

UCSF Weill Institute for Neurosciences

Memory and Aging Center

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

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- 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 K23NS408855 (2005-2010)

Article abstract—A 58-year-old man developed a selective supranuclear paralysis of downgaze, which was repeatedly documented until it completely resolved after 6 weeks. At autopsy, there was a bilaterally symmetric old infarct in the mesodiencephalic region. In common with four previous similar reports, the lesion involved structures bordering the dorsomedial aspect of the red nucleus. This same region has been implicated in the control of vertical eye movements in recent neuroanatomic and physiologic experiments in nonhuman primates.

NEUROLOGY 30: 605-610, June 1980

#### 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.



Adam L. Boxer, MD, PhD; Siobhan Garbutt, PhD; William W. Seeley, MD; Aria Jafari, BS; Hilary W. Heuer, PhD; Jacob Mirsky, MS; Joanna Hellmuth, MD, MHS; John Q. Trojanowski, MD, PhD; Erik Huang, MD, PhD; Steven DeArmond, MD; John Neuhaus, PhD; Bruce L. Miller, MD





Figure 5. Transverse section through ventral 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



Kretzschmar, *Nat. Rev. Neurosci.* 2009, 10: 70-77; Williams, *Brain* 2007, 130: 1566-1576; McKee, *Brain* 2013, 136: 43–64



# Tau plays a central role in neurodegeneration: tauopathies





# Tau genetics: strong links to primary tauopathies (but not AD)



Brunden ..... **Trojanowski**, Nat Rev Drug Dis 2009, 8: 783; Hoglinger, Nat Genet 2011; 43: 699; Khouri, Nat Comm 2015, 6:7247; Tabuzini, Hum Mol Gen 2012, 21: 4094



# JQT's pioneering work in tau therapeutics: MT stabiliztion

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

Bin Zhang\*, Arpita Maiti<sup>‡</sup>, Sharon Shively\*, Fara Lakhani<sup>†</sup>, Gaye McDonald-Jones<sup>†</sup>, Jennifer Bruce\*, Edward B. Lee\*, Sharon X. Xie<sup>‡</sup>, Sonali Joyce\*, Chi Li\*, Philip M. Toleikis<sup>†</sup>, Virginia M.-Y. Lee\*, and John Q. Trojanowski\*<sup>§</sup>

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

#### Epothilone 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

Kurt R. Brunden,<sup>1\*</sup> Bin Zhang,<sup>1\*</sup> Jenna Carroll,<sup>1</sup> Yuemang Yao,<sup>1</sup> Justin S. Potuzak,<sup>2</sup> Anne-Marie L. Hogan,<sup>2</sup> Michiyo Iba,<sup>1</sup> Michael J. James,<sup>1</sup> Sharon X. Xie,<sup>3,4</sup> Carlo Ballatore,<sup>1,2</sup> Amos B. Smith III,<sup>2</sup> Virginia M.-Y. Lee,<sup>1</sup> and John Q. Trojanowski<sup>1,3</sup> Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial Lancet Neurol. 2014 May 23. pii: \$1474-4422(14)70088-2. doi: 10.1016

Adam L Boxer, Anthony E Lang, Murray Grossman, David S Knopman, Bruce L Miller, Lon S Schneider, Rachelle S Doody, Andrew Lees, Lawrence I Golbe, David R Williams, Jean-Cristophe Corvol, Albert Ludolph, David Burn, Stefan Lorenzl, Irene Litvan, Erik D Roberson, Günter U Höglinger, Mary Koestler, Clifford R Jack Jr, Viviana Van Deerlin, Christopher Randolph, Iryna V Lobach, Hilary W Hever, Illana Gozes, Lesley Parker, Steve Whitaker, Joe Hirman, Alistair J Stewart, Michael Gold, Bruce H Morimoto, for the AL-108-231 Investigators\*



# Basket trial: Abeotaxane in 3 tauopathies





Tsai, JAMA Neurol, 2019 Nov 11. doi: 10.1001/jamaneurol.2019.3812

# Effects of MT stabilizer in 4R tauopathy group only





# Tau is a multi-functional protein in health and disease



#### Mitochondrial protein binding & dysfunction



#### Synaptic vesicle protein binding & dysfunction



#### RNA binding & cytosolic condensates





# Tau reduction as a therapeutic strategy



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



# 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?





# Three potential tauopathy indications Each has clinical development advantages—AD has the inside track

Diagnosis	Relationship to <i>MAPT,</i> preclinical models	Size/speed of clinical efficacy study	Tau biomarker availability	Prevalence
AD	+/-	~1000's/18 months	+++	Common
PSP	+	~100's/12 months	(+)	Uncommon
MAPT	+++	<100/ unknown	(+)	(very) Rare





## Tau biomarkers to inform therapeutic effects (mostly in AD)



<sup>16</sup> Sato C, et al, *Neuron*. 2018; Horie et al, *Brain*, 2021; Thijssen et al, *Lancet Neurol*, 2021



# Tau biomarker changes with donanemab (anti-A $\beta$ ) treatment



Mintun et al, NEJM, 2021; Mintun et al, AAIC abstract, 2021; Janelidze et al, JAMA Neuro, 2020

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# 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  $\rightarrow$  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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Tau

Consortium

Turning Discovery Into Health

The Association for Frontotemporal Degeneration Opening the gateway to help and a cure

