The utility of biomarkers in CNS drug development

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Global burden of CNS disorders and CNS medicines research

Global disease burden

Proportion of drugs and drug candidates

Non-CNS  CNS

Non-CNS  CNS

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Cumulative success rates to market by therapeutic area

- **Infectious diseases**
  - PHASE I: 33%
  - PHASE II: 47%
  - PHASE III: 75%

- **Cardiovascular diseases**
  - PHASE I: 6%
  - PHASE II: 9%
  - PHASE III: 32%

- **Cancer**
  - PHASE I: 6%
  - PHASE II: 8%
  - PHASE III: 2%

- **CNS disorders**
  - PHASE I: 1%
  - PHASE II: 2%
  - PHASE III: 14%

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Biomarkers in drug development

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

• Patient selection and stratification
  – Improves the likelihood of patient 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

MRI diffusion-perfusion mismatch to select stroke patients with a penumbra
Neuroimaging

- **Structure**
  - MRI
- **Molecular probes of structure**
  - SPECT
  - PET
- **Functional measures**
  - $[^{18}\text{F}]\text{Fludeoxyglucose}$
  - EEG
  - MEG
  - fMRI
    - Blood oxygen level-dependent contrast
Visualising amyloid plaques in the intact brain

- $[^{18}\text{F}]$ Florbetapir
  - FDA approval in 2012
  - Strictly limited to “ruling out AD”
Defining prodromal disease

Clinically isolated syndrome
- A transient impairment in motor or sensory function
- White matter abnormalities shown by MRI
- IFNβ drugs and glatiramer delay the conversion of CIS to RRMS

Mild cognitive impairment
- Mild memory loss (MMSE: 26-30)
- Some indication of AD pathology
  - Increased CSF $[\text{A}\beta_{42}]$
  - PET amyloid imaging
  - Cortical/hippocampal atrophy (MRI)
  - Pyramidal cell loss (FDG-PET)
  - Increased CSF [Tau]

## Clinical trials of premanifest AD (autosomal dominant 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>
Confidence in patient selection in Phase 2b studies

Cook D et al (2014)

<table>
<thead>
<tr>
<th>Percentage of projects</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Active**
- **Closed**
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The blood-brain barrier
Paul Ehrlich (1884-1915)

The blood-brain barrier (BBB)

- Separates the blood and brain compartments
- It severely constrains potential CNS therapeutics
- Generally, blood biomarkers do not reflect drug activity in the brain

Interstitial fluid is the key compartment for CNS drugs.
The three pillars of success

3 pillars
• Tissue exposure
• Target engagement
• Pharmacodynamic action

Brain ISF concentration is key

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Human</td>
<td>✓</td>
<td>?</td>
</tr>
</tbody>
</table>
Target engagement

Pharmacodynamic biomarkers

- Biochemical
- Physiological
- Behavioural
- Imaging
A PK-PD relationship is essential for successful CNS medicines research.
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MRI has revolutionised the diagnosis and management of MS

• **Diagnosis**
  – Greater accuracy and precision
  – The MacDonald criteria: more weight to MRI data

• **Can measure:**
  • White matter damage
  • Grey matter damage
  • BBB breakdown
  • New lesion formation

• **Used as:**
  – Primary endpoint in POC clinical trials
  – Surrogate endpoint in Phase III trials

Receptor occupancy studies
Measurement of disease activity

- Loss of dopaminergic neurons from the striatum of the intact brain of a PD patient

Striatum

Substantia nigra
The progression of Alzheimer’s disease

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

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

Severe
- Cortical association areas + amygdala + thalamus, + striatum
- Extensive deficits not restricted to cognition
- 0-9
The three cardinal pathologies of Alzheimer’s disease

Plaques and tangles
- Neurofibrillary tangles
- Amyloid plaques

Pyramidal cell loss
- 70% of all neurons
  - Corticocortical pathways
  - Corticofugal pathways
The loss of pyramidal cells is progressive (Mann D et al 1988)
Correlations between neuropathology and clinical measures

<table>
<thead>
<tr>
<th>Clinical measure</th>
<th>Plaques</th>
<th>Tangles</th>
<th>Pyramidal cells In layer III</th>
<th>Pyramidal cells in layer V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical rating*</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>WAIS verbal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>WAIS performance</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Token test</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Visual reaction time</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*A rating of magnitude of dementia (0-9)
- Language (0-3)
- Perceptuo-spatial functions (0-3)
- Memory (0-3)

PET markers of pyramidal cells and tangles

- $[^{18}\text{F}]$MPPF hippocampal binding
- Tau ligands
  - $[^{18}\text{F}]$-T808
  - $[^{18}\text{F}]$-THK523
  - $[^{11}\text{C}]$PBB3

The utility of biomarkers in CNS drug development

• Patient selection and stratification
  – Improves homogeneity of patient population
• Target engagement
  – Indirect measure of brain penetration
• Pharmacodynamics
  – PK-PD relationship
• Disease and disease modification
  – Surrogate markers of disease progression
# The utility of biomarker in AD clinical trials

<table>
<thead>
<tr>
<th>Method</th>
<th>Biomarker</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI (manual)</td>
<td>Hippocampal volume (and rate of atrophy)</td>
<td>Diagnosis, patient stratification, disease modification</td>
</tr>
<tr>
<td>MRI (automated)</td>
<td>Whole brain volume</td>
<td>Diagnosis, patient stratification, disease modification</td>
</tr>
<tr>
<td>fMRI</td>
<td>Blood oxygen-dependent level signal</td>
<td>Diagnosis, patient stratification</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Glucose uptake</td>
<td>Diagnosis, patient stratification, disease modification</td>
</tr>
<tr>
<td>Amyloid PET</td>
<td>Amyloid</td>
<td>Diagnosis, patient stratification, disease modification, target engagement</td>
</tr>
<tr>
<td>Aβ in CSF</td>
<td>Amyloid</td>
<td>Diagnosis, patient stratification, disease modification, target engagement</td>
</tr>
<tr>
<td>Tau in CSF</td>
<td>Tau</td>
<td>Diagnosis, patient stratification, disease modification, target engagement</td>
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</tbody>
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Summary and future prospects

• Biomarkers have the potential to:
  – Reduce clinical trial time
  – Increase the power of clinical trials
  – Improve diagnosis, including for prodromal (and premanifest) disease
  – Establish the optimal dosing regimen
• Genomics, proteomics, metabonomics are providing many biomarker candidates
• The clinical need for effective biomarkers is huge
  – Particularly for biomarkers of disease progression