET scans and lower CSF levels of ß42
- *Neurodegeneration markers* include brain atrophy on MRI, hypometabolism on PET-FDG, higher CSF levels of phospho-tau, spread of tau pathology on PET

AD PROGRESSION USING BIOMARKERS

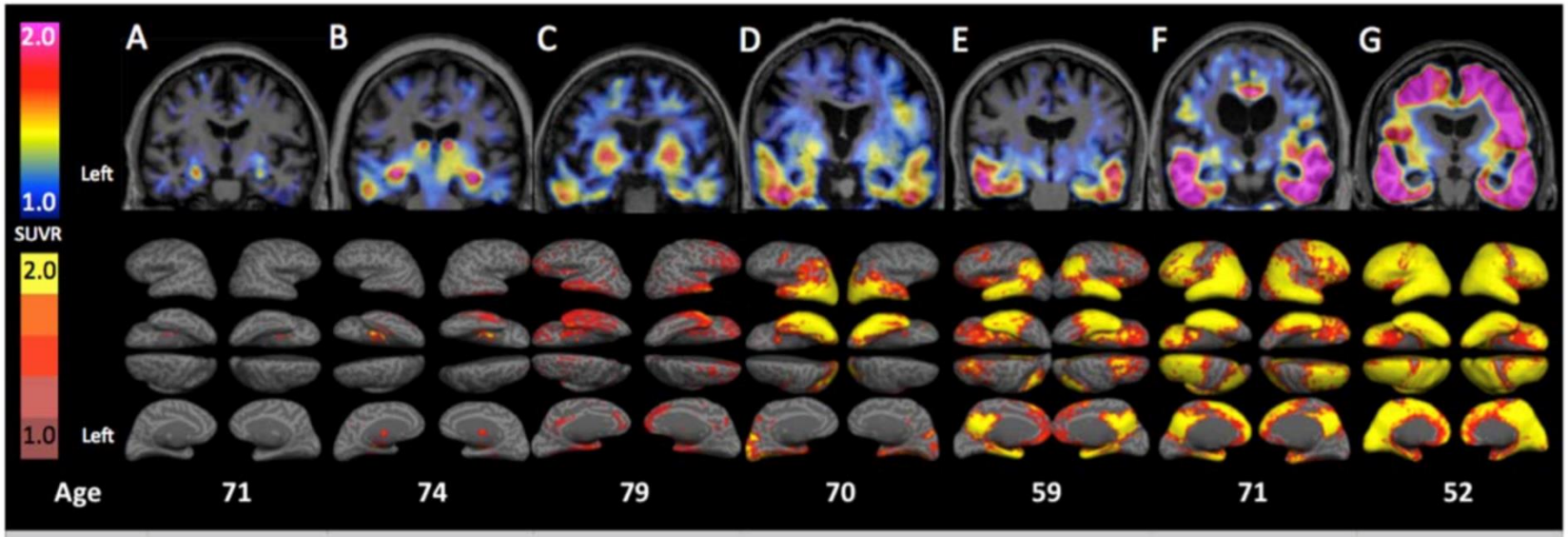


Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

AMYLOID PET IN MUTATION CARRIERS



Courtesy of Mark Mintun and Randy Bateman



MMSE	30	30	29	27	26	23	11
PiB (DVR)	Low (1.0)	High (1.2)	High (1.8)	High (1.5)	High (1.7)	High (1.5)	High (1.5)
Dx	CN	CN	CN	MCI	MCI	AD	AD
PET Braak	0, I-II	III-IV	III-IV	III-IV	III-IV	V-VI	V-VI

FIGURE 1: Cortical patterns of 18F T807 binding. Coronal 18F T807 positron emission tomographic (PET) images (top row) and whole-brain surface renderings of standardized uptake value ratio (SUVR; cerebellar reference; second row) from 3 clinically normal (CN) and 4 impaired (2 mild cognitive impairment [MCI] and 2 mild Alzheimer dementia [AD] dementia) participants. Top: (A) A 71-year-old CN subject with low amyloid b (Ab) by Pittsburgh compound B (PiB) PET (mean cortical distribution vol- ume ratio [DVR]51.0) had low, nonspecific 18F T807 binding in cortex, consistent with a Braak stage less than III/IV. (B) A 74- year-old CN subject with high Ab (DVR51.2) with 18F T807 binding in inferior temporal cortex, left>right, consistent with Braak stage III/IV. (C) A 79-year-old CN subject with high Ab (DVR 5 1.8) had binding in inferior temporal neocortex, consistent with Braak stage of III/IV. B and C show focally intense subcortical uptake that is likely due to off-target binding (see Discus- sion). (D–G) Cognitively impaired participants all with high Ab and with successively greater levels of cortical 18F T807 binding successively involving temporal, parietal, frontal, and occipital cortices. Bottom: 18F T807 SUVR calculated at vertices (see Sub- jects and Methods) indicating the extent of cortical binding, with left hemisphere views (lateral, inferior, superior, medial) at left. The 52-year-old AD dementia patient (G) showed confluent 18F T807 binding that is nearly pancortical, sparing only por- tions of primary cortex and consistent with Braak stage V/VI. Dx5classification; MMSE5Mini-Mental State Examination; PET Braak 5 estimate of Braak stages based on the anatomic pattern of T807 binding assessed visually and quantitatively in regions and full volume data.

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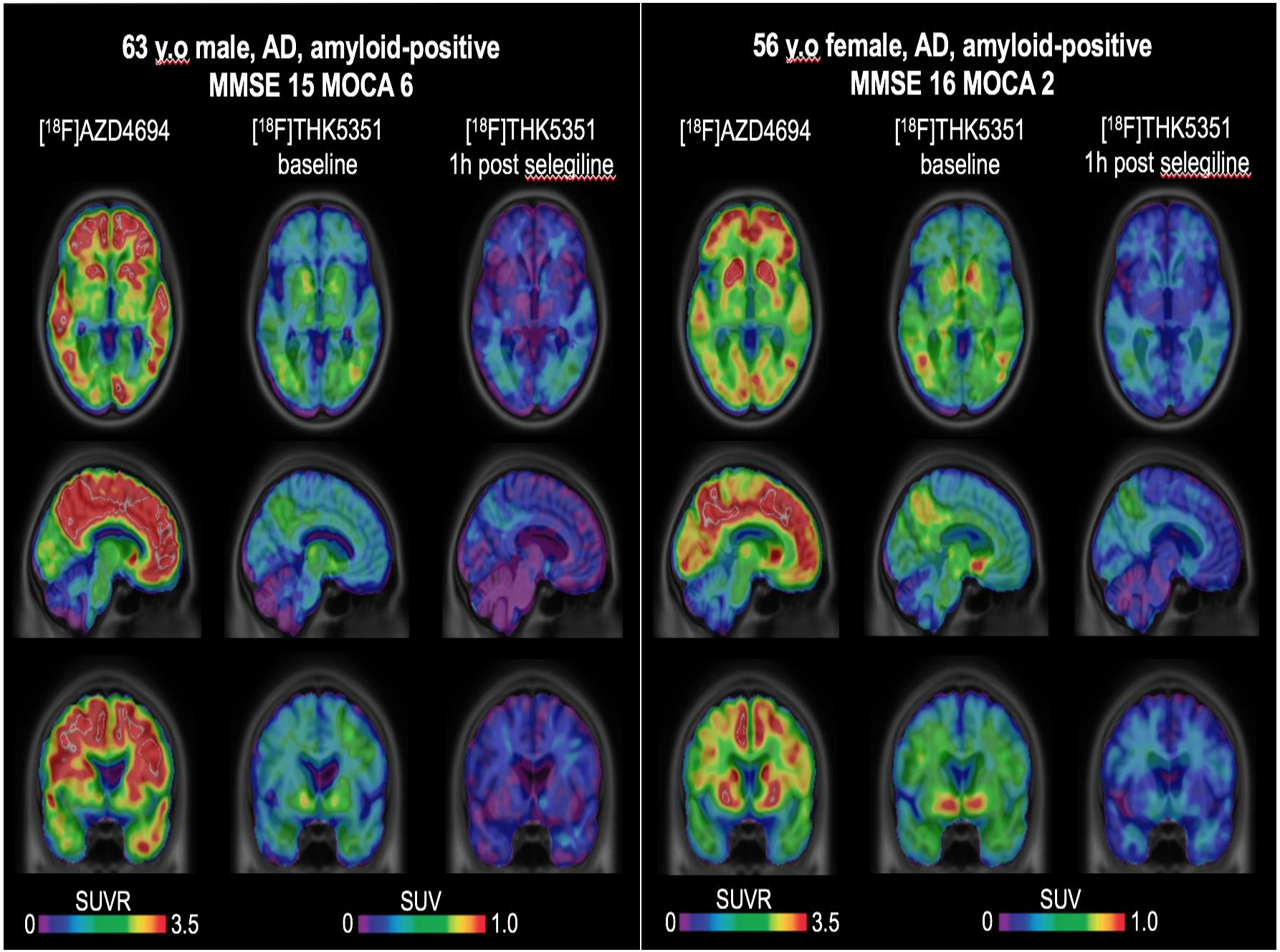

Ng et al; Alzheimer's Research & Therapy 2017

In summary...

- Biomarkers of AD pathology are essential tools for research, but are not ready for use in clinical practice outside very specialized centers
- There is still uncertainty about the specificity of Tau ligands, since MAO-B inhibition reduces the apparent tau binding by 40%

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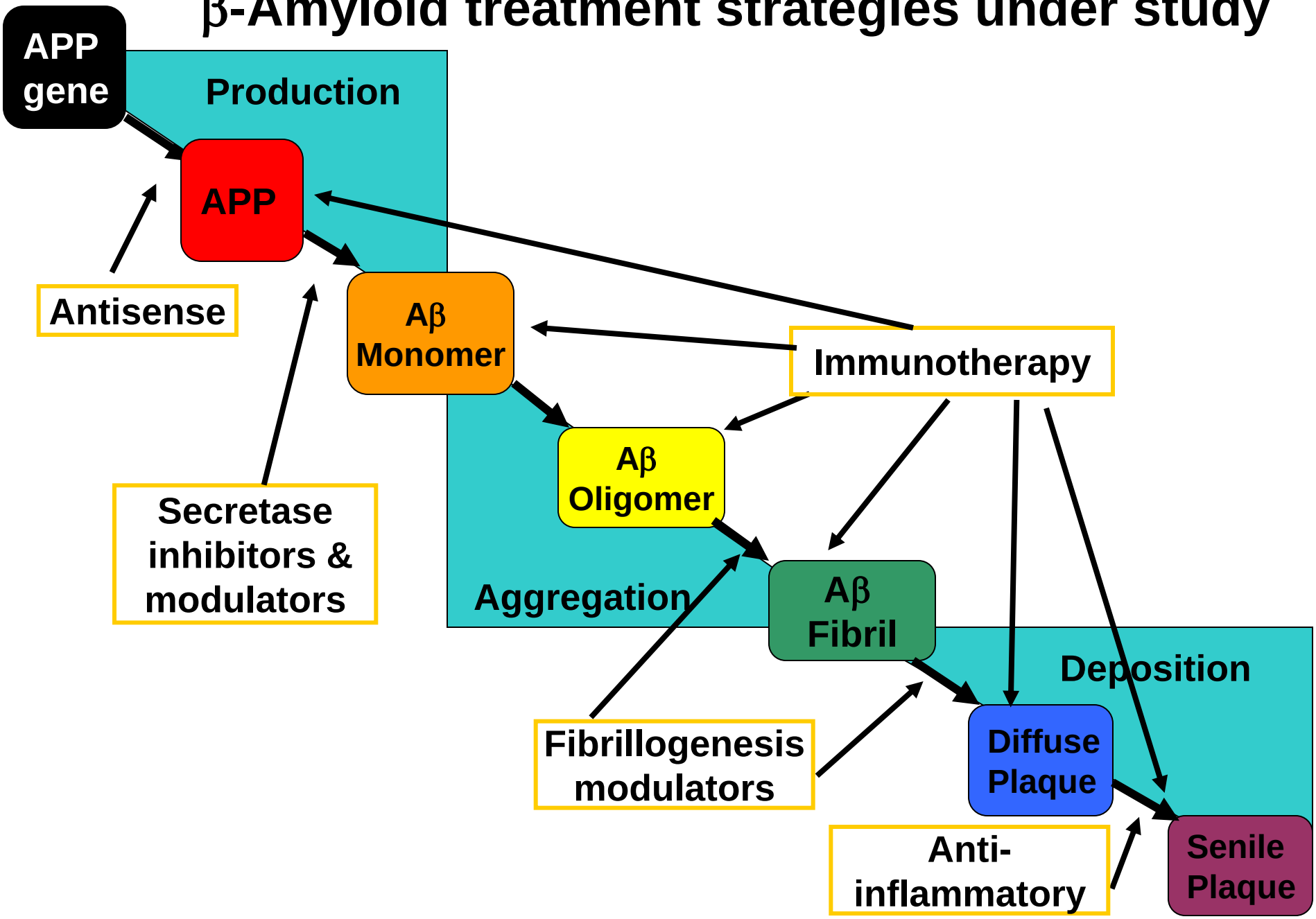
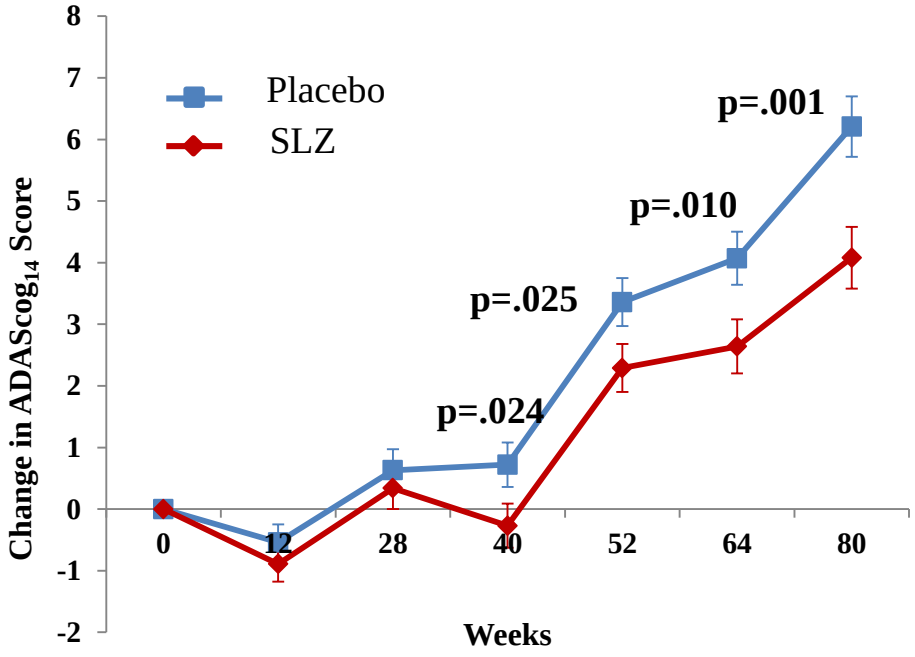
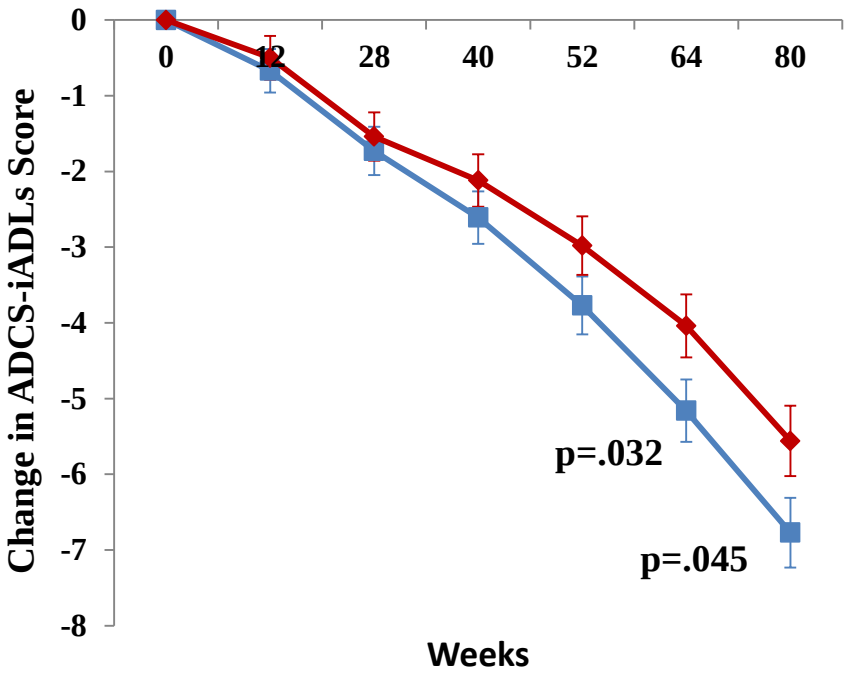
β-Amyloid treatment strategies under study



Pooled Mild AD Patients: EXP1 + EXP2





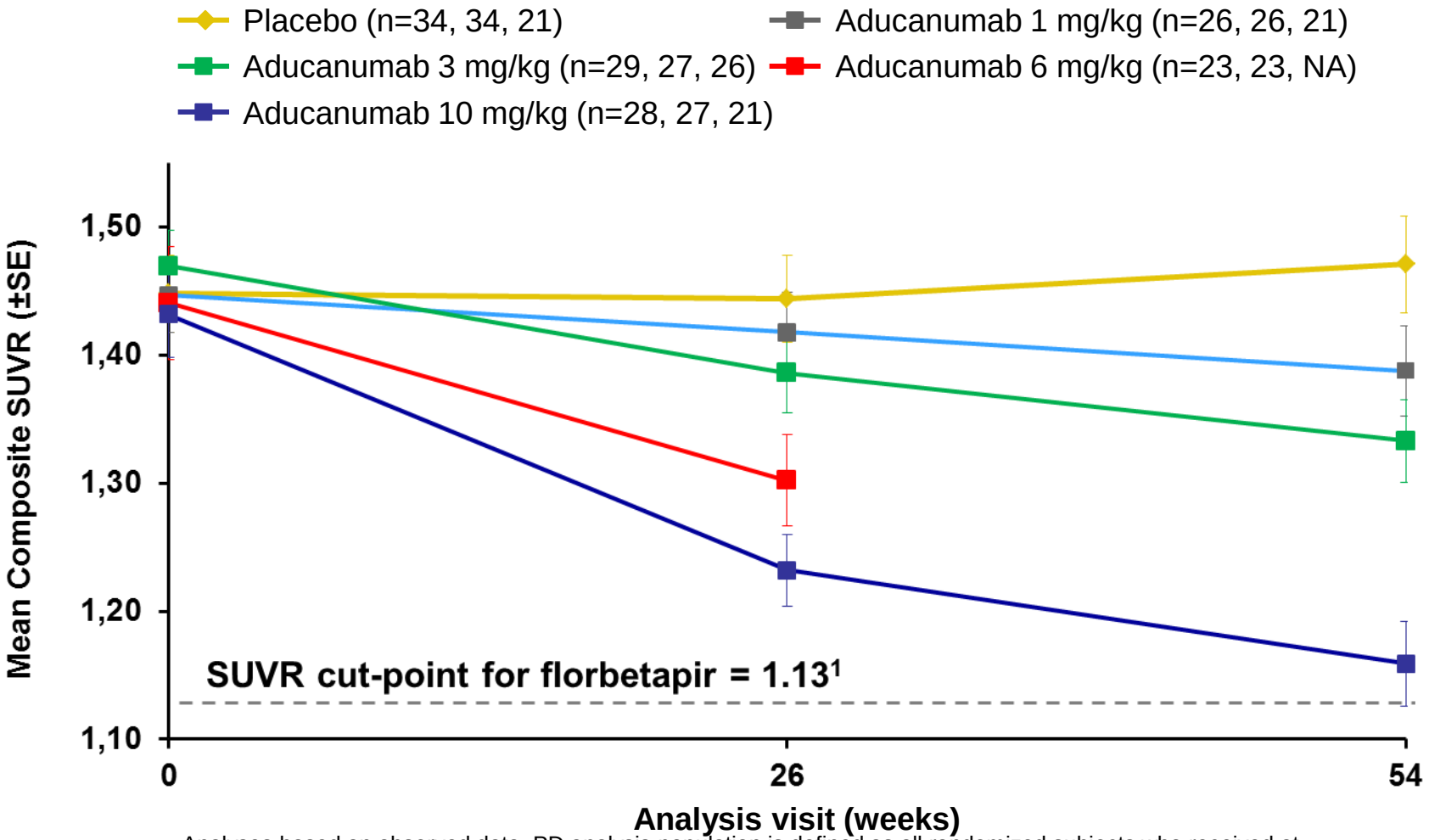
ADAS-Cog$_{14}$: 34% slowing in cognitive decline at Week 80

ADCS-iADLs: 18% slowing in functional decline at Week 80

Negative Phase III Amyloid Study

- Solanezumab, in mild AD (still tested in familial early-onset AD, asymptomatic E4/4): is the dose to low, or given to late?

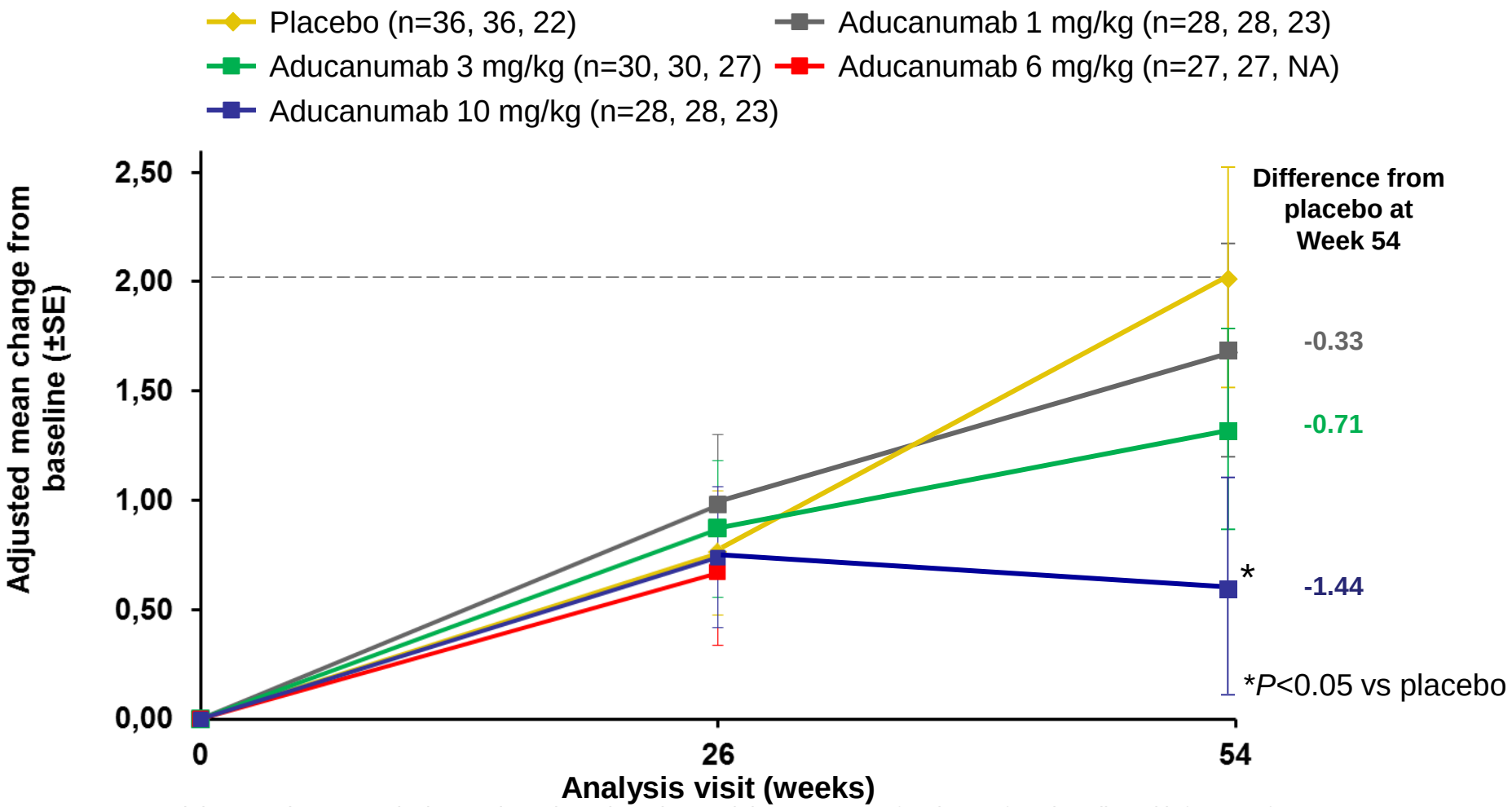
Amyloid Plaque Reduction with Aducanumab



Analyses based on observed data. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

1. Landau et al. J Nucl Med 2013

Aducanumab Effect on CDR-sb



CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

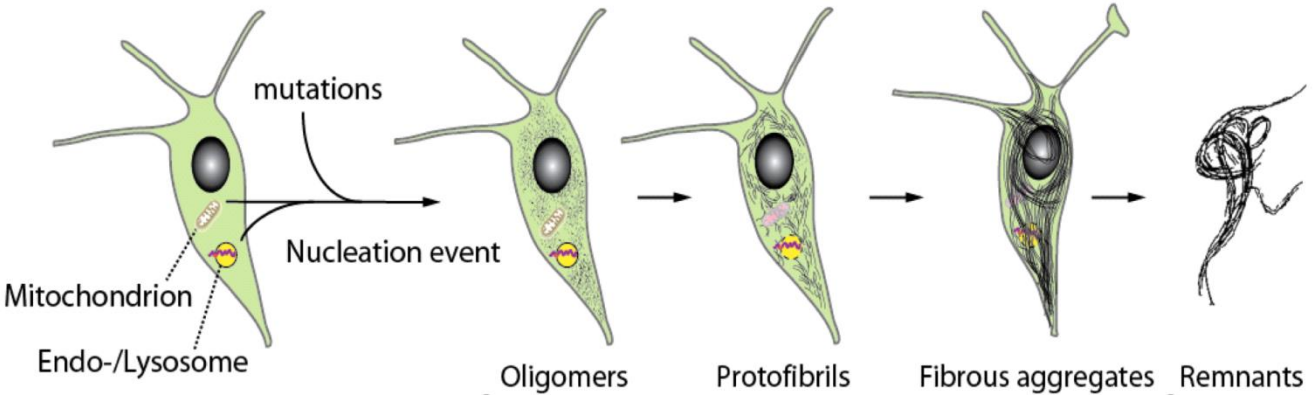
The tau protein pathology of Alzheimer's disease

Tau protein normally stabilised axonal microtubules in cortical neurones

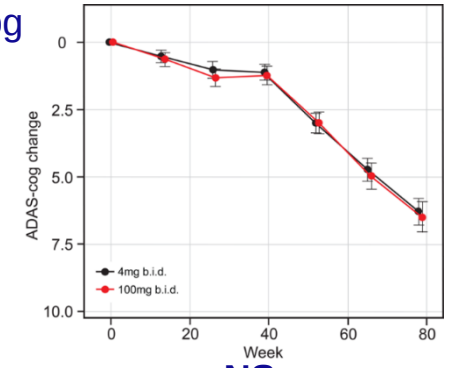
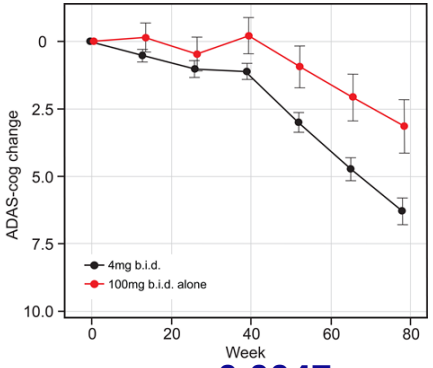
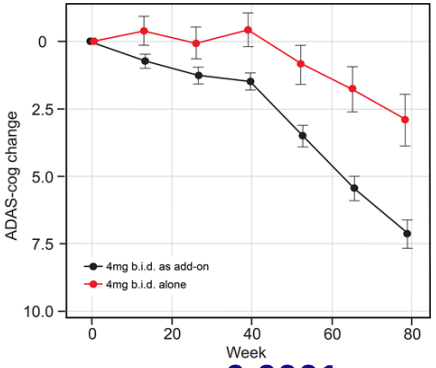
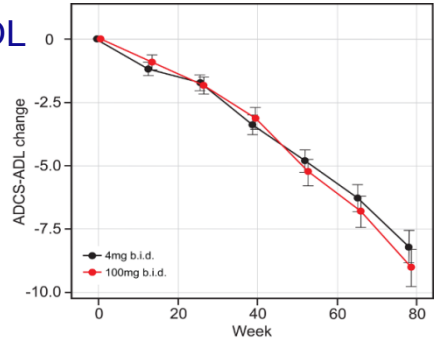
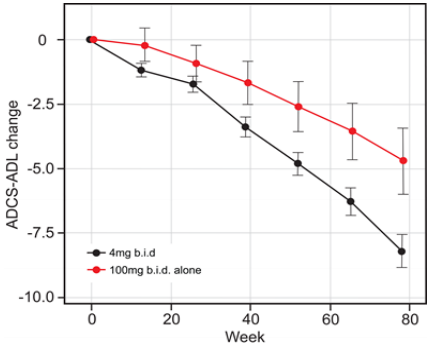
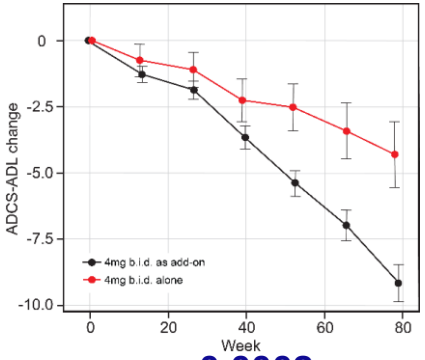
In AD, tau undergoes processing to form proteolytically stable aggregates and filaments making up the neurofibrillary tangles discovered by Alzheimer

These aggregates propagate prion-like throughout the brain

LMTM inhibits tau aggregation



Second Phase 3 LMTM study in mild AD compared 200 mg/day vs 8 mg/day in patients taking or not taking standard AD treatments
Primary analyses modified prior to database lock in view of results of first study

	As-randomised analysis 8 mg vs. 200 mg/day (exploratory in final Statistical Analysis Plan)	Primary analysis A: LMTM 100mg/day vs 8mg/day as randomised	Primary analysis B: LMTM 8mg/day as monotherapy vs 8mg/day as add-on
ADAS-cog			
	NS	**p = 0.0047**	**p < 0.0001**
ADCS-ADL			
	NS	**p = 0.0157**	**p = 0.0002**

- **Primary analyses confirmed same pattern of results as earlier study with strong control of type I error:**
  - **LMTM ineffective as add-on, but might be effective as monotherapy**
  - **Minority of patients received LMTM as monotherapy (155 overall, 22% of patients in trial)**
  - **No dose-response: 8mg/day might be as effective as 200mg/day**
  - **Primary comparisons not as randomised**

Negative Tau Phase III Studies

- The anti-aggregation tau agent LMTM, in mild to moderate AD, and in mild AD: is there a negative interaction with other AD drugs such as donepezil?

In summary…

- Anti-amyloid drugs need to show adequate `target engagement` (such as ARIA, changes in amyloid amounts using PET or CSF) in Phase II before going in Phase III
- Anti-tau treatments need further work – possible negative interaction with other drugs

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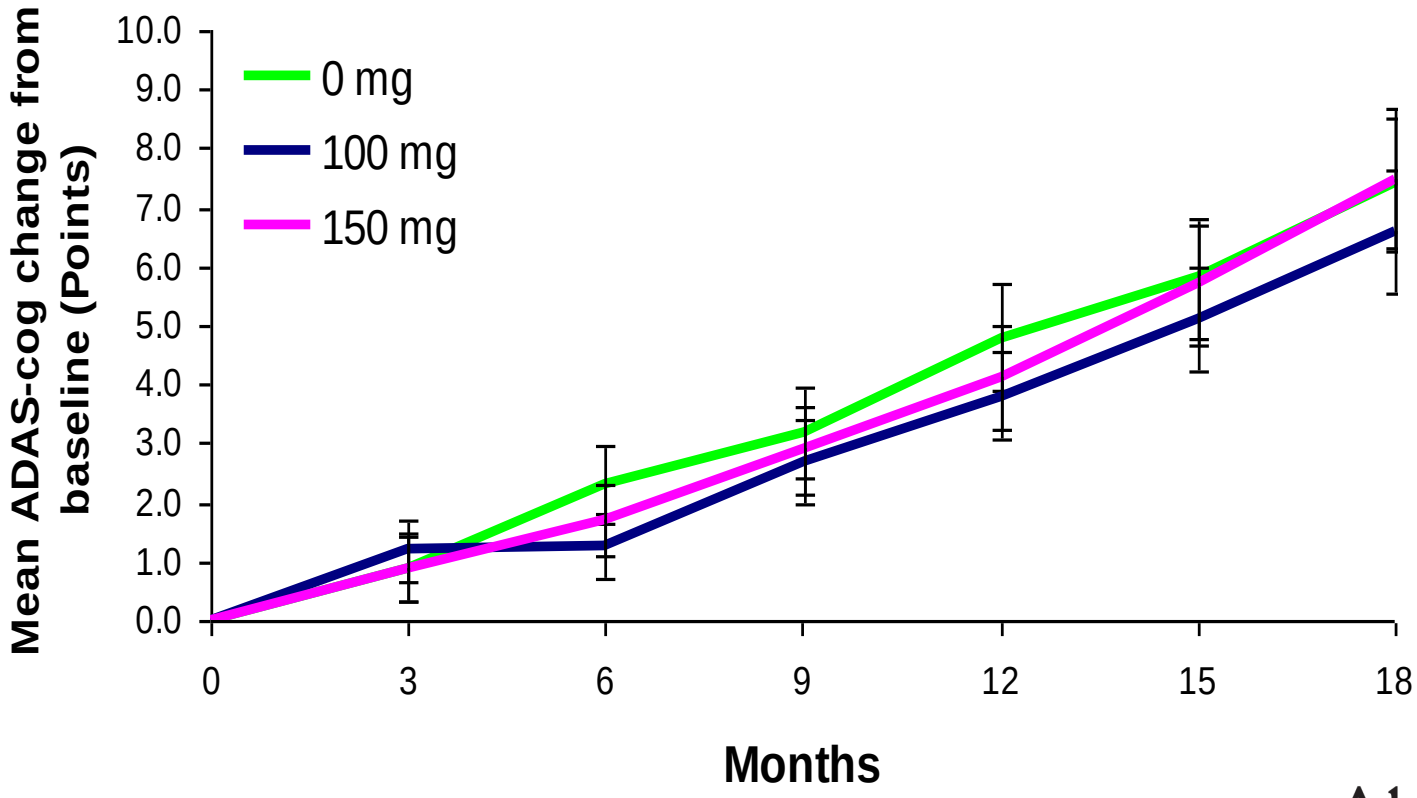
New look at old drugs - 1

- Tramiprosate was tested in mild to moderate AD: reanalysis showed a potential disease stabilization effect in E4/4 homozygous patients

Tramiprosate vs placebo, 18 months, cognition (ADAS-cog)

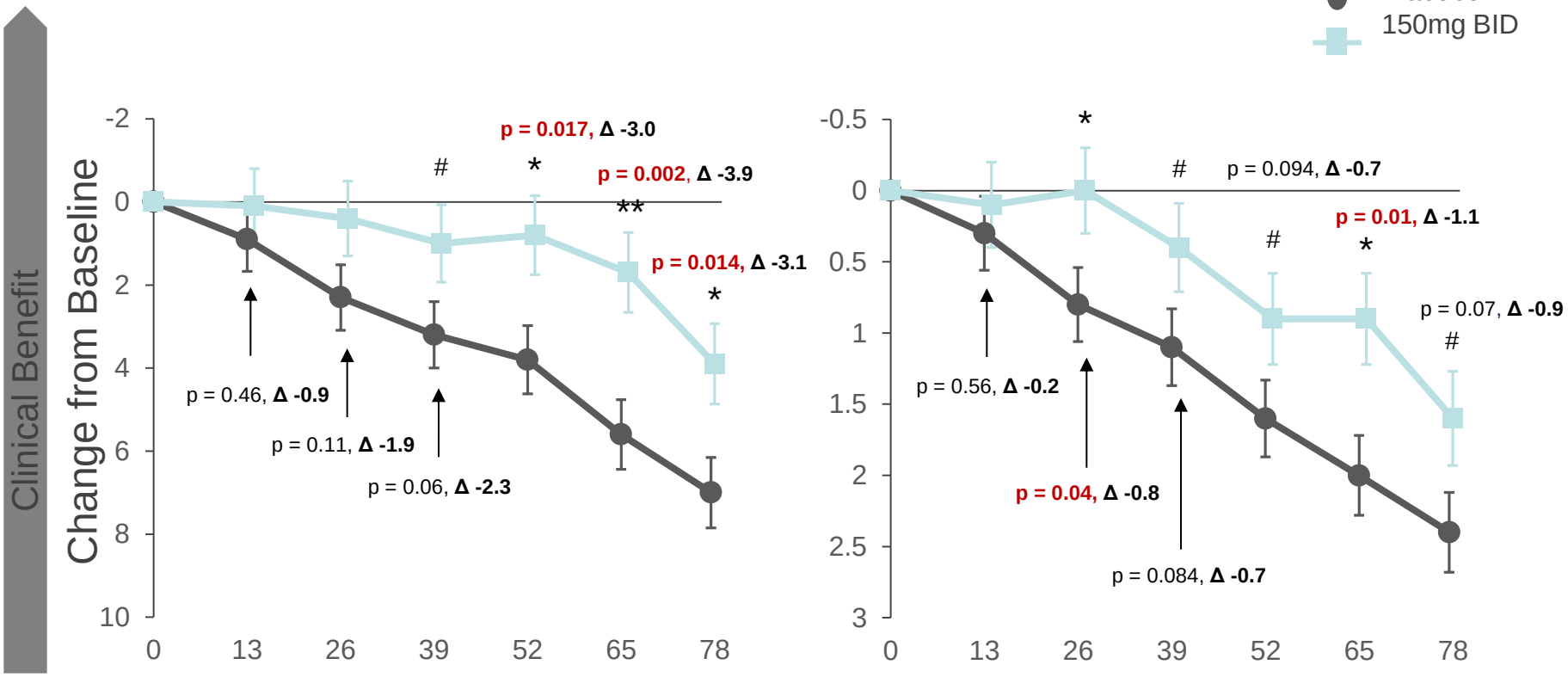


*Arithmetic mean +/- 95% CI

Alphase III Study

Effects in Mild to Moderate AD E4/4

North American Study: APOE4/4, Age ≤85 Years, MMSE 16-26



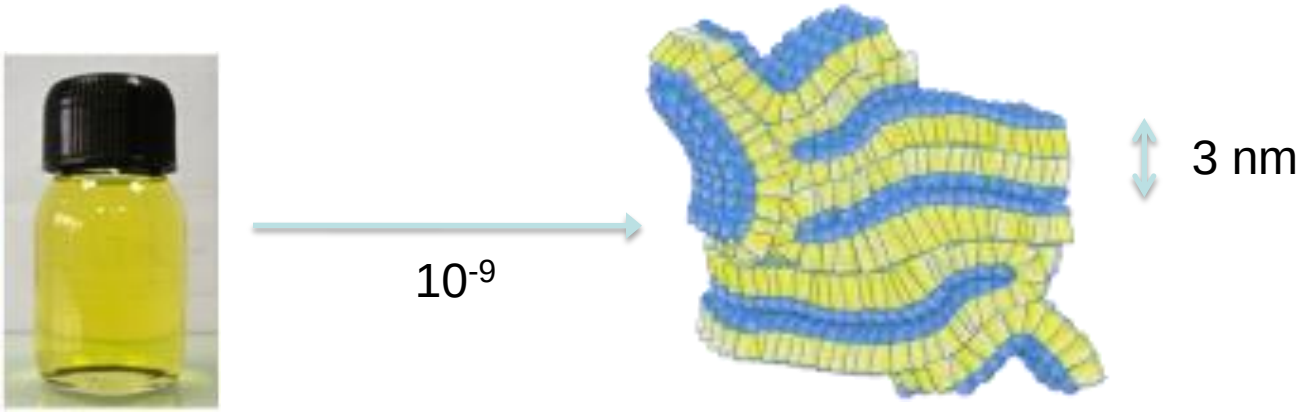
* p < 0.05
** p < 0.01
\# p = 0.05 - 0.1 (trend)

N per Group			
Visit	Placebo	100	150
Baseline	54	47	40
Week 52	47	40	34

New look at old drugs - 2

- Lithium may have symptomatic and disease stabilization effects, but needs better tolerated doses: possible with new “NanoLithium” NP03 formulation

Aonys® Technology



Aonys® is a unique nanotechnology shared by all products under development
Aonys® is protected by 8 **international patents**
A pharmaceutical microemulsion composed of water and specific lipids
The active pharmaceutical ingredient is dissolved in the water phase
Administration is via buccal mucosa, transported by HDL lipoproteins and delivered directly in cells in all tissue types, including the brain

New look at old drugs - 3

- Working group led by Robert Howard looking at all available data on

  (1) angiotensin receptor blockers

  (2) angiotensin convesting enzyme inhibitors

  (3) liraglutide/exenatide

  (4) lithium (5) infliximab/etanercept

  (6) fasudil (7) metformin

In summary…

- We need to think about alternative approaches in AD treatment
- Old drugs have the advantages of known pharmacology, alone or in combination

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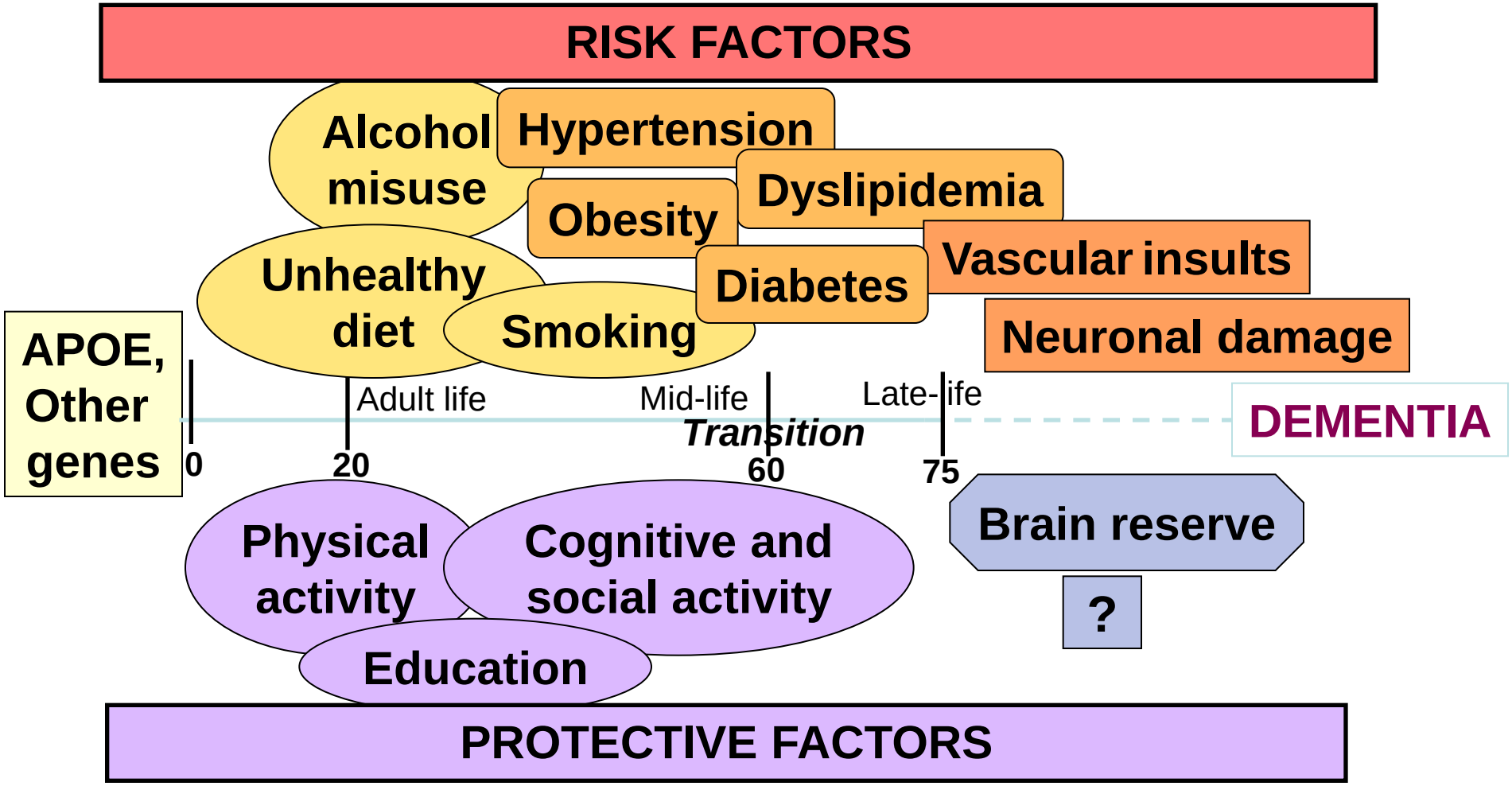
WHAT IS ALZHEIMER'S DISEASE? RISK AND PROTECTIVE FACTORS

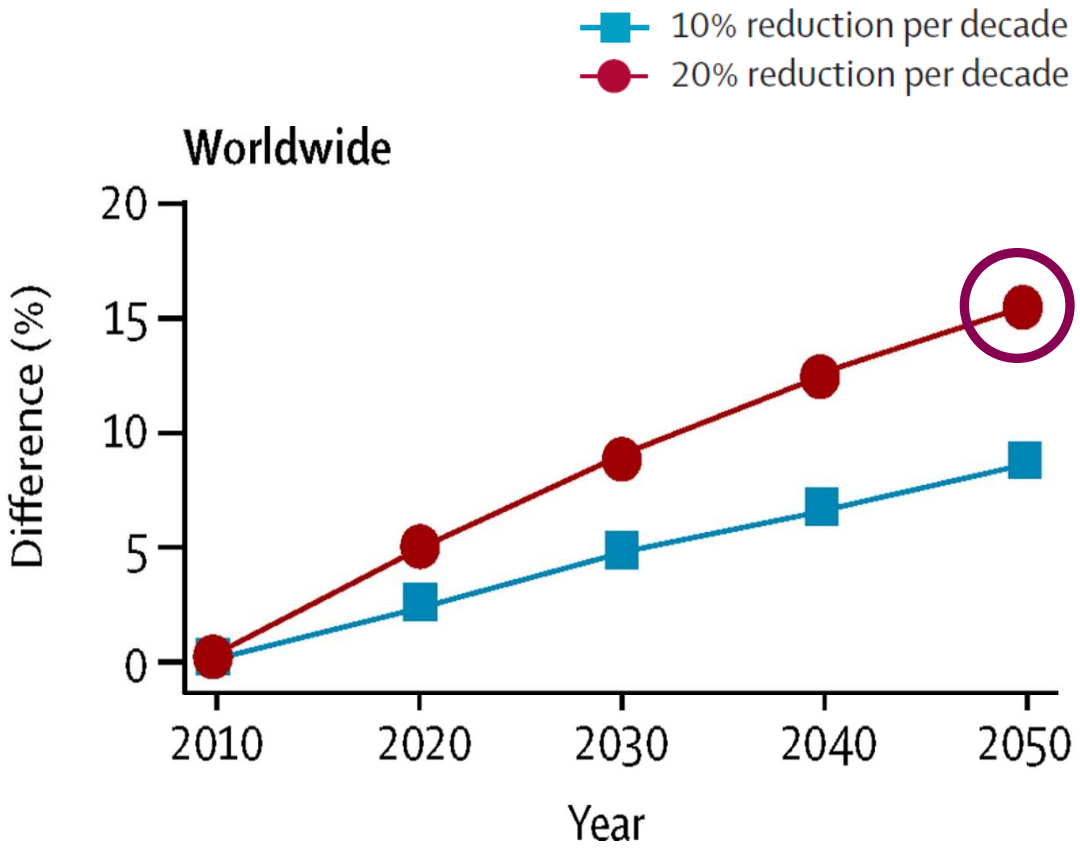


Mangialasche, Kivipelto et al., 2012

To what extent can Alzheimer dementia be prevented?

Risk factor	PAR
Diabetes mellitus	2.9%
Midlife hypertension	5.1%
Midlife obesity	2.0%
Physical inactivity	12.7%
Depression	7.9%
Smoking	13.9%
Low education	19.1%
Combined PAR*	28.2%

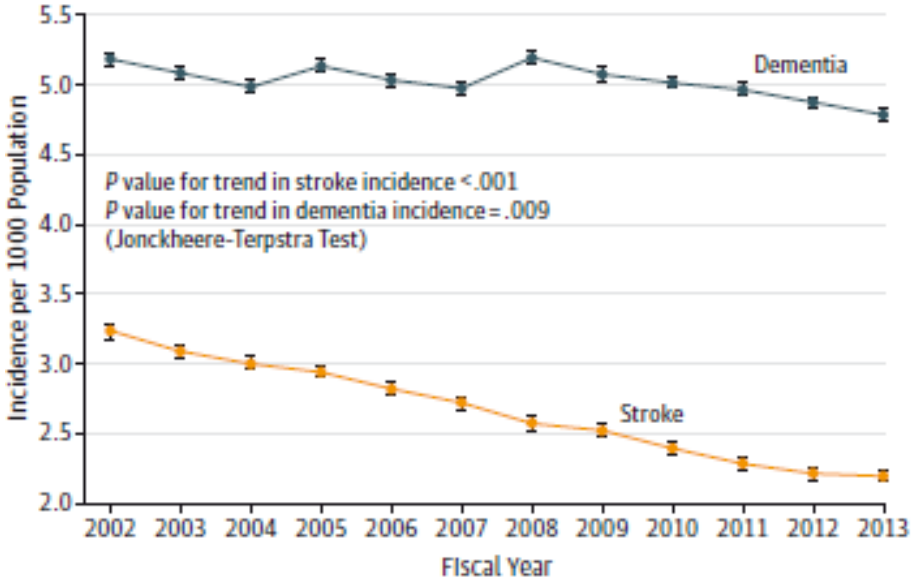
PAR=population-attributable risk.
*Adjusting for non-independence of the risk factors.



Norton et al., Lancet Neurol, 2014; Kivipelto and Mangialasche, Nature Neurol Rev, 2014

Decrease in stroke incidence leading to decrease in dementia

Figure. Trends in Stroke and Dementia Incidence Rates, Ontario 2002-2013



The error bars represent 95% CIs.

In summary…

- Primary and secondary prevention is the best way to reduce the incidence of AD, VaD and mixed dementia
- This requires a national policy with changes towards healthy habits and control of vascular risk factors

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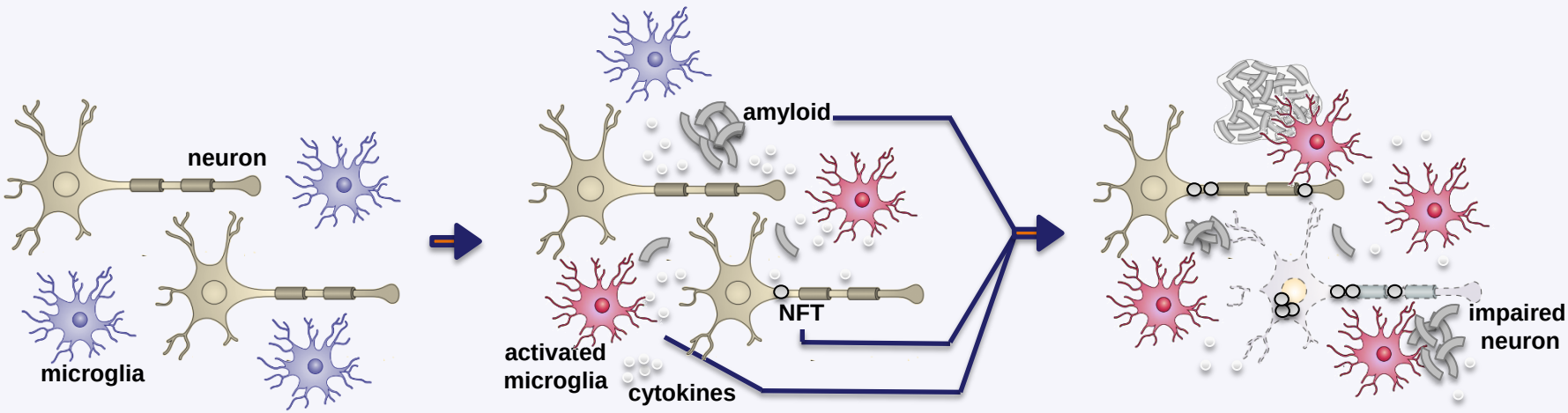
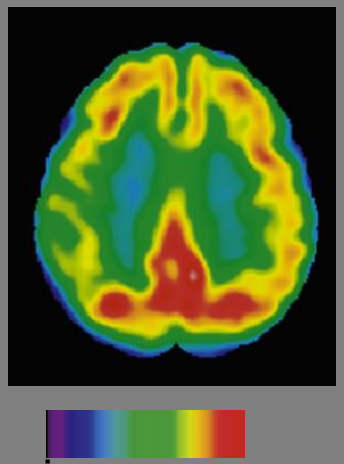
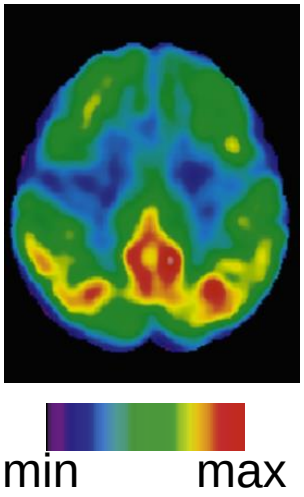
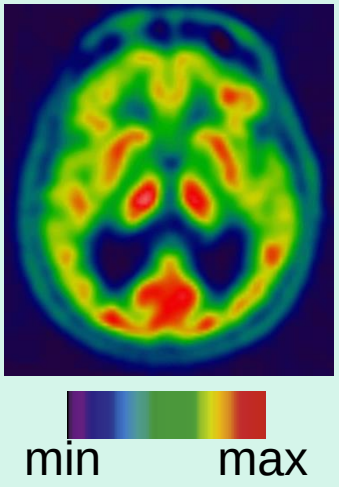
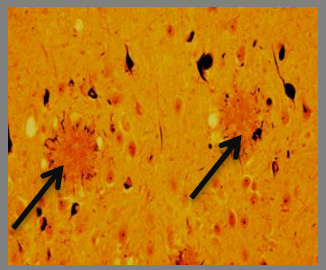
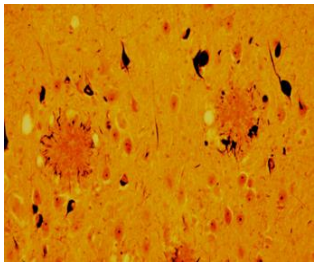
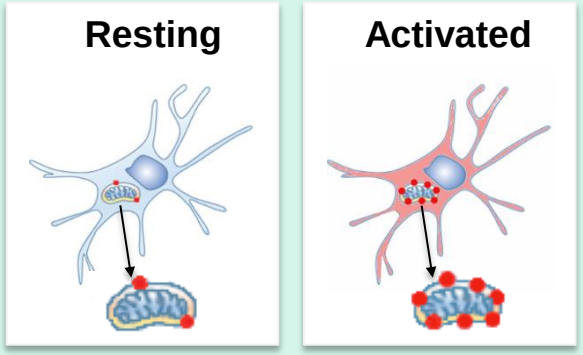
Interactions between pathological processes drive disease progression in preclinical AD



Increased tissue concentrations of amyloid in preclinical Alzheimer's disease will activate microglia.

We hypothesize that the interaction between regional amyloid, local NFT and levels of microglial activation will drive propagation of NFT and cognitive decline (see statistical methods).

Figure 1 - Summary of the imaging agents and PET outcomes proposed

	Amyloid imaging	Tau imaging	TSPO imaging
tracer	[^{11}C]PIB SUVR	[^{18}F]THK5351 SUVR	[^{11}C]PBR28 SUVR
Image			
Interpretation	**Amyloid plaques**  Tissue availability of Fibrillary amyloid	**Neurofibrillary tangles**  Tissue availability of Paired Helical Filaments	**Microglia**  Tissue availability of TSPO expression

- TSPO =Translocator protein (18kDa) - mitochondrial cholesterol transporter

In summary…

- The brain inflammatory component of AD is being studied with new imaging technique combined with CSF markers
- Hope for anti-inflammatory therapy prior to symptoms emergence

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Canadian efforts under way

- CCNA with ASC partnership
- National Dementia Plan – Bill C233
- Observational cohorts: COMPASS (CCNA), ADNI, GENFI
- Multi-centric studies against amyloid: BACE inhibitors, monoclonal antibodies
- Validation of PET ligands: amyloid, tau, inflammation

CONCLUSIONS

- The study of AD and related dementias is a fast moving field
- There is hope for a personalized and stage-specific therapy in the near future for persons at high risk
- There is already evidence for reduction of incidence with control of risk factors, principally vascular