LATEST RESEARCH IN ALZHEIMER’S DISEASE THERAPIES

Associate Professor Michael Woodward
Austin Health
Alzheimer’s Australia national conference
Brisbane
May 2011
“Third generation” immunotherapy

- Beyond active immunization and current mAbs
- Agadjanyan’s group have developed epitope vaccines that add a foreign T-cell interacting sequence to the Aβ fragment-containing antigen
  - so there is no induction of the unwanted human T cell response that causes meningoencephalitis
  - His group prefers DNA rather than protein vaccines
  - Requires additional efforts need to ensure adequate immunogenicity
    - include placing an adjuvant patch, using an electrical field over the vaccination site, “gene gun” therapy and following the DNA vaccine by a protein vaccine
- His third generation immunotherapy has been taken up by Lundbeck and is being trialled in monkeys
- Aβ_{1-24} is the fragment that is being utilized- the vaccine is called VAR 24.
DUALITY OF INTEREST

§ Member of Alzheimer’s Advisory Boards for Novartis, Pfizer, Janssen-Cilag, Lundbeck
  § Paid honorarium for these
§ Financial support from several companies to attend and report on international conferences on dementia
§ Honorarium from several companies for speaking
§ Dementia research – Hospital paid for Principal Investigator duties for several trials
Relative Prevalence of Dementia
Australia

Rate per 100,000 population

PREVALENCE

[AIHW & Other Sources]
OUTLINE

§ Latest research impacting on therapies
§ New symptomatic therapies
§ Disease-modifying approaches
§ What the future holds
LATEST RESEARCH

Impact on therapies

• Improved understanding of the amyloid cascade
• Better biomarkers and understanding of their significance
• AD as a continuum- a risk state
Potential Molecular Targets for AD Therapies

- Ab40
  - Accumulates
  - Acutely Neurotoxic

- Ab Oligomers
- Ab Fibrils

- Amyloid Precursor Protein (APP)
- Soluble Ab40
- Gamma-Secretase Complex
- Beta-Secretase

- Mitochondrial Dysfunction
- Nucleus
- Amyloid Plaque
  - Inflammation
  - Oxidative stress
  - Neuronal cell death
The amyloid cascade

• The peptide Aβ is the initiator of AD
  – Why it is produced in pathogenic amounts in some older individuals remains unclear
• Probably has direct effects on neurones and on memory
  – Esp the oligomers (small aggregates of Aβ)
• Also increases tau production/pathology
  – Hyperphosphorylated/misfolded/truncated tau recruits normal tau to create toxic fibrils and then tangles
  – This tau is also toxic to mitochondria
• Most new disease-modifying approaches target the amyloid cascade
  – If they fail, it will place the importance of the cascade under severe stress
Biomarkers

• Increasingly essential to diagnosis of early stages of AD
• The earliest changes reflect Aβ pathology
  – CSF and plasma Aβ
  – Amyloid imaging
• Later biomarkers can detect neurodegeneration
  – MRI atrophy
  – CSF (and possibly plasma) tau
• Newer ones being developed
  – Proteomics, genetic, other
IS MCI EARLY AD?

§ Almost all with specific episodic memory disorder and one other phenotypic feature progress to AD
  § So (this subtype of) MCI is really early AD
§ We need to see AD as a continuum, not a discrete sudden-onset illness
  § Aβ deposits 10-15 years before subject fulfils current clinical criteria for AD
§ Dubois et al\(^1\) criteria for AD include much of what we currently call MCI
  § Cued recall deficit
  § One or more of
    § Hippocampal atrophy
    § FDG or PIB PET abnormality
    § Biomarker positive (eg raised CSF p-tau)
    § Known AD gene or strong family history
  § Note- not prodromal/early AD if no biomarker
    § Problematic if poorer country

Presymptomatic AD

• Stage one- asymptomatic cerebral amyloidosis
  – PIB-PET positive
  – CSF Aβ reduced
• Stage two- amyloidosis plus evidence of neurodegeneration
  – MRI atrophy or elevated tau
• Stage three- the above plus subjective memory complaint
  – May have abnormality on sophisticated neuropsychological testing- eg Cog State
Disease modifying trials- endpoints

• Most early MCI trials failed
  – Too few conversions to AD

• New criteria for prodromal AD as a continuum to AD allow new measures of disease modification
  – eg biomarker modification

• Likely that new criteria will select those that have more conversion annually to AD
  – Around 20-25%/year
Rx OF aMCI/ PRODROMAL AD

§ Huge effort
  § Target of many current/planned trials
    § BMS gamma-secretase inhibitor trial
    § Roche mAb trial
    § both here in Australia
§ No drug demonstrated beneficial as yet in earlier trials
  § Trial of donepezil showed no effect at 3 years; partial benefit at 18 months
§ Cognitive training may be useful
§ Prevention even more relevant (diet, depression, diabetes and control of vascular risk factors)
  § Recent BMJ¹ and NIH reviews
§ AD disease modifying treatment may be used here

1. BMJ 2010; 341:c3885
New symptomatic therapies

- 5-HT$_6$ receptor antagonists
  - Improved cognition in preclinical studies
  - Two under trial here
- Histamine-3 receptor agonists
  - Several under trial, here
- Partial nicotine $\alpha$4$\beta$2 agonist, ABT-089
  - Phase II trial terminated due to futility
  - Probably the end to nicotinic receptor approach
- New selective M$_1$ and M$_5$ agonists/allosteric activators being developed
  - should avoid SLUDGE
- Newer disease-modifying agents will likely also be symptomatic therapies
Disease Modification

• Targeting amyloid
• Targeting tau
• Combined approaches
• Others
  – Mitochondria
**STATUS OF INVESTIGATIONAL DISEASE-MODIFYING TREATMENTS FOR AD**

<table>
<thead>
<tr>
<th>IMMUNOTHERAPY</th>
<th>Solanezumab (Lilly)</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive immunisation</td>
<td>Bapineuzumab (Elan Wyeth)</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Ponezumab (Pfizer)</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Ganteneruzumab (Roche)</td>
<td>Phase II (pro AD)</td>
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<tr>
<td></td>
<td>Intravenous immunoglobulin (Baxter)</td>
<td>Phase III</td>
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<tr>
<td>Active immunisation</td>
<td>ACC-001 (Elan Wyeth)</td>
<td>Phase I</td>
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<td></td>
<td>CAD-106 (Novartis)</td>
<td>Phase II</td>
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<tr>
<td>SECRETASE INHIBITORS</td>
<td>Semagacestat (Lilly)</td>
<td>Phase III (negative)</td>
</tr>
<tr>
<td>Gamma secretase inhibitors</td>
<td>MK-0752 (Merck)</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>BMS-708163</td>
<td>Phase II (pro/early AD)</td>
</tr>
<tr>
<td>Beta secretase inhibitors</td>
<td>KMI-429</td>
<td>early Phase</td>
</tr>
<tr>
<td>ANTI-AGGREGATION AGENTS</td>
<td>Tramiprosate (Neurochem)</td>
<td>Phase II (negative)</td>
</tr>
<tr>
<td></td>
<td>Curcumin (John Douglas)</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>PBT-2 (Prana)</td>
<td>Phase III (planned)</td>
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</tbody>
</table>
# OTHER DISEASE-MODIFYING APPROACHES
( Mostly targeting amyloid)

<table>
<thead>
<tr>
<th>Category</th>
<th>Compound</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SELECTIVE AMYLOID-LOWERING AGENTS</strong></td>
<td>Tarenflurbil (Myriad)</td>
<td>Phase III (negative)</td>
</tr>
<tr>
<td></td>
<td>Posiphen</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>PPAR - AGONISTS</strong></td>
<td>Rosiglitazone (GSK)</td>
<td>Phase II (negative)</td>
</tr>
<tr>
<td><strong>RAGE LIGAND INHIBITORS</strong></td>
<td>Several (eg Pfizer)</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>PHOPHODIESTERASE (PDE9A) INHIBITORS</strong></td>
<td>PF 0447943 (Pfizer)</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>STATINS (several mechanisms)</strong></td>
<td>Atorvastatin (Pfizer)</td>
<td>Phase II (negative)</td>
</tr>
<tr>
<td><strong>DUAL AChEI/AMYLOID PRODUCTION REDUCER</strong></td>
<td>Phenserine (Axonyx)</td>
<td>Phase II (negative)</td>
</tr>
</tbody>
</table>
### OTHER DISEASE-MODIFYING THERAPIES

| NEURORESTORATIVE | NGF & RELATED THERAPIES | Cerebrolysin  
| Gene therapy | Transplantation / Infusion  
| Neurotrophic Factor Enhancer | Genetically engineered cells expressing NGF  
| Stem cells | Xaliproden (negative) |
Newer gamma secretase inhibitors

- Semagacestat failed
  - Greater decline in group receiving active drug
  - Also toxicity - skin cancer, rash, gastrointestinal
- BMS 708163
  - Phase II trial
  - CSF Aβ_{42} decreased
- Safe, well tolerated so far
- Soon to be trialled here
  - Both in AD and MCI/prodromal AD
Advances in secretase therapies

- The 3 APP secretases have been the target of a huge drug development program
- But the recent failure of semagacestat, a γ secretase inhibitor is very concerning
- It is surprising that these have become a target as in sporadic AD there is only a very slight increase in Aβ production
  - the main problem is oligomeric toxicity, and reduced Aβ clearance.
Alpha secreatase therapies

• The “good” secretase that prevents Aβ production
• When ADAM-10, an α secretase, is overexpressed in APP Tg mice, they no longer deposit excess amyloid
• Retinoic acid, and various related retinoids, activate ADAM-10
  – provides a therapeutic option using a drug that is already marketed
  – Acitretin, one retinoid, has reached Phase II trial stage in Germany
  – In Osaka tamibarotene, a retinoic acid receptor activator, is also being evaluated
  – Intriguingly, caloric restriction, which prevents amyloid toxicity in animal models, induces ADAM-10 activity, possibly by an epigenetic mechanism.
B Secretase inhibition

• For many years it was thought that it was impossible to make an inhibitor of this very large protein complex
  – any drug able to block the catalytic sites would be too large to cross the Blood Brain Barrier (BBB)
• Encouragingly, BACE knock out (KO) mice have a normal phenotype
• Amyloidogenic Tg mice with BACE KO also do not form excess amyloid, showing the benefit of reducing β-secretase activity.
• LY2811376, a non-peptide BACE inhibitor developed by Lily and the Clinical Research Organization Parexel, has undergone preclinical trials and certainly looked promising
  – binds to several catalytic pockets of the BACE-1 enzyme, and has good BBB and cellular penetration
  – in mice and beagles it reduces Aβ deposition
  – Phase I trials showed a reduction in plasma Aβ42 and good pharmacokinetics
  – Continuous (36hr) CSF catheterization in healthy volunteers also showed reduced central Aβ42 levels
  – Preliminary safety efficacy was also good….but
  – changes in animal retinal epithelium were seen
    • an “off mechanism” effect
    • results with the drug provide a proof of concept
    • but due to this retinal effect, development has been halted.
SECOND GENERATION IMMUNOTHERAPY

§ Several approaches
  § Aβ fragments
  § Monoclonal antibodies
    § Over 10 companies developing these
  § Should avoid the T-cell response that led to the unwanted inflammation

§ Aβ fragments could be delivered mucosally
  § Effective antibody response in mice when given weekly this way
  § Also an oral vaccine developed

§ Anti- Aβ DNA vaccination also promising
§ Olgomeric targeting
§ Human IgG
Aβ Fragment Immunotherapy

• Could be last shot at active immunotherapy
• Novartis Phase I CAD 106 vaccination.
• Aβ\textsubscript{1-6} fragment inserted into a biosphere to increase immunogenicity
  – doesn’t stimulate full Aβ-reactive T cells.
• 2 small cohorts tested, using 50 and 150 microgram doses, with MMSE 16-26.
  – Each of the subjects received 3 injections
  – followed for 12 months
  – clinical, MRI and CSF endpoints.
• Eighteen of 22 actively treated patients developed detectable antibodies
• No serious adverse events.
• Cognitive endpoints negative
• Other endpoints not yet reported
Aβ Monoclonal Antibody Programs

Solanezumab
Targets AA 16-24; IgG\textsubscript{1}

Bapineuzumab
Targets AA 1-5; IgG\textsubscript{1}

Ponezumab
Targets AA 13-40; IgG\textsubscript{2Da}

Gantenerumab targets Aβ aggregates

Sources: Cowen and Company Dec 17, 2007; Siemers et al, International Conference on Alzheimer’s disease; Madrid, Spain 2006; Natixis Bleichroeder; http://www.alzforum.org/newsdetail.asp?id=1793
Solanezumab

- Mid-terminus mAb
  - does cross the BBB
- Aβ fragments, which are normally only found in the brain, appear in the plasma by day 80, in a dose-dependent manner.
- Phase II trial in progress, including here
Ponezumab

- 2 Phase I single dose studies presented at ICAD 2010 (one 10 min infusion, one 2hr)
- Pharmacokinetics favourable
- CSF Aβ increased
  - No effects on CSF tau
- No safety issues
  - No Vasogenic Oedema reported yet (including ongoing Phase II study)
Bapineuzumab

- Wyeth / Elan N-terminus monoclonal Ab
- Phase II results
- N = 234
- Mean baseline MMSE = 20
- Mean age 70
- 10 endpoints (ADAS-Cog & DAD) did not significantly improve
  - But moved in expected direction
  - Did achieve significance in Apo E4 non-carriers, especially for completers
    - ADAS-Cog $\Delta = 7.3$
- In CSF, only p-tau affected (not $A\beta_{42}$)
- Less brain volume loss
Clinical Efficacy Endpoints: Total Population (MITT)

Bapineuzumab - results, all patients

**ADAS-cog**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Improvement Over Placebo at Week 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>3.3</td>
</tr>
<tr>
<td>0.5</td>
<td>4.3</td>
</tr>
<tr>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>2.0</td>
<td>2.8</td>
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<tr>
<td>All Doses</td>
<td>2.3</td>
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</table>

p = 0.078

**DAD**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Improvement Over Placebo at Week 78</th>
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<tbody>
<tr>
<td>0.15</td>
<td>2.1</td>
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<td>0.5</td>
<td>2.8</td>
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<tr>
<td>1.0</td>
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<td>5.1</td>
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<tr>
<td>All Doses</td>
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p > 0.10

**NTB**

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<tr>
<th>Dose</th>
<th>Improvement Over Placebo at Week 78</th>
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<tbody>
<tr>
<td>0.15</td>
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<tr>
<td>0.5</td>
<td>0.28</td>
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<tr>
<td>1.0</td>
<td>0.09</td>
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<tr>
<td>2.0</td>
<td>-0.03</td>
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<tr>
<td>All Doses</td>
<td>0.13</td>
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</table>

p = 0.068

**CDR-SB**

<table>
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<tr>
<th>Dose</th>
<th>Improvement Over Placebo at Week 78</th>
</tr>
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<tbody>
<tr>
<td>0.15</td>
<td>0.7</td>
</tr>
<tr>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>1.0</td>
<td>-1.1</td>
</tr>
<tr>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>All Doses</td>
<td>0.3</td>
</tr>
</tbody>
</table>

p > 0.10

MITT analyses using repeated measures model without assumption of linearity
Bars above zero indicate improvement relative to placebo
Patient populations for “all doses” comparisons: bapineuzumab range, N = 115-119; placebo range, N = 102-106
Clinical Efficacy Endpoints: Total Population (Completer)

**Bapineuzumab- Apo E₄ non-carrier results**

**ADAS-cog**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Improvement Over Placebo at Week 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
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<tr>
<td>0.5</td>
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</tr>
<tr>
<td>1.0</td>
<td>3.4</td>
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<tr>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>All Doses</td>
<td>4.3</td>
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*p = 0.003*

**DAD**

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<th>Improvement Over Placebo at Week 78</th>
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<tbody>
<tr>
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<tr>
<td>0.5</td>
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<tr>
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<td>-0.1</td>
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<td>2.0</td>
<td>6.4</td>
</tr>
<tr>
<td>All Doses</td>
<td>6.1</td>
</tr>
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*p = 0.041*

**NTB**

<table>
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<tr>
<th>Dose</th>
<th>Improvement Over Placebo at Week 78</th>
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<tr>
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<tr>
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<td>-0.05</td>
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<tr>
<td>All Doses</td>
<td>0.16</td>
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</table>

*p = 0.045*

**CDR-SB**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Improvement Over Placebo at Week 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>1.2</td>
</tr>
<tr>
<td>0.5</td>
<td>2.2</td>
</tr>
<tr>
<td>1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>2.0</td>
<td>1.6</td>
</tr>
<tr>
<td>All Doses</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*p > 0.10*

Completer: patient who had all 6 infusions and an efficacy assessment at Week 78
Bars above zero indicate improvement relative to placebo
Patient populations for “all doses” comparisons: bapineuzumab, N = 78; placebo, N = 78
Change in MRI Brain Volume*: ApoE4 Non-carrier Population (MITT)

10.7 cc less brain volume reduction over 71 weeks

Rx difference at Week 71 = 10.7 cc
\( p = 0.004 \)

\( N = 46 \)

\( N = 31 \)

*B brain volume as measured by brain boundary shift integral (BBSI)
MITT analyses using RM model without assumption of linearity, adjusted for whole brain volume at baseline, MMSE at baseline and ApoE4 status
Bapineuzumab - Safety

- Vasogenic oedema in 9.7% (N = 12)
  - Mostly in higher dose cohort
  - Usually just MRI finding
    - One had lethargy and confusion
  - ICAD 2010 presented theory that may be due to blockage of perivascular brain interstitial fluid drainage

- 3 deaths (all on active treatment)
  - Not considered drug-related

- Largest ever AD Phase III trial program in progress (N=4,000)
  - Stratified for Apo E4 (actually as 2 separate trials)
  - Using lower doses than in the Phase II, to reduce adverse events
Bapineuzumab-results from 3D6

• 3D6 is the murine equivalent of bapineuzumab
• Not only does the N-terminus binding 3D6 act against the amyloid plaques, it also is active against Aβ oligomers
  – these are the entities that are most toxic in AD
  – a C-terminus equivalent mAb had no such effect on oligomers
    • interesting as the same company that has an interest in bapineuzumab, Pfizer, is also is developing a C-terminus mAb, ponuzemab
• D6 also blocks oligomeric Aβ-induced tau phosphorylation
• In Tg mice, 3D6 increased synapse formation and reversed memory/behavioural deficits
• If bapineuzumab proves to be effective, it may well be due to this effect on oligomeric Aβ rather than on the monomeric or plaque form.
Monoclonal Ab’s from Reverse Translational Medicine

• From sera of a cohort of individuals with mild cognitive impairment (MCI) that had improved on cognitive testing over time Hock’s Geneva team isolated anti Aβ antibodies
  – selected ones that bound to aggregated Aβ
  – using RTM created monoclonal Abs
  – in transgenic (Tg) mice (genetically changed to overexpress Aβ) these human mAbs reduced Aβ levels by 50% through activation of microglia
  – seem to be acting against a conformational epitope of these Aβ aggregates rather than a linear sequence on the monomers
  – most encouragingly, there was increased dendritic branching and neuronal connectivity, along with neurogenesis.
  – memory also improved

• Human trials with these unique human mAbs planned.
Aβ oligomeric immunotherapy

• Arctic APP mutation is not associated with amyloid plaque formation
• This mid-APP mutation is, instead, associated with increased Aβ protofibril formation
  – and it does cause AD
• Lars Lannfelt, from Uppsala, has developed a humanized mAb against these Arctic mutation protofibrils
• Licensed to Eisai in 2007 after demonstrated efficacy in mouse models
• Phase I study of BAN 2401 completed
• A Phase II study is planned
  – Biomarker endpoints will include MRI volumetrics and CSF
• Gives us a fall-back option if current mAb trials, directed largely against Aβ monomers and amyloid plaques, fail.
Human IgG

- Contains anti-A Abs
  - Given IV
- Original trial positive
- Nine month data (poster at ICAD 2008)
  - Results:
    - Improvement in ADAS-Cog
      - Only significant at 9 months
- Phase III trial in progress
Scylloinositol

- Binds to the c-terminus of Aβ
- This induces phagocytosis
- Numerous beneficial effects in Tg mice
  - reduced cortical Aβ
  - reduced CSF Aβ
  - Improved memory
- Seems to induce many genes related to Aβ degradation
- An amyloid imaging ligand is also being developed, based on this product
Attacking tangles – tau protein

..but- tau is downstream from amyloid
Recent discoveries have moved the tau-ists more towards centre-field

- eg the finding that endogenous tau is necessary for $\text{A}\beta$- induced neuronal, synaptic and cognitive impairment
- reducing tau production reduces learning deficits in APP Tg mice (over-expressing amyloid), without affecting amyloid deposition- just making the amyloid much less toxic.
- This neuroprotective effect of tau depletion seems to be $\text{A}\beta$-dependent as tau reduction is not neuroprotective in other models of neurotoxicity
  - $\text{A}\beta$ may be causing a toxic gain of function of tau, or at least permitting tau to become toxic
  - the truncated and hyperphosphorylated forms of tau seem to be the toxic entity

Therapeutic approaches suggested by this understanding of the interdependence of $\text{A}\beta$ and tau include:

- directly inhibiting tau
- reducing tau expression
- inhibiting tau hyperphosphorylation
  - Increased tau acetylation seems to be associated with tau hyperphosphorylation, so another therapeutic approach could be to use acetylation inhibitors
- inhibiting tau aggregation
- stabilizing microtubules in a tau-independent way.
Rember
Leuko-methylthiominium chloride
(methylene blue)

- Inhibitor of tau aggregation
- N = 321
- T = 84 weeks
- Primary
  - ADAS-Cog $\Delta 5$
    - significant
  - CDR also significant
Rember
Neuroimaging studies

• SPECT in 125
  – No decline in 60mg group
  – Placebo did decline
• FDG PET in 19
  – Impressive results
Rember

- Safety
  - diarrhoea (poorly absorbed)
  - UTI / urgency / dysuria
- Phase III to commence
- By 2050, 600 million will be BRAAK II (tau staging) or above
- Succor for the tau-ists
  - But baptists not yet in retreat
- We may need both pathologies targeted
OTHER ANTI-TAU THERAPIES

• Selenium
  – Promotes tau dephosphorylation

• Phosphorylation inhibitors

• Anti-tau immunotherapy
  – Microtubule-binding region of tau
  – Phospho-tau itself
    • ie active tau immunotherapy
  – Truncated tau seems most toxic
    • need to develop drugs targeting this
  – only in animal models so far, but promising

• Aβ immunotherapy also lowers CSF tau

May be useful for other tau-relayed dementias, such as frontotemporal lobar degeneration
Other disease-modifying approaches

• Dimebon
  – Ietredipine
  – Targets mitochondria
• Metal binding agents
  – PBT-2
• Bacterial phages
• Nerve growth factors
• Stem cell therapies
• Anti-TNF therapy
Dimebon (letreditpine)

- N = 183, RCT (2 arms)
- Russian sites
- Not on AChEI
- T = 26 weeks
- 1\textsuperscript{st} outcome result (one only)
  - ADAS-Cog positive
    - $\Delta$ 4.0 ($p=\leq0.0001$)
- Well tolerated
ADAS-Cog

- **Dimebon**
- **Placebo**

**Clinical improvement**

**Clinical deterioration**

- *p* < 0.0001 Dimebon versus placebo
- *p* < 0.001 Dimebon improved over baseline
- *p* = 0.002 Placebo worsened from baseline

**Mean change from baseline**

- Baseline
- Week 12
- Week 26
Dimebon

• Two large phase III trials
  – One ongoing (add-on to AChEI)
    • CONCERT trial
    • Worldwide, including here
  – Recent monotherapy trial (CONNECT) negative
    • No decline in placebo group
    • Probably has implications for add-on trial
    • But only 6 month
    • New mechanisms of dimebon effects on mitochondria
      presented at ICAD 2010
PBT-2 (‘son of chloquinol’)

- Binds zinc and copper
  - Required for Aβ aggregation and synaptic function
- Phase IIa trial
  - Sweden, Australia
- N = 78
- T = 12 weeks
- 3 arms (placebo, 50mg, 250mg)
- Mean age = 72
- Mean MMSE = 23
PBT-2

Results
- Non significant for cognition
  - significant for 2 executive subscales for 250mg dose
  - Reduced CSF Aβ42 (250mg, p=0.006)
    - but ? significance

Phase IIb/III to begin soon
- will have PIB (amyloid) PET as primary endpoint
PDE9A Inhibition

• Modulate cGMP and cAMP signalling
  – affect gene expression that impact on memory
• First In Humans study reported at ICAD 2010
  – Only safety and PK presented
  – Safe, well tolerated
  – Half life 13-30 hr
Other therapies- Human Nerve Growth Factor

• Phase I trial completed
• 8 patients with mild AD
• Intracerebral injections of their own primary fibroblasts genetically modified to make NGF into the region of basal forebrain cholinergic neurons
• Mean MMSE decline = 3.0 ± 1.0 points per yr (↓ 51%); no AEs

Other NGF approaches

• Direct CSF infusion caused axial pain and neuraesthения/ weight loss

• New approach uses capsule containing human retinal epithelial cells transfected with human NGF gene
  – Phase Ib study implanting into both medial basal forebrains (N= 6 only)
  – Safe (no pain or wt loss)
  – Cog function improved in 2 of the 6
Other therapies-continued

• Anti-TNF monoclonal antibodies
  – Unblinded single-centre study with 12 subjects
    • 6 month endpoint
  – Etanercept infused perispinally weekly
    • Need to invert subject
  – Marked improvement in all cognitive endpoints
    • esp letter fluency (in FAS)
    • 2 aphasic subjects began talking within minutes
      – lots of publicity
  – RCT said to begin soon

• Trial of a different new generation anti-inflammatory agent planned for here soon

1. Tobinick et al. BMC Neurology 2008; 8: 27
Other therapies

• Many presented at ICAD 2010
  – Phenolics (myricetin (red wine), curcumin, rosemary)
    • All inhibit Aβ fibril formation and destabilize formed fibrils
    • Also antioxidative and anti-inflammatory effects
  – Tideglusib (GSK 3 inhibitor)
    • Effects on both Aβ and tau in mice
    • Phase I studies completed
      – 7% had ALT elevations
      – also seen in phase II studies
  – Shen-Wu (ginseng+)
    • Mitochondrial effects
  – Lipoic acid
    • Mitochondrial antioxidant
    • Only animal studies to date
Epigenetics- another target for therapies

• Regulation of genes is through epigenetic mechanisms
  – Gene expression necessary for the production of hippocampal synapses in memory formation
• Largely occurs through acetylation and deacetylation of histone proteins that condense the DNA
• Two opposing enzymes- histone acetyl transferase (HAT) and histone deacetylase (HDAC)
• Inhibiting the latter is beneficial for learning and memory
  – in a mouse model of dementia and neurodegeneration (CK-p25), even after a year of neurodegeneration the use of a HDAC inhibitor restored learning- a remarkable observation.
• Suggests numerous new targets for AD therapies
Recently failed therapies

- Eight in a row presented at ICAD 2009 (Vienna)
- Tarenflurbil
  - Initially developed as anti-inflammatory
  - All anti-inflammatory therapies have failed
  - May still have a role in prevention
  - Also anti-amyloid (modulates γ secretase)
  - Both placebo and active groups declined
- Alzhemed
  - Large phase III trial showed insignificant benefits
    - A glycosaminoglycan (GAG) mimetic
    - Binds to Aβ, leading to disaggregation
- Atorvastatin
  - Atorvastatin add-on to donepezil
  - LEADe trial
  - Insignificant ADAS-Cog effect
- Tamoxifen / Raloxifen ("Co Star")
Reasons for failed trials

• wrong targets
• too simplistic an approach to AD therapies
  – we may need to hit several targets simultaneously
• wrong trial designs
• wrong patients
• wrong endpoints
  – we use those for symptomatic AD whereas many new trials are for disease modification
Trial endpoints

- Need better endpoints
  - Group working with FDA developing a better CIBIC-like tool
    - Probably will incorporate Goal Attainment Scaling-like dimension
- “PROCOG” developed for MCI/prodromal AD
- NTB also favoured by European Medicines Authority
- Fascinating presentation on the challenges of multinational trials at ICAD 2010
  - 3 stage command has 42 syllables in Japanese cf 26 in English
  - “no ifs ands or buts” can be very challenging.
Conclusions

- Both exciting and disappointing times
- 25 years after original tacrine report, we still only have 4 modestly effective symptomatic therapies
  - not for want of trying!
- Likely that we will have a disease-modifying therapy within 5-10 years
  - will be expensive
  - probably most effective if used earlier (prodromal AD)
  - add-on to symptomatic therapies
  - possibly used sequentially, or in combination
  - toxicity may be a limiting factor
- Most advanced are monoclonal antibodies, IgG and gamma-secretase inhibitors
- Still very few advances in other dementias
- We must better recruit into trials
  - for the next generation if not for the person with dementia
  - clinicians should support research into trial methodology and recruitment, and create model centres of recruitment