# AC4R ASM 2019

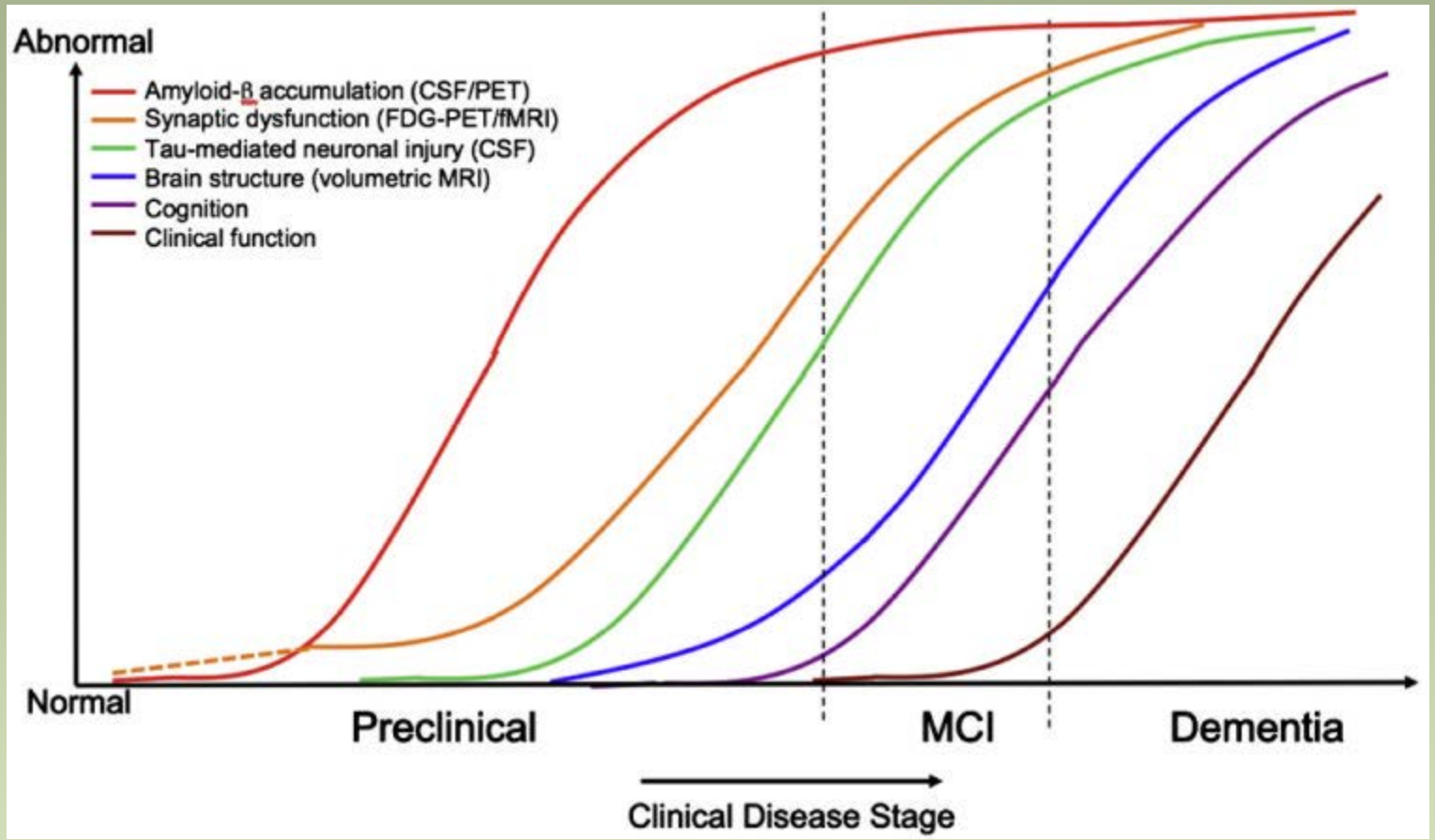
- **Clinical AD Trials in Australia**
- **Current status**
- Roger Clarnette

# 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 – 1,128 active studies of/for AD in USA (101 in Australia – 78 completed or terminated) www.clinicaltrials.gov
- Alternating current stimulation, stem cell infusions, coconut oil, laser light and sound stimulation, oral fecal microbiota transplant, grape seed, TMS, direct current, total brain irradiation.
- AD drug trials 2002-2012, 99.6% failure rate


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

# Current Treatment

- Cholinesterase inhibitors
- NMDA receptor anatagonists
- Memantine 50mg modified release – safety evaluation
- Donepezil transdermal patch 87.5/25cm$^2$ – AD dementia, 50-85 years, MMSE 10-26

# Amyloid Based Therapy

- Monoclonal antibodies
- Biogen Engage - Aducanumab – terminated
- Roche – Crenezumab - terminated
- Eli Lilly – Solanezumab – terminated

- 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

# 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

- A4 study – anti-amyloid treatment in asymptomatic AD
- Cognitively normal (age 65-85), CDR 0 with brain amyloid (florbetapir), MMSE 25-30
- Solenezumab vs placebo
- Primary outcome - change from baseline of the ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC) to Week 168

# Amyloid Based Therapy

- Novartis Generation 1 - active immunotherapy CAD106
- Contains Aβ fragments coupled to a carrier protein
- Inclusion – age 60-75, homozygous APOE ε4, MMSE ≥24
- CAD106 immunotherapy and CNP520 (BACE inhibitor)
- - im injections quarterly
- - oral capsule
- - placebo:active 3:5
- Outcome –
- 1. Time to diagnosis of MCI due to AD
- 2. Change in APCC score at 60 months

# Amyloid Based Therapy

- BACE inhibitors (β site APP cleaving enzyme)
- Up stream interference with the amyloid cascade
- Show >80% reductions of amyloid β peptides in CSF

- JNJ-54861911 (liver toxicity) – terminated
- Eisai (Mission AD) –terminated
- Novartis Generation 1/2 – terminated
- Eli Lilly – Amaranth - termionated
- Merck – verubecestat - terminated

# Anti-tau immunotherapy

- ABBV-8E12 mab – binds to human microtubule associated tau in CSF
- MMSE 22-30, age 55-85
- Current trial – monthly iv infusions (active:placebo 3:1)
- Aim - reduce accumulation of phosphorylated tau
- CDR SOB is primary outcome measure

- Biogen (Tango) – mab (BIIB092) binds tau at amino terminus
- MMSE 22-30
- Monthly iv infusions (Active:placebo 3:1)

- Genentech (RO7105705) – phase 2, anti-tau IgG4 mab
- iv infusion, MMSE>20. Outcome –CDR SOB at 12 months
- Not recruiting but active

# Sigma Receptor Modulators

- Cognition Therapeutics – CT1812
- Prevents Aβ oligomer binding to receptors – sigma 2PGRMC1 antagonist, high brain penetrance
- Phase 2 study, MMSE 18-26, amyloid PET +ve, treatment for six months
- Two active doses vs placebo
- ADASCog/CGIC

# Sigma Receptor Modulators

- ANAVEX®2-73, 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.
- Current study phase 2b/3
- MMSE 20-28, Primary outcome - ADASCog, 48 weeks duration

# Drugs in Other Categories

- Neuroscience Trials Australia – (3D) Deferiprone (to delay dementia) 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

- Tricaprillin – phase 1
- Lipid multiparticulate formulation

# Drugs in Other Categories

- Avanir - Treatment of agitation in dementia with AVP-786
- Phase 2 study with AVP-923 – significant reduction in agitation based on NPI (non-deuterated form of drug)
- Phase 3 trial – no sites active in Australia
- Actinogen (Xanadu) – Xanamem – completed ?another phase 2 study at a higher dose
- Alector – iv AL002 – single dose, immune modulator, one site in Melbourne

# Drugs in Other Categories

- AZTherapies (Cognite) – inhaled/oral Aβ polymerisation inhibitor
- CDR 0.5 and CSF Aβ c/W AD
- 55-79 years
- CDR SOB is primary outcome measure

- NeuroActiva – oral tranuerocin, MMSE >23, 24 week duration

# InmuneBio – Xpro 1595

- Inhibitor or TNF – selectively neutralises soluble TNF
- Phase 1b open label, sc injection weekly for 12 weeks
- Inclusions: +ve amyloid biomarker, hsCRP >2mg/l, MMSE 13-24
- LP x 2 required

# Roger's Rants

- Repudiate Ridiculous Research Requirements (ACR4)

- **Technocracy** is a system of governance where decision-makers are selected on the basis of technological knowledge. Scientists, engineers, technologists, or experts in any field, exert control, instead of elected representatives.
- Have clinical trials been taken over by technocrats?
- *"In the realm of clinical trials it is evident that technocrats have taken over many aspects of research. These people have high intelligence but often display little wisdom. They are embedded in the middle layers of large complex systems and usually eschew common sense. They are unaccountable for their actions and like politicians are promoted after reducing the productivity of and wasting the time of honest professionals. They insist that the people that they consider to be serfs do their bidding to ensure that the integrity of the system remains intact."* Anonymous 2017

# Roger's Rants

- 1. Anonymous email instructions to do 'training' – no indication of sponsor, study, web address, author and 'do not reply to this email'.
- 2. Training provides little useful information and does not lead to practical skill acquisition
- 2. Blackmail – complete the training or the study will not go ahead
- 3. Medical monitors – unnecessary scrutiny of everything investigators do. Lack of flexibility

# How to Legally Own Another Person

- *Skin In The Game* – Nassim Nicholas Taleb 2018
- 'Bureaucracy (technocracy) is a construction by which a person is conveniently separated from the consequences of his or her actions.'
- To survive, organisations need a certain number of people associated with it to be deprived of a share of their freedom. How do organisations own people?
- 1. conditioning and psychological manipulation
- 2. by conferring skin in the game – so the person has something to lose if they disobey

# How to Legally Own Another Person

- ‘Someone who had been employed for a while is giving you a strong evidence of submission’
- ‘What matters is not what a person has or does not have; it is what he or she is afraid of losing’

# Roger's Rants

- Options for managing training requirements
- 1. Submit
- 2. Start a 'Whipped Dog' 12 step program
- 3. Coordinate a plan to change the technocracy

# Why We Make Sacrifices

- **A psychological perspective of submission to training**
- 12 Rules for Life – Jordan Peterson
- Rule 7 – Pursue what is meaningful
- The curse of work – means delay of gratification
- The ancients articulated the discovery of time
- That is; if we behave well now, rewards may come in the future
- This allowed society to be organised and motivated the social contract
- Sacrifice now to gain later.


RAGE AGAINST THE MACHINE

# Conclusions

- Dementia stage studies now much less common
- PET imaging – diagnosis and outcomes
- Less trials available now
- ADNet should help recruitment
- Multiple vendors
- Training requirements remain burdensome and annoying