Prana Alzheimer's disease Development Program update

MELBOURNE, AUSTRALIA, JULY 17, 2014: Prana Biotechnology (ASX:PBT) has today provided an update on its clinical development program for Alzheimer's disease.

Professor Colin Masters, the Florey Institute of Neuroscience and Mental Health, The University of Melbourne, will today include data from Prana's Phase 2 IMAGINE and EURO trials in his presentation at the Alzheimer's Association International Conference in Copenhagen, Denmark.

The presentation is entitled: *"How to change and monitor the rates of Aβ amyloid accumulation and cognitive decline in Alzheimer's disease"*. The presentation is attached.

The IMAGINE trial top-line draft results were released on 31 March 2014. Further sub-analyses of the top line imaging data have been performed, including PiB-PET, MRI and FDG analysis of the effects of a once daily, 250 mg dose of PBT2 over 12 months. IMAGINE enrolled 42 patients, 27 in the PBT2 group and 15 in placebo.

The primary objective of the IMAGINE trial was to explore whether amyloid burden, as measured by PiB-PET would decrease in participants treated with PBT2 relative to placebo. However, in contrast to published literature, the average amyloid burden in the placebo group fell during the trial.

Prana conducted a sub-analysis to better understand the behaviour of the placebo group and what can be learned in the trial about the utility of such exploratory biomarkers for future trials.

In Professor Masters' presentation, he noted that the starting amyloid burden level (baseline) in the PBT2 treated participant group had an important bearing on the decrease of amyloid over time in that participant ($p=0.035$), whereas there was no such correlation in the placebo group.

Prof Masters further investigated the response of participants with baseline amyloid burden levels above and below the mean for the IMAGINE cohort (SUVR of 2.5). He showed that in the subgroup of PBT2 treated participants with a baseline of SUVR above 2.5, there was a significant decrease in amyloid burden that was not observed in participants on placebo nor PBT2 participants with a SUVR less than 2.5. In summary, whilst the utility of PiB in small trials may be questioned, it was interesting to note the impact of baseline SUVR amyloid burden level on the response of a cohort, for future trial design.

Separately, Prana has confirmed the top line finding that there is a very promising trend towards the preservation of brain volume (as measured by MRI) in PBT2 treated patients compared to placebo patients.

Mechanism of action of PBT2 in AD

PBT2 prevents formation and toxicity of pathological Aβ species (primarily soluble oligomers) and promotes their clearance. In Professor Masters' presentation he proposes the observed effect upon amyloid burden is due to increased clearance by PBT2 of pools of PIB-detectable non-fibrillar soluble and membrane bound Aβ.

Through its metal chaperone activity, PBT2 activates intracellular signalling pathways which promote neuronal health and plasticity and suppress pathobiological processes including the abnormal phosphorylation of tau. The trend towards reduced hippocampal atrophy seen in the PBT2 treatment group mirrors the Company's preclinical observations and reinforces a similar trend observed in the Reach2HD Huntington's disease study.

"Understanding the limitations of a small trial, the atypical placebo group response, previous clinical findings (the EURO trial), the strong body of peer reviewed science, along with the sub-analyses of IMAGINE, the company remains enthusiastic about the prospects of a large trial statistically powered to demonstrate cognitive benefit," Prof. Masters said.

IMAGINE EXTENSION TRIAL UPDATE

Patients who completed the full 12-month term of the IMAGINE trial were eligible for participation in an open-label Extension study. All participants in the Extension study receive a 250mg once daily oral dose of PBT2 for an additional 12 months during which PiB-PET and MRI imaging will continue.

Thirty three patients elected to join the Extension trial and of these, 30 remain on the trial. Of those participants, 21 have now been identified as being randomized to the PBT2 treatment arm in the IMAGINE study. Of these, all 21 patients have completed 14 months of PBT2 administration, 20 have completed 18 months of PBT2 administration and nine have completed 21 months of PBT2 administration.

We are very pleased with the continuing safety profile of the drug. The data safety monitoring board has met a further two times and has not expressed any concerns in relation to adverse events.

- ENDS-

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About Prana Biotechnology Limited

Prana Biotechnology was established to commercialise research into Alzheimer's disease, Huntington disease and other neurodegenerative and movement disorders. The Company was incorporated in 1997 and listed on the Australian Stock Exchange in March 2000 and listed on NASDAQ in September 2002. Researchers at prominent international institutions including The University of Melbourne, The Mental Health Research Institute (Melbourne) and Massachusetts General Hospital, a teaching hospital of Harvard Medical School, contributed to the discovery of Prana's technology.

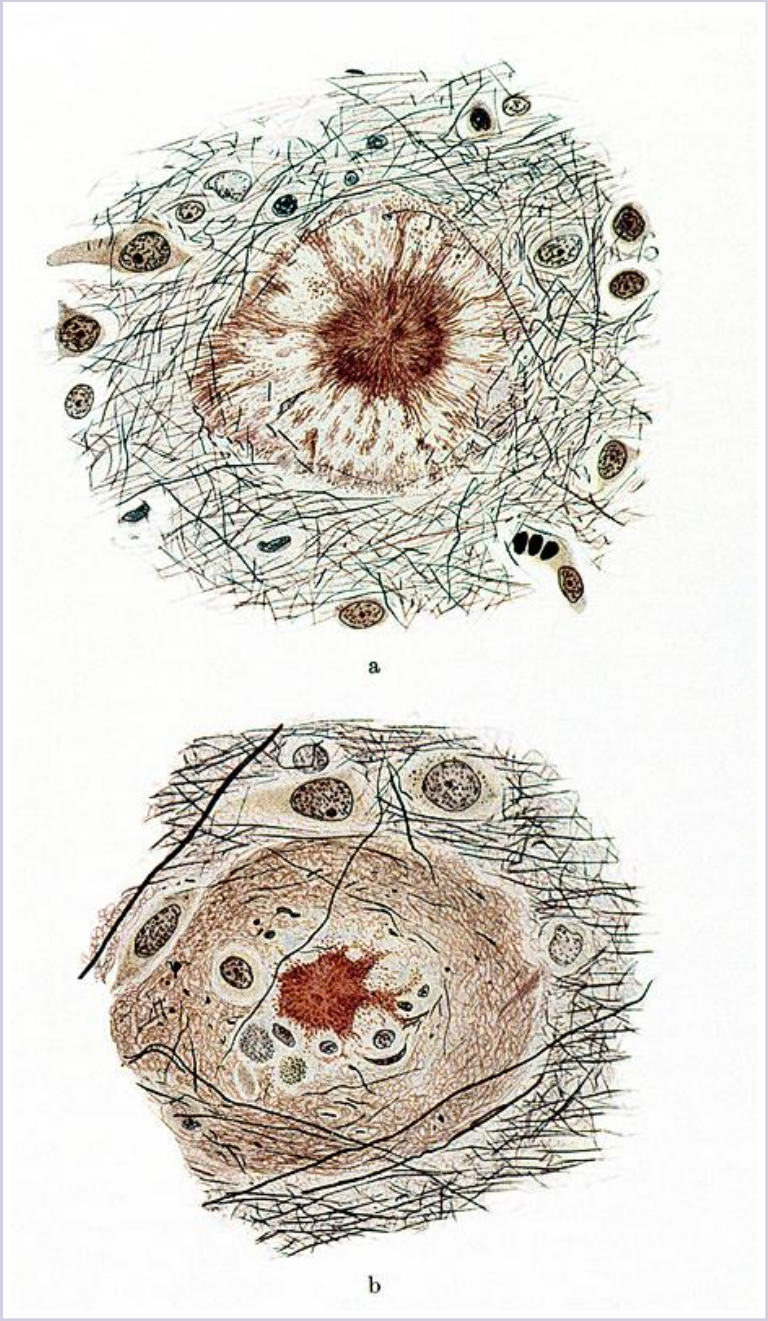
Forward Looking Statements

This press release contains "forward-looking statements" within the meaning of section 27A of the Securities Act of 1933 and section 21E of the Securities Exchange Act of 1934. The Company has tried to identify such forward-looking statements by use of such words as "expects," "intends," "hopes," "anticipates," "believes," "could," "may," "evidences" and "estimates," and other similar expressions, but these words are not the exclusive means of identifying such statements. Such statements include, but are not limited to any statements relating to the Company's drug development program, including, but not limited to the initiation, progress and outcomes of clinical trials of the Company's drug development program, including, but not limited to, PBT2, and any other statements that are not historical facts. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to the difficulties or delays in financing, development, testing, regulatory approval, production and marketing of the Company's drug components, including, but not limited to, PBT2, the ability of the Company to procure additional future sources of financing, unexpected adverse side effects or inadequate therapeutic efficacy of the Company's drug compounds, including, but not limited to, PBT2, that could slow or prevent products coming to market, the uncertainty of patent protection for the Company's intellectual property or trade secrets, including, but not limited to, the intellectual property relating to PBT2, and other risks detailed from time to time in the filings the Company makes with Securities and Exchange Commission including its annual reports on Form 20-F and its reports on Form 6-K. Such statements are based on management's current expectations, but actual results may differ materially due to various factions including those risks and uncertainties mentioned or referred to in this press release. Accordingly, you should not rely on those forward-looking statements as a prediction of actual future results.

How to change and monitor the rates of Aβ amyloid accumulation and cognitive decline in Alzheimer's disease

AAIC, Copenhagen, July 2014

The Amyloid Plaque



From W Spielmeyer,
Histopathologie des Nervensystems.
1922

Abb. 201 a und b. Zwei senile Plaques. Bielschowskysche Silberimprägnation. In 201 a gehen von dem amorphen Kerne Strahlen aus, welche wie Kristallnadeln einen hellen Hof durchsetzen und am Rande in einer schmalen, ringartigen Zone ansetzen. In 201 b ist der Kern massiger, ebenfalls amorph, stellenweise etwas ausgezogen. In dem hellen Hof liegen Gliazellen und dürftige Achsenzylinderauftreibungen. Die Außenzone besteht aus einem breiten dichten Wall.

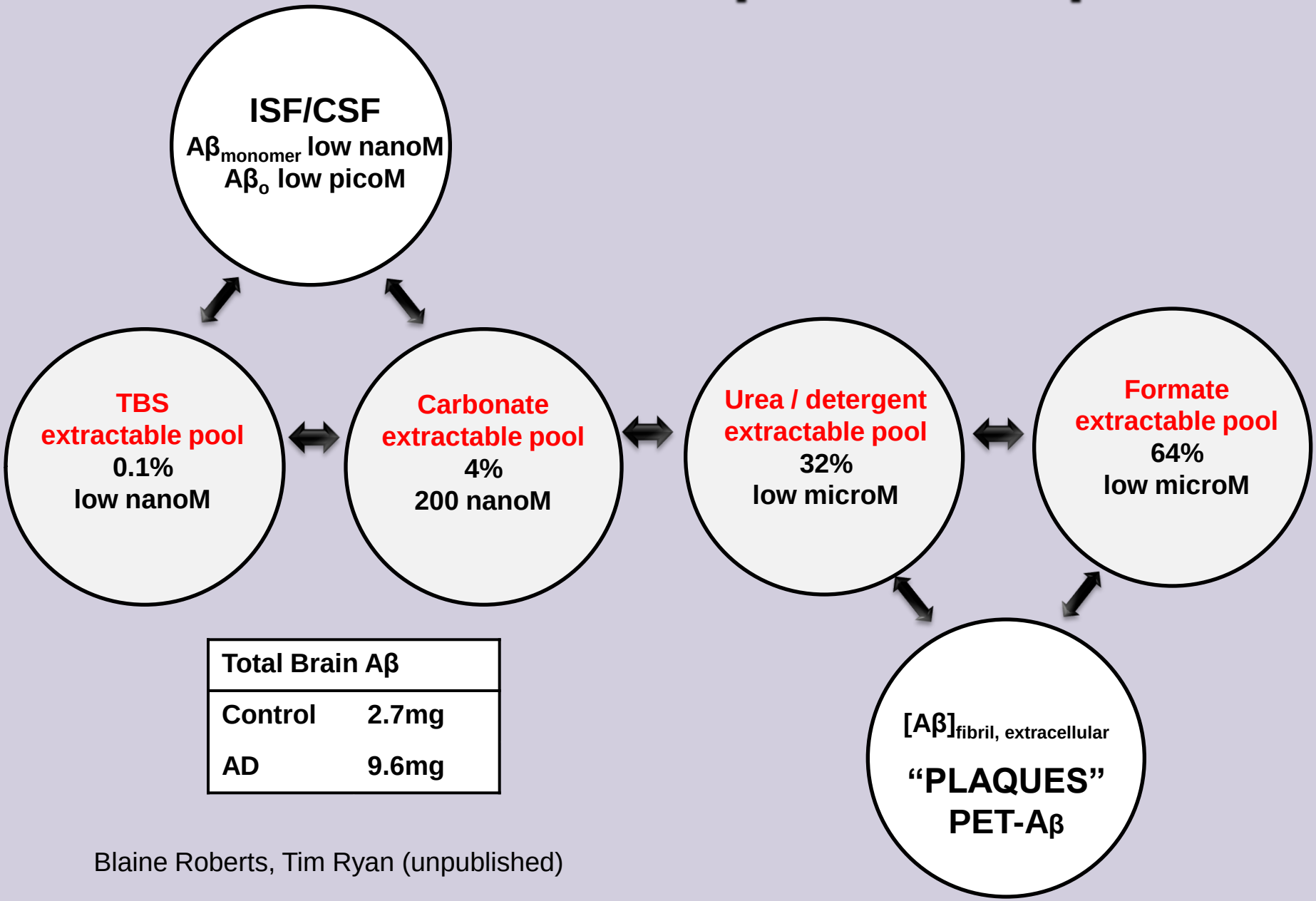
Disclosures

Consultant to Eli Lilly and
ad hoc consultant
to Prana Biotechnology

How to monitor Aβ accumulation?

- What does PET-Aβ and CSF-Aβ actually report?
- Why are we having such difficulty in achieving a link between cognitive variables and these two markers?

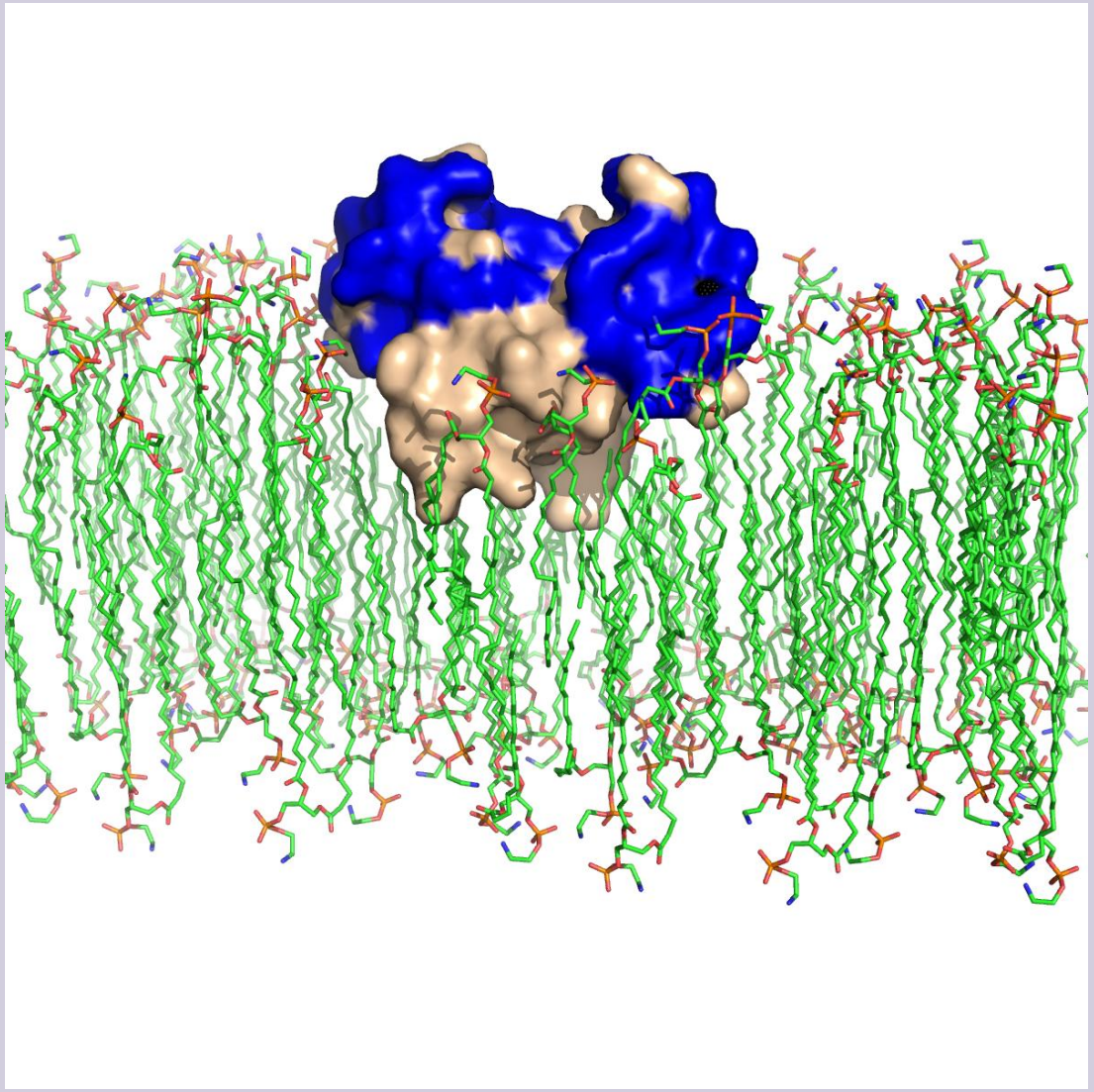
The metabolic pools of Aβ



Total Brain Aβ	
Control	2.7mg
AD	9.6mg

Blaine Roberts, Tim Ryan (unpublished)

P3 oligomer model based on crystal structure: the toxic Aβ-oligomer target?

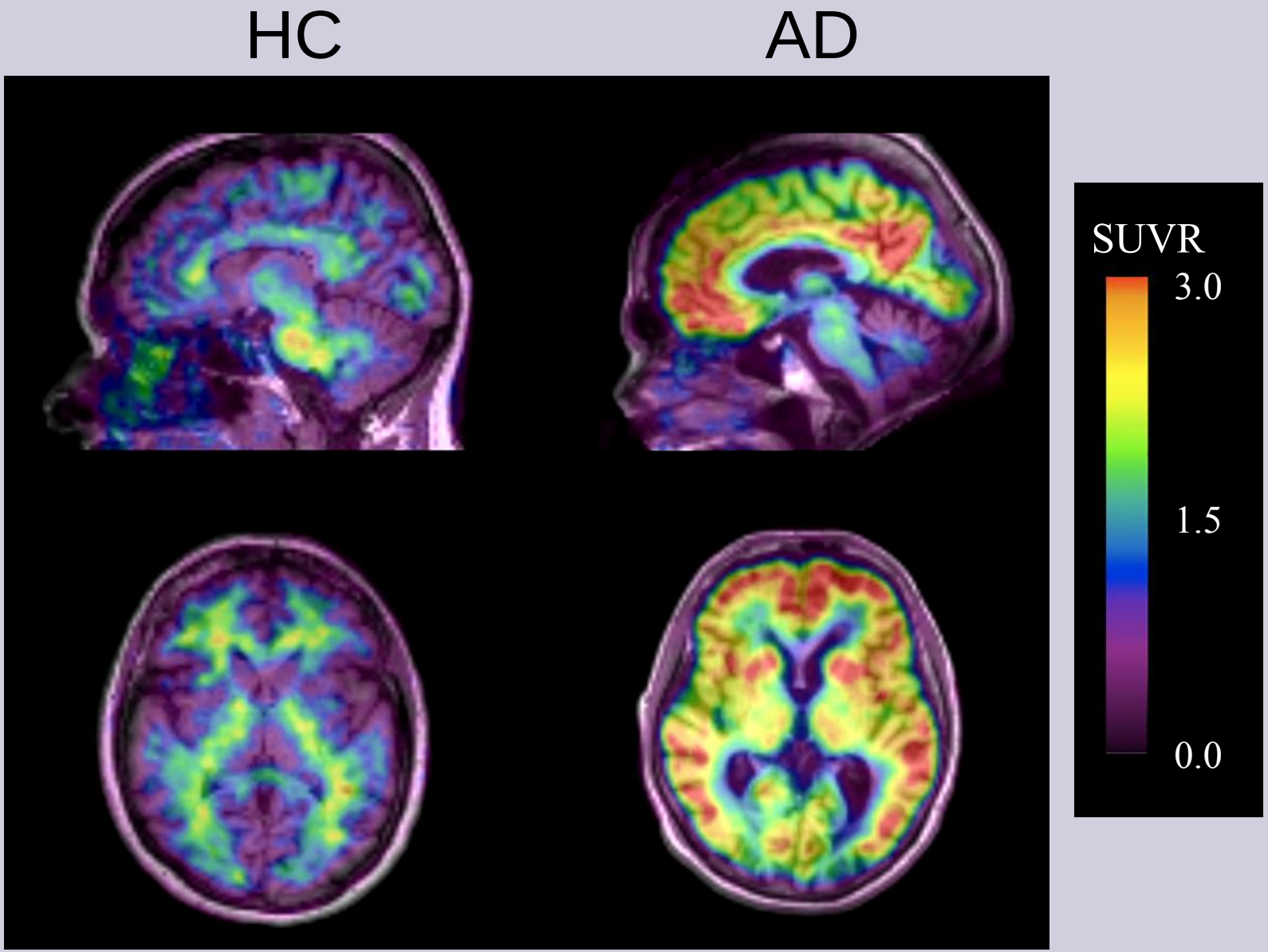


Streltsov, Nuttall 2011

The Australian Imaging, Biomarkers and Lifestyle Study of Aging

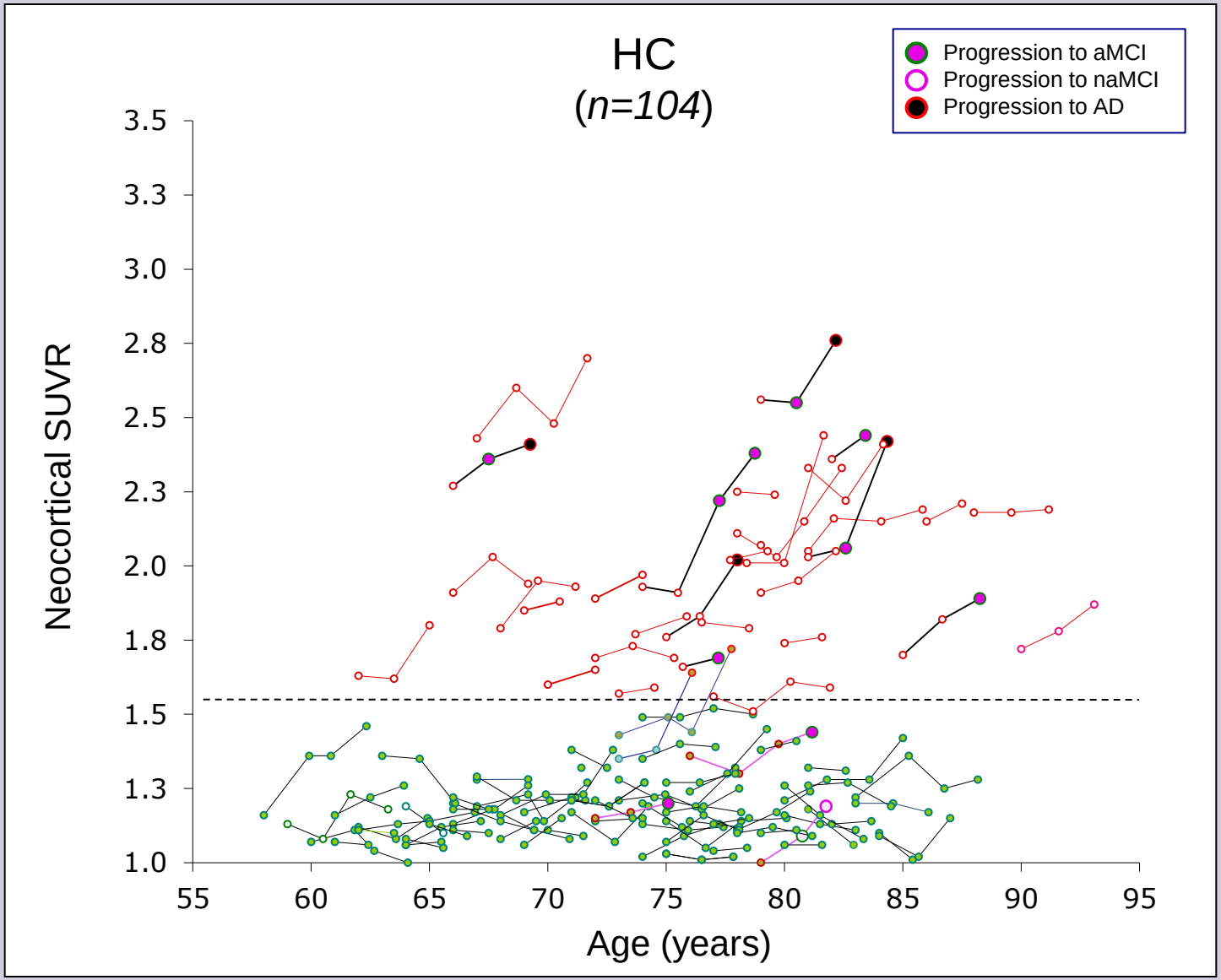
(Australian ADNI)

^{11}C-PIB for Aβ imaging



Villemagne / Rowe

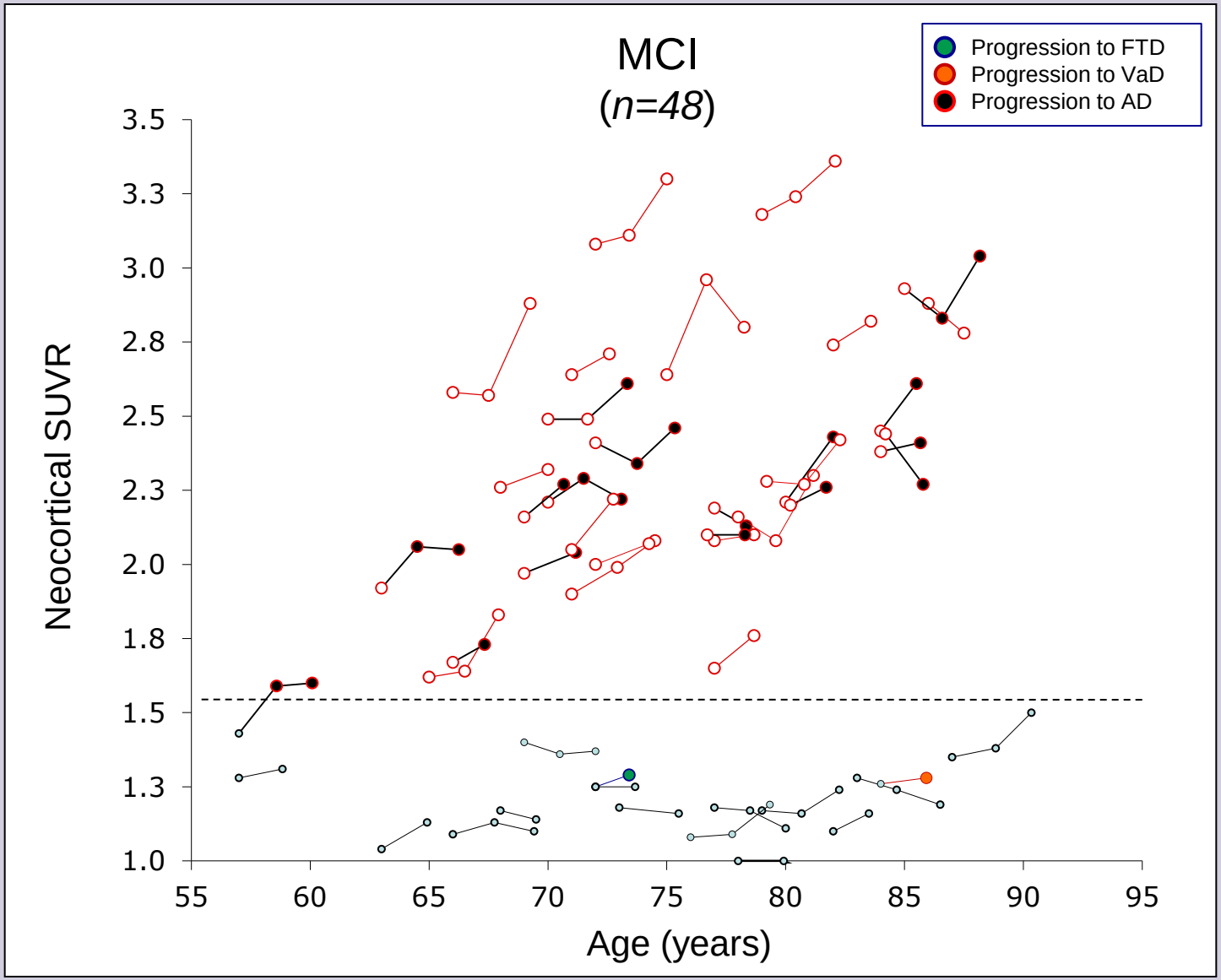
Longitudinal PiB PET follow-up



* *PiB+/PiB- SUVR cut-off = 1.5*

Villemagne / Rowe

Longitudinal PiB PET follow-up



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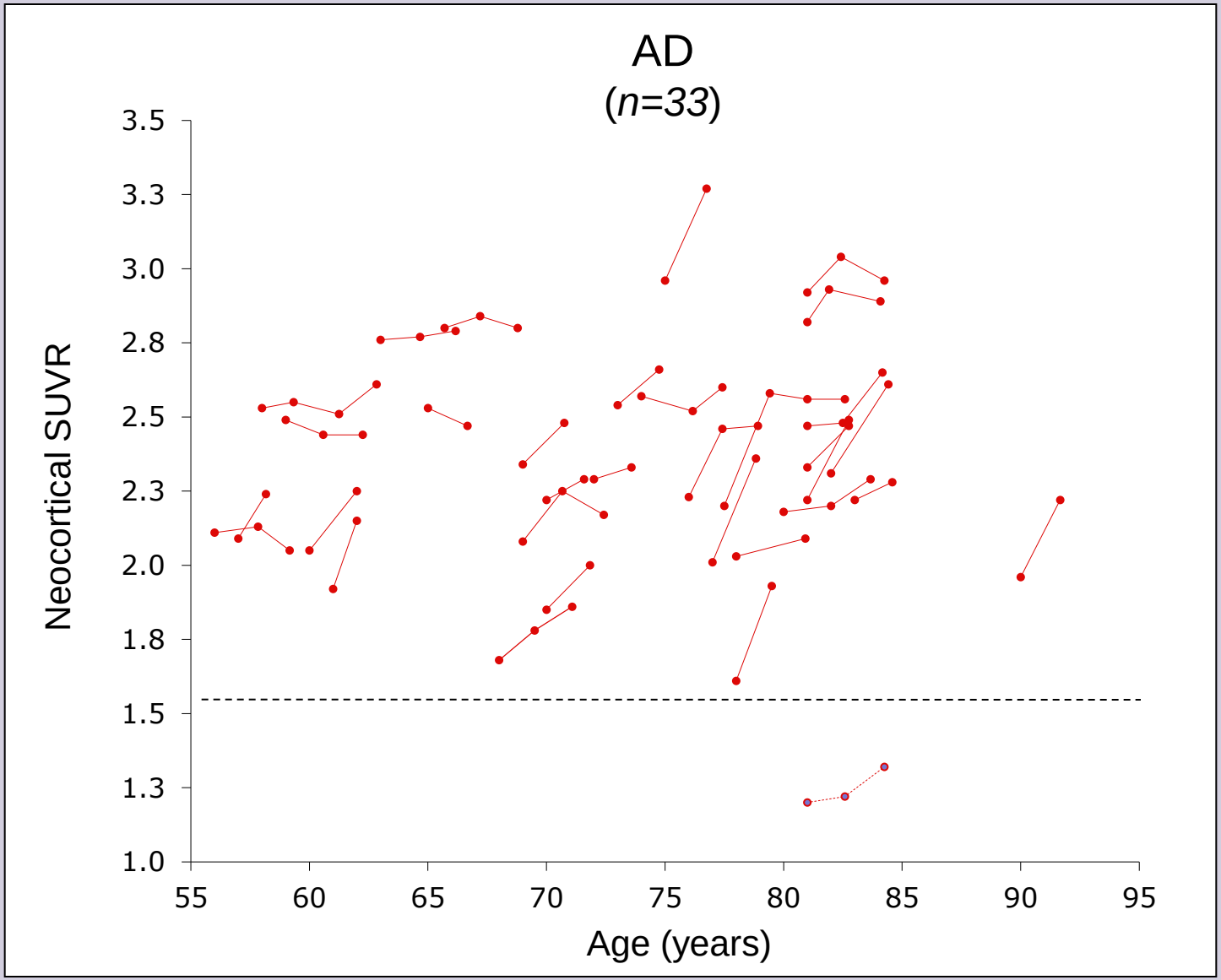
Villemagne / Rowe

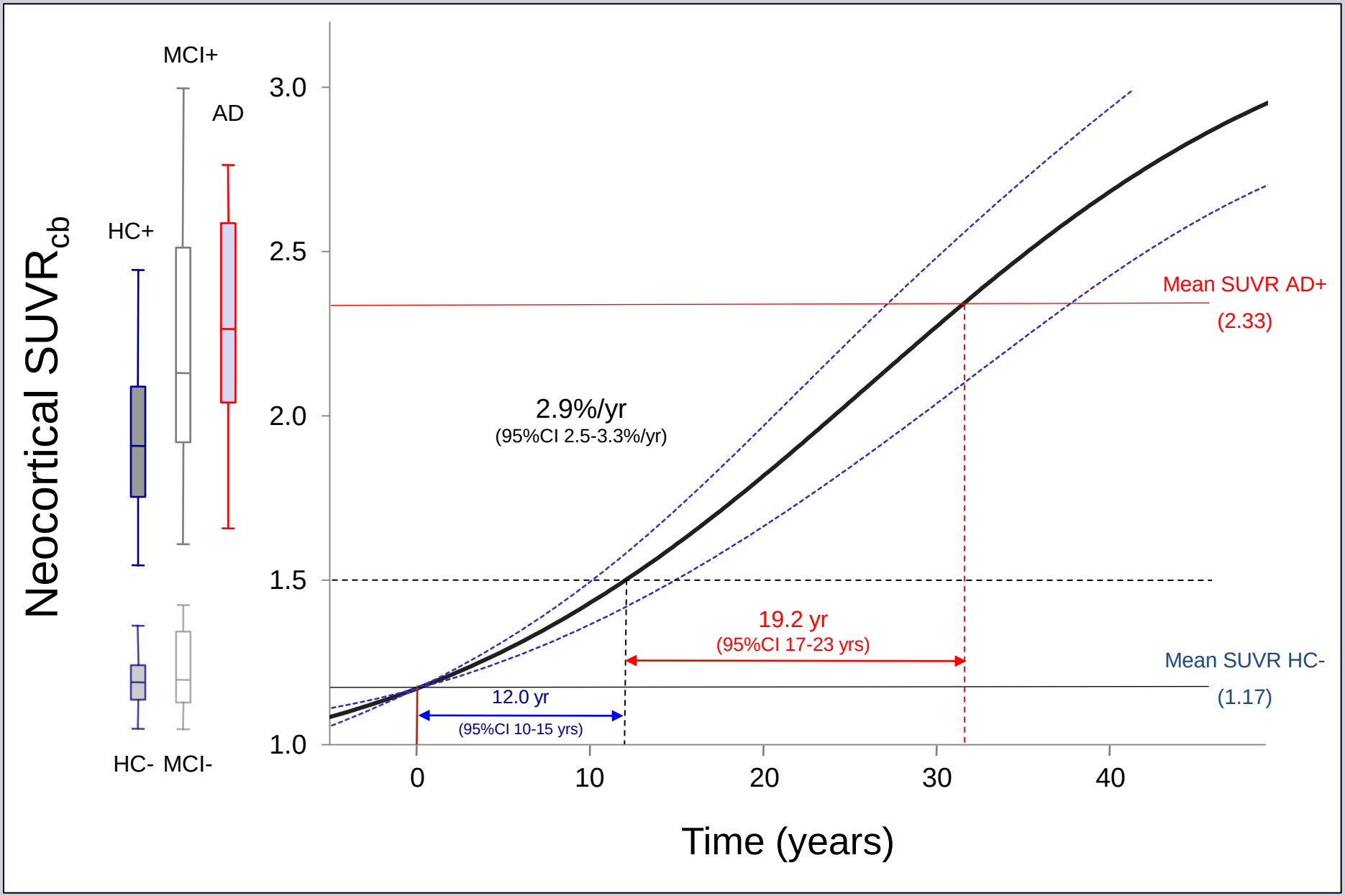
Longitudinal PiB PET follow-up



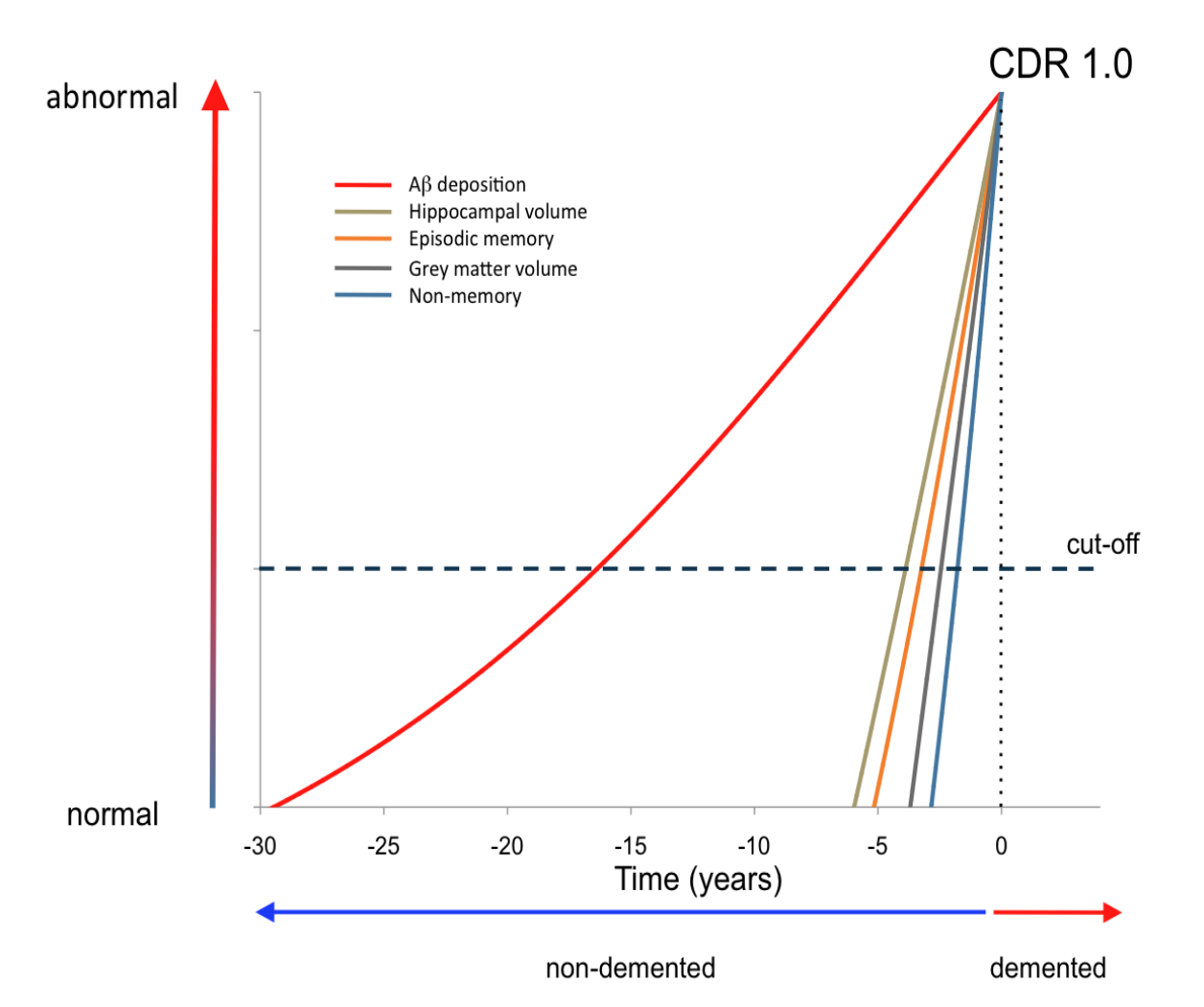
* PiB+/PiB- SUVR cut-off = 1.5

Villemagne / Rowe

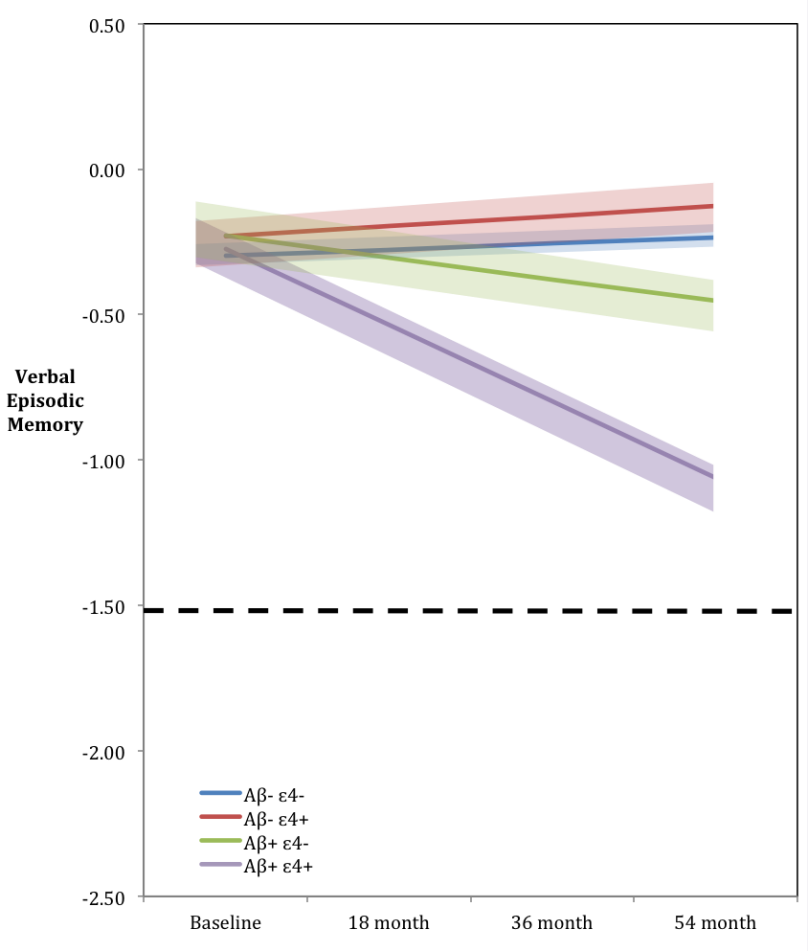
AIBL: Aβ deposition over time

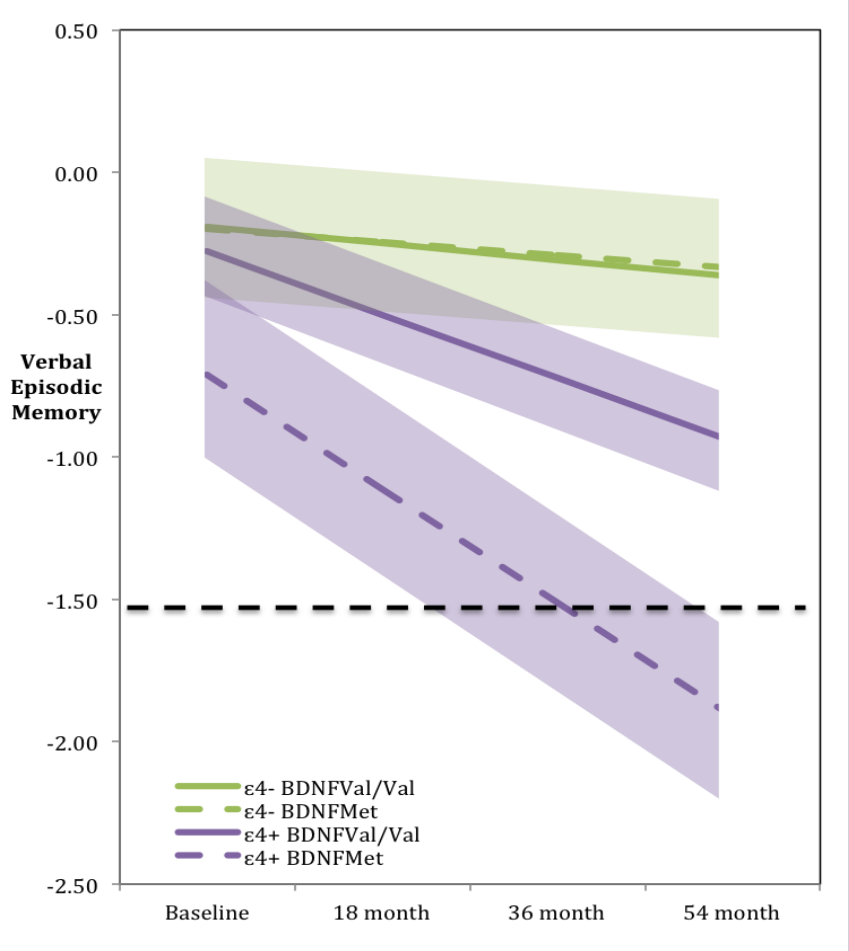


AIBL: Relationship between "abnormality" and CDR of 1.0



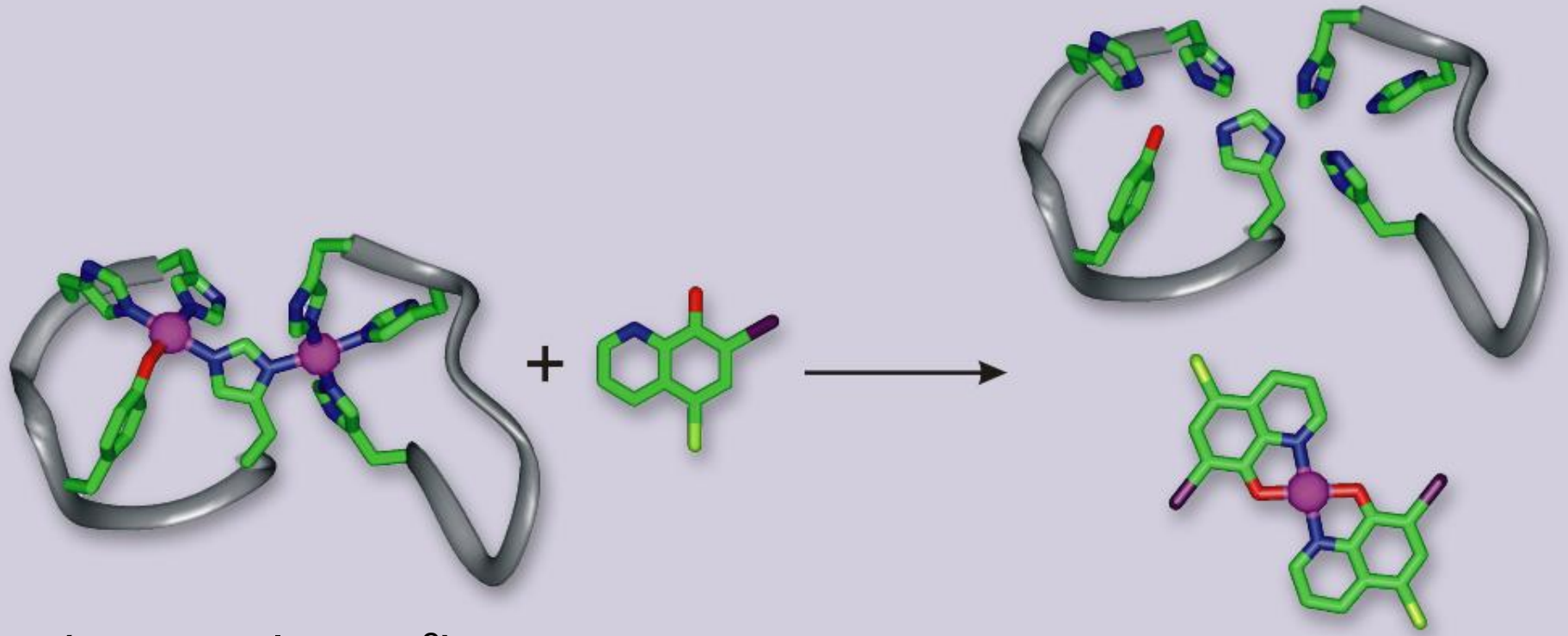
Trajectories of cognitive decline over 54 months in preclinical AD: effect of ApoE and BDNF polymorphisms





Lim, Maruff et al. unpublished

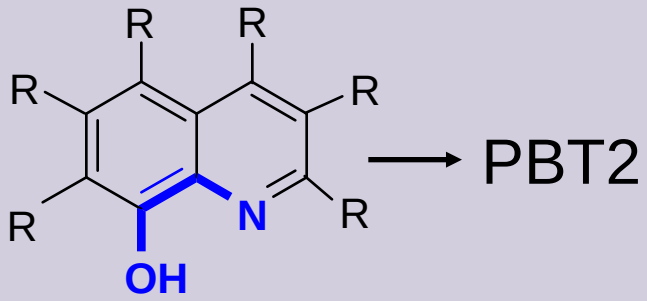
Case Study:
Metal-chaperones with moderate affinity



(nanomolar 10^{-9})

(low picomolar 10^{-11})

Xilinas, Barnham, Bush, Curtain



→ PBT2

fused ring scaffold with
transition metal binding motif
(dissociation constant Cu/Zn/Fe low picomolar 10^{-11})

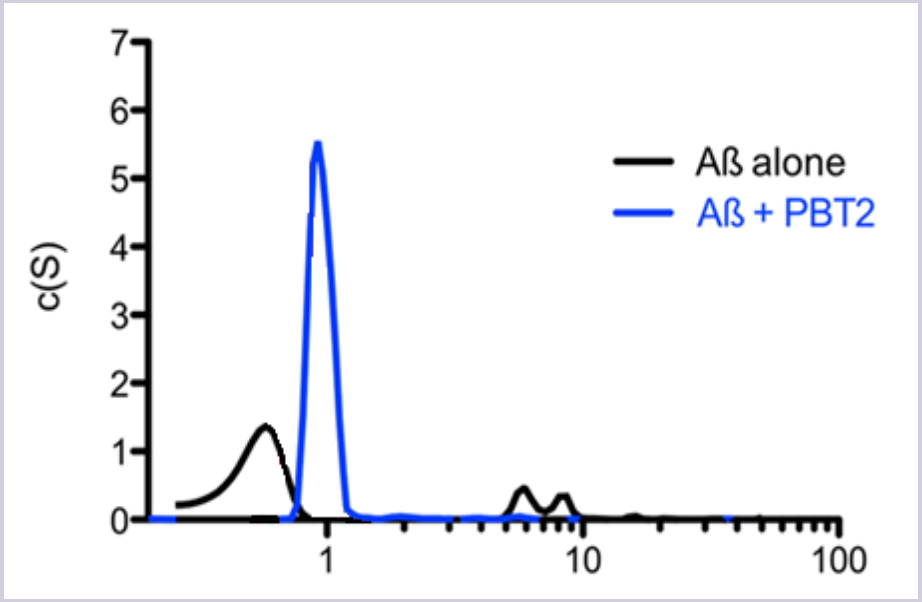
Substituent "R" groups influence:
- solubility
- Hydrophobicity
- BBB permeability
- metal chaperone "ionophore" property
- metal binding affinity

***in vitro* screening:**
- inhibition of metal mediated ROS
- Inhibition of formation of cross-linked oligomeric Abeta
- transition metal uptake by cultured neurons
- inhibition of Abeta mediated hippocampal LTP suppression

***In vivo* screening (APP/PS1 and Tg2576):**
- total soluble and insoluble Abeta, Tau, pTau
- interstitial Abeta (*in vivo* brain microdialysis)
- cognition (morris water maze)
- neuronal architecture (dendritic spines, hippocampal volume)
- molecular substrates of memory and neuronal function (NMDAr etc)

PBT2 inhibits the formation of high order Aß oligomers in vitro and promotes Aß clearance in vivo

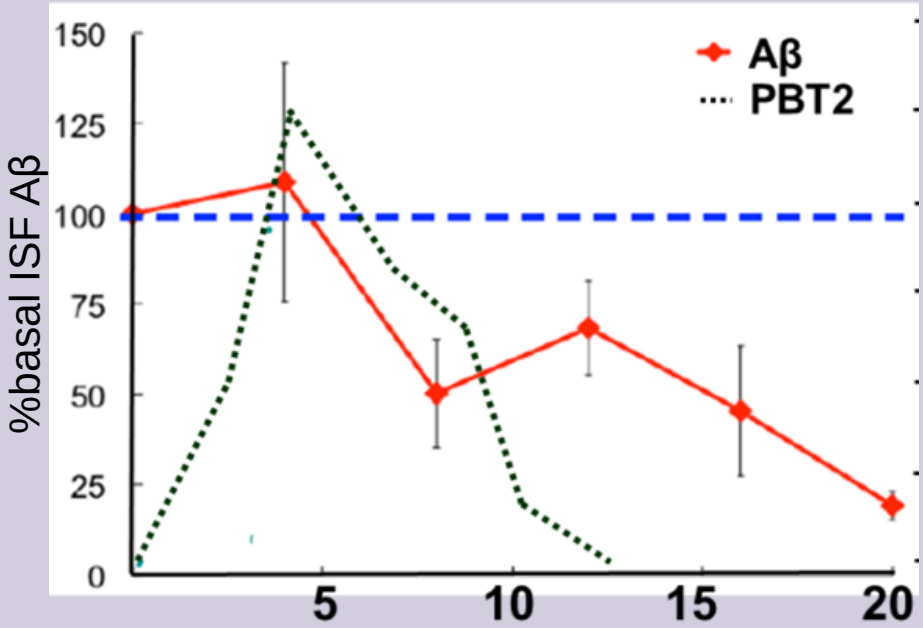
Aß 1-40
(analtyical ultacentrifugation)



Sedimentation coefficient (S)

Tim Ryan, Blaine Roberts, unpublished

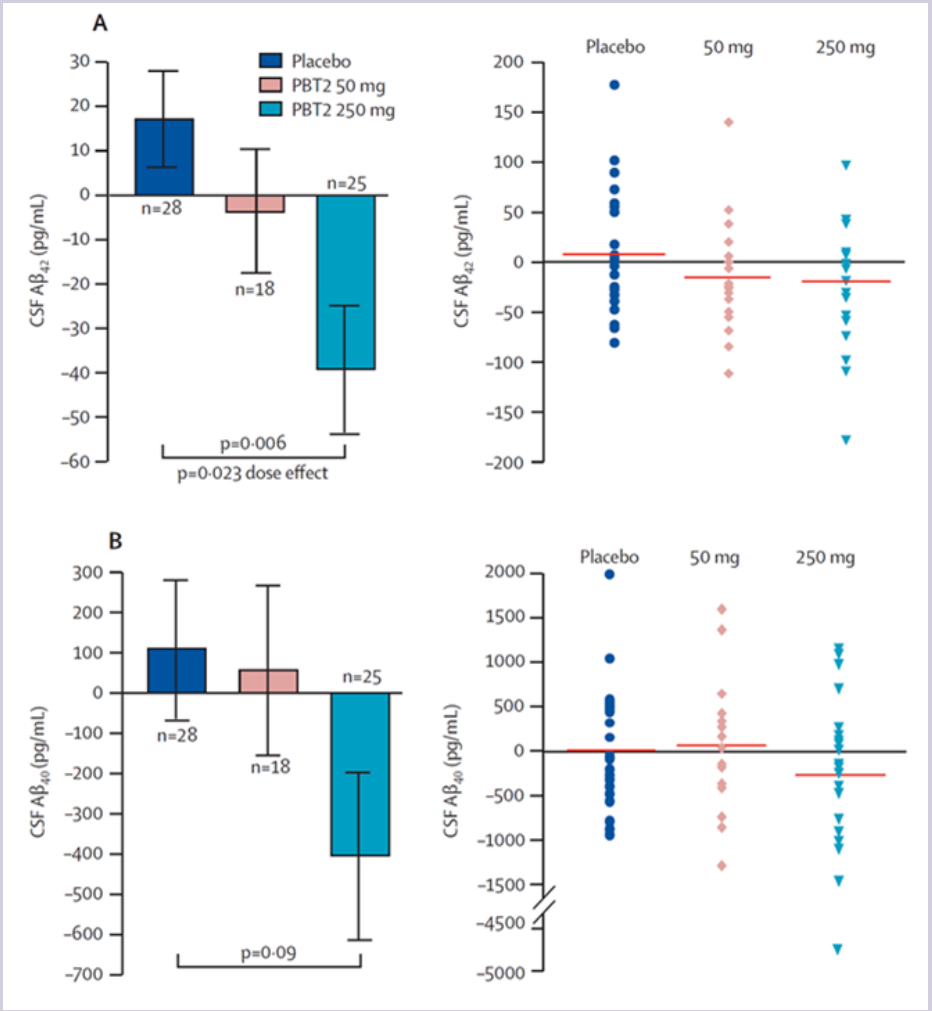
ISF Aß in tg mice
(*in vivo* microdialysis)



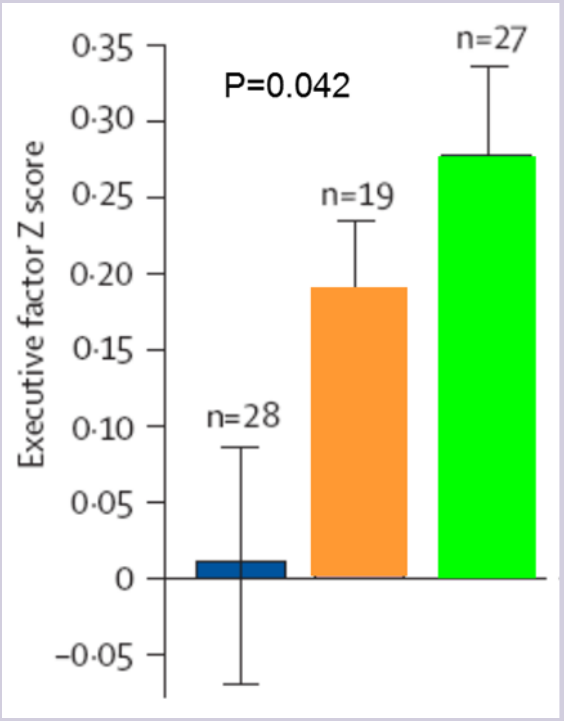
Time post administration (hr)

Adlard et al., Neuron 2008

PBT2 reduces soluble Aβ 42 in human CSF ("Euro" Phase IIa, 12 Weeks)



13% fall in CSF Aβ42 from baseline



Dose dependent improvement in executive function

Lannfelt et al., Lancet Neurology (2008)

PBT2 reduced CSF Aβ in Phase IIa study; is that relected in plaque burden?

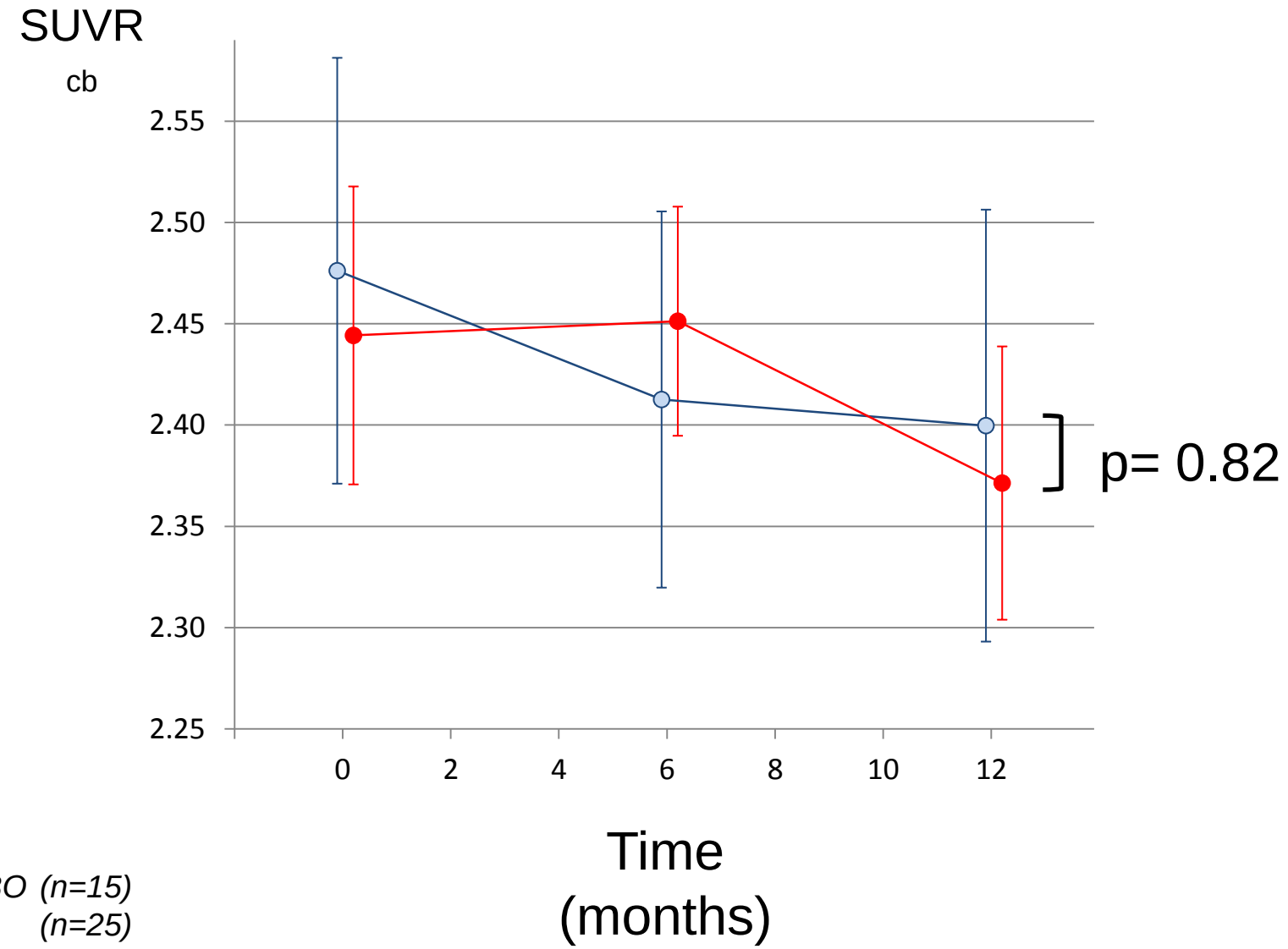
PBT2-204 (Imagine)

RCT, Phase IIa, prodromal or mild AD,
Inclusion criteria PiB-PET > 1.7, MMSE >20,
12 months, n=40 (placebo 15, drug 25),

Sponsor: Prana Biotechnology with support from ADDF.

- Primary objective: effect of PBT2 on PiB-PET
- Secondary objectives: safety and tolerability; effect of PBT2 on FDG, MRI volumetrics, cognition (NTB), functional abilities (ADCS-ADL-23), and blood Aβ-related markers

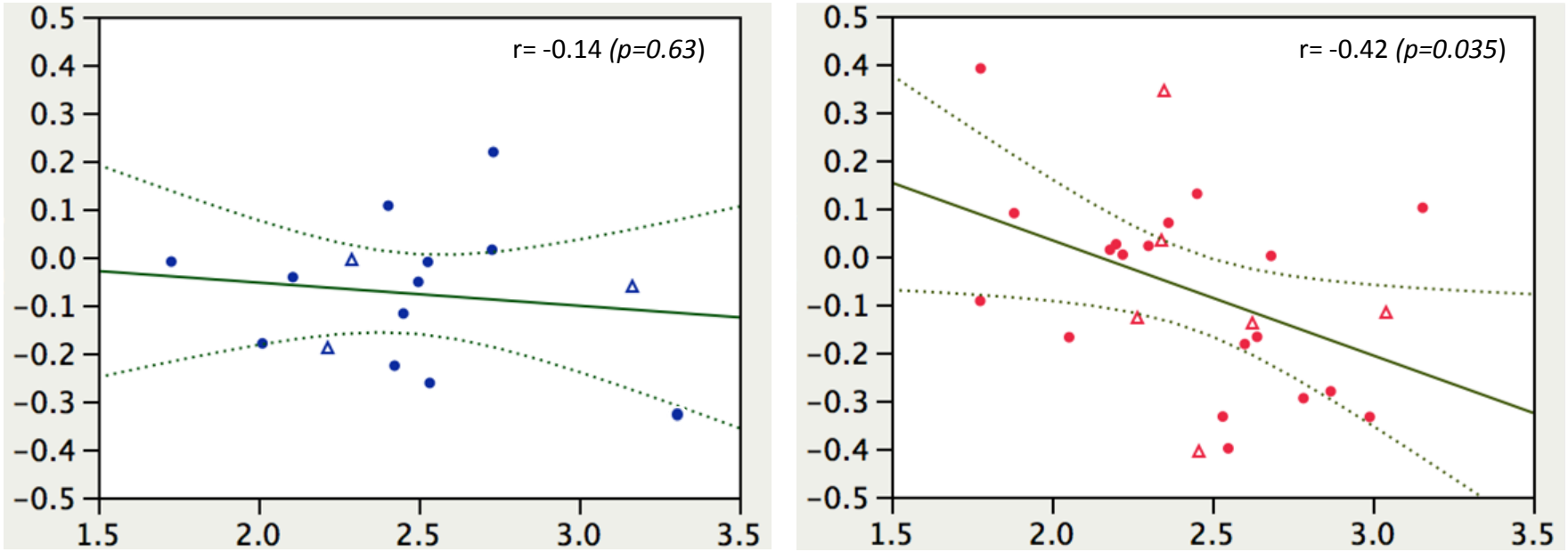
PiB PET


SUVR
cb
2.55
2.50
2.45
2.40
2.35
2.30
2.25
0
2
4
6
8
10
12
Time
(months)
p= 0.82
PLACEBO (n=15)
PBT2 (n=25)

Relationship between baseline Aβ burden and change at 12 months

PLACEBO

PBT2

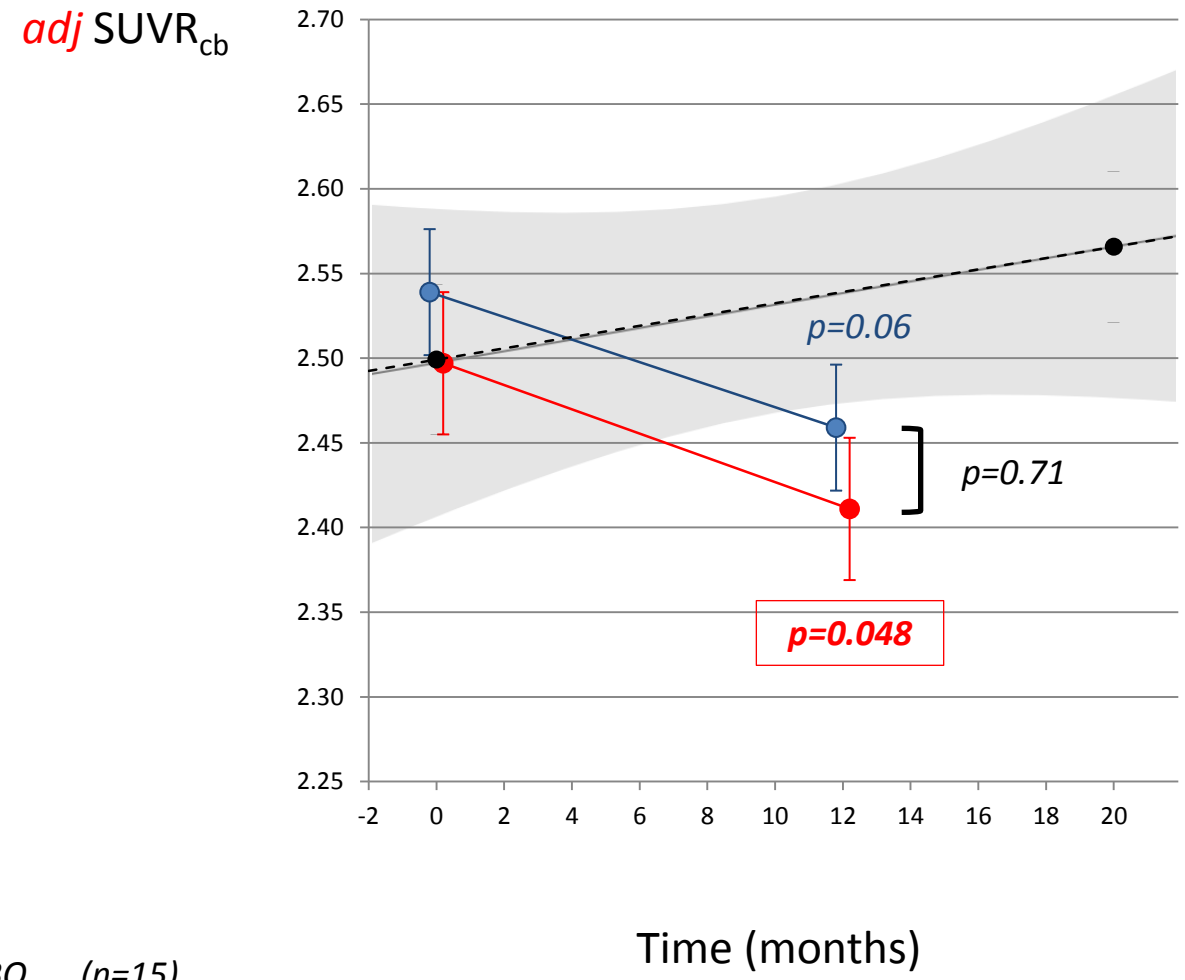


Slope Placebo= -0.048 (sem 0.097)
Slope PBT2 = -0.240 (sem 0.107)
(*p=0.2*)

PLACEBO (n=15) ε4 non-ε4
PBT2 (n=25) ε4 non-ε4

PiB PET

(adjusted for baseline SUVR)

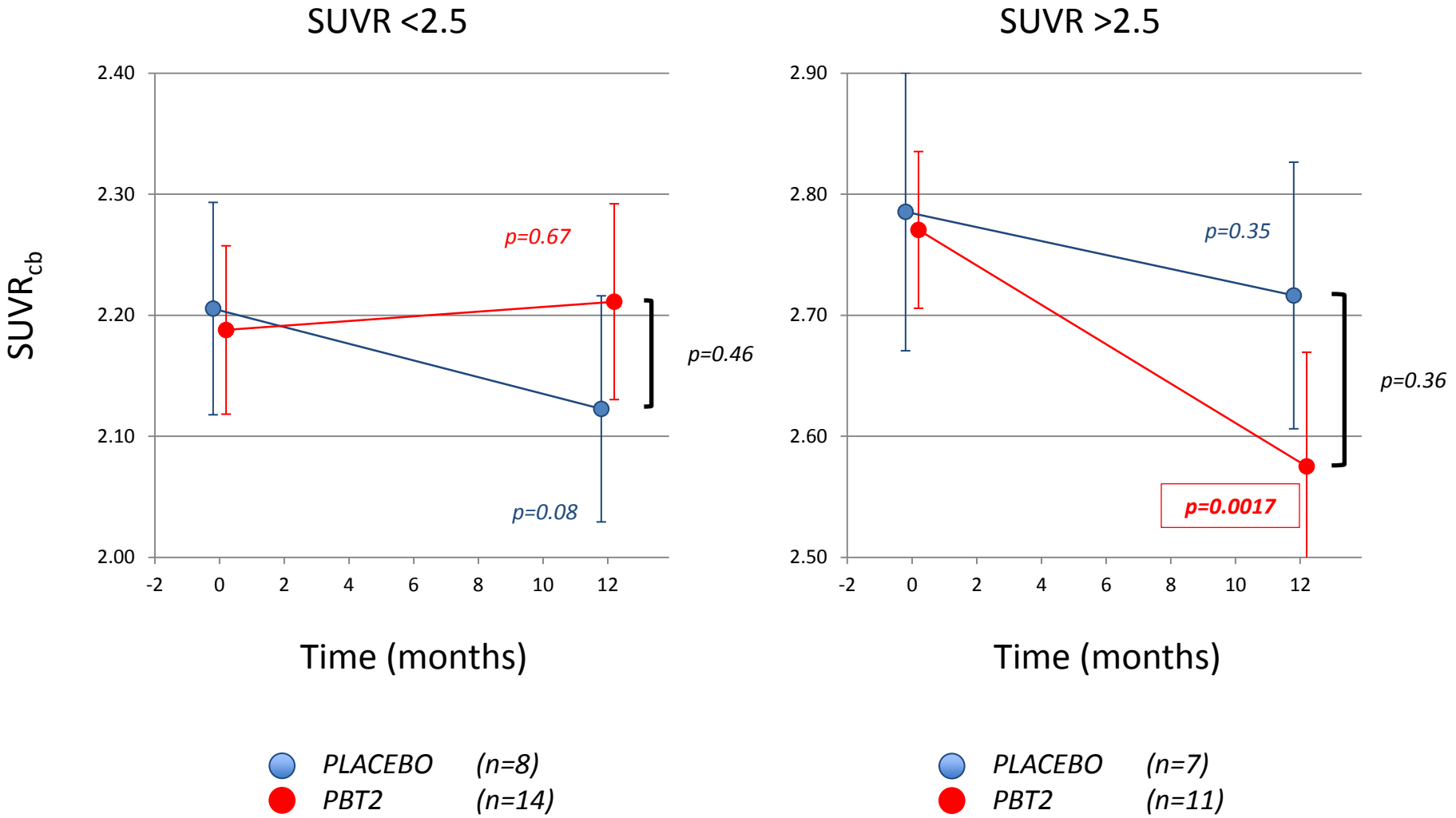


PLACEBO *(n=15)*

PBT2 *(n=25)*

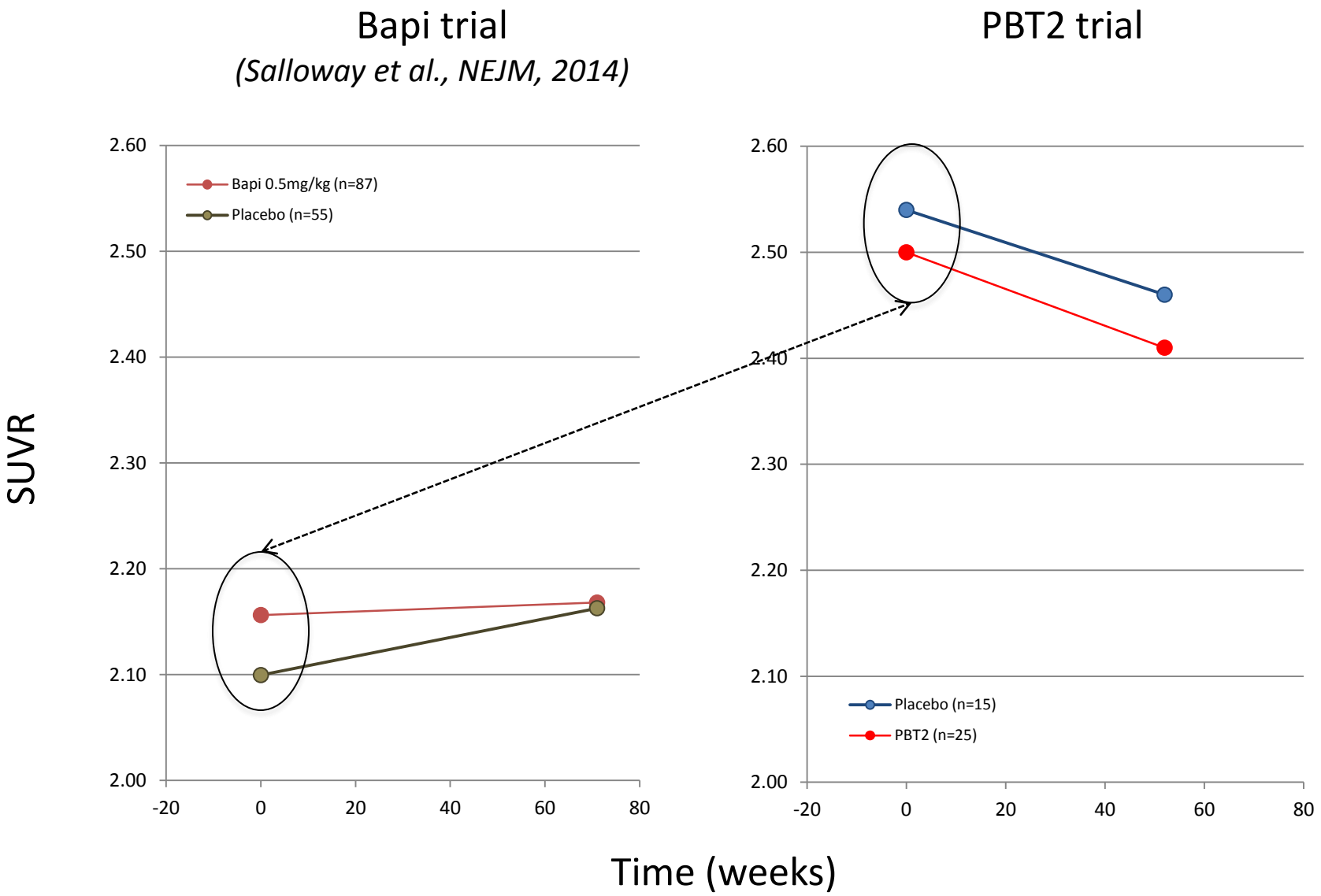
AIBL [shaded area 95% CI] (MCI or AD, SUVR>1.7*; MMSE>20; matched for baseline SUVR (n=46))*

Changes in Aβ burden



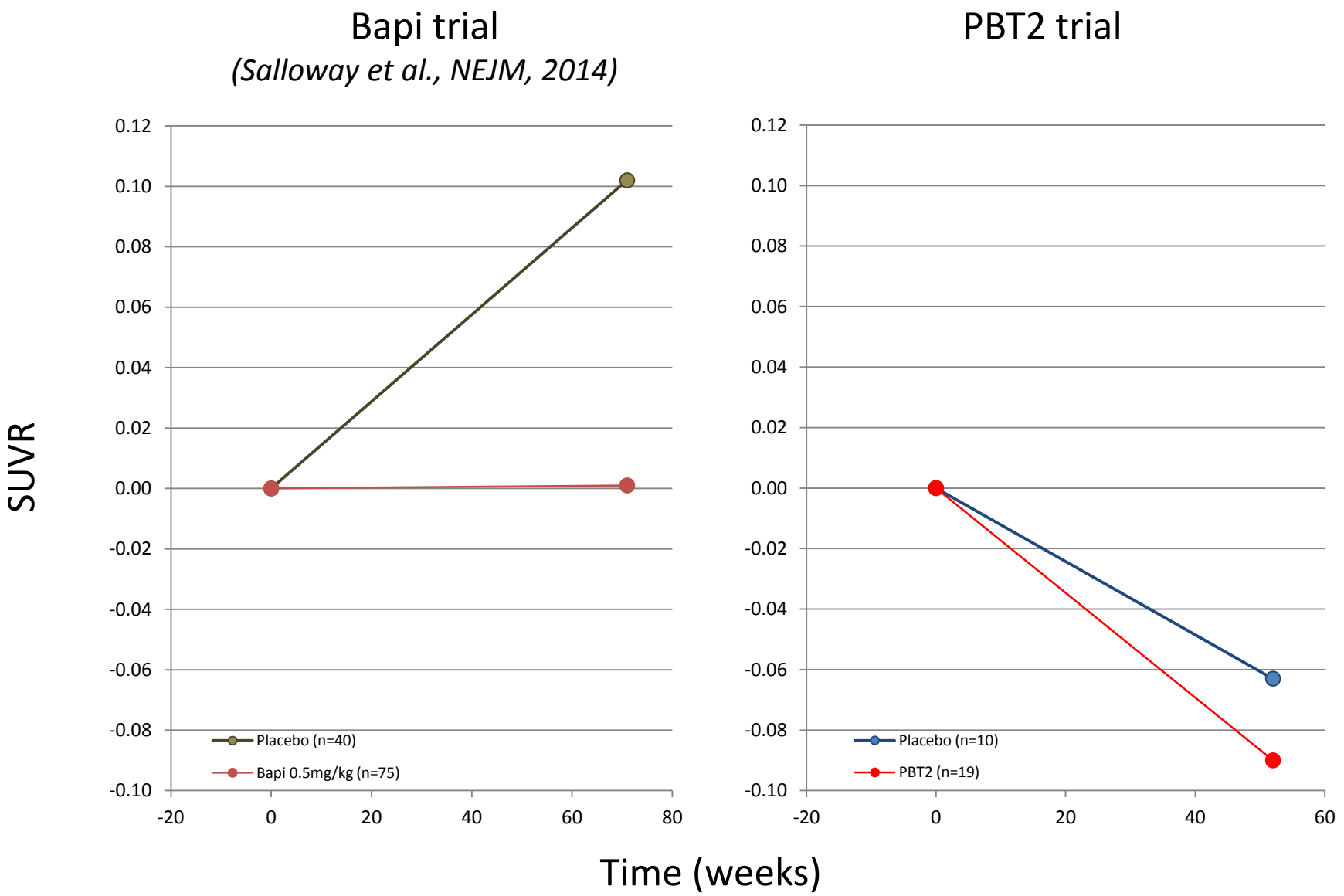
Changes in Aβ burden

(ε4 & non-ε4)

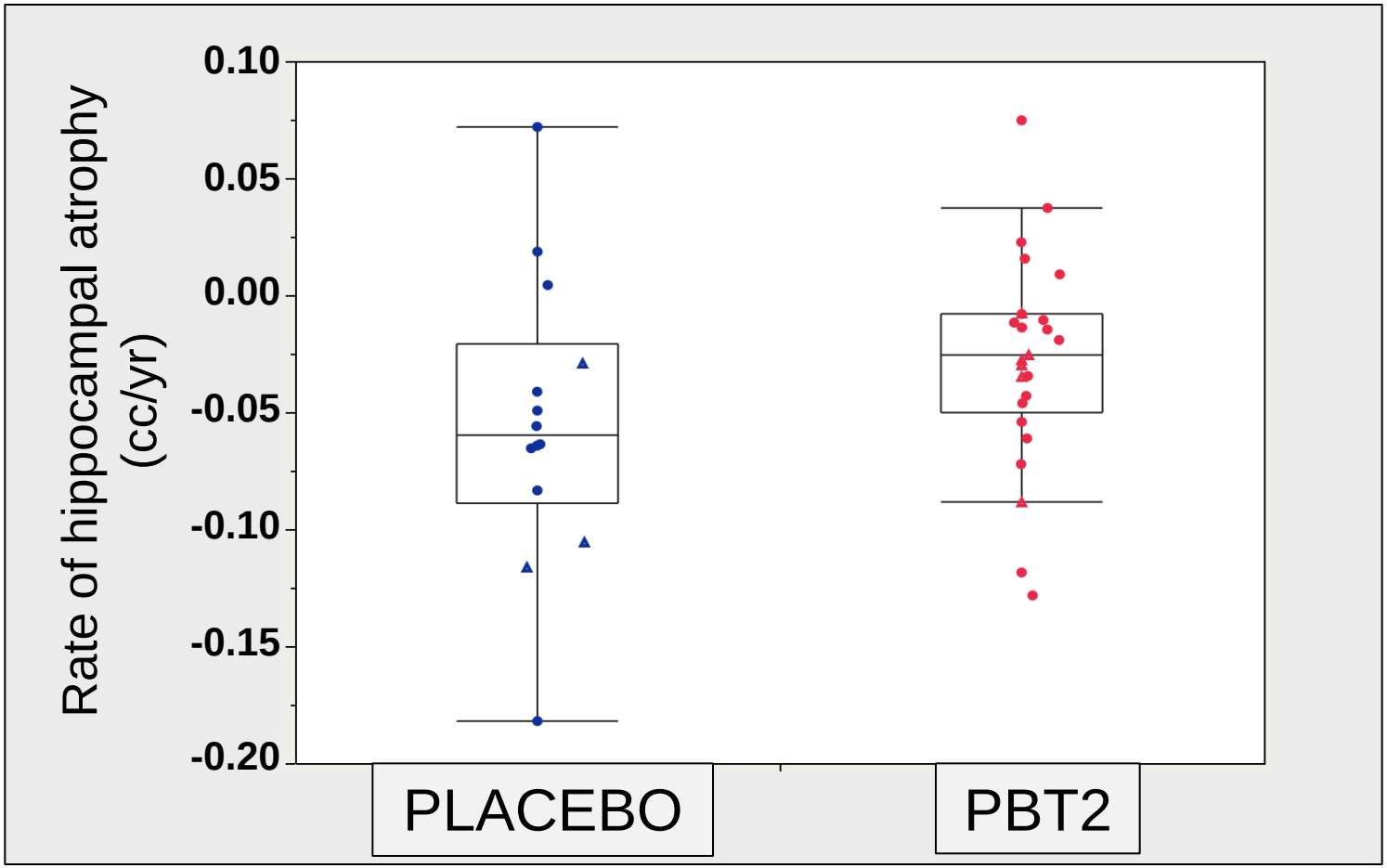


Changes in Aβ burden

(ΔLMM – ε4)



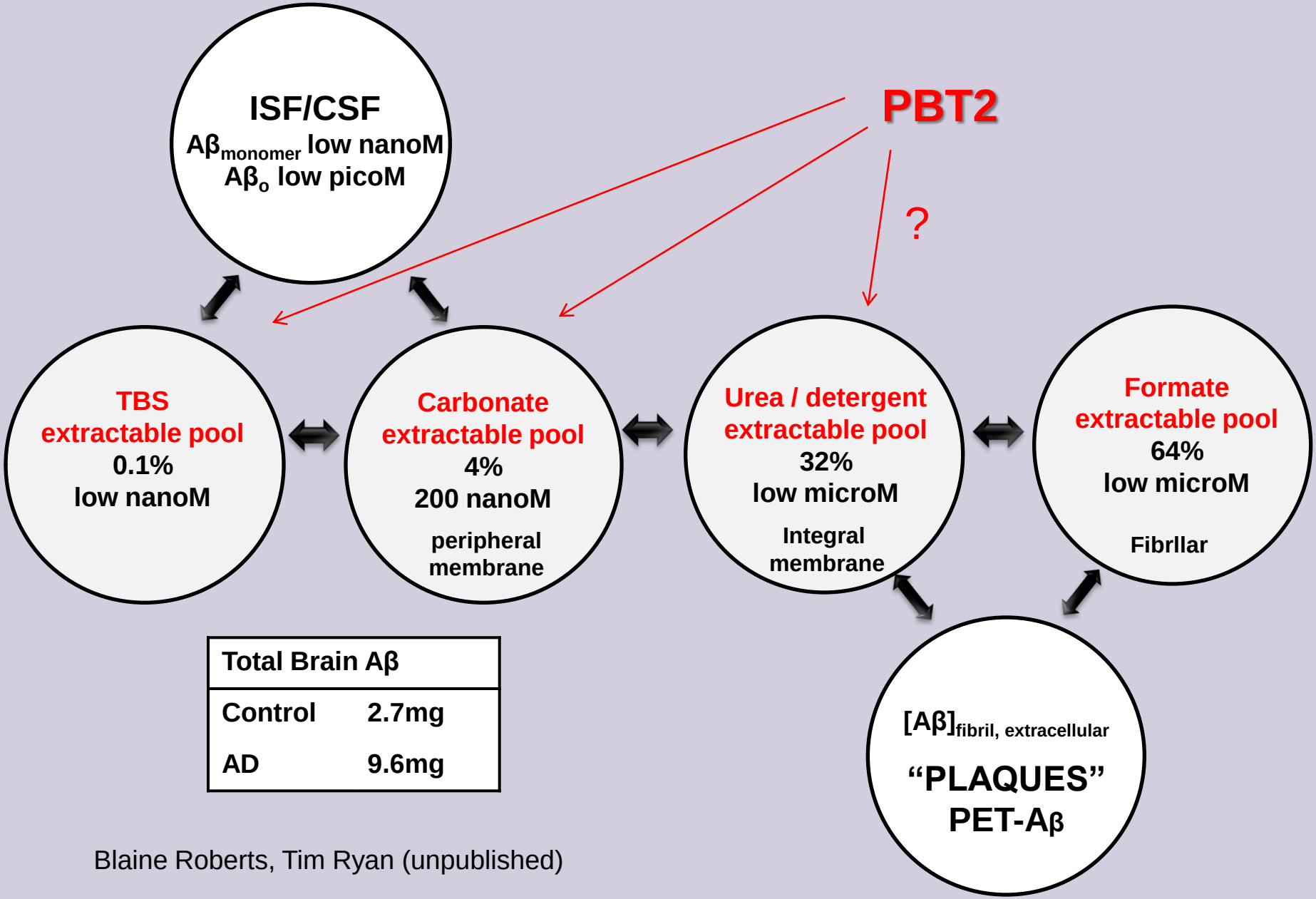
Rates of hippocampal atrophy



PBT2 declined at almost half the rate of the placebos (-0.055 vs -0.028 cc/yr for placebo and PBT2, respectively. ns). **Neuroquant software*

PLACEBO (n=15) ε4 *non-ε4*
PBT2 (n=25) ε4 *non-ε4*

The metabolic pools of Aβ



Total Brain Aβ	
Control	2.7mg
AD	9.6mg

Blaine Roberts, Tim Ryan (unpublished)

Preliminary conclusions from PBT2-204 Trial (Imagine)

- Significant correlation between baseline SUVR and change over 12 months in PBT2 group (decline in SUVR with higher baseline [>2.5], not seen in placebo), and significant decrease in PBT2 group after adjusting for baseline
- BUT intake SUVR values higher than expected (2.46); placebo group declined (n.s.) over 12 months whereas comparator groups (AIBL and Bapi) increased significantly; individual variability large; relatively small numbers: these factors contributed to group means not differing

General conclusions

- Some Aß-directed therapies are shifting the PET/CSF signals, but the effect so far is weak: Mcabs to the N-terminus (Bapi) promote plaque clearance but may not affect toxic species (no cognitive effect); Mcabs to the mid-region (Sola) may neutralize soluble toxic species (with cognitive benefit) but have no effect on “plaques”; compounds which target toxic oligomers (PBT2) lower the membrane-pool (principal PiB-PET read-out?) with some cognitive benefit (EURO trial).
- Failure to stratify by genetic determinants which control rates of change may lower signal:noise ratio
- Need better characterizations of the metabolic pools of Aß and specific therapies for lowering production, shifting their equilibria, or promoting clearance. Combinations of drugs targeting different components of these pools should be explored.
- Clearing the AD brain of 10mg of aggregated Aß should not be an insurmountable objective!

The AIBL Study Team

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- Cogstate: Paul Maruff
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