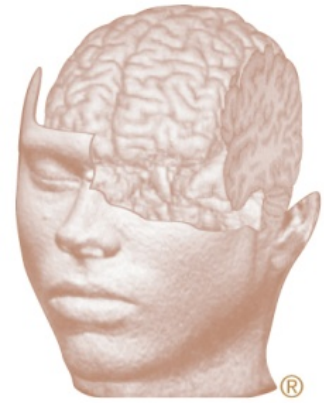
Development of Novel Biotherapeutics for the Treatment of Tauopathies



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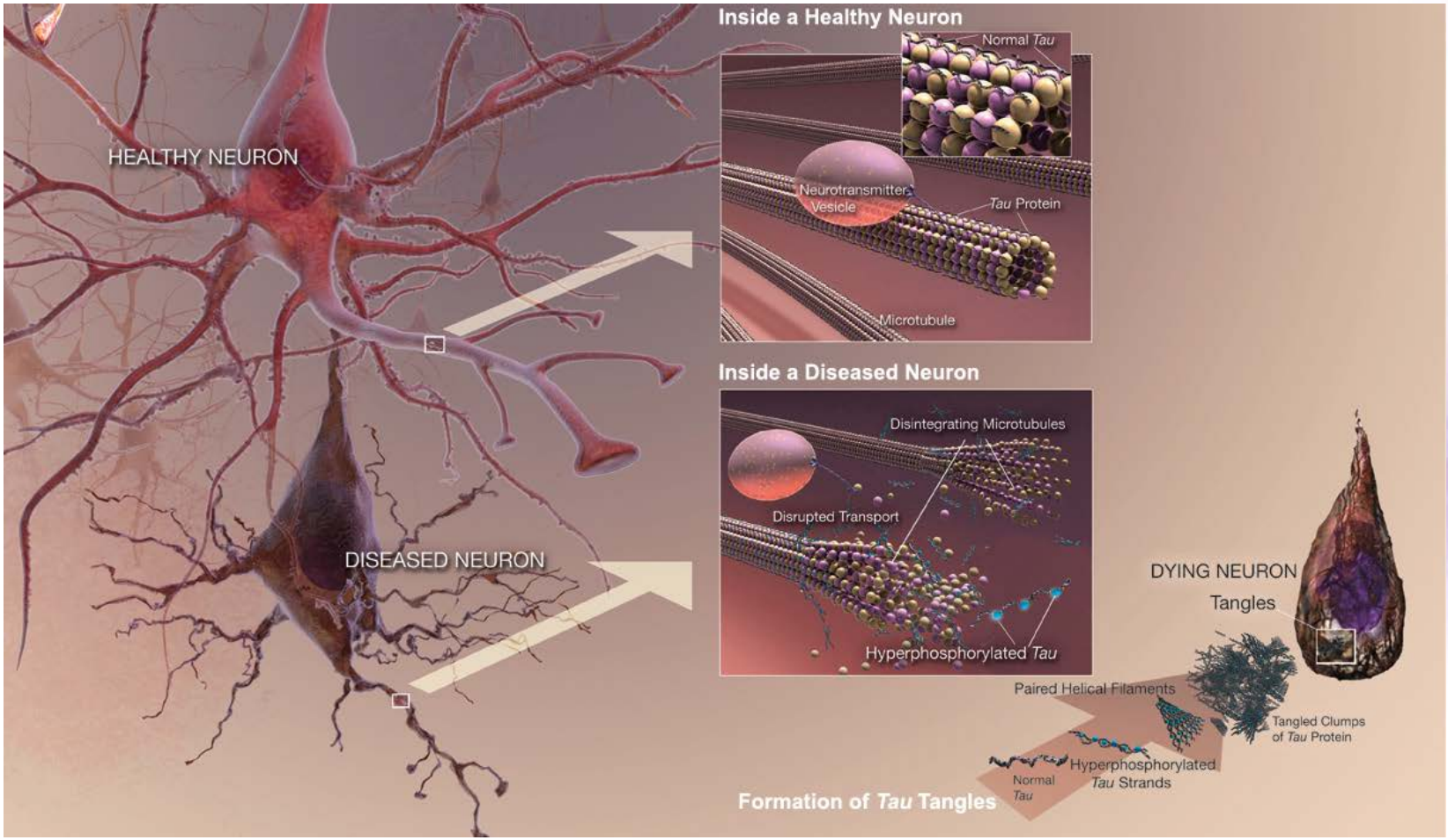
Neurodegenerative Tauopathies

Tauopathies are age-related neurodegenerative diseases characterized by the presence of aggregates of abnormally phosphorylated Tau. They are clinically characterized by *dementia* and include:

- Alzheimer's disease (AD)
- Frontotemporal dementia (FTD) or Pick's disease
  - Mutations in the Tau gene microtubule associated protein Tau (MAPT) cause familial frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)
  - Aβ plaques are not found in patients with FTDP-17
- Chronic traumatic encephalopathy (CTE) or dementia pugilistica (DP)
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- Parkinson's disease dementia (PDD)
- Posttraumatic stress disorder (PTSD)

Hyperphosphorylation of Tau Destabilizes Microtubules Leading to Neurodegeneration and Cell Death



Pathologies of Dementias

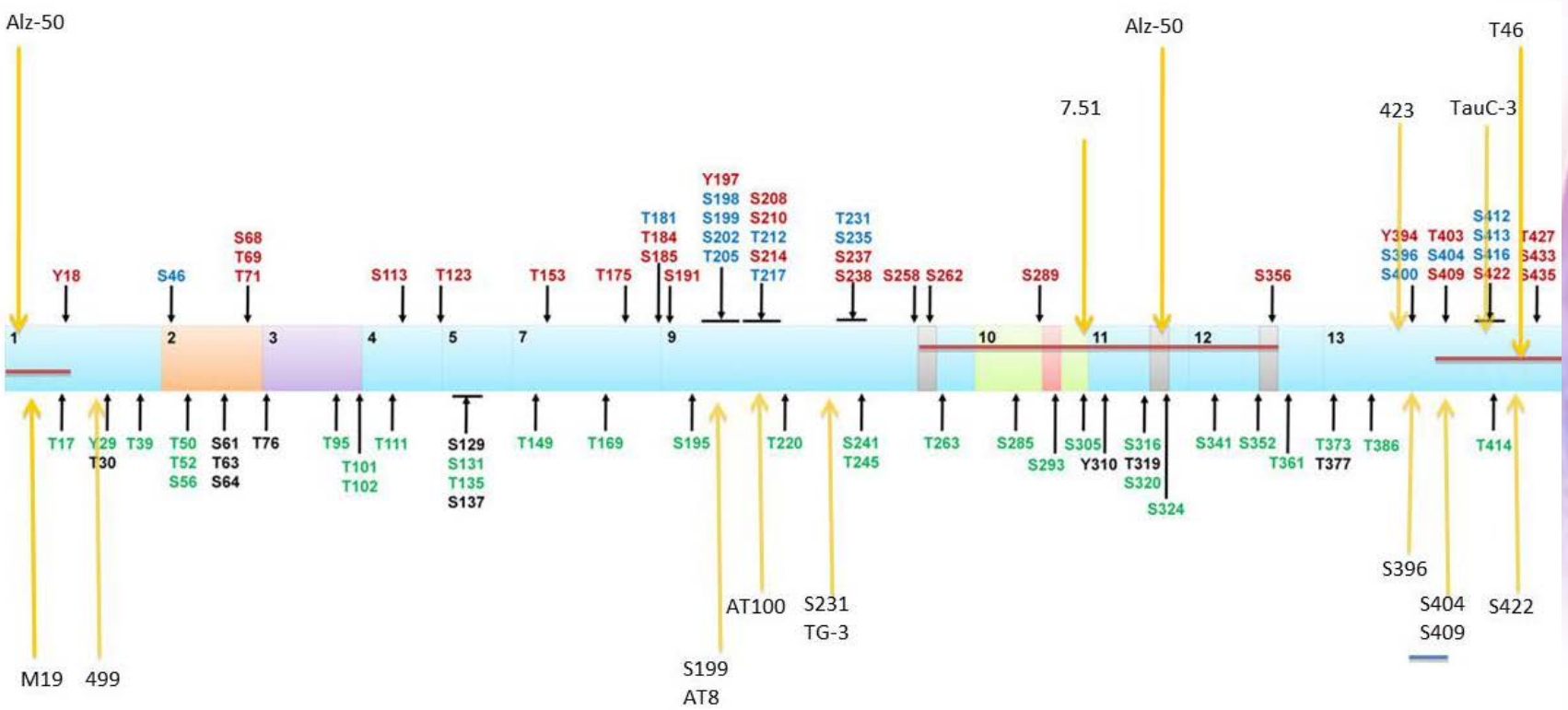
- All dementias are characterized by two or more hallmarks
- All dementias are characterized by localized neuronal loss (cell death)

Neurodegenerative Disorder	Pathological Hallmarks*
Alzheimer's Disease	NFTs, Aβ plaques, and cell death
Frontotemporal Dementia	NFTs and cell death
Chronic traumatic encephalopathy	NFTs and cell death
Corticobasal degeneration	NFTs and cell death
Progressive supranuclear palsy	NFTs and cell death

*NFTs are neurofibrillary tangles of Tau protein. Aβ plaques are largely composed of beta-amyloid protein.

All of these conditions are related to Tau

Multiple Epitopes of Tau as Potential Therapeutic Targets for Tauopathies



Importance of the Tau *N*-Terminus

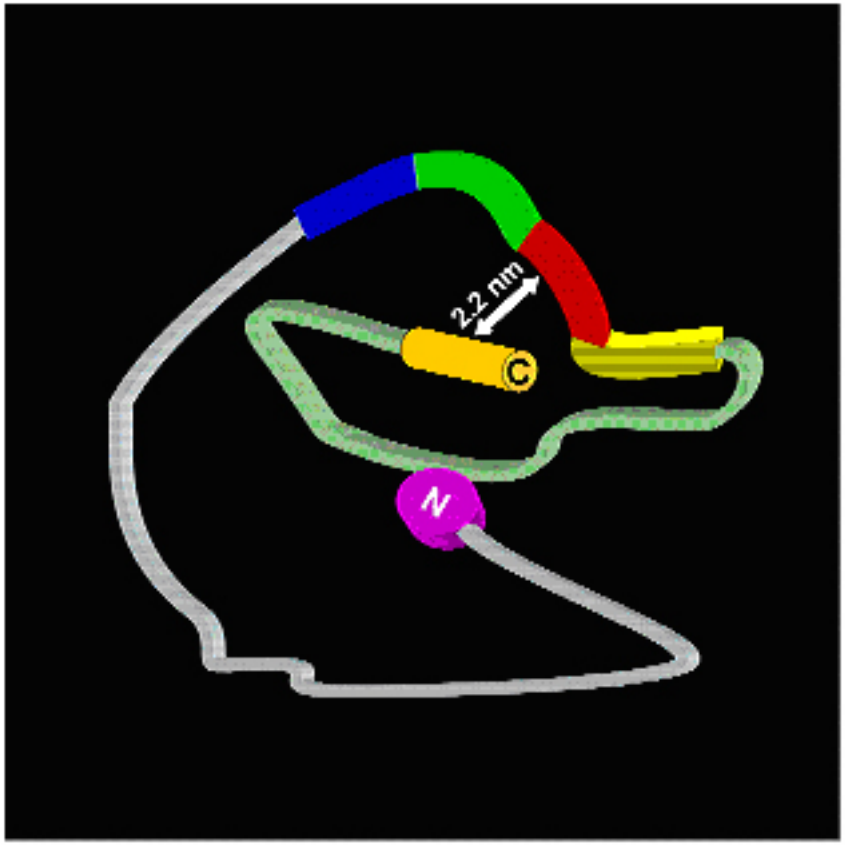
- In its native shape, Tau maintains a "paperclip" conformation shielding the *N*-terminus
- The phosphatase activating domain (PAD) sequence is 100% identical between 6 isoforms (amino acids 2-18):

AEPRQEFEVMEDHAGTY

- Exposure of the *N*-terminus is a *necessary first step* in conversion of normal physiological Tau to pathological Tau (amongst the earliest alterations in the development of AD and other tauopathies)
- Aberrant exposure of *N*-terminus leads to inhibition of fast axonal transport (FAT) through a signaling cascade involving PP1 and GSK3
- Immunization against this PAD sequence should have no effect on native Tau and should only bind to pathological Tau preventing adverse downstream pathology[1,2,3,4]

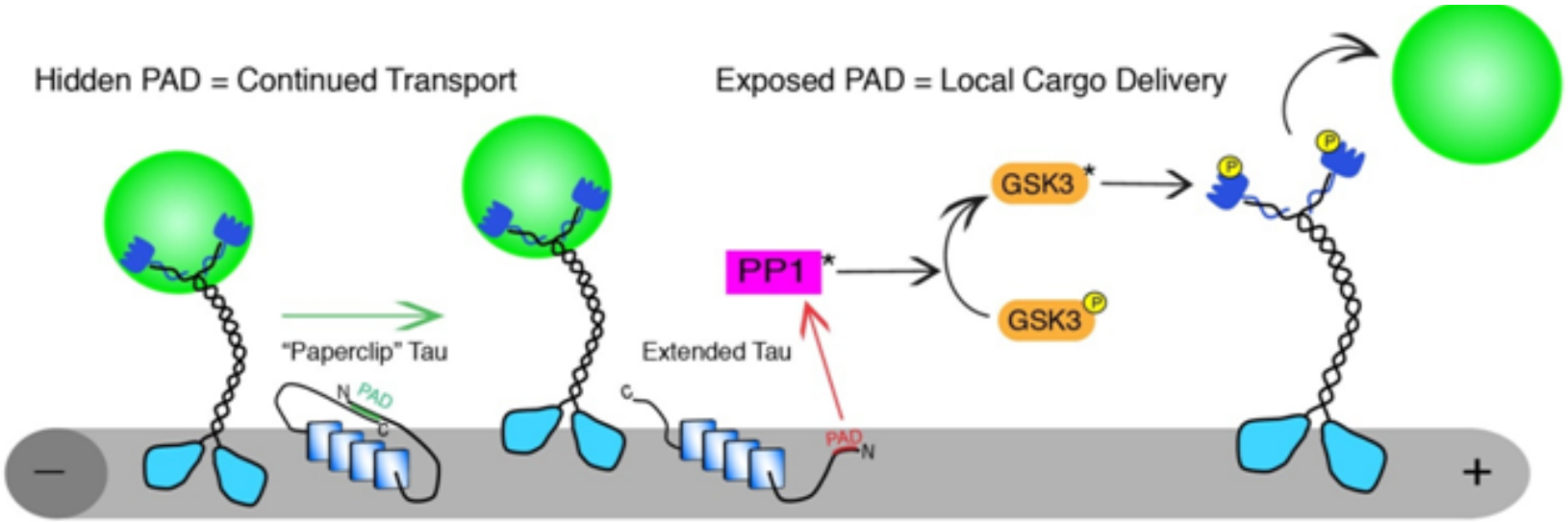
Experimental Conformation of Tau

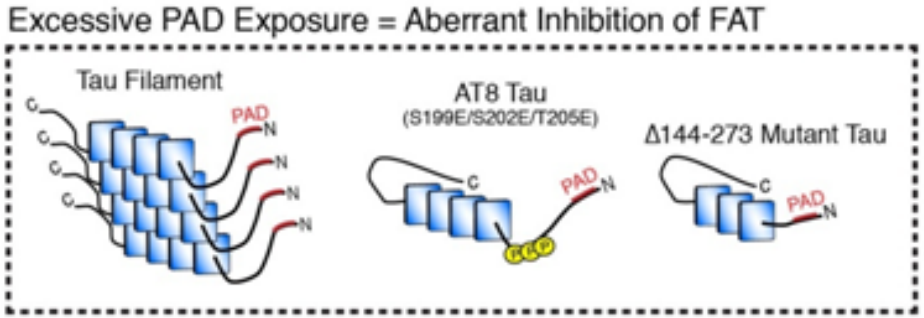
In solution, Tau normally adopts a closed “paperclip-like” conformation



- *N*-terminus
- *C*-terminus

Fast Axonal Transport (FAT) and Tau



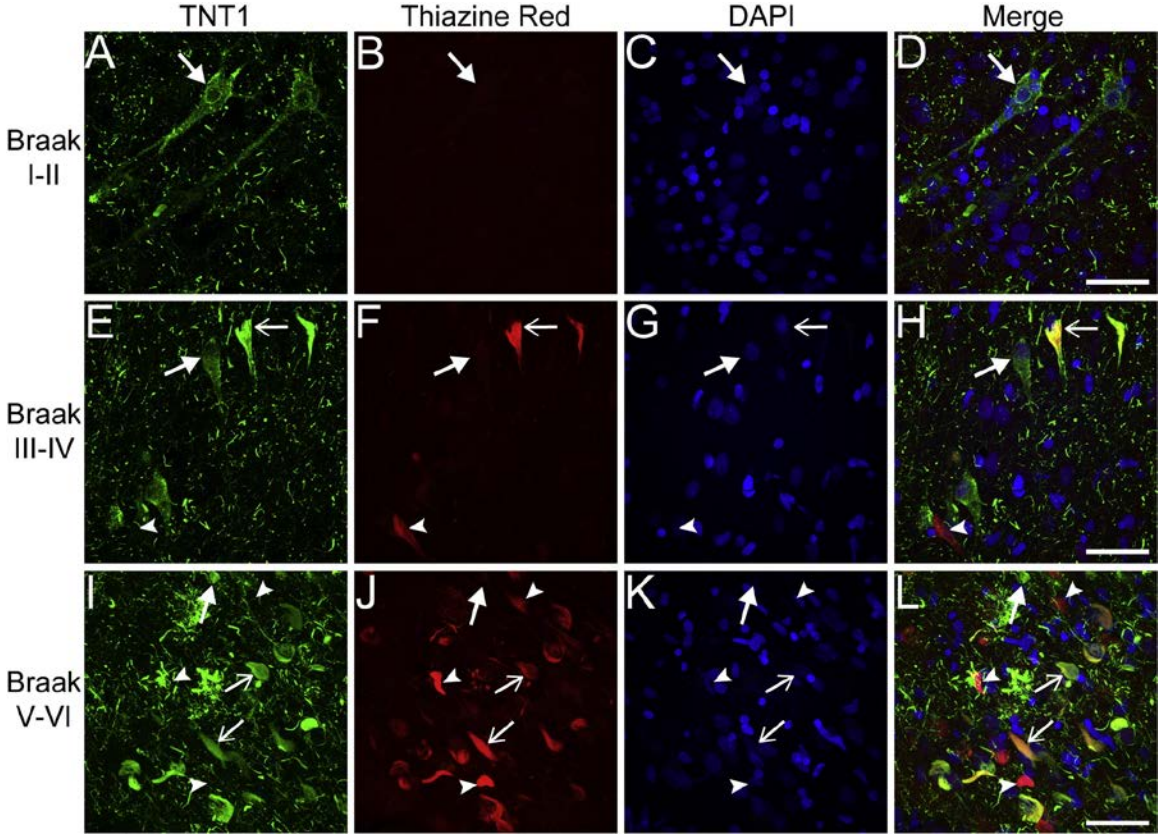


** FAT is critical to neuron function and viability*

INT-1 & INT-2: PAD-derived mAbs

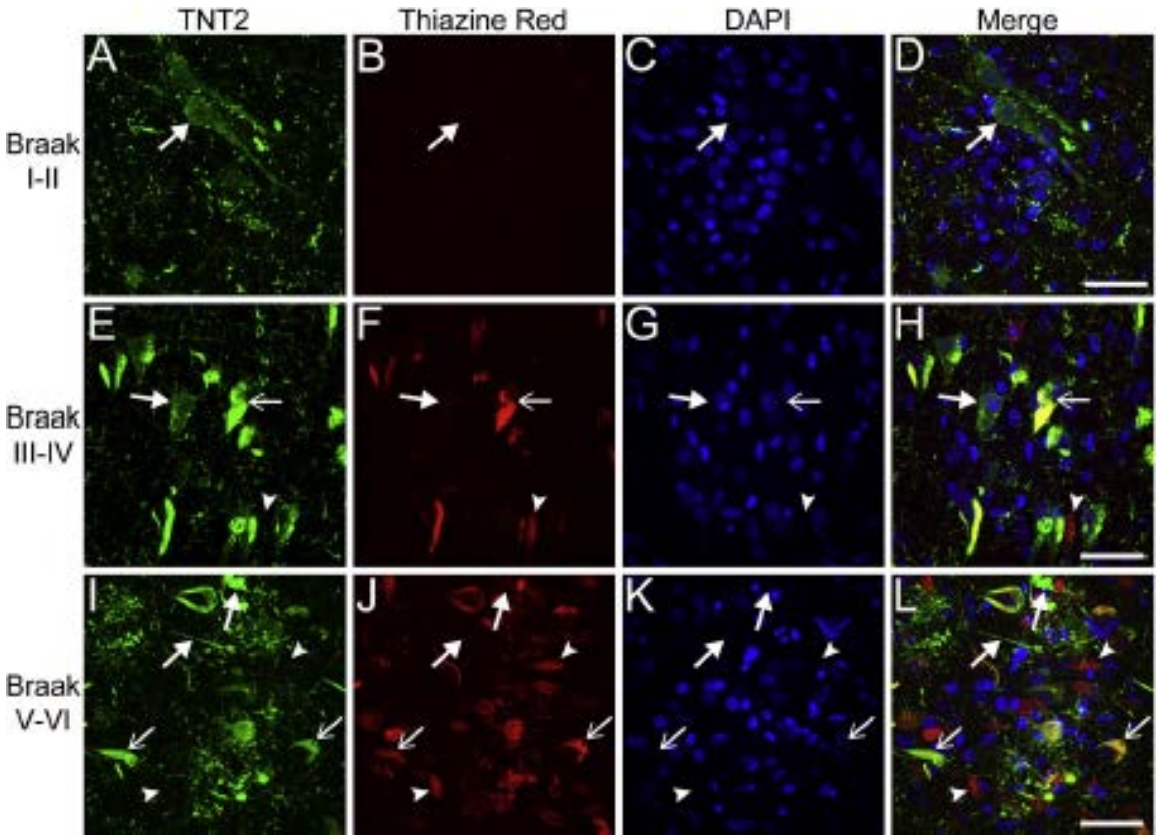
- Both recognize discrete regions within the N-terminus
- Display strong, conformation-dependent reactivity with pathological forms of Tau, but not normal Tau in non-denaturing assays
- Label diffuse, pre-tangle pathology in hippocampal tissue sections from Braak stages I-VI cases
- Co-localize with pathology identified by very early, conformation-specific Alz50 antibody
- Do not co-label in thiazine red-positive late-stage neurofibrillary tangles (NFTs) or ghost tangles
- Thus, INT-1 and INT-2 mAbs are *central* in differentiating between normal and pathological Tau; PAD exposure is a very early conformational change in Tau that occurs as pathology begins to accumulate in neurons[1]
- **Patent No. US 2012/014602 A1**

INT-1 mAb Detects Early Tau Pathology in Disease



- Multi-label fluorescent stain reveals that INT-1 (TNT1) mAb detects early Tau pathology in the hippocampus and the extend of pathology increases with Braak stage

INT-2 mAb Detects Early Tau Pathology in Disease



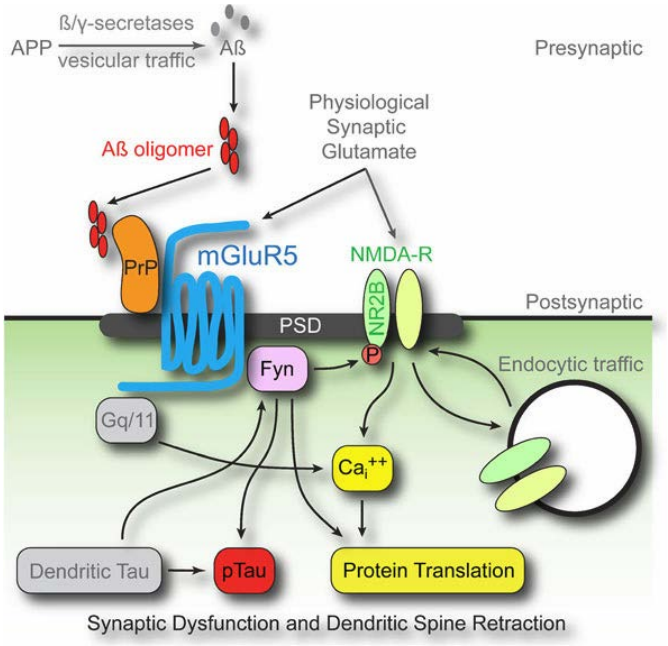
- Multi-label fluorescent stain reveals that INT-2 (TNT2) mAb detects early Tau pathology in the hippocampus and the extend of pathology increases with Braak stage

INT-3: Phospho-Tyr18-tau (PY18) mAb

- Tau is phosphorylated on Tyrosine-18 at its amino terminus by Fyn, Src and LcK, and members of the Src family non-receptor tyrosine kinase family (SFK)[5]
- Immunohistochemical studies have indicated that tyrosine phosphorylation of Tau at Tyrosine-18 is present in paired helical filaments (PHFs) and NFTs of AD brain[6]
- Fyn has been proposed to have a *key role* in disease pathogenesis based on data obtained from AD patients
- Fyn depletion confers protection against neurotoxicity induced by Aβ and reduces the synaptotoxicity and neurotoxicity in human amyloid precursor protein (hAPP) trangenic mice over-expressing Aβ[7,8]
- Fyn over-expression in this same mouse model potentiates behavioral deficits[9]
- Fyn and Tau interact genetically to modulate synapse loss, behavioral deficits, and electroencephalographic abnormalities in APP transgenic mice[10]
- This suggests an important role for *Fyn-Tau interaction* in the neurodegenerative process for AD and other related tauopathies

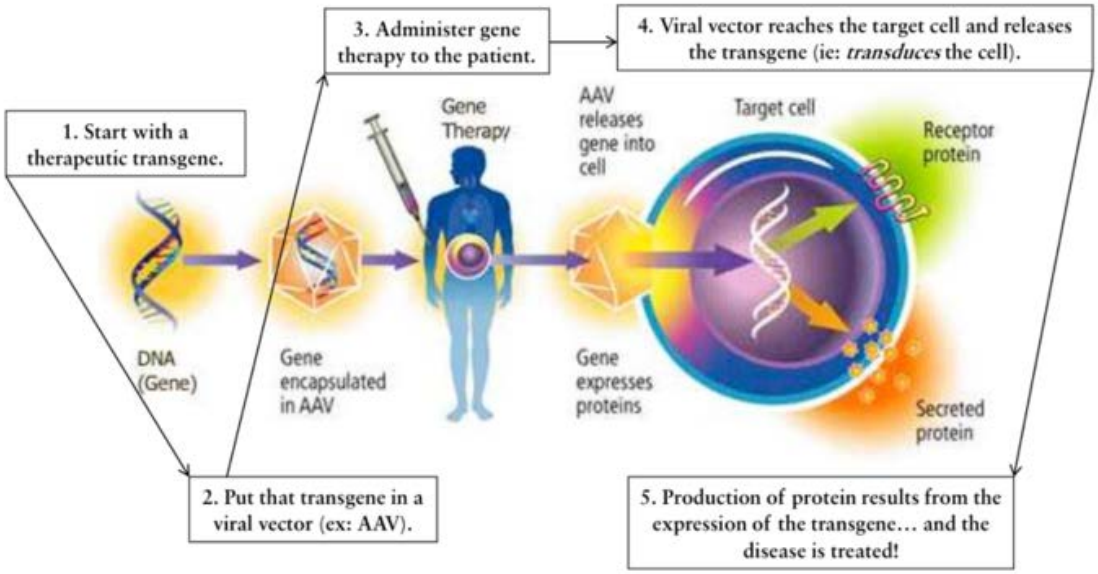
INT-3: Phospho-Tyr18-tau (PY18) mAb

- Schematic illustrating the central role of Fyn in amyloid-beta oligomer (Aβo) signaling



- Net result of aberrant cellular prion protein (PrP^c)-mGluR5-Fyn signaling is *synaptic malfunction and loss*
- Tau also appears to play a dendritic function at the postsynaptic density (PSD) and can mediate Aβ toxicity when AD is initiated
- This suggests a putative model for the Fyn-Tau-Amyloid "Toxic Triad" in the pathogenesis of AD, in which Tau and Aβ pathologies are directly *linked* through the actions of Fyn
- **Patent No. US 7,238,788 B2**

Adeno-Associated Viral (AAV) Vectors for Gene Therapy



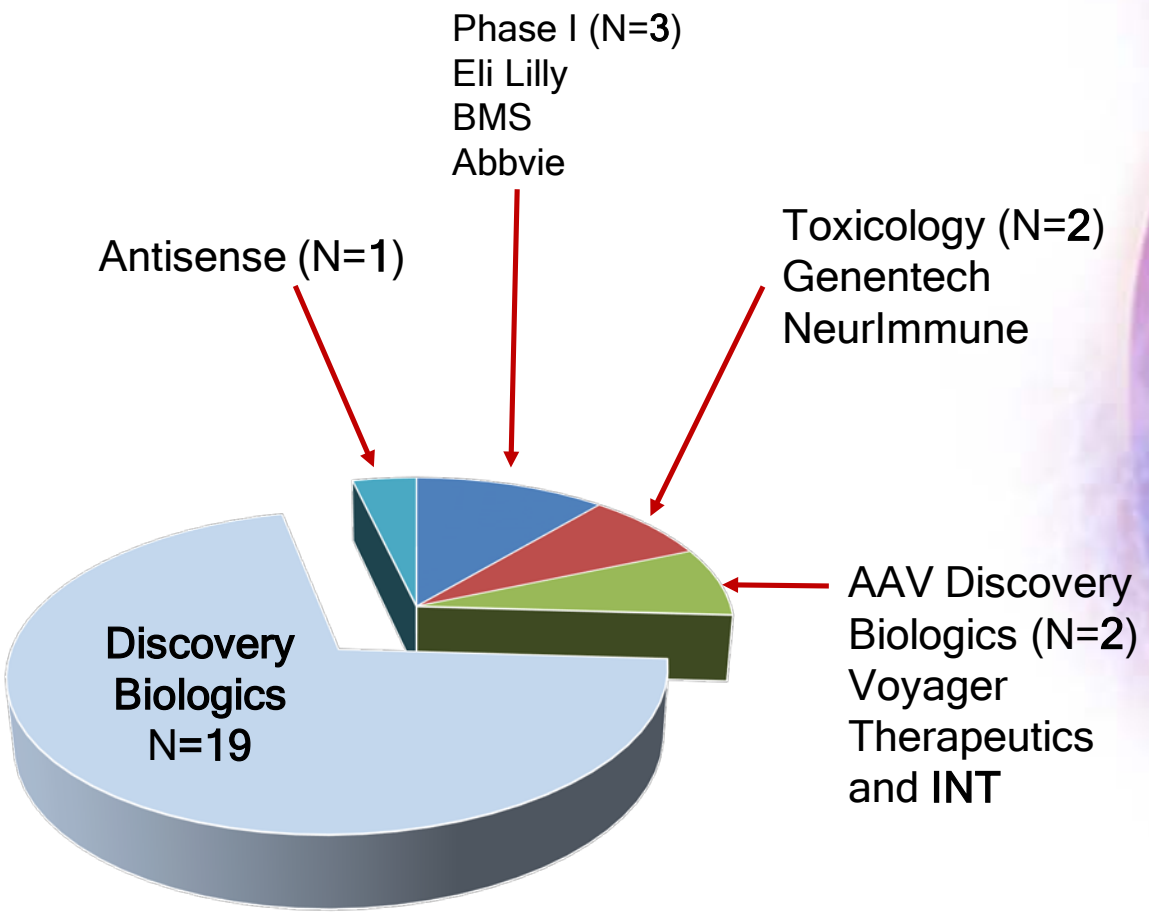
- Over the last decade, AAV has emerged as a highly promising and attractive approach to gene therapy with *proven safety* in clinical trials
- AAV is a *common, naturally occurring* virus that is not currently known to cause disease
- Advances in AAV vector design and related dosing techniques have made AAV *particularly well-suited* for the treatment of CNS disorders (e.g., AD, FTD, and PD)
- Since the targeted cells in the CNS are long-lived, non dividing neurons, therapy can potentially be delivered via a *single dose and be a long-lasting* (or even a lifelong) treatment
- It is possible that more than 8 years of durable expression be observed in the brain following AAV treatment

Tau-based Biotherapeutics in Development

09/2015 BMS initiated a Phase I clinical trial for PSP with their *N*-terminal mAb.

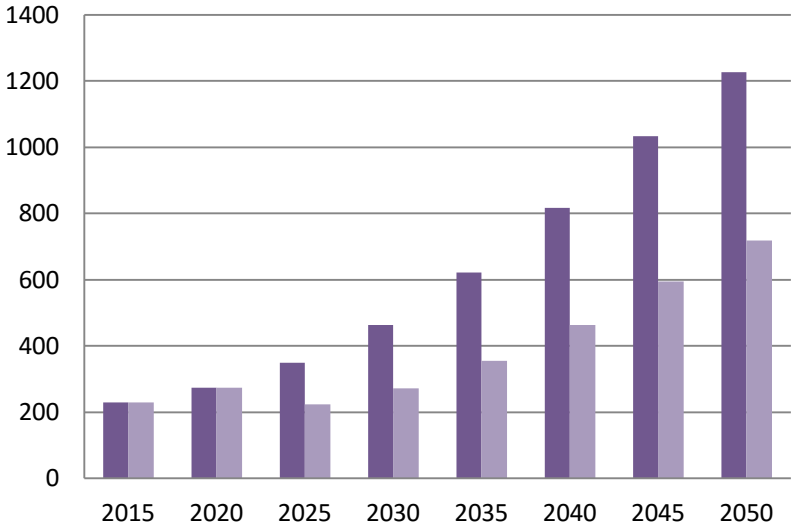
06/2016 Abbvie was granted orphan drug designation for treatment of PSP with their *N*-terminal mAb.

06/2016 Eli Lilly announced that they had entered a mAb in Phase I.



N=number of companies

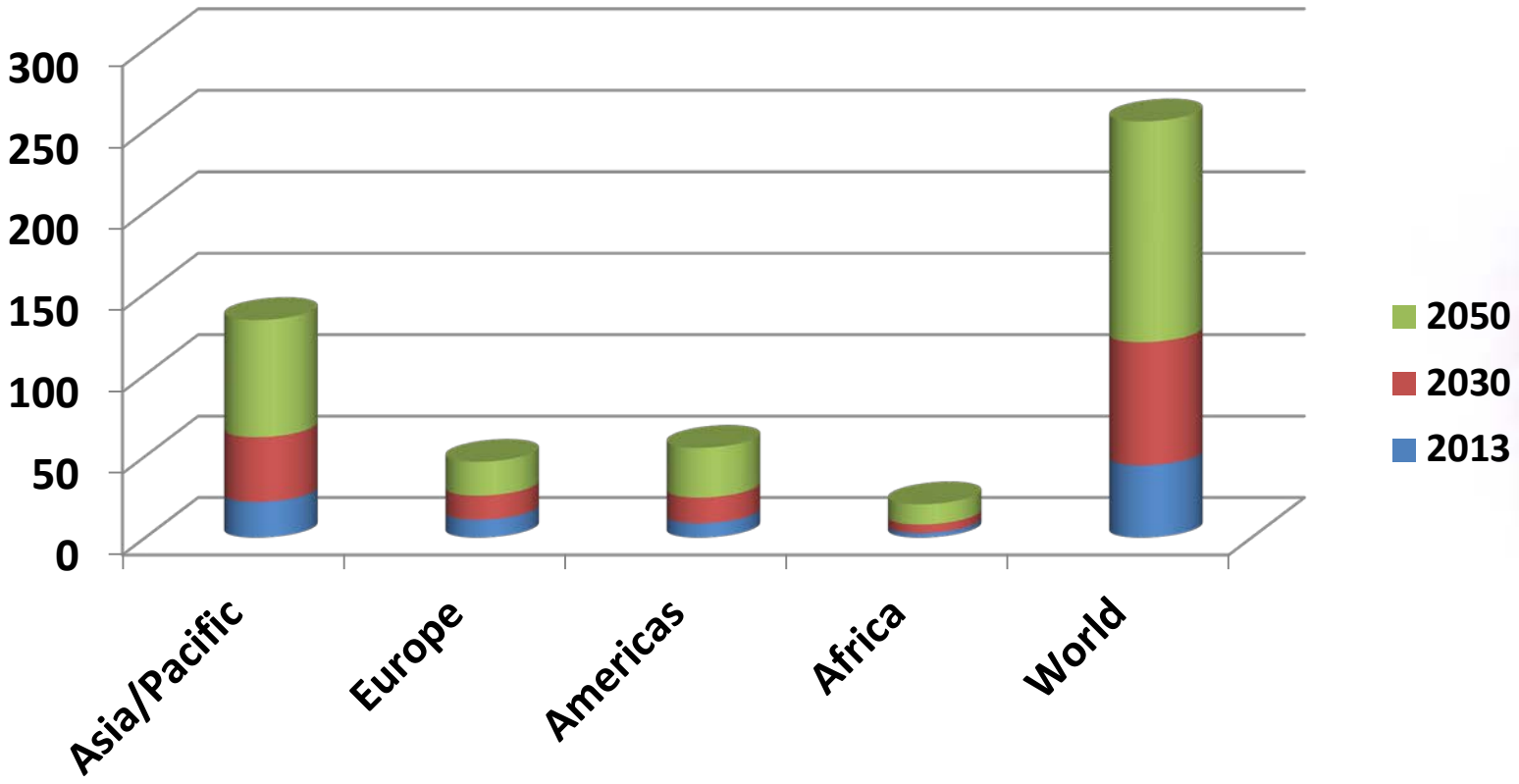
Impact of a 5-year Delay on Costs (in billions), Americans Age 65 and Older with AD 2015-2050



- In 2013, 44.4 million people globally suffered from dementia and a new case is diagnosed every 7 seconds
- The total estimated worldwide costs of AD and other dementia were over $604 billion in 2010

- The total U.S. costs of AD and other dementias were over $214 billion in 2013
- Alzheimer's will cost an estimated $1.2 trillion (in today's dollars) in 2050.
- An estimated 5.5 million Americans are currently diagnosed with AD, and AD is the *6th leading cause of death* in the U.S.
- **In the U.S. alone, introduction of a drug that delayed the onset of AD by 5 years would result in savings of $150 billion over the first 20 years of use**

Global Costs of Dementia by Region (in 2013 millions of USD)



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