Clinical Trials in Frontotemporal Lobar Degeneration: Focus on Tau

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Summary

- FTLD has advantages for clinical trials
- This is particularly true for FTLD-tau
  - More similar to tau Tg mice than AD
  - Less competing brain pathology
  - Potentially more efficient trials; Orphan incentives
- Established methods for progressive supranuclear palsy (PSP) trials
- Genetic tauopathies (FTDP-17) may allow prevention approaches
- New biomarkers available (tau PET)
Tau is an ideal target

Alzheimer Mice

Neurotoxin seizures

Roberson et al. Science 2007;316:750-754

Trans-synaptic (prion-like) spread

1. Fross and Diamond Nature Rev Neuroscience 2010;316:750-754
3. de Calignon, Neuron 2012; 73, 685–697
Tau drug targets and leads

- Methylene blue
- Tideglusib (GSK 3β inhibitor)
- Lithium
- Thiamet-G
- HSP90 inhibitors
- Proteasome
- Tau kinase or O-GlcNAcase inhibitors
- Tau assembly inhibitors
- Autophagy enhancers
- Transmission inhibitors
- Anti-oxidants
- Anti-microglial agents
- Microtubule stabilizers
- Coenzyme Q-10
- Rasagiline
- Mitochondrial cocktail
- Anti-tau mAb vaccine
- Davunetide
- Epothilone D
- TPI-287
- Anti-inflammatory

Brunden, Nat Rev Drug Discov, 2009
Tau diseases (tauopathies)

- Alzheimer’s disease
- Chronic traumatic encephalopathy (CTE)
- Frontotemporal dementia
- Progressive Supranuclear Palsy (PSP)
- Corticobasal degeneration
- (Parkinson’s disease)

Neurofibrillary tangles

tau protein
Neuropathology of FTLD

- ALS
- TDP-43
- bvFTD
- Tau
- MAPT
- PSEN
- C9ORF72
- GRN
- PSP
- CBD
- Alzheimer's
- Tau + Aβ
Improving precision for molecular targets

Probable AD at autopsy

Schneider, Ann Neurol 2009; 66

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>DLB</th>
<th>PD</th>
<th>FTD</th>
<th>PSP</th>
<th>CBD</th>
<th>ALS</th>
<th>svPPA</th>
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<td>Tau</td>
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TDP-43 proteinopathies (FTLD-TDP)

FTD ALS svPPA

Tauopathies (FTLD-tau)
FTLD Clinical development advantages

- Precise clinical-molecular links improve targeting of molecular therapies in humans
- Rapid FTLD progression allows more efficient trials
  - faster, smaller, cheaper than AD
- FTLD patients younger, healthier
  - fewer concomitant illnesses, medications
- Regulatory (FDA): orphan drug incentives, accelerated approval possible
- Marketing advantages (no competition) for any company with an effective therapy

Boxer et al., Alzheimer’s and Dementia 2013
Current FTD Therapeutics

• Galen’s view on off-label treatment (180 AD):
  o “All who drink of this remedy recover in a short time except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.”

slide courtesy Lon Schneider, MD
Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial


www.thelancet.com/neurology Published online January 2, 2013 http://dx.doi.org/10.1016/S1474-4422(12)70320-4

Neuropsychiatric inventory

Clinician’s Global Impression Change
2 times rate of decline in Alzheimer’s
H1 Tau haplotype: OR 5.46 (4.72–6.31) p = 1.5 × 10^{-116}

Hoglinger, Nat. Genetics (2011)
PSP = Tau

Steele JC, Richardson JC, Olszewski J. 1964


Williams and Lees; Lancet Neurol 2009; 8: 270–79
Davunetide for PSP phase 2/3 sites

N = 317 subjects followed for 1 year
Davunetide not efficacious for PSP

- Groups well matched at baseline; 94.2% H1/H1 haplotype (c/w PSP)
- No treatment effects on, CGIC, brain atrophy rate (n=215), RBANS, CSF, sensitivity analyses
- 11 deaths davunetide, 9 placebo group; 54 serious AEs in each. Nasal AEs more frequent in davunetide.

PSP Rating Scale

Schwab and England Scale

\[ p = 0.41 \]

\[ p = 0.92 \]
**Tau-directed therapeutics**

Potential approaches:
- Mitigate microtubule effects (MT stabilizers)
- Decrease tau (antisense oligos, autophagy mod.)
- Alter tau posttranslational (kinase inhib; aggregation)
- Block spread of tau (tau mAb, vaccine)

### Phase 1a
- **safe?**

### Phase 1b
- **PD effect?**

### Phase 2/3
- **efficacy?**

<table>
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<tr>
<th>Syndrome</th>
<th>PSP</th>
<th>FTDP-17</th>
<th>MAPT carrier</th>
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<tr>
<td>Recruitment</td>
<td>+++</td>
<td>+ ?</td>
<td>?</td>
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<tr>
<td>PD biomarker</td>
<td>CSF tau?</td>
<td>??</td>
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<th>Clinical Efficacy</th>
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<tr>
<td>Surrogate outcomes</td>
<td>vMRI</td>
<td>vMRI?</td>
<td>Delay onset</td>
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<tr>
<td></td>
<td>vMRI CSF?</td>
<td>vMRI?</td>
<td>?</td>
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</table>
Volumetric MRI in PSP

Whitwell (2012) Parkinsonism Related DO
Josephs (2012) Movement DO
CSF tau in primary tauopathies

- Standard CSF assays normal or low
  - Neuronal injury marker?
- Similar to tau transgenic mice (P301S)
- Newer tau assays reveal low CSF tau in PSP

Rosso, Arch Neurol 2003;60:1209-13
Hall, Arch. Neurol 2012; 69:1445-52
4 Repeat Tauopathy Neuroimaging Initiative

- 120 PSP / CBD
- 80 Controls

sites: UCSF, MGH (Dickerson), Toronto (Tartaglia/Lang), UCSD (Litvan)
Annual atrophy PSP from AL-108-231

n = 188 PSP (mean age 68.0 years)
n = 102 NC (mean age 68.1 years)

Shubir Dutt, Priyanka Bhatt, Richard Binney, Howie Rosen; on behalf of the AL-108-231 Investigators
FDDNP-PET in PSP

Kepe, et al., JAD, 2013
T807 Tau PET in Alzheimer’s Disease

Healthy  Very Mild AD  Mild AD  Severe AD
T807 Tau PET in PSP

Midbrain

Dentate nucleus of cerebellum

Thalamus

Slide courtesy of Brad Dickerson, MD; MGH FTD Unit
## Tau therapeutics: populations

<table>
<thead>
<tr>
<th>Clinical</th>
<th>AD</th>
<th>PSP/CBD</th>
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<td>Diagnosis</td>
<td>++</td>
<td>++++</td>
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<tr>
<td>Market</td>
<td>++++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Unmet need</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
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<tr>
<td>CT experience</td>
<td>++++</td>
<td>++</td>
<td>(-)</td>
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<tr>
<td>Recruitment (2014)</td>
<td>++</td>
<td>++++</td>
<td>+</td>
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<tr>
<td>Pre-symptomatic Tx</td>
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<td>+</td>
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<td>++++</td>
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<tr>
<td>Fluid biomarkers</td>
<td>++</td>
<td>+</td>
<td>(+/-)</td>
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<tr>
<td><strong>Tau mouse relevance</strong></td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Tau &gt; other neuropath</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Bedside to bench</td>
<td>+</td>
<td>++</td>
<td>+++</td>
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  o Potentially more efficient trials
• Established methods for progressive supranuclear palsy (PSP) trials
• Genetic tauopathies (FTDP-17) prevention approaches
• New biomarkers available (tau PET)
Davunetide/ Memantine Trials
David Knopman
Lon Schneider
Rachelle Doody
Murray Grossman
Erik Roberson
Dan Kaufer
Chiadi Onyike
Neill Graf-Radford
Mario Mendez
Jill Shapira
Diana Kerwin
Alan Lerner
Chuang-Kuo Wu
M. Marsel Mesulam
Mary Koestler
Kathryn Sullivan
Kristen Klepac
Scott Fields
John Neuhaus
Charlie Toohey
Joe Hesse
Chiara Corbetta-Rastelli

Eye Movements
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Dana Wagshal
Judy Pa
Shubir Dutt
Erwin Kong
John Fesenko
Eric Fine
Siobhan Garbutt
Joanna Hellmuth
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