Plaque and tangle distribution at different stages of Alzheimer’s disease progression (Braak staging)

Prodromal
transentorhinal
I - II

Early-Moderate
limbic
III - IV

Moderate -Late
isocortical
V - VI

Tangles

Amyloid plaques
Spread of tau pathology follows a distinct neuroanatomical path that suggests network connectivity.
MC1 antibody – human specific, recognizes an abnormal conformation of tau

EC directed expression of (mutant) tau

Young (~10 mo)

Old (~22 mo)
POSSIBLE MODES OF SPREAD

1) Dysfunction in cell A induces dysfunction and 
de novo patholgy in neighboring cell B

2) Secretion of tau molecules from cell A induces dysfunction and 
de novo pathology in neighboring cell B

3) Secretion or transfer of tau molecules from cell A to neighboring cell B

Propagation to new cells follows abnormal tau conformation “templating” to normal tau and repeat of cycle

(c) somatodendritic/synapse degeneration releasing tau into the extracellular space?
Tau pathology spreads to monosynaptically connected neurons that do not express human tau - evidence for cell-cell propagation.

Tau pathology can also spread to glia (Hyman et al. 2012).
Small tau aggregates are taken up by neurons and transported anterogradely

Cell bodies

Axons in grooves

Axon terminals

β-tubulin III (neuron specific)

DAPI

0.4uM hTau40 dimer and trimers for 12 h
…and retrogradely where it coalesces in the cell bodies
Accumulation of neurotoxic forms of tau in somatodendritic compartments of EC neurons

Disturbance of Tau metabolism - Hyperphosphorylation? Altered clearance of pathological forms?

Impedance of axonal transport
Degeneration of axons in pp
Degeneration of somatodendritic compartment in the EC

Release of tau into extracellular space from axons, then cell bodies

Uptake of tau by surrounding cells

Only low molecular weight/small fibrils - monomer, or large fibrils from mature tangles cannot bind to recipient cells

 Templating to endogenous tau

trans-synaptic then transneuronal propagation of pathological tau → Widespread tauopathy

IMMUNOTHERAPY to remove extracellular tau
“Diseases of neural networks”

- Differences between distribution of Abeta/amyloid and tau.

- Interactions between Abeta and tau?

- Functional outcomes and ordering of events – pathology – function correlations?

- Disconnect between where tau or Abeta is generated, and where pathology manifests.

- Why do 4R tauopathies (PSP, CBD AGD) affect different regions?

- Type of tau (conformers) and impact on cells, or networks affected?

- Why is the EC affected first? Why are layer II stellate neurons affected first?
20+ month old neuropsin-tTA-APP mice make mature and diffuse plaques
Pathology distribution in tau and APP mice different – expression pattern of APP/Abeta does not match deposition pattern

MC1 antibody

6E10 antibody