The utility of biomarkers in CNS drug development

A focus on Alzheimer’s disease
R&D outsourcing penetration in the global pharma and biotech industries

Drug discovery - $17 bn
Clinical trials - $33 bn
Biomarkers in drug development

- A biological variable with a statistically significant relationship with parameters of
  - disease states
  - drug activity
The utility of biomarkers in drug development

• Patient selection and stratification
  – Improves the likelihood of patients to respond (or not) to the compound

• Target engagement
  – Indirect measure of CNS penetration

• Pharmacodynamics
  – Define the consequences of a compound's interaction with its target

• Disease and disease modification
  – Biomarkers that correlate with disease progression

Dementia
AD neuropathology

The cardinal changes

- Neuritic plaques
- Neurofibrillar changes
  - Neurofibrillary tangles
  - Neurophil threads
- Neuronal loss
  - Cholinergic
  - Noradrenergic
  - Serotonergic
  - Pyramidal cells

Plaques and tangles

The incidence of dementia
The progression of Alzheimer’s disease

Mild
- MMSE: 20-25
- Episodic memory
- Entorhinal cortex (ECX)

Moderate
- MMSE: 10-19
- Executive function + working memory
- ECX + cortex + LC + RN + nbM

Severe
- MMSE: 0-9
- Extensive deficits not restricted to cognition
- Cortical association areas + amygdala + thalamus + striatum
The progression of AD
Strategies to reduce the burden of dementia

- Pharmacotherapy
  - Symptomatic drugs
  - Disease modifying drugs
Hypothesis-based AD drug discovery

The cholinergic hypothesis

• 1976
  – The cholinergic deficit described
• 1997
  – The first AChE inhibitor lunched
    • Donepezil

The amyloid hypothesis

• 1991
  – The amyloid hypothesis proposed
• 2015
  – No amyloid-based therapy launched
Evidence to support the amyloid hypothesis

- Mutations in certain genes
  - cause early-onset familial AD
  - lead to the accumulation of Aβ
- Confer protection
  - Coding mutation (A6373T) in APP

- Aβ peptide found in
  - diffuse plaques
  - neuritic plaques
- Plaques and tangles seen in Down’s syndrome (trisomy 21)
Amyloid precursor protein (APP) processing
The predicted effect of a drug to reduce $A\beta$ concentration
The search for drugs to reduce Aβ-peptide in AD

**Approaches**

- Increased Aβ-peptide clearance
  - Active immunisation
  - Anti-Aβ-peptide antibodies
  - Metal protein attenuating compounds
- Increased non-amyloidogenic metabolism
- Inhibition Aβ-peptide formation
  - β-secretase inhibitors
  - γ-secretase inhibitors

**Anti-Aβ mAbs**

- Bapineuzumab
  - No efficacy in two large phase III trials
- Solanezumab
  - No efficacy in two large phase III trials
- Gantenerumab
  - No efficacy in a large phase III trial
- Aducanumab
Two phase 3 trials of bapineuzumab in patients with mild-to-moderate AD

<table>
<thead>
<tr>
<th>APOE ε4 carriers (432 v 658)</th>
<th>0.5 mg/kg</th>
<th>1 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog11 total score</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>DAD total score</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Clinical Dementia Rating Scale–Sum of Boxes total score</td>
<td>NS</td>
<td>-</td>
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<tr>
<td>Neuropsych. test Battery total score</td>
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<tr>
<td>MMSE total score</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Dependence Scale</td>
<td>NS</td>
<td>-</td>
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<table>
<thead>
<tr>
<th>ε4 non-carriers (493 v 307 v 314)</th>
<th>0.5 mg/kg</th>
<th>1 mg/kg</th>
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<td>ADAS-cog11 total score</td>
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Two phase 3 trials of solanezumab in patients with mild-to-moderate AD


<table>
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<tr>
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<th>EXPEDITION 1 (n = 506 v 506)</th>
<th>EXPEDITION 2 (n = 519 v 521)</th>
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<tbody>
<tr>
<td>ADAS-cog11 score</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ADAS-cog14 score</td>
<td>NS</td>
<td>p = 0.04 (1.6)</td>
</tr>
<tr>
<td>ADCS-ADL score</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CDR-SB score</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NPI score</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>NS</td>
<td>p = 0.01 (0.8)</td>
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</table>
Pharmacodynamic biomarkers

<table>
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<th>CSF concentration</th>
<th>EXPEDITION 1 (n = 506 v 506)</th>
<th>EXPEDITION 2 (n = 519 v 521)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free Aβ40</td>
<td>p = 0.01</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>Total Aβ40</td>
<td>p = 0.002</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Free Aβ42</td>
<td>NS</td>
<td>p = 0.06</td>
</tr>
<tr>
<td>Total Aβ42</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

The progression of AD
Mild cognitive impairment

• Subtle problems in one or more of the following domains
  – Memory
  – Planning
  – Language
  – Attention
  – Visuospatial skills

• Develop AD at a higher rate
  – Control 1–2%/year
  – MCI - 10–15%/year

• Mild AD neuropathology often present

• Amnesic
  – Single domain
  – Multiple domains

• Non-amnesic
  – Single domain
  – Multiple domains
Gantenerumab in prodromal AD

Mild cognitive impairment
- Mild memory loss (MMSE: 26-30)
- Some indication of AD pathology
  - Increased CSF $[\alpha_42]$ 
  - PET amyloid imaging 
  - Cortical/hippocampal atrophy (MRI)
  - Pyramidal cell loss (FDG-PET)

Gantenerumab
- Phase 3 clinical trial
  - Due to complete in 2018
  - Halted in 2015
    - No hope for benefit
Visualising amyloid plaques in the intact brain

$^{18}$F-Labeled Aβ Imaging Agents

- Florbetapir
  - FDA approval in 2012
  - Strictly limited to “ruling out AD”
Aducanumab

Phase 1 study
• 166 patients
• MCI/mild AD
• Positive amyloid PET

Presented at AD/PD Congress held in March 2015 (Nice)
## Premanifest familial AD

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Drug candidate</th>
<th>Selection</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Prevention Initiative</td>
<td>Crenezumab</td>
<td>PS1-positive subjects within 10 years before apparent cognitive decline</td>
<td>PET- Aβ, PET-FDG, Structural MRI, Cognitive tests</td>
</tr>
<tr>
<td>Dominantly Inherited Alzheimer Network</td>
<td>Solanezumab and gantenerumab</td>
<td>Confirmed family pedigree for autosomal dominant AD (mutations in APP, PS1 and PS2)</td>
<td>PET- Aβ, PET-FDG, Structural MRI, Cognitive tests</td>
</tr>
</tbody>
</table>
The classification of Alzheimer’s disease

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<tr>
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<th>Early onset AD (Autosomal dominant inheritance)</th>
<th>Early-onset AD (Multifactorial inheritance)</th>
<th>Late-onset AD (Multifactorial inheritance)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Inherited genetic mutations in APP, PS1 or PS2</td>
<td>Genetic and environmental risk factors</td>
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</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>Mostly 30-60 years</td>
<td>&lt;65 years</td>
<td>&gt;65 years</td>
</tr>
<tr>
<td><strong>Proportion of cases</strong></td>
<td>1%</td>
<td>4%</td>
<td>95%</td>
</tr>
</tbody>
</table>
Conclusions

- Over 400 clinical trials of disease-modifying disease candidates but no drug approved
- Early treatment is key
- Therefore, early detection is essential
Conclusions

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• Early treatment is key
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• Digital games to help detect early signs of dementia
Thanks for your attention

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