Neuropathology Contributions to Clinical Trials and Drug Development: A Trialist’s View

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Dr. Cummings has provided consultation to MedAvante, Neurotrax, and UBC assessment companies.

Dr. Cummings owns the copyright of the Neuropsychiatric Inventory

Dr. Cummings has stock options in Prana, Neurokos, ADAMAS, Medavante
Cleveland Clinic Lou Ruvo Center for Brain Health

LRCBH; Folded Architecture

Misfolded Amyloid Protein

Frank Gehry, architect
Neuropathology Contributions to Clinical Trials

- Target validation
- Animal model pathology
- Patient selection
- Biomarkers
- Adverse events
- Verification of drug effect
- Hypothesis generation of drug effects
- Emphasis on morphologic and histopathology
Stages of Drug Development and Neuropathology Relationships

- Target Identification; Hypothesis Generation
- Preclinical Studies; Animal Models
- Clinical Trials; Patient Selection
- Biomarkers
- Adverse Events
- Clinical Outcomes
Stages of Drug Development and Neuropathology Relationships

Target Identification; Hypothesis Generation

Preclinical Studies; Animal Models

Clinical Trials; Patient Selection

Biomarkers

Adverse Events

Clinical Outcomes

Amyloid, p-tau, drug effects, etc

Tg animal pathology

Dx, ddx, comorbidity

Amyloid PET, FDG PET, MRI, MRS, etc

Inflamm, CAA, etc

Treatment verification: amyloid removal, etc
Neuropathology Contributions to Clinical Trials: Target Validation

- Amyloid protein in vessels
  - George Glenner, 1984
- Amyloid protein in plaques (AD, DS)
  - Wong, Glenner (1985)
- Hyperphosphorylated tau in NF tangles
  - Iqbal, 1974
Amyloid-Based Clinical Trials

- Immunotherapies
- Beta-secretase inhibitors
- Gamma-secretase inhibitors
- Alpha secretase enhancers
- Aggregation inhibiting agents
- BBB agents (inhibit import; facilitate export)
- Degradation enhancers
Neuropathology Contributions to Clinical Trials: Animal Models

- APP transgenics
- APP/PS1 2x tg
- APP/PS1/tau 3x tg
- Arctic mutations
- Effect of e4
- Tau mutants
- Tau knockouts
- Time effects
- Microhemorrhages
Neuropathology Contributions to Clinical Trials: Patient Selection

- Clinical-pathological correlations in AD diagnosis and differential diagnosis
  - Exclude non-AD dementias
- Exclude comorbid condition
  - Cerebrovascular disease
  - Microhemorrhages in immunotherapy trials
## Neuropathology Contributions to Clinical Trials: Biomarkers

<table>
<thead>
<tr>
<th>Neuritic and diffuse plaques</th>
<th>Amyloid imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuritic and diffuse plaques</td>
<td>Decreased CSF A-beta 42</td>
</tr>
<tr>
<td>Neurofibrillary tangles</td>
<td>FDDNP</td>
</tr>
<tr>
<td>Synaptic pathology</td>
<td>FDG PET</td>
</tr>
<tr>
<td>Neuropathology Contributions to Clinical Trials: Biomarkers</td>
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<tr>
<td>----------------------------------------------------------</td>
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<tr>
<td><strong>Cell loss (NAA content)</strong></td>
<td><strong>MRS</strong></td>
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<tr>
<td><strong>Cell loss</strong></td>
<td><strong>CSF total tau</strong></td>
</tr>
<tr>
<td><strong>Extracellular NFTs</strong></td>
<td><strong>CSF p-tau</strong></td>
</tr>
<tr>
<td><strong>Neurodegeneration; cell loss</strong></td>
<td><strong>MRI atrophy; cortical thinning</strong></td>
</tr>
</tbody>
</table>
Neuropathology Contributions to Clinical Trials: Biomarkers

- Cell loss correlates with MRI atrophy

Neuropathology Contributions to Clinical Trials: Amyloid Imaging

- PIB binds to fibrillar amyloid: neuritic plaques and diffuse plaques

Neuropathology Contributions to Clinical Trials: Treatment Verification

- **AN 1792**
  - Plaque removal
  - Increase in congophilic angiopathy (at least early in the course of treatment)
  - No change in neurofibrillary tangles
  - Reduction in neuritic dystrophy
  - Encephalitis features
AN 1792: Neuropathology Provides Insight into Drug Activity

Weller RO et al. Acta Neuropath 2009 (on line)
Evolution of Cerebral Angiopathy Following AN1792 Vaccination

(Broche D et al. Brain 2008)
# Neuropathologic Correlations with Clinical Trial Measures

<table>
<thead>
<tr>
<th>Trial Instrument</th>
<th>Neuritic Plaques</th>
<th>Braak Stage</th>
<th>Total Neuropath Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>-0.29 (0.0001)</td>
<td>-0.35 (0.0001)</td>
<td>-0.39 (0.0001)</td>
</tr>
<tr>
<td>Logical memory</td>
<td>-0.39 (0.0001)</td>
<td>-0.50 (0.0001)</td>
<td>-0.54 (0.0001)</td>
</tr>
<tr>
<td>FAQ</td>
<td>0.54 (0.0001)</td>
<td>0.56 (0.0001)</td>
<td>0.56 (0.0001)</td>
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<tr>
<td>NPI-Q</td>
<td>0.16 (0.04)</td>
<td>0.43 (0.0001)</td>
<td>0.36 (0.0001)</td>
</tr>
<tr>
<td>CDR-sb</td>
<td>0.54 (0.0001)</td>
<td>0.63 (0.0001)</td>
<td>0.64 (0.0001)</td>
</tr>
</tbody>
</table>

CDR0sb – Clinical Dementia Rating sum of the boxes; FAQ – Functional Activity Questionnaire; NPI-Q – Neuropsychiatric Inventory Questionnaire

Cummings JL et al. ICAD 2010
Neuropathology Contributions to Clinical Trials: Adverse Events

- Encephalitis in the AN 1792 trials

Treatment-Related Observations

- The following pathology observations have been reported in relation to treatment.
- These are not based on comparison of treatment and placebo groups in trials and are subject to bias.
Treatment-Related Observations

- Reduced plaque burden in DLB patients treated with cholinesterase inhibitors
- Increased plaque burden with chronic anticholinergic therapy
- Reduced plaque burden in patients treated with statins
- Other
Cholinesterase Inhibitors May Reduce Aβ in DLB

Anticholinergic Treatment Has Been Associated with Increased Plaque and Tangle Burden

Statins May Reduce Tangle Burden

Li G et al. Neurol 2007; 69: 878-885
Neuropathology Contributions to Clinical Trials: Critical Importance

- Neuropathology studies are critical to better understand the neurobiological effects of disease-modifying therapies
  - Type
  - Magnitude
  - Sequence
  - Relationships
    - Biomarkers
    - Clinical outcomes
  - Adverse events