Tau protein as a therapeutic target and biomarker for neurologic disease (and JQT)

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Outline

- John Trojanowksi: a pioneer of tau therapeutics and K23 mentor from afar

- **Tauopathies**: diseases with tau accumulation in the brain
- Tau biology: not just for microtubule binding
- Tau-directed therapies in clinical trials for tauopathies
- Tau biomarkers: insoluble (PET); soluble (CSF, plasma)
Ocular motor function … in FTLD

Saccade Abnormalities in Autopsy-Confirmed Frontotemporal Lobar Degeneration and Alzheimer Disease

Adam L. Boxer, MD, PhD; Siddham Garbutt, PhD; William W. Seeley, MD; Aria Jafari, BS; Hilary W. Heuer, PhD; Jacob Morsky, MS; Joanna Hellmann, MD, MIFS; John Q. Trojanowski, MD, PhD; Erik Huang, MD, PhD; Steven DeArmond, MD; John Neuhaus, PhD; Bruce L. Miller, MD

Vertical gaze ophthalmoplegia: Selective paralysis of downgaze

John Q. Trojanowski, M.D., Ph.D., and Shirley H. Wray, M.D., Ph.D., F.R.C.P.

Figure 5. Transverse section through central diencephalon. The bilateral infarcts have nearly disappeared. Hematoxylin and eosin plus luxol fast blue. × 4.5. See text and list of abbreviations.
Insoluble tau correlates with clinical features in tauopathies

Tau plays a central role in neurodegeneration: **tauopathies**

**Primary**
- MAPT mutation
- PSP, CBD, Pick’s

**Secondary**
- Aβ (Alzheimer’s)
- ApoE

**Contributory**
- synuclein (PD), epilepsy

**Pathways**
- Tau gain of function
  - Altered splicing
  - Altered folding
  - Altered expression
  - Other factors

- Clearance/autophagy
- Overproduction
- Misfolding
- Spread
- Strains

**Results**
- Neuronal (± glial) dysfunction
- Death
Tau genetics: strong links to primary tauopathies (but not AD)

JQT’s pioneering work in tau therapeutics: MT stabilization

Microtubule-binding drugs offset tau sequestration by stabilizing microtubules and reversing fast axonal transport deficits in a tauopathy model

Bin Zhang, Arpita Matli, Sharon Shivley, Fara Lakhani, Gaye McDonald-Jones, Jennifer Bruce, Edward B. Lee, Sharon X. Xie, Sonali Joyce, Chi Li, Philip M. Toleikis, Virginia M.-Y. Lee, and John Q. Trojanowski

PNAS | January 4, 2005 | vol. 102 | no. 1 | 227–231

Ephitholone D Improves Microtubule Density, Axonal Integrity, and Cognition in a Transgenic Mouse Model of Tauopathy

The Journal of Neuroscience, October 13, 2010 | 30(41):13861–13866 | 13861

Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial


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8 Presentation Title

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Basket trial: **Abeotaxane** in 3 tauopathies

Effects of MT stabilizer in 4R tauopathy group only

*\( p = 0.03 \)

**\( p = 0.022 \)

remains sig. after removing outlier

Tau is a multi-functional protein in health and disease

Cytoskeletal regulation

Synaptic vesicle protein binding & dysfunction

Mitochondrial protein binding & dysfunction

RNA binding & cytosolic condensates

Tau reduction as a therapeutic strategy

Alzheimer Mice

![Graph showing percent survival over age (months).]  
- hAPP/Tau^{+/+}
- hAPP/Tau^{+/−}
- hAPP/Tau^{−/−}

Neurotoxin seizures

![Graph showing tonic-clonic seizures (%) against kainate dose (mg/kg).]  
- Tau^{+/+}
- Tau^{+/−}
- Tau^{−/−}

Human AD patients treated with *MAPT* antisense oligonucleotide (ASO) to reduce tau by 50%

![Graph showing CSF total tau (% change from baseline) over time.]


Mummery et al. *AAIC abstract; 2021 #51871*
Mechanisms of action: anti-tau therapeutics in or near the clinic

1. **Genetically targeted therapies**: Antisense oligonucleotides (ASOs), RNAi, gene therapy
2. **Small molecule enzyme inhibitors**: Kinase (GSKi, DYRK1A), O-glcNACase (OGNi), Acetylation (salsalate), Nicotinamide
3. **Small molecule aggregation blockers**: Methylene blue derivatives, other aggregation inhibitors
4. **Small molecule enhancers**: Proteolysis targeting chimeras (PROTACs), Farnesyl transferase inhibitors
5. **Immunotherapies**: Active vaccines, Anti-tau monoclonal antibodies (mAbs)

Disease specific tau aggregate structures: impact on treatments?

Alzheimer’s Disease

Progressive Supranuclear Palsy

# Three potential tauopathy indications

Each has clinical development advantages—AD has the inside track

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Relationship to MAPT, preclinical models</th>
<th>Size/speed of clinical efficacy study</th>
<th>Tau biomarker availability</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>+/-</td>
<td>~1000’s/18 months</td>
<td>+++</td>
<td>Common</td>
</tr>
<tr>
<td>PSP</td>
<td>+</td>
<td>~100’s/12 months</td>
<td>(+)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>MAPT</td>
<td>+++</td>
<td>&lt;100/unknown</td>
<td>(+)</td>
<td>(very) Rare</td>
</tr>
</tbody>
</table>

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 ![Clinical development diagram]

**Clinical development**

**Tau**

**AD**

**PSP**

**MAPT**

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*UCSF*
Tau biomarkers to inform therapeutic effects (mostly in AD)

Brain

- Soluble tau
- Tau production
- Aggregates
- Post translational modification
- Clearance
- Tau fragments

CSF

- C-terminal cleaved
- Tau fragments
- CSF assays
  - P-tau181
  - P-tau217
  - "total tau"

Blood

- Blood assays
  - P-tau181
  - P-tau217
  - "total tau"

New IPMS assays

Horie et al, Brain, 2021; Thijssen et al, Lancet Neurol, 2021
Tau biomarker changes with donanemab (anti-Aβ) treatment

Clinical composite (iADRS)  Plasma P-tau217  Flortaucipir PET

Amyloid PET

Timing?
Conclusions

- Tau protein strongly implicated in many neurological diseases
  - AD, PSP and MAPT mutation carriers are focus of clinical trials
- Reducing tau gain of function is a therapeutic strategy
- Tau biomarkers important for diagnosis and clinical trials
  - Blood tests (P-tau217) transformative for AD clinical care & research
- So far, no successful tau therapies
- Donanemab: less tau by PET, plasma P-tau → better clinical status
- Early days for tau therapeutics … new insights into tau biology are rapidly leading to new biomarkers and therapies
- John Trojanowski was a pioneer in tau therapeutics
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