DTAus ASM 2021

- **Clinical AD Trials in Australia**
- **Current status**
- Roger Clarnette

Conflicts of Interest

- I receive advisory board participation fees from
- Biogen
- Roche

Treatment of AD

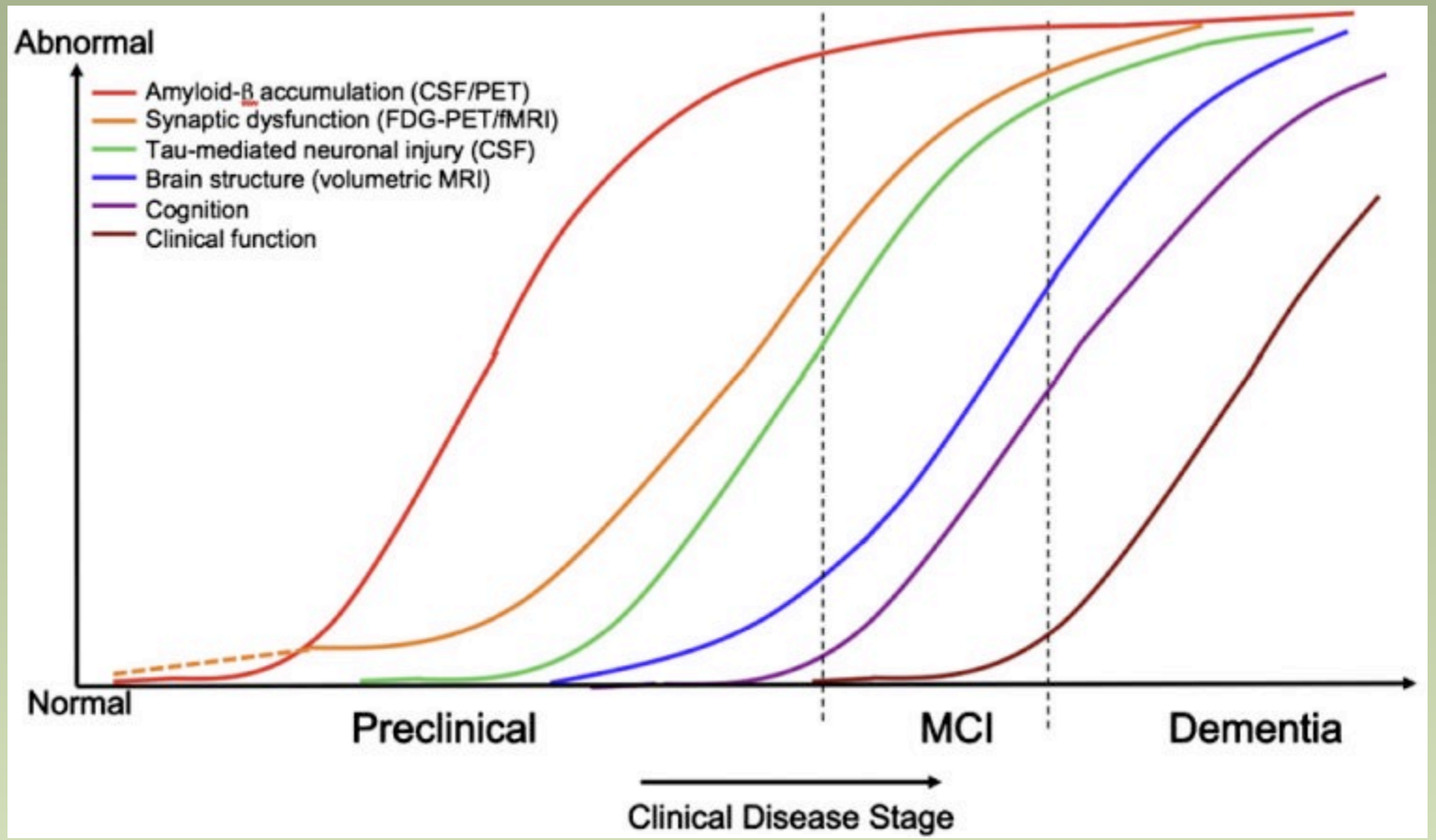
- 1. Current drugs
- 2. Amyloid based therapy
- 3. Tau based therapy
- 4. Sigma receptor modulators
- 5. Drugs in other categories
- 6. Nutritional/Lifestyle

AD Drug Trials

- Currently – 1,387 active studies of/for AD in USA (117 in Australia – 117) www.clinicaltrials.gov
- Stem cell infusions
- Ketogenic diet
- Glutathione
- Partnered rhythmic rehabilitation (dancing)
- Coconut oil
- Laser light and sound stimulation
- Oral fecal microbiota transplant
- Grape seed
- TMS
- Focused ultrasound, AC/DC stimulation, total brain irradiation
- IF-5:2 diet (reduction of IR)

Miscellaneous

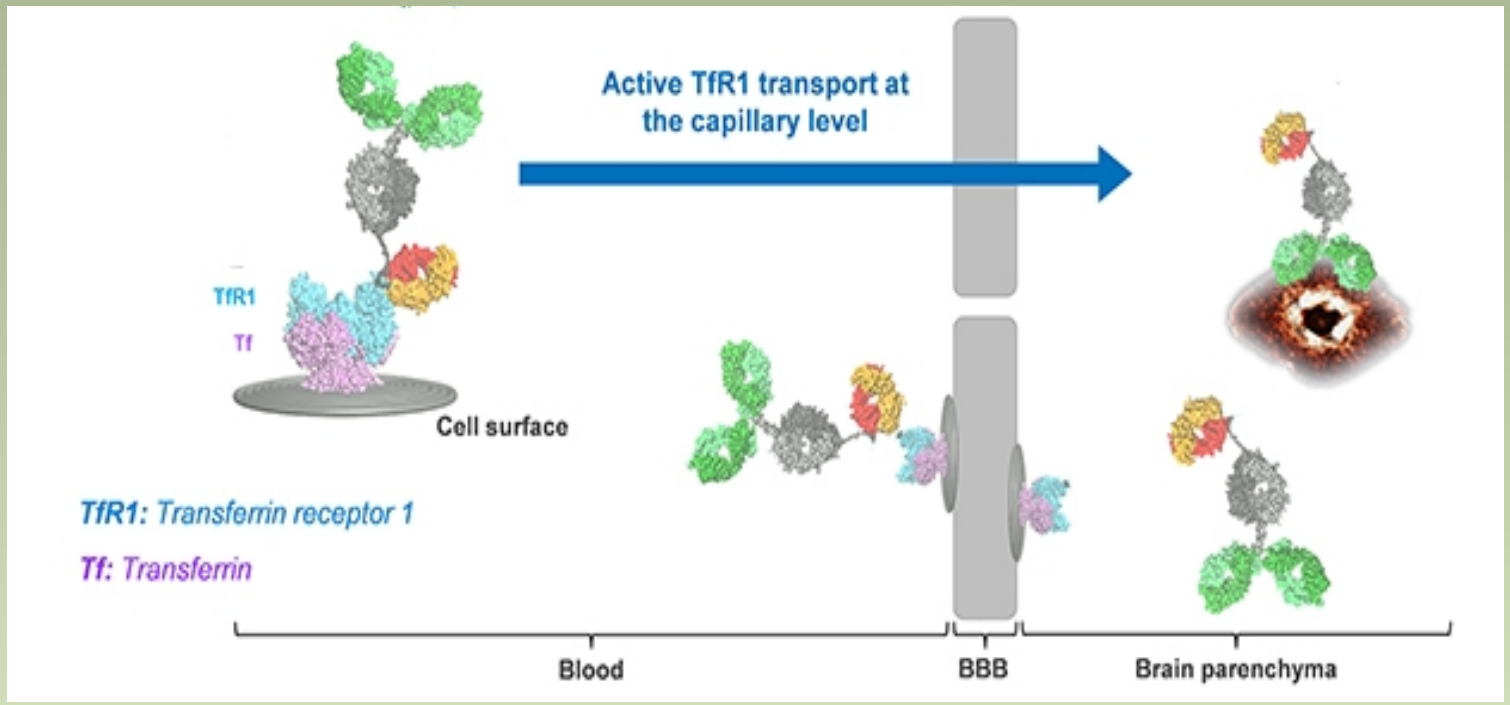
- BDNF gene therapy vector - adeno-associated virus serotype 2 (AAV2) stereotaxically administered into the brain under MRI guidance.
- Nicotinimide mononucleotide – improve mitochondrial function
- Combination of 40Hz light and cognitive therapy (ALZLIFE)
- Rapamycin and influence on downregulating mTOR
- Intra-cisternal administration of adeno-associated virus (AAV) gene transfer vector expressing cDNA coding for human APOEε2


Abnormal
Amyloid-β accumulation (CSF/PET)
Synaptic dysfunction (FDG-PET/fMRI)
Tau-mediated neuronal injury (CSF)
Brain structure (volumetric MRI)
Cognition
Clinical function
Normal
Preclinical
MCI
Dementia
Clinical Disease Stage

Amyloid Based Therapy

- Monoclonal antibodies
- Roche (Graduate) gantenerumab, MMSE ≥ 22, CDR 0.5/1, abn FCSRT, sc inj Q4W
- Similar to bapineuzumab, gantenerumab binds primarily fibrillar, deposited Aβ, not soluble monomeric Aβ as solanezumab does
- Roche Brain shuttle
- A Phase Ib/IIa, study of RO7126209 iv infusion in patients with prodromal or mild/moderate **AD (**7 doses 4 weekly).
- Large molecules ferried into the brain - conjugates a cargo to a Fab antibody fragment that recognizes transferrin receptor on endothelial cells lining the brain's blood vessels. They take up transferrin floating by in the blood and pass it through into the brain. This technique able to boost brain uptake of a generic anti-amyloid antibody 50-fold in mice

Roche Brainshuttle study



Amyloid Based Therapy

- Monoclonal Antibodies
- DIAN TU - sponsor Washington Uni, St Louis
- PS1, PS2 and APP mutations
- Treatment with gantererumab and solanezumab
- Eligibility – (-)15 to (+)10 years parental age
- CDR range 0, 0.5, 1
- Outcomes – gantenerumab PIB PET, solanezumab free CSF Aβ42
- Planned BACE inhibitor arm abandoned because of liver toxicity
- Tau imaging is planned

Amyloid Based Therapy

- AHEAD – anti-amyloid treatment in asymptomatic AD
- 1. Is lecanemab (BAN2401) superior to placebo on change from baseline of the Preclinical Alzheimer Cognitive Composite 5 (PACC5) at 216 weeks (A45 Trial)?
- 2. Is lecanemab superior to placebo in reducing brain amyloid measured by PET at 216 weeks (A3 Trial)?
- Participants – age 55-80, for those 55-64 must have one of:
- 1. first degree relative with dementia onset <75 years
- 2. one ε4 APOE allele
- 3. known +ve amyloid biomarker

Amyloid Based Therapy

- **Eisai (Clarity)**
- BAN2401 (lecanemab)(breakthrough therapy designation by FDA)
- Iv infusion every two weeks 18 months
- 50-90
- CDR 0.5 and memory domain 0.5 or greater
- **Eli Lilly (Trailblazer)**
- Mab targets a form of beta amyloid plaque called N3pG
- TRAILBLAZER-ALZ 2 mild Alzheimer's disease patients. TRAILBLAZER-ALZ 3, prevention, will donanemab prevent clinical progression of AD before clinical impairment begins.

Anti-tau immunotherapy

- ABBV-8E12 mab – binds to human microtubule associated tau in CSF
- Study terminated early 2021

- Biogen (Tango) – mab binds tau at amino terminus
- Study terminated June 20121

- Janssen (Autonomy)
- Anti – tau mab, (binds to phosphorylated tau) phase 2, 1:1
- Iv 4 weekly for four years
- Primary outcome - ADAS cog 13

Sigma Receptor Modulators

- Cognition Therapeutics – CT1812
- Prevents Aβ oligomer binding to receptors – sigma 2PGRMC1 antagonist, high brain penetrance
- **COG0203 study:**540-person Phase 2 study in early Alzheimer's disease in collaboration with the Alzheimer's Clinical Trials Consortium (ACTC).
- Supported by a $80 million grant from the National Institute on Aging (NIA) of the National Institutes of Health (NIH).
- Expected to commence in 2021.

Sigma Receptor Modulators

- ANAVEX®3-73, mechanism of action via sigma-1 receptor activation and M1 muscarinic allosteric modulation,
- Enhances neuroprotection and cognition in AD.
- Effective in very small doses in transgenic (3xTg-AD) mice - cognitive deficits, amyloid and tau pathologies, and also has beneficial effects on inflammation and mitochondrial dysfunctions.
- Therapeutic advantages in Alzheimer's and potentially other protein-aggregation-related diseases given its ability to enhance neuroprotection and cognition via sigma-1 receptor activation and M1 muscarinic allosteric modulation.
- MMSE 20-28, Primary outcome - ADASCog, 48 weeks duration
- Now OLE

Drugs in Other Categories

- Neuroscience Trials Australia – (3D) Deferiprone in MCI due to AD (Australia only)
- Iron chelator
- MMSE ≥ 22
- 15mg/kg bd po for 52 weeks vs placebo
- Must have +ve amyloid PET

Drugs in Other Categories

- Actinogen (Xanadu – phase 2) – Xanamem 10mg - completed and failed to show a clinical effect. Phase 3 did not proceed.
- Volunteer subjects - randomly assigned to 1 of 3 treatment groups, either 5 mg Xanamem®, 10 mg Xanamem® or placebo in the ratio of 1:1:1, 35 subjects in each treatment group (approximately 30 subjects per treatment group to complete the study).
- Short dose finding study – 10 weeks
- XanMIA study - ?status

Drugs in Other Categories

- Nucleus Network Victoria, (NTA)
- ASN51-101 - a randomized, double-blind, placebo-controlled, phase 1 first in human (FIH) safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) study of oral ASN51 in healthy young adult and elderly subjects and elderly subjects with AD.
- **OGA inhibitors as multimodal drugs for intracellular proteinopathies"** Pharmacological Inhibition of O-GlcNAcase Enhances Autophagy in Brain through an mTOR-Independent Pathway
- **Alector** - Phase 2 Study of AL002 in Participants With Early **AD**
- Iv infusion 4 weekly
- Humanized IgG1 - partnership between Alector and AbbVie. Binds microglial receptor TREM2, activates signalling, increases phosphorylation of TREM2's downstream effector Syk, induces microglia proliferation. AL002a, reportedly doubled the number of CD11b-positive microglia in cortex and hippocampus 72 hours after injection in APP/PS1 mice. Microglia expressed more pro-inflammatory and repair genes, and nearby amyloid deposits were nearly halved

Drugs in Other Categories

- **Athira**
- This study will assess the correlation of the functional translational biomarker P300 latency and change in ADAS-Cog11 induced by ATH-1017 therapy, over 26-week randomized, double-blind treatment.
- Daily sc injection – hepatocyte growth factor MET system.
- Primary outcome is event related potential P300 latency
- MMSE 14-24
- CDR 1 and 2
- **Evoke (Novo Nordisk)**
- Semaglutide – GLP1 receptor agonist
- Duration 173 weeks maximum
- Primary outcome- CDR sob at week 104
- MMSE >21
- CDR 0.5 or 1

Drugs in Other Categories

- Probucol in AD (PIA study) – originally synthesised as an antioxidant and then found to lower cholesterol.
- Investigator sponsored – Curtin University.
- Funded by MRFF grant
- Probucol suppresses secretion of lipoprotein-amyloid; preserves cerebrovascular integrity and supports cognitive function in murine models of AD and diabetes
- Probucol
- suppresses lipoprotein amyloid secretion
- Promotes lipoprotein amyloid clearance
- Prevents capillary dysfunction

InmuneBio – Xpro 1595

- Inhibitor of TNF – selectively neutralises soluble TNF
- (AD is an immunological disease)
- Phase 1b open label, sc injection weekly for 12 weeks
- Inclusions: +ve amyloid biomarker, hsCRP >2mg/l, MMSE 13-24
- LP x 2 required
- Phase 1 completed and phase 2 study is now imminent.

Potential Trials

- **Seelos Therapeutics**
- Investigational drug SLS-005, weekly iv infusion in 32 subjects
- Target population – MCI and mild dementia due to AD, MMSE 18-27, CDR 0.5 - 2
- Safety is primary endpoint
- **Vaxxinity**
- Phase 2b study, mild AD MMSE 22-30
- Immunological therapy

Why Most Published Research Findings are False

- High non-replication rate due to claiming significance based on a single study assessed using a p value
- Bias reduces the chance that a research finding is true
- Small n = reduced power and less likelihood of research finding being true
- Small effect size influences likelihood of findings being true
- Flexible designs in trials results in bias

Why Most Published Research Findings are False

- Financial interests and prejudices affect likelihood of research finding truth
- Expert evidence is extremely unreliable
- Peer review can suppress true research
- Large data sets are associated with very low PPV

- *Ioannidis J, PLoS 2005;2:696*

P values and How Not to be Wrong

- The standard methods of assessing results (the way we determine a threshold between a real phenomenon and random static) come under dangerous pressure in an era of massive data sets.
- How do we rule out the possibility that an intervention does nothing? - the null hypothesis significance test. (RA Fisher) Seeing better results with a new drug cf placebo says very little, since this is not at all unlikely, even under the null hypothesis.
- *In reference to the effect of a new drug, the null hypothesis is that there is no effect at all; so to reject the null hypothesis is merely to make the judgement that the effect of the drug is not zero. "So the effect could be very small, so small that the drug is not effective in any sense that an ordinary non-mathematical person would call significant. "*

P values and How Not to be Wrong

- With respect to drugs the null hypothesis is just about always false because any drug will have some influence on a biological pathway in some form. Just because we detect an effect does not mean it matters.
- "Humans are prone to perceive patterns when they do not exist and to overestimate their strength when they do"
- "A better term is statistically 'noticeable' or 'detectable' – not statistically 'significant'"
- $P<0.5$ - if the null hypothesis is true for a particular experiment, then the chance that the experiment will nonetheless return a statistically significant result is only one in 20
- In medicine most interventions we try will not work and most associations we test for are going to be absent

P values and How Not to be Wrong

- P hacking is when data is tortured until it confesses
- p of 0.05 is purely arbitrary, a convention chosen by Fisher. It is not the case that $p<0.05$ means true and $p>0.05$ means false.
- Neyman and Pearson – statistics are not about what to believe but what to do – what to do about answering questions
- **"A 'significant' finding gives a clue suggesting a promising place to focus further research energy"**
- Fisher - "a scientific fact should be regarded as experimentally established only if a properly designed experiment rarely fails to give this level of significance". The replication process is science's 'immune system'

- *Ellenberg J. How Not To Be Wrong The Power of Mathematical Thinking. Penguin NY 2014*