Viewing Alzheimer's disease in the brain.

Professor Christopher Rowe FRACP MD
Director ADNeT
Director Molecular Imaging Research, Austin Health & University of Melbourne

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SAVE THE DATE – 29-31 May 2023

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Topics

- MRI
- Imaging metabolism with ^{18}F-FDG PET
- Beta-amyloid plaque imaging in AD
- Tau imaging in AD

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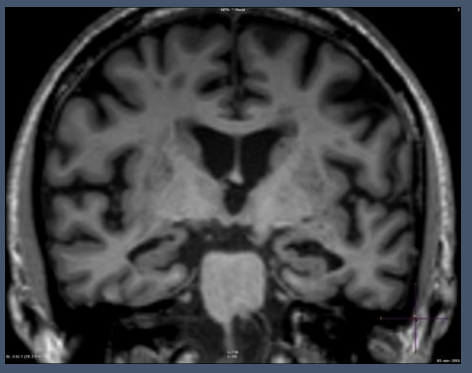
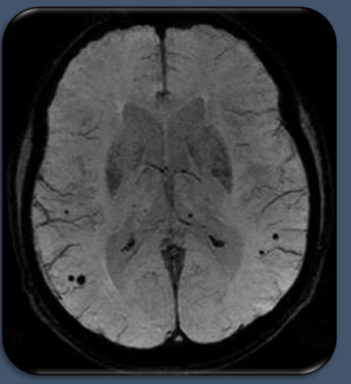
MRI

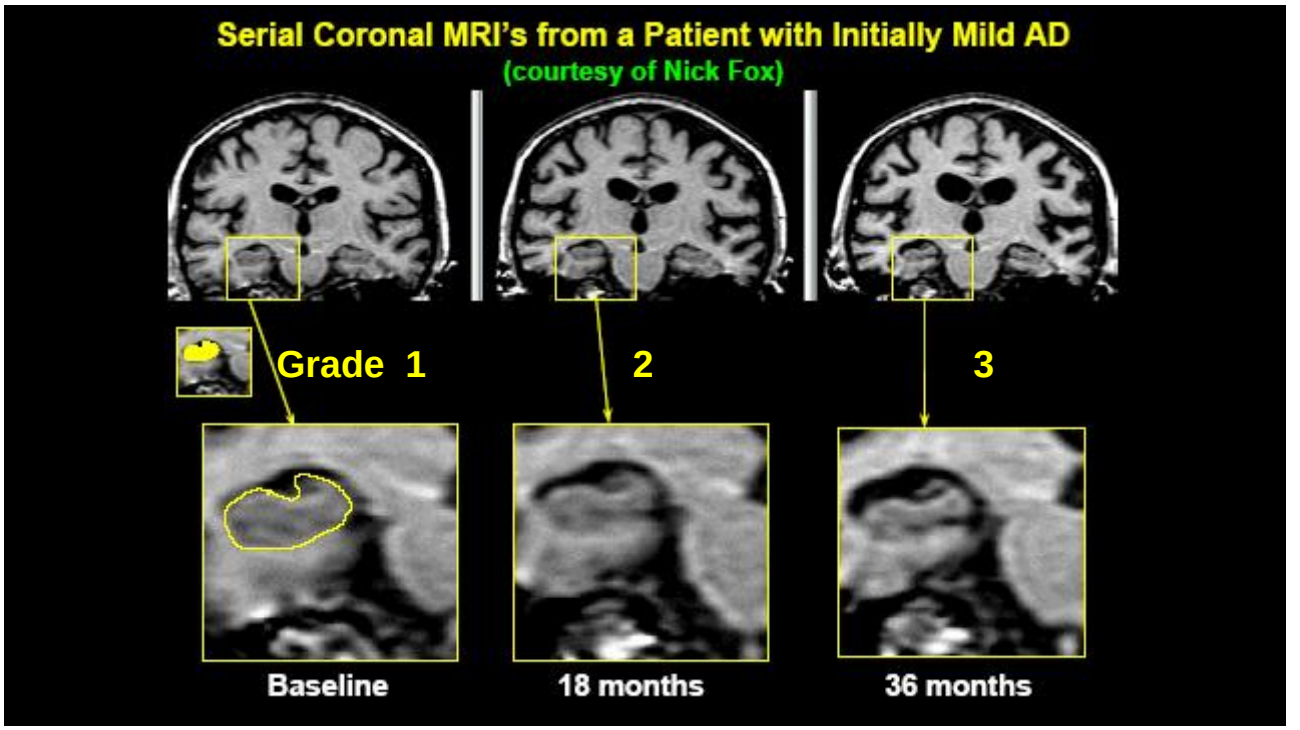
Hippocampal atrophy (Left Image) is the most established structural imaging sign of AD but it is also seen in LATE (hippocampal sclerosis) and Frontotemporal dementia. Lobar microbleeds may be seen (Right Image).





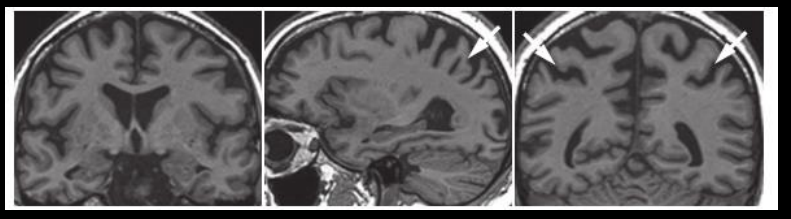
DRIVING CHANGE
Mild Cognitive Impairment

4

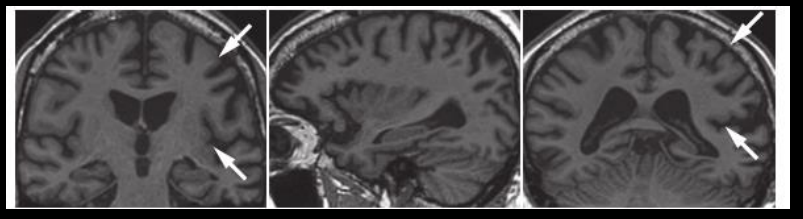


5

Atypical AD Atrophy Patterns



Parietal Lobe atrophy in Posterior Cortical Atrophy



Left side atrophy in Logopenic Aphasia

Note: Hippocampal atrophy may not be seen in AD variants

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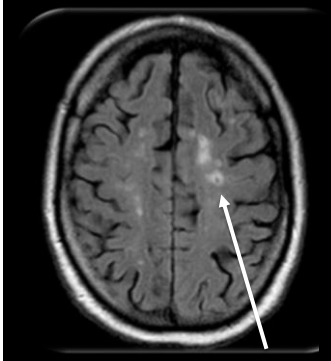
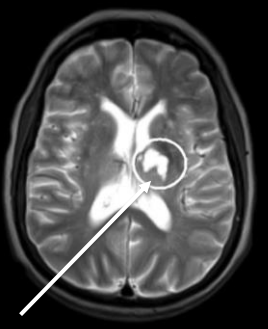
Vascular Changes are Common with AD

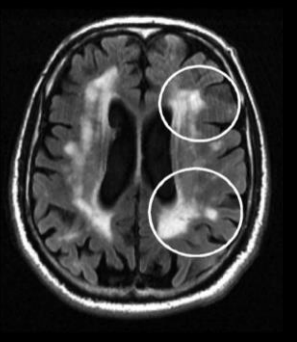
Small Vessel Disease



Lacunar Infarction



White matter hyperintensity



Dilated peri-vascular spaces

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Medicare rebate for FDG PET for AD available since November 2021
- now 800 performed per month in Australia

Medicare Benefits Schedule - Item 61560

Search Results for Item 61560

Category 5 - DIAGNOSTIC IMAGING SERVICES

61560

Group I4 - Nuclear Medicine Imaging

Subgroup 2 - PET

FDG PET study of the brain, performed for the diagnosis of Alzheimer's disease, if:

a. clinical evaluation of the patient by a specialist, or in consultation with a specialist, is equivocal; and

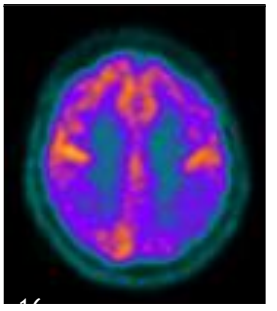
b. the service includes a quantitative comparison of the results of the study with the results of an FDG PET study of a normal brain from a reference database; and

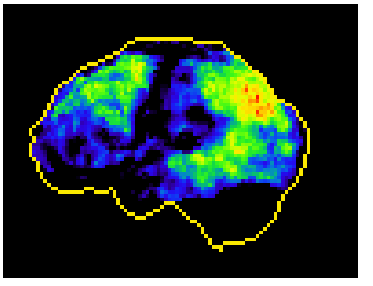
c. a service to which this item applies has not been performed on the patient in the previous 12 months; and

d. a service to which item 61402 applies has not been performed on the patient in the previous 12 months for the diagnosis or management of Alzheimer's disease

Applicable not more than 3 times per lifetime (R)

Typical AD pattern of hypometabolism





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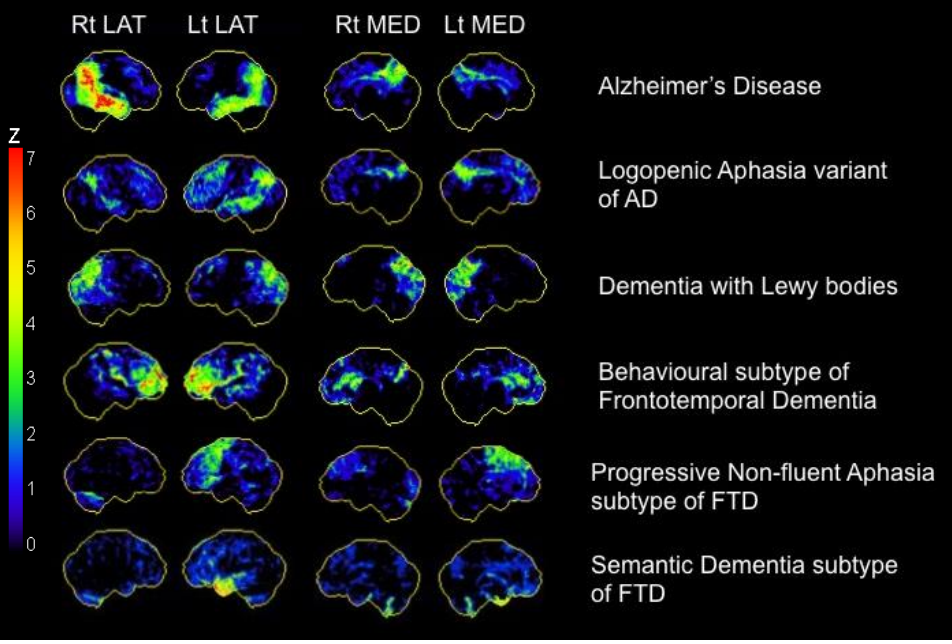
Comparison to normal database. *e.g. Neurostat*



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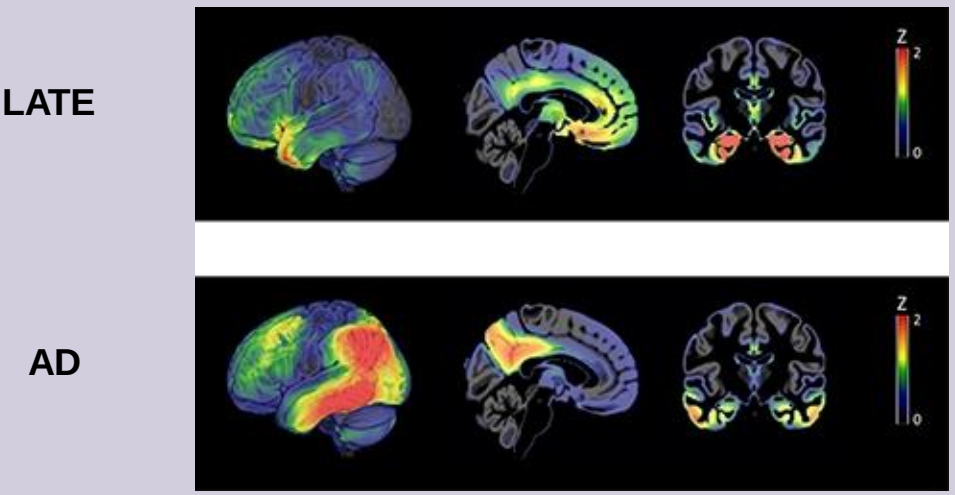
A condition that mimics Alzheimer's disease

Limbic predominant Age related TDP-43 Encephalopathy (LATE)



Alzforum 2022

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Case

- 74 year old with progressive speech difficulty
- Language difficulty was the most prominent feature for first two years but now some memory impairment
- MMSE 22/30

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Primary Progressive Aphasia
International Consensus Criteria

1. Semantic → FTLD (TDP43)
2. Nonfluent/agrammatic → FTLD (Tau > TDP43)
3. Logopenic → Alzheimer's Disease (beta-amyloid and tau)

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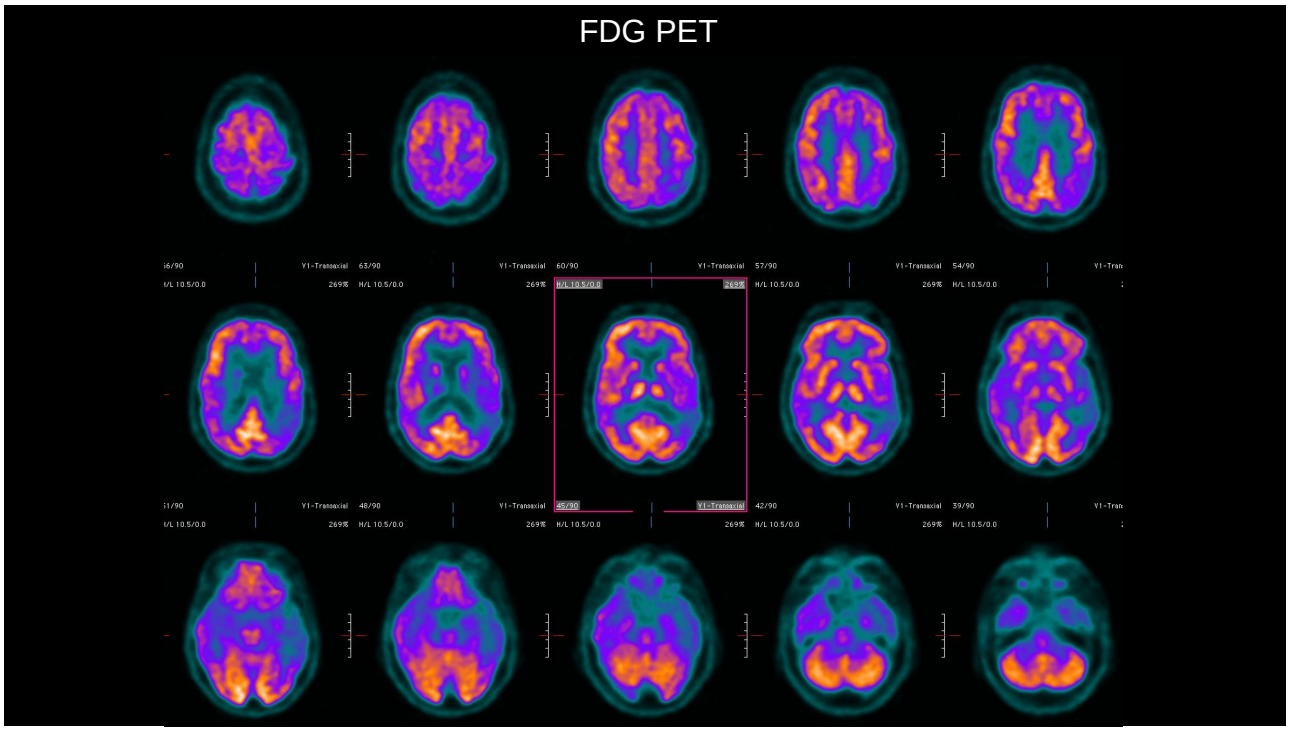
FDG PET

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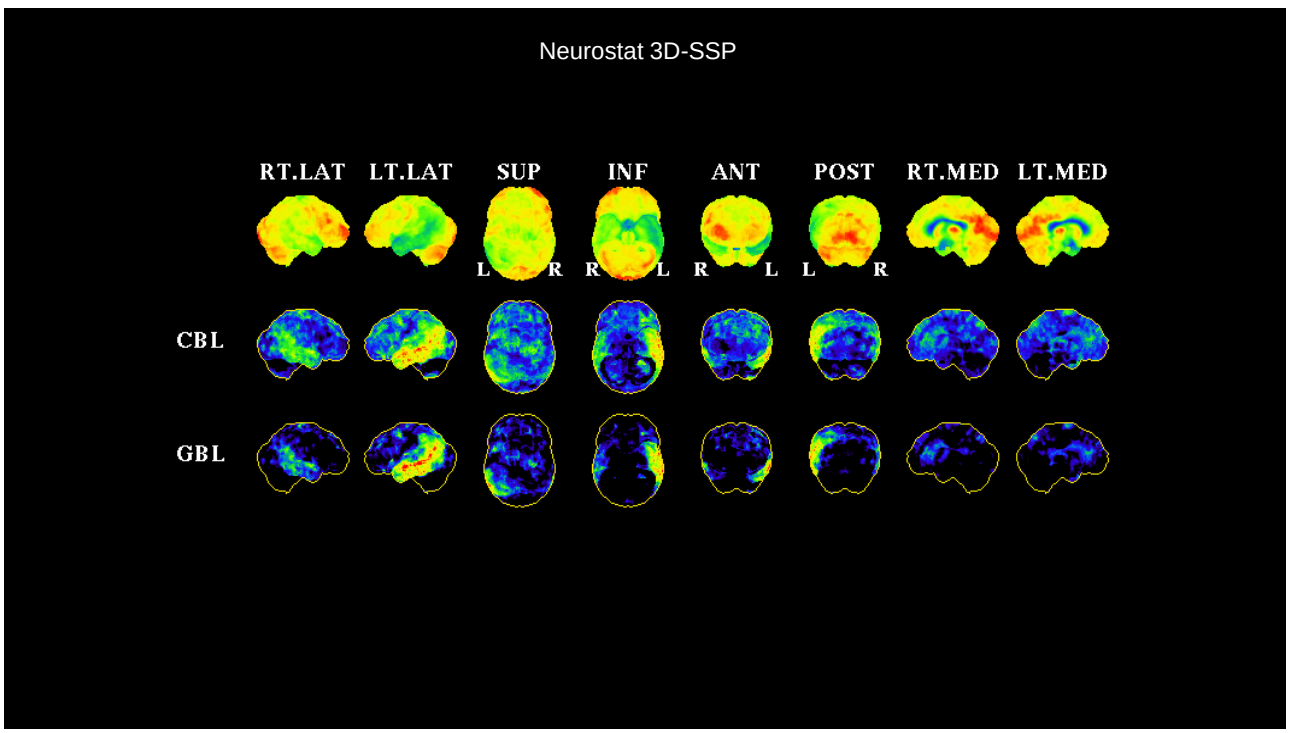
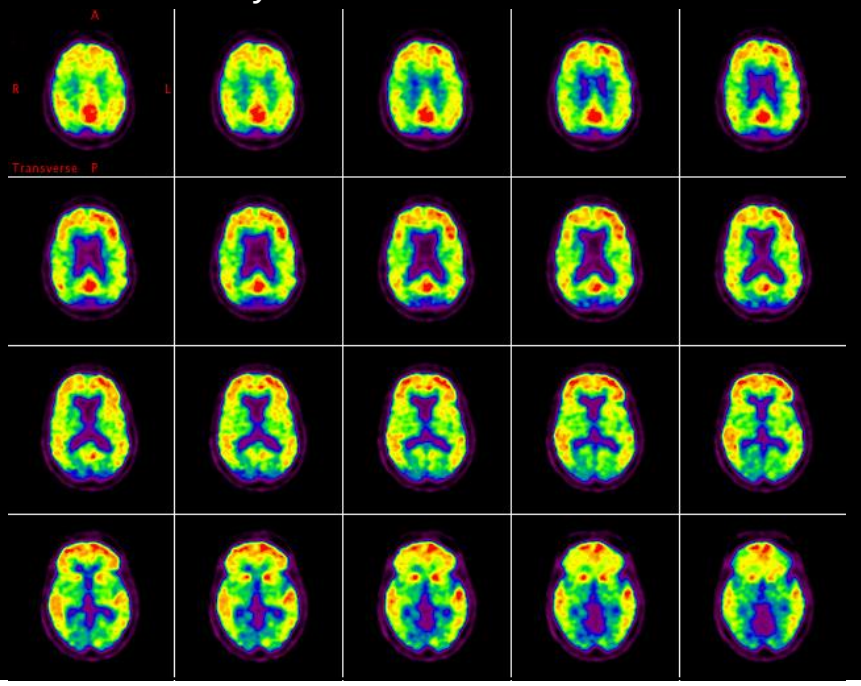

Neurostat 3D-SSP
RT.LAT
LT.LAT
SUP
INF
ANT
POST
RT.MED
LT.MED
L R
R L
R L
L R
CBL
GBL

14

Amyloid PET was Positive



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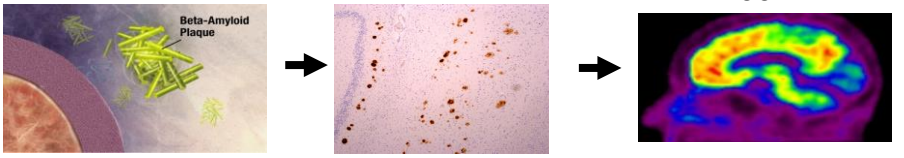
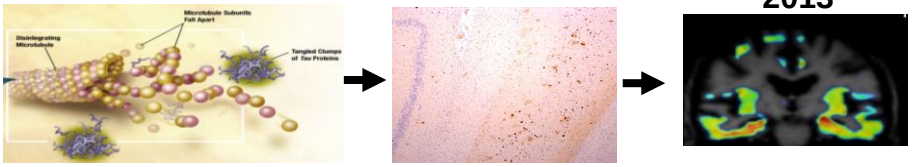
Alzheimer's Pathology

1. Extracellular Beta-amyloid Plaques



2. Intracellular Neurofibrillary Tangles (tau aggregates)



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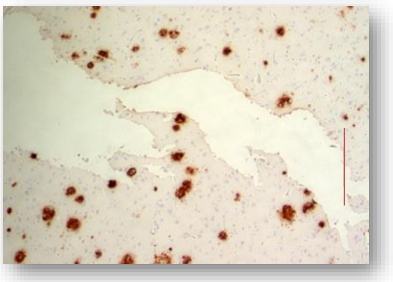
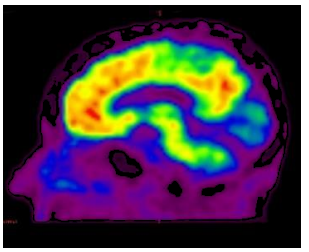
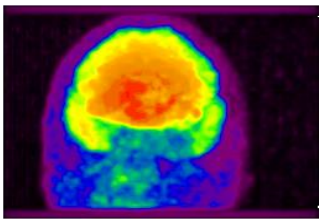
Beta-amyloid PET Scan

first performed in Uppsala, Sweden in 2002







^{11}C-PiB

Alzheimer's Disease

Inventors:
Chet Mathis
William Klunk
University of Pittsburgh

Klunk W, et al. Ann Neurology 2004;55:519–527.

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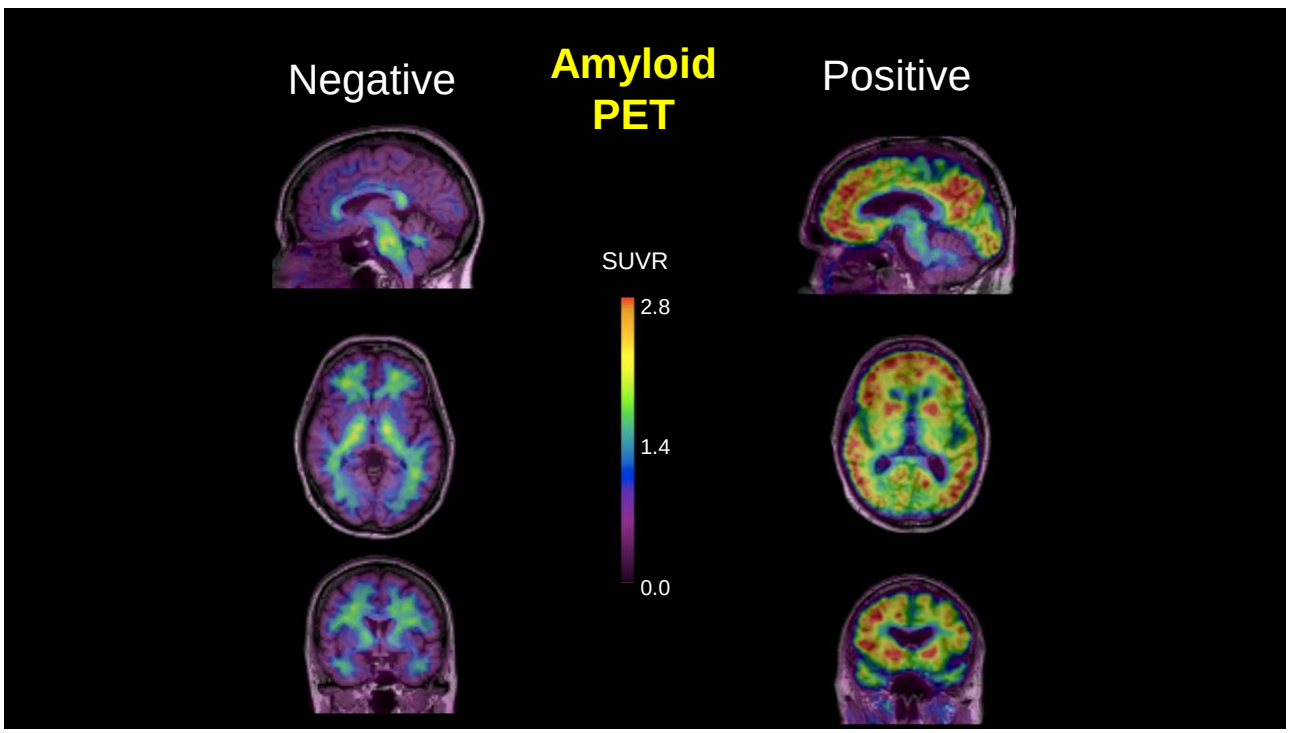

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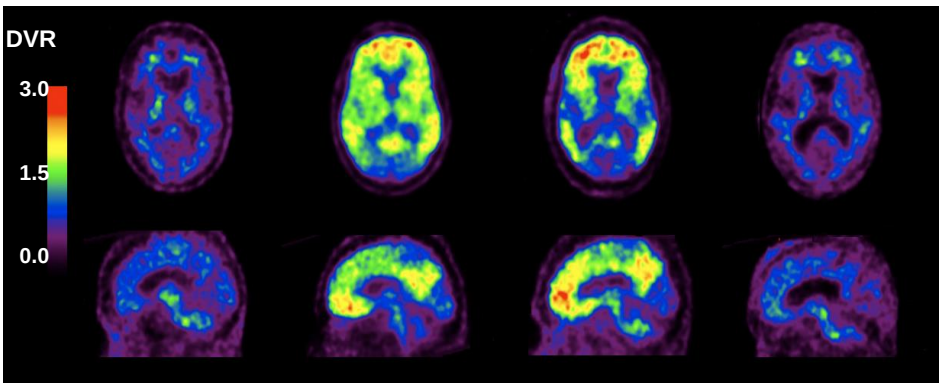
Dementia Specific Patterns



HC DLB AD FTD

Rowe CC, et al. ***Neurology*** *2007. (1,203 citations)*

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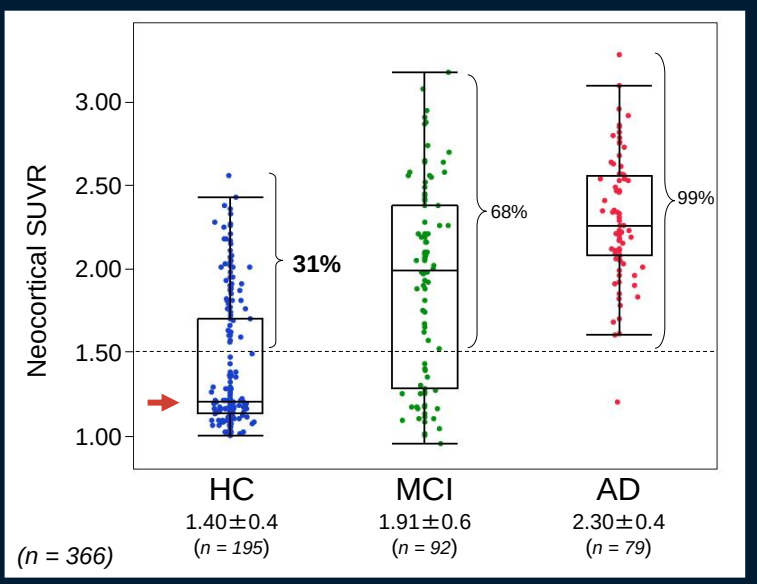
Amyloid PET SUVR



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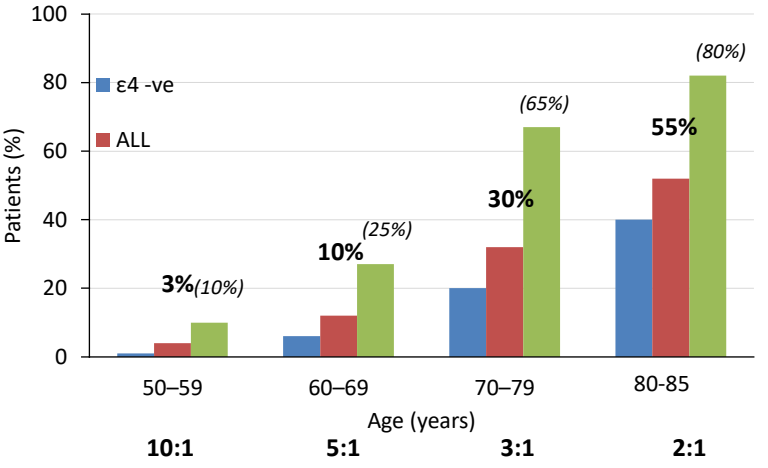
Prevalence of amyloid PET +ve by age and APOE-ε4



Data for <60 years of age from Washington University

Rowe CC, et al. Neurobiology of Aging 2010. (1025 citations)

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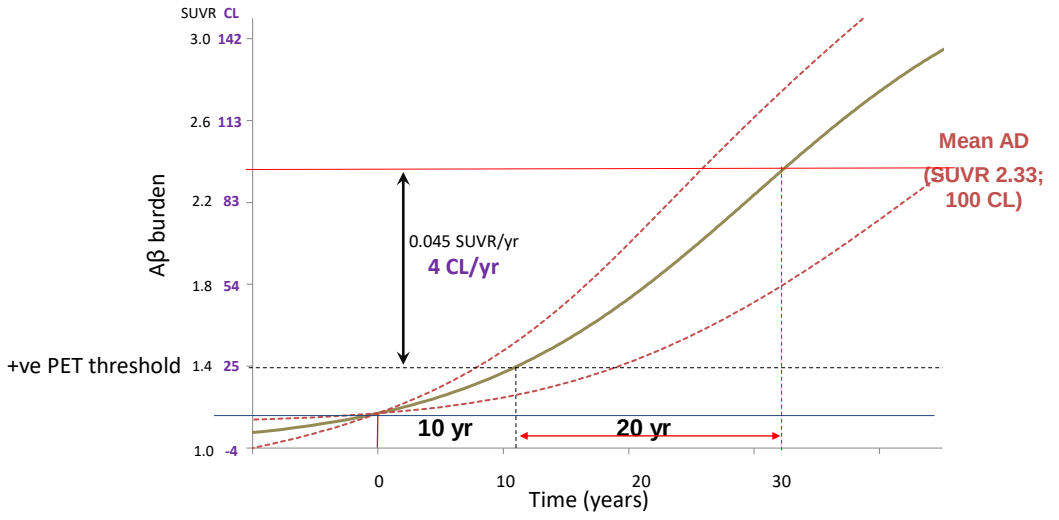
Aβ Deposition Rate



Villemagne VL, et al. **Lancet Neurology.** 2013. (1,820 citations)

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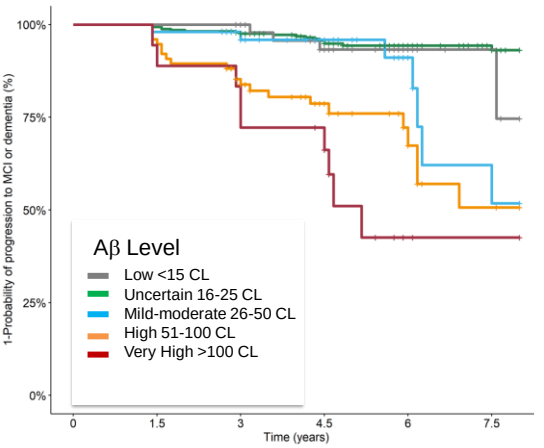
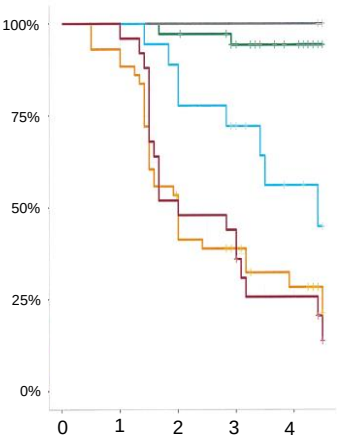
Aβ level vs disease progression

Normal to Mild Cognitive Impairment:



Time (Years)

MCI to dementia:



Time (Years)

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IWG-2 research criteria for AD

Dubois B, et al. Lancet Neurology ***2014****.*

- Objective episodic memory impairment

plus

- Pathophysiological biomarker for AD

i.e. CSF (low $A\beta_{42}$ with high tau) or **positive Aβ PET**

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Aβ PET Diagnostic Impact is Massive

- **Concordance between pre-PET diagnosis and PET results**
  - Pre-PET diagnosis AD: 61.2% amyloid PET+
  - Pre-PET diagnosis non-AD: 54.5% amyloid PET+
- **PET led to changes in diagnosis**
  - In patients with *positive* scan, rate of AD diagnosis *increased* from 78.5% pre-PET to 95.2% post-PET
  - In patients with *negative* scan, rate of AD diagnosis *decreased* from 73.0% pre-PET to 14.5% post-PET

IDEAS-Study.org

iDEAS Imaging Dementia—Evidence For Amyloid Scanning

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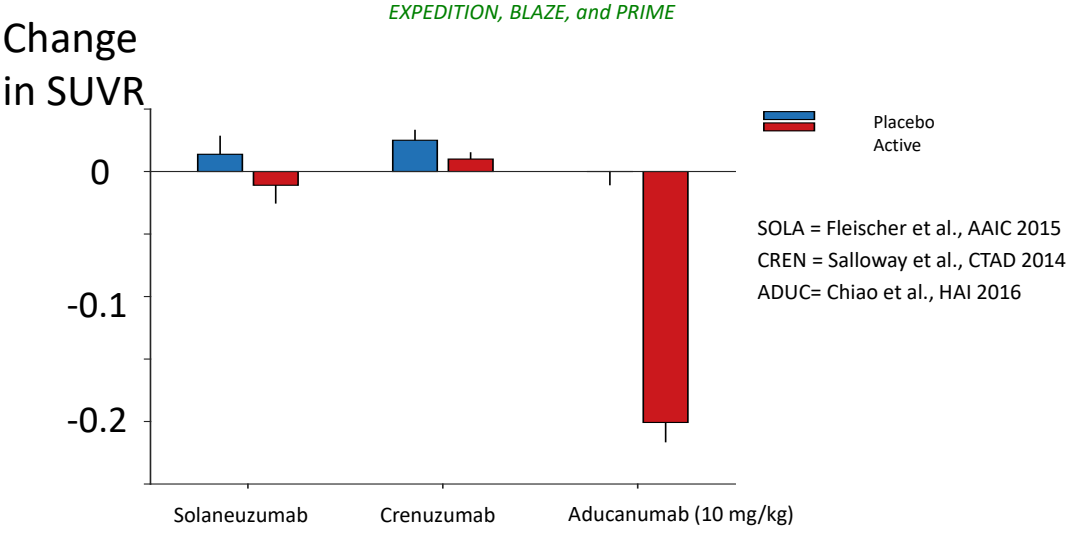
Aβ PET in early monoclonal Aβ antibody AD trials in Mild-Moderate Dementia

EXPEDITION, BLAZE, and PRIME



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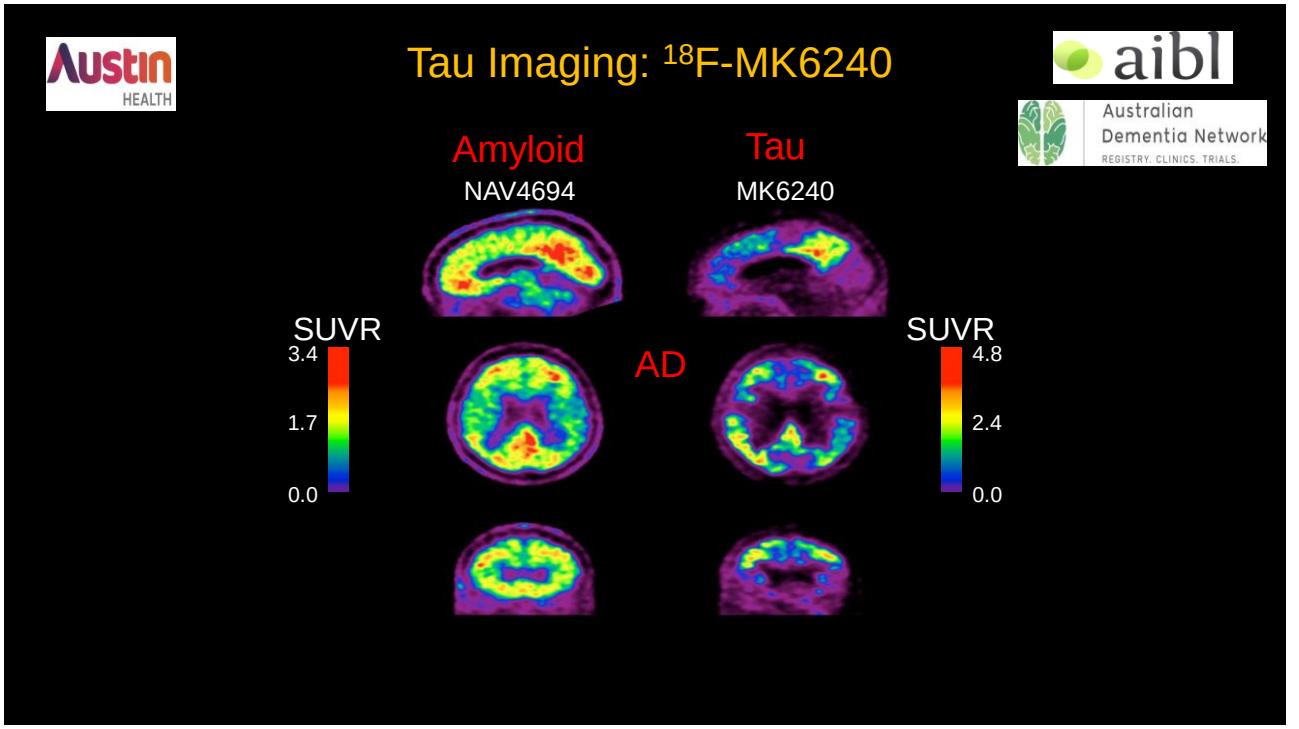
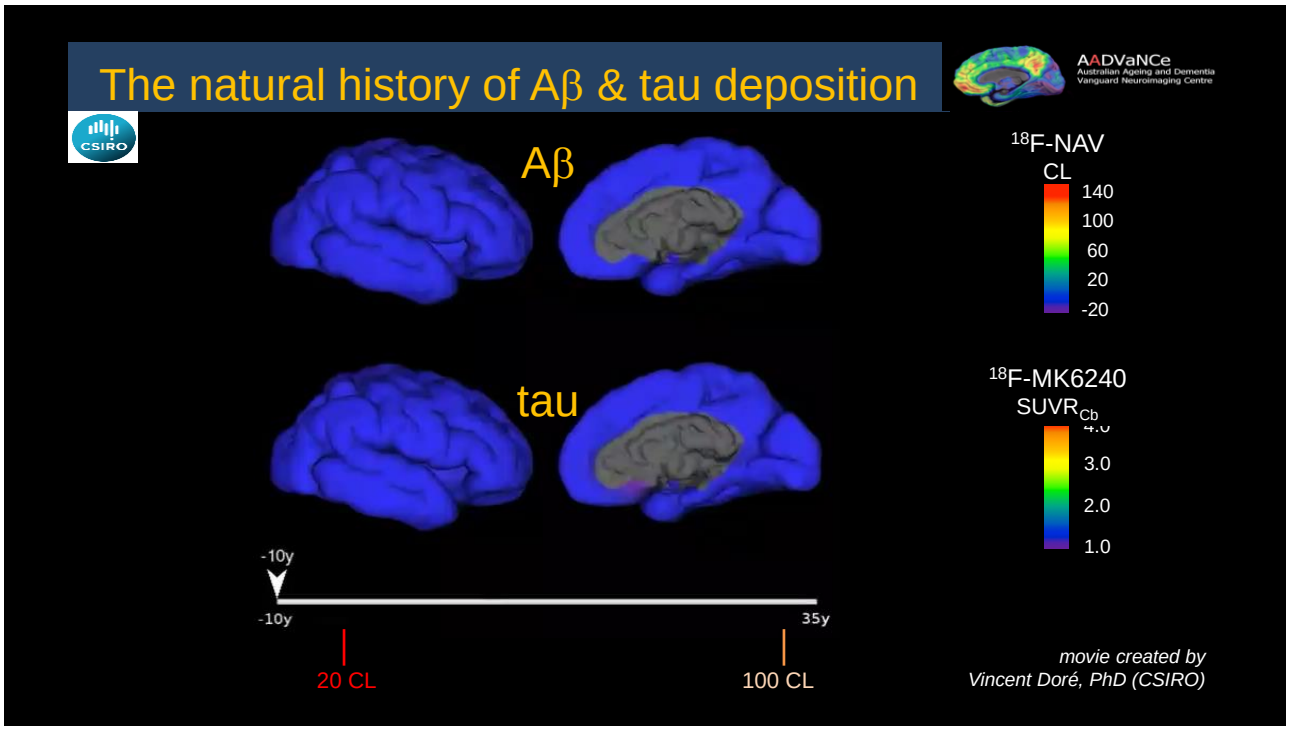

Tau Imaging: 18F-MK6240
Amyloid
NAV4694
Tau
MK6240
SUVR
3.4
1.7
0.0
AD
SUVR
4.8
2.4
0.0

27


The natural history of Aβ & tau deposition
AADVaNCe
Australian Ageing and Dementia Vanguard Neuroimaging Centre
Aβ
tau
18F-NAV
CL
140
100
60
20
-20
18F-MK6240
SUVRCb
3.0
2.0
1.0
-10y
-10y
35y
20 CL
100 CL
movie created by
Vincent Doré, PhD (CSIRO)

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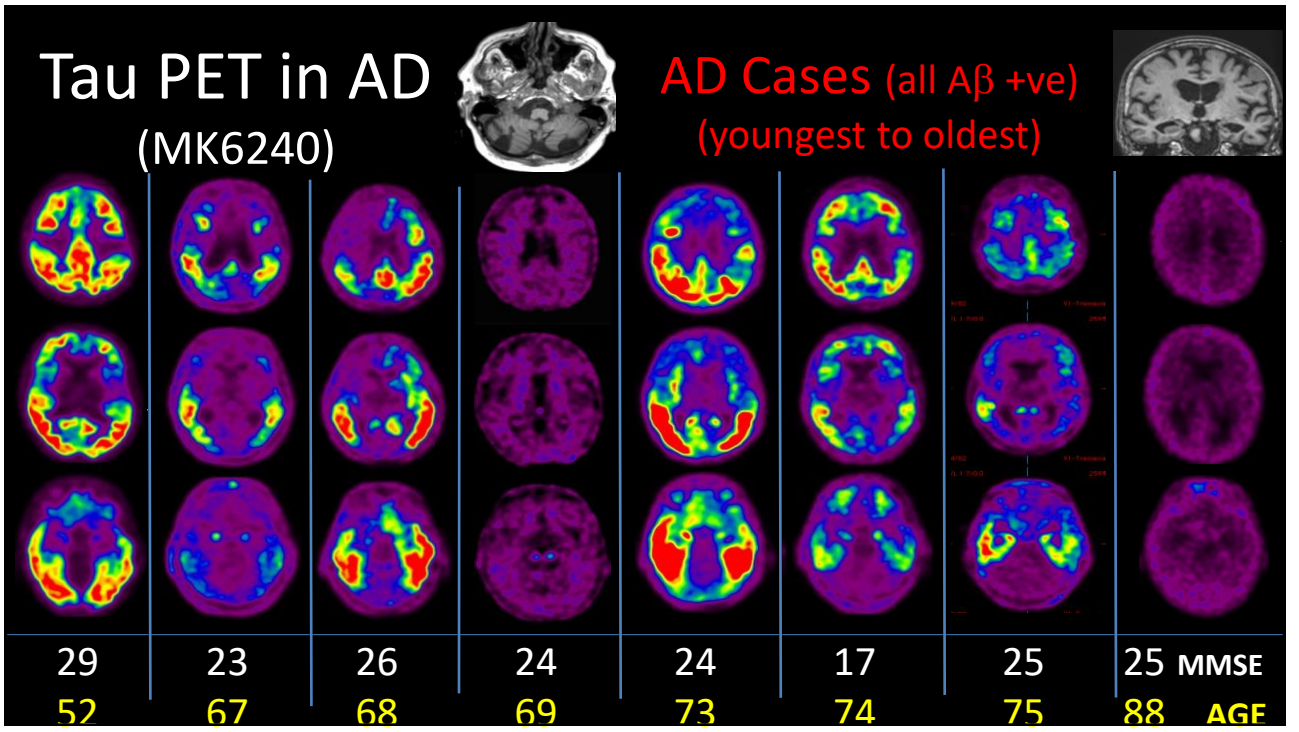
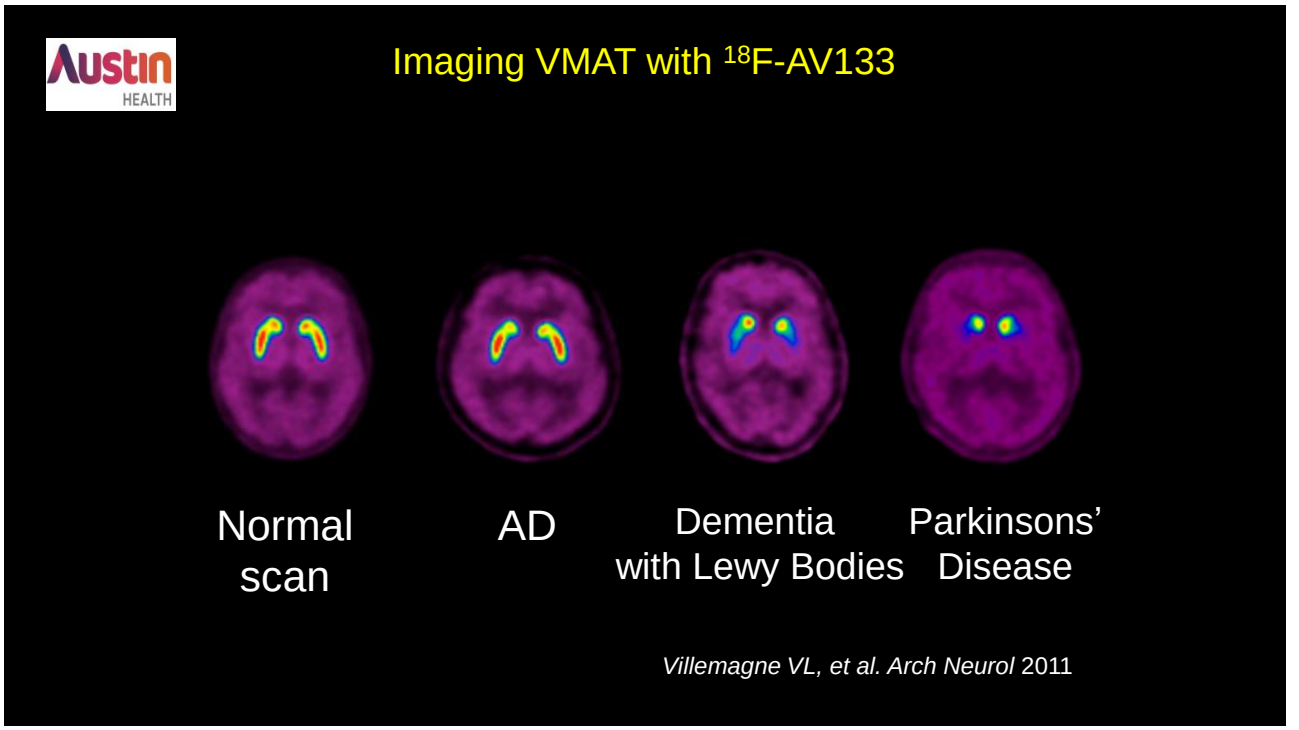

Tau PET in AD
(MK6240)
AD Cases (all Aβ +ve)
(youngest to oldest)
29 23 26 24 24 17 25 25 MMSE
52 67 68 69 73 74 75 88 AGE

29


Austin HEALTH
Imaging VMAT with 18F-AV133
Normal scan
AD
Dementia with Lewy Bodies
Parkinsons' Disease
Villemagne VL, et al. Arch Neurol 2011

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Clinical status of Aβ PET for AD and dopamine transporter (DAT) imaging for PD/DLB

- Aβ imaging in AD approved by the US FDA in 2011 and Europe in 2013.
- DATScan (^{123}I FP-CIT aka ^{123}I-ioflupane) marketed by GE Healthcare was approved in Europe in 2000 and in USA in 2011 for PD and DLB.
- MBS listing for Aβ PET could occur if TGA approves Lecanemab (anti-amyloid antibody therapy for AD).

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Detecting Alzheimer's disease in fluids

Christopher Fowler

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AIBL Biobank

- One of best characterised AD cohorts in the world
- >150 researchers/companies world wide have accessed biospecimens
- Supporting basic research
- Validating new tests for clinical diagnosis

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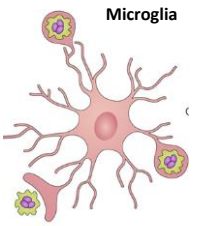
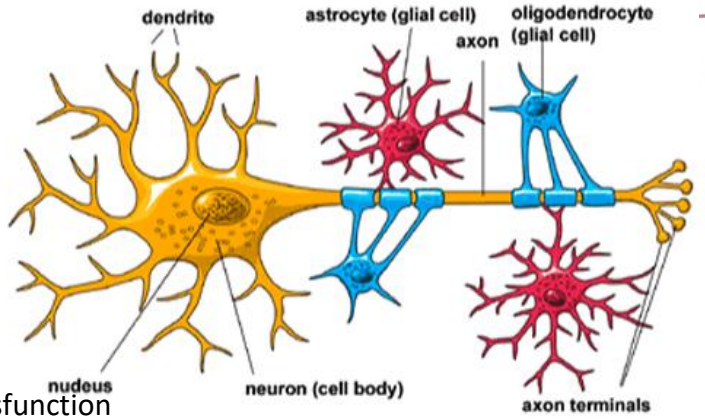
Cellular environment of AD pathology

Cells of the Brain

- nerve cells
- support cells
  - nutrition
  - immune function
  - nerve maintenance





AD neurodegeneration

- Terminal/Synaptic disfunction
- Axonal damage
- Cell body loss

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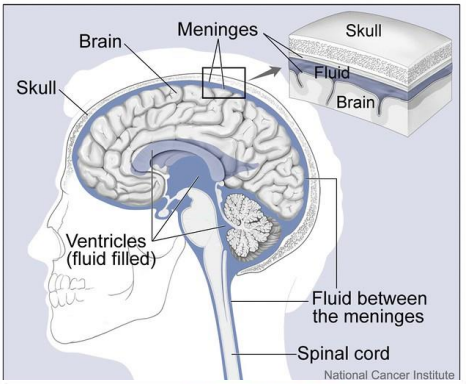
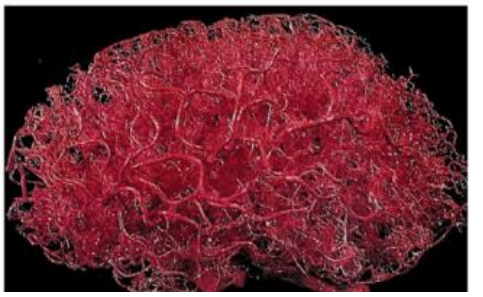
Available biofluids

- Blood, Urine, Saliva, Tears, CSF

Blood brain barrier

- Brain needs to be highly protected.
  - Thick skull
  - Protective fluid around brain and spinal cord = **Cerebral Spinal Fluid (CSF)**
  - Meninges membrane
  - Blood vessels provide nutrients, but have specialised endothelia that prevents toxins, infection crossing into the brain.
    - Also makes it difficult for material to exit the brain to the blood





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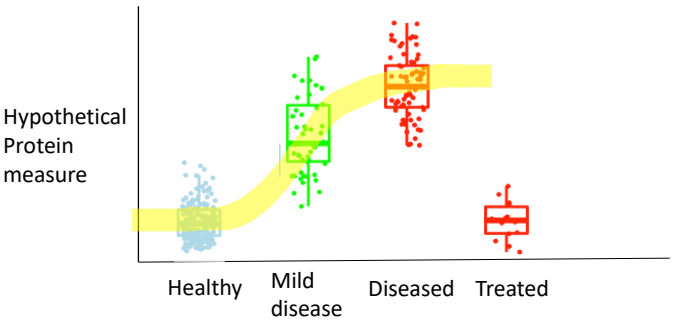
Biomarkers and disease chemistry

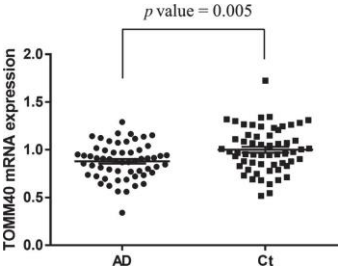
- Characteristics of optimal biomarker



- Real life measurements

- often no clear threshold

- provides information on disease molecular pathways



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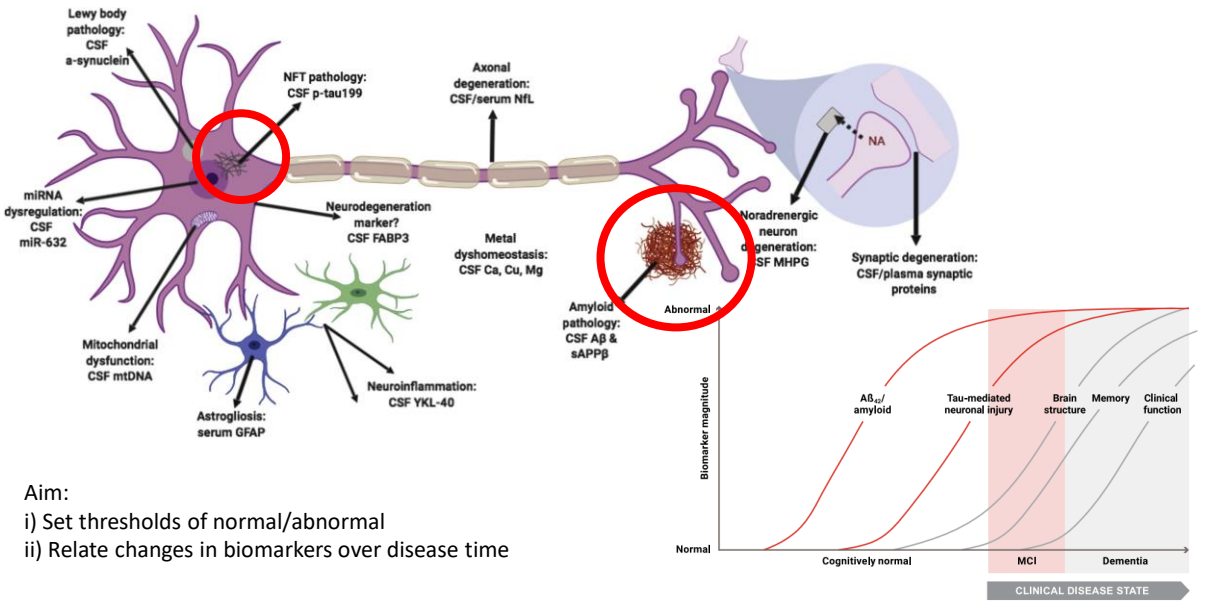
Hallmark pathologies: Amyloid plaque, Tau tangles



Aim:
i) Set thresholds of normal/abnormal
ii) Relate changes in biomarkers over disease time

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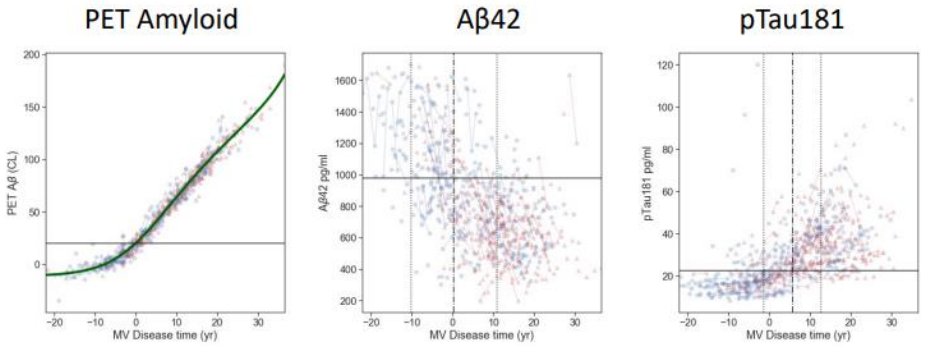
Directly measuring Aβ and Tau in CSF

- Protein of these markers in CSF 100x higher than in blood
- Have established positivity threshold: National Dementia Diagnostic Laboratory (NDDL - Florey) analyses clinical samples
- Work with international consortia to combine data and analyse time frame of biomarker change
- Abeta – lots of soluble fragments in CSF of healthy; aggregate into plaques (soluble markers disappear) while plaques increase (measured by PET)



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Directly measuring Aβ – evolution in detection devices

- Lower limit of detection:
  - ELISA (100 pg/mL)
  - SIMOA (5 pg/mL)
  - Mass Spec (3 pg/mL)

ELSEVIER

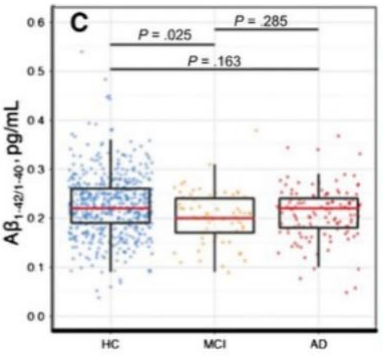
Alzheimer's & Dementia 10 (2014) 53–61

Alzheimer's & Dementia

Changes in plasma amyloid beta in a longitudinal study of aging and Alzheimer's disease

Alan Rembach[a,*], Noel G. Faux[a], Andrew D. Watt[a], Kelly K. Pertile[a], Rebecca L. Rumble[a], Brett O. Trounson[a], Christopher J. Fowler[a], Blaine R. Roberts[a], Keyla A. Perez[a], Qiao-Xin Li[a], Simon M. Laws[b,c], Kevin Taddei[b,c], Stephanie Rainey-Smith[b,c], Joanne S. Robertson[a], Manu Vandijck[d], Hugo Vanderstichele[d,e], Kevin J. Barnham[a], Kathryn A. Ellis[a,f,i], Cassandra Szoeke[f,i], Lance Macaulay[g], Christopher C. Rowe[h], Victor L. Villemagne[a,h], David Ames[i], Ralph N. Martins[b,c], Ashley I. Bush[a], Colin L. Masters[a]; the AIBL research group[†]

2014 analysis ELISA



No strong effect observed

39

Directly measuring Aβ – evolution in detection devices

- Lower limit of detection:
  - ELISA (100 pg/mL)
  - SIMOA (5 pg/mL)
  - Mass Spec (3 pg/mL)

2018 MASS SPEC

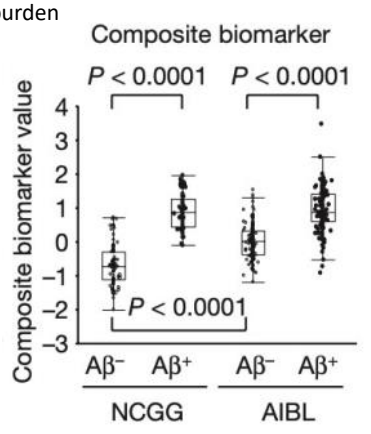
Key results:
- Confirmed the plasma-CSF relationship
- Confirmed association with cerebral amyloid burden

LETTER

doi:10.1038/nature25456

High performance plasma amyloid-β biomarkers for Alzheimer's disease

Akinori Nakamura[1], Naoki Kaneko[2], Victor L. Villemagne[3,4], Takashi Kato[1,5], James Doecke[6], Vincent Doré[3,6], Chris Fowler[4], Qiao-Xin Li[4], Ralph Martins[7], Christopher Rowe[3,4], Taisuke Tomita[8], Katsumi Matsuzaki[9], Kenji Ishii[10], Kazunari Ishii[11], Yutaka Arahata[5], Shinichi Iwamoto[2], Kengo Ito[1,5], Koichi Tanaka[2], Colin L. Masters[4] & Katsuhiko Yanagisawa[1]

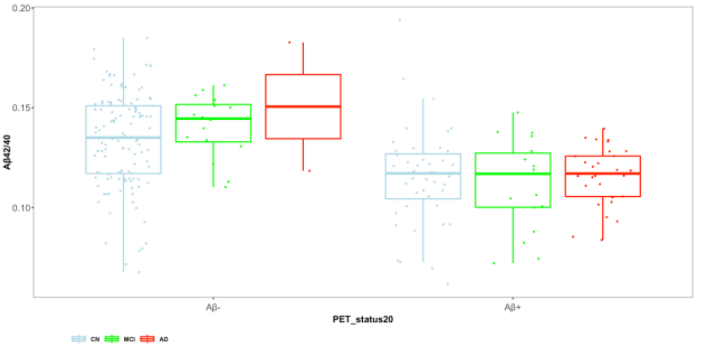


40

Directly measuring Aβ – evolution in detection devices

- Lower limit of detection:
  - ELISA (100 pg/mL)
  - SIMOA (5 pg/mL)
  - Mass Spec (3 pg/mL)

2022 SIMOA
Cheaper than mass spec
Less expertise to run



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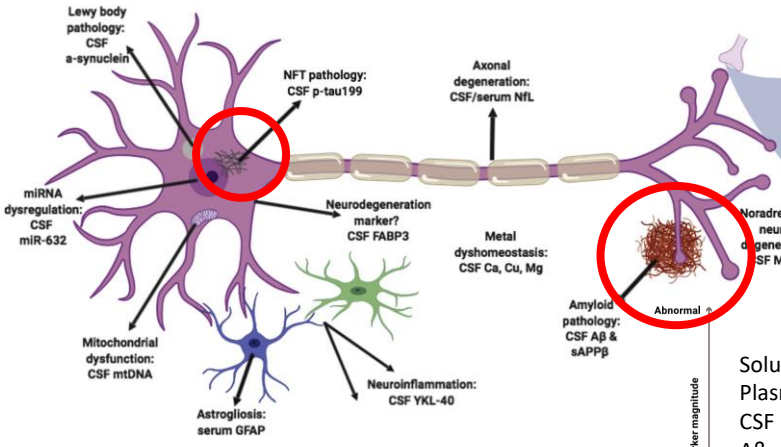
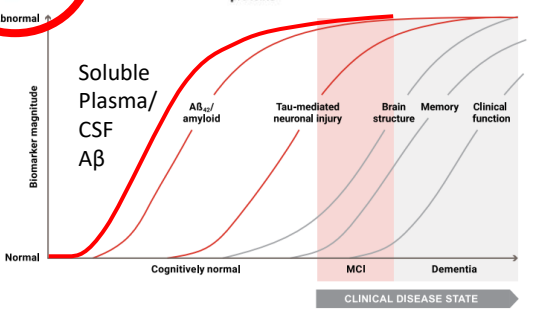
Hallmark pathologies: Amyloid plaque, Tau tangles





Aim:
i) Set thresholds of normal/abnormal
ii) Relate changes in biomarkers over disease time

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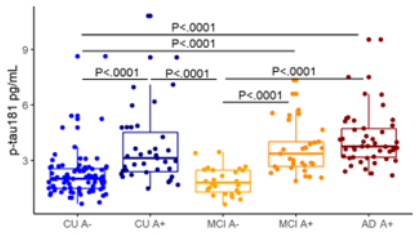
Hallmark pathology – tau in plasma



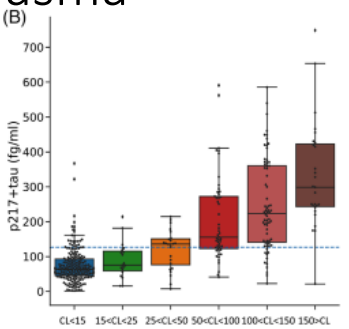
Received: 8 February 2022 | Revised: 22 May 2022 | Accepted: 23 May 2022
DOI: 10.1002/alz.12724

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Plasma Aβ42/40 ratio, p-tau181, GFAP, and NfL across the Alzheimer's disease continuum: A cross-sectional and longitudinal study in the AIBL cohort

Pratishtha Chatterjee[1,2] | Steve Pedrini[2] | James D. Doecke[3] | Rohith Thota[1,4] | Victor L. Villemagne[5,6] | Vincent Doré[3,6] | Abhay K. Singh[7] | Penghao Wang[8] | Stephanie Rainey-Smith[2,9,10,11] | Christopher Fowler[12] | Kevin Taddei[2,9] | Hamid R. Sohrabi[1,2,9,13,14] | Mark P. Molloy[15,16,17] | David Ames[18,19] | Paul Maruff[12,20] | Christopher C. Rowe[6,12] | Colin L. Masters[12] | Ralph N. Martins[1,2,9,13] | the AIBL Research Group



Received: 4 March 2022 | Accepted: 6 March 2022 | Published online: 8 April 2022
DOI: 10.1002/dad2.12307

RESEARCH ARTICLE

Diagnosis, Assessment & Disease Monitoring

Plasma p217+tau versus NAV4694 amyloid and MK6240 tau PET across the Alzheimer's continuum

Vincent Doré[1,2] | James D. Doecke[3] | Ziad S. Saad[4] | Gallen Triana-Baltzer[4] | Randy Slemmon[4] | Natasha Krishnadas[2] | Pierrick Bourgeat[3] | Kun Huang[2] | Samantha Burnham[1] | Christopher Fowler[5] | Stephanie R. Rainey-Smith[6] | Ashley I. Bush[5,7] | Larry Ward[5] | Jo Robertson[5] | Ralph N. Martins[6,8,9] | Colin L. Masters[5] | Victor L. Villemagne[2,10] | Jurgen Fripp[3] | Hartmuth C. Kolb[4] | Christopher C. Rowe[2,5,7]

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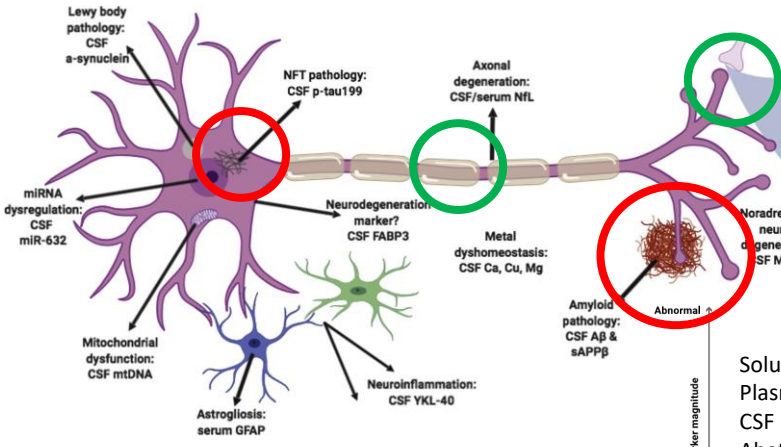
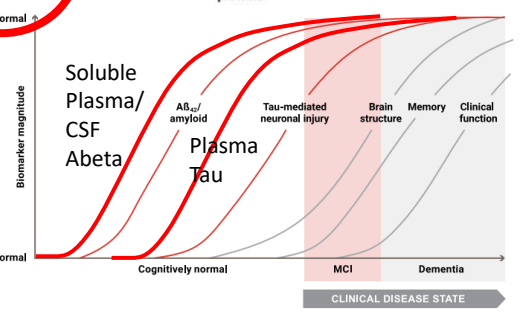
Pathologies: Synaptic dysfunction





Aim:
i) Set thresholds of normal/abnormal
ii) Relate changes in biomarkers over disease time

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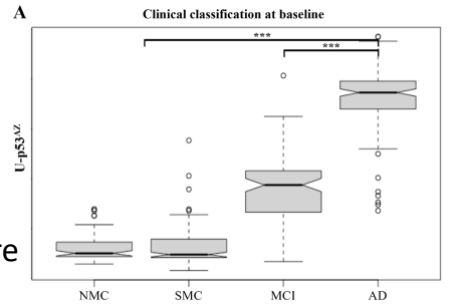
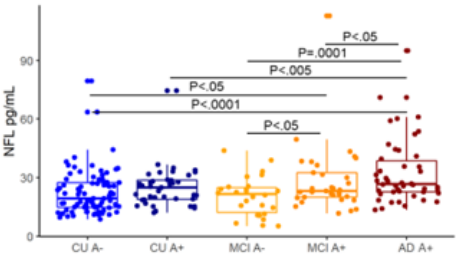
Synapse disruption

- Unfolded p53
- Marker of oxidative stress at synapse
- Starting longitudinal analysis
- Unsure if specific for AD, but indicates future cognitive decline



Nerve damage

- NfL – part of cell scaffolding
- Marker of axon damage
- Good marker for neurodegeneration in general vs psychosis



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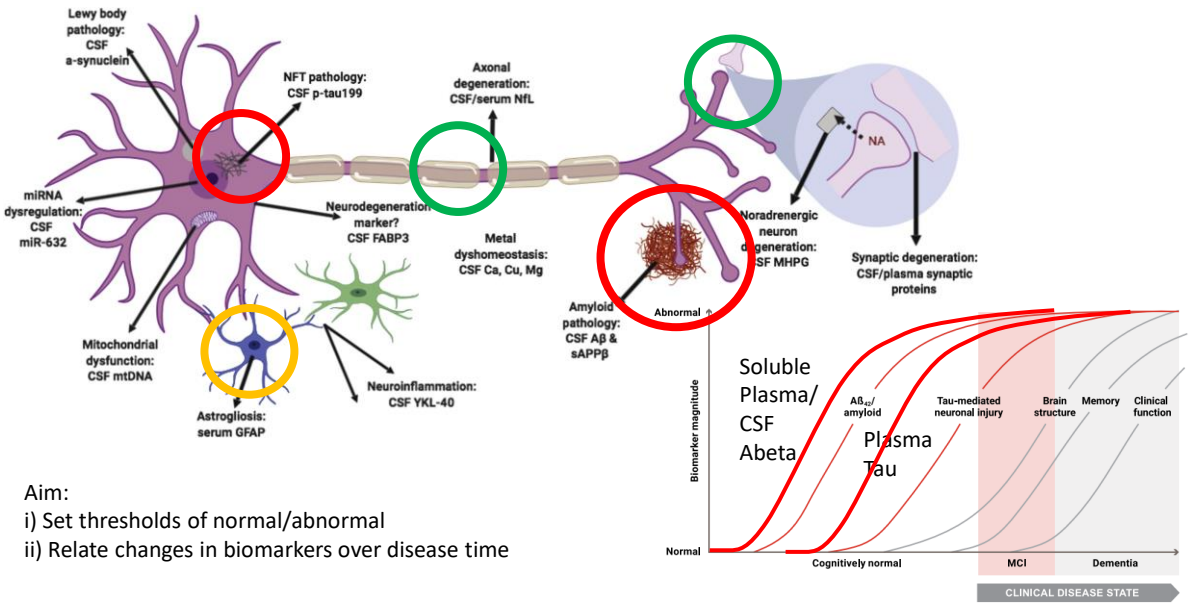
Pathologies: Support cells



Aim:
i) Set thresholds of normal/abnormal
ii) Relate changes in biomarkers over disease time

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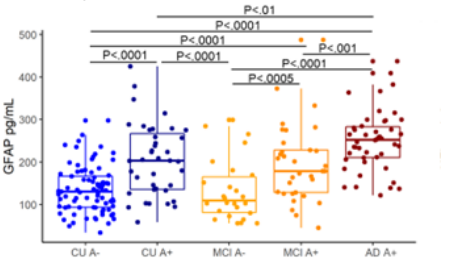
Changes of the immune response

- Over-activation of support cells
  - Reactive astrogliosis
    - Prevents damage to nerves
    - Activated for too long
  - Protein marker GFAP



- Do blood immune cells also show changed properties?
  - Evidence of changed prevalence of subtypes of blood immune cells
  - Reduced phagocytosis (immune cells eating debris) rates in AD.

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Urine

- Measure Aβ – need more samples
- Measure plastics – need more samples
- Exosomes
  - Small blebbings/bubbles separate from nerve cells and contain a selection of protein and RNA. These exosomes move into fluids all around the body, including urine. Investigate a snap-shot of DNA expression in the brain nerve cells.

More blood

- Lipids and cell membrane composition
- Lots more synaptic markers – new antibodies – being developed
- More sensitive platforms
- Integrating genetics and rates of change of biomarkers

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Conclusions

- Have established thresholds in CSF to support clinical diagnosis
- Have supported plasma Aβ assay development to the point that companies are preparing datasets/platforms for FDA application
- Starting to plot longitudinal biomarker changes covering many aspects of disease pathway
- Not all markers are specific for AD, but when taken in conjunction with Aβ and Tau measurements will help understand “disease age”
- Longitudinal follow up has been critical in developing our understanding of disease time frame
- What precedes amyloid accumulation? – moving into younger cohorts

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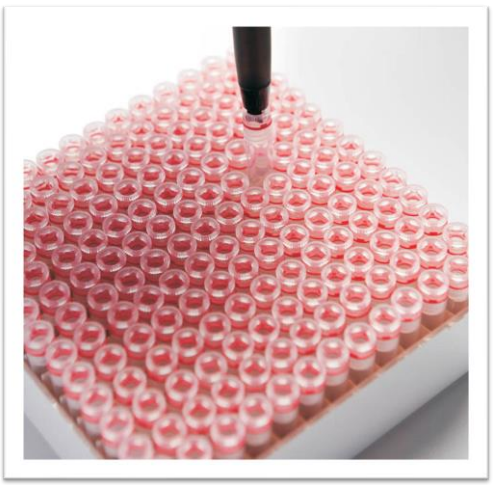
Thank you for donating biofluids – both on-site and home visits



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Australia's National Science Agency

Reducing your risks – Can lifestyle modification help

Jurgen Fripp
Group Leader of Biomedical Informatics
Health & Biosecurity
The Australian e-Health Research Centre
June 2022

Innovative medical technologies for the discovery of meaningful patterns and biomarkers from biomedical data.

THE AUSTRALIAN E-HEALTH RESEARCH CENTRE

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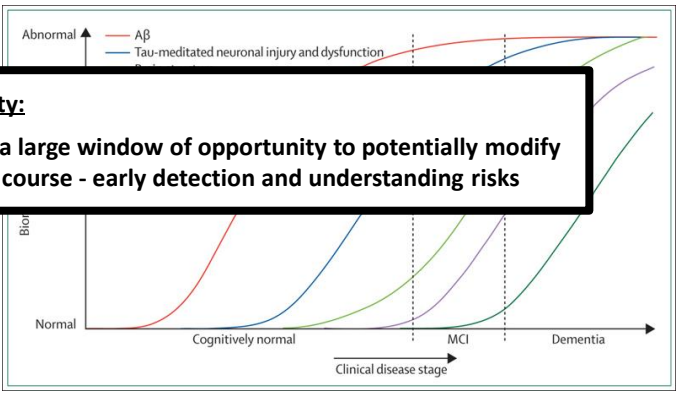
Alzheimer's – understanding disease course

aibl ADNI

MRI

Aβ

tau



Opportunity:

There's a large window of opportunity to potentially modify disease course - early detection and understanding risks

Rowe, Villemagne, Jack

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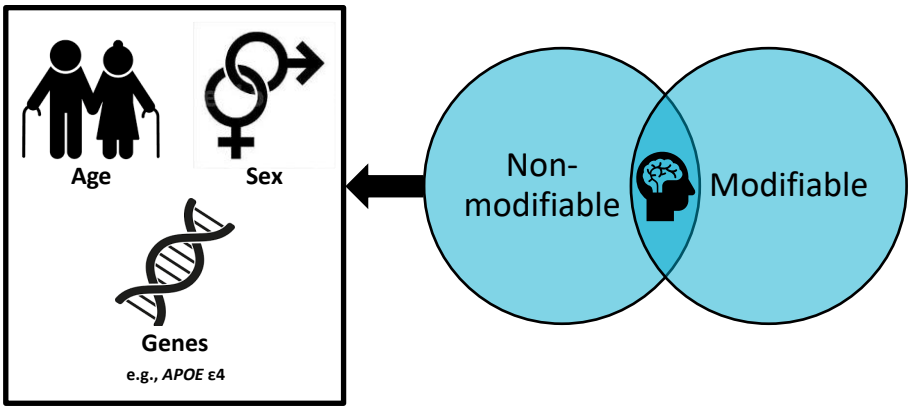
Risk factors: Dementia (Alzheimer's, Vascular…)



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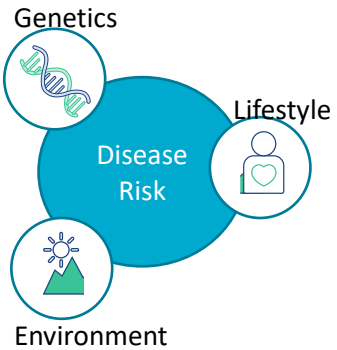
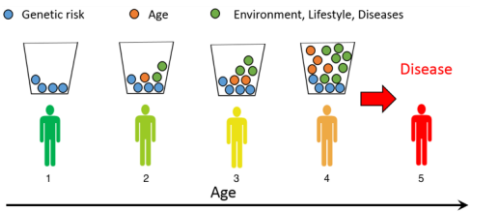
AIBL long term goal: Precision medicine





Visualisation by Krista Fischer

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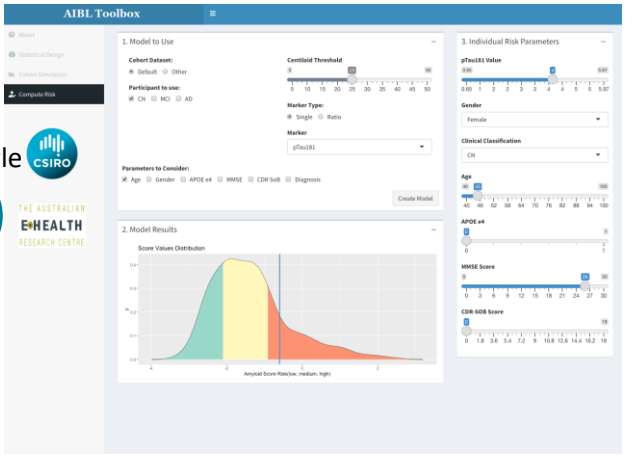
AIBL long term goal: Precision medicine



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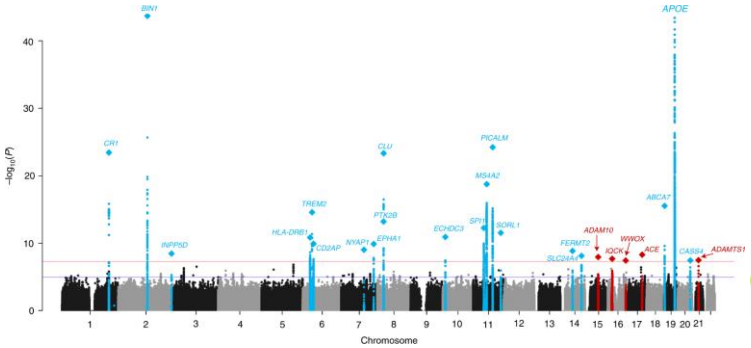
CSIRO

Australia's National Science Agency

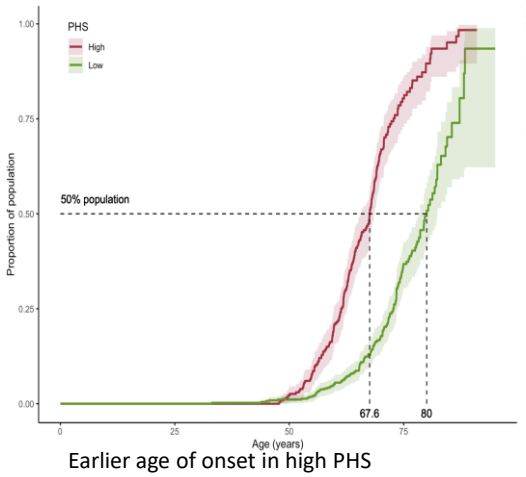
AIBL Genetics Stream – contributing to non-modifiable risk factor evidence base….AD



A/Prof. Simon Laws

aibl

Non modifiable: Polygenic risks



Earlier age of onset in high PHS

BMC Genomics

RESEARCH Open Access

Assessment of a polygenic hazard score for the onset of pre-clinical Alzheimer's disease

Michael Vacher[1,2,3*], Vincent Doré[4,5], Tenielle Porter[2,3,6], Lidija Milicic[2,3], Victor L. Villemagne[2,7], Pierrick Bourgeat[8], Sam C. Burnham[2,3], Timothy Cox[4], Colin L. Masters[9], Christopher C. Rowe[2], Jurgen Fripp[8], James D. Doecke[2,3] and Simon M. Laws[2,3,6]

Genome-wide association studies indicate > 40 loci are associated with AD

Polygenic scores provide a measure of your disease risk due to your genes.

Dr Michael Vacher

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Modifiable dementia risk factors

'Dementia prevention, intervention, and care: 2020 report of the Lancet Commission' **12 modifiable risk factors** account for around **40%** of worldwide dementia cases

…but likely to be more as evidence base builds for factors not yet included

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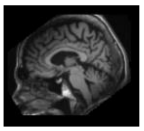
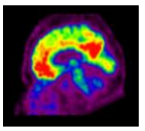
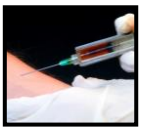
Australia's National Science Agency

AIBL Lifestyle Stream – contributing to modifiable risk factor evidence base….AD

- Hearing Loss
- Physical Activity
- Diet
- Sleep
- Vascular risk factors
- Other modifiable risk factors

A/Prof. Stephanie Rainey-Smith

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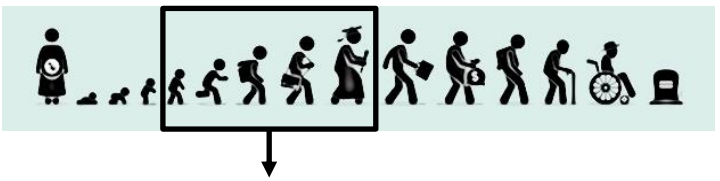
Modifiable dementia risk factors – early life



Life Stage	Modifiable Risk Factor	Case reduction if risk factor eliminated
Early life	Less education	7%

"Provide all children with primary and secondary education."
Note: *continual mental stimulation throughout life is also beneficial.*

Livingstone et al., Lancet 2020; 396: 413–46.

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Modifiable dementia risk factors – midlife

Life Stage	Modifiable Risk Factor	Case reduction if risk factor eliminated	
Midlife	Hearing loss	8%	
Midlife	Traumatic brain injury	3%	
Midlife	Hypertension	2%	CV
Midlife	Obesity	1%	L
Midlife	Alcohol > 21 units per week	1%	L

Livingstone et al., Lancet 2020; 396: 413–46.

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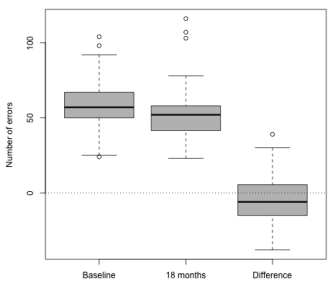
Cognitive improvement: Hearing aids

Executive function



Journal of Clinical Medicine

MDPI

Article

The Effect of Hearing Aid Use on Cognition in Older Adults: Can We Delay Decline or Even Improve Cognitive Function?

Julia Sarant [1,*], David Harris [2], Peter Busby [3], Paul Maruff [3], Adrian Schembri [3], Ulrike Lemke [4] and Stefan Launer [4]

Significant improvement in group mean EF score

- EF scores improved by 9% of mean baseline score (p = 0.010)
- 92% of participants stable or improved
- Females, who used their HAs much more than males (54% vs 29%) had far greater improvement in EF scores (19.8% vs 0.5%)

A/Prof. Julia Sarant

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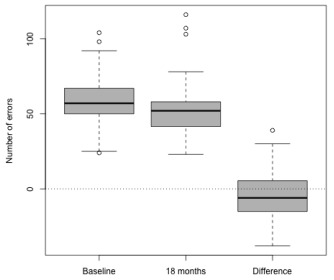
Cognitive improvement: Hearing aids

Executive function



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- 92% of participants stable or improved
- Females, who used their HAs much more than males (54% vs 29%) had far greater improvement in EF

No Influence of Age-Related Hearing Loss on Brain Amyloid-β

Julia Z. Sarant[a,*], David C. Harris[a], Peter A. Busby[a], Christopher Fowler[b], Jurgen Fripp[c], Colin L. Masters[b] and Paul Maruff[b]

A/Prof. Julia Sarant

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Modifiable dementia risk factors – later life

Life Stage	Modifiable Risk Factor	Case reduction if risk factor eliminated	
Later life	Smoking	5%	L
Later life	Depression	4%	
Later life	Social isolation	4%	L
Later life	Air pollution	2%	
Later life	Physical inactivity	2%	L
Later life	Diabetes	1%	

Livingstone et al., Lancet 2020; 396: 413–46.

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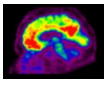
Modifiable dementia risk factors – diet

- 5 of the 12 modifiable risk factors can be positively impacted by a healthy diet:
  - Hypertension
  - Obesity
  - Alcohol intake
  - Diabetes (type 2)
  - Depression

Diet rich in vegetables (green, leafy), fruits (berries), fish, whole grains, olive oil, such as Mediterranean or MIND diet, best for brain health?

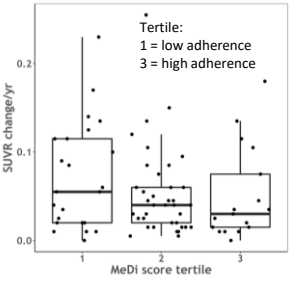
Mediterranean diet adherence is associated with slower Aβ accumulation in the brain

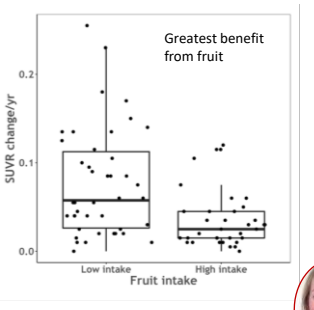


Amyloid beta levels

World First Study

aibl



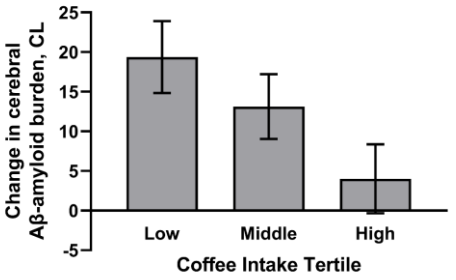


Generalised Linear Modelling, accounting for age, gender, education, Apolipoprotein E ε4 allele status, body mass index and total energy intake; $p = 0.0070$; $p = 0.00036$.

Rainey-Smith et al., Translational Psychiatry, 2018.

A/Prof. Stephanie Rainey-Smith

Higher coffee consumption is associated with slower cognitive decline and Aβ accumulation



Higher coffee consumption was associated over 126 months with:

- Slower cognitive decline in executive function, attention, and AIBL PACC,
- Lower likelihood of transitioning to MCI or AD,
- Slower brain Aβ accumulation.

aibl

Gardener, Rainey-Smith et al., Frontiers of Aging Neuroscience, 2021.

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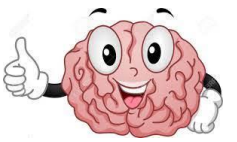
Risk reduction - summary

- AIBL is providing a key window into understanding how underlying biology, modifiable and non modifiable risk factors interact.
- 12 modifiable risk factors account for around 40% of dementia cases worldwide.
- Exercise, eat well, sleep well, engage socially, and intervene if cardiovascular risk factors (e.g., hypertension), or hearing loss manifest
- **"Be ambitious about prevention."**
- **"… it is never too early or too late."**



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Thank you

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ACKNOWLEDGEMENTS

AIBL would like to thank the study participants and their families

AIBL Study team:

David Ames
Alex Barac
Mary Barnes
Kevin Barnham
Pierrick Bourgeat
Sveltana Bozinovski (nee Pejoska)
Belinda Brown
Samantha Burnham
Lesley Cheng
Steven Collins
James Doecke
Josie Domingo
Vincent Dore
Denise El-Sheikh
Kathryn Ellis
Binosha Fernando
Christopher Fowler
Jurgen Fripp
Shaun Frost
Sam Gardener
Simon Gibson
Rob Grenfell
Rodney Guzman
Bronwyn Hall
David Hanson
Elise Harrison
Jacqui Hayem
Andy Hill
Eugene Hone
Maryam Hor
Jill Hwang
Yogi Kanagasingam
Neil Killeen
Fiona Lamb
Nicola Lautenschlager
Simon Laws
Hugo Leroux
Qiao-Xin Li
Yen Ying Lim
Florence Lim
Lucy Lim
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Lucy Mackintosh
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Amanda Niu
Steve Pedrini
Kayla Perez
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Jo Robertson
Mark Rodrigues
Christopher Rowe
Rebecca Rumble
Ian Saunders
Greg Savage
KaiKai Shen
Brendan Silbert
Harmid Sohrabi
Kevin Taddei
Tania Taddei
Christine Thai
Philip Thomas
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Irene Volitakis
Larry Ward
Mike Weinborn
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Michael Woodward
Paul Yates
Luz Fernanda Yevenes Ugarte
George Zisis

AIBL is a large collaborative study and a complete list of contributors can be found at www.aibl.csiro.au

The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

Collaborators

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Cognitive decline & hearing loss

HL independently associated with an accelerated rate of cognitive decline in older adults
-> 30-40% higher rate even for mild HL

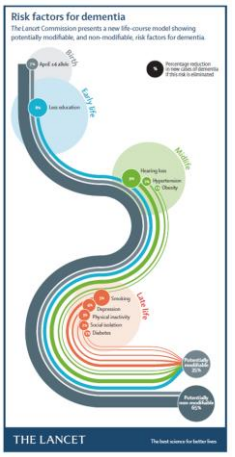
Lancet Commissions Expert Reviews (2017 & 2020):

- **Hearing loss contributes 8-9% to risk of dementia**
- Largest single potentially modifiable risk factor for dementia but has received the least scientific attention to date

Relative risks of dementia:
Normal hearing = 1.0
Mild loss = 1.89
Moderate loss = 3.0
Severe loss = 4.94

Hearing loss leads to greater cognitive decline in an older adults, but the reasons are unclear

Need to investigate methods of risk reduction / prevention



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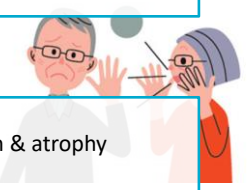
Mechanisms: HL & cognitive decline?

Mechanisms unknown, but likely to be multiple

Theories:



- Common neuropathic pathology: e.g., decline in brain function & atrophy with both HL & dementia
- Increased cognitive load: resources needed for thinking and memory are recruited to speech processing
- Sensory deprivation: leads to cortical re-organization/atrophy
- HL leads to social isolation & depression/anxiety (risk factors for dementia)
- Changes in brain activity due to HL cause irreversible molecular damage: increased protein pathology associated with AD
- Genetic relationship between HL and cognitive decline: shared genes & immune response pathways between both conditions

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Cognitive function in older adults with HL who use HAs can not only remain stable but may improve significantly after HA use

- Improved executive function & visual learning after 18 months of HA use
- At 36 months, most participants stable except for psychomotor function, despite reduced use & likely negative effects of repeated / extended COVID lockdowns
- No change in cognitive function over time in comparative groups at 18-month follow up

Hearing loss and AIBL biomarkers in healthy subjects

- Amyloid burden is not increase with HL.

No Influence of Age-Related Hearing Loss on Brain Amyloid-β

Julia Z. Sarant[a,*], David C. Harris[a], Peter A. Busby[a], Christopher Fowler[b], Jurgen Fripp[c], Colin L. Masters[b] and Paul Maruff[b]
[a]The University of Melbourne, Melbourne, Australia
[b]The Florey Institute, Melbourne, Australia
[c]Commonwealth Scientific and Industrial Research Organization, Queensland, Australia
[d]Cogstate, Melbourne, Australia

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Late onset (sporadic) Alzheimer's disease: caused by defective innate immunity and treated with adaptive immunity

- Where and when does AD start?
- Are the default mode network, synaptic plasticity, and the normal function of APP involved?
- What molecular species of Aβ cause synaptic degeneration?
- Is impaired innate immunity responsible for failure of Aβ clearance?
- What are the biomarker cutpoints of normality vs the preclinical, prodromal and clinical stages of AD?
- What are the best disease modifying therapeutic strategies?

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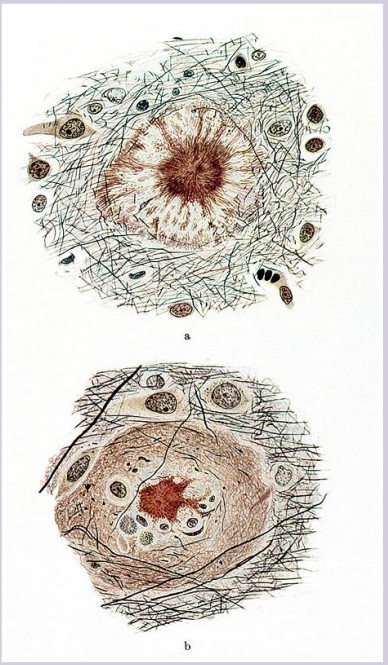
The Amyloid Plaque



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.

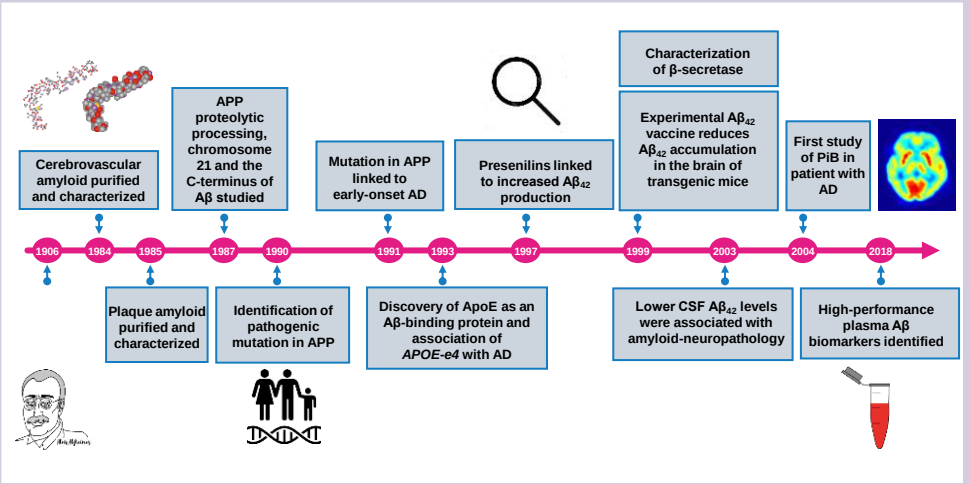
Disclosures

PRANA BIOTECHNOLOGY Limited

(*Ad hoc* consultancies with
Actinogen, Acumen, Alterity/Prana,
Biogen, Cytox, Eisai, Lilly, Roche)

75

Timeline: Key Findings to Support the Central Role of Aβ Amyloid in AD



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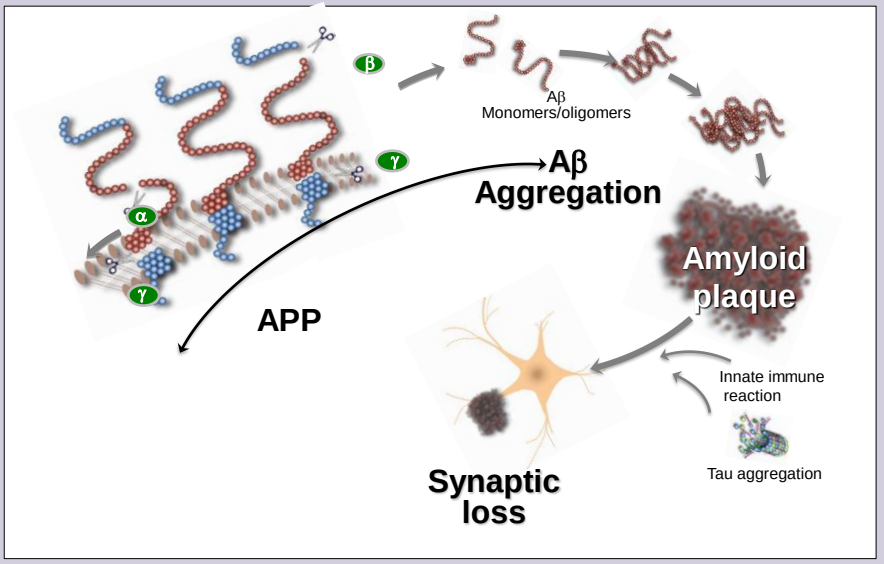
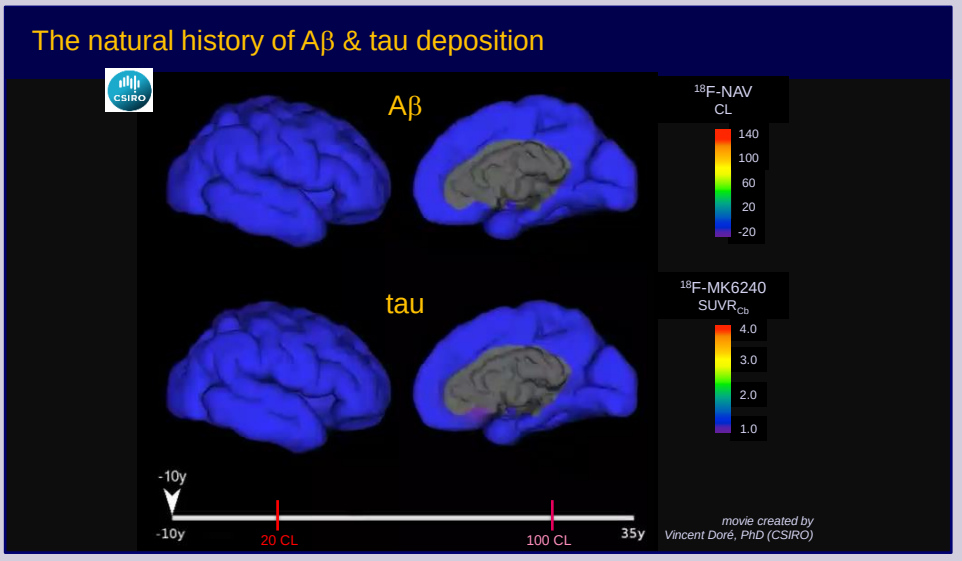
From little things, big things grow
(Kelly and Carmody 1991)



77



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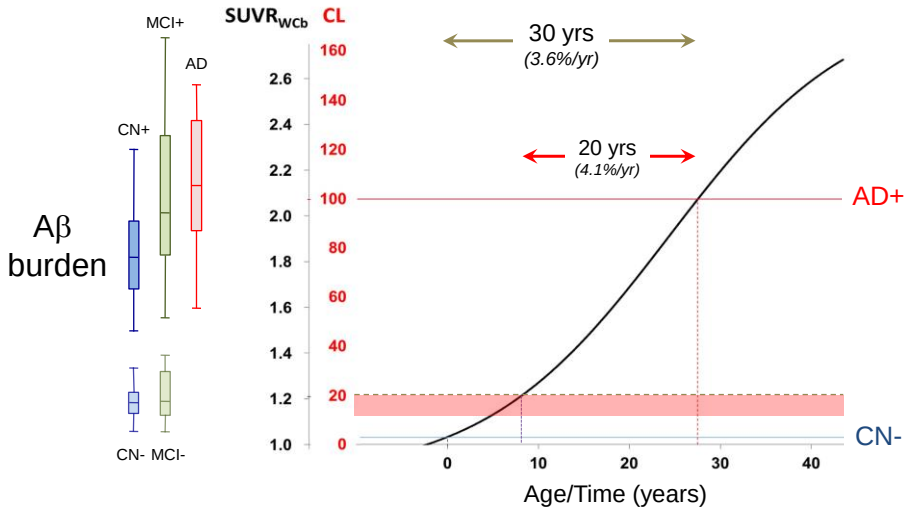
Aβ deposition over time

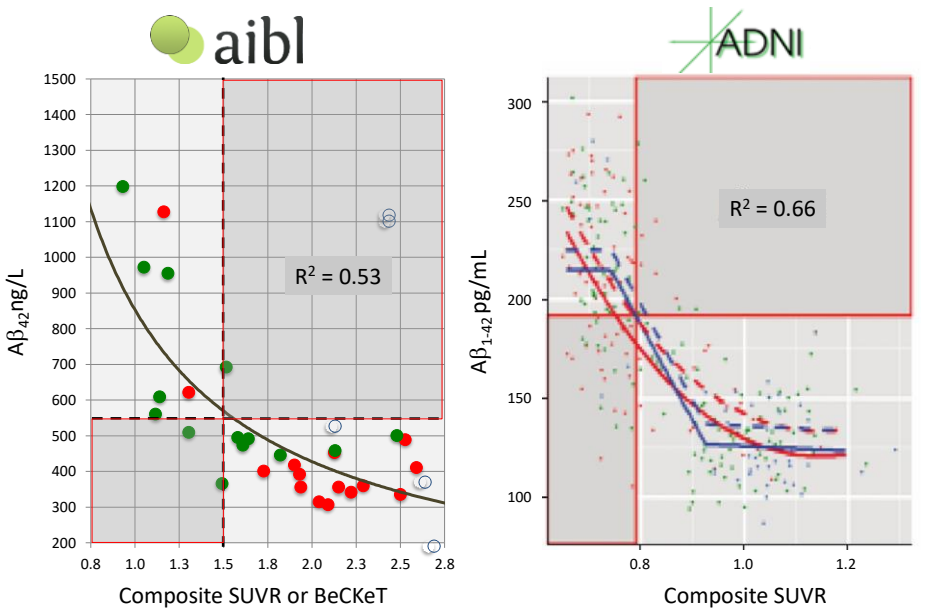
5-9 year follow-up (PiB/NAV)



(Villemagne and Rowe)

79

Relationship between brain Aβ and CSF $Aβ_{42}$



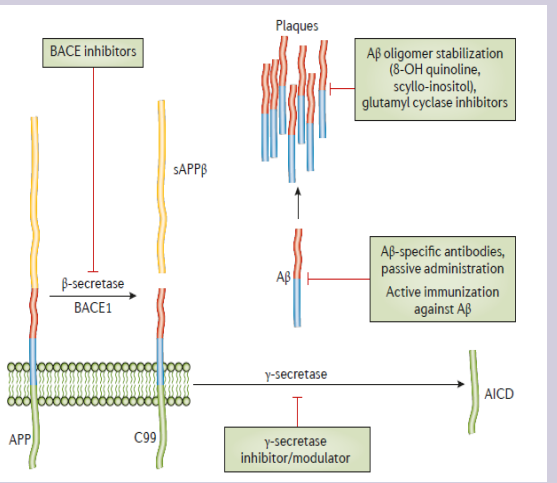
80

High performance plasma $A\beta_{42}$ assays in current development

- Shimadzu (+NCGG): IP-MS (MALDI-TOF)
- C_2N (+Wash U): IP-MS (LC-MS/MS Thermo Lumos)
- Araclon (Zaragoza, Spain): Dissociation + ELISA
- Quanterix (Lexington MA): Single molecule array on paramagnetic beads (SIMOA +ADx)
- Roche Diagnostics (Basel): COBAS Elecsys automated immunoassay
- Sysmex (Kobe, Japan): HISCL automated immunoassay
- MagQu (Taiwan): Immuno-Magnetic reduction-superconducting quantum interference device (IMR-SQUID)
- Amplified Plasmonic Exosome (APEX); (Singapore)
- Immuno-Infrared Sensor (IIS); (Bochum)
- Aβ complexes ApoE, ApoJ, ATIII (MagArray)

81

Potential strategies to manipulate Aβ in Alzheimer's disease



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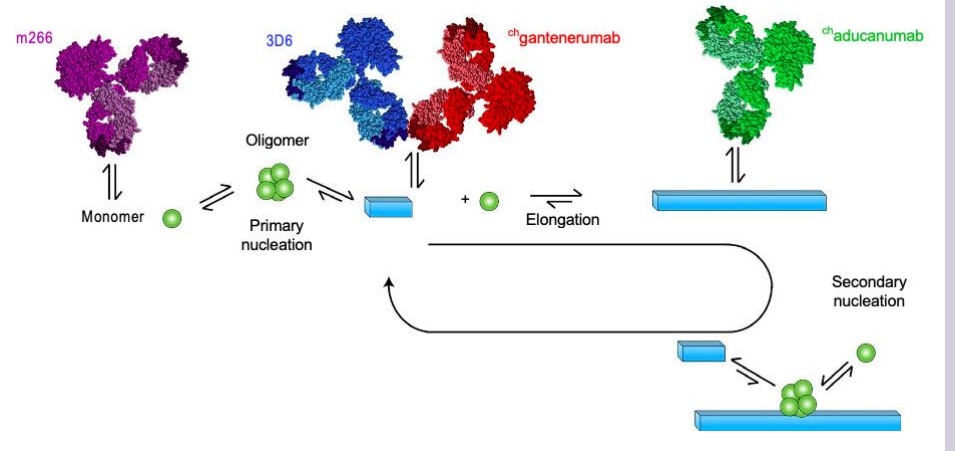
Targeting Aβ: passive immunization and % reduction in PET signal

- Aducanumab (Biogen/Eisai/Neurimmune) 70%
- Gantenerumab (Roche/MorphoSys) 70%
- Lecanemab (Ban2401, Eisai/BioArctic) >70%
- Donanemab (N3pG, Lilly) >85%
- Bapineuzumab (J&J/Pfizer/Janssen) 12-25%
- Solanezumab (Lilly) ??
- Crenezumab (Roche/Genentech/AC Immune) ??

83

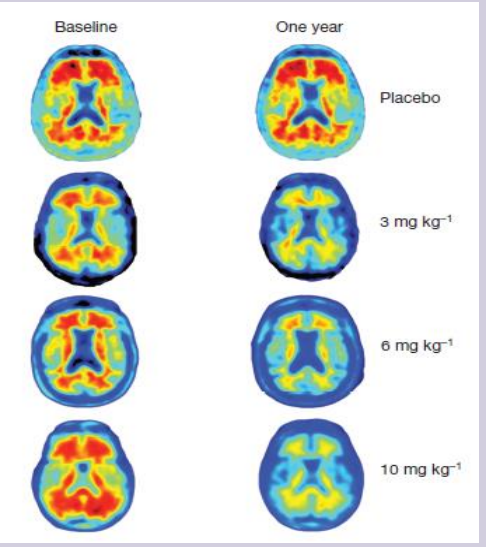
Effects of Mabs on the kinetics of aggregation of Aβ42 (m266 solanezumab; 3D6 bapineuzumab). Major effect of aducanumab on secondary nucleation flux of oligomers



Linse et al 2020

84

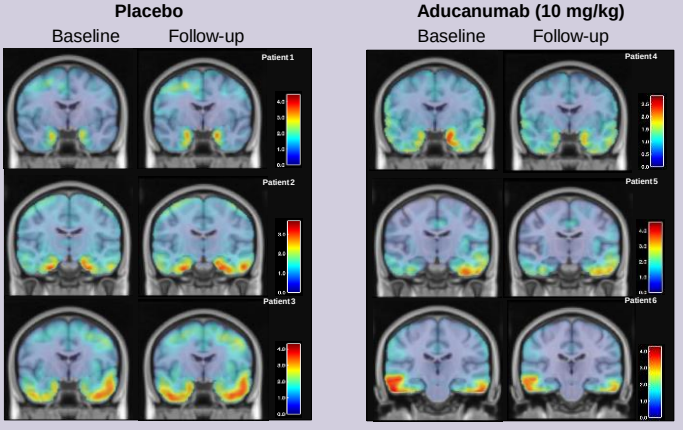
Aβ amyloid reduction with aducanumab: example florbetapir PET images at baseline and week 54



Sevigny et al, Nature, September 2016

85

Tau deposition in representative patients



CTAD 2019

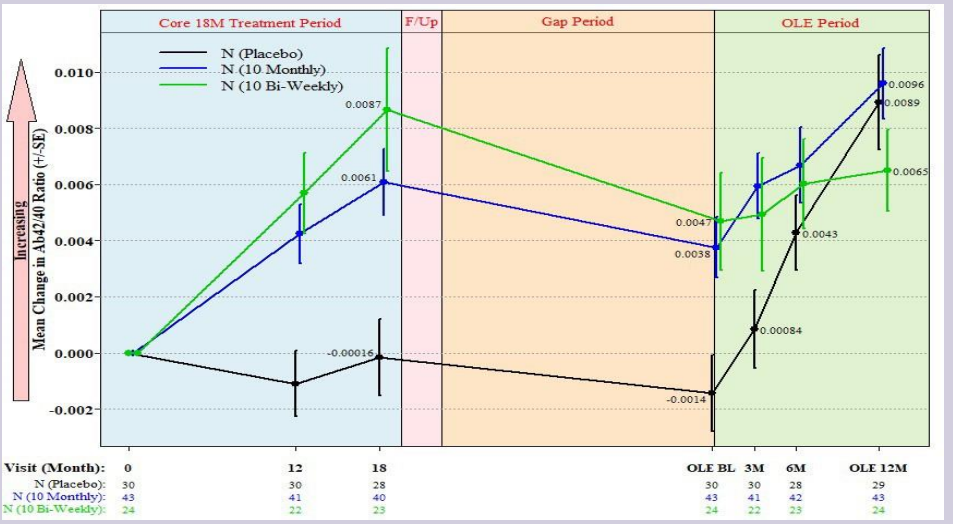
86

First disease modifying drug for Alzheimer's disease (June 7, 2021)

Biogen 2021

87

Change in plasma Aβ42/40 ratio (C2N Precivity) by lecanemab in core treatment, gap, and OLE



Swanson 2021

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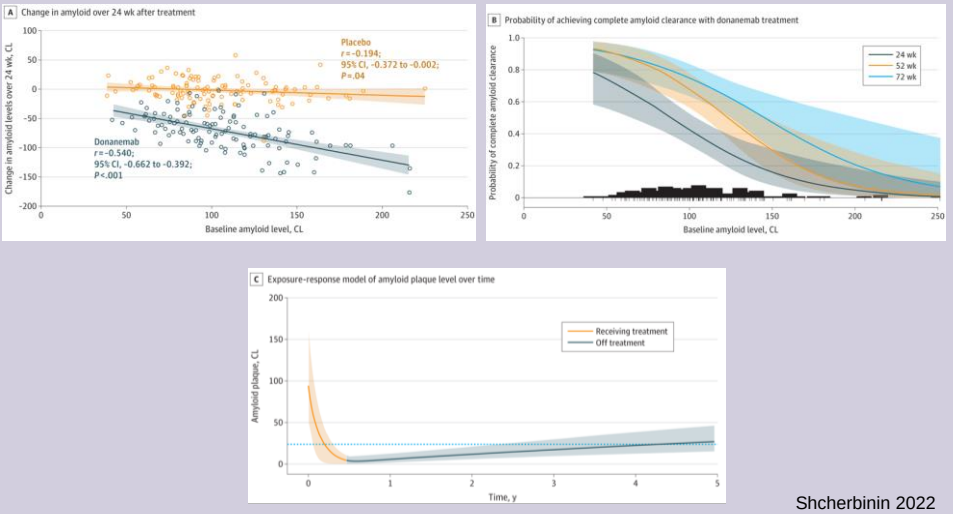
Donanemab (TRAILBLAZER-ALZ): Aβ-PET Amyloid Responses to Initiation and Discontinuation of Treatment



Shcherbinin 2022

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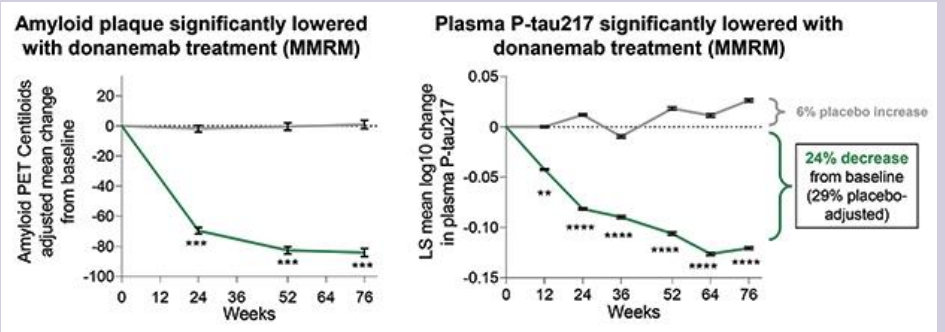
Donanemab: concomitant Aβ load and plasma p-tau217 lowering



Lilly, AAIC, 2021

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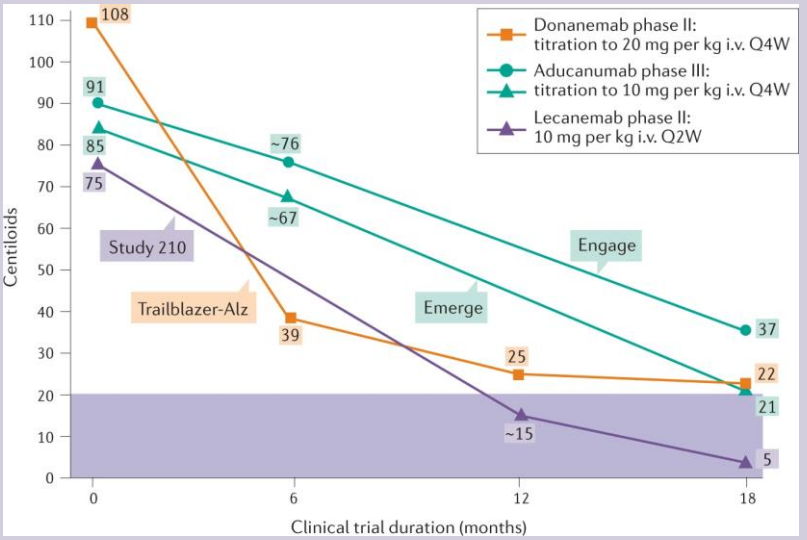
Amyloid-β removal profiles for aducanumab, donanemab and lecanemab



Karran 2022

91

Current state of play (June 2022)

- Highly significant relationship of lowering Aβ with slowing of cognitive decline (CDR-SB) with multiple Mcabs targeting N-terminus of Aβ, with clear dose-response effect.
- Sample size calculated to have 90% power to detect difference of 0.5 CDR-SB, representing 25% slowing assuming placebo change of 2.0. The observed placebo change was 1.5-1.7, and the effect size was 0.39 (exactly 25% of 1.6).
- Some critics expected an effect size of 1.0 or 2.0 (62.5% or 125%) reduction, but this would be “a totally unrealistic expectation for the first drug in two decades”.
- Clear evidence of continued plasma p-tau181 reduction beyond two years.
- Global tau-PET reduction is mediated by early Aβ reduction (62% of tau lowering is mediated by Aβ lowering in first 24 weeks.

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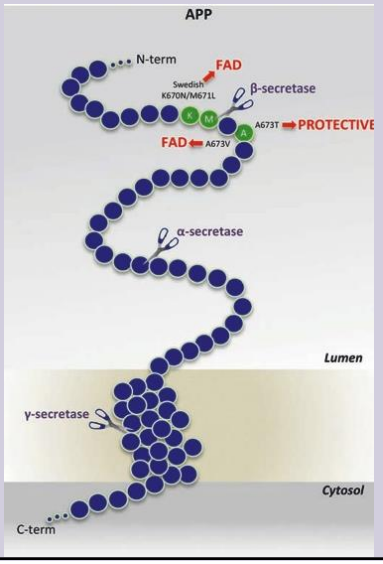
Icelandic APP A673T mutation protects against AD and decreases Aβ levels by reducing BACE1 cleavage of APP



APP A673T carriers have 28% lower levels of Aβ40 and Aβ42 in plasma compared to controls; proof of concept that ~30% lower Aβ levels via BACE1 inhibition should prevent AD

Jonsson 2012

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BACEi's (July, 2019)

1. **Verubecestat (Merck)** EPOCH/APECS

   BACE1>BACE2 (x0.17); CSF Aβ 70-80%↓; Aβ-PET 10-20%↓; MRI atrophy; Cognition: worse

2. **Lanabecestat (Lilly/AZD)** AMARANTH/DAYBREAK

   BACE1>BACE2 (x2.0); Aβ-PET 20%↓ at higher dose; SUVR baseline 95-98 CL; CSF tau↓; Cognition: futile

3. **Atabecestat (Shionogi/Janssen)** EARLY

   Biomarkers pending; Hepatotoxic; Cognition: worse

4. **LY3202626 (Lilly)** NAVIGATE

   MRI atrophy; cognition: futile

5. **Elenbecestat (Eisai/Biogen)** MISSION 1+2

   BACE1>BACE2 (x3.5); Aβ-PET 25%↓; CDR-SB 31% slowing.

6. **Umibecestat (CNP520) (Novartis/Amgen)** GENERATION

   BACE1>BACE2 (x3.0).

All too much, too late, with on-target side effects for both β/ɣ secretases

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Estimates of amount of inhibition of Aβ production (BACE1/2i, GSI/GSM) required over the 20 year natural history of preclinical/prodromal phases of AD

- **Rates of Aβ accumulation (i.e. failure of clearance):**

  28 ng/hr (PET/post mortem assay Roberts/Masters 2017)

  31 ng/hr (CSF SILK kinetics Patterson/Bateman 2015)

- **Normal production rate of total Aβ based on CSF SILK kinetics (Potter/Bateman 2013):**

  $A\beta_{38}$ 106

  $A\beta_{40}$ 418 = 581 ng/hr total Aβ

  $A\beta_{42}$ 57

- Therefore, accumulation of 30 ng/hr is 5% of normal Aβ production (580 ng/hr). Depending on the species of Aβ selectively deposited (e.g. $A\beta_{42}$>$A\beta_{40}$), a first approximation would be that a 5-10% lowering of production over the 20 year window should abrogate the effect of this degree of clearance failure. Higher levels of inhibition would be required over shorter time intervals closer to the onset of prodromal AD.

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Alzheimer's disease: future strategies for disease modification

- Develop rational combination therapeutics:

  Lower production by 10-20% (β/γ secretase inhibitors)
  Stabilize and neutralize (8OH-quinolines)
  Clearance pathway activators (ApoE, microglial scavenger receptors, TREM2, CD33, etc)

- Design "super-adaptive" trials with frequent, interim, quantitative real-time biomarker evaluations

- Consider lowering Aβ burden to baseline (using Mcab) in earliest stage, followed by maintenance therapy with inhibitors of production and aggregation, dimer stabilization, and improved clearance strategies

- May require use of "co-morbid disease-free" subjects

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ACKNOWLEDGEMENTS

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Simon Laws
Hugo Leroux
Qiao-Xin Li
YFlorence Lim
Lucy Lim
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Ralph Martins
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Paul Maruff
Colin Masters
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The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

Collaborators