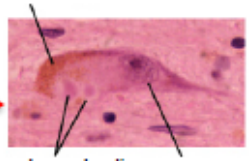
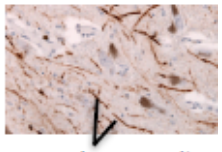
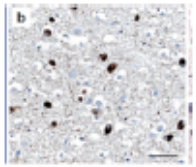
LEC 1- ALZHEIMER'S DISEASE

- **dementia diagnosis**: at least 2 of memory, communication + language, ability to focus and pay attention, reasoning and judgment, visual perception
- **types of dementia**: AD (60-80%), vascular dementia (10%), PD or dementia w LB, frontotemporal dementia, frontotemporal lobar degeneration (worse than AD), mixed dementia (AD + vascular), CJD, HD, Wernicke-Korsakoff syndrome (thiamine vit B1 deficiency), hydrocephalus
- **dementias classified by protein deposit**: tauopathies (AD, CBD, FTD), synucleinopathies (PD, DLB)
- **proteinopathies**- commonality in pathology of age-related neurodegenerative disease

Disease	Protein Deposit	Toxic Protein
Alzheimer's Disease	extracellular plaques intracellular tangles	Aβ tau
Parkinson's Disease	Lewy bodies	α-synuclein
Prion Disease	Prion plaque	PrP^{Sc}
Polyglutamine disease eg. Huntingtons	nuclear and cytoplasmic inclusions	Polyglutamine – containing protein
Pick's disease	cytoplasmic deposits	tau
Familial amyotrophic lateral sclerosis	Bunina bodies	SOD1

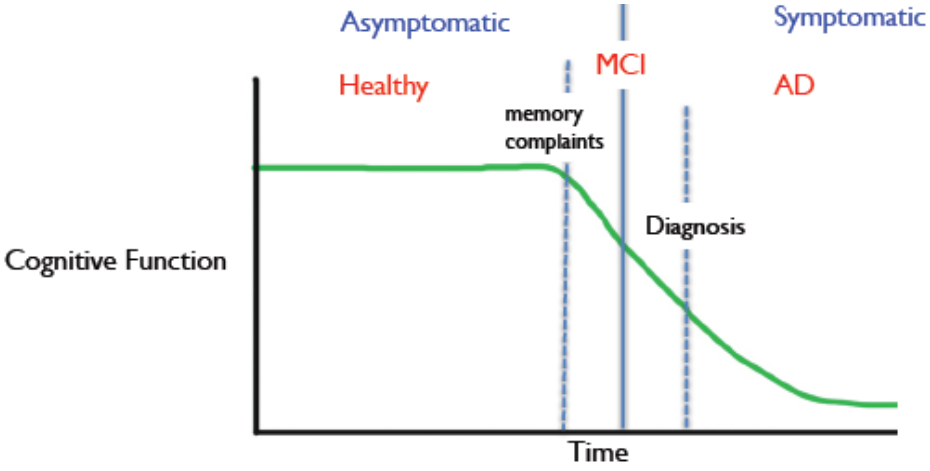

Lewy bodies


Lewy neurites


Pick bodies

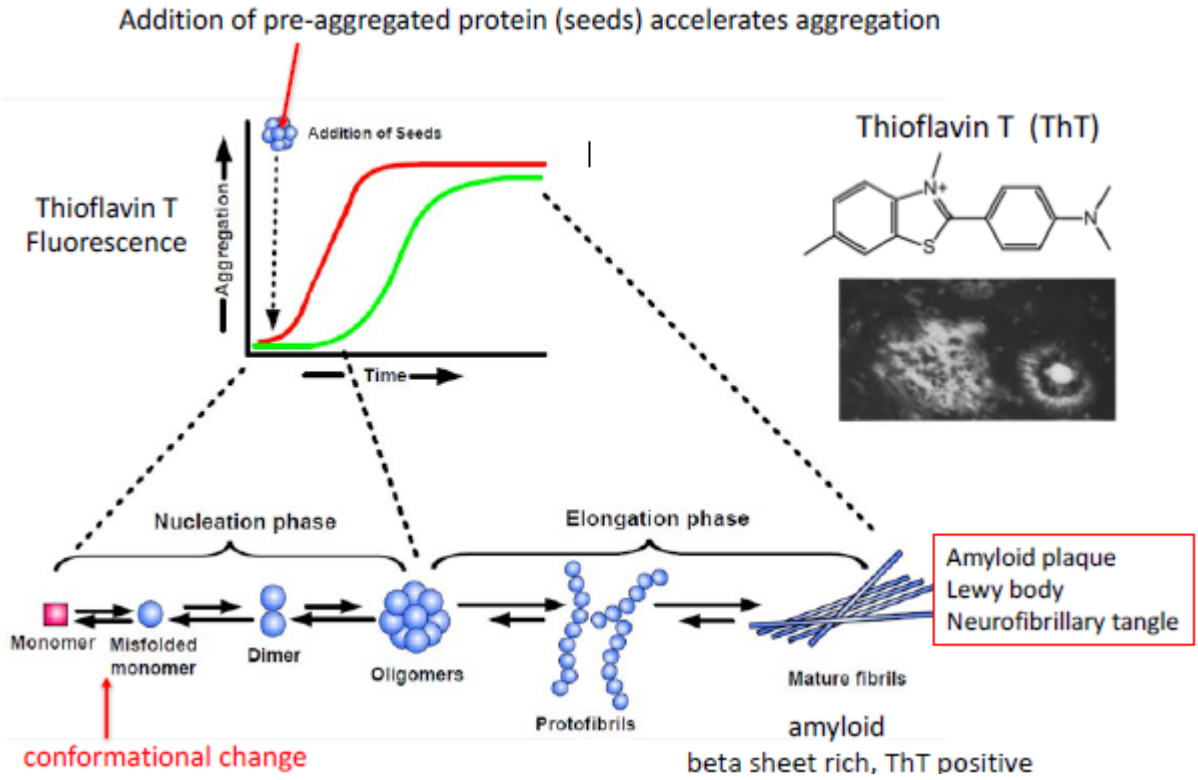
AD

- **3 stages:**
  - prodromal: preclinical with no symptoms, up to 30 years, decline in cognition
  - MCI
  - clinical AD: mild- typically diagnosed, moderate, severe- body shuts down



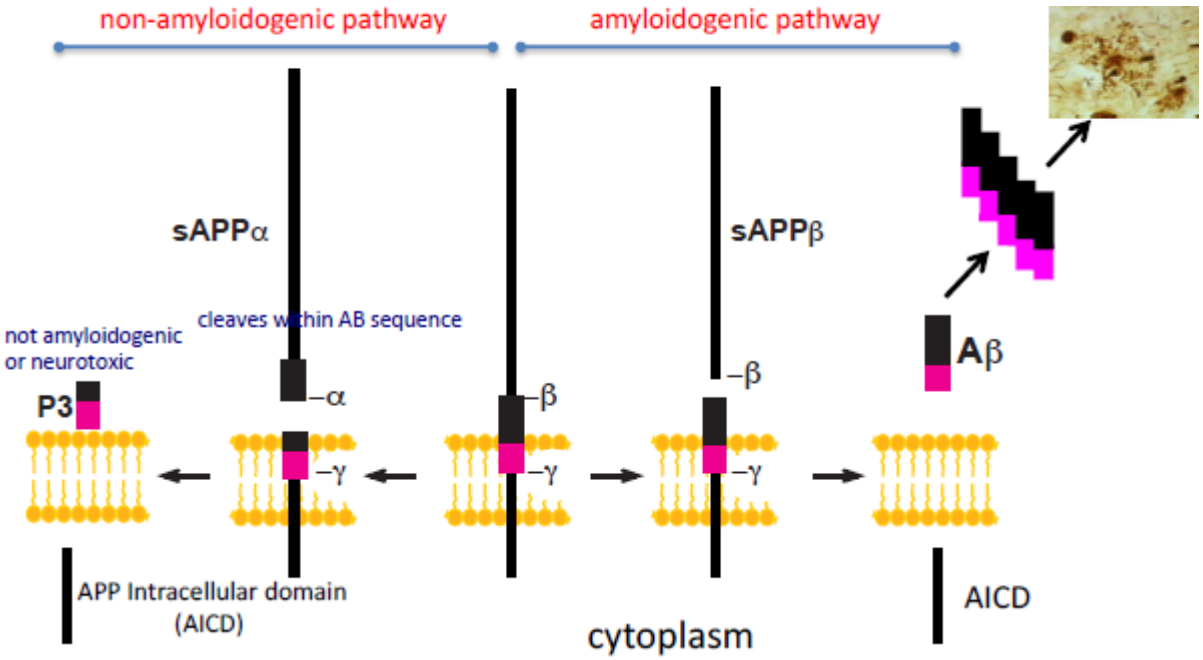
- 90% sporadic: >65
  10% familial: early onset, rare but high risk
- twin studies show heritability of AD is 60% > thus AD is genetic + non-genetic
- **risk factors**: ageing, women, hypertension + CVD, head injury, lower education, genetics (apoE 4 allele increases risk, KO mice protected from AB deposition; Down syndrome- 3 copies of APP)
- **pathology**
  - loss of synapses/neurons (cell body) > atrophy of cerebral cortex and hippocampus, enlarged ventricles
  - protein aggregates:
    - NFT- intracellular, hyperphosphorylated tau
    - amyloid plaque- extracellular, AB peptide

- **cholinergic pathway**
    - loss of cholinergic function, damage to cholinergic neurons in the hippocampus, frontal cortex, amygdala, nucleus basilis, medial septum
    - cholinergic pathways project to thalamus > role in conscious awareness, attention, working memory
    - downregulation of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) is assoc w onset of cognitive impairment
    - major alterations in cholinergic system: choline uptake, impaired ACh release, downregulation of nicotinic and muscarinic receptors, dysfunctional neurotrophin support, deficits in axonal transport
    - AB peptide interacts w cholinergic receptors and affects their function
    - symptomatic treatment- AChE inhibitors to increase ACh, doesn't treat pathology
- **protein aggregation**



Amyloid beta peptide

- **APP > AB42 and AB40 > amyloid plaque- amyloidogenic pathway**
    - APP is cleaved first by β-secretase, which releases sAPPβ
    - then ɣ-secretase cleaves, which releases AB and APP intracellular domain
    - (cleavage by α-secretase is non-amyloidogenic)
- **familial AD mutations increase the AB42:AB40 ratio - early onset, dominant**
    - AB40 is more abundant but AB42 is more amyloidogenic and neurotoxic
    - occur near b-secretase sites (increase AB levels), ɣ-secretase (increase AB42), α-secretase (decrease a-secretase activity or affect aggregation)
    - protective mutation near b-secretase- A673T carriers have better cognition scores than non-carriers
    - APP (21), presenilin 1 (14), presenilin 2 (1), duplication of APP
        - APP has a direct causal role in AD
        - presenilin (ɣ-secretase complex) mutations promote increase in AB42 production
- **AB is toxic**- decreases cell viability, decreases LTP and causes synaptotoxicity (loss of spines from neurites)



Tau

- tau is a microtubule binding protein which interacts with tubulin to stabilize microtubules and regulates axonal transport
    - affects transport of motor proteins dynein and kinesin along microtubules
    - can bind to mt and modulate interaction between microtubules and mt
- **tau phosphorylation state determined by balance of kinase-phosphatases**
    - tau phosphorylation decreases with aging
    - increased phosphorylation decreases interaction with microtubules
    - hyperphosphorylated tau and truncated tau detach from microtubules > aggregate into NFT
- **tau mutations**- spread across the protein, can affect phosphorylation and splicing
- **deposition of tau into NFT positive stages 1 to V1**
    - prodromal I-II: transentorhinal
    - early to moderate III-IV: limbic
    - moderate to late V-VI: isocortical
- **rship between AB and tau**
    - sporadic AD starts with intraneuritic pretangle tau in lower brainstem
    - tau pretangles develop into NFT from stage I onwards
    - first plaques occur in the neocortex, after onset of tauopathy in brainstem
    - thus tau pathology (increased phospho-tau immunoreactivity, not NFT) precedes amyloid plaque pathology; this spreads thru the brain and correlates w clinical changes
        - a tauopathy possibly beginning in childhood (tau can aggregate by itself)
        - or exacerbation by AB after a given threshold level of AB is reached (AB accelerates NFT)
    - tau is required for AB mediated toxicity
- **changes in AD biomarkers over time**
    - increase in: AB deposition, CSF tau
    - decrease in: CSF AB (bc retained in brain), hippocampal volume, glucose metabolism (neuronal loss)

Pathological hallmarks of AD

- **oxidative stress**
    - increased production of ROS and RNS by mitochondrial dysfunction
- **metal dyshomeostasis and oxidative stress**- Amyloid plaques have high levels of copper, zinc and iron
    - **Zinc**: increased bulk Zn, but reduced synaptic Zn (bc in plaques > interact badly w receptors) > reduces synaptic function, cognitive decline
        - binds AB and can promote its aggregation into ThT-positive aggregates
        - can promote tau aggregation and phosphorylation