Hallmarks of Alzheimer's disease

Clinical features and diagnosis of Alzheimer's disease

- Progressive, unremitting neurodegenerative disease
- Dementia which leads to difficulty with daily life activities
- Affects 1 – 3 % of overall population
- Overall prevalence 10 – 30 % in the elderly (>65y)

- Early, prodromal phase with mild cognitive deficits
- Moderate, progressive memory impairment
- Severe, late stage requiring continuous assistance

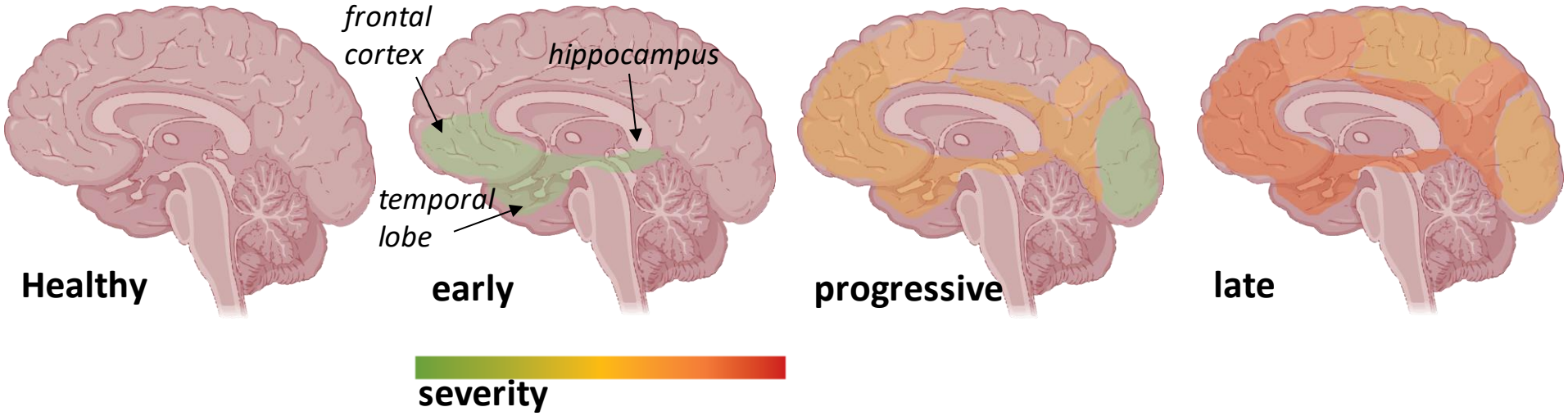
- <1% of persons affected have an autosomal dominant form
- 99% have sporadic, often genetically-linked disease

Early onset: ***APP*, *PSEN1*, *PSEN2***

Sporadic: ***APOE4, TREM2, ABCA7, CLU, CR1, PICALM, PLD3, SORL1, PSMC5, ADAM10, ADAMTS1, WWOX, CD55, HLA-DPA1, …***

Neurological examination, genetic testing, biomarkers in CSF, brain imaging

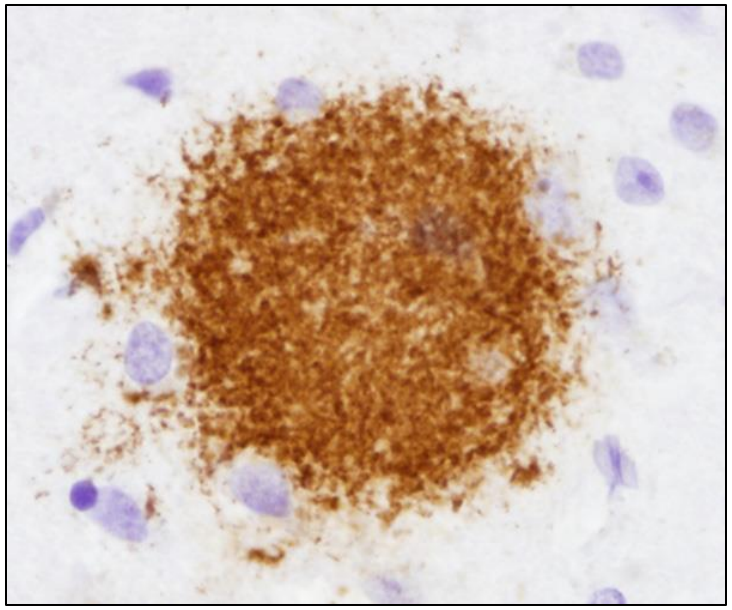
Adapted from Masters, C. L. et al. Nat. Rev. Dis. Prim. 2015



Imaging diagnostics:

- FDG-PET
- Aβ and tau PET
- structural MRI

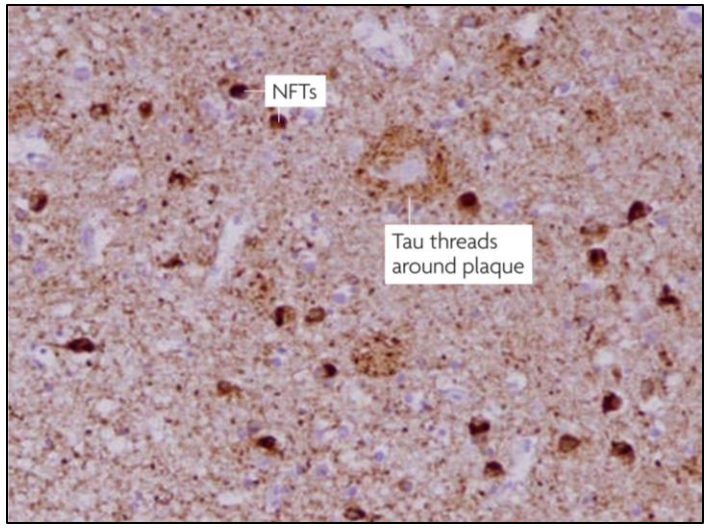
Histopathological observations in Alzheimer's disease



Advanced stage senile plaque

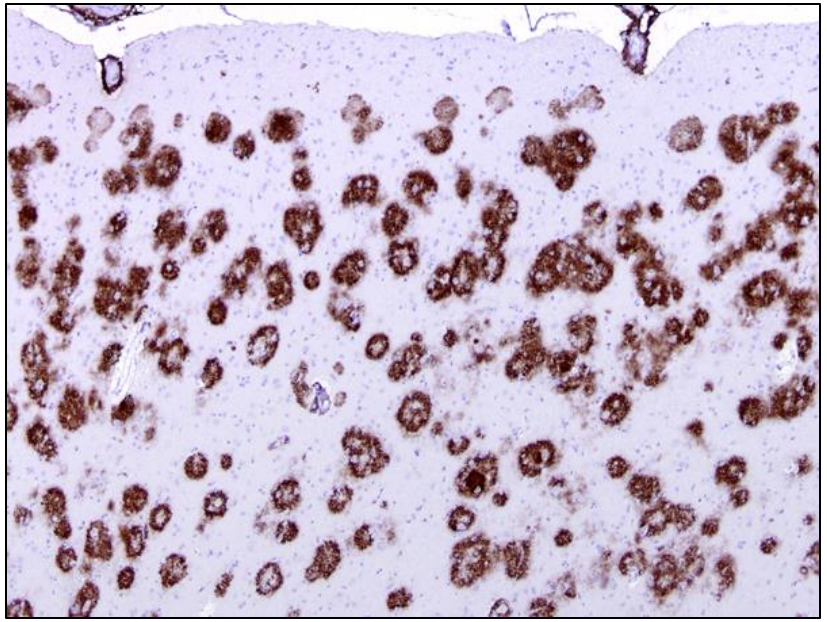
- **Deposits of Aβ fibrils**
- **Coalesce into amyloid plaques**

Brunden, K., Trojanowski, J. & Lee, Nat Rev Drug Discov 2009



Neurofibrillary tangles

- **Inclusions of microtubule-associated protein tau**
- **Tau aggregation initiated by misfolded Aβ deposits**
- **Tau fibrils deposit along neurons, causing neurotoxic inclusions**



Widespread plaque deposits

- **Amyloid plaques deposit throughout brain cortex**
- **Up to 100micron in diameter**

Biomarkers of Alzheimer's disease

Time progression

- **Genetic testing for familial mutations and single nucleotide polymorphisms (SNPs)**

- **Aβ detected in cerebrospinal fluid (CSF)**
- **Aβ positron emission tomography (PET)**
- **Tau detected in CSF**

} ***Precede clinical symptoms***

- **Brain hypometabolism detected by fluorodeoxyglucose (FDG) PET**
- **Brain atrophy detected by magnetic resonance imaging (MRI)**

} ***Often precede clinical symptoms***

- **Detection of mild cognitive deficits (MCI)**
- **Full-blown dementia**

<u>Blood and plasma</u>

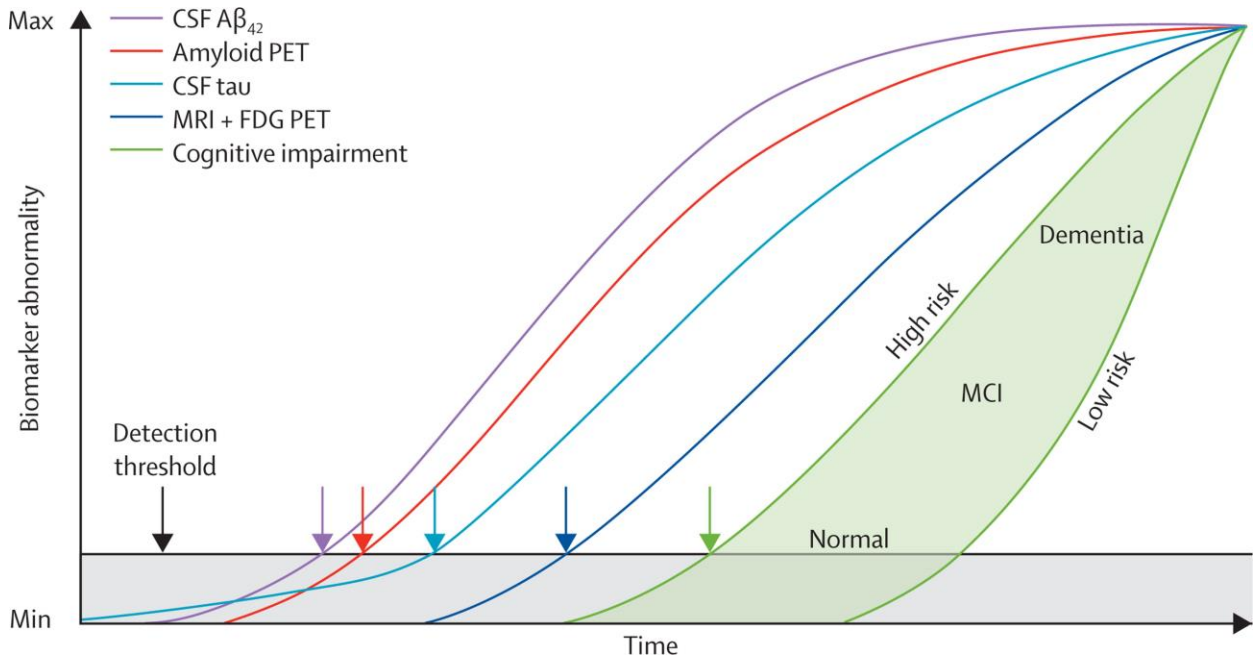
- **Aβ**
- **Tau**
- **Metabolites?**

} ***Variably reliable***
May precede symptoms
Experimental

<u>Post-mortem histology</u>

- **Brain atrophy, Aβ, senile plaques, tangles,…**

Jack C., Knopman D. et.al The Lancet Neurol. 2013

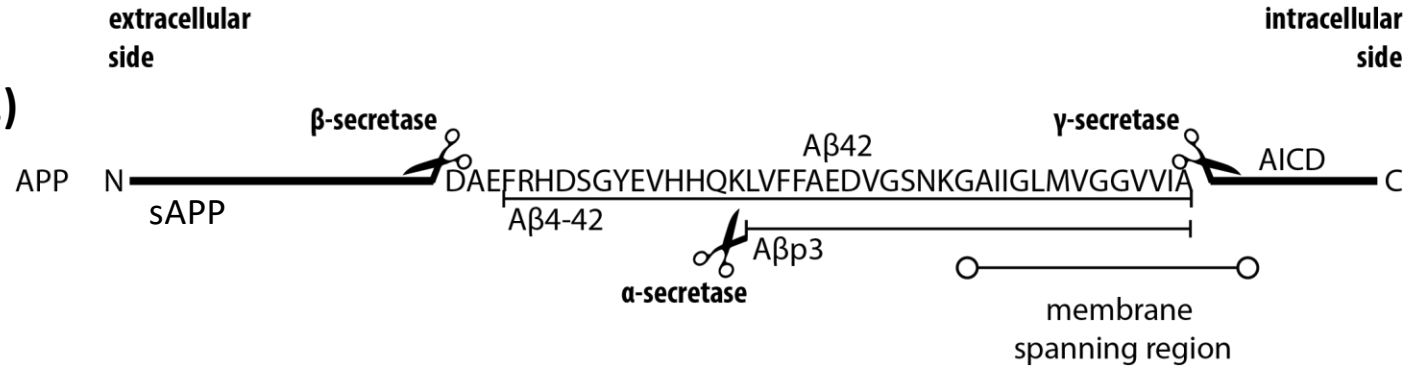


Amyloid hypothesis – APP biochemistry

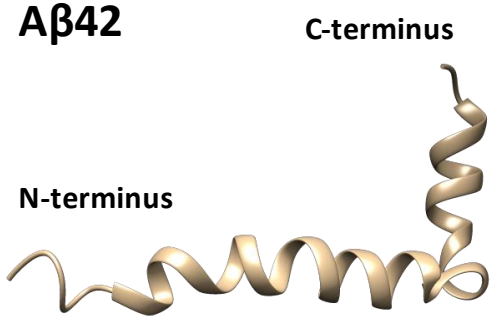
- Three enzymes can cleave APP
  - α-secretase (ADAM10, ADAM17,…)
  - β-secretase (BACE1)
  - γ-secretase (PSEN1, PSEN2, PEN2,…)
- Give rise to AICD, sAPP, and Aβ

- Aβ42 is alpha helical
- Aβ fibrils form as aggregated beta-pleated sheets

APP: Amyloid precursor protein
Aβ: Amyloid beta
sAPP: soluble APP
AICD: APP intracellular domain

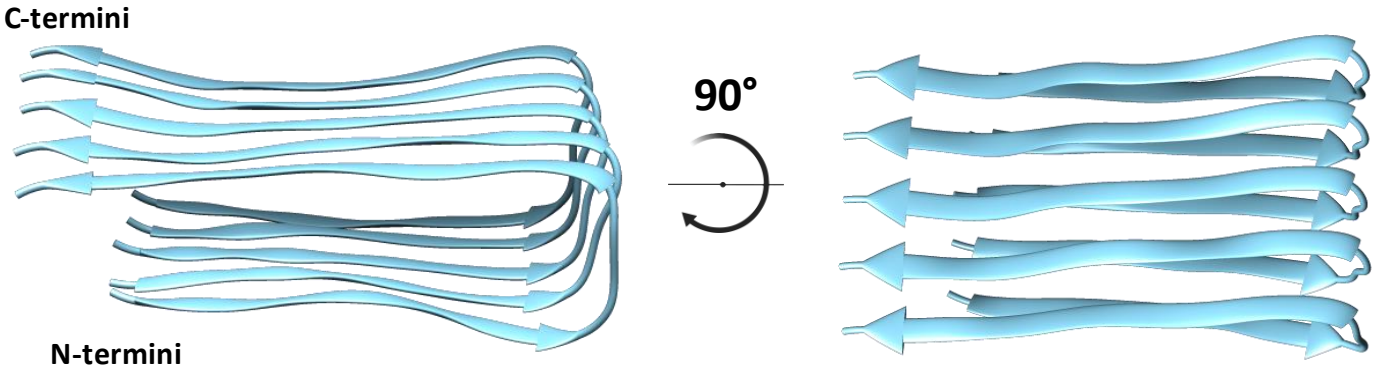


Aβ42

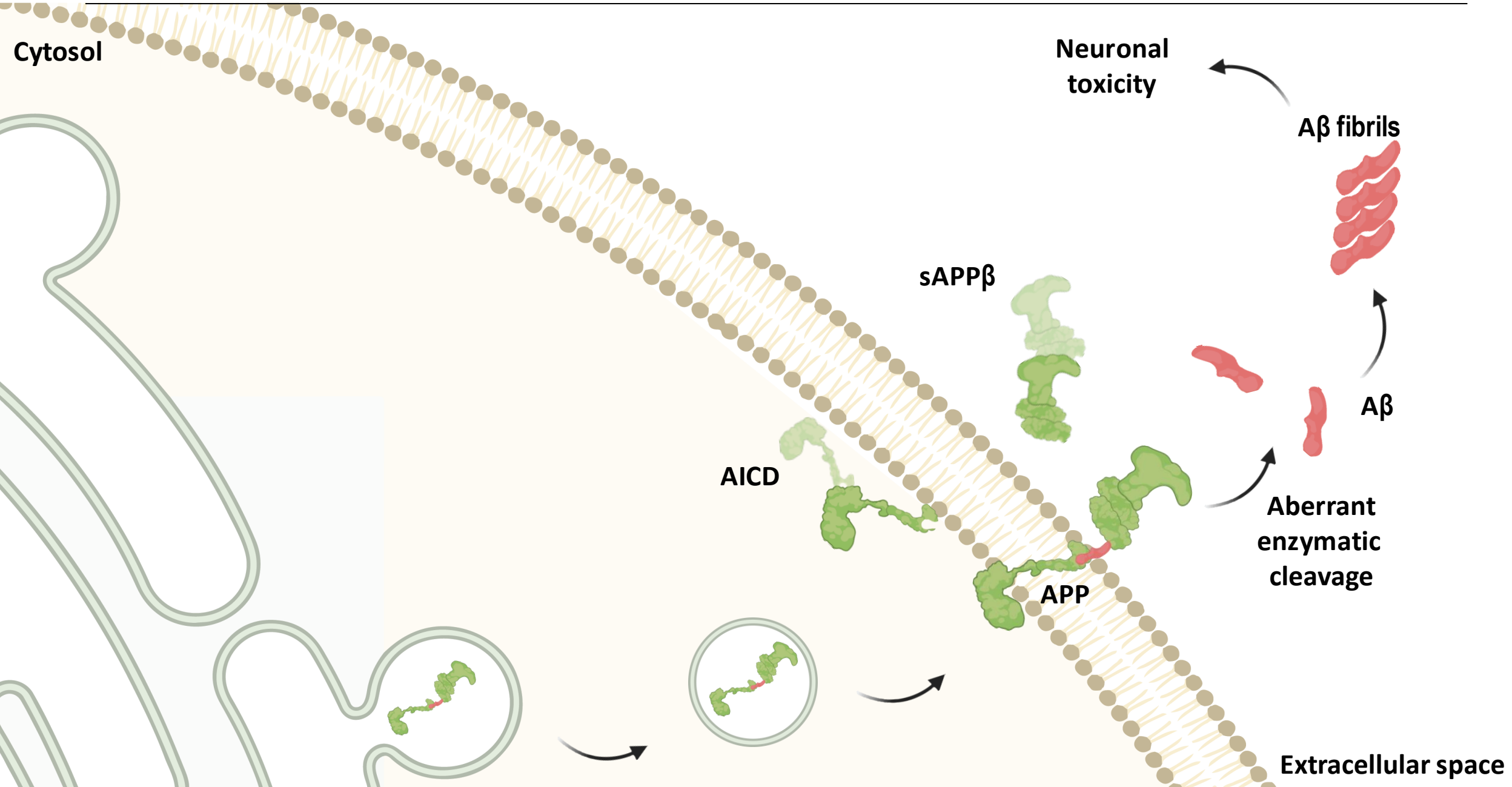


spontaneously

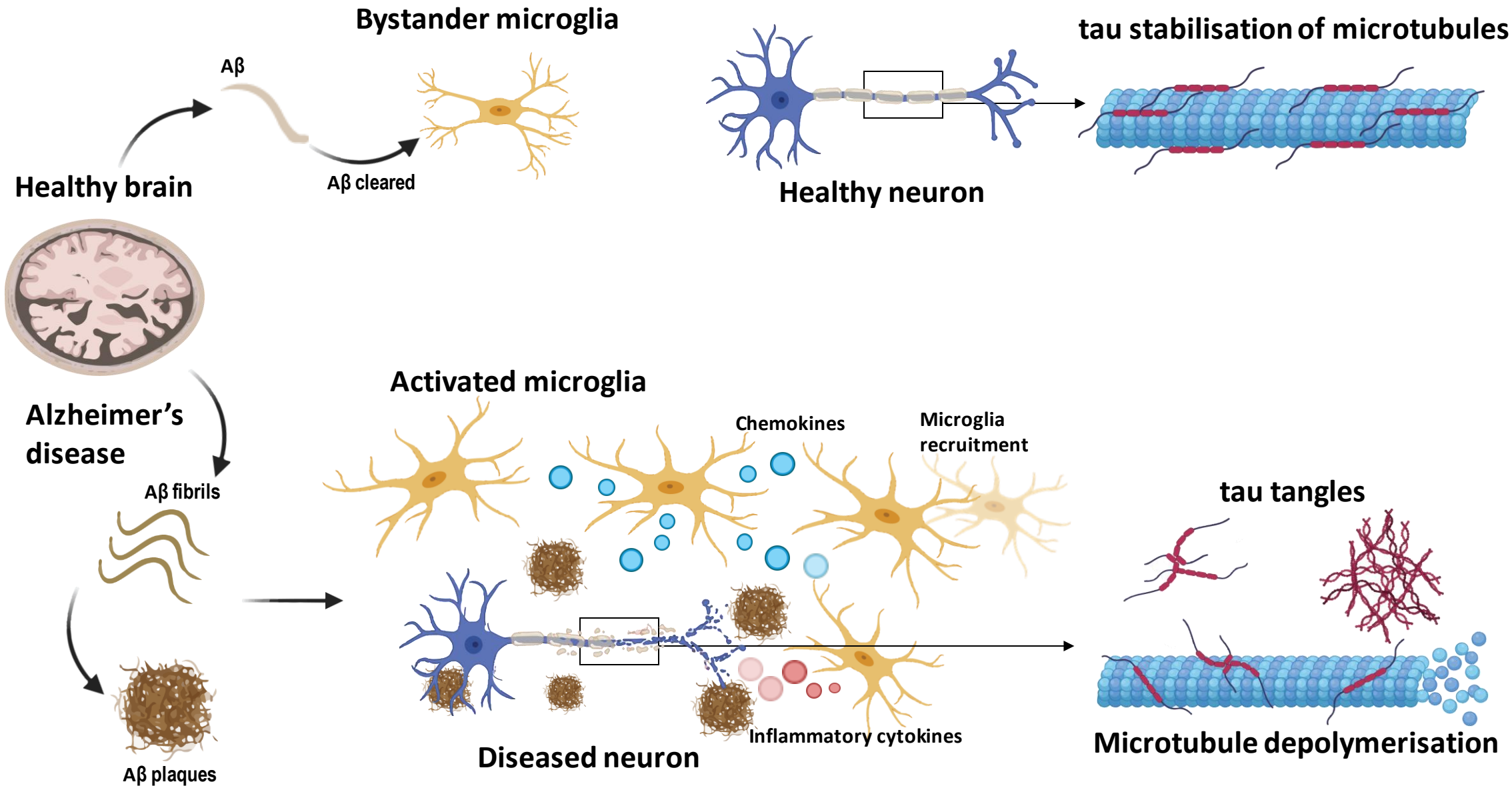
Aβ fibrils



Amyloid hypothesis – cellular pathway



Amyloid hypothesis – pathogenic mechanisms

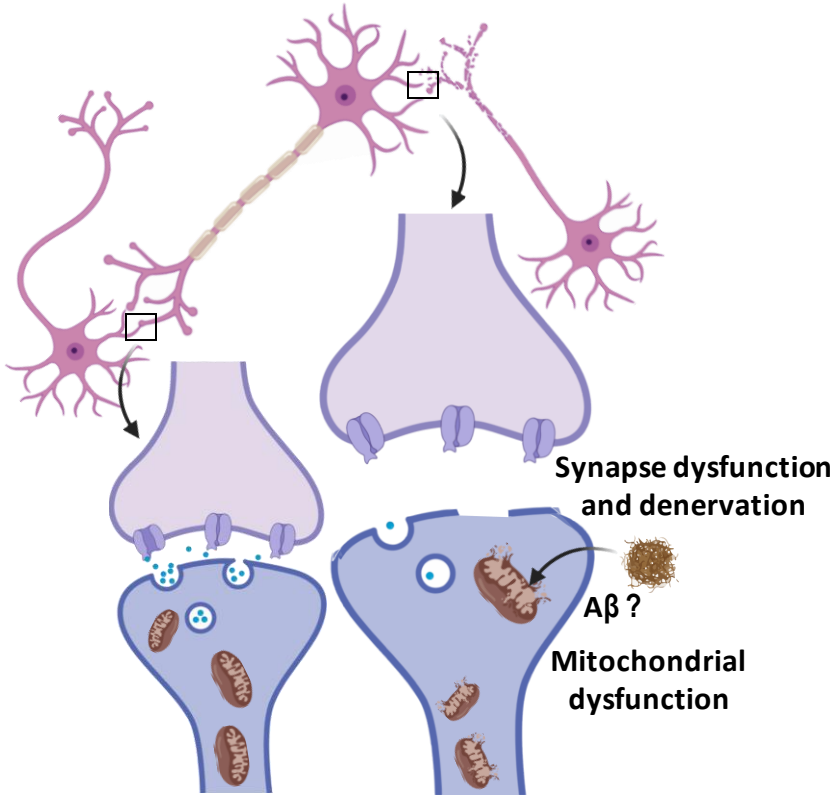


Beyond the amyloid hypothesis

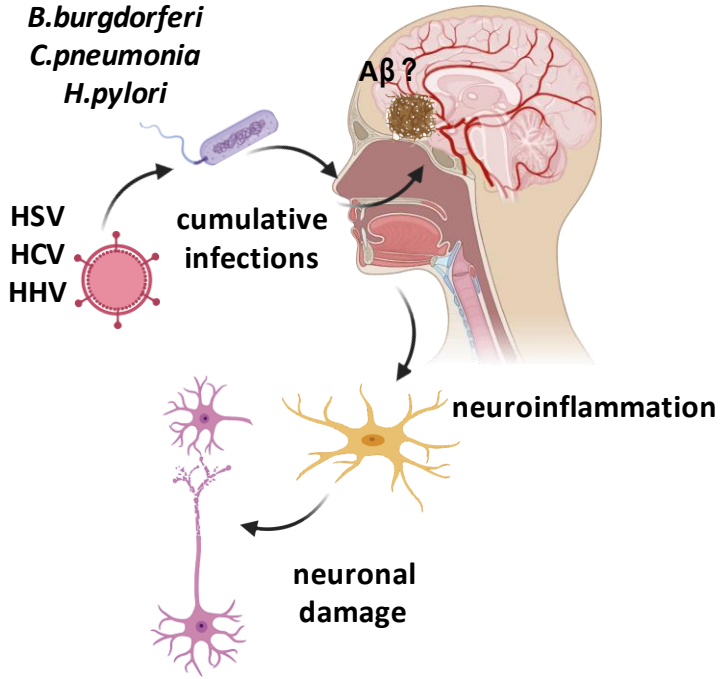
- Role of Amyloid deposition undisputable as key factor in familial AD
- Yet almost 30 years of unsuccessful attempts to target Amyloid and its processing

- Either damage is irreversible by time of cognitive decline
- OR other factors implicated

Mitochondria dynamics and aging



Infectious organisms



Metabolic defects

γ-secretase involvement

Systemic inflammation

…

Literature referenced and further reading

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