TauRx Pharmaceuticals Ltd

Therapies and Diagnostics for Neurodegenerative Disease

The place of Tau in the pathology, treatment and prevention of Alzheimer's disease and Frontotemporal Dementia

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Professor of Old Age Psychiatry, University of Aberdeen
& Chairman TauRx Therapeutics

Tau vs amyloid-β biomarker sequence

General agreement that AD has long prodrome over at least 20 years

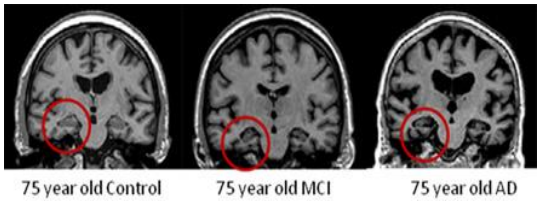
Pre-clinical	Prodromal	Mild	Moderate	Severe
Cognition	**Cognition**	**Cognition**	**Cognition**	Cognition
Function	Function	**Function**	**Function**	**Function**
Global	Global	**Global**	**Global**	**Global**
Behaviour	Behaviour	Behaviour	Behaviour	**Behaviour**

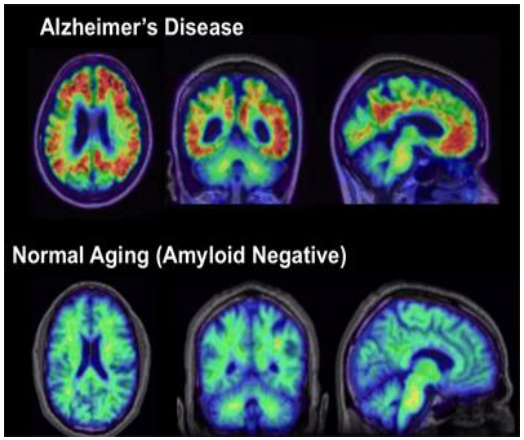
Biomarkers will increasingly play a critical role in definitions of populations for clinical trials and evidence of efficacy in Preclinical and Prodromal AD

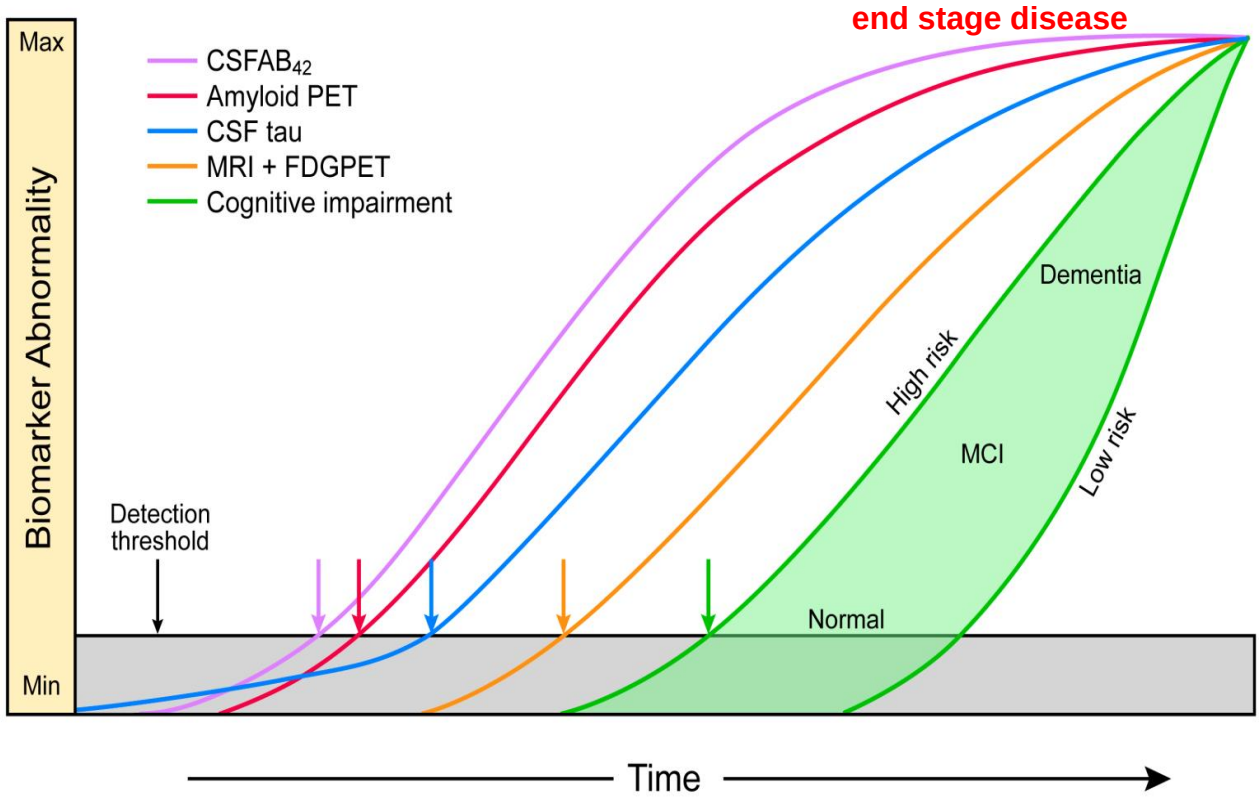
Major opportunities and challenges for development and validation of companion biomarkers

Conjectured biomarker sequence assumed to validate amyloid-β theory of pathogenesis

- Positioning of amyloid-β changes as prior to others



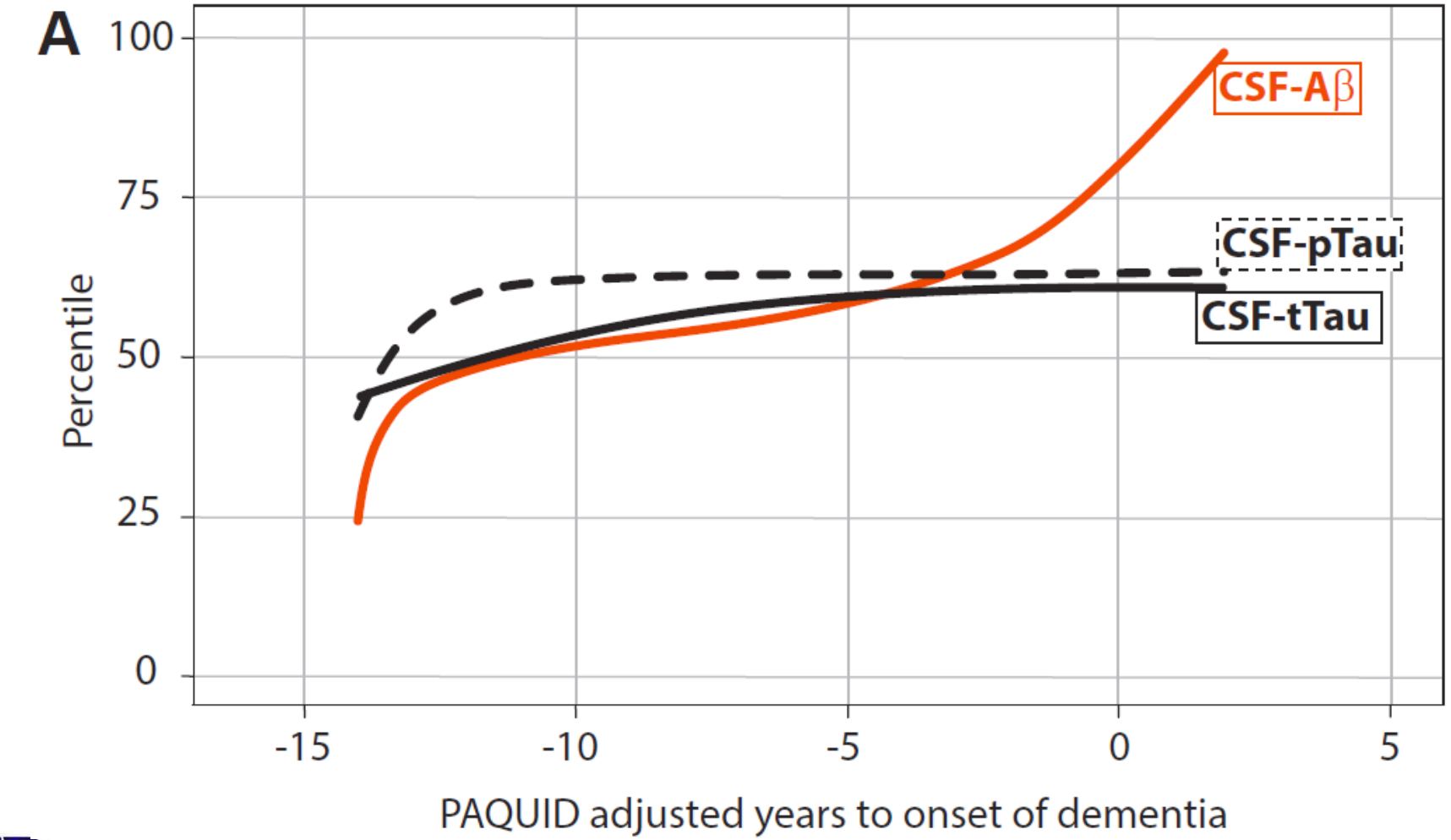




The Jack et al. (Lancet Neurology, 2013) model emphasises temporal priority of early amyloid changes

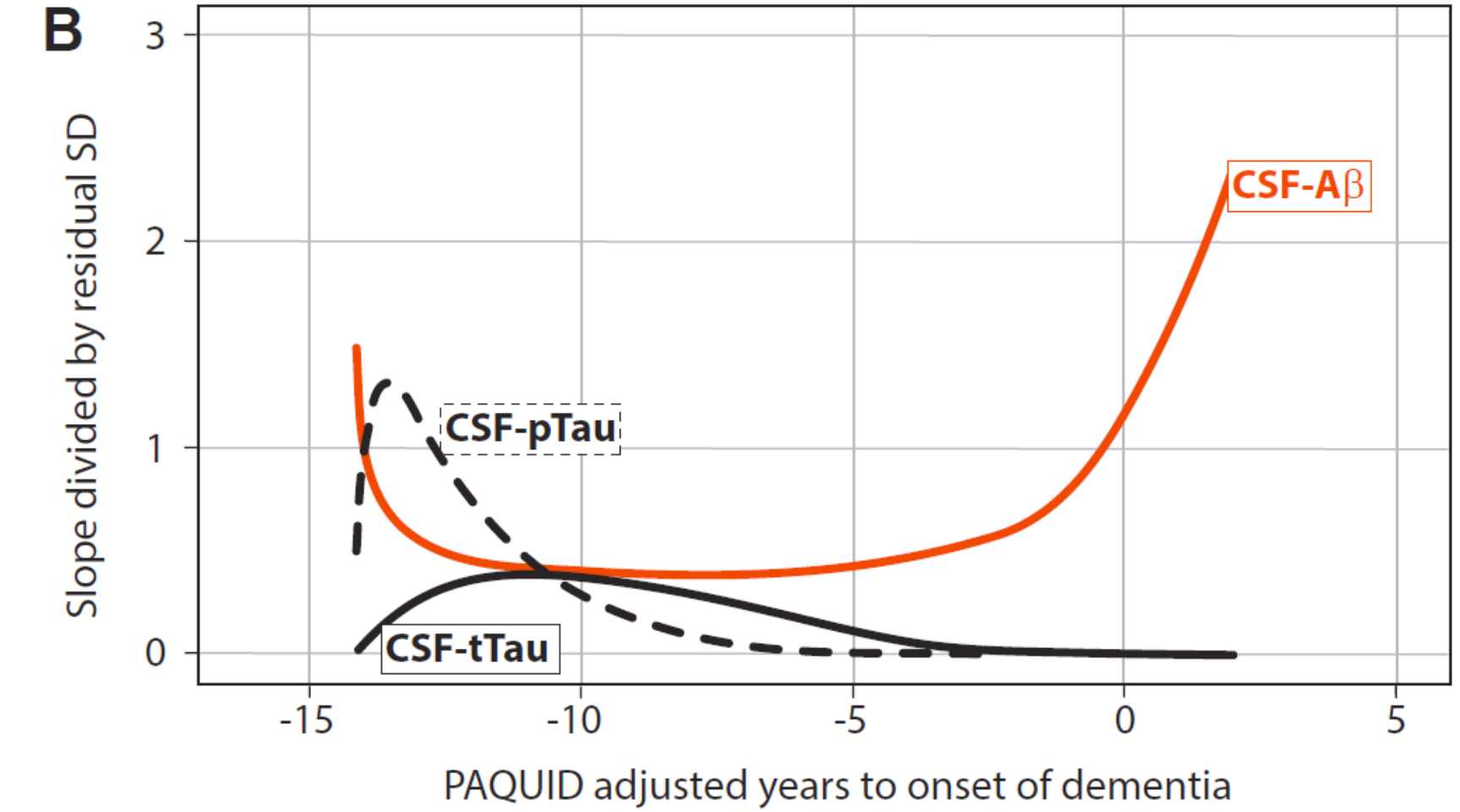
Widespread neurodegeneration and irreversible neuronal loss with progressive cognitive and functional impairment

However, estimates of long-term multivariate projection calibrated to MMSE progression produce different picture



From Donohue et al., Alzheimer's and Dementiia, 2014, 10: S400-S410,

Rate of change of biomarker changes suggest that Tau changes are very early

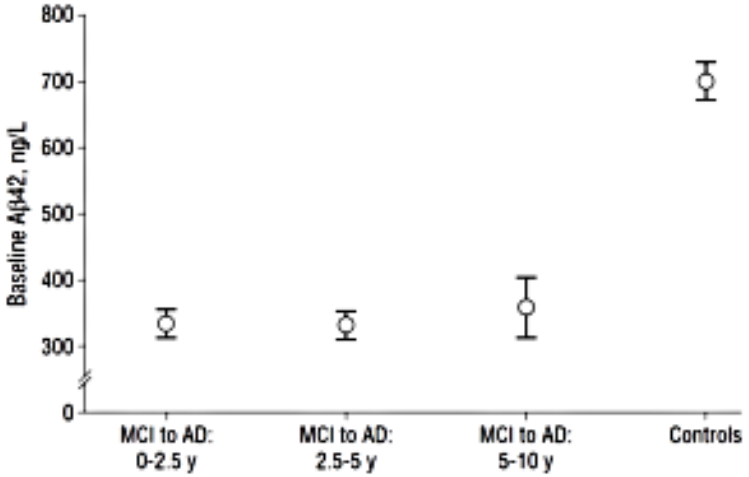


From Donohue et al., Alzheimer's and Dementiia, 2014, 10: S400-S410,

CSF changes in sporadic MCI → AD

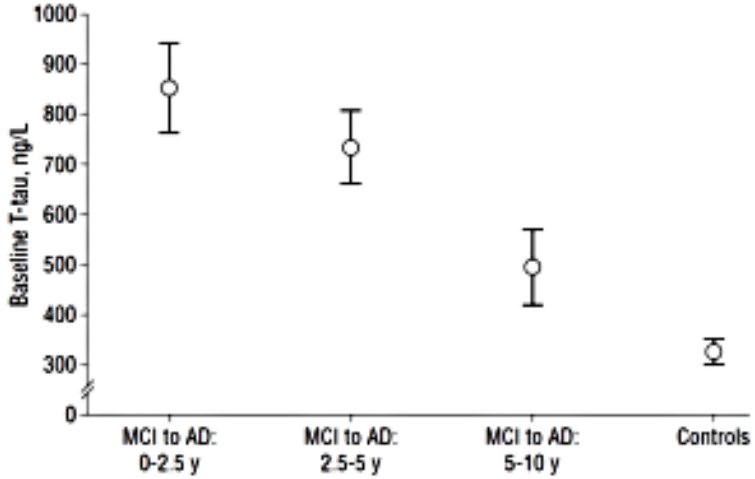
- 137 MCI patients followed for 9.2 yrs
- CSF Aß decreases 5 – 10 yrs before conversion to AD
- CSF tau increases steadily with disease progression
- First evidence of change in Tau and amyloid-ß occurs at same stage

CSF ß-amyloid



← Disease progression

CSF P-Tau

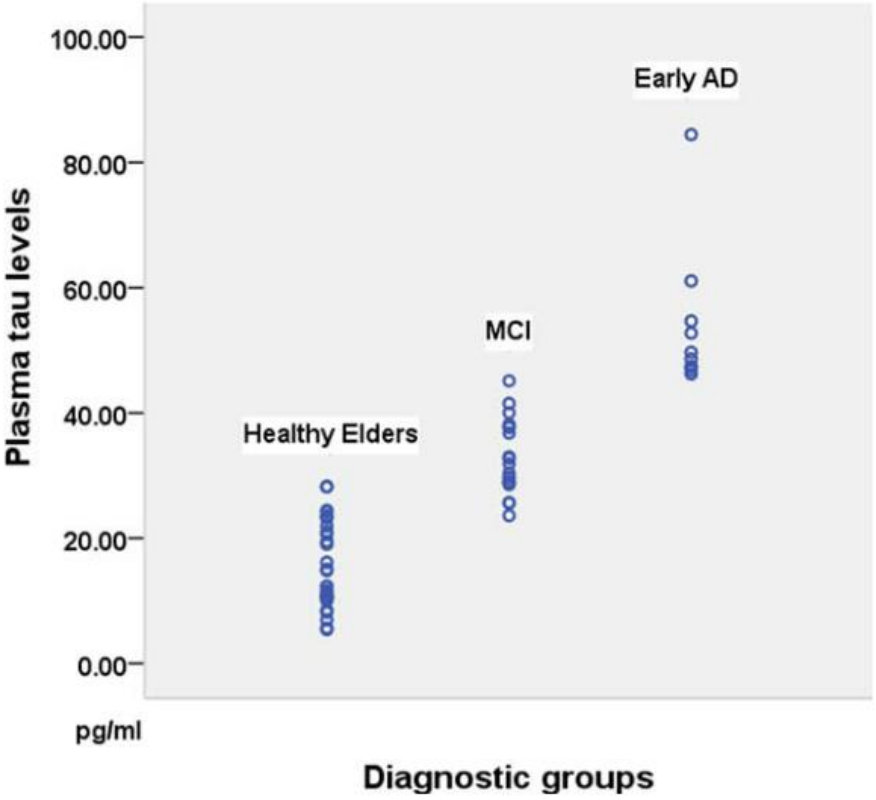


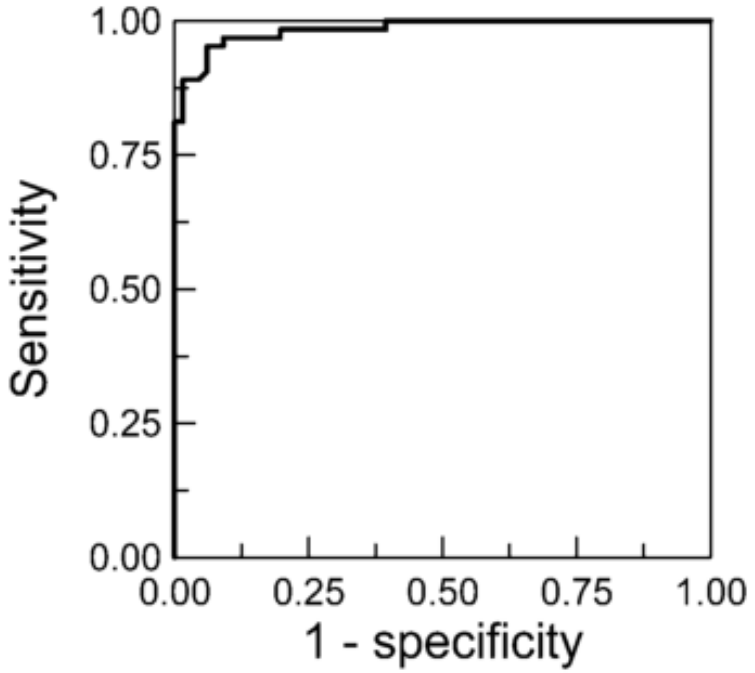
← Disease progression

Buchhave et al., Arch Gen Pysch 2012; 69:98-106

Plasma Tau marker[1] disriminatory and correlates with cognitive changes[2] irrespective of Aβ PET status[3]

	r	p
Correlation with HC volume	0.638	<0.0001
Correlation with logical memory	0.825	<0.0001





	HC vs MCI/AD	MCI vs AD
Sensitivity	0.97	0.82
Specificity	0.91	0.80

Chiu et al., ACS Chem Neurosci 2013; 4:1530-1536

[2]Chiu et al., Hum Br Mapp 2014; 35:3132-3142
[3]Tzen et al., 2014, ACS Chem. Neurosci. 5:830

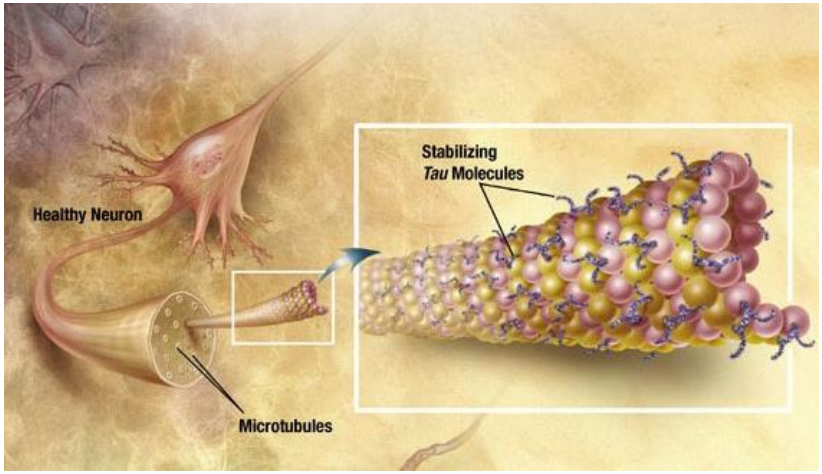
[1]Note that antibody used binds C-terminal tau46 and MAP2

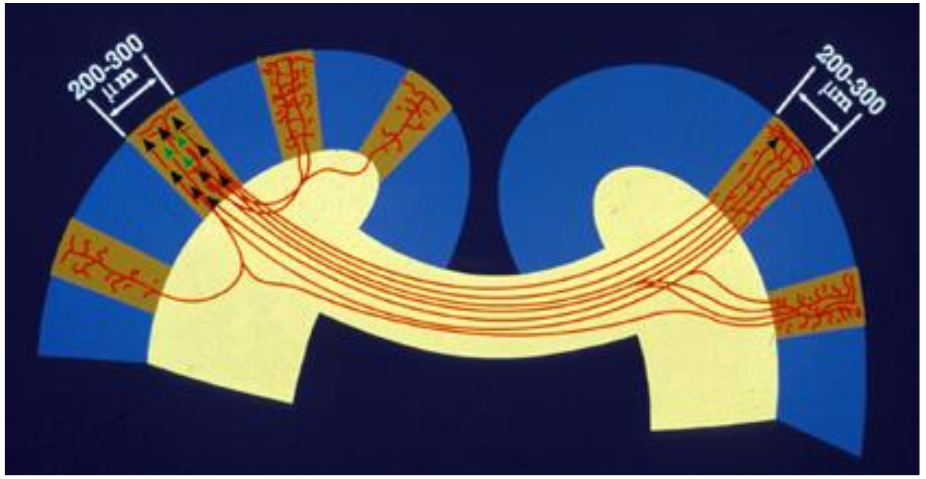
The Tau Pathology of AD

Tau protein normally stabilises axonal microtubules: but polymerises to form Paired Helical Filaments in AD

Tau protein normally functions to stabilize axonal microtubules

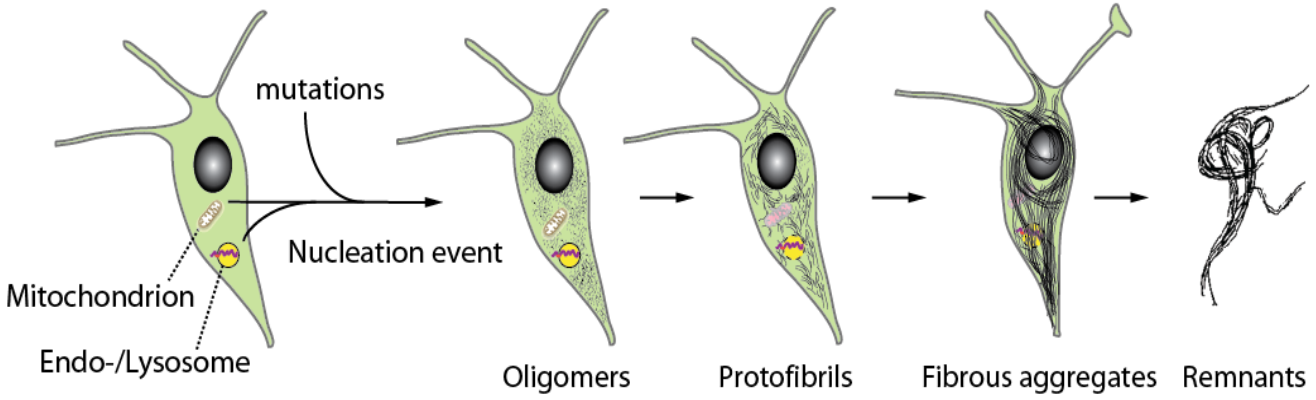
These are critical for axonal transport in cortico-cortical association circuits



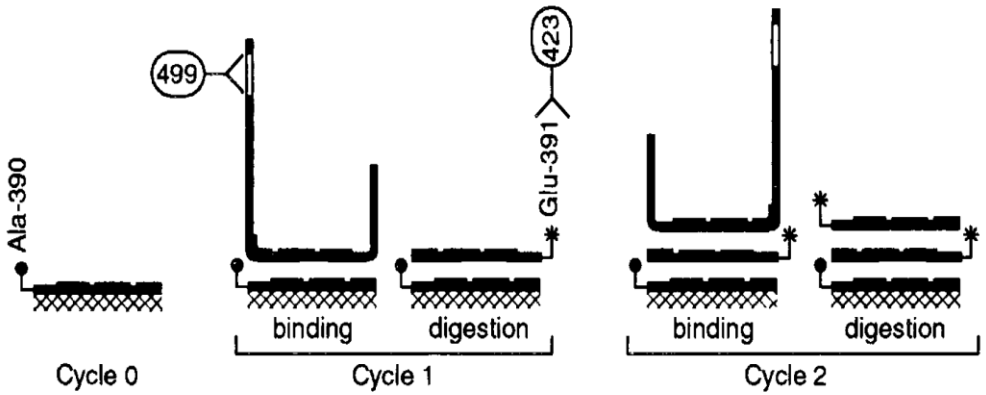


In AD Tau aggregates to form first oligomers then fibrous aggregates composed of de novo Tau polymers - Paired Helical Filaments (PHFs)

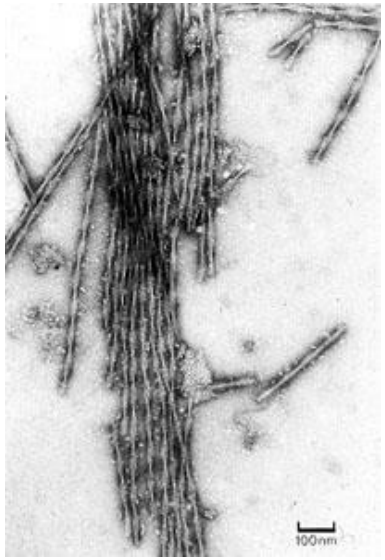
Alzheimer called these fibrous aggregates “neurofibrillay tangles”

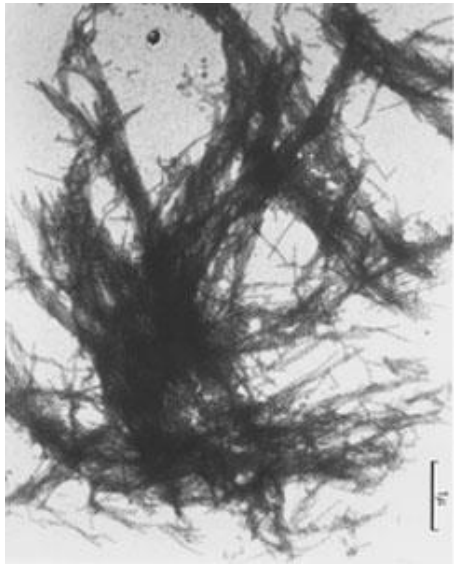


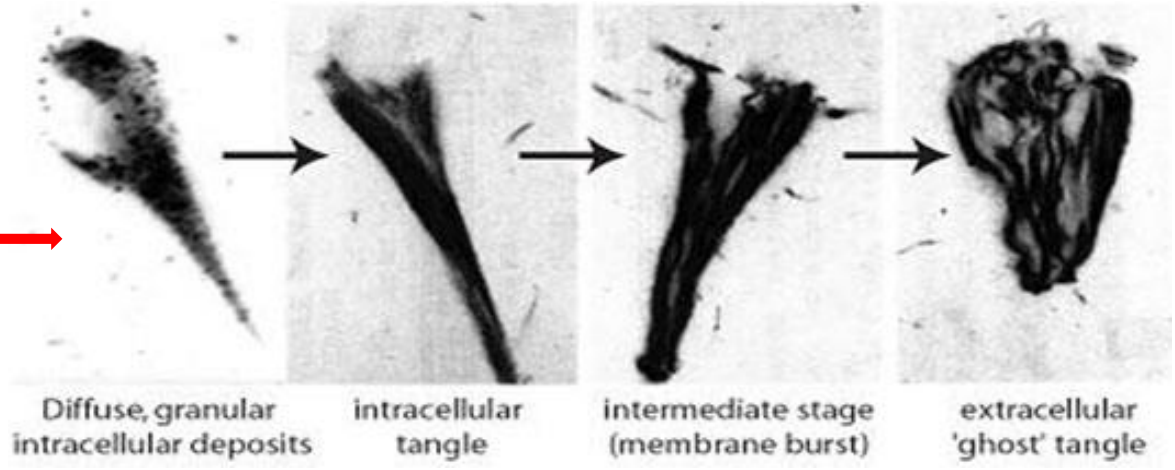
Core-oligomer of PHF Tangle is proteolytically stable and self-replicating[1] (ie prion-like[2])



[1] Wischik et al., PNAS, 1996, 93:11213–11218



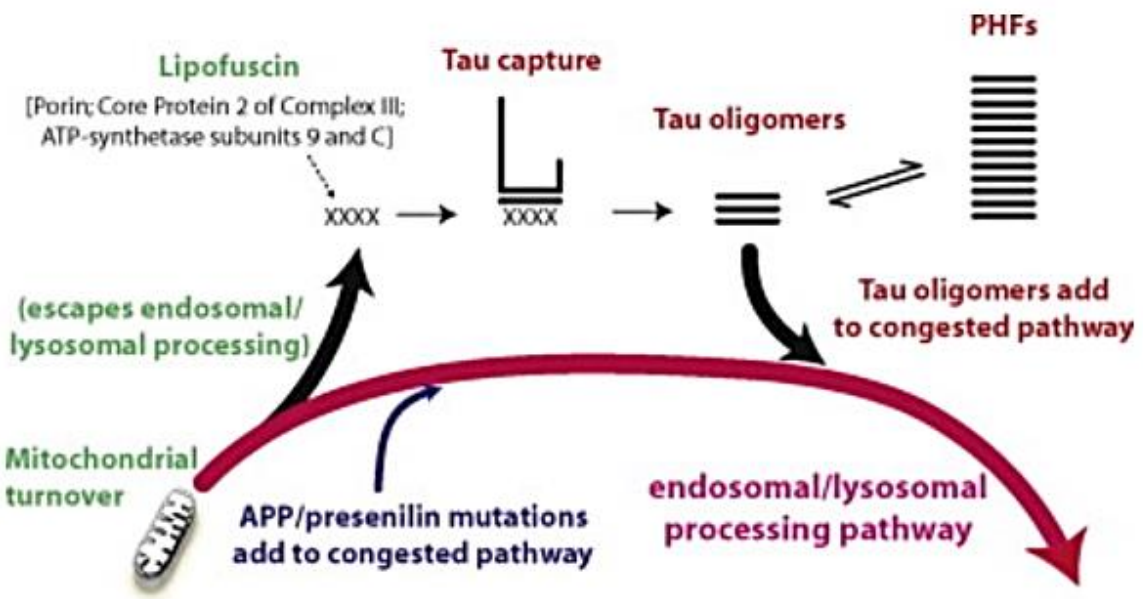


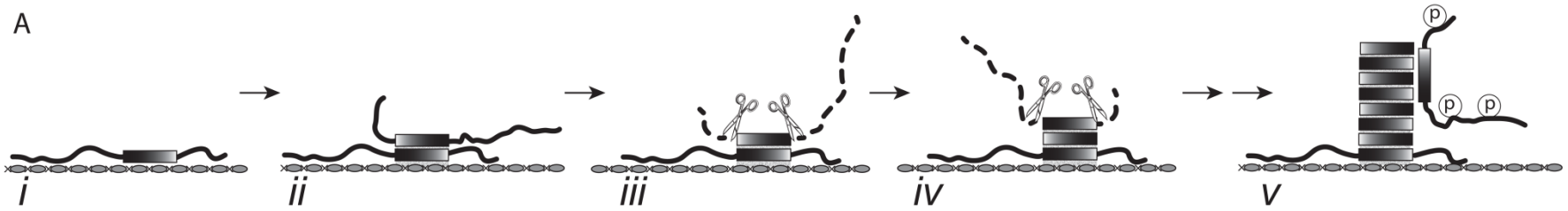


[1] Wischik et al., 1996, PNAS 93:11213-11218;
[2] Wischik et al., 1997, in Microtubule-Associated Proteins: Modifications in Disease., ed. J. Avila, R. Brandt, K. S. Kosik. pp. 185-241

Importance of age-related impairment of mitochondrial turnover by endosomal-lysosomal pathway

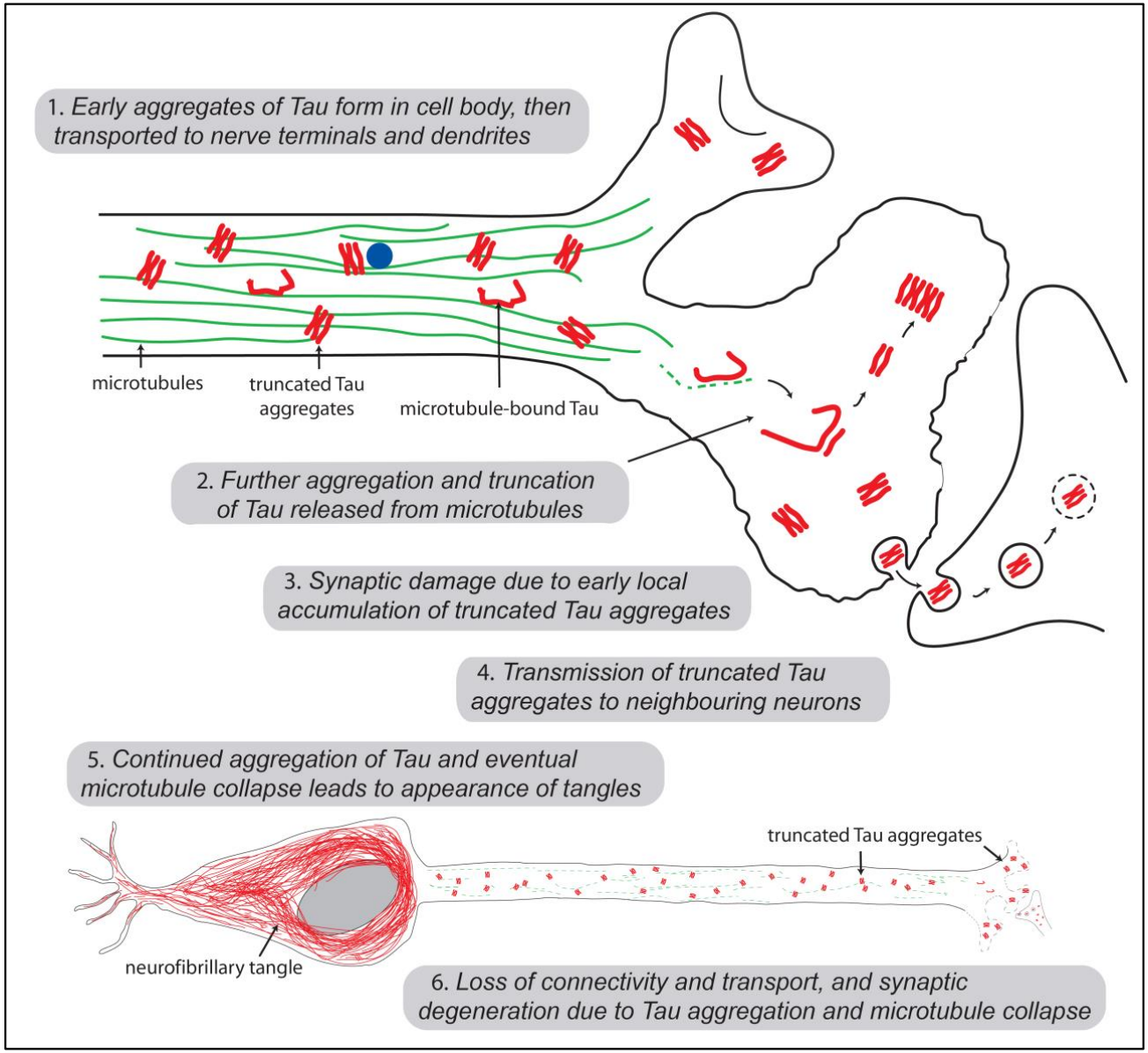
- Potential to identify markers of up-stream endosomal-lysosomal dysfunction



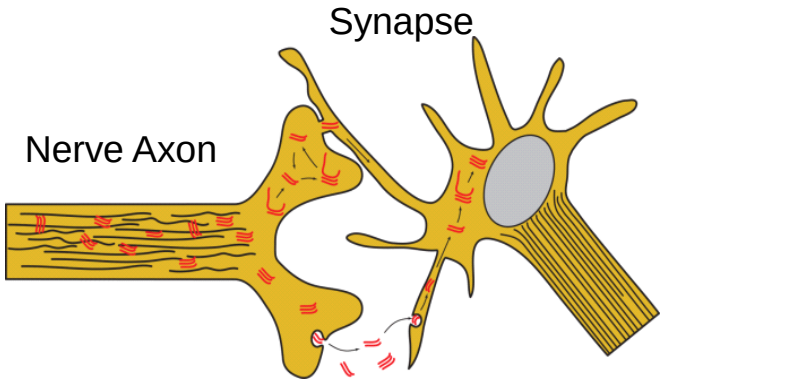


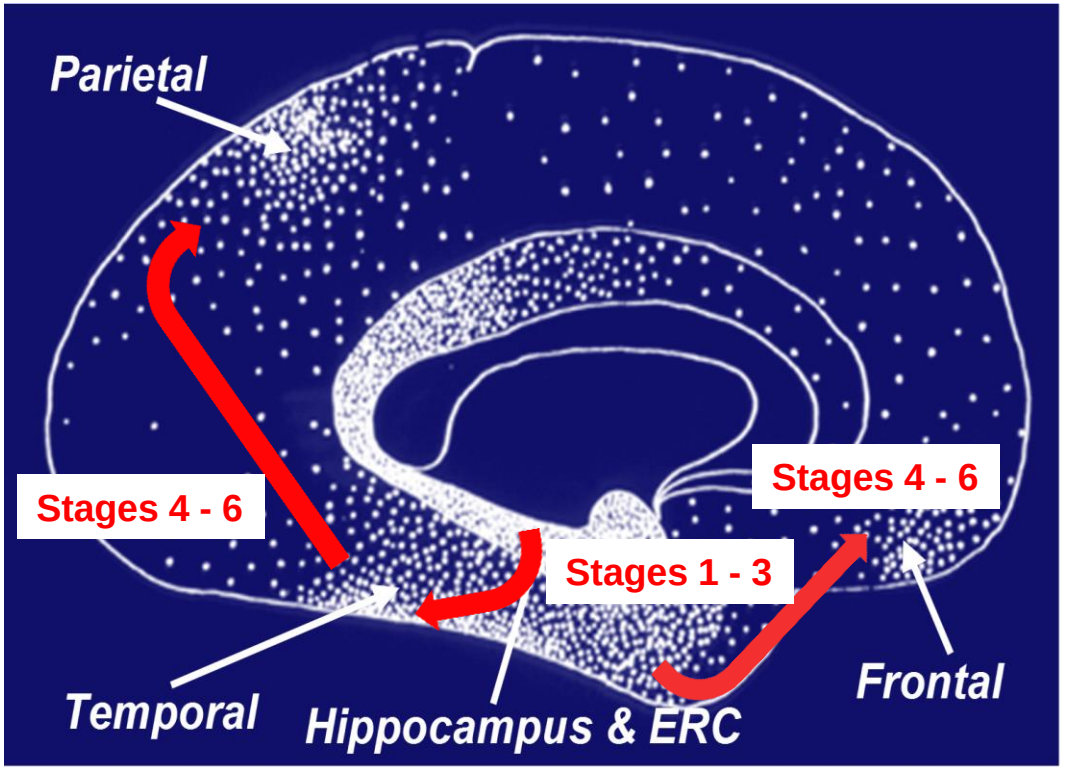
[1] Wischik et al. Tau-aggregation inhibitor therapy for Alzheimer's disease. Biochem Pharmacol (2014), 88:529-539

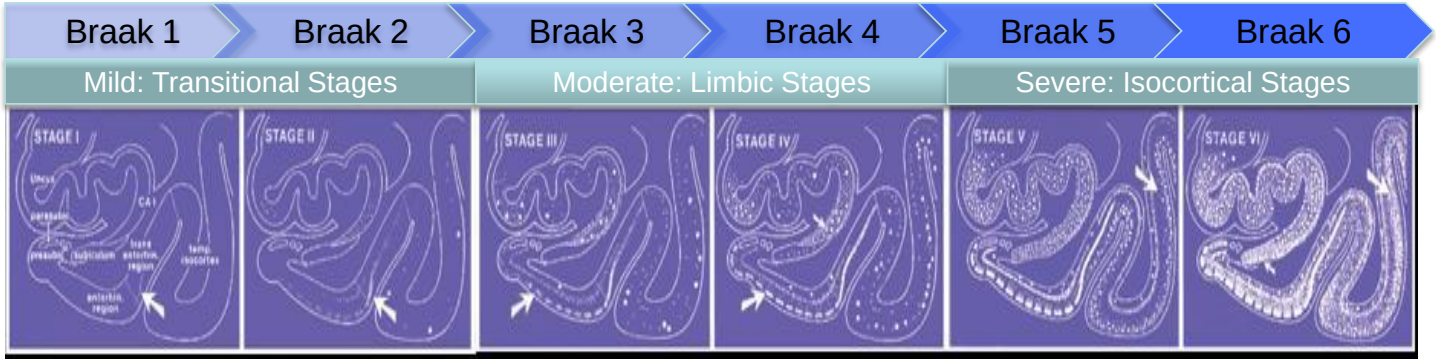
Tau oligomers damage synapses and transmit the aggregation process – ie infectious



Spread of pathology and Braak staging[1]



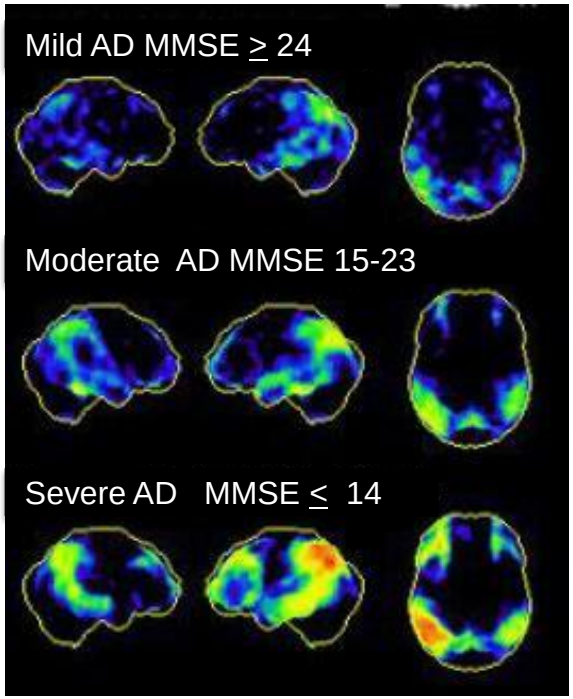




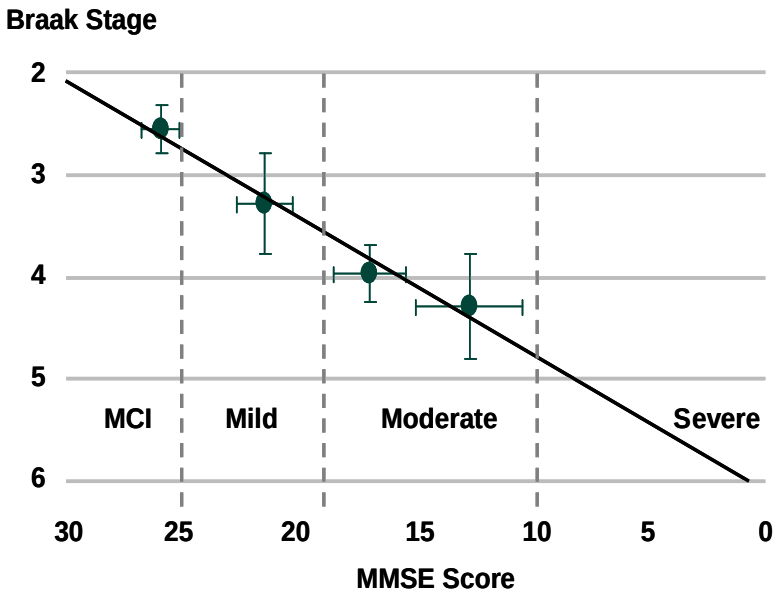
[1] Braak and Braak., 1991, Acta Neuropathol, 82:239-259

Relationship between Brain Scan, MMSE and Braak

Scan deficits correlate with Braak stage[1]



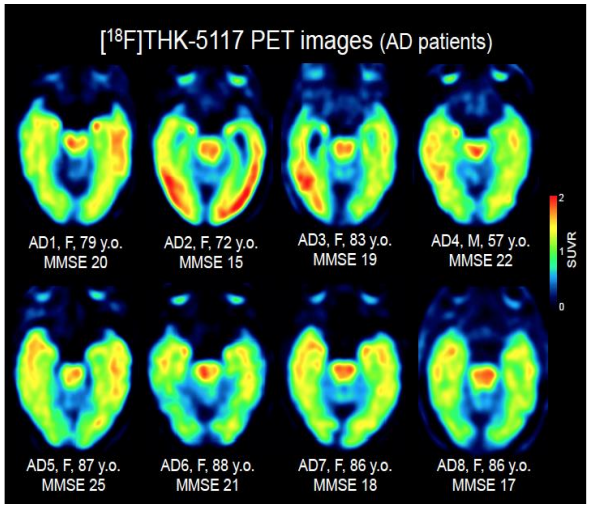
Clinical progression correlates with Braak stage[2]



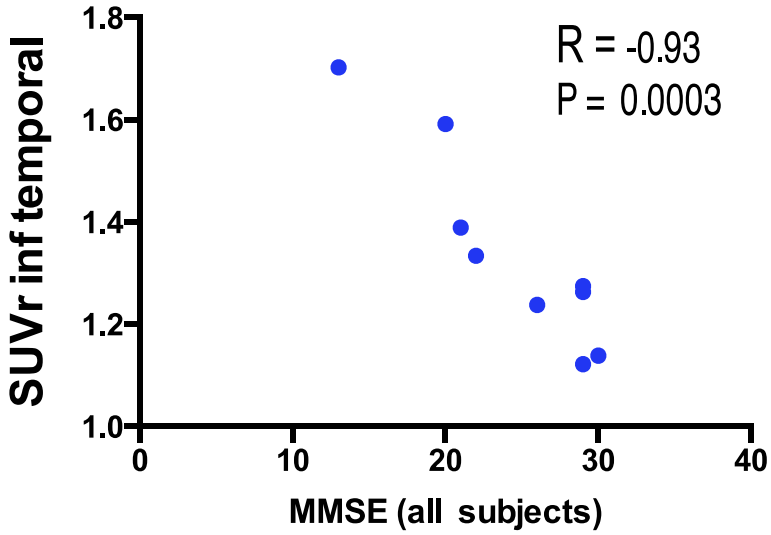
[1] Jobst et al., 1992, J Neurol Neurosurg Psychiat
Bradley et al., 2002, Brain, 125, 1772-1781
Nishimura et al. 2007, Ann Nuc Med

[2] Mukaetova et al., 2000, Am J Pathol, 157: 623-636

Tau-PET ligand uptake correlates with cognitive status in AD and in normal elderly

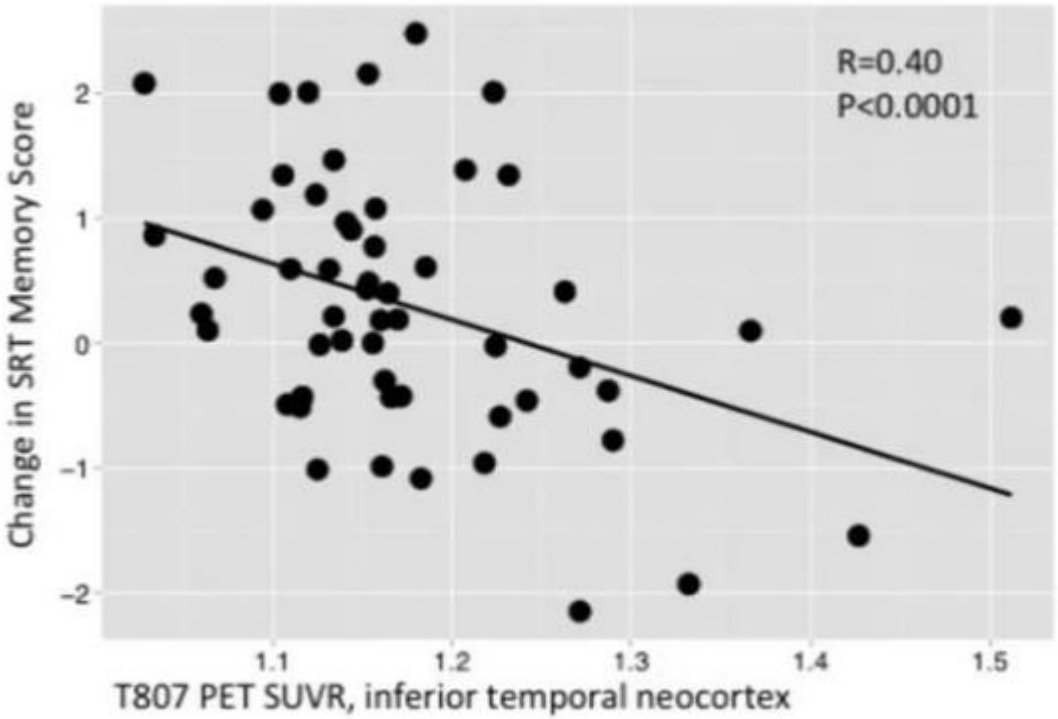


THK(R,S)-5117



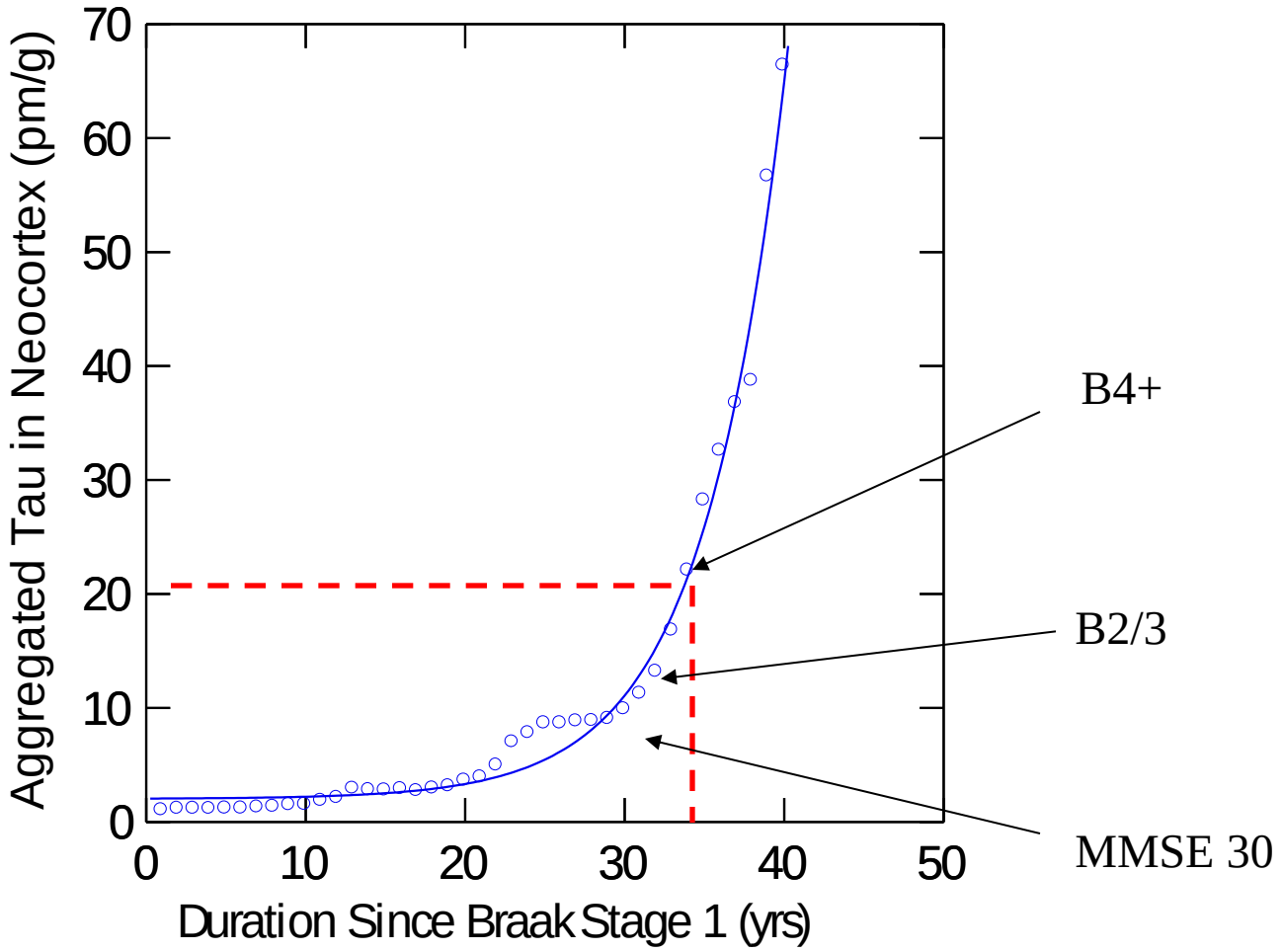
MNI data in AD using THK-5117, kindly provided by John Seibyl and Ken Marek

Temporal neocortical tau deposition measured by PET (T807) is associated with longitudinal decline in memory performance among clinically normal elderly



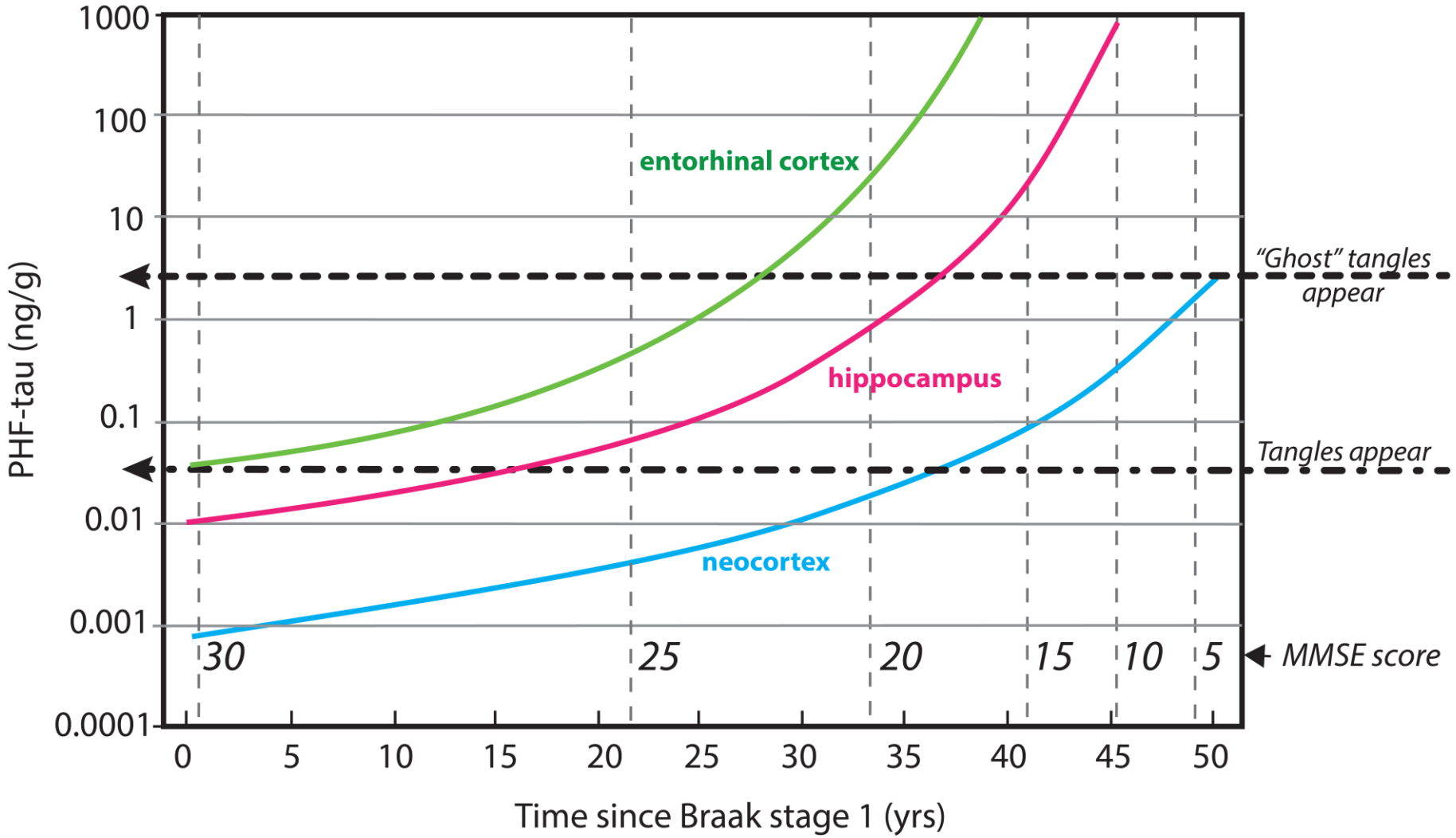
Johnson et al., (2014) AAIC presentation, DT-01-02

Tau accumulation is exponential with respect to Braak stage, MMSE and time



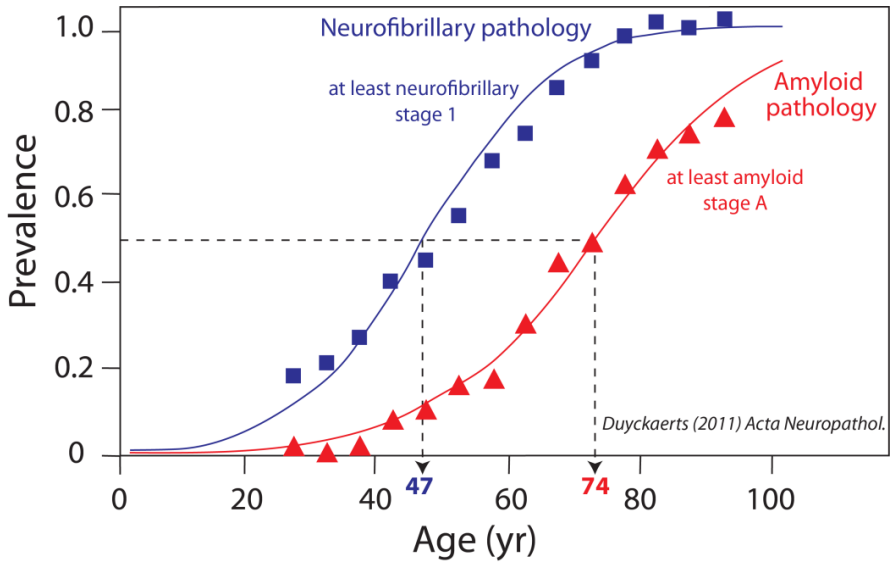
Wischik et al., (2015) In press in: Progress and Challenges in Developing Therapeutics for Alzheimer's Disease (Edited by M.S. Wolfe)

Tau aggregation, pathology and cognitive impairment in AD



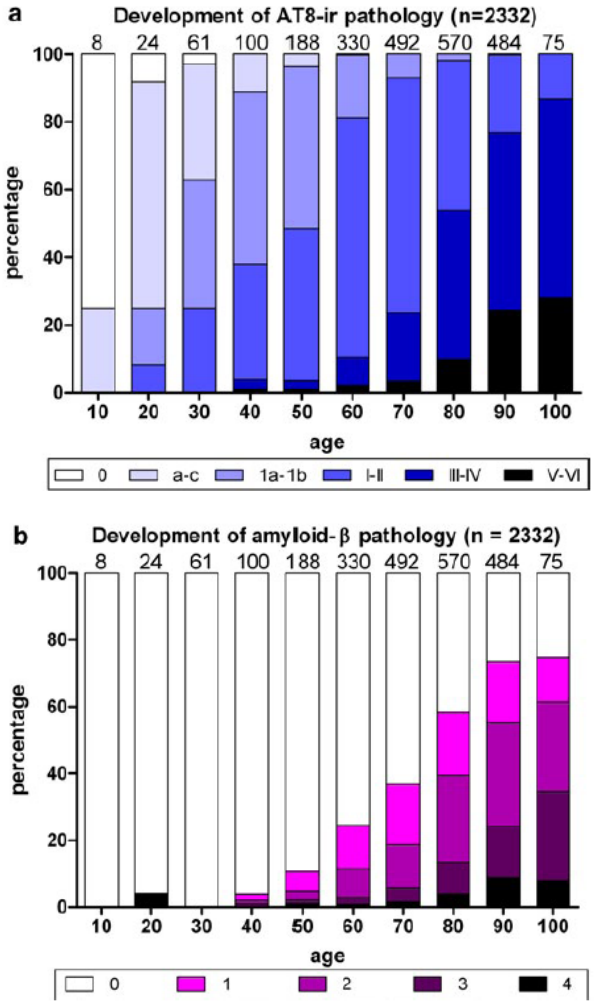
Wischik et al., (2015) In press in: Progress and Challenges in Developing Therapeutics for Alzheimer's Disease (Edited by M.S. Wolfe)

Tau pathology PRECEDES amyloid-β pathology



Duyckaerts (2011) Lancet Neurology 10, 774-775.

Tau pathology at Braak stage 1 precedes amyloid-β pathology by 20 years in the brain

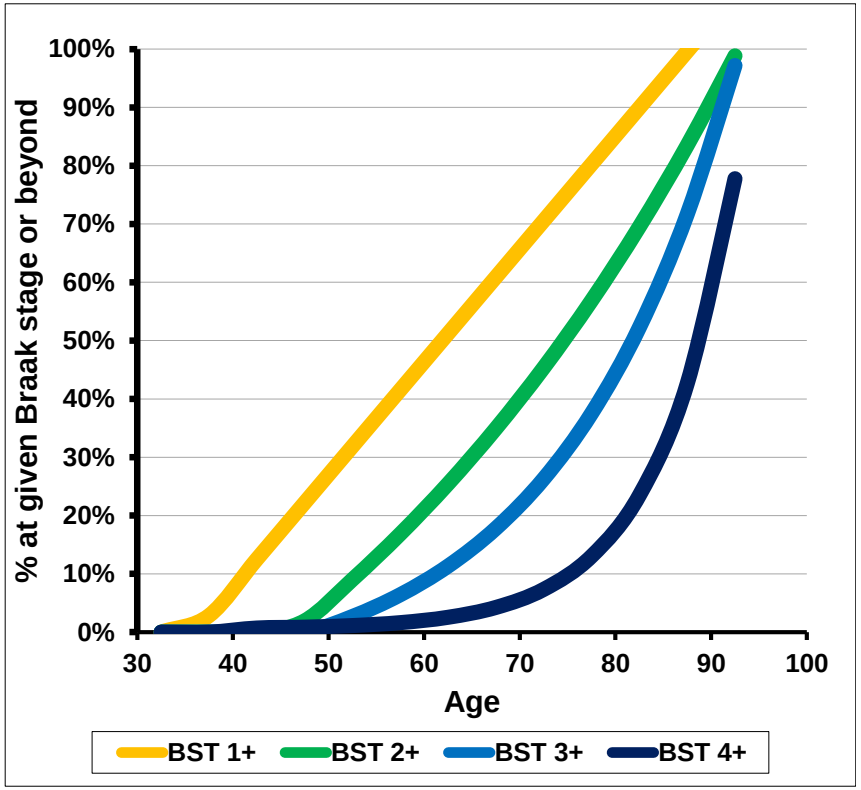


Braak et al (2013), Acta Neuropath,126:631-41

Demographics of Braak Staging

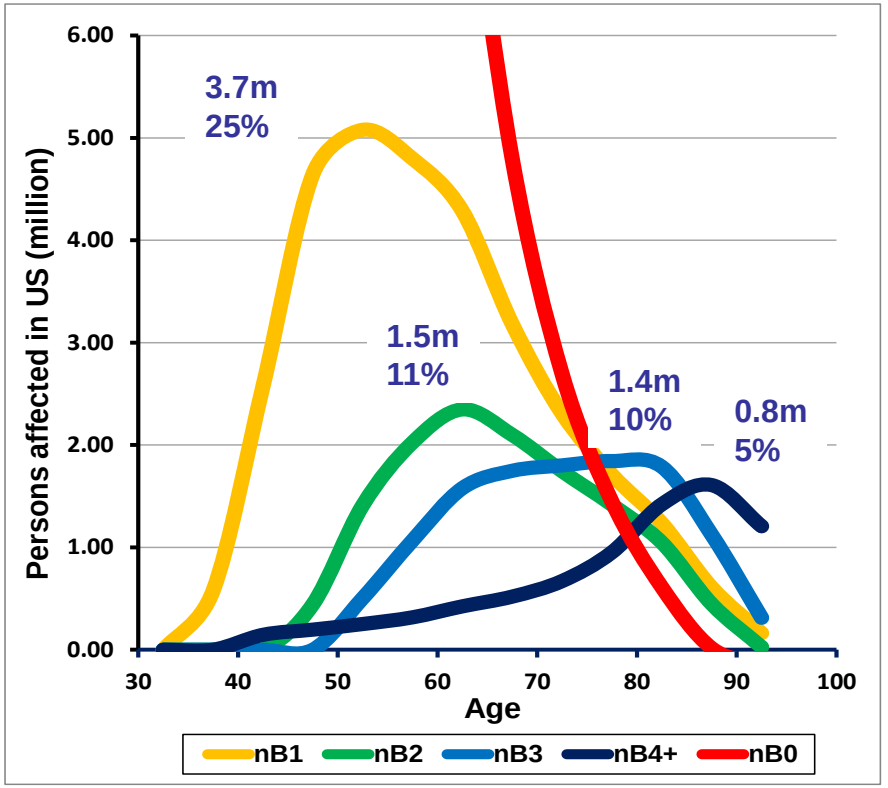
(Estimates based on Canada 2010 population)

Age-specific probability of Braak stage transitions, calculated from Ohm et al. (1995)[1] data from 847 post-mortems ages 45 – 95 with ~17 cases per year of life



Estimated Canada population prevalence by Braak stage and age[2]

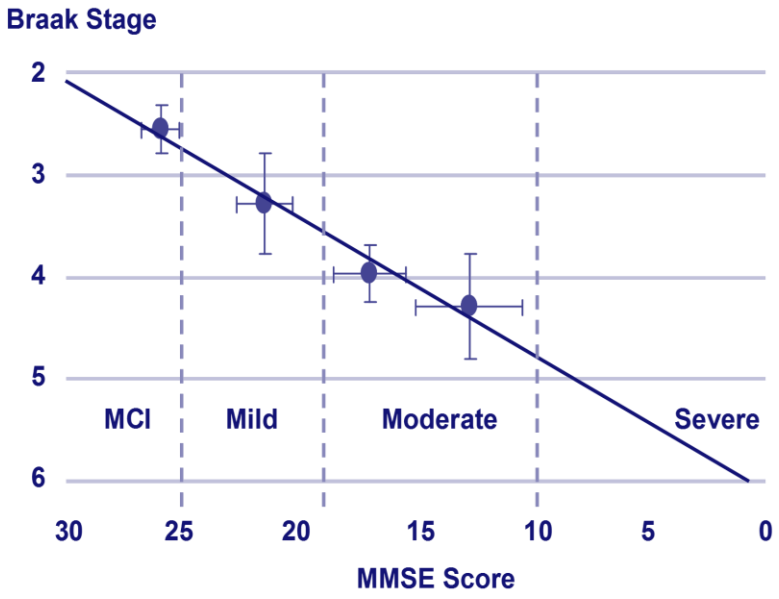
Of age >45 population (14.5m), **51%** have Tau pathology at B1+ (7.5m)



[1] Ohm et al. (1995), Acta Neuropathol ;64:209-217

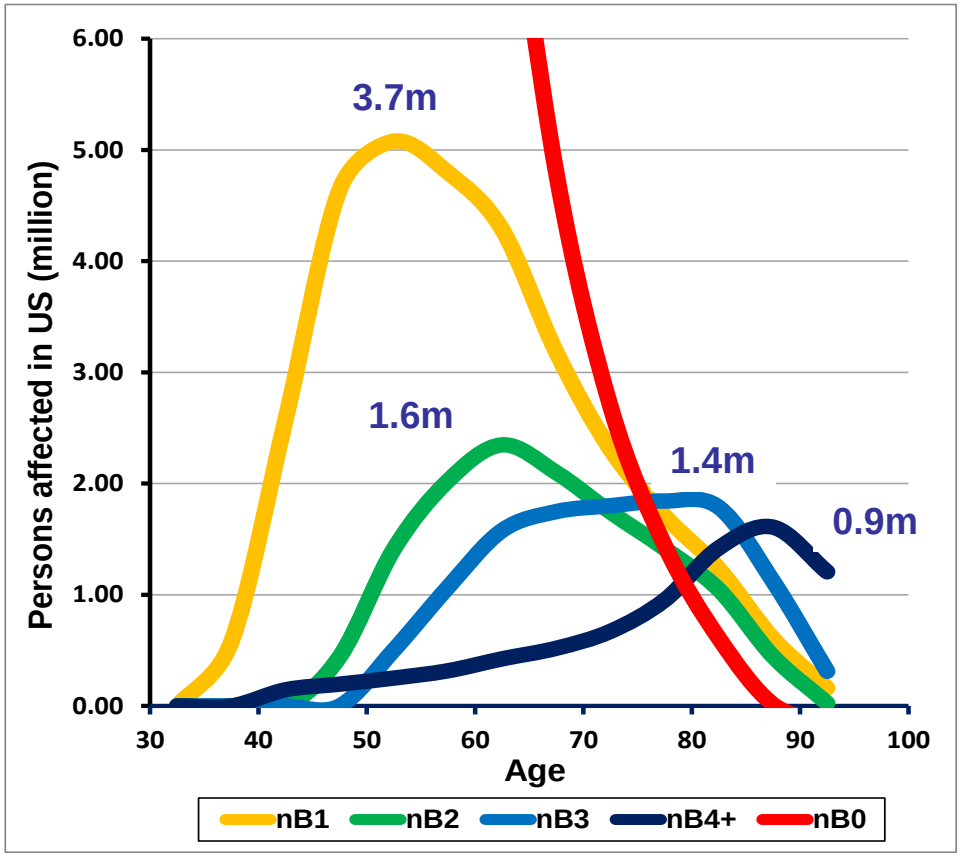
[2] Wischik et al. Tau-aggregation inhibitor therapy for Alzheimer's disease. Biochem Pharmacol (2014), 88:529-539

Tau Pathology is not late-stage:
Begins in middle age and progresses relentlessly



Predicted ages of onset and peak ages by Braak stage are:

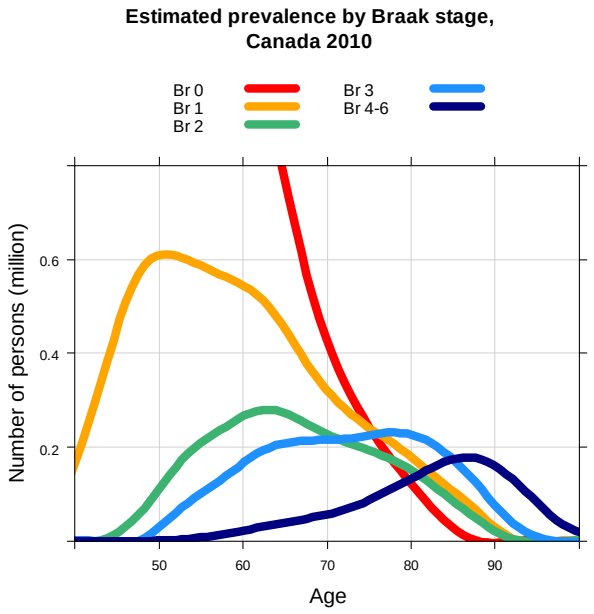
		Onset	Peak
stage	1	38	58
stage	2	48	63
stage	3	53	68 - 78
stages	4-6	43	88

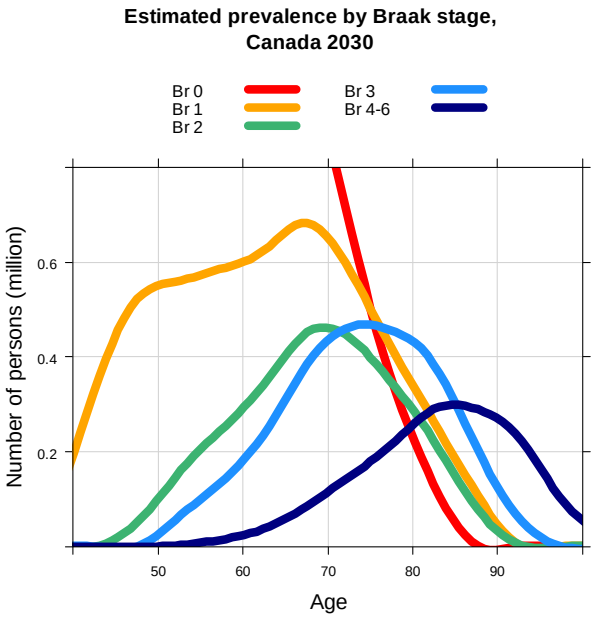


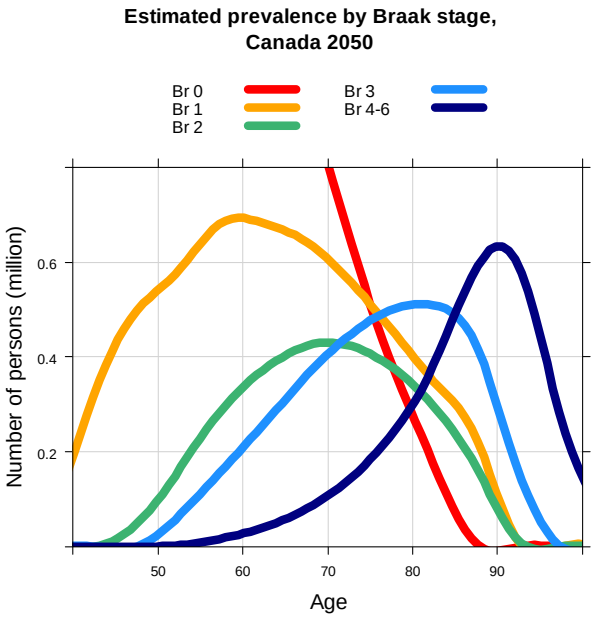
Canada affected population (2010)

(Calculated from Ohm et al., 1995) study of 847 post-mortems with 17 cases per year of life)

Braak stage prevalence, Canada 2010 - 2050







	2010	2030	2030	2050	2050
Br 1	3,696	4,761	129%	5,087	138%
Br 2	1,549	2,344	151%	2,573	166%
Br 3	1,426	2,395	168%	2,879	202%
Br 4+	782	1,435	183%	2,411	308%
Total	7,454	10,935		12,950	

Estimated prevalence of Tau aggregation in Canada

51% of over-45 population (7.5 / 14.5m) have some degree of tau aggregation pathology in the brain

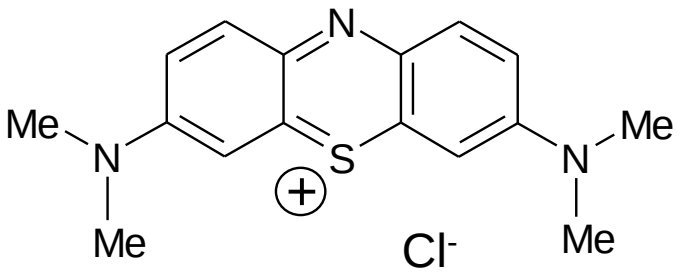
Of these:	**(peak age)**	
25% are at Braak stage 1	**(53)**	**3.7m**
11% are at Braak stage 2	**(63)**	**1.5m**
10% are at Braak stage 3	**(70)**	**1.4m**
5% are at Braak stage 4+	**(87)**	**0.8m**
51%		**7.5m**

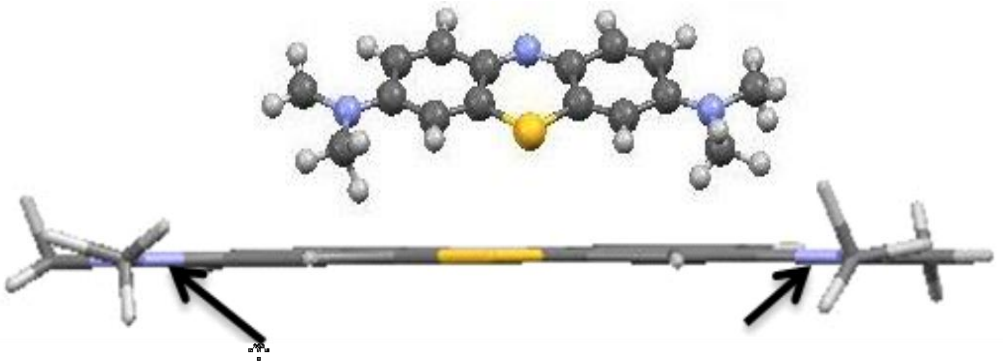
Inhibition/prevention of tau aggregation pathology is a potential pharmaceutical target for BOTH TREATMENT AND EARLY PREVENTION

Potential efficacy of
Tau Aggregation Inhibitor (TAI) Therapy

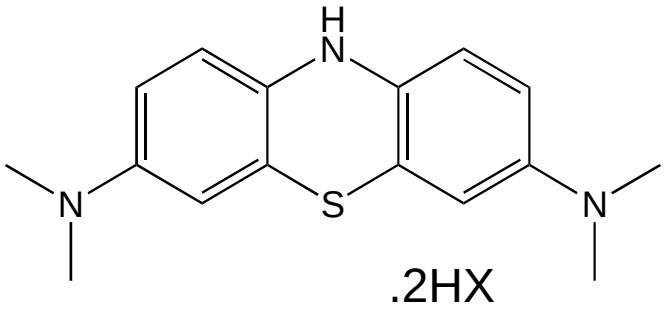
LMTX™ (stable reduced form of MT) overcomes absorption and tolerability limitations of MTC (methyl thioninium chloride)

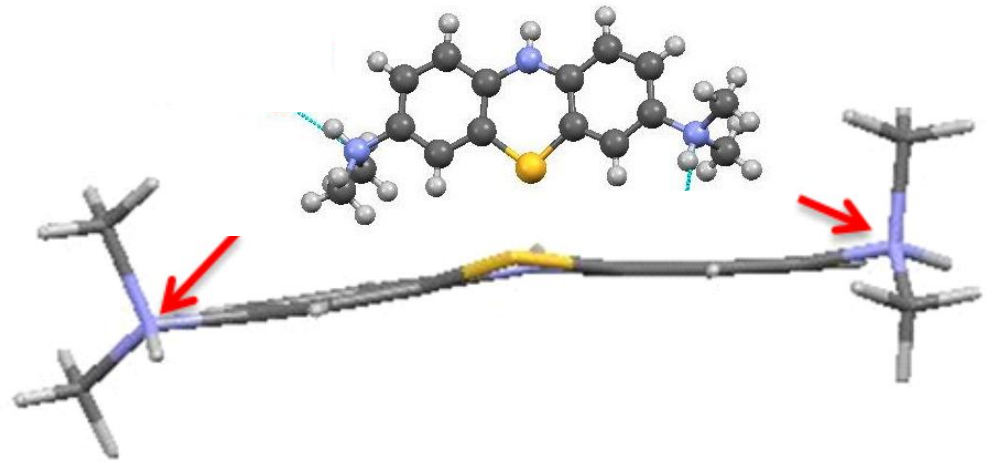
MTC





LMTX™



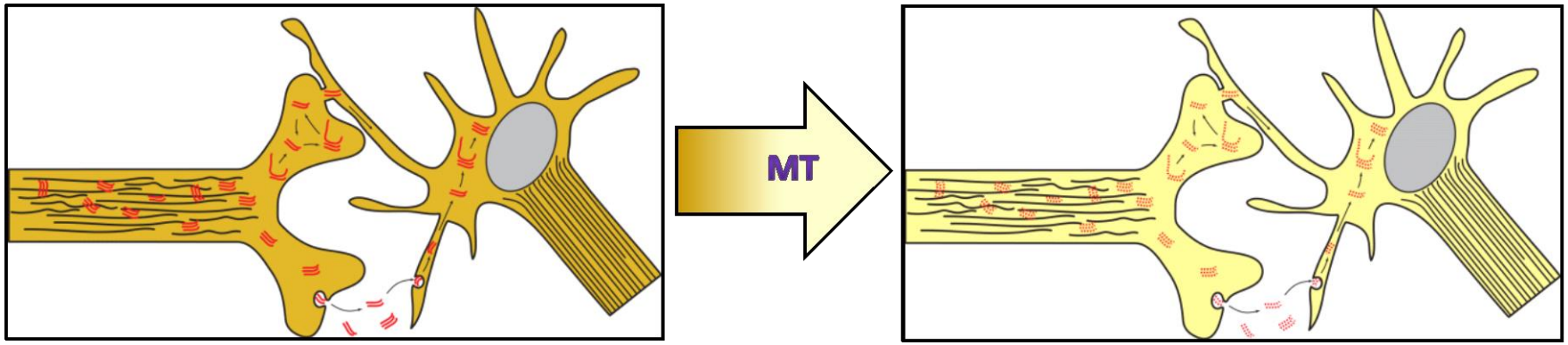


MTC is oxidised MT^+ and suffers from dose-dependent food interference with absorption, but poorly tolerated in the fasted state

LMTX is a distinct chemical entity which delivers the same active moiety

Baddeley et al. J Pharmacol Exp Therap (2015) 352:110-118
Harrington et al. submitted

Rationale for treatment with methylthionine (MT) in AD



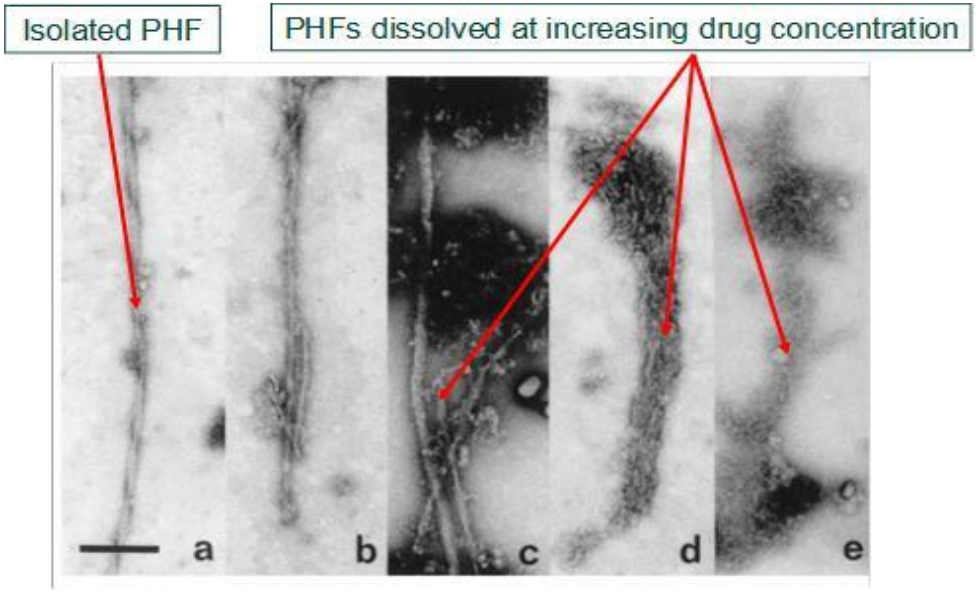
Tau aggregation is highly correlated with clinical dementia in AD

Tau aggregation is self-propagating, recruiting normal Tau and spreading pathology throughout the brain in a stereotyped cascade

MT is the first Tau Aggregation Inhibitor (TAI) in clinical development

MT dissolves and enhances clearance of pathological Tau polymers and oligomers isolated from AD brain

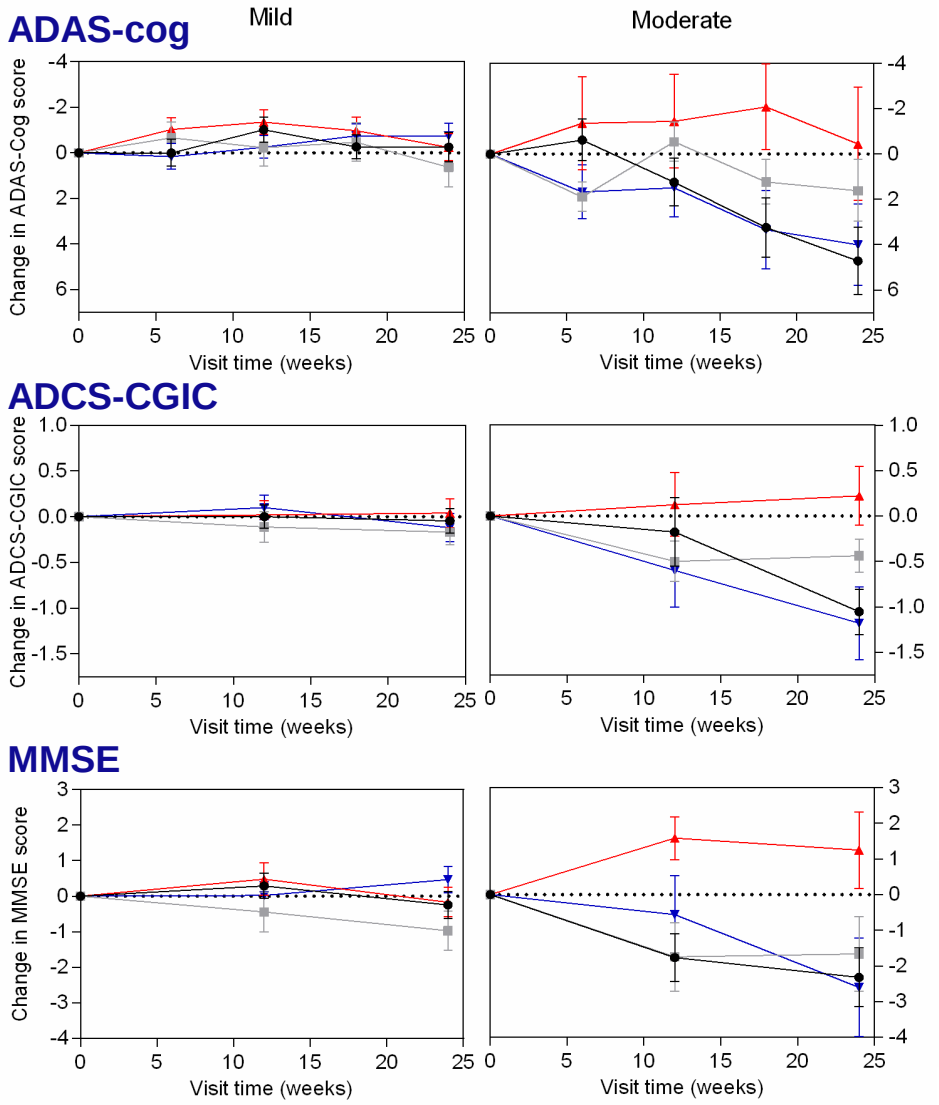
Therefore treatment with MT has potential as a Tau-based disease-modifying treatment for AD as an alternative to amyloid-based approaches



MT converts proteolytically stable Tau aggregates into proteolytically susceptible monomers by 'melting' the para-crystalline Tau polymer (Wischik et al., 1996, PNAS 93:11213)

TauRx Phase 2 data – mild/moderate AD, 321 subjects

Primary efficacy endpoint: ADAS-cog change at 24 weeks according to severity



Significant benefit at 24w in moderate AD:

	effect size	p	corr. p
ADAS-cog	-5.42	0.0080	0.046
ADCS-CGIC	1.29	0.0036	0.021
MMSE	3.79	0.0048	0.028

Minimum effective dose 138 mg/day

228 mg/day not effective due to problems with absorption:

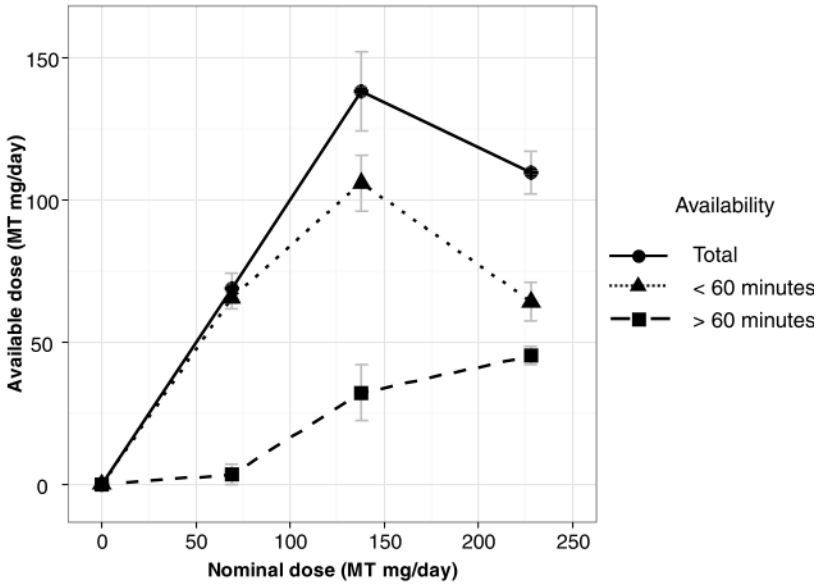
- formulation defect &
- dose-dependent food-impairment

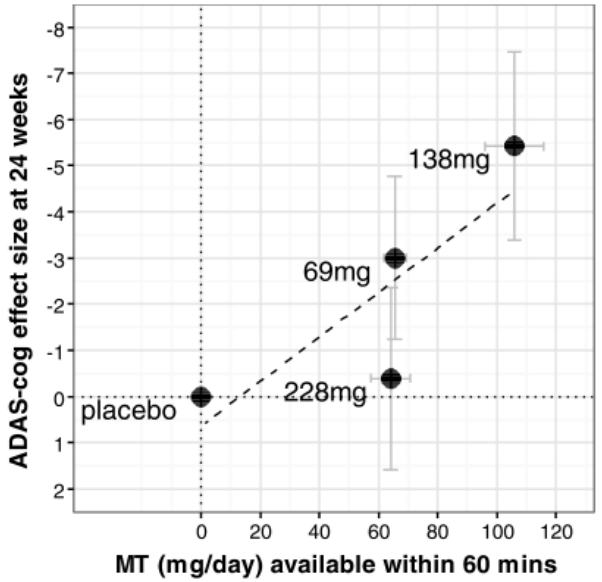
No placebo decline at 24w in mild AD

- Placebo
- 69 mg MT/day
- 138 mg MT/day
- 228 mg MT/day

Wischik et al. J Alz Dis (2015) 44: 705-720

Availability limitations of MTC: Dose-response for available dose rather than nominal dose



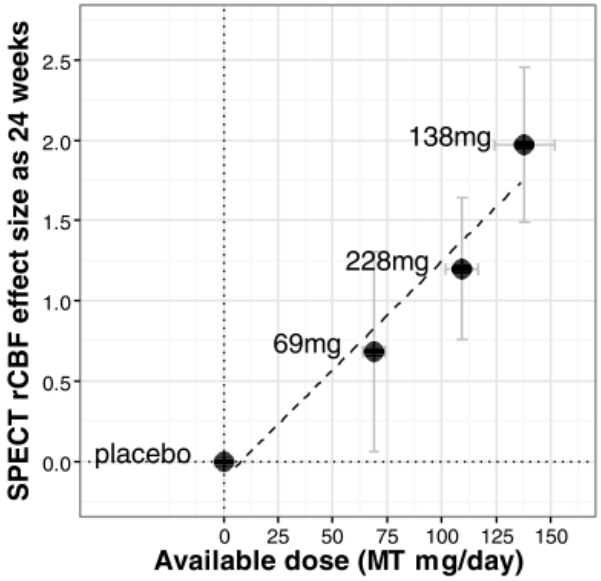


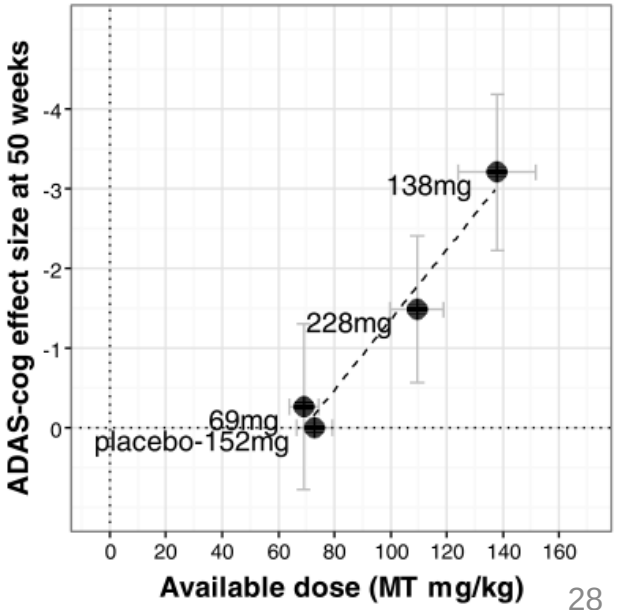
Baddeley et al. J Pharmacol Exp Therap (2015) 352:110-118

Minimum effective dose is highest available dose, 138 mg MT/day

228 mg/day not effective due to problems with absorption:

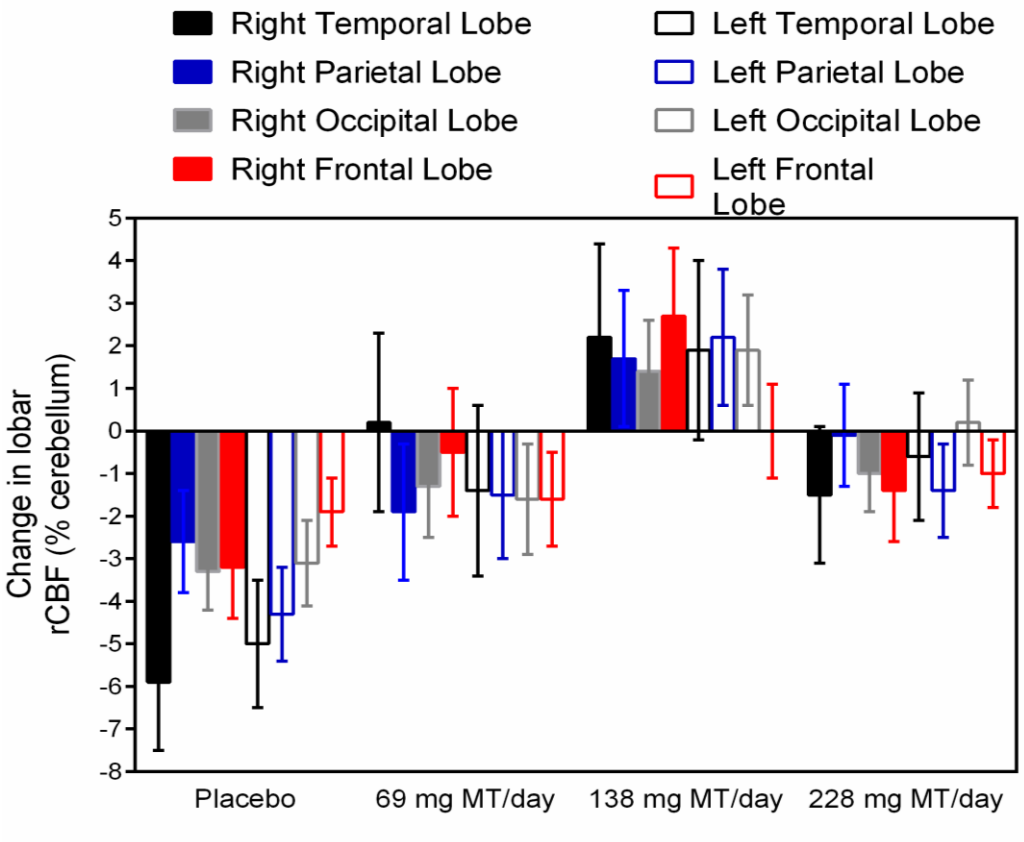
- **formulation defect &**
- **dose-dependent food-impairment**

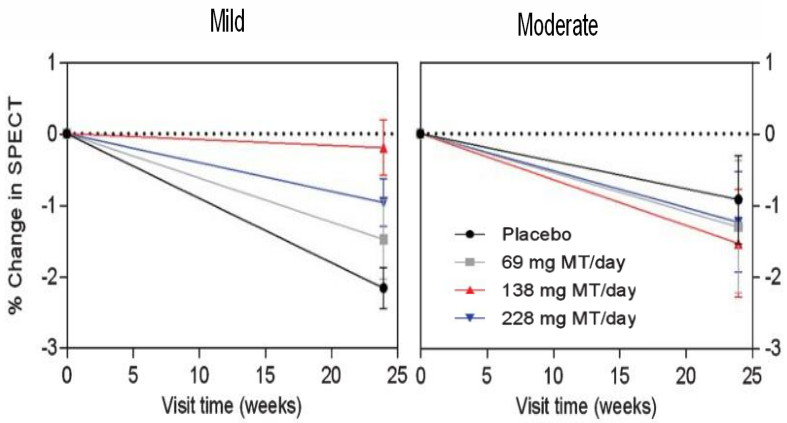


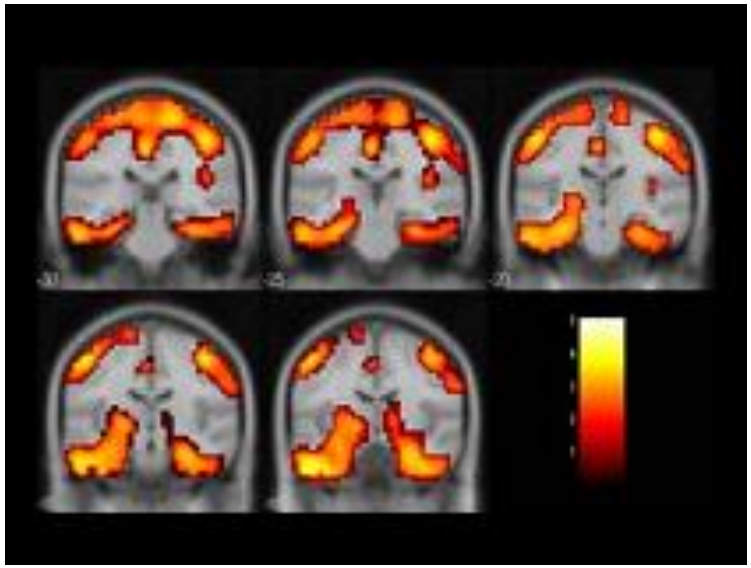


Wischik et al. J Alz Dis (2015) 44: 705-720

TauRx Phase 2 data – Efficacy supported by HMPAO-SPECT

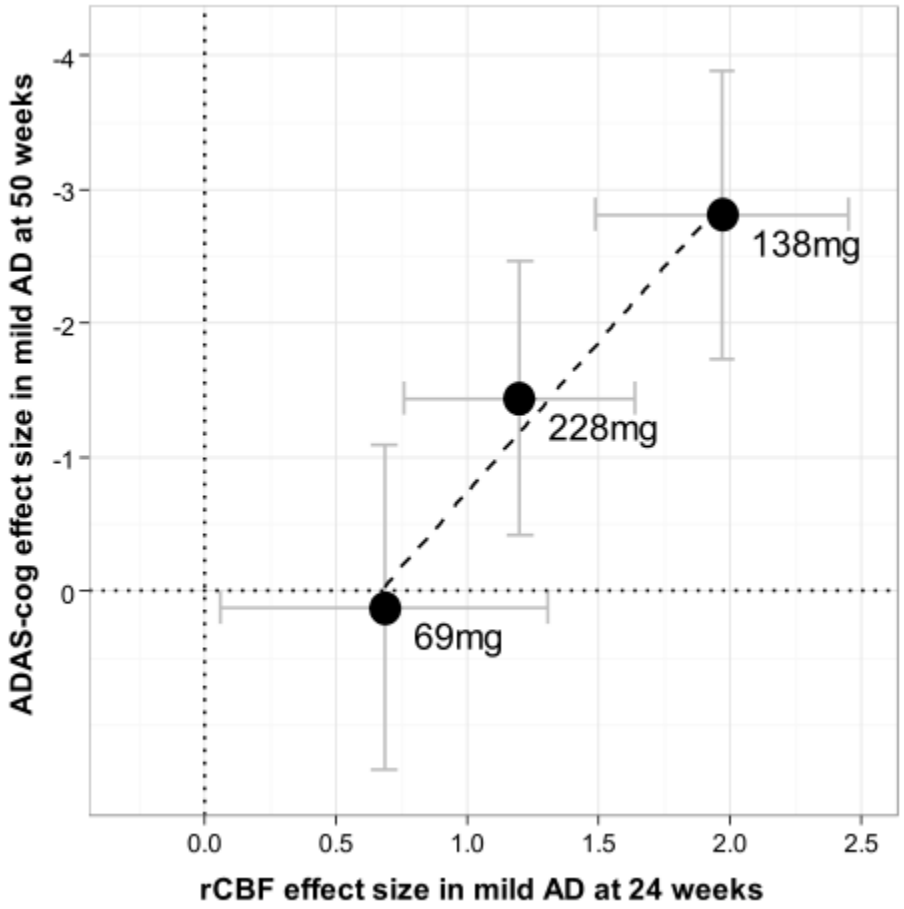






Wischik et al. J Alz Dis (2015) 44: 705-720

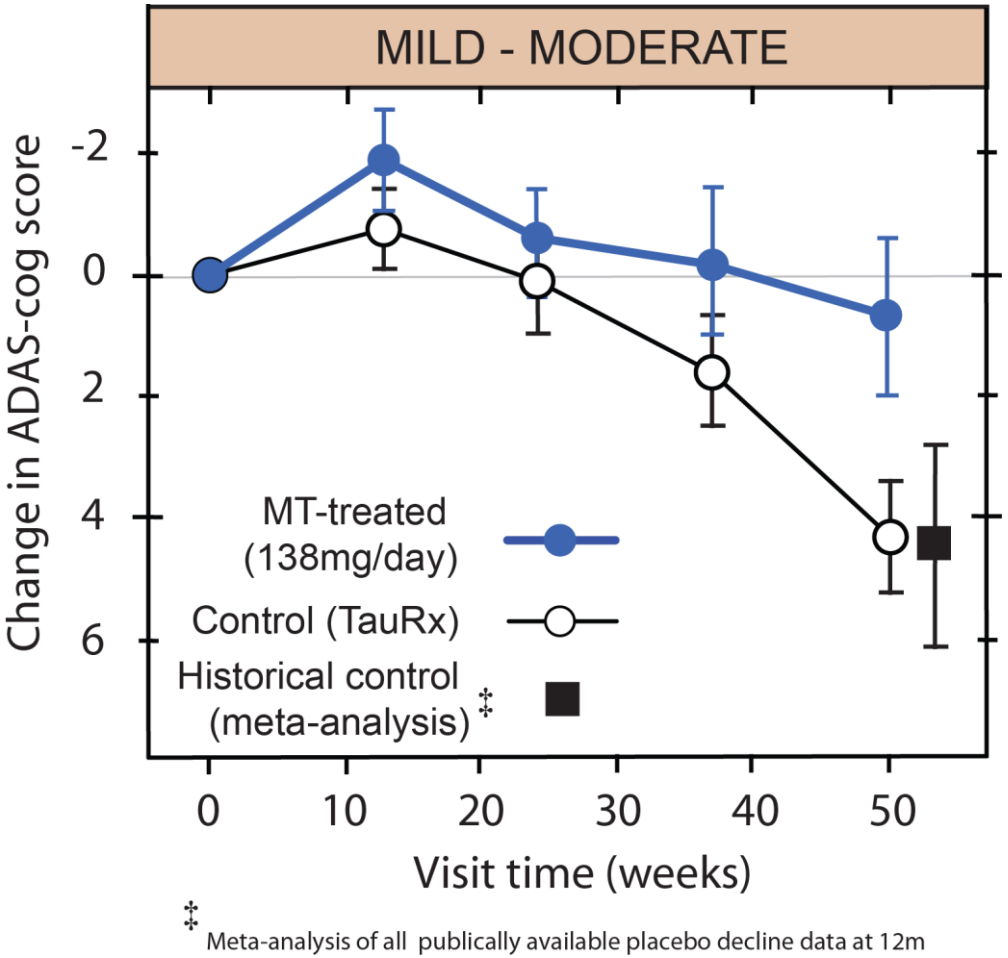
Imaging at 24 weeks predicts clinical benefit at 50 weeks: potential utility as early biomarker surrogate of response



Wischik et al. J Alz Dis (2015) 44: 705-720

TauRx Phase 2 data – mild/moderate AD (12m), 321 subjects

FDA analysis model (mixed effects, mITT, no imputation, unstructured correlation matrix)



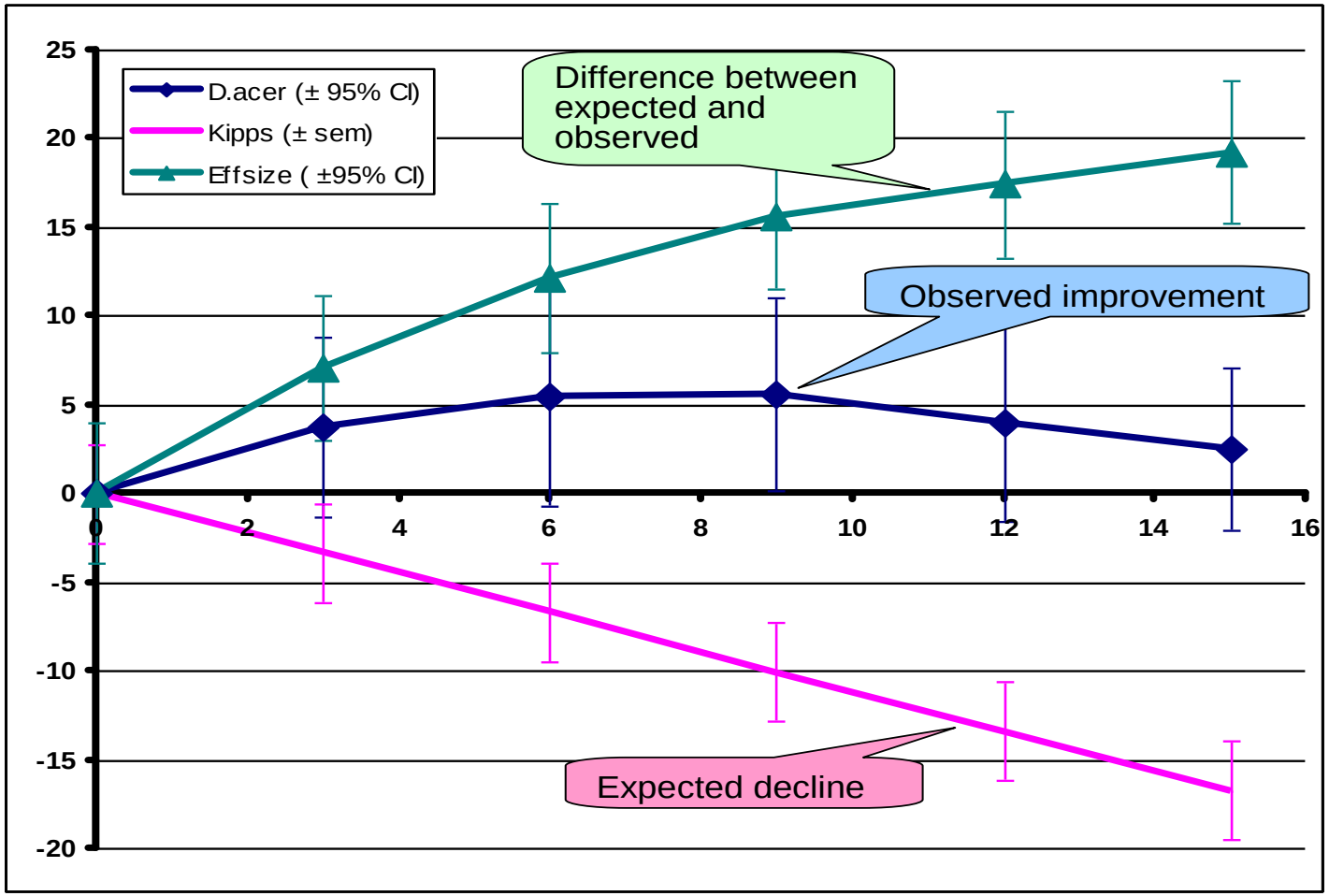
Placebo decline (50 weeks) **= 4.26 ± 0.94**

Effect size **= 3.63 ± 1.29** **p = 0.0053**

Effect size as % placebo decline **= 85.1% ± 30.3%**

Fronto Temporal Dementia in Pilot Study of MT

Seven FTD patients dosed with rember®, first generation tau aggregation inhibitor



Phase 3 program – 3 trials in parallel

- TRx-015: mild/moderate AD, N = 890, 15m, 150mg & 250mg LMTX vs placebo
- TRx-005: mild AD, N = 800, 18m, 200mg LMTX vs placebo
- TRx-007: bvFTD, N = 220, 12m, 200mg LMTX vs placebo

- First results to be available first half of 2016

Conclusions

- The presumption of temporal and aetiological priority of altered processing of APP is unproven
- The genetic data for APP could be understood as an accelerating factor in an underlying age-related pathway of molecular pathogenesis rather than as a rate-critical causative factor
- There is no basis for the presumption that Tau pathology is late stage
- Intervention in the Tau aggregation pathway is a valid pharmaceutical target for both prevention and treatment irrespective of the amyloid-β theory
- **Phase 2 trial demonstrated feasibility of Tau Aggregation Inhibitor (TAI) therapy in mild and moderate AD**
- **Phase 3 trials ongoing, results available in 2016**
- Implications for other prion-like neurodegenerative disorders (PD, PSP, CBD, CTE, HD)