A quantitative approach to the use of biomarkers in studying the etiology, natural history, diagnosis and treatment of Alzheimer's disease:
progress in blood-based screens and gene-environment interactions

1. How much Aβ amyloid accumulates in the AD brain?
2. 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?

November, 2018
The Amyloid Plaque

From W Spielmeyer,
Histopathologie des Nervensystems.
1922

Disclosures

(and current consultancies with
Eli Lilly, Neuro-Bio, 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
The metabolic pools of Aβ

TBS extractable pool
- 0.2%
- low nanoM
- 200 nanoM

Carbonate extractable pool
- 7%
- 200 nanoM

Urea / detergent extractable pool
- 48%
- low microM

Formate extractable pool
- 45%
- low microM

ISF/CSF
- Aβmonomer low nanoM
- Aβo low picoM

Blood

Total Brain Aβ

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AD</th>
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<tbody>
<tr>
<td>[Aβ]fibril, extracellular</td>
<td>1.7mg</td>
<td>6.5mg</td>
</tr>
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</table>

“PLAQUES”

PET-Aβ

(Roberts et al., Brain, 2017)
The Australian Imaging, Biomarkers and Lifestyle Study of Aging

(Australian ADNI)
Australian Dementia Network (ADNeT) Trials Screening – Melbourne (TMS)

- Screening program to facilitate entry of patients with prodromal and mild Alzheimer’s disease dementia into therapy trials
- Patients aged 50-85
- Mild cognitive impairment or early dementia (MMSE >20)
- Undergo medical and cognitive screening, MRI, amyloid PET, tau PET
- Amyloid PET result provided to referring clinician
- Clinician or ADNeT-TSM staff refer appropriate patients to therapy trial

Email: ADNeTscreening@florey.edu.au
Call: Jo Robertson on (03) 9389 2937 or 0408 508 121
AIBL enrollment status
End of December 2017

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>MCI</th>
<th>AD</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>1456</td>
<td>344</td>
<td>384</td>
</tr>
<tr>
<td>18 month</td>
<td>980</td>
<td>166</td>
<td>275</td>
</tr>
<tr>
<td>36 month</td>
<td>770</td>
<td>98</td>
<td>215</td>
</tr>
<tr>
<td>54 month</td>
<td>663</td>
<td>65</td>
<td>121</td>
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<tr>
<td>72 month</td>
<td>500</td>
<td>48</td>
<td>60</td>
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<tr>
<td>90 month</td>
<td>419</td>
<td>34</td>
<td>44</td>
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<tr>
<td>108 month</td>
<td>374</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>126 month</td>
<td>60</td>
<td>6</td>
<td>2</td>
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</table>

Person contact years

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>MCI</th>
<th>AD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2017</td>
<td>5649</td>
<td>693</td>
<td>1134</td>
<td>7476</td>
</tr>
</tbody>
</table>

Total enrolments 2254; currently enrolled 1335
The natural history of Aβ deposition

$^{11}$C-PiB/$^{18}$F-NAV

3 (min) to 11 (max) year follow-up

Villemagne, Burnham, Bourgeat et al. (In preparation)
Aβ and Tau Imaging in AD (¹⁸F) (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 $\text{A}\beta^-$ 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

0.058 SUVR/yr
0.059 SUVR/yr

17 years

Aβ Burden (SUVR)

Age 75
Age 60

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

Aβ⁺ E⁺ BDNFval 10yrs;  Aβ⁺ E⁺ BDNFmet 3yrs
Relationship between brain $\text{A}\beta$ and CSF $\text{A}\beta_{42}$

$R^2 = 0.53$

Composite SUVR or BeCKeT

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

$R^2 = 0.66$

Composite $\text{A}\beta_{1-42} \text{pg/mL}$
Shimadzu blood test (Nakamura, et al., 2018)
High performance plasma Aβ-amyloid biomarkers for Alzheimer’s disease

IP- MALDI-TOF MS

\[
\begin{align*}
[Aβ_{42}]_{\text{plasma}} & = 38.5 \pm 5.7 \text{ ng/L (Aβ-)} & [Aβ_{40}]_{\text{plasma}} & = 233.5 \pm 43.1 \text{ ng/L (Aβ-)} \\
28.5 \pm 2.5 \text{ ng/L (Aβ+)} & & 220.7 \pm 36.8 \text{ ng/L (Aβ+)}
\end{align*}
\]

(26% lowering : 8.6 pm to 6.3 pm)

Composite ratios of: \( (\text{APP}_{669-711}) (Aβ_{(-3)-40}) / Aβ_{1-42} + Aβ_{1-40}/Aβ_{1-42} : \)

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

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

For preclinical AD (30\% prevalence)  
Sensitivity 88%  
Specificity 87%  
PPV 74%  
NPV 94%

For prodromal AD (66\% prevalence)  
Sensitivity 90%  
Specificity 87%  
PPV 74%  
NPV 94%
Potential strategies to manipulate Aβ in Alzheimer’s disease

- BACE inhibitors
- sAPPβ
- β-secretase
- BACE1
- γ-secretase
- Aβ
- Aβ-specific antibodies, passive administration
  - Active immunization against Aβ
- Aβ oligomer stabilization
  - (8-OH quinoline, scylo-inositol, glutamyl cyclase inhibitors)

APP
C99
AICD
γ-secretase inhibitor/modulator
Aβ amyloid reduction with aducanumab: example florbetapir PET images at baseline and week 54

Effect of aducanumab on Aβ-PET (centiloid scale), 36 month OLE

Haeberlein, 2018 (Biogen)
Effect of aducanumab on CDR-SB, 36 month OLE

Haeberlein, 2018 (Biogen)
Aducanumab (Biogen)

- human monoclonal antibody selective for aggregated forms of Aβ
- derived from human memory B cell pool isolated from cognitively normal and impaired subjects with unusually slow decline
- binds Aβ_{3-7}, with interface primarily with Phe4 and His6
- shallow and compact epitope may account for binding to aggregated Aβ without targeting monomers
- comparatively weak binding of monomers compared to gantenerumab and bapineuzumab
- tolerates a greater conformational diversity in Aβ than other N-terminal antibodies (modelling data)

(Arndt et al, AAIC, Toronto, August 2016)
Solanezumab (Lilly) Expedition 1 and 2 Mcab to Aβ 16-23

Liu-Seifert et al. *Alz & Dement.* 2015

30% cognitive benefit
Crenezumab (Roche/Genentech): High dose (15 mg/kg) in mild/moderate (MMSE 18-26, 17% reduction), mild (MMSE 20-26, 24% reduction), and very mild (MMSE 22-26, 35% reduction in cognitive decline) AD
BAN2401 Reduces Amyloid Burden

- Dose dependent reduction in amyloid PET values (Florbetapir tracer)
- BAN2401 significantly reduced amyloid PET values across all doses

- Similar results with SUVr and Centiloid measures across all reference regions analyzed
  - Reference regions analyzed: SWM, WC mask, WC derived, WC/WM correction, CG, Composite
- Top dose: observed baseline mean (74.5), observed 18-month mean (5.5)

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**PET SUVr**

- Adjusted Mean Change from Baseline (±SE)

**Centiloid**

- Adjusted Mean Change from Baseline (±SE)

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**Global Cortical Average versus Whole Cerebellum Reference**

*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. †Adjusted mean change from baseline by Mixed Model Repeated Measures (MMRM).

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group by visit interaction as factors, and baseline value as covariate.

For PET analysis N=306 at 12 months and N=277 at 18 months.
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/Early with solanezumab or JNJ-54861911 in sporadic preclinical AD
Pre-AD: the challenge of primary prevention
Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (the A4 Study): the Melbourne Composite Site

• 65 – 85 years
• Evidence of Aβ amyloid on PET
• Asymptomatic (CDR = 0)
• Following screening, 4 weekly solanezumab/placebo (1:1) infusions (IV) for 3 yrs
• Cognitive testing
• Aβ amyloid and tau (PET and CSF)
• Blood for biomarkers (AIBL protocol)
# A4 PET Screening Demographics

<table>
<thead>
<tr>
<th></th>
<th>Not Elevated (n=2685)</th>
<th>Elevated Amyloid (n=1115)</th>
<th>Group differences p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.9 (4.5)</td>
<td>72.0 (4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Female</td>
<td>59%</td>
<td>58%</td>
<td>0.447</td>
</tr>
<tr>
<td>% Minority</td>
<td>12%</td>
<td>8%</td>
<td>0.001</td>
</tr>
<tr>
<td>Education</td>
<td>16.6 (2.9)</td>
<td>16.6 (2.8)</td>
<td>0.999</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 (1.2)</td>
<td>28.8 (1.3)</td>
<td>0.455</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>11.8 (3.2)</td>
<td>11.5 (3.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Family History</td>
<td>68%</td>
<td>74%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% APOE ε4</td>
<td>25%</td>
<td>58%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PET SUVr</td>
<td>1.00 (0.07)</td>
<td>1.33 (0.18)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Alzheimer’s disease: future strategies for disease modification

- Determine and use Maximum Tolerated Dose (MTD)

- Develop rational combination therapeutics:
  
  Lower production by 50% (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
The Aging Brain

• Define normality and sub-threshold changes, to distinguish from three major classes of disease:
  • AD/DLB/PD spectrum (Aβ, tau, α-syn)
  • FTD/ALS/HS spectrum (TDP-43, tau, SOD1, PGRN, C9Orf72 dipeptide repeats, fus, etc)
  • Vascular impairments (atherosclerotic, thrombotic, embolic, intrinsic small vessel disease)
ACKNOWLEDGEMENTS

AIBL would like to thank the study participants and their families

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- Vicky Lawson
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- CSIRO: Sam Burnham, James Doekke, Olivier Salvado
- University of Edinburgh: Craig Ritchie
- Mass General Hospital / Harvard Med School: Rudy Tanzi, Reisa Sperling
- Network Aging Research (Heidelberg): Konrad Beyreuther