Australian Imaging, Biomarkers and Lifestyle Study of Ageing
Participant Information Day 2019

Kaele Stokes
Executive Director of Consumer Engagement, Policy and Research
Dementia Australia

Friday 21 June 2019
Dementia in Australia

447,115 Australians living with dementia
Dementia Australia

• Works with individuals and families, all levels of government, and other key stakeholders.
• We are an important representative for those impacted by dementia.
• We provide input on policy matters.
• We collaborate with a range of stakeholders.
• We provide support services, education and information.
Activity

• Established the Centre for Dementia Learning.
• Memory Walk & Jog – 9 events this year.
• Dementia Action Week.
• Research - $1 million in funding.
• Suite of technology using virtual reality.
• Royal Commission into Aged Care Quality and Safety.
• Federal election campaign.
Highlights from last financial year

- 22,000 calls to the National Dementia Helpline.
- 28,000 people who attended community education, information and awareness sessions.
- 447,000 Help Sheets downloaded.
- 644,000 visits to the Dementia Australia website.
Australian Imaging, Biomarkers and Lifestyle Study of Ageing

- One of the most recognised longitudinal study of Alzheimer’s disease.
- Contributes to incredible clinical advances.
- Works towards early diagnosis.
Thank you
dementia.org.au
National Dementia Helpline
1800 100 500
For language assistance call 131 450
AIBL Feedback Day 2019

Emeritus Professor David Ames AO, AIBL Chair
University of Melbourne Academic Unit for Psychiatry of Old Age, National Ageing Research Institute and Florey Institute for Neuroscience and Mental Health
dames@unimelb.edu.au
Running order

• Welcome – Kaele Stokes Dementia Australia
• Introduction - David Ames
• PET Imaging – Chris Rowe
• Blood, CSF Biomarkers & trials – Colin Masters AO
• Cognitive and brain change in the absence of Alzheimer’s disease – Krista Dang
• Questions
• Tea
AIBL Publications in peer-reviewed journals to November 2017

- 2007 – 4
- 2008 – 1
- 2009 – 8
- 2010 – 8
- 2011 – 16
- 2012 – 21
- 2013 – 37
- 2014 - 31
- 2015 - 31
- 2016 – 25
- 2017 – 25
- 2018 - 58
- 2019 - TBA
- Total – at least 265
The eye is a window to the brain

Amyloid beta accumulates in neural tissue of people with Alzheimer’s disease 10-20 years before the onset of symptoms.

Amyloid beta in the retina (at the back of the eye)

Advantages of eye imaging

✓ Convenient: quick, non-contact, non-invasive
✓ Low cost
✓ Safe
✓ Can be repeated as often as needed
Amyloid beta scatters light in a characteristic way…

... the scatter varies with different colours of light

✓ We can use this property as a measure of amyloid beta in the retina
✓ We have shown that the eye imaging signal corresponds with the amount of amyloid beta in the brain
It’s as simple as a rainbow-coloured flash

The imaging process is very similar to a standard photo of the eye, but with a rainbow-coloured flash.

The imaging is performed by our team at the Royal Victorian Eye and Ear Hospital in East Melbourne.
NeuroVision

• Another simple eye-test for early detection of Alzheimer’s disease
• Investigating whether β amyloid plaques can be identified in the retina at an earlier age before symptoms emerge or in people with MCI
• Correlation between retinal β amyloid and those in the brain
• *Curcumin* allows fluorescence of retinal β amyloid, so it is visible to the camera
NeuroVision Update

• Study closed December 2018
• 145 participants enrolled
  – 2 sessions of retinal imaging
    • one at screening/baseline
    • one after 3 doses of Curcumin and Vitamin E
      – Vit E known to enhance absorption of curcumin
• In the process of data analysis
• Results to follow...
The Australian Imaging Biomarkers and Lifestyle Study of Ageing

Professor Christopher Rowe
Director – Molecular Imaging and Therapy, Austin Health
Director – Australian Dementia Network
The Australian Imaging Biomarkers and Lifestyle Study of Ageing

Commenced 2006
Amyloid PET + MRI with follow-up in 288 of the 1100 original participants.

Now in 75% of 2,335 participants
Biomarkers to assist diagnosis of AD

Pathology Markers
• Beta-amyloid imaging with PET
• CSF Aβ_{42} assay

Neuronal damage markers
• MRI
• FDG PET
• CSF Tau assay
Neuronal Injury Biomarkers on MRI: Hippocampal Atrophy

Hippocampal atrophy

Normal hippocampi
Positron Emission Tomography (PET)
Alzheimer’s Pathology

1. Extracellular Beta-amyloid Plaques

2. Intracellular Neurofibrillary Tangles (tau aggregates)
Neuropathology of AD

• β-Amyloid

• Phospho-tau tangles

Braak and Braak 1991
Beta-amyloid PET

Inventors:
Chet Mathis
William Klunk
University of Pittsburgh

First Publication 2004.

$^{11}$C-PiB

Alzheimer’s Disease
% of cognitively healthy population who have plaques

Rowe CC, et al. Neurobiology of Aging. 2010 (680 citations)
% of persons with elevated amyloid as a function of the APO-E gene

YEARS OF AGE

12% overall
32% overall
52% overall

60-69
70-79
80+

e4-
e4+
Aβ deposition in sporadic AD

(587 citations)

PiB SUVR

Time (years)

Average AD (2.33)

Average Healthy (1.17)

Detectable (1.5)

0.043 SUVR/yr
(95%CI 0.037-0.049 SUVR/yr)

19 yrs
(95%CI 17-23 yrs)

12 yrs
(95%CI 10-15 yrs)

0
1.0
2.0
3.0

0.0
10
20
30
40

Time (years)

PiB SUVR_{cb}
Memory decline and amyloid: Effect of APOE & BDNF

EM = AIBL Episodic Memory Composite
New diagnostic criteria for Alzheimer’s disease


• Progressive memory impairment
  plus
• **Positive Aβ PET** or CSF (low Aβ42 with high tau)
A little amyloid plaque is not so bad
Achievements of Aβ PET imaging

• Improved diagnosis of AD vs FTD
• Earlier diagnosis of AD in MCI phase (“Prodromal” AD)
• Opened a broad window (15 years) for preclinical intervention
• Improved subject selection for therapeutic trials
• Measures effectiveness of anti-Aβ agents
• Permits the study of AD related pathology in non-demented persons and its relationship to genetic and potentially modifiable environmental factors.
Tau Imaging: $^{18}$F-MK6240

HC

AD

SUVR

0.0

3.5

7.0
Patterns of MK-6240

A is an Older Control, B-D are MCI/early AD
In the MCI/early AD group, the Limbic Predominant had mildly reduced MMSE, moderately reduced memory function and relatively intact non-memory cognitive functions.
4.5 year data release

amyloid scan status known in 371 subjects with 4.5 yrs of follow-up and 250 new recruits

www.adni.loni.usc.edu

- Data and Samples
- Access Data
1550 research groups granted access to AIBL@LONI through ADNI website

Includes access granted to the following companies:
What is ADNeT?

- **Australian Dementia NeTwork = ADNeT**

- Funded by $18 Million NHMRC-NNIDR (Boosting Dementia Research Grant)

- Network of national dementia research experts
ACKNOWLEDGEMENTS

AIBL would like to thank the study participants and their families

AIBL Study team


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 Study of Ageing

Professor Colin Masters
Laureate Professor of Dementia Research

Florey Institute and The University of Melbourne
Molecular origins of Alzheimer’s disease: when does it start, and what strategies for primary prevention?

1. How much Aβ amyloid accumulates in the AD brain?
2. When does it start and how long does it take?
3. How much is the clearance mechanism impaired in sporadic AD?
4. Can quantitative real-time biomarker read-outs be used in clinical trial design to monitor drug efficacy?
5. How to quantitatively define the onset of AD using biomarkers?
The Amyloid Plaque

From W Spielmeyer,
Histopathologie des Nervensystems.
1922


Disclosures

(and current consultancies with Prana/Alterity, NeuroBio, Recuerdo and Actinogen)
Two types of Alzheimer’s disease

Autosomal/Dominantly Inherited (Early Onset):
Over-production of Aβ
Mean age dementia onset: 45 y
Mutations in APP/PSEN1,2
18% increased production of $[\text{Aβ}_{42}]_{\text{CSF}}$
Aβ-PET accumulation rates same as sporadic AD (below)

Sporadic (Late Onset):
Failure of Aβ clearance
Mean age dementia onset: 78 y ($\varepsilon_4^{+/+}$ 68y, $\varepsilon_4^{+/+}$ 76y, $\varepsilon_4^{+/-}$ 86y)
$[\text{Aβ}]_{\text{CSF}}$: turnover 19h (13h control): 49% slower than control
$T_{1/2} 9.4$ h (3.8 h young control)
Aβ-PET: accumulation 0.048 SUVR/y; 28 ng/hr
MALDI-MS imaging

Ikegawa/Ihara: 2019
The Australian Imaging, Biomarkers and Lifestyle Study of Aging

(Australian ADNI)
AIBL cohort (now collecting 144 month/12 year data)
Total enrollments: 2502

<table>
<thead>
<tr>
<th>Time point (n)</th>
<th>CN</th>
<th>MCI</th>
<th>AD</th>
<th>Non-AD</th>
<th>Excl.</th>
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<td>1488</td>
<td>411</td>
<td>437</td>
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<td>18 month (1582)</td>
<td>1103</td>
<td>182</td>
<td>292</td>
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<td>36 month (1181)</td>
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<td>111</td>
<td>227</td>
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<td>54 month (910)</td>
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<td>80</td>
<td>130</td>
<td>12</td>
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<td>72 month (675)</td>
<td>539</td>
<td>59</td>
<td>69</td>
<td>8</td>
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<tr>
<td>90 month (503)</td>
<td>419</td>
<td>34</td>
<td>44</td>
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<tr>
<td>108 month (439)</td>
<td>377</td>
<td>28</td>
<td>30</td>
<td>4</td>
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<tr>
<td>126 month (322)</td>
<td>290</td>
<td>21</td>
<td>8</td>
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Person contact years

<table>
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<th>CN</th>
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<th>AD</th>
<th>Total</th>
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<tr>
<td>Years</td>
<td>6373</td>
<td>772</td>
<td>1200</td>
<td>8418</td>
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</table>
Aβ and Tau Imaging in AD ($^{18}$F) (Villemagne and Rowe)
Aβ deposition over time

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

(Villemagne and Rowe)
Preclinical AD age at onset of episodic memory decline: effect of APOE4; quadratic curve fits, differences from $A\beta^-$ subjects compared to inflexion points (Lim et al., JAMA Neurol 2018).
Impact of ε4 carriage on the progression of Aβ-amyloid accumulation (AIBL)

ε4 carriers
ε4 non-carriers

Aβ Burden (SUVR)

0.058 SUVR/yr
0.059 SUVR/yr

17 years

Age 60
Age 75

(Burnham & Villemagne)
Trajectories of cognitive decline over 54 months in preclinical AD: effect of ApoE and BDNF polymorphisms (Lim et al. 2015)

Aβ+ E4- BDNF+/− 30 yrs; Aβ+ E+ BDNFval 10 yrs; Aβ+E+BDNFmet 3 yrs
Relationship between brain $\text{A}\beta$ and CSF $\text{A}\beta_{42}$

$$R^2 = 0.53$$

Composite SUVR or BeCKeT

$\text{A}\beta_{42}$ ng/L

$\text{A}\beta_{1-42}$ pg/mL

$R^2 = 0.66$
Shimadzu blood test (Nakamura, et al., 2018)

IP- MALDI-TOF MS

\[
[A\beta_{42}]_{\text{plasma}} = 38.5 \pm 5.7 \text{ ng/L (Aβ-)} \\
[A\beta_{40}]_{\text{plasma}} = 233.5 \pm 43.1 \text{ ng/L (Aβ-)} \\
28.5 \pm 2.5 \text{ ng/L (Aβ+)} \\
220.7 \pm 36.8 \text{ ng/L (Aβ+)}
\]

(26% lowering : 8.6 pm to 6.3 pm)

Composite ratios of: \((\text{APP}_669-711) (A\beta_{(3)-40}) / A\beta_{1-42} + A\beta_{1-40}/A\beta_{1-42}:

- AUC 94-97%
- Accuracy 90%
- Sensitivity 88%
- Specificity 87%

Compared to \(^{11}\text{C-PiB}, 10\%\ lower\ accuracy\ with\ \(^{18}\text{F\ tracers\ (FLUTE, FBP)}\)

For preclinical AD (30\% prevalence)       For prodromal AD (66\% prevalence)

<table>
<thead>
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<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<td>87%</td>
<td>74%</td>
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<td>94%</td>
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Primary vs secondary prevention of AD

• Primary (pre-AD) in populations who fall below the Aβ cut-offs for CSF/PET. Subjects who meet prognostic algorithm of “age x genes x PET/CSF” change over three years. Characterised as “Aβ accumulators”. Design of trial in development recruiting from failed screens in A4.

• Secondary prevention in subjects with preclinical AD (over the threshold for Aβ PET/CSF) now underway: DIAN-TU in pathogenic mutation carriers and A4 with solanezumab in sporadic preclinical AD
Alzheimer’s disease: future strategies for disease modification

- Determine and use Maximum Tolerated Dose (MTD)

- Develop rational combination therapeutics:
  - Lower production by 10-20% (β/γ secretase inhibitors)
  - Stabilize and neutralize (8OH-quinoline; Mcab to mid-region)
  - Clear (Mcab to N-terminus)

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

- Consider lowering Aβ burden to baseline (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
The burden of age-associated cognitive impairment lies in the co-morbidities of only a few major disease pathways; these need to be controlled in clinical trial designs.

ACKNOWLEDGEMENTS

AIBL would like to thank the study participants and their families

AIBL Study team:

David Ames    Shaun Frost    Qiao-Xin Li    Jo Robertson    Rob Williams
Alex Barac    Sam Gardener    Yen Ying Lim    Mark Rodrigues
Mary Barnes   Simon Gibson    Florence Lim    Christopher Rowe
Kevin Barnham Rob Grenfell    Lucy Lim        Rebecca Rumble
Pierrick Bourgeat Rodney Guzman    Kathy Lucas    Ian Saunders
Svetlana Bozinovski (nee Pejoska) Bronwyn Hall    Lucy Mackintosh    Greg Savage
Belinda Brown David Hanson    Ralph Martins    KaiKai Shen
Samantha Burnham Elise Harrison    Georgia Martins    Brendan Silbert
Lesley Cheng    Jacqui Hayem    Paul Maruff    Harmid Sohrabi
Steven Collins Andy Hill    Colin Masters    Kevin Taddei
James Doecke    Yogi    Tania Taddei
Josie Domingo    Kanagasalingam    Tash Mitchell    Christine Thai
Vincent Dore    Neil Killeen    Amanda Niu    Philip Thomas
Denise El-Sheikh Fiona Lamb    Steve Pedrini    Brett Trounson
Kathryn Ellis    Nicola    Kayla Perez    Regan Tyrell
Binosa Fernando    Lautenschlager    Kelly Pertile    Jackie Uren
Christopher Fowler Simon Laws    Malcolm Riley    Victor Villemagne
Jurgen Fripp    Hugo Leroux    Stephanie Rainey-Irene Volitakis

AIBL is a large collaborative study and a complete list of contributors can be found at www.aibl.csiro.au
Cognitive and brain aging in the absence of preclinical Alzheimer’s disease
Alzheimer’s disease (AD)
Amyloid-β and preclinical AD

- Aβ+ is associated with higher risk of AD, and faster rates of cognitive decline\(^1\) and cortical atrophy\(^2\)

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Hypothetical model for the pathological–clinical continuum of Alzheimer’s disease

MCI=mild cognitive impairment
Aging

• AD or any cause of dementia is NOT a normal part of aging
• Aging is thought to be associated with declines in cognition and loss of brain volume
  • But not to the same extent as observed in AD
  • BUT MAYBE NOT TRUE
Age-associated cognitive decline

Memory Performance

Age

Aβ-

Normal aging?

Aβ+

Harrington et al. Neurobiol Aging, 2018
What does successful aging look like?
SuperAgers

- Older adults (≥60) who exhibit **verbal memory** performance equivalent to, or better than, that of individuals 20-30 years younger, with no impairment in any other cognitive domains\(^1\)
- SuperAgers may be able to resist age-associated cognitive decline and neurodegeneration\(^2,3\)
- SuperAging = aging without disease (i.e. normal aging)?

Rate of change is the same for SuperAgers

Poorer performance

Dang et al. Arch Clin Neuropsych. 2018

Aβ+ SuperAgers

Aβ− SuperAgers

Aβ− Cognitively normal for age

Aβ+ Cognitively normal for age
SuperAgers don’t have less Aβ

39% SUPERAGERS & 37% Cognitively normal for age WERE Aβ+
Key takeaways

• Aβ is a better predictor of future outcomes than being classified as SuperAger
  • Aβ- showed preserved cognition and reduced rates of brain volume loss
  • No difference in rates of change for SuperAgers
• Having exceptionally good memory is not as important to your future as it is to reach old age without accumulating a lot of Aβ
What does this all mean?

• Normal aging is NOT associated with memory loss!
• It is possible to age well without developing signs of AD
• You don’t need to have had a fantastic memory to age well
THANK YOU!