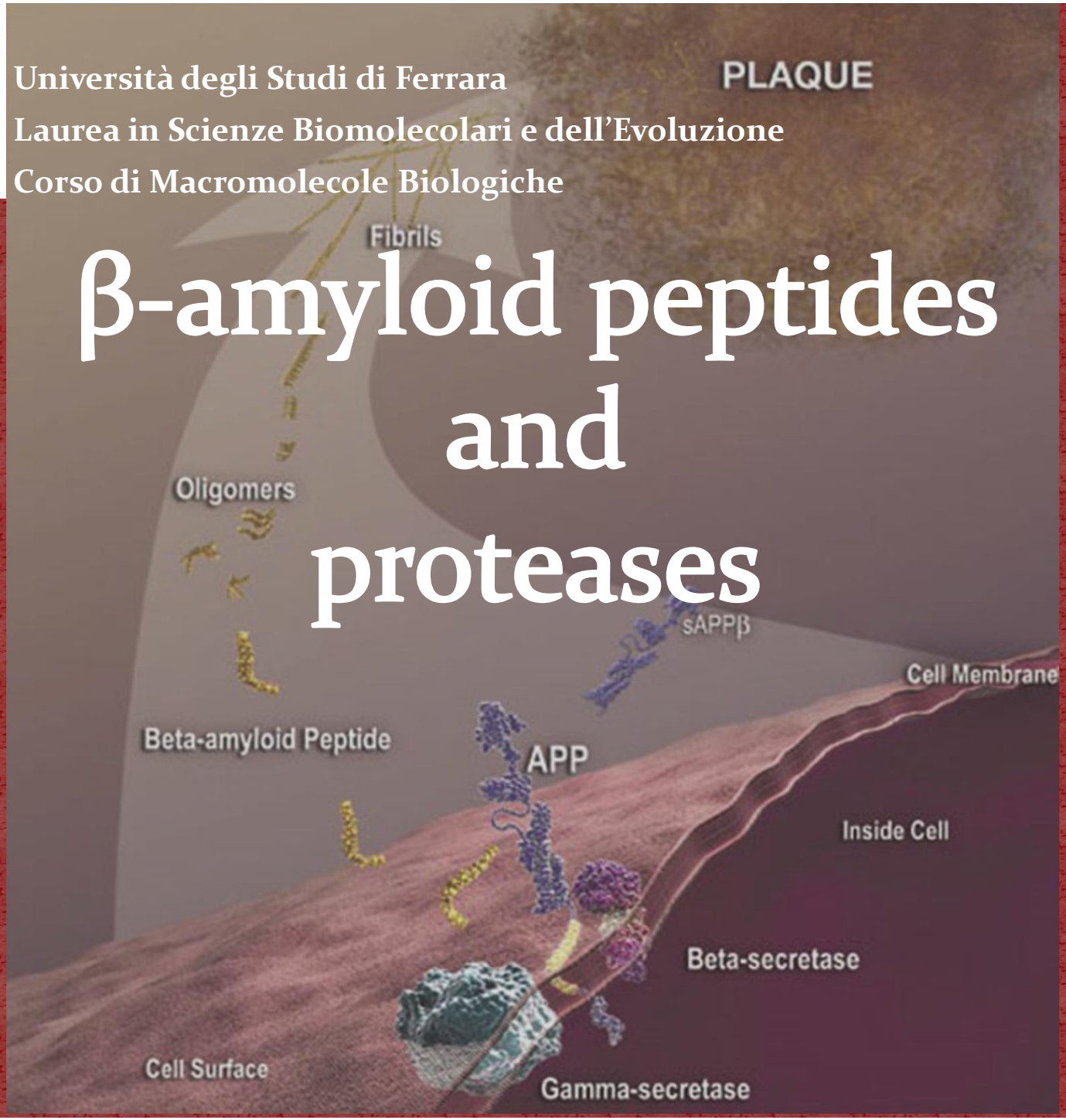
Università degli Studi di Ferrara

Laurea in Scienze Biomolecolari e dell'Evoluzione

Corso di Macromolecole Biologiche

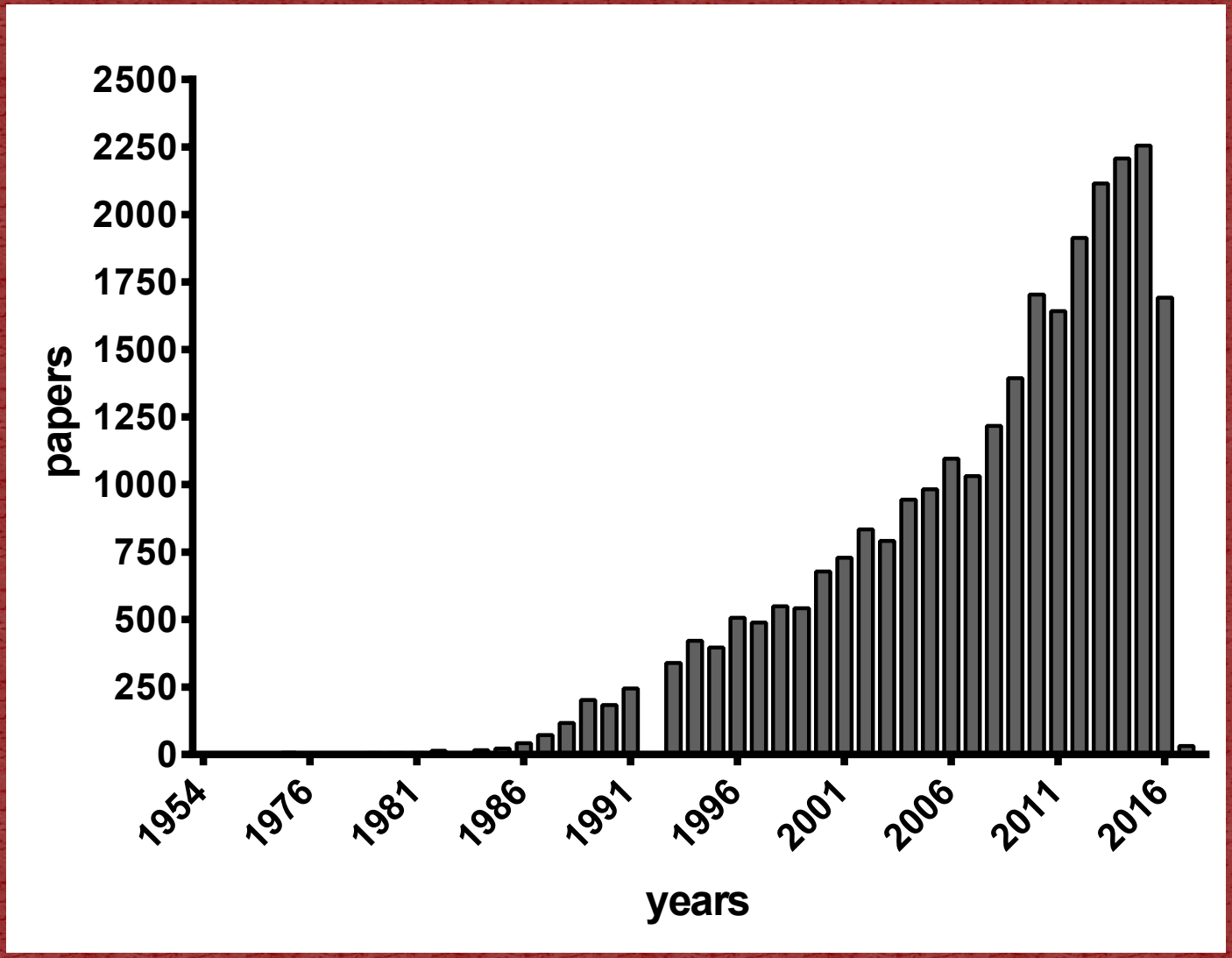
β-amyloid peptides and proteases



Nicole Ziliotto

04/04/2017

Articles about "Alzheimer amyloid" over the years



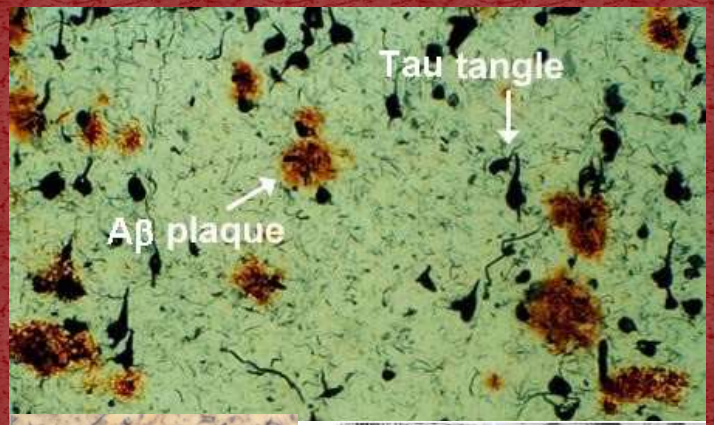
Problem statement

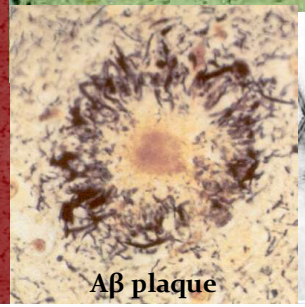
- 46.8 million people living with dementia in 2015 , this number is projected to reach 131.5 million by 2050.
- One new case of dementia every 3 seconds
- 1 in 10 people over age 65 and nearly half of people over 85 have Alzheimer's disease (AD).
- AD is the most common form of dementia with 60 to 80% of cases.
- Curative therapies are absent.

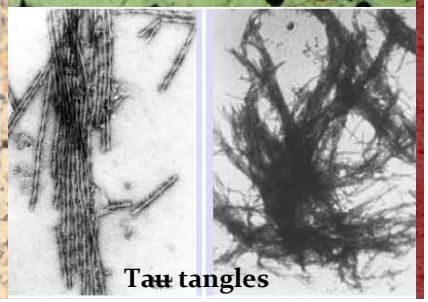
World Alzheimer Report 2016
2016 Alzheimer's Disease facts and figures

Abundance of two abnormal structures in the brains of people with AD:

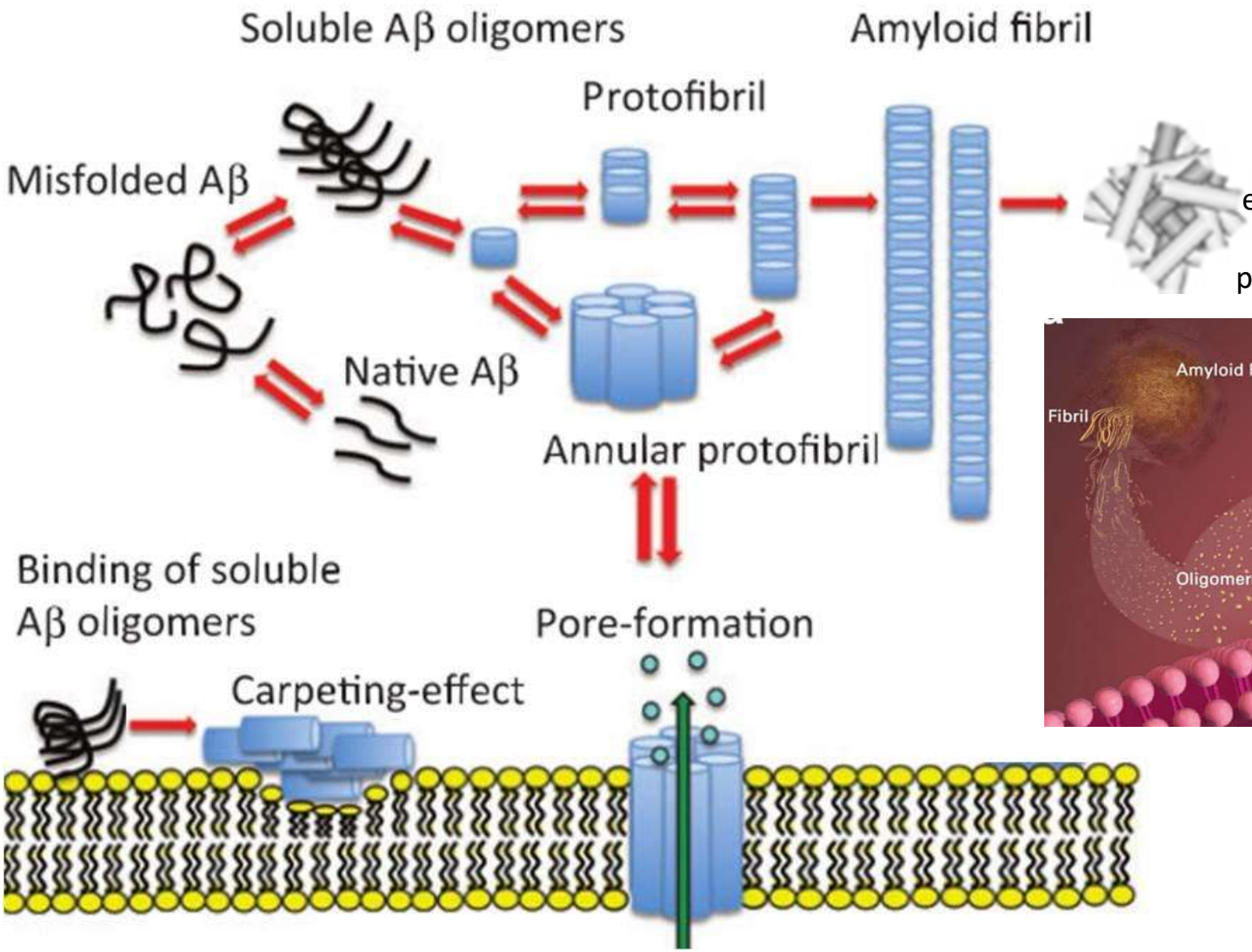
- Amyloid-β (Aβ) plaques, which are dense deposits of protein and cellular material that accumulate outside and around nerve cells
- Neurofibrillary TAU tangles, which are twisted fibers that build up inside the nerve cell




Aβ plaque

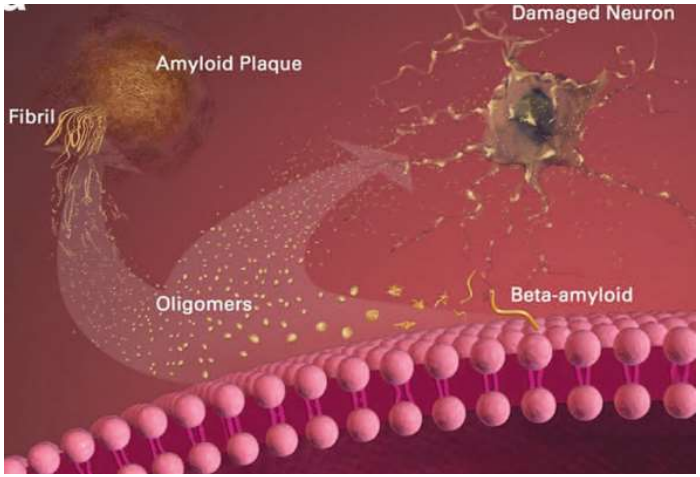

Tau tangles

β-amyloid self-aggregating structure



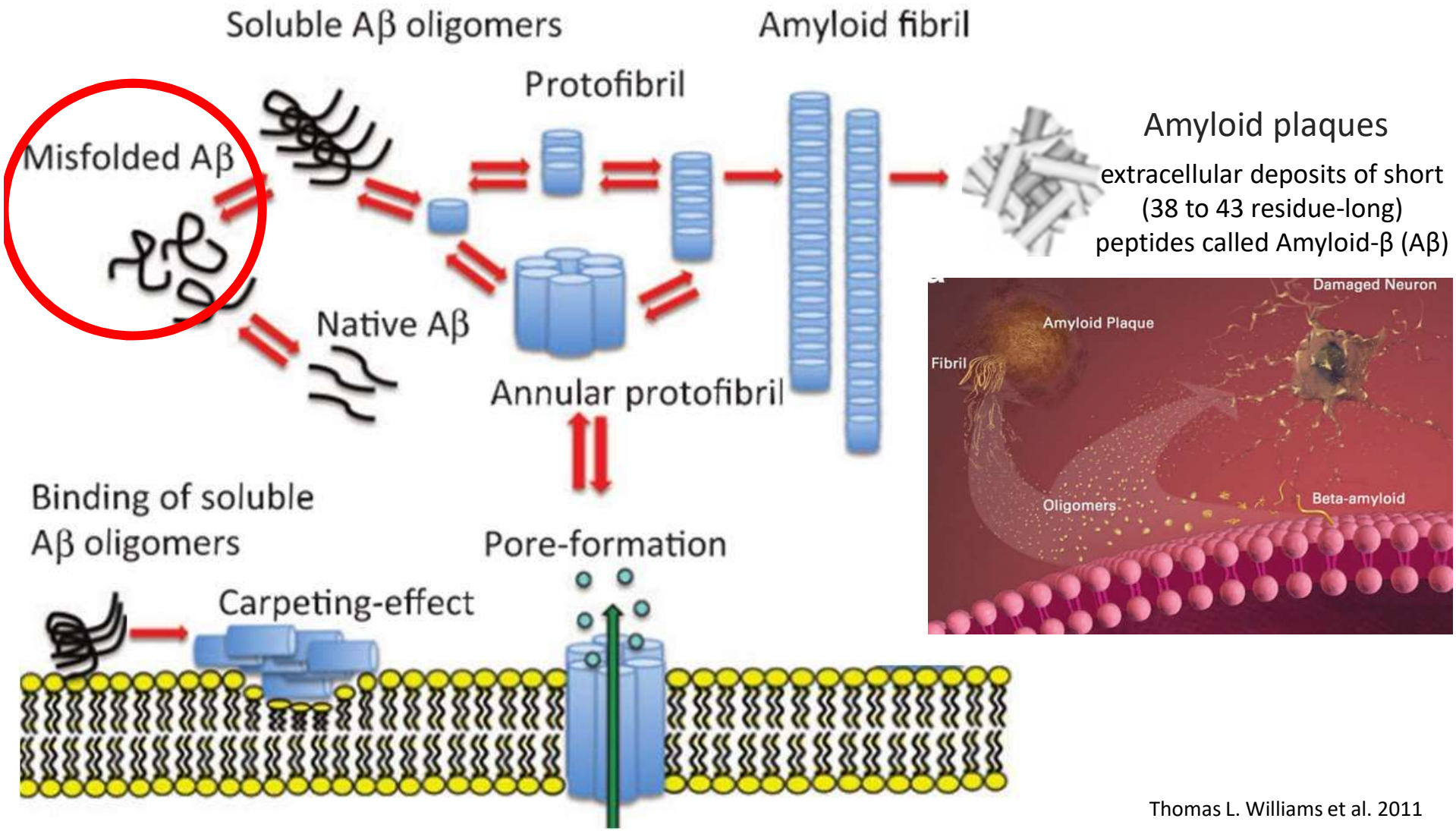
Amyloid plaques

extracellular deposits of short (38 to 43 residue-long) peptides called Amyloid-β (Aβ)



Thomas L. Williams et al. 2011

β-amyloid self-aggregating structure



Amyloid plaques

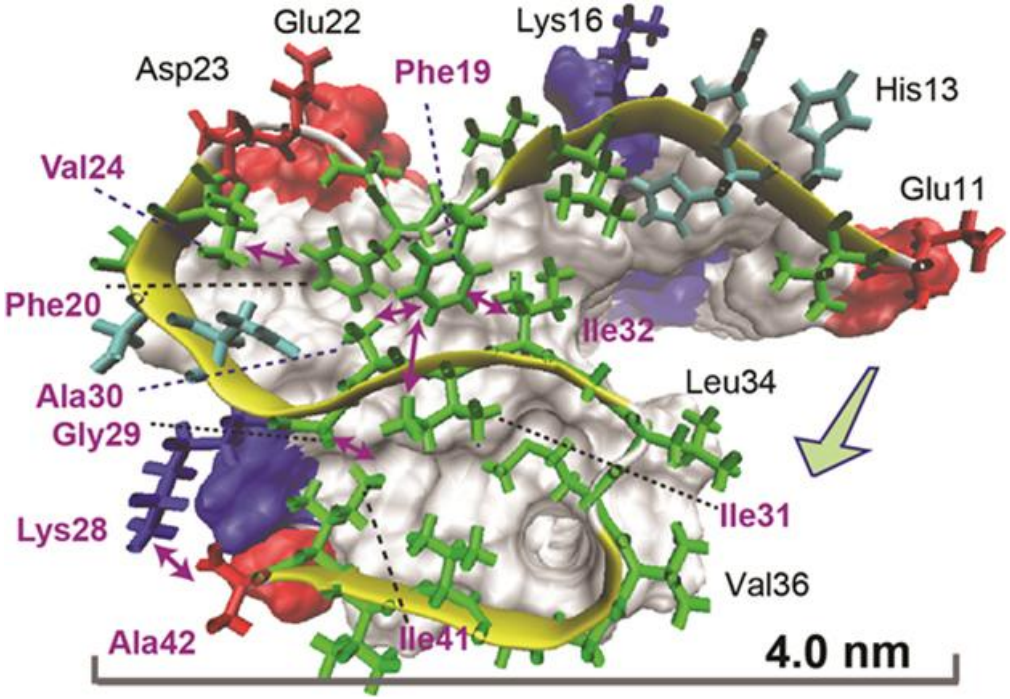
extracellular deposits of short (38 to 43 residue-long) peptides called Amyloid-β (Aβ)

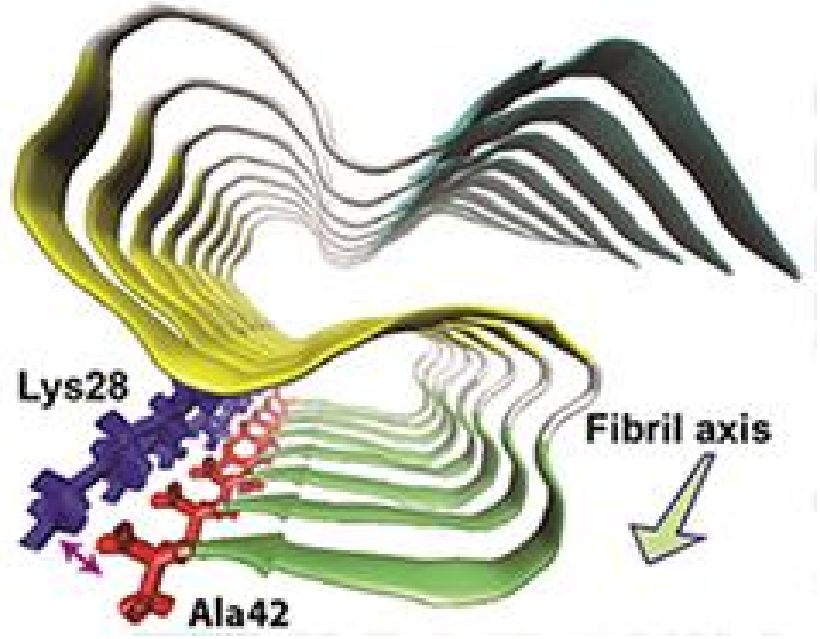
Thomas L. Williams et al. 2011

Atomic structure model of Aβ(1–42) fibrils

Aβ1-42 aggregates at a faster rate than Aβ1–40 due to its highly hydrophobic isoleucine and alanine at C-terminus

4 KDa





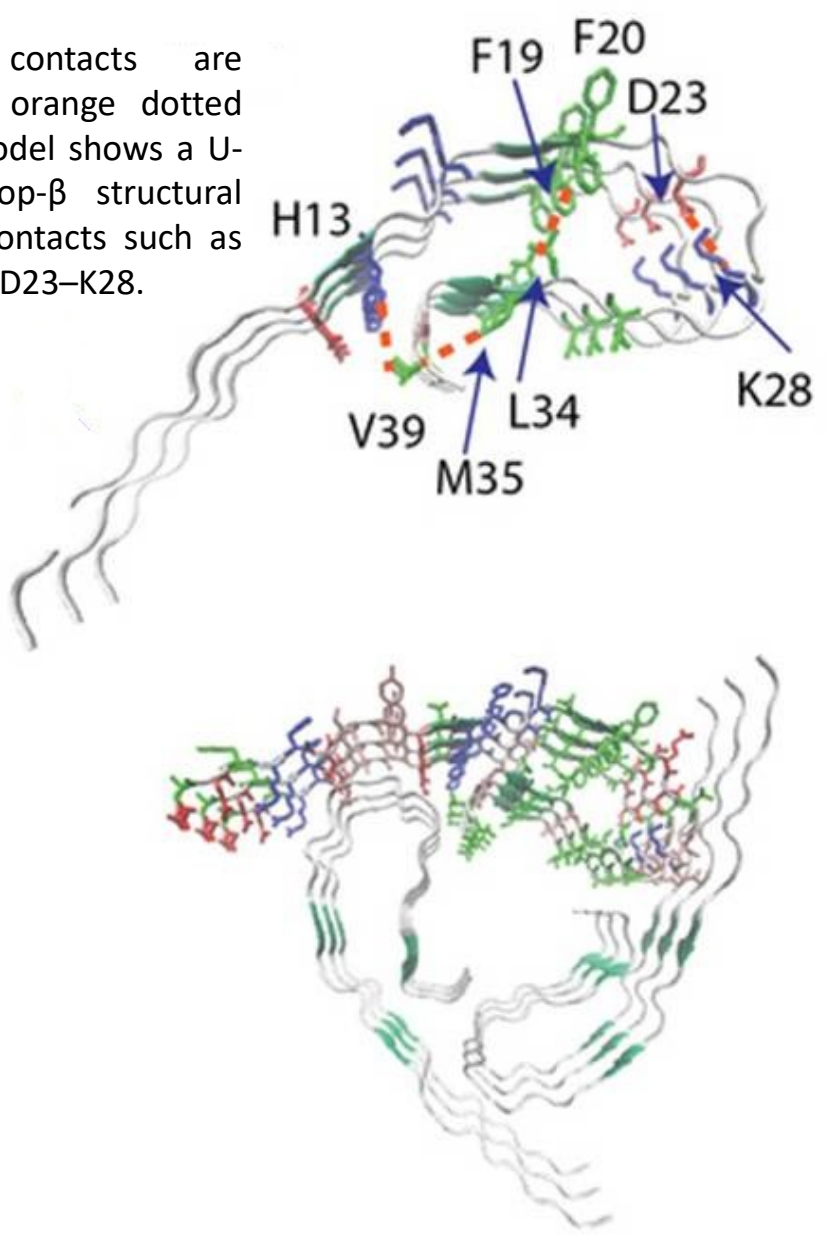
An atomic view of an Aβ42 molecule within a fiber reveals intramolecular connections (double-headed purple arrows) between residues in different parts of the S-shaped structure. Residues are colored as green, hydrophobic; cyan, polar; red, acidic; and blue, basic.

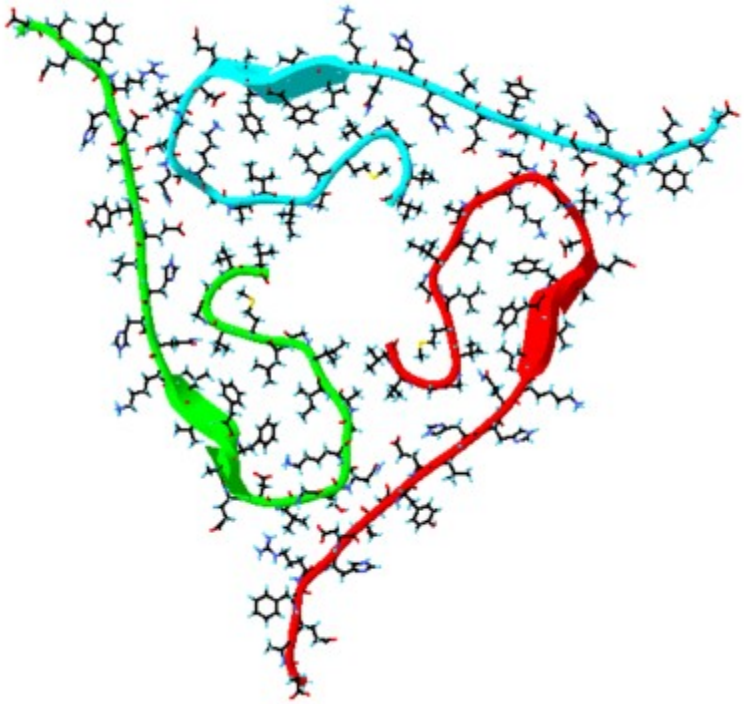
Three β-strand regions (cyan, residues 12–18; yellow, 24–33; green, 36–40) connected by two short coil or turn (white) regions. A salt bridge between Ala42 and Lys28 stabilizes the structure.

Xiao Y. Et al. 2015

Atomic structure model of Aβ(1–40) fibrils

Side-chain contacts are denoted by orange dotted lines. The model shows a U-shaped β-loop-β structural motif with contacts such as F19–L34 and D23–K28.





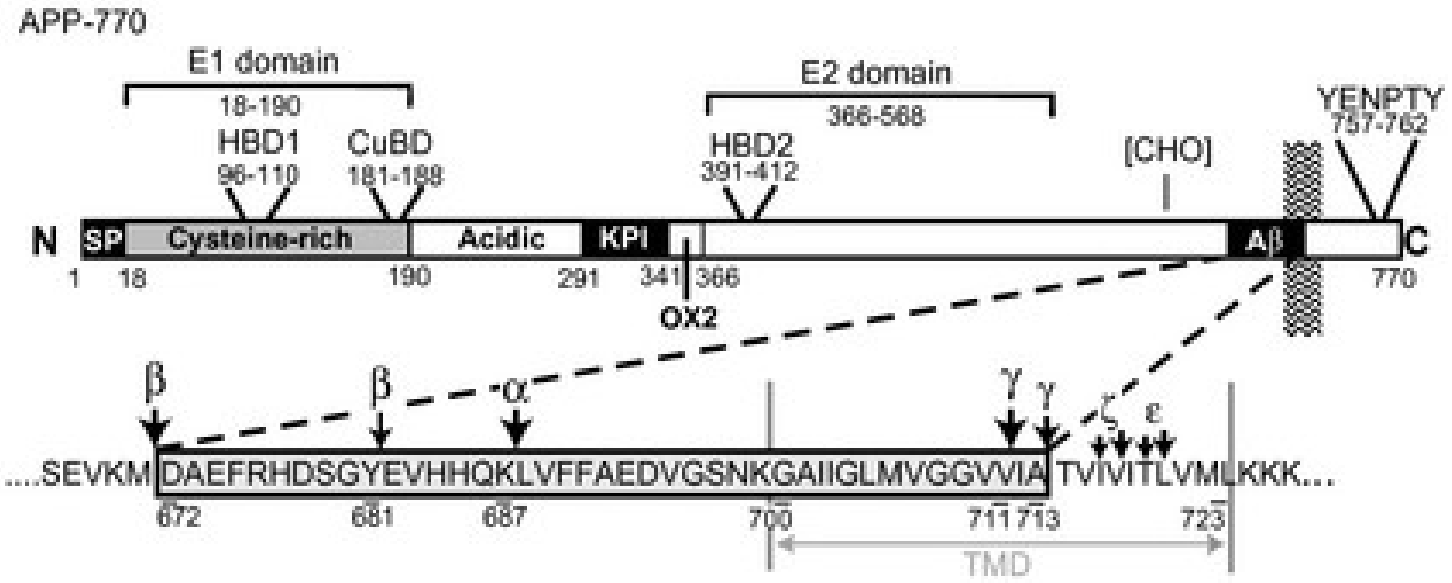
Aβ40 peptide monomers tend to aggregate in oligomers multiple of three units (trimers, hexamers, nonamers and dodecamers), where the N-termini are exposed to the solvent, while the hydrophobic C-termini, are buried in the trimer core.

Xiao Y. Et al. 2015
Montoliu-Gaya L et al. 2015

Amyloid Protein Precursor (APP)

Protein Function:

- Cellular proliferation and differentiation
- Neurite outgrowth
- Synaptogenesis
- Synaptic plasticity
- Inibition blood coagulation
- Signal transduction
- Gene regulation
- Trafficking



HBD: Heparin-binding domain
KPI: Kunitz protease inhibitor
CHO: Copper-binding domain

110-135 KDa

Dawkins E. et al. 2014

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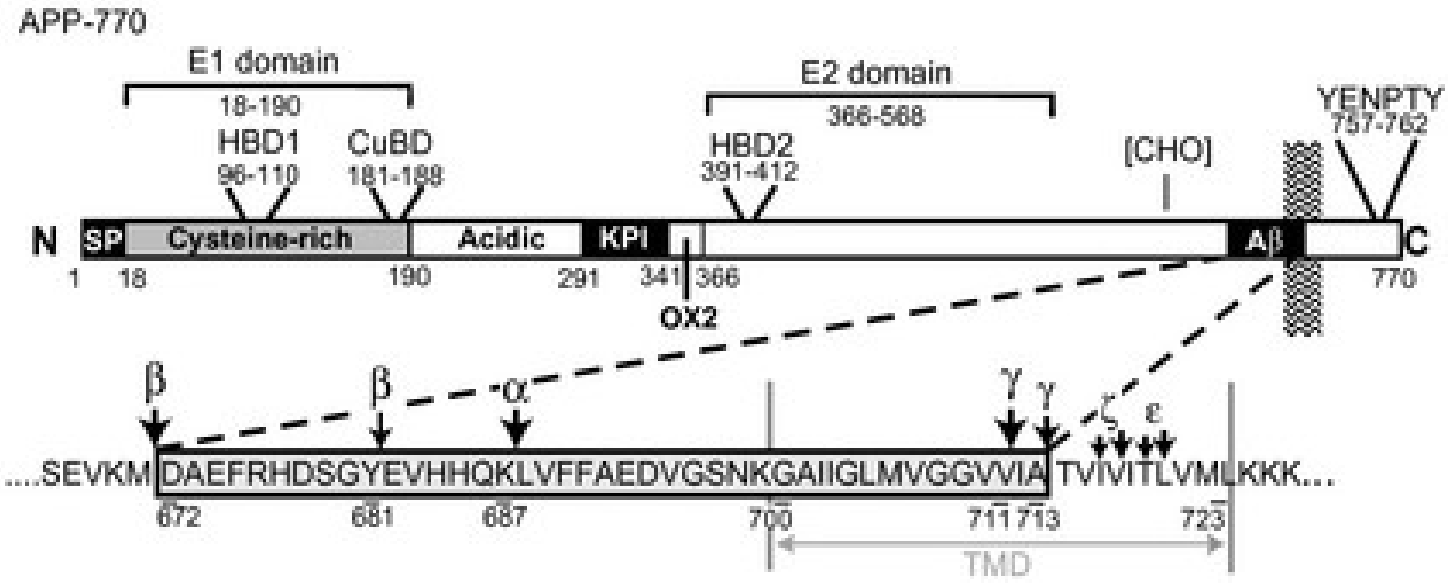

mutations in APP increase Aβ deposition (e.g. Swedish mutation)

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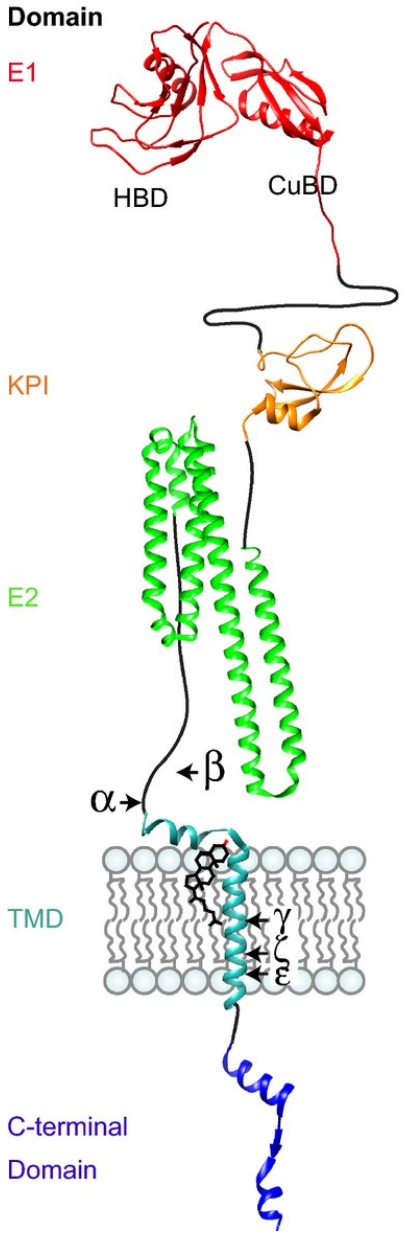
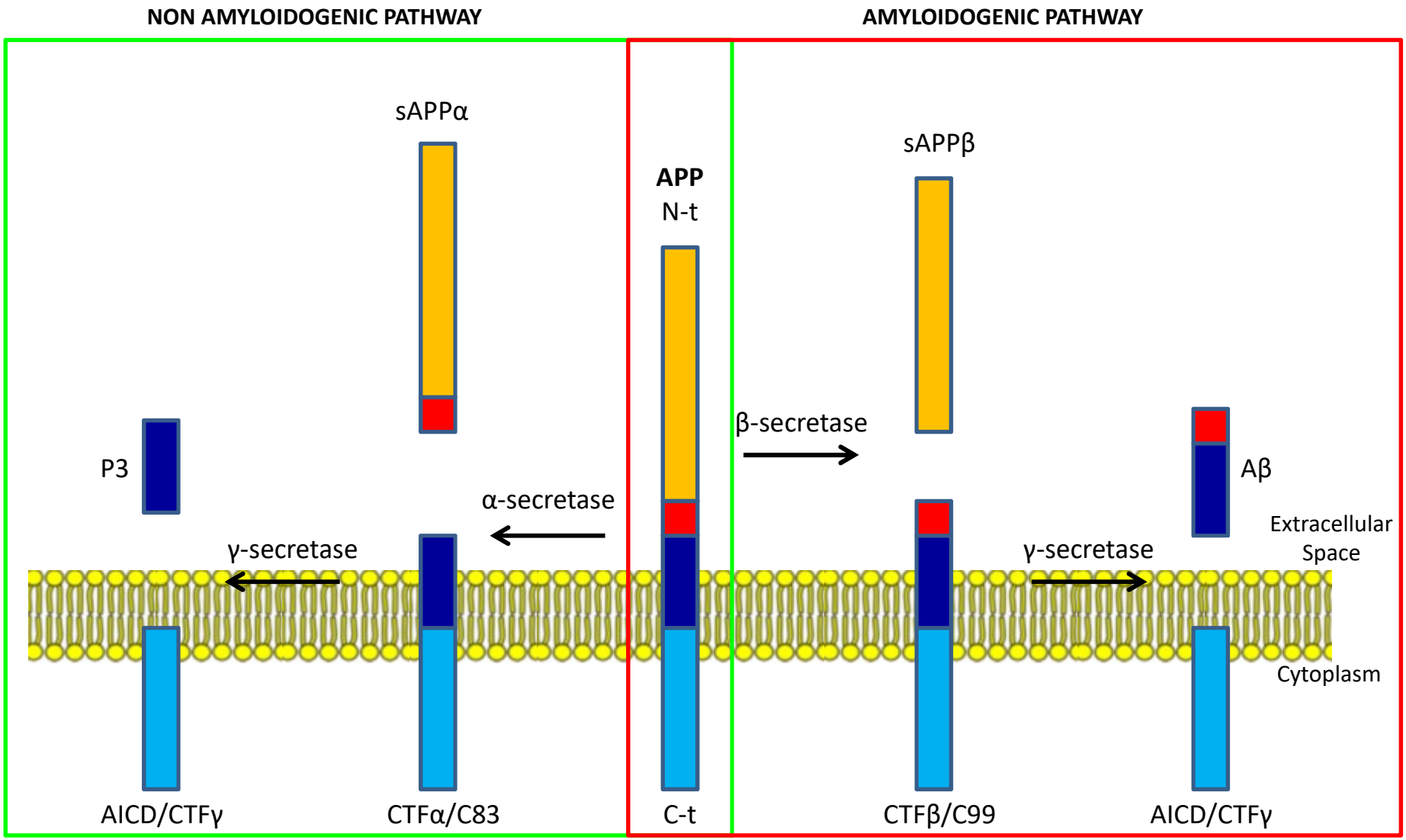


Dawkins E. et al. 2014

Amyloid Plaque Formation

- Amyloid plaques are extracellular deposits of short (38 to 43 residue-long) peptides called amyloid-β (Aβ).
- Aβ peptides derived from amyloid precursor protein (APP).
- APP is a membrane glycoprotein that normally behave in the brain as a cell surface signaling molecule.
- The hydrophobicity, net charge and the sequence propensity to form secondary structures, have been shown to modulate amyloidogenicity. In fact Aβ42 aggregates at a faster rate than Aβ40.
- Neurotoxic Aβ assemblies contain a high level of b-sheet conformation.
- Aβ oligomers are capable of seeding their own replication and may be analogous to different strains of prions.

Amyloid Hypothesis



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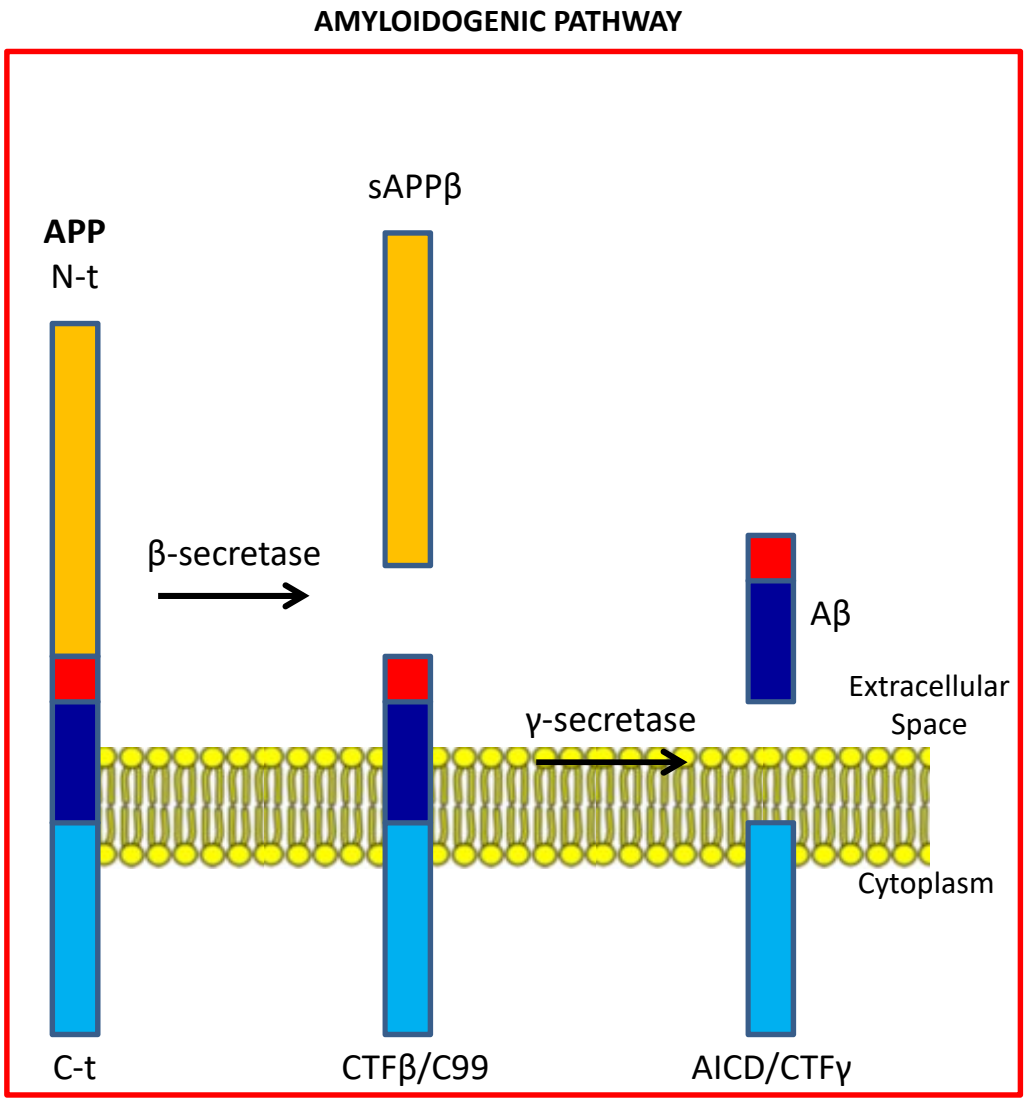

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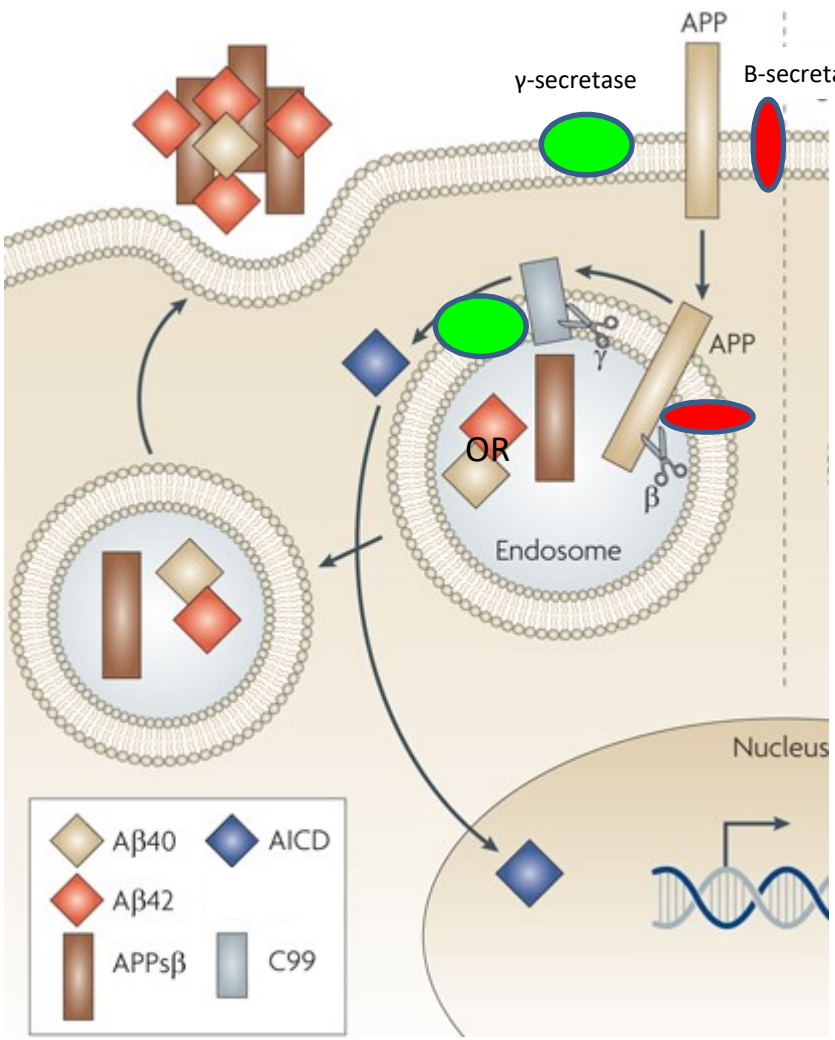

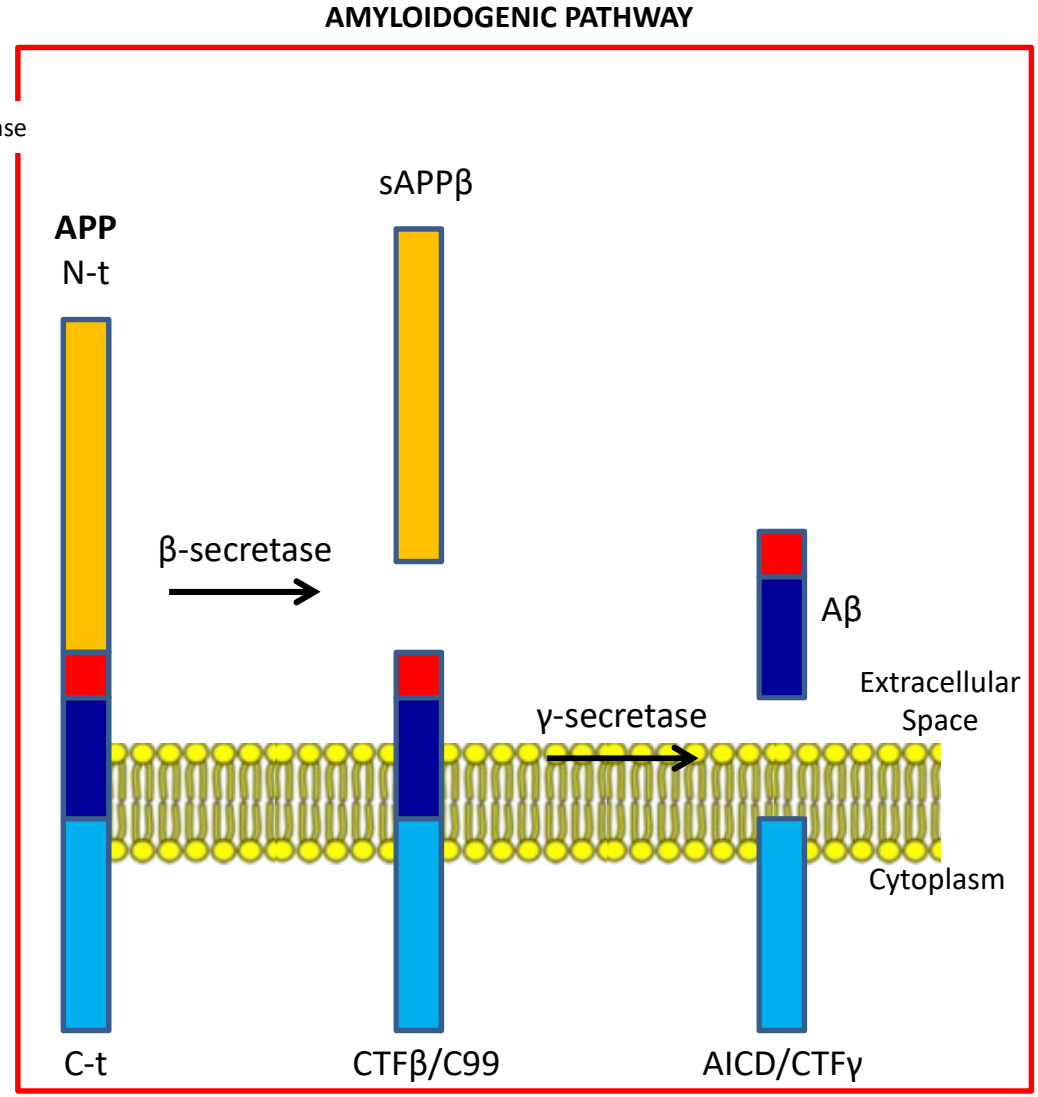

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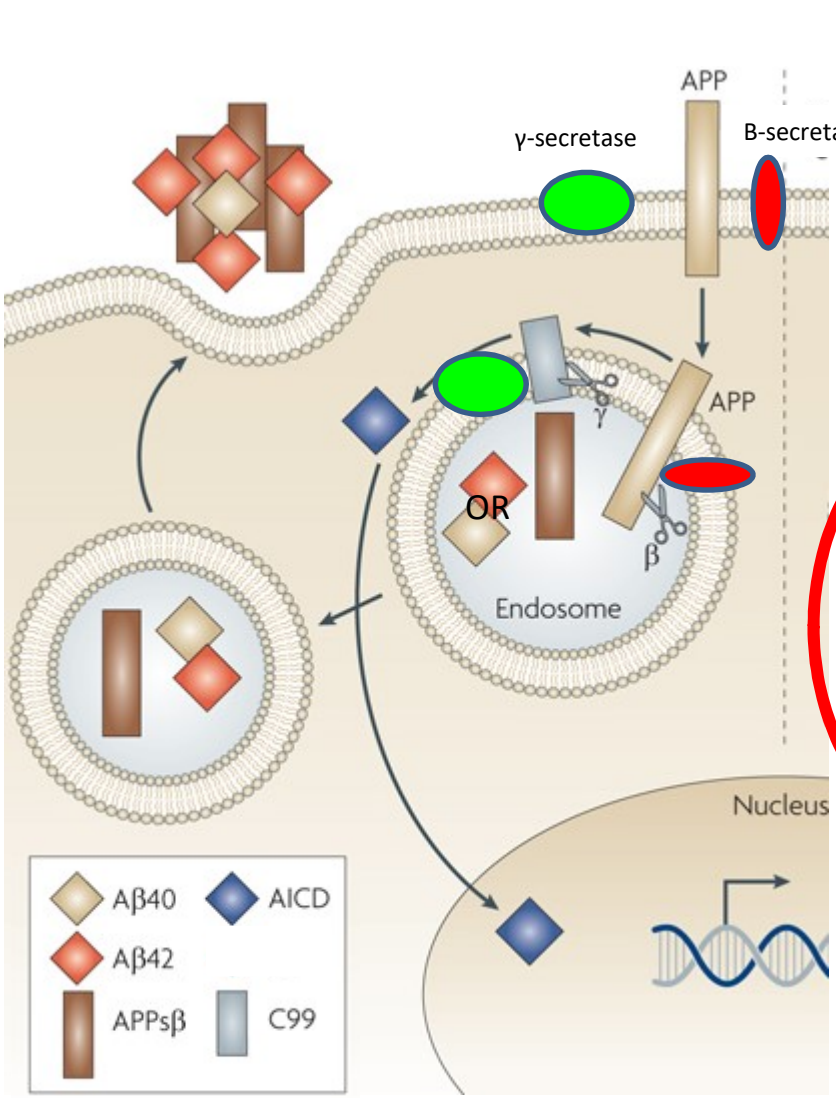
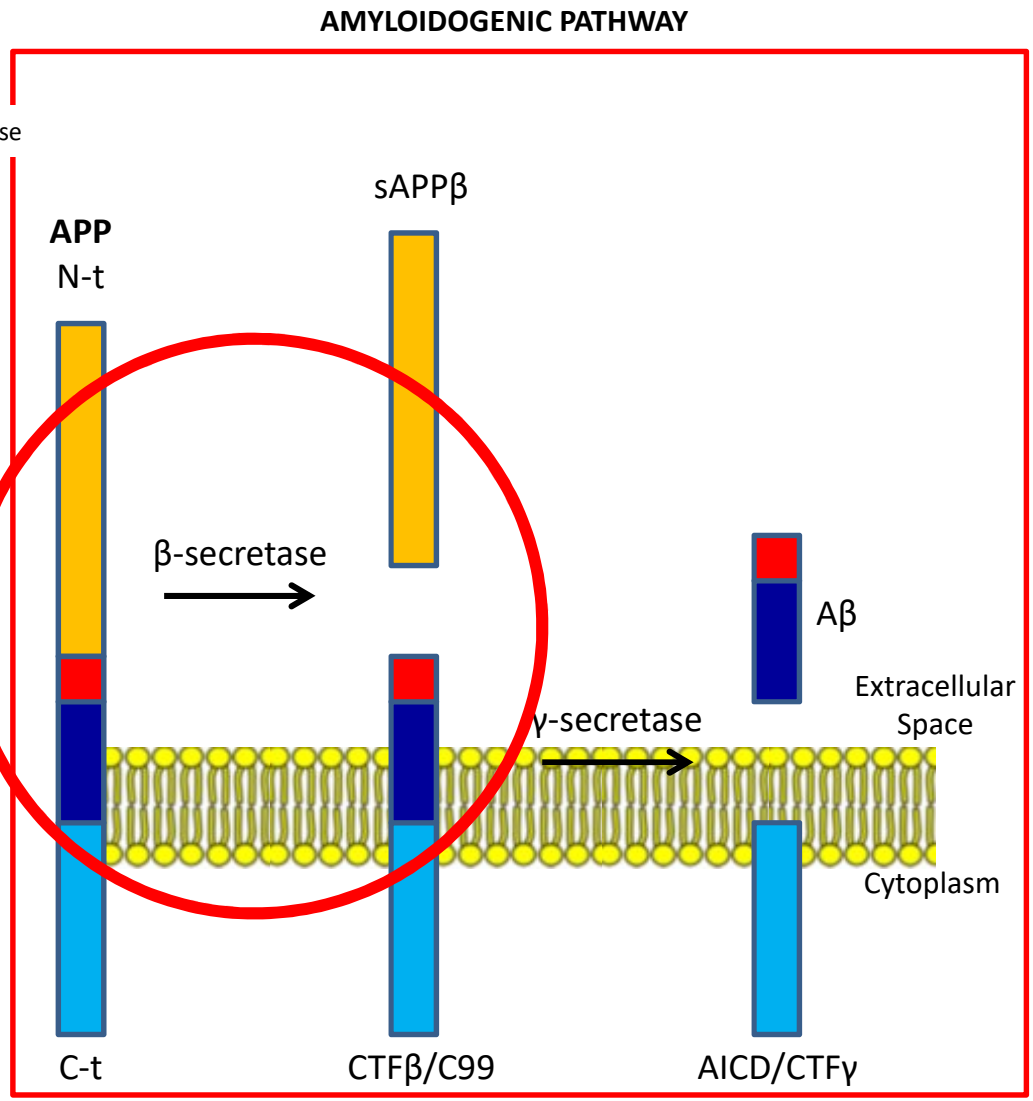
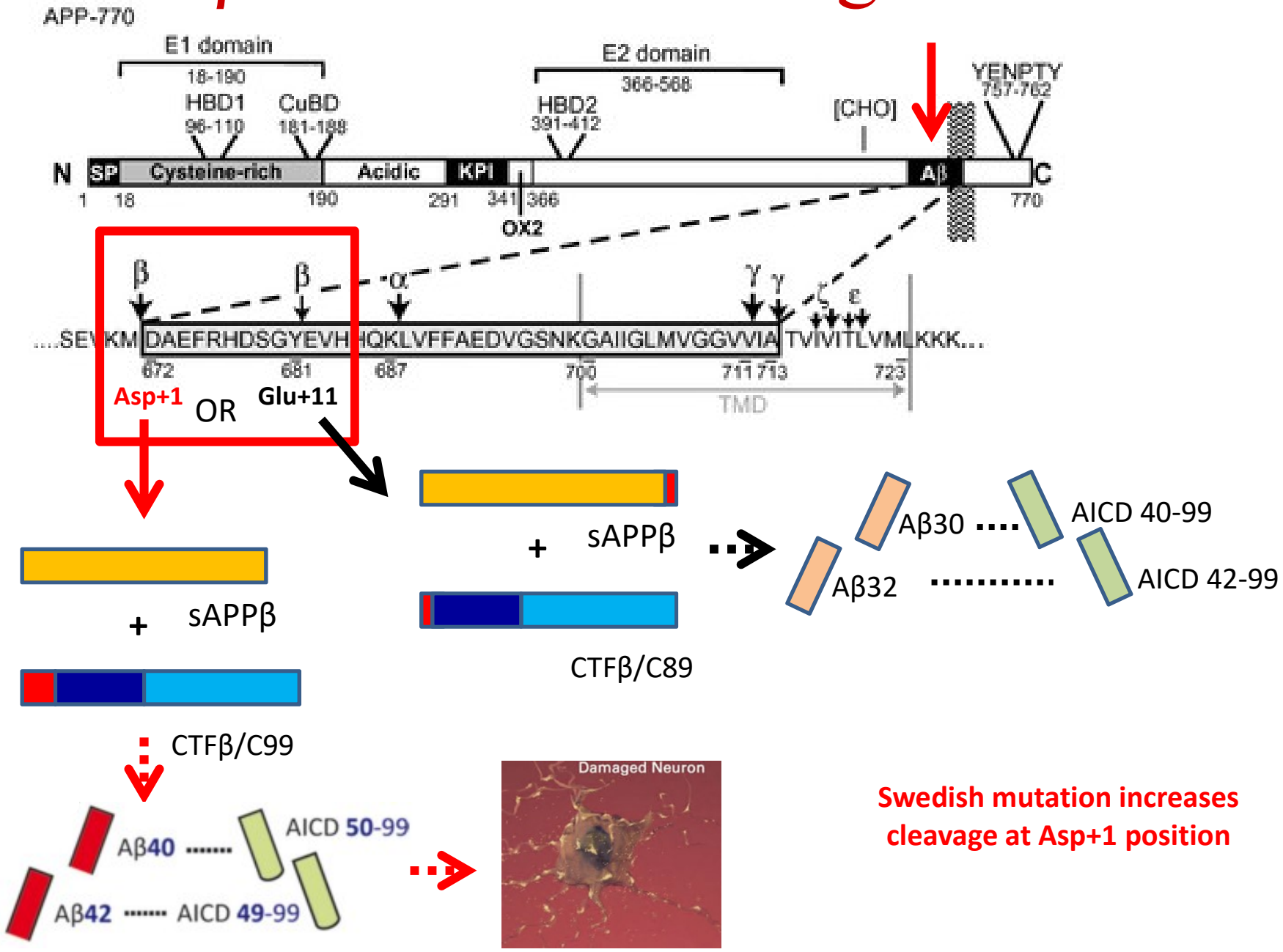


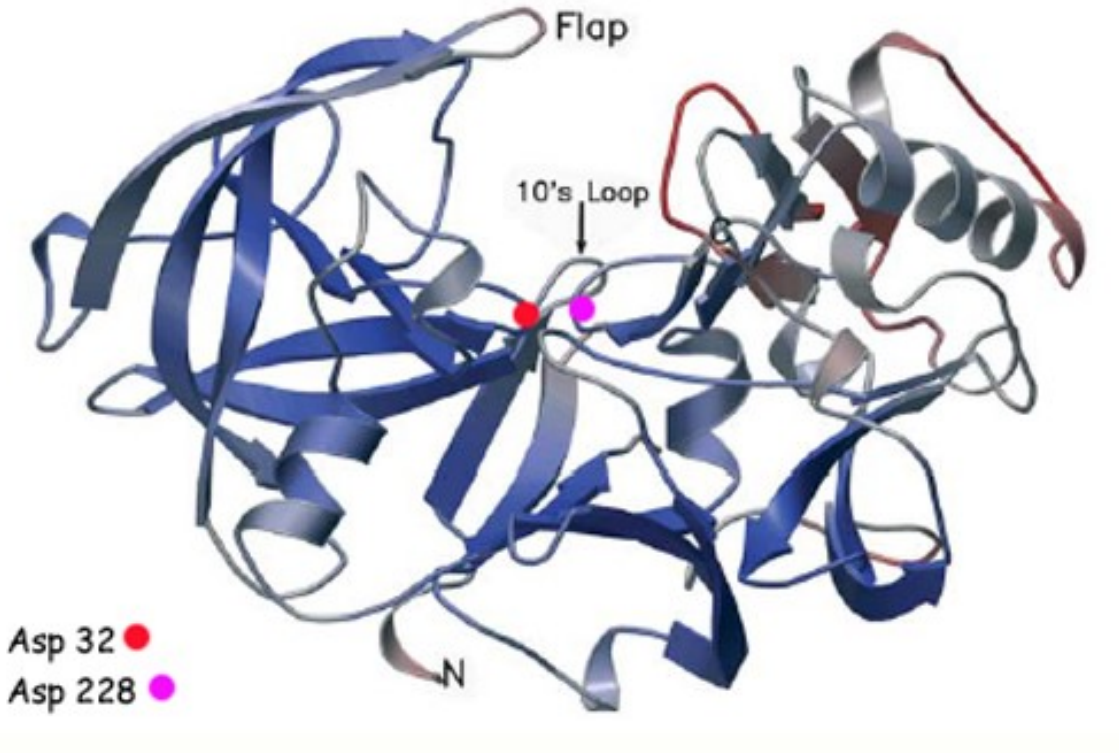


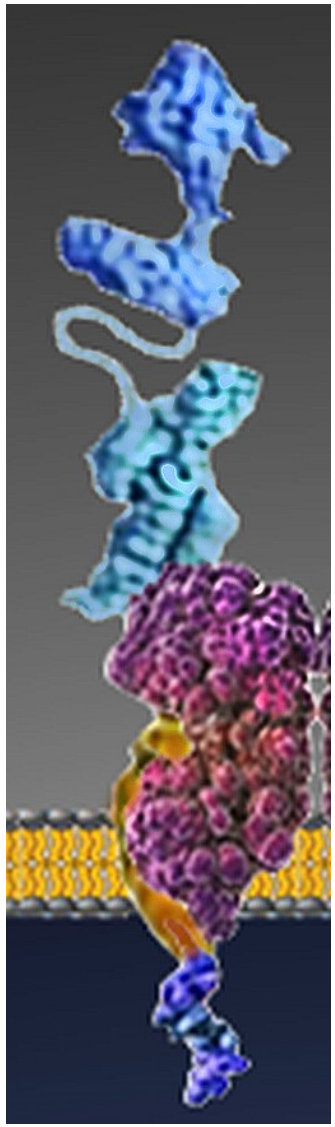
β-secretase cleavage of APP



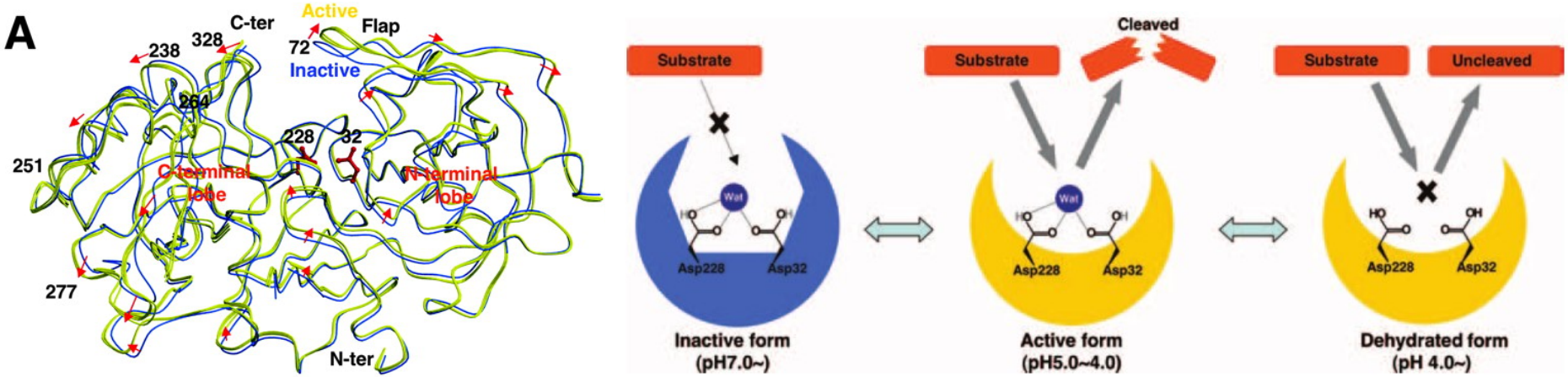
Swedish mutation increases cleavage at Asp+1 position

β-Secretase: Beta Amyloid-site-Cleaving Enzime 1 (BACE1)





Conformational changes associated with activation of BACE1



Shimizu et al. 2008

In the aspartic proteases there are two conserved water molecules. The first water molecule (Wat1) is located between the Asp pair of Asp32 and Asp228 of BACE1. The second water molecule (Wat2) is involved in the hydrogen bond, with a conserved Tyr residue in the flap. Wat2 also participates in a conserved hydrogen-bonding network Wat2-Ser35-Asp32-Wat1-Asp228 and was proposed to assist in the catalytic reaction.

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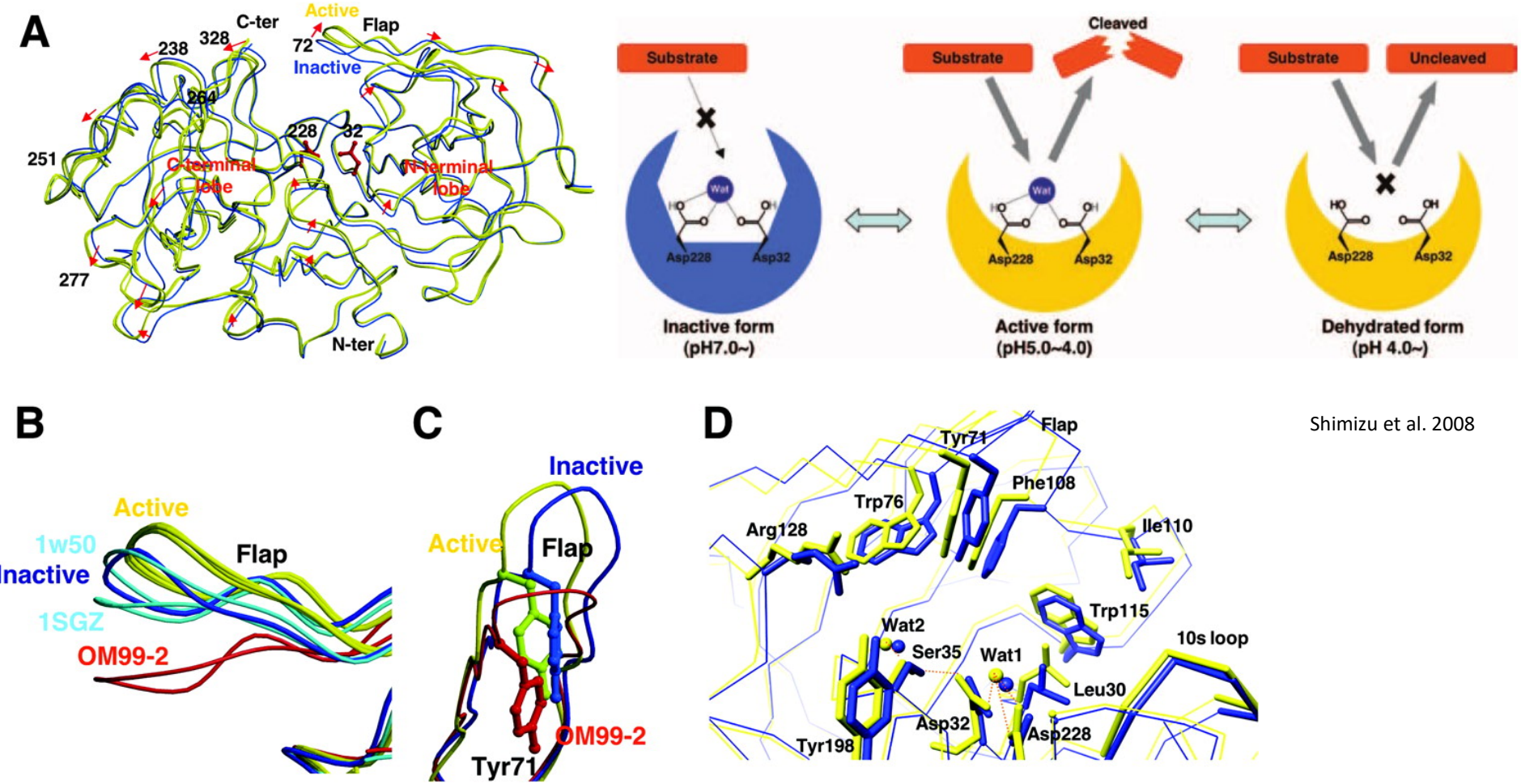

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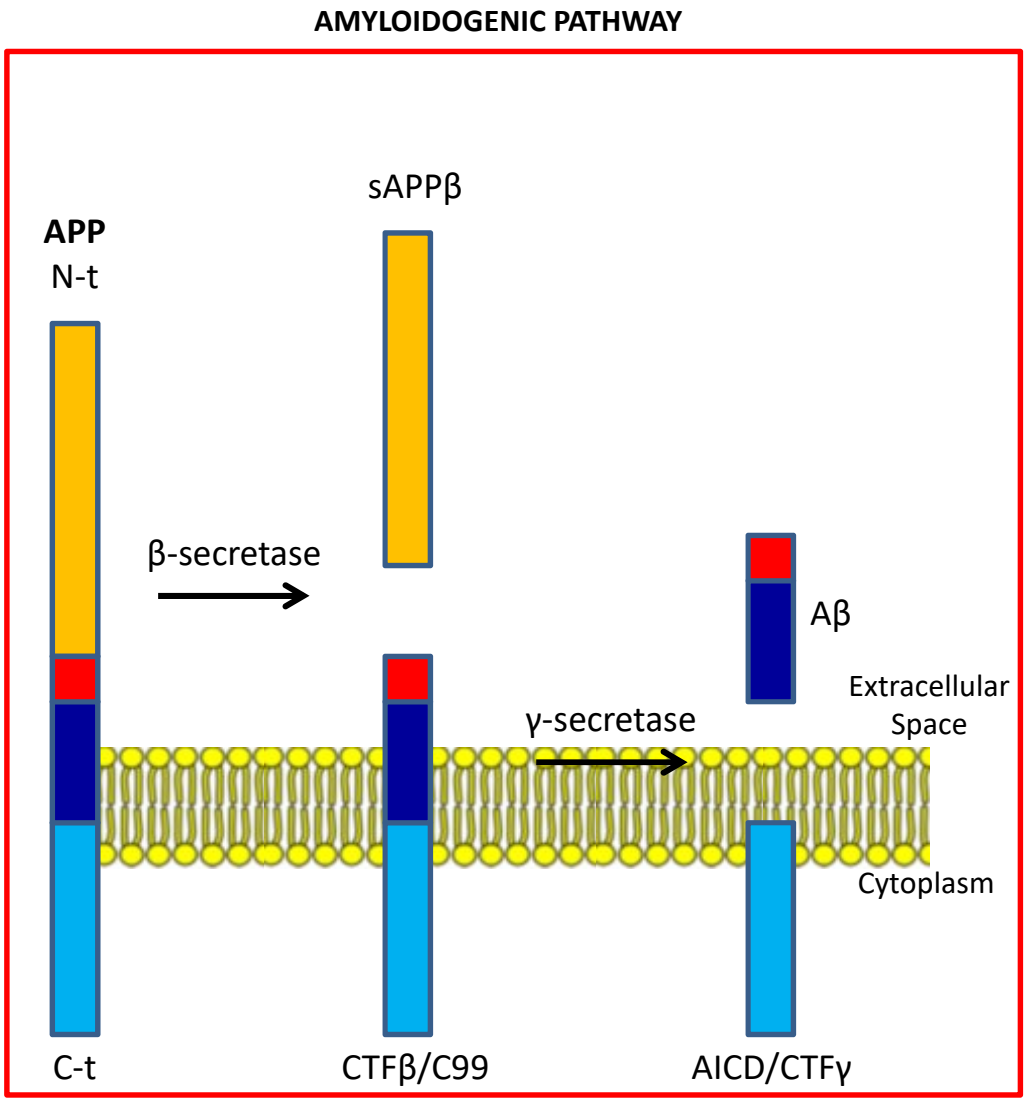
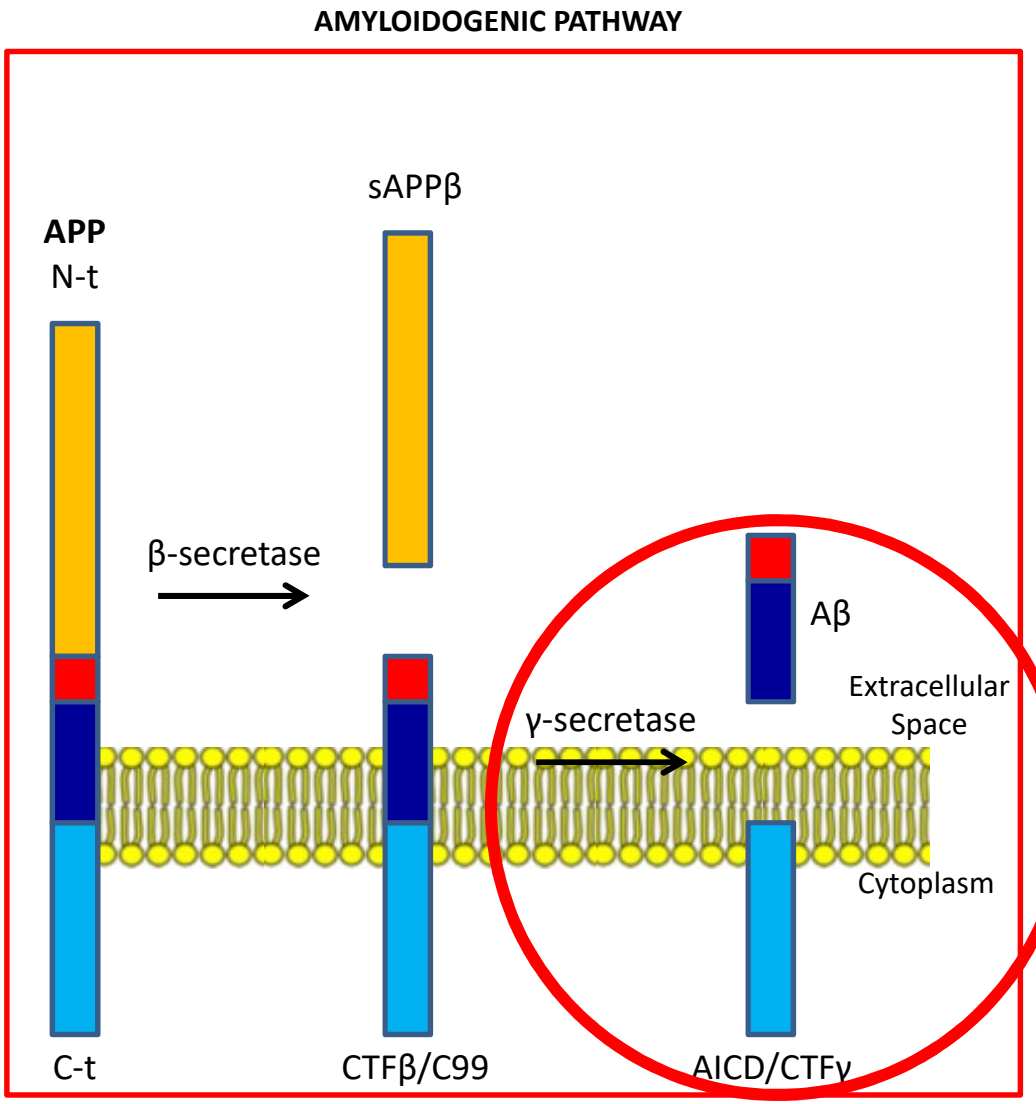
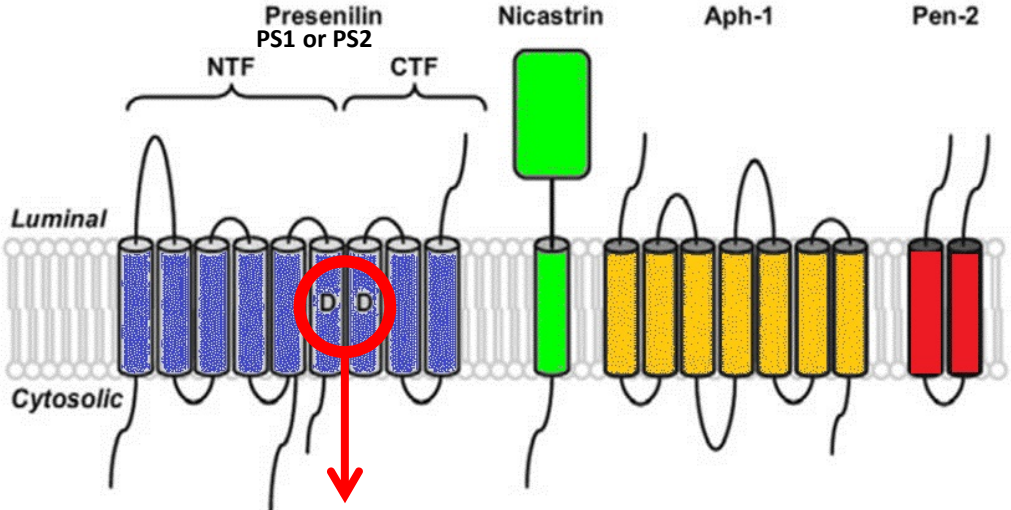
Amyloid Hypothesis



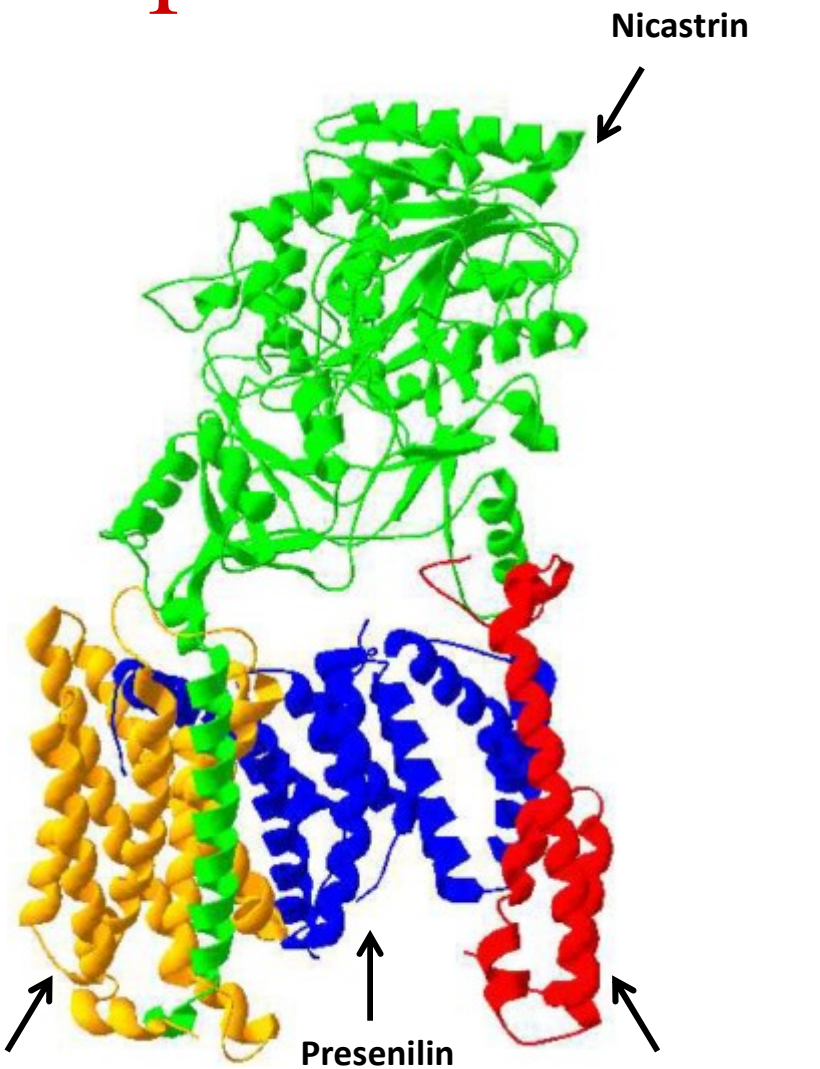
Amyloid Hypothesis



γ-Secretase Complex



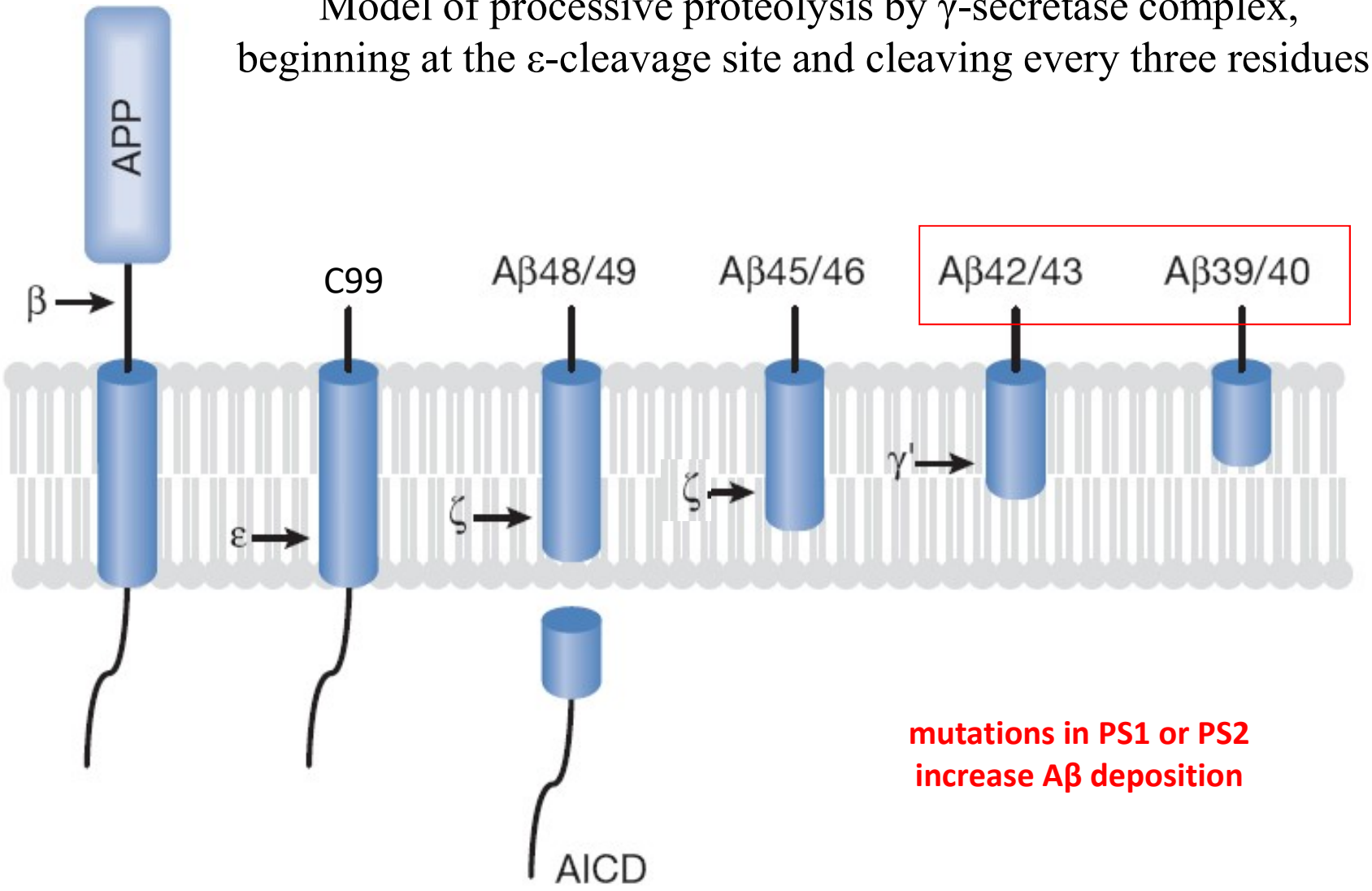
Asp257 and Asp385 are the PS1 catalytic residue



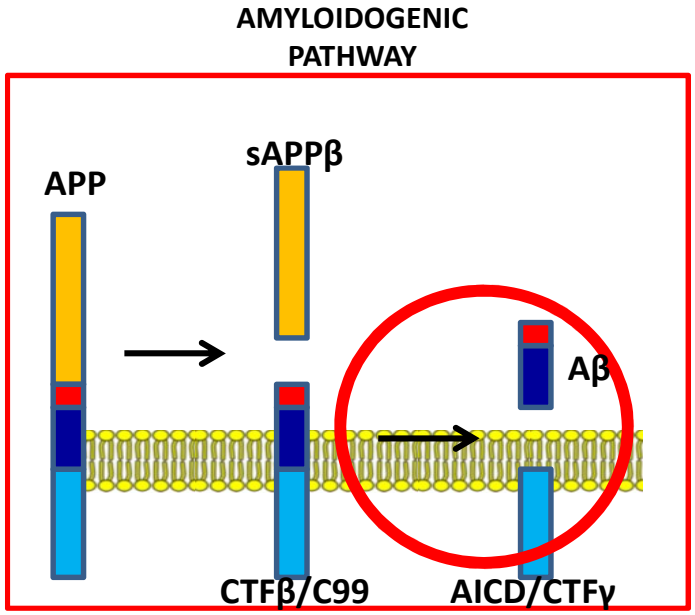
Barage SH et al. 2015
Montoliu-Gaya L et al. 2015

γ-Secretase cleavage

Model of processive proteolysis by γ-secretase complex, beginning at the ε-cleavage site and cleaving every three residues.



mutations in PS1 or PS2 increase Aβ deposition



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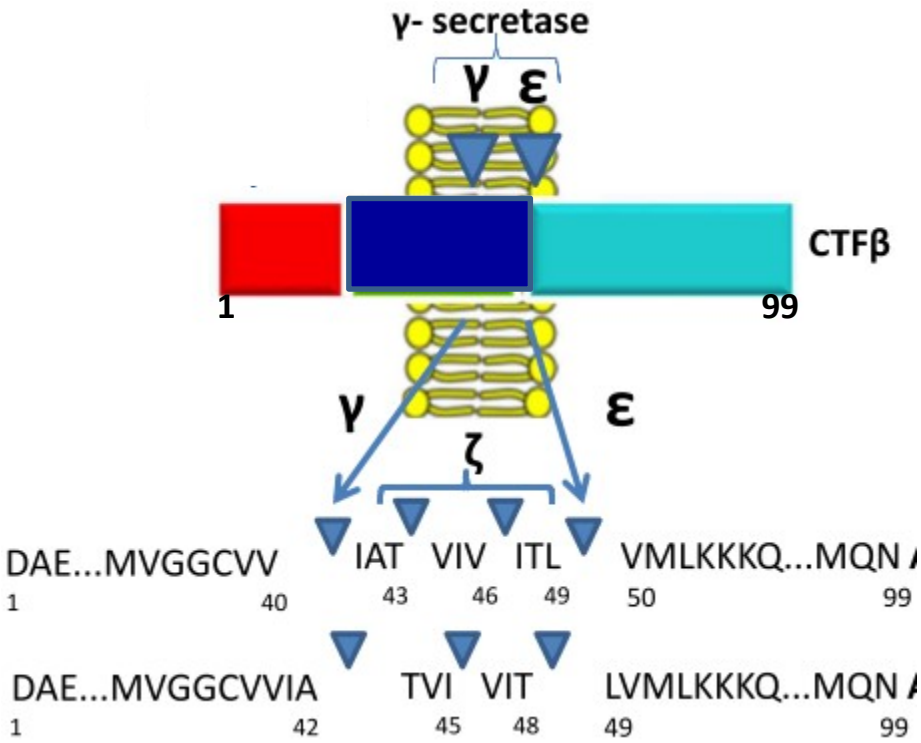


Three cleavages:

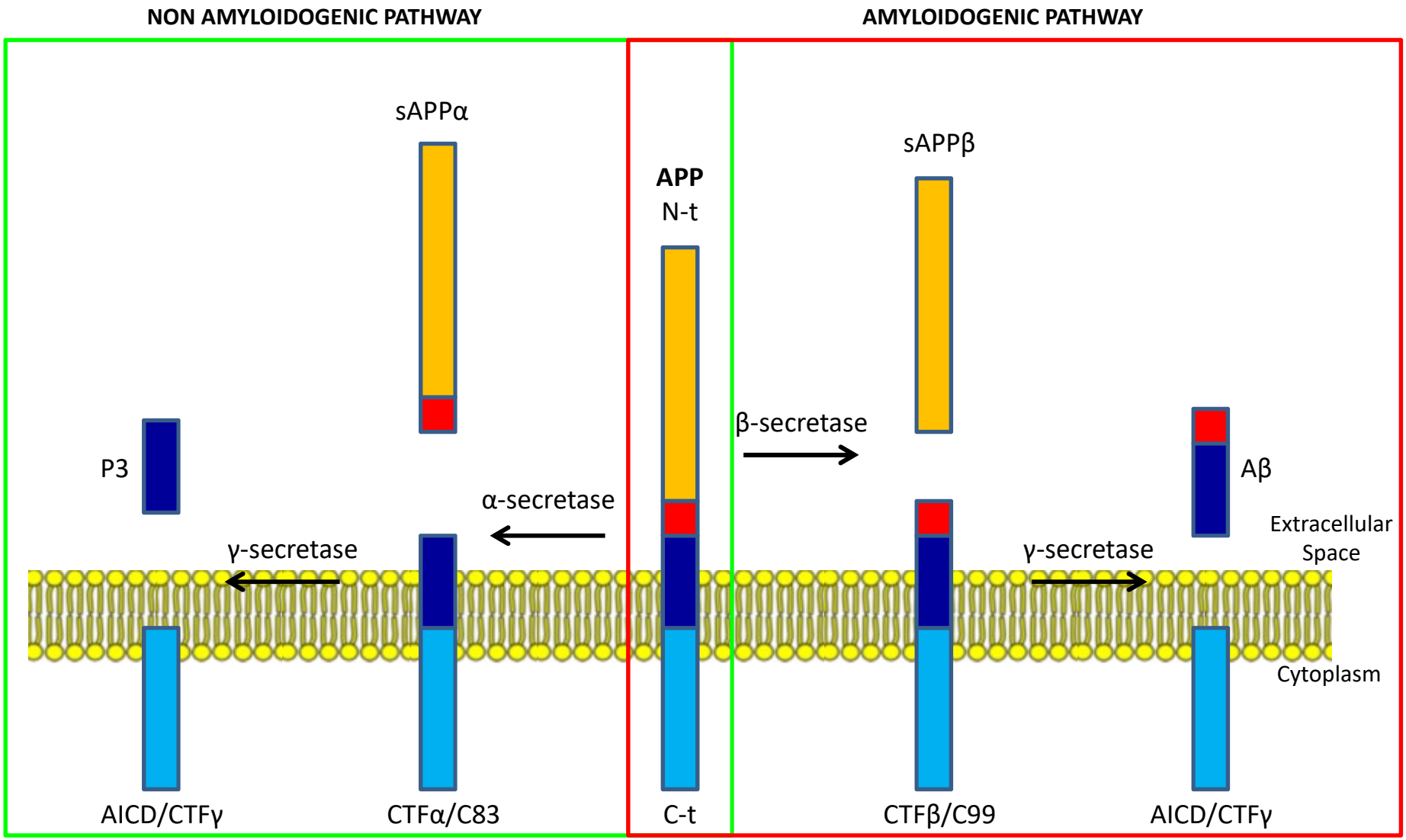
1st the ε

2nd the ζ

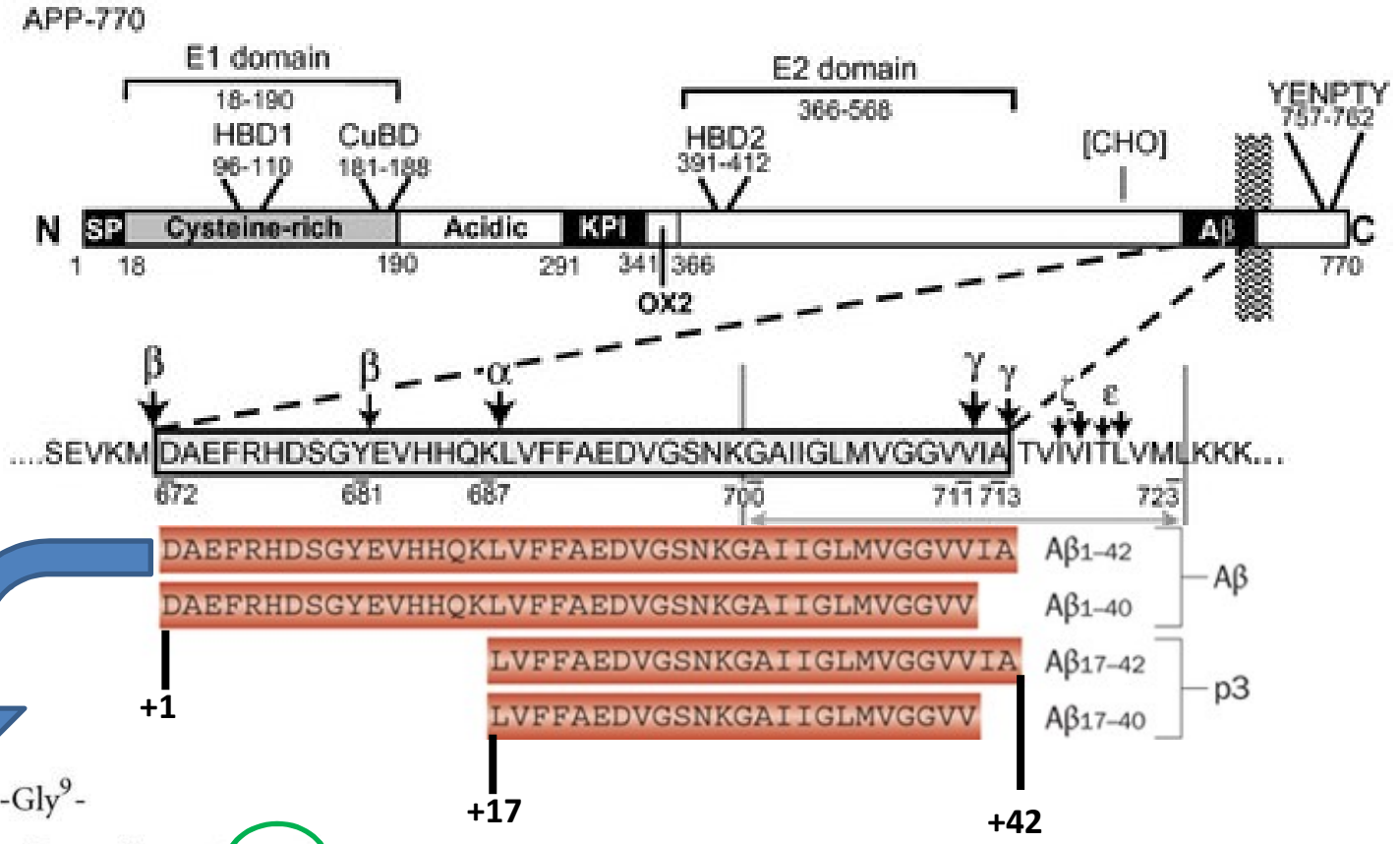
3rd the γ

Alternative products:

Amyloid Hypothesis



Comparison between fragments



Aβ(1–42)

H_2N-Asp[1]-Ala[2]-His[6]-Asp[7]-Ser[8]-Gly[9]-
Tyr[10]-Glu[11]-Val[12]-His[13]-His[14]-Gln[15]-Lys[16]-Leu[17]-
Val[18]-Phe[19]-Phe[20]-Ala[21]-Glu[22]-Asp[23]-Val[24]-Gly[25]-
Ser[26]-Asn[27]-Lys[28]-Gly[29]-Ala[30]-Ile[31]-Ile[32]-Gly[33]-
Leu[34]-**Met[35]**-Val[36]-Gly[37]-Gly[38]-Val[39]-Val[40]-Ile[41]-Ala[42]-COOH

ALZHEIMER'S DISEASE

Amyloid Hypothesis

Tau Hypothesis

Calcium Hypothesis

Cholinergic Hypothesis

Oxidative Stress Hypothesis

Problems with the amyloid hypothesis

- In some cases, individuals without symptoms of AD have many cortical Aβ deposits. However, in these cases, these are diffuse amyloid plaques that are not associated with surrounding necrotic and glial pathology.
- The degree of dementia appears to correlate with soluble Aβ species. Several lines of evidence demonstrate that soluble Aβ oligomers, instead of monomers or insoluble amyloid fibrils, may be responsible for synaptic dysfunction in the brains of AD patients and in animal models.


Dendrite
Synapse
THE END
Oligomers
Neuron
A-beta
Intermediate
Amyloid-beta
Plaque
Amyloid
precursor
protein
Fibrils