Repositioning Dementia

Progress in Biomarker and Therapy Research

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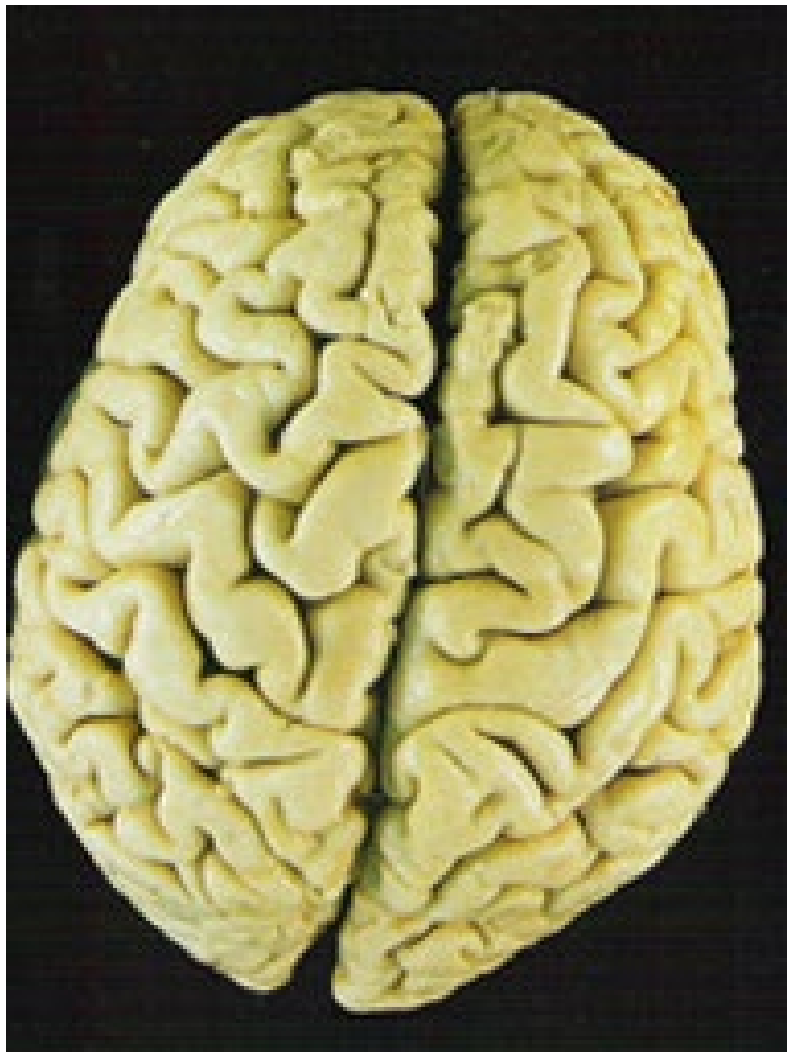
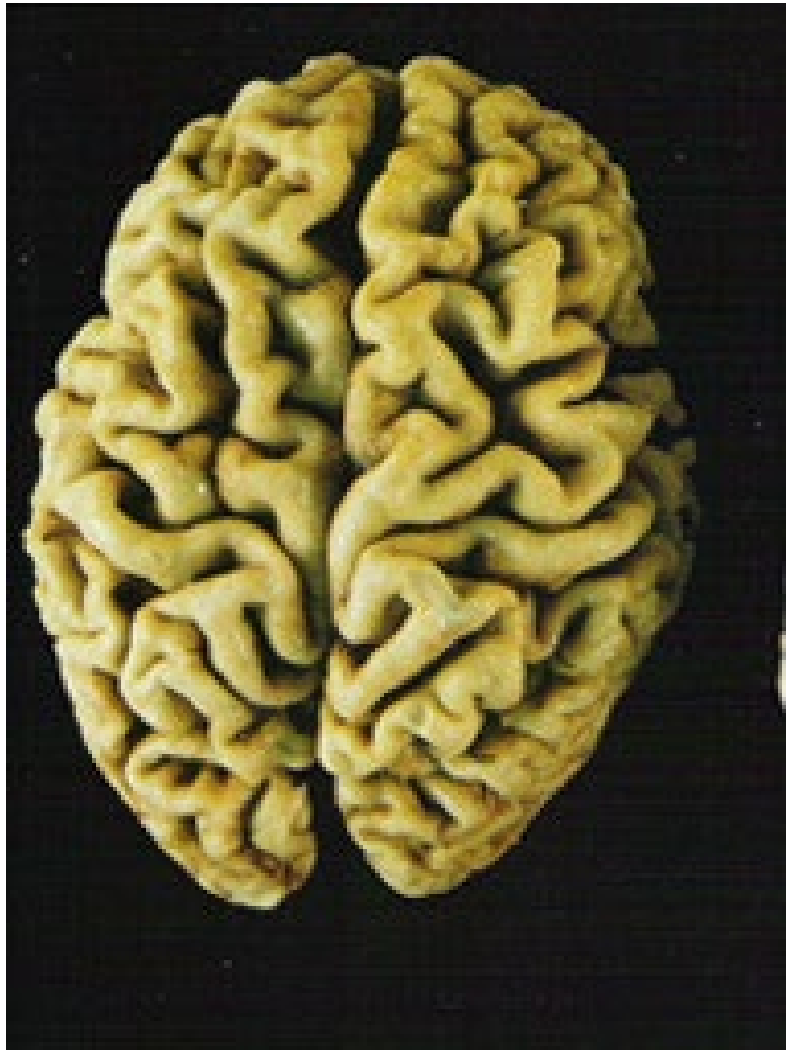
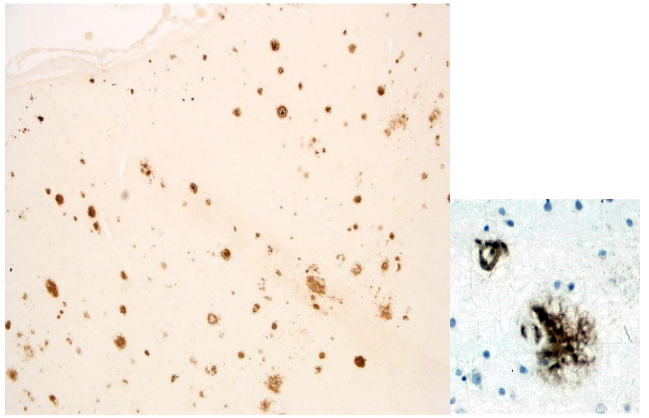
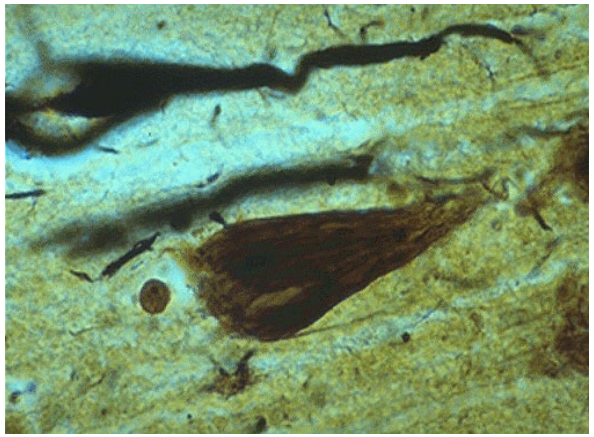
Alzheimer’s disease







Plaques (amyloid-β)



Tangles (tau protein)

neuroinflammation

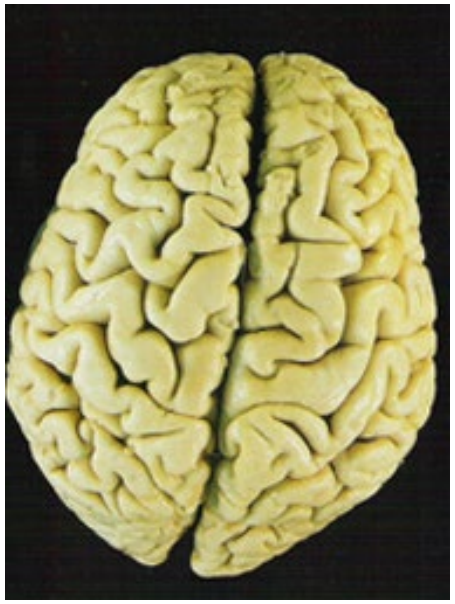
The Big Issues

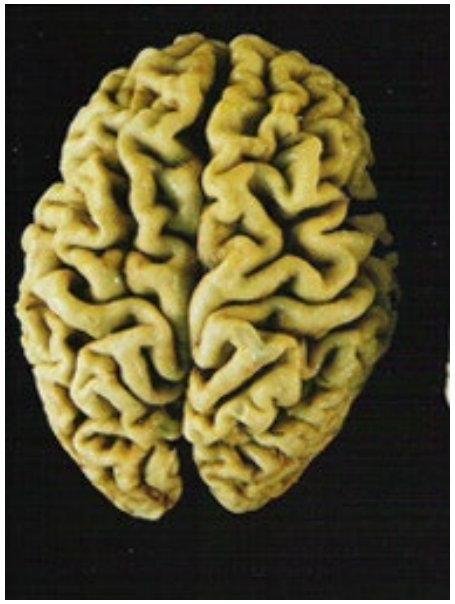
(from a research perspective)

Prevention
Delay

Early Detection

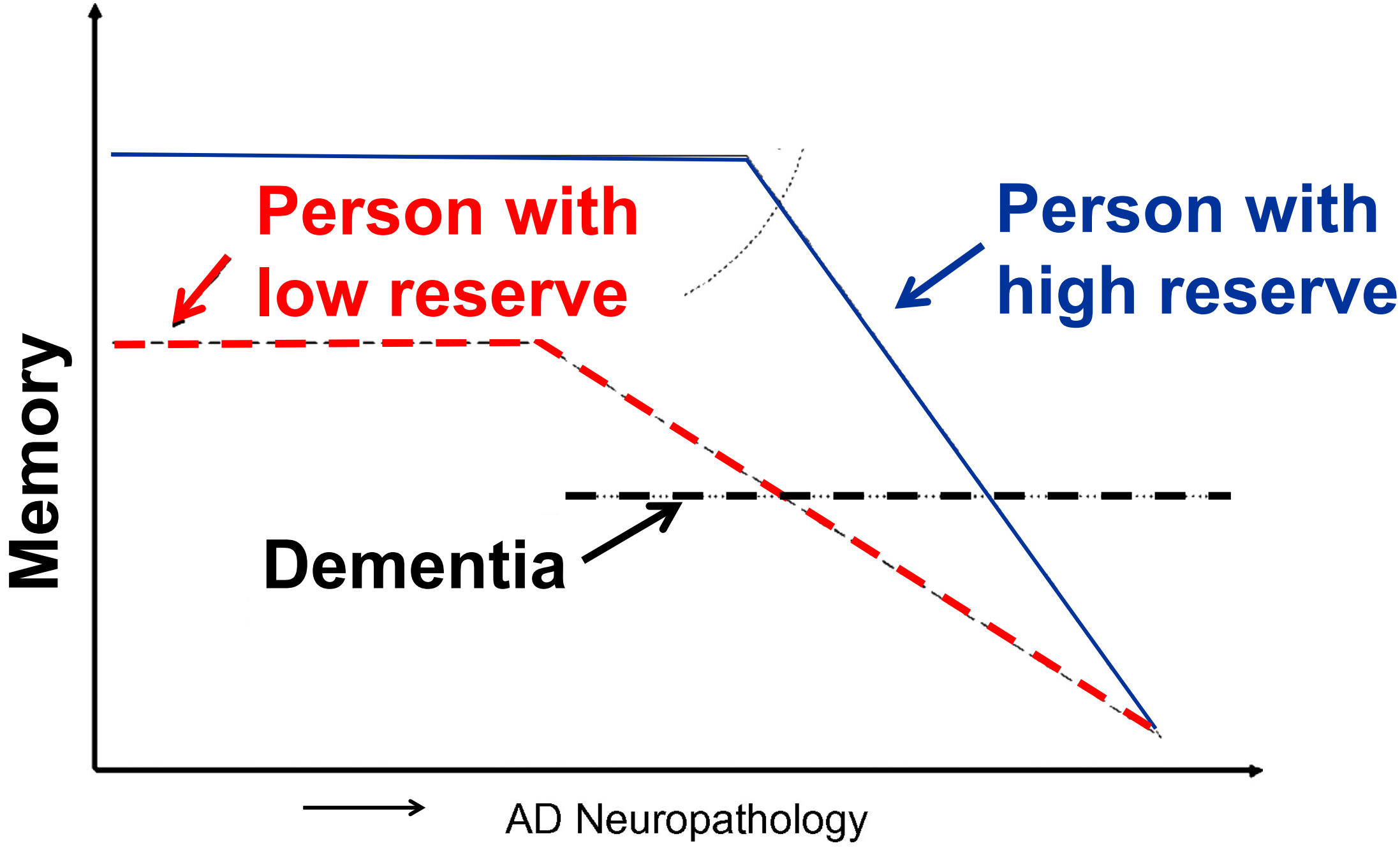
Effective Treatment





Prevention / Delay: Use or it lose it

Prevention / Delay


Person with
low reserve
Person with
high reserve
Memory
Dementia
AD Neuropathology

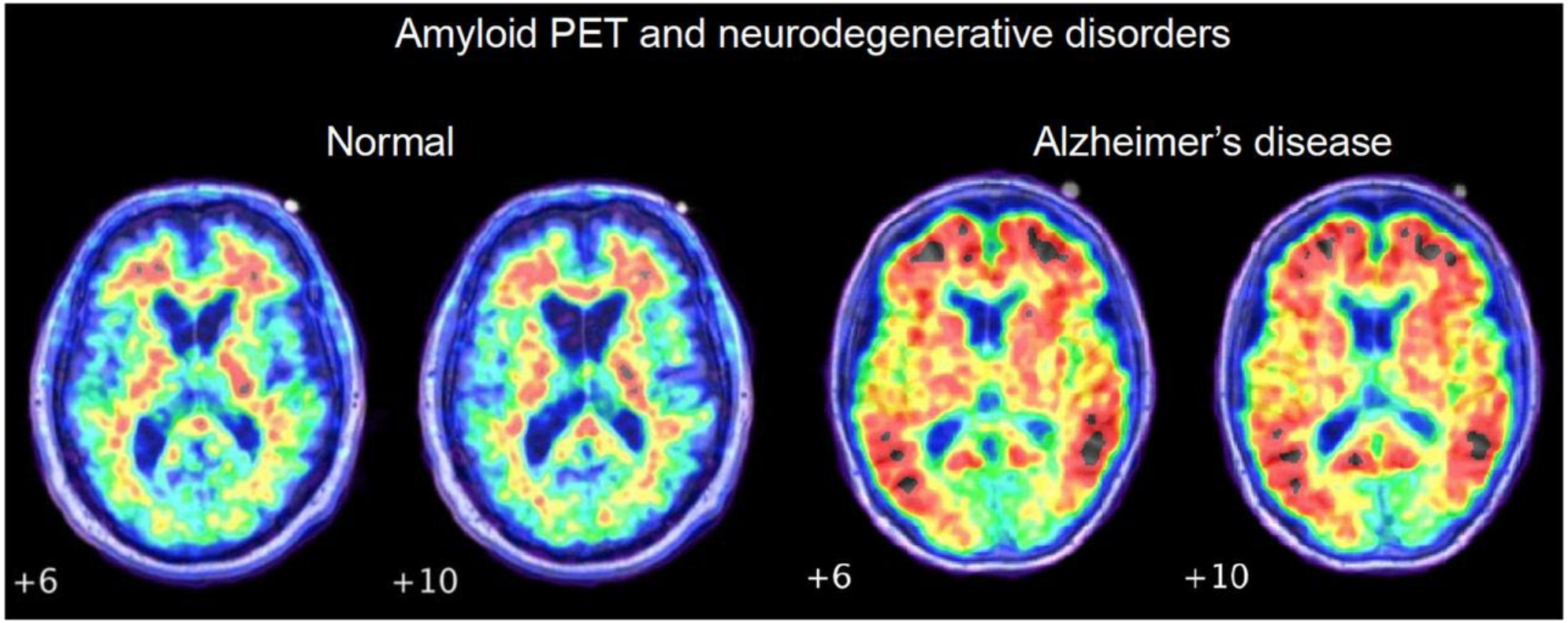
The All Blacks' bench has something 'no other team' has

By Ned Lester

39 days ago

Damian McKenzie with ball in hand for the All Blacks. Photo by Catherine Ivill/Getty Images

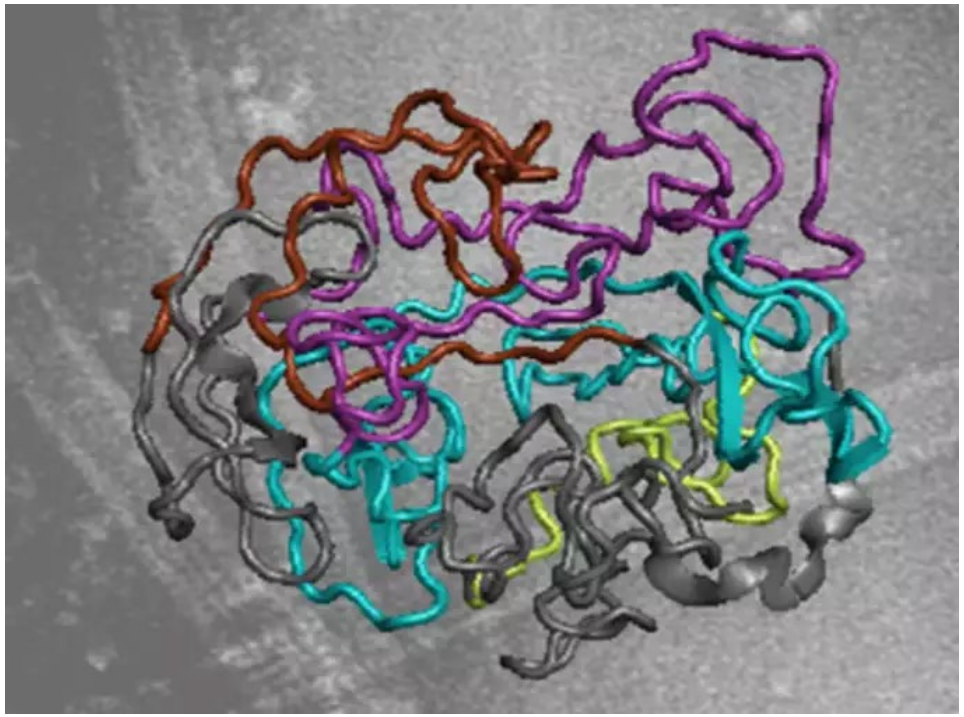
Early Detection? Amyloid “PET” scan



Marianne Chapleau, et al, Journal of Nuclear Medicine June 2022, 63 (Supplement 1) 13S-19S; DOI: https://doi.org/10.2967/jnumed.121.263195

Early Detection? A New Hope?

Blood tests for early stage AD - tau protein



Alzheimer's disease-related modifications of tau protein found in plasma

1. pTau-181 (+amyloid-β)
2. pTau-217

Early Detection? A New Hope

A blood test for early stage AD: “microRNA”

86% Specificity
80% Sensitivity

Provisional Patent #766493

OTAGO INNOVATION
A UNIVERSITY OF OTAGO COMPANY

Neurological Foundation
A pathway to hope


Assoc Prof Joanna Williams


Diane Guévremont


Prof Warren Tate


Dr Nick Cutfield

Treatment: all Challenge, or is there New Hope?

FDA-approved Treatments

Increase levels of Acetylcholine by blocking its breakdown

- tacrine (Cognex®), approved in 1993 but now discontinued
- donepezil (Aricept®. Donepezil-Rex® approved in 1996
- rivastigmine (Exelon®, Rimane®), approved in 2000
- galantamine (Razadyne®, Reminyl®), approved in 2001

Increase brain “tone”

About half of the people who take these drugs experience a modest improvement in cognition.

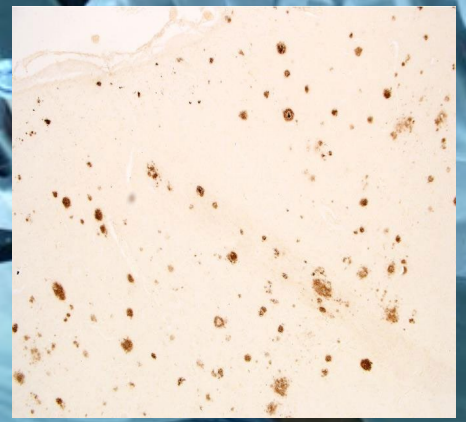
Treatment: considerations

- Effective !
- Long-lasting
- Non-invasive
- Brain-wide delivery
- Cross the blood-brain barrier
- Few if any side-effects
- Affordable

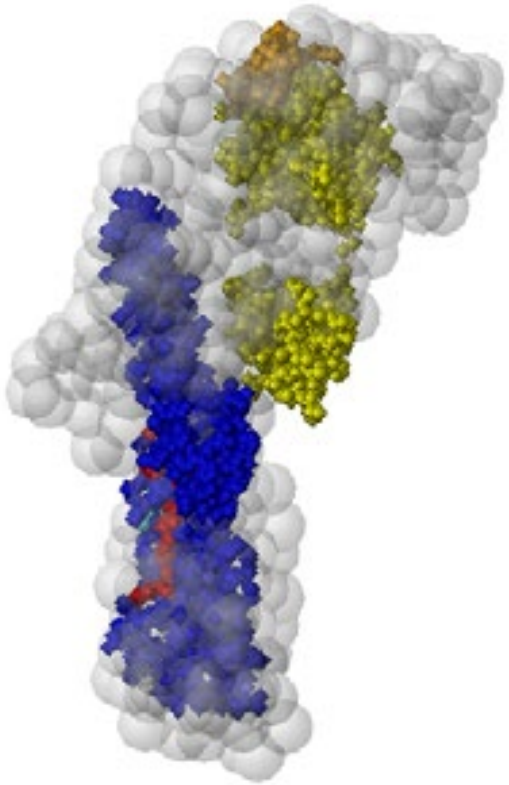
Aducanumab (Aduhelm™) – FDA approved but selling stopped

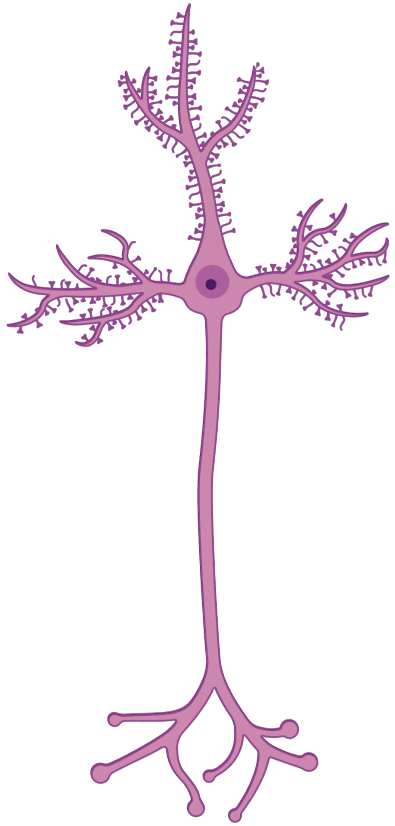
Lecanemab – FDA approved

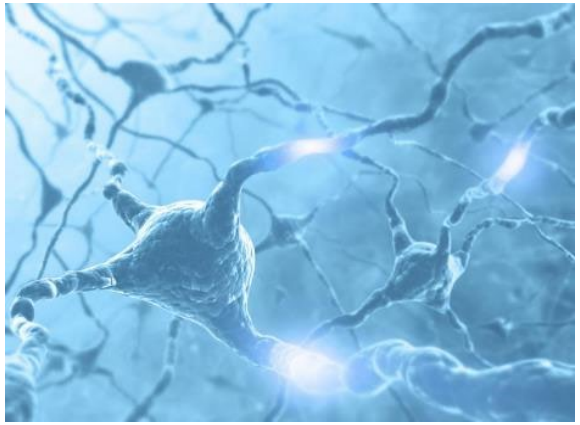
Donanemab – not yet FDA approved



A new treatment target



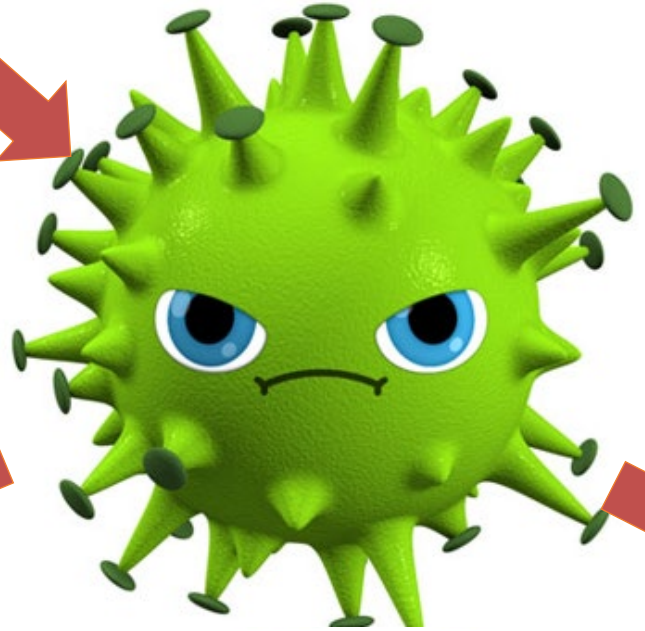


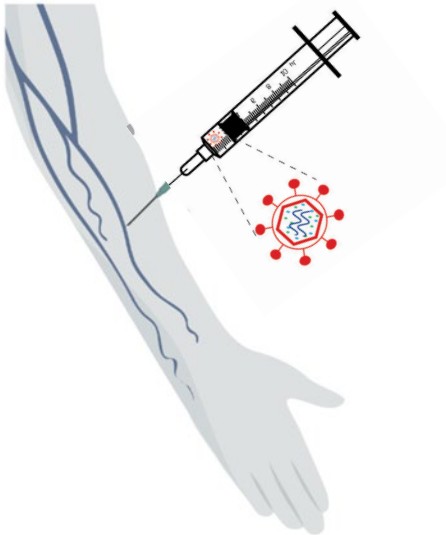


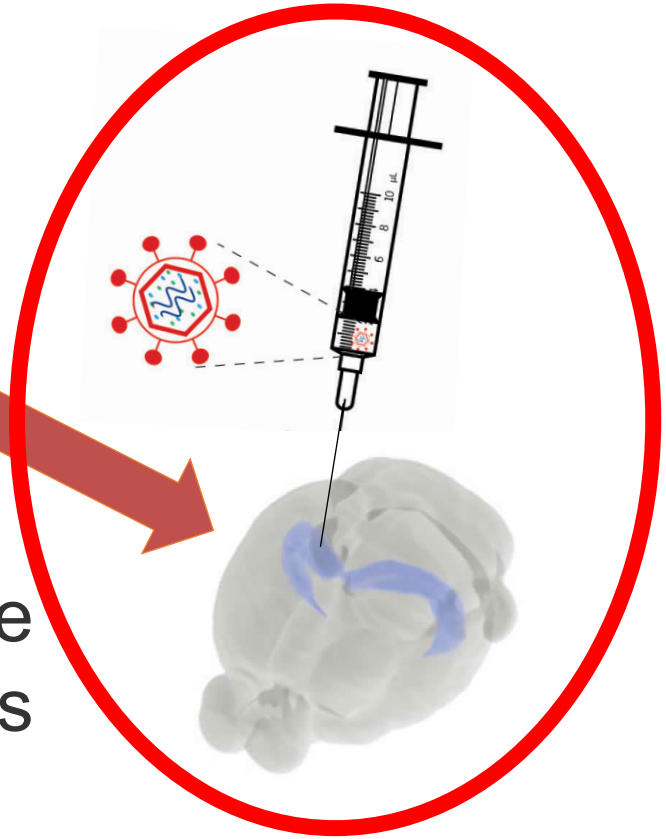
Gene Therapy - a one-time fix?

Therapeutic gene

Package into a virus envelope

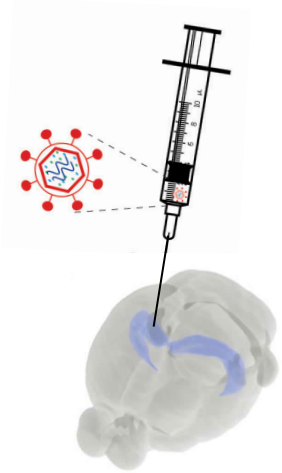


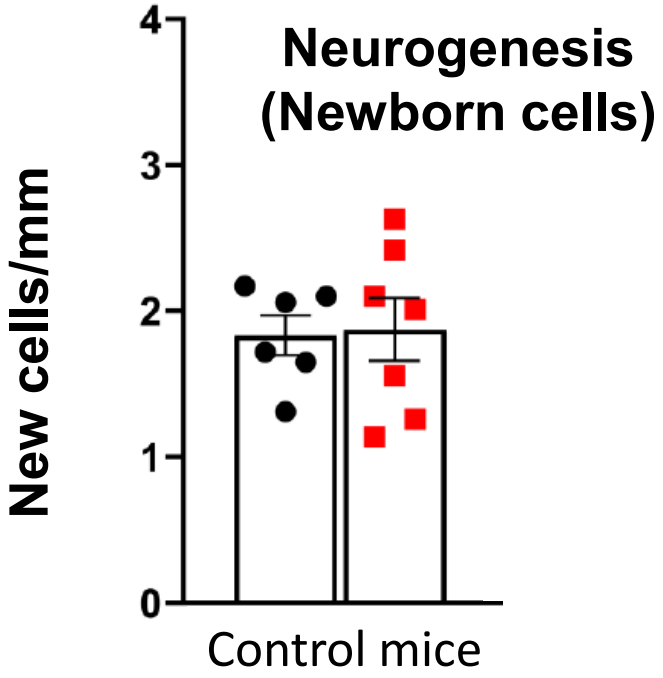


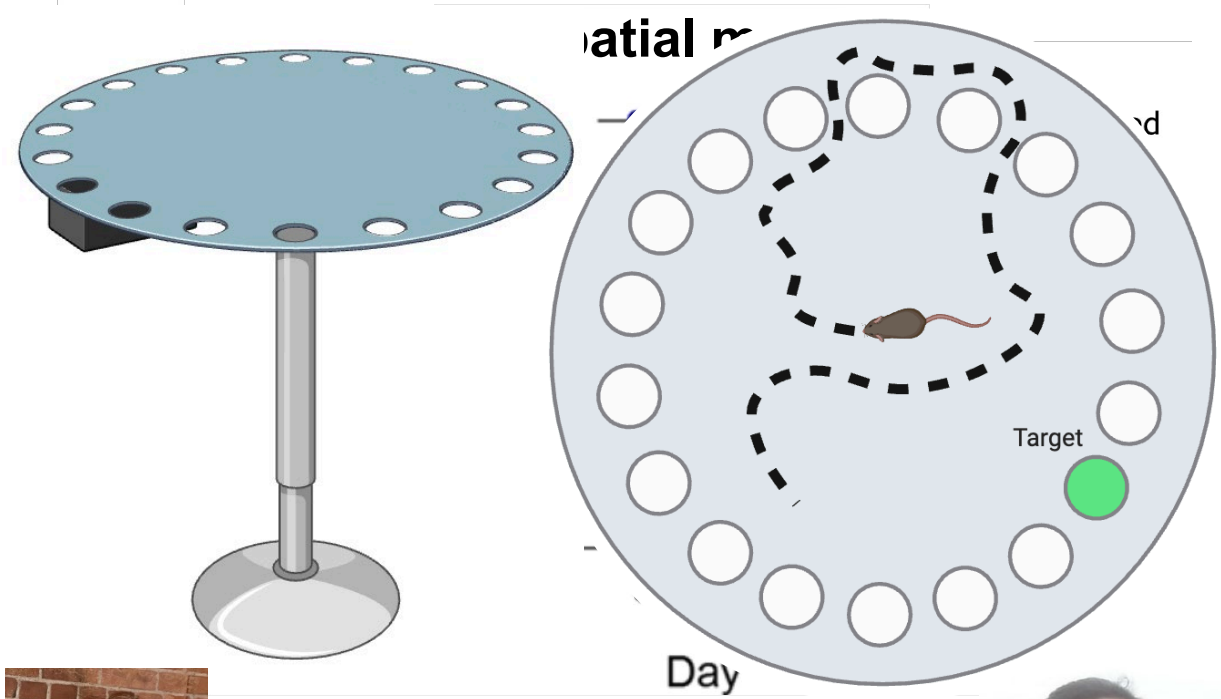


Inject into the hippocampus

Mouse model of AD







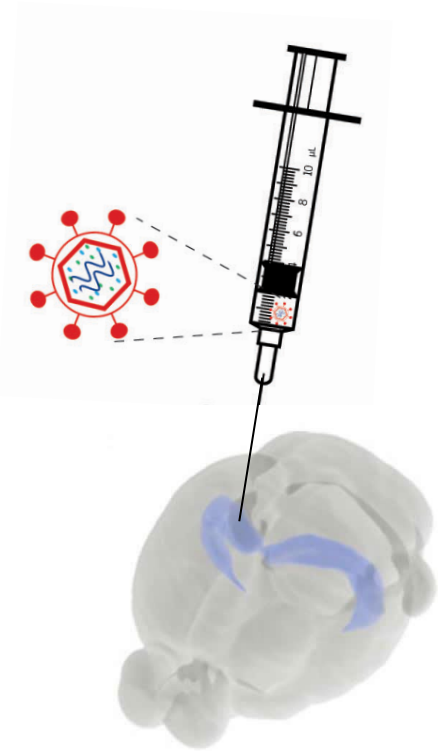

Connie Chan

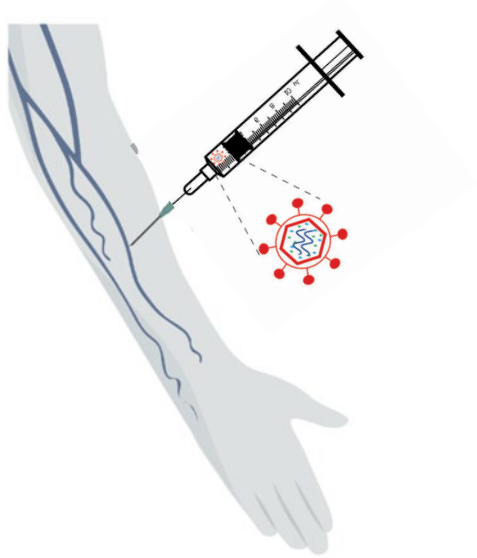

Dr Shane Ohline

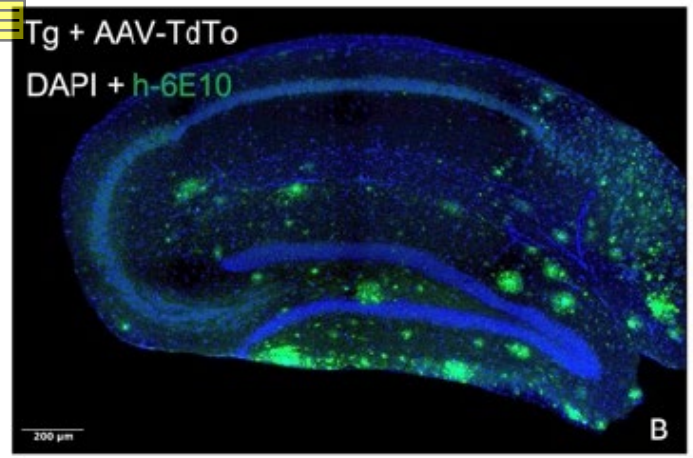

Barbara Logan


Dr Valerie Tan

Intravenous injection







Sophie Mathiesen

Dr Emily He

The Hope

More neuroprotective proteins in the brain

=

Greater Brain Resilience

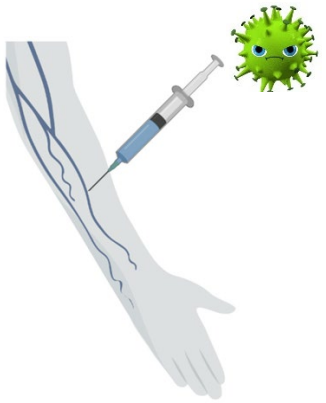
More Cognitive Reserve

Reduced pathology

Delayed symptoms

Longer Healthspan

With what you can do, and what we can do, working together we can add life to years

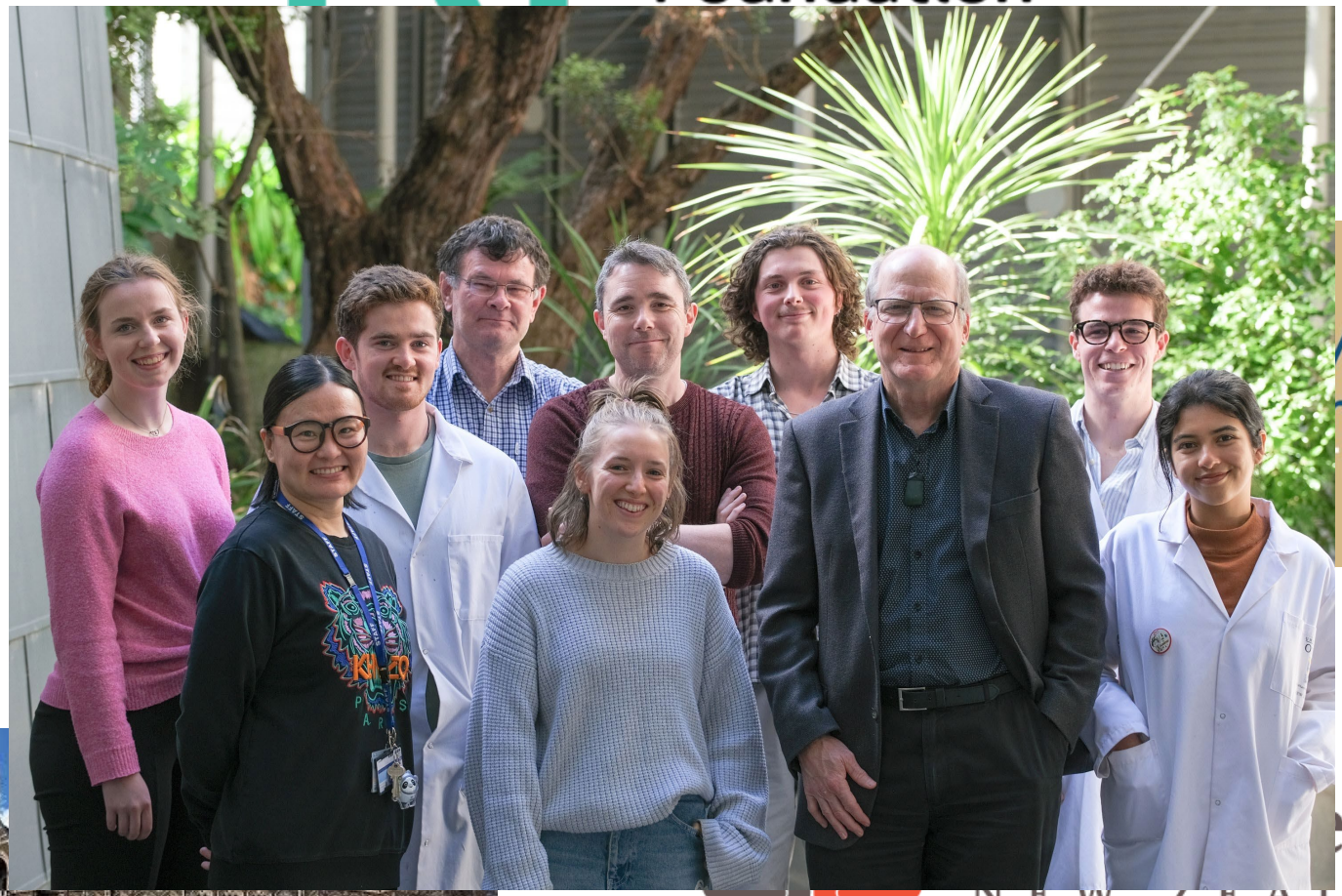


Prof Stephanie Hughes

Dr Luci Schweitzer

Prof Warren Tate

Neurological Foundation



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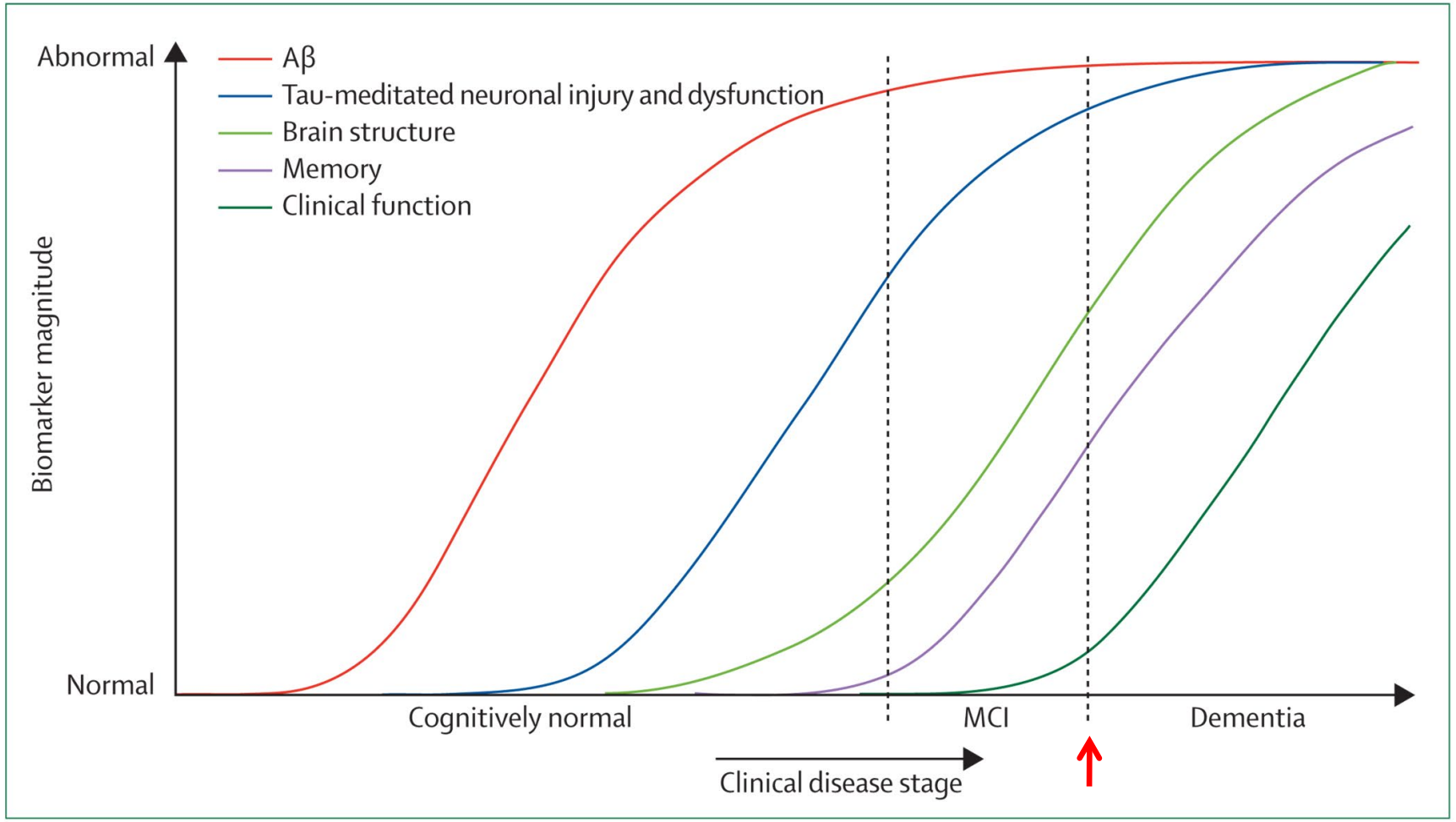
Timelines for AD Biomarkers and Clinical Function



AD may begin up to 25 yr prior to clinical diagnosis

FDA-approved Treatments

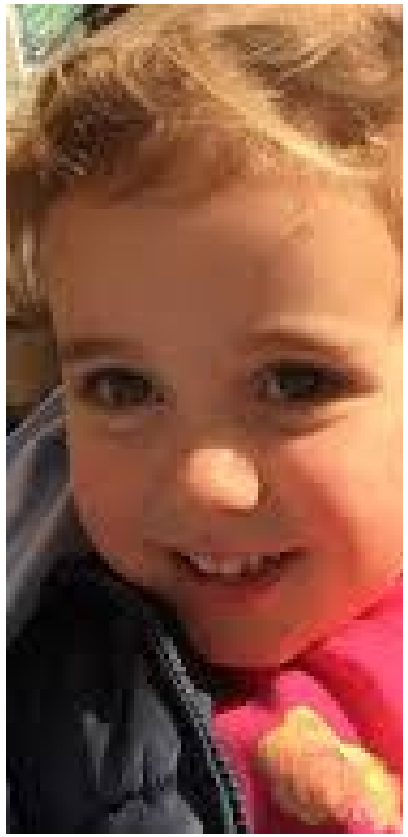
Attenuate over-excitation of nerve cells

Memantine (Ebixa®,Namenda®)
- approved 2003 by the FDA for treatment of moderate to severe AD

Memantine may protect cells against toxicity arising from nerve cells becoming too highly activated. However, the exact reason for its effectiveness is not known.

Has gene therapy worked yet?

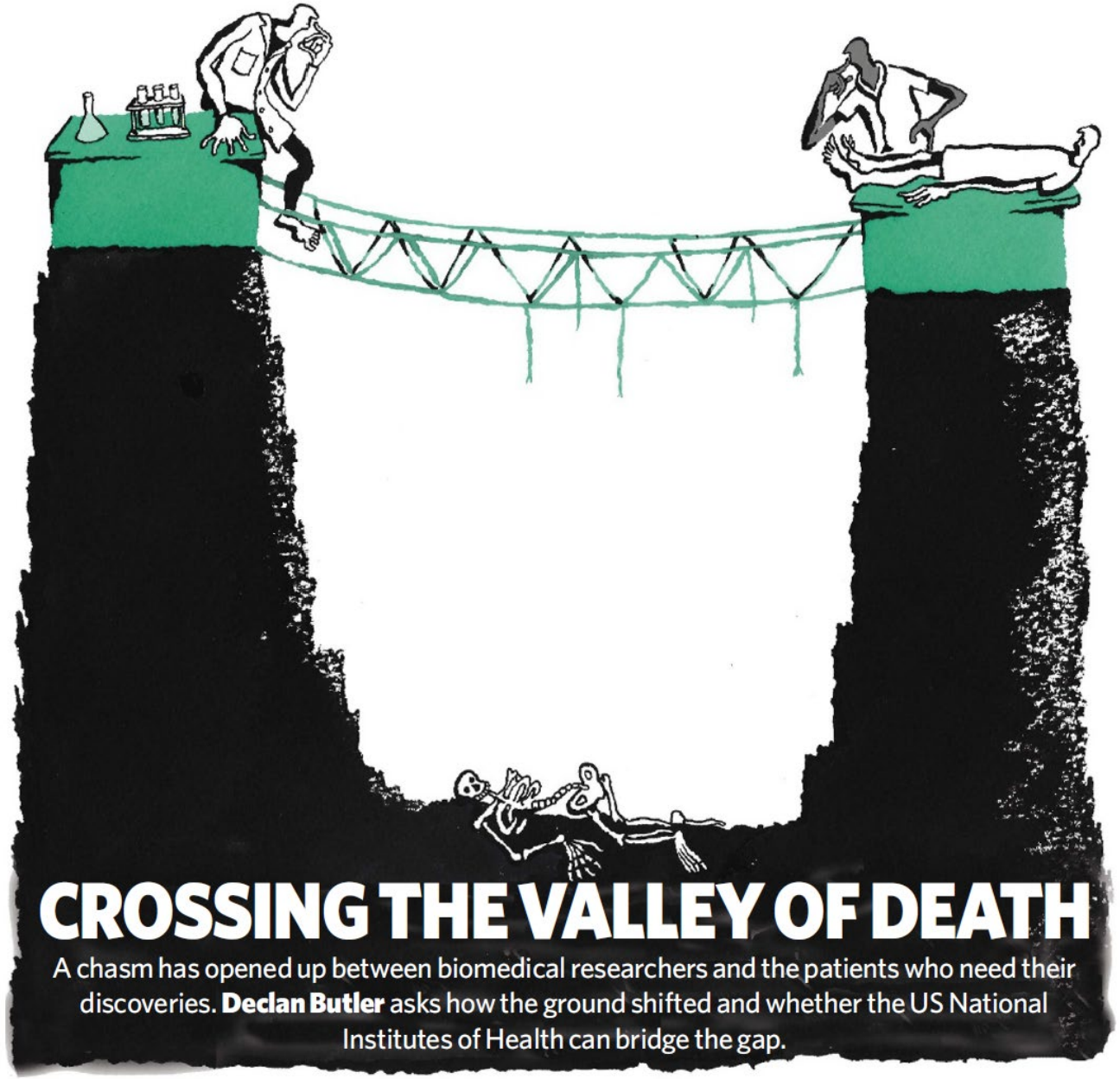
Childhood blindness



Spinal muscular atrophy

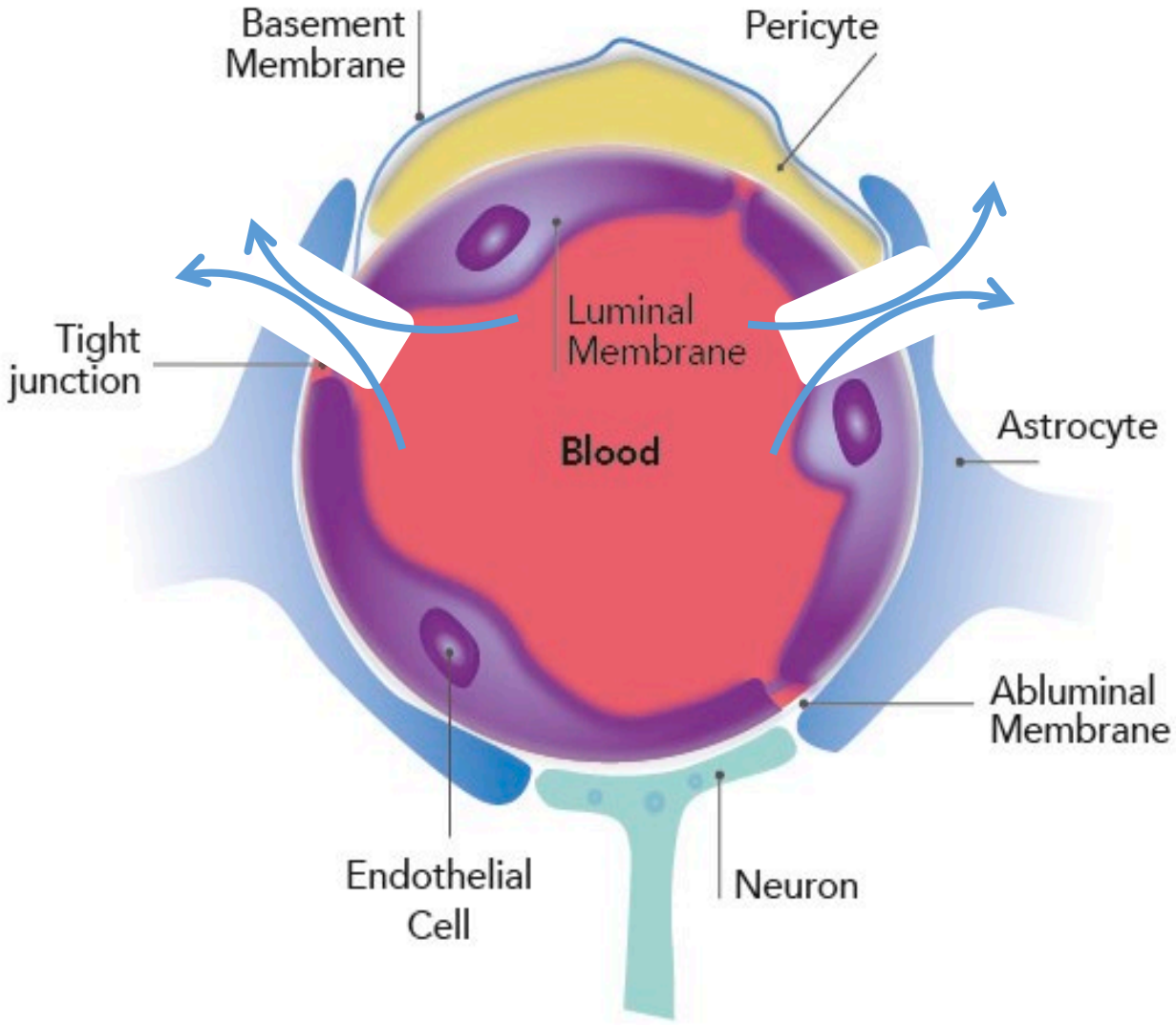
https://sofiasees.org/living-lca-vickys-story/

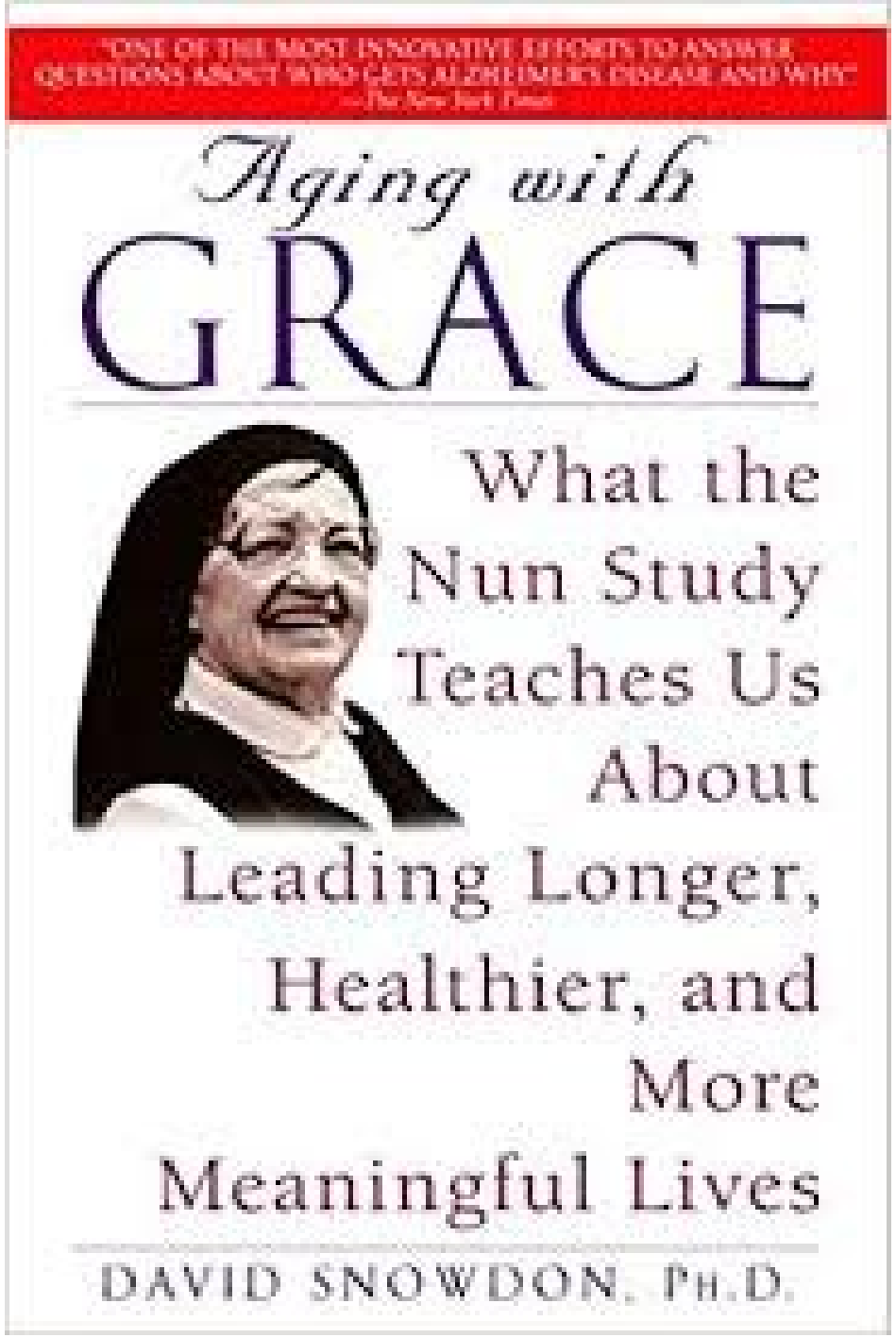
https://www.zolgensma.com/family-videos/



Butler (2008) Nature, 453, 840–842

Leaky blood-brain barrier





Clues from the Nun study

School Sisters of Notre Dame, MN

Building brain resilience can build "Cognitive Reserve"

Autobiographical essays written by the nuns at ~22 years of age.

….an essay's lack of **linguistic density** (e.g., complexity, vivacity, fluency) was a significant predictor of the risk for Alzheimer's.

~80% of nuns whose writing lacked linguistic density went on to develop Alzheimer's disease in old age;

…of those whose writing was not lacking, only 10% later developed the disease.

Resources

Neurological Foundation
https://neurological.org.nz/

BRNZ funded Website: Living well with MCI
https://www.goodhealthdesign.com/projects/living-well-with-mild-cognitive-impairment-mci

Alzheimer's NZ
http://www.alzheimers.org.nz/
Dementia NZ
https://www.dementia.nz/
N.B. many other ageing-related disorders and support societies

ABP site, https://www.aotearoabrainproject.nz
BHRC site, https://www.otago.ac.nz/bhrc