Malalties neurodegeneratives: Un problema de plegament proteic

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Seminari de Recerca de la Facultat de Farmàcia– 2013

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FACULTAT DE FARMÀCIA

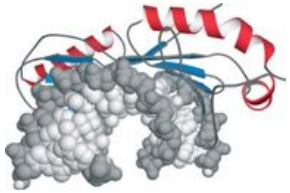
Malalties Conformacionals: Proteïnes com a responsable final de les agregacions amiloides

Funcions i arquitectura de les proteïnes

Binding

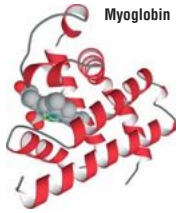
Specific recognition of other molecules is central to protein function. The molecule that is bound (the ligand) can be as small as the oxygen molecule that coordinates to the heme group of myoglobin, or as large as the specific DNA sequence (called the TATA box) that is bound—and distorted—by the TATA binding protein. Specific binding is governed by shape complementarity and polar interactions such as hydrogen bonding.

TATA binding protein



The TATA binding protein binds a specific DNA sequence and serves as the platform for a complex that initiates transcription of genetic information. (PDB 1tgh)

Myoglobin

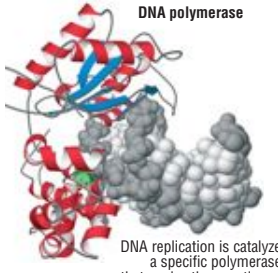


Myoglobin binds a molecule of oxygen reversibly to the iron atom in its heme group (shown in grey with the iron in green). It stores oxygen for use in muscle tissues. (PDB 1a6k)

Catalysis

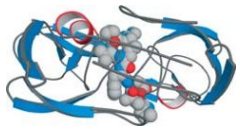
Essentially every chemical reaction in the living cell is catalyzed, and most of the catalysts are protein enzymes. The catalytic efficiency of enzymes is remarkable: reactions can be accelerated by as much as 17 orders of magnitude over simple buffer catalysis. Many structural features contribute to the catalytic power of enzymes: holding reacting groups together in an orientation favorable for reaction (proximity); binding the transition state of the reaction more tightly than ground state complexes (transition state stabilization); acid-base catalysis, and so on.

DNA polymerase



DNA replication is catalyzed by a specific polymerase that copies the genetic material and edits the product for errors in the copy. (PDB 1pbx)

HIV protease



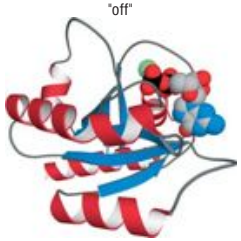
Replication of the AIDS virus HIV depends on the action of a protein-cleaving enzyme called HIV protease. This enzyme is the target for protease-inhibitor drugs (shown in grey). (PDB 1a8k)

Switching

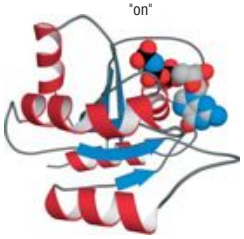
Proteins are flexible molecules and their conformation can change in response to changes in pH or ligand binding. Such changes can be used as molecular switches to control cellular processes. One example, which is critically important for the molecular basis of many cancers, is the conformational change that occurs in the small GTPase Ras when GTP is hydrolyzed to GDP. The GTP-bound conformation is an "on" state that signals cell growth; the GDP-bound structure is the "off" signal.

Ras

"off"



"on"



The GDP-bound ("off"; PDB 1pll) state of Ras differs significantly from the GTP-bound ("on"; PDB 121p) state. This difference causes the two states to be recognized by different proteins in signal transduction pathways.

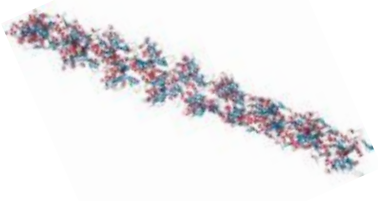
Structural Proteins

Protein molecules serve as some of the major structural elements of living systems. This function depends on specific association of protein subunits with themselves as well as with other proteins, carbohydrates, and so on, enabling even complex systems like actin fibrils to assemble spontaneously. Structural proteins are also important sources of biomaterials, such as silk, collagen, and keratin.

Silk

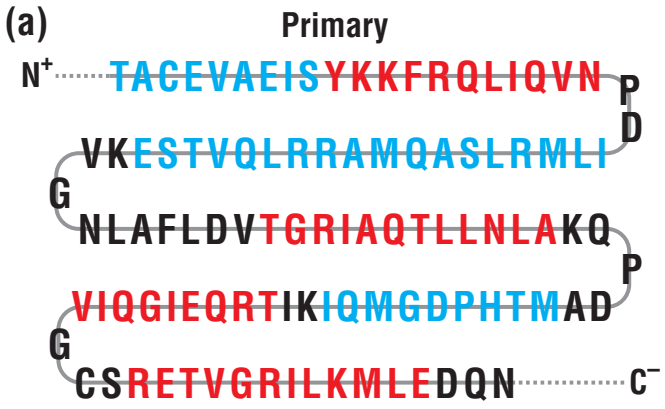
Silk derives its strength and flexibility from its structure: it is a giant stack of antiparallel beta sheets. Its strength comes from the covalent and hydrogen bonds within each sheet; the flexibility from the van der Waals interactions that hold the sheets together. (PDB 1slk)

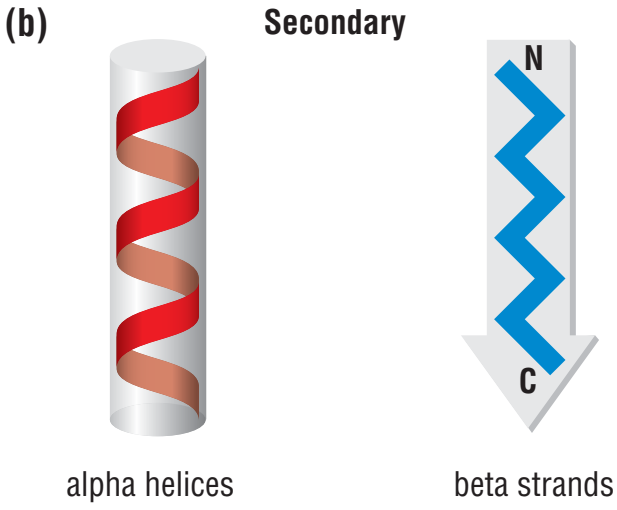
F-actin

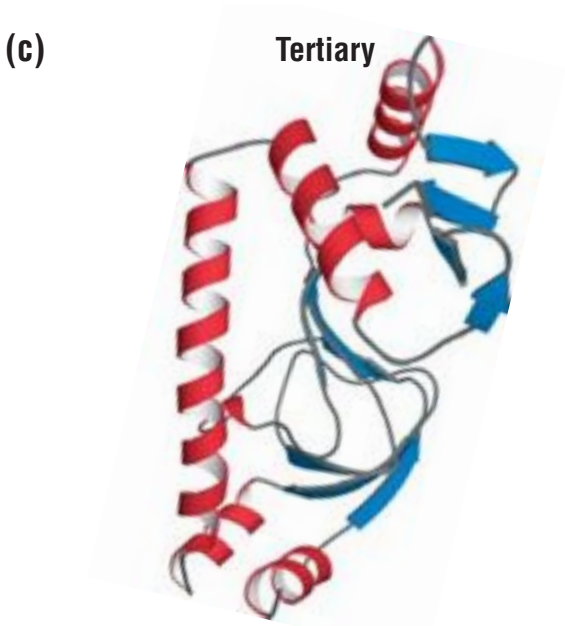


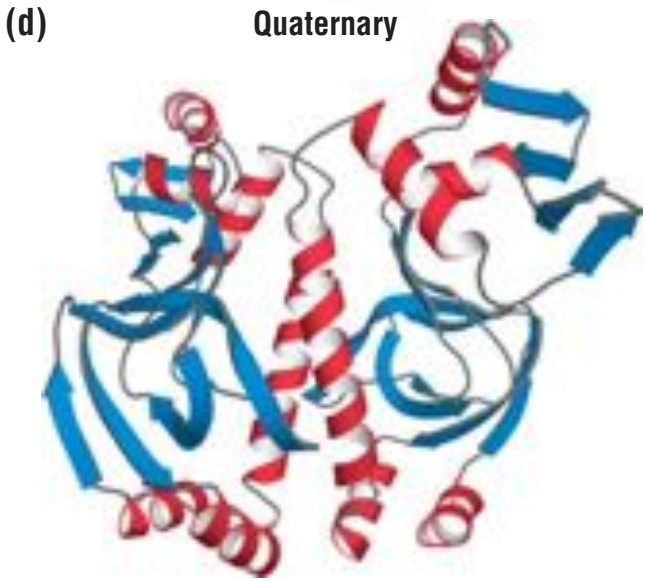
Actin fibers are important for muscle contraction and for the cytoskeleton. They are helical assemblies of actin and actin-associated proteins. (Courtesy of Ken Holmes)

De la seqüència a l'estructura









Funcions i arquitectura de les proteïnes

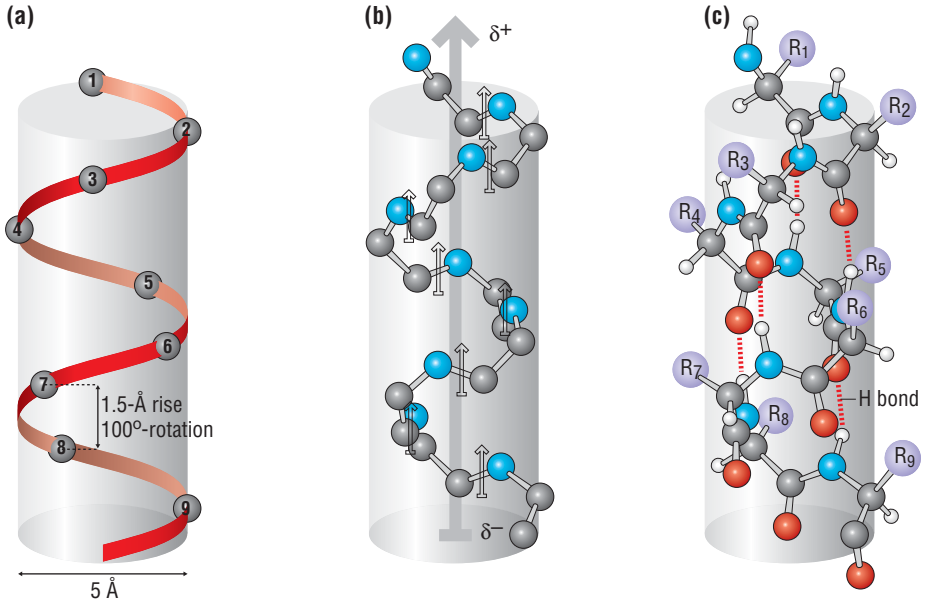


Figure 1-13 **The alpha helix** The chain path with average helical parameters is indicated showing **(a)** the alpha carbons only, **(b)** the backbone fold with peptide dipoles and **(c)** the full structure with backbone hydrogen bonds in red. All three chains run from top to bottom (that is, the amino-terminal end is at the top). Note that the individual peptide dipoles align to produce a macrodipole with its positive end at the amino-terminal end of the helix. Note also that the amino-terminal end has unsatisfied hydrogen-bond donors (N–H groups) whereas the carboxy-terminal end has unsatisfied hydrogen-bond acceptors (C=O groups). Usually a polar side chain is found at the end of the helix, making hydrogen bonds to these donors and acceptors; such a residue is called a helix cap.

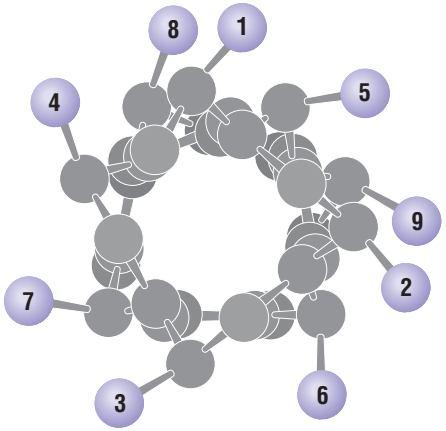


Figure 1-15 **View along the axis of an idealized alpha-helical polypeptide** The view is from the amino-terminal end. Side chains project outward from the helical axis at 100° intervals. Note that side chains four residues apart in the sequence tend to cluster on the same face of the helix, for shorter helices. For long helices any such pattern would slowly coil about the helix axis, so if two long helices had a pattern of hydrophobic groups four residues apart they would interact by forming a coiled coil (see Figure 1-67).

Funcions i arquitectura de les proteïnes

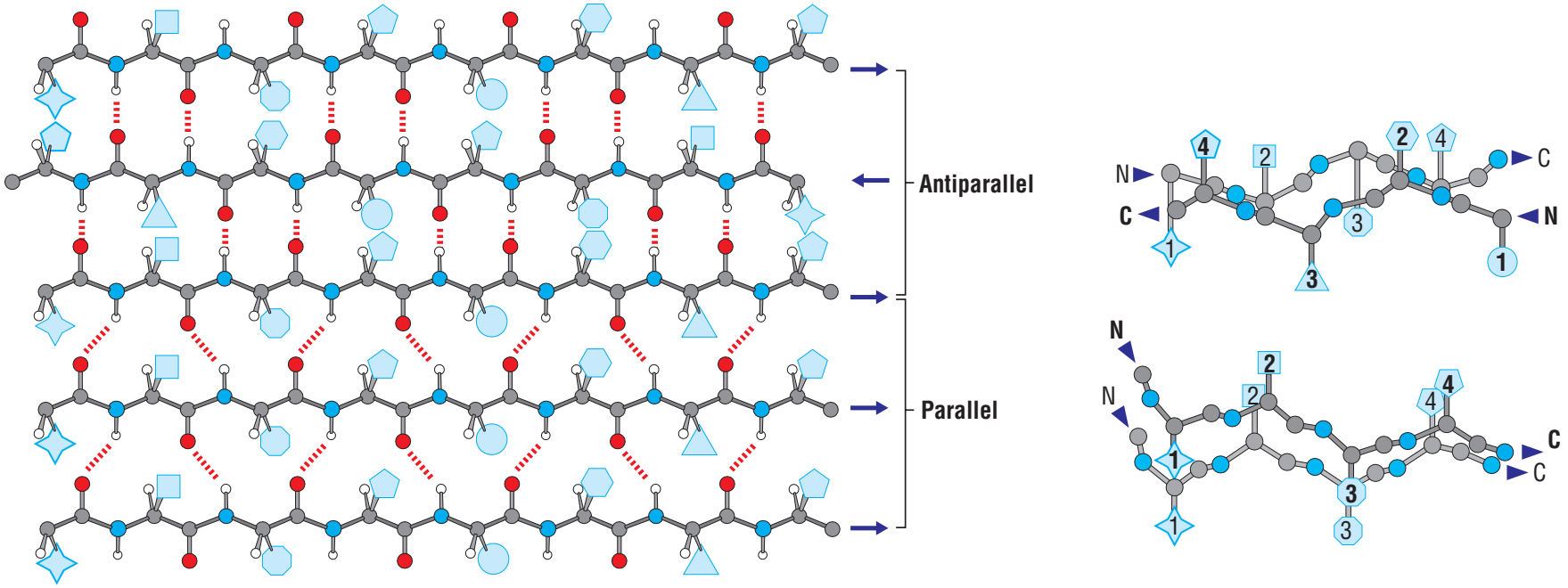


Figure 1-17 **The structure of the beta sheet** The left figure shows a mixed beta sheet, that is one containing both parallel and antiparallel segments. Note that the hydrogen bonds are more linear in the antiparallel sheet. On the right are edge-on views of antiparallel (top) and parallel sheets (bottom). The corrugated appearance gives rise to the name "pleated sheet" for these elements of secondary structure. Consecutive side chains, indicated here as numbered geometric symbols, point from alternate faces of both types of sheet.

Plegament proteic: Levinthal's paradox

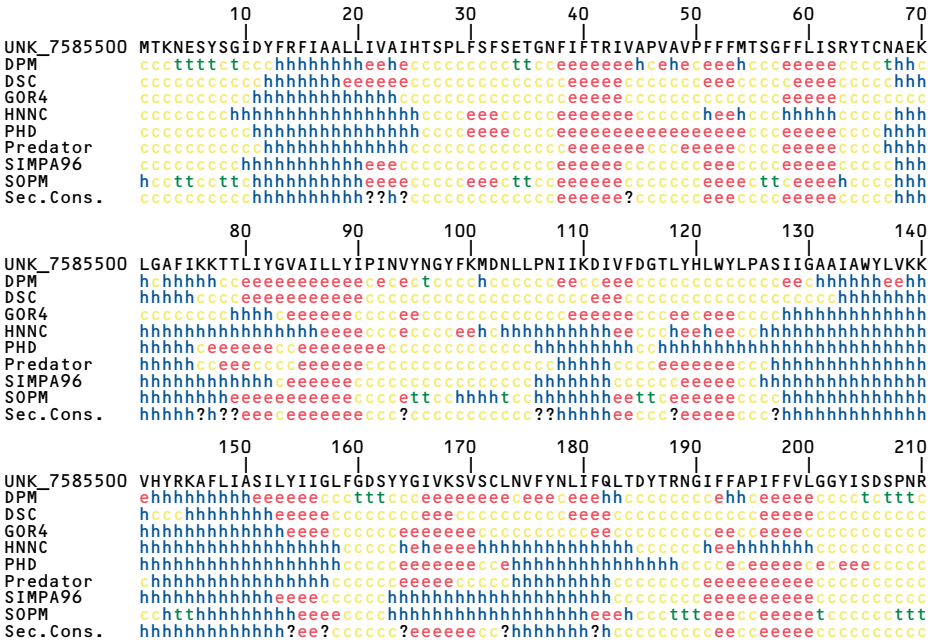


Figure 1-21 An example of secondary structure prediction An example of the prediction of secondary structure from sequence for a protein of unknown function from the *Enterococcus faecalis* genome. Only the first 490 residues are shown. Eight different statistical prediction schemes have been applied to this sequence. What is striking is that all of the schemes agree on the approximate locations of the alpha helices (h) and beta strands (e), but they disagree considerably on the lengths and end positions of these segments. Note also that the probable positions of loops (indicated by a c) and turns (indicated by a t) are very inconsistently predicted. Such results are typical, but the application of many methods is clearly more informative than the use of a single one. The bottom line shows the consensus prediction.

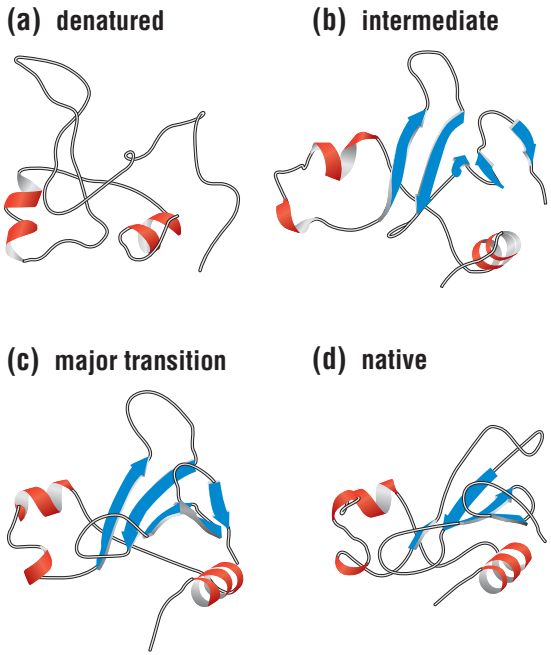
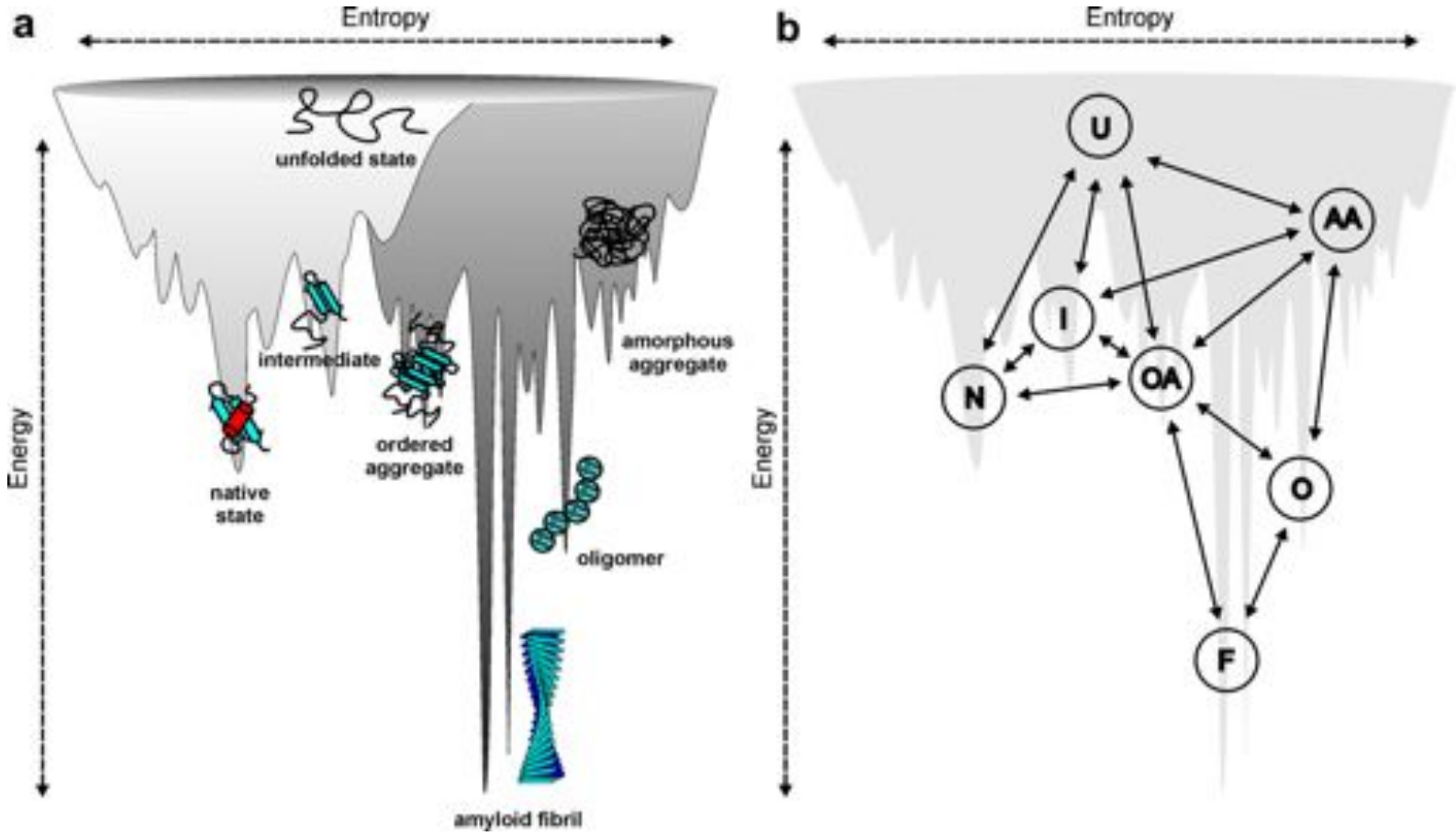
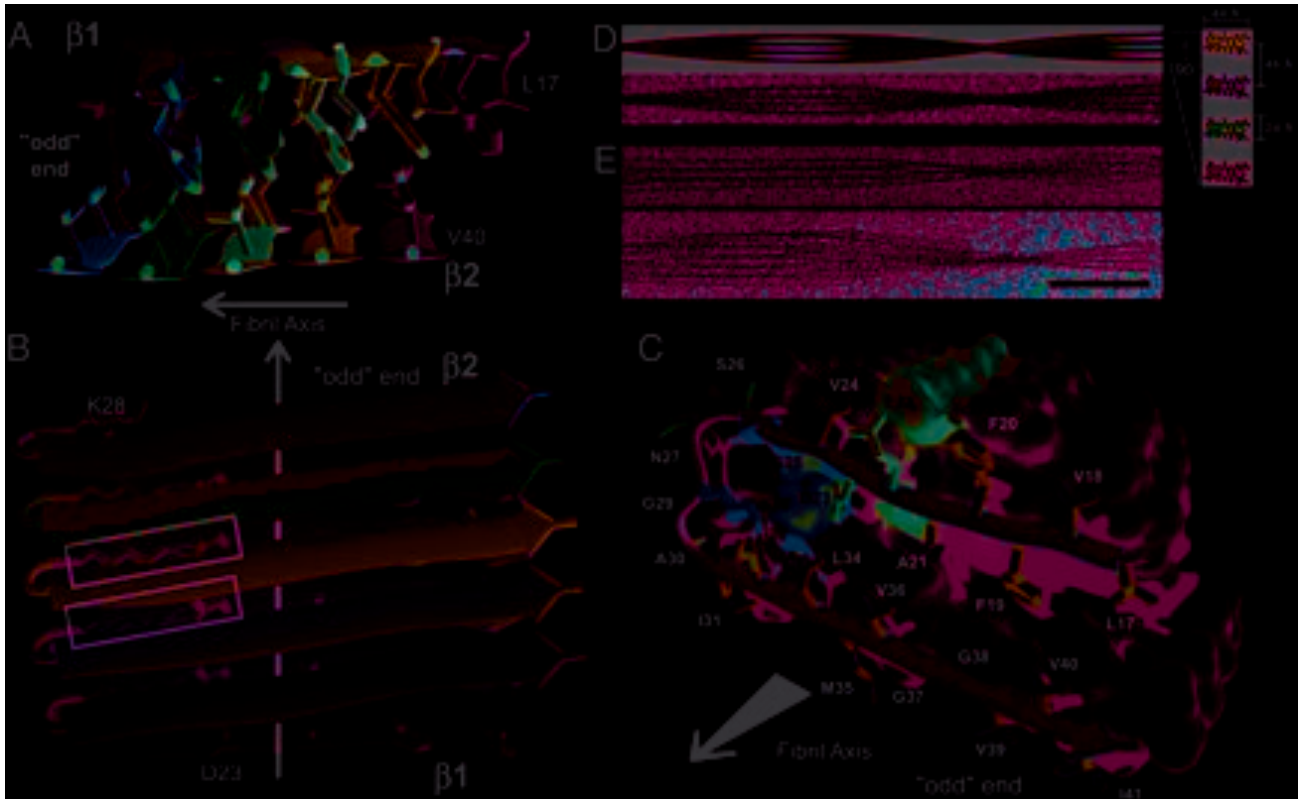


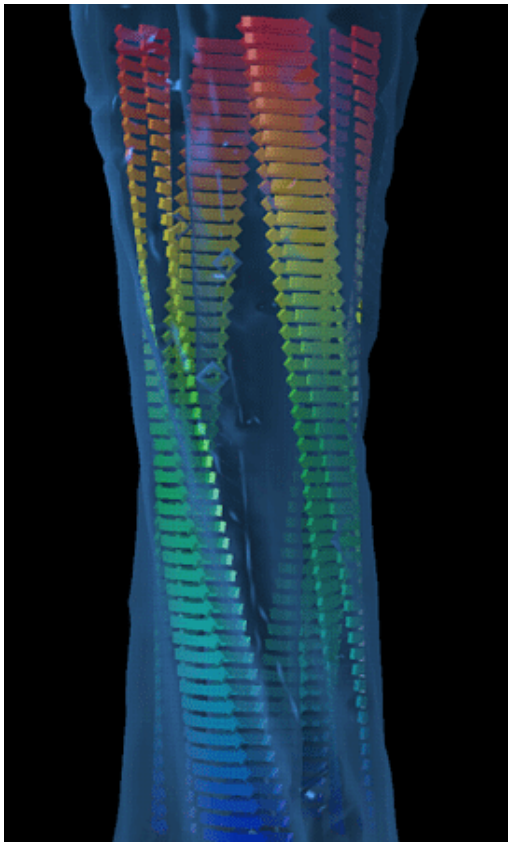
Figure 1-22 Folding intermediates Structures of **(a)** denatured, **(b)** intermediate, **(c)** major transition and **(d)** native states of barnase. Structures were determined from molecular dynamics calculations and NMR experiments, illustrating a possible folding pathway. Note that during folding, segments of secondary structure form that do not completely coincide with their final positions in the sequence, and that the non-native states are considerably expanded and more flexible relative to the final folded form. These characteristics appear to be common to most, if not all, protein-folding pathways. (Bond, C.J. *et al.*: *Proc. Natl Acad. Sci. USA* 1997, **94**:13409–13413.)

De la seqüència a l'estructura: Diferents camins de plegament



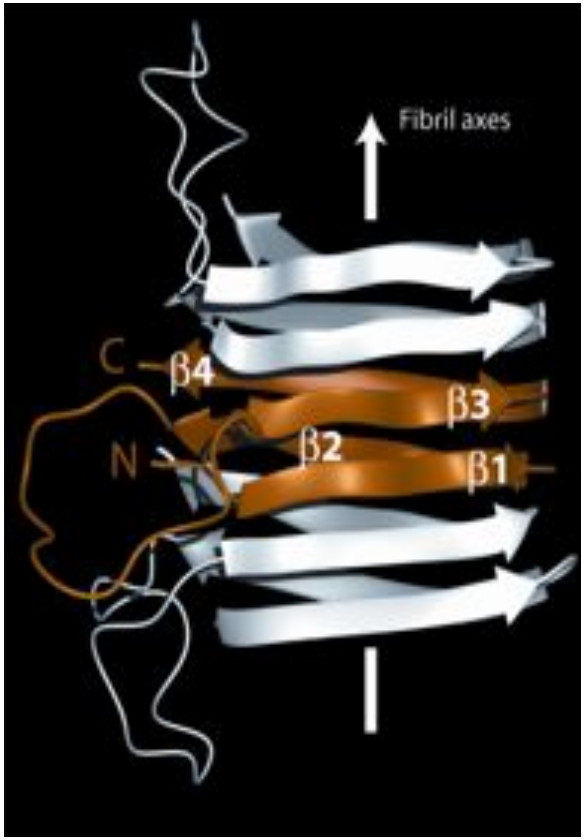
Conformació Amiloide





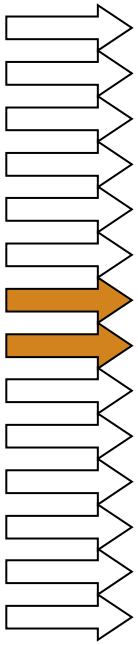
Core en estructura de fulla-β formant fibres

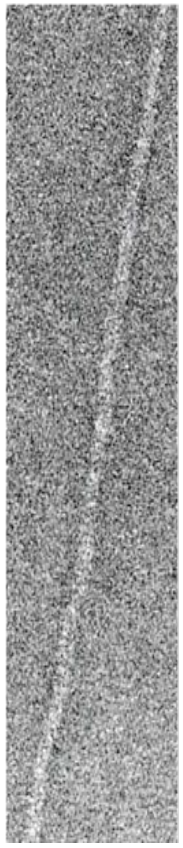
Conformació Amiloide



3,85 nm

0,95 nm





1 nm

5 nm

Malalties Conformacionals en humans

Disease	Aggregating protein or peptide	Number of residues[a]	Native structure of protein or peptide[b]
Neurodegenerative diseases			
Alzheimer's disease[c]	Amyloid β peptide	40 or 42[f]	Natively unfolded
Spongiform encephalopathies[c,e]	Prion protein or fragments thereof	253	Natively unfolded (residues 1–120) and α-helical (residues 121–230)
Parkinson's disease[c]	α-Synuclein	140	Natively unfolded
Dementia with Lewy bodies[c]	α-Synuclein	140	Natively unfolded
Frontotemporal dementia with Parkinsonism[c]	Tau	352–441[f]	Natively unfolded
Amyotrophic lateral sclerosis[c]	Superoxide dismutase 1	153	All-β, Ig like
Huntington's disease[d]	Huntingtin with polyQ expansion	3144[g]	Largely natively unfolded
Spinocerebellar ataxias[d]	Ataxins with polyQ expansion	816[g,h]	All-β, AXH domain (residues 562–694); the rest are unknown
Spinocerebellar ataxia 17[d]	TATA box-binding protein with polyQ expansion	339[g]	α+β, TBP like (residues 159–339); unknown (residues 1–158)
Spinal and bulbar muscular atrophy[d]	Androgen receptor with polyQ expansion	919[g]	All-α, nuclear receptor ligand-binding domain (residues 669–919); the rest are unknown
Hereditary dentatorubral-pallidoluysian atrophy[d]	Atrophin-1 with polyQ expansion	1185[g]	Unknown
Familial British dementia[d]	ABri	23	Natively unfolded
Familial Danish dementia[d]	ADan	23	Natively unfolded

Malalties Conformacionals en humans

Disease	Aggregating protein or peptide	Number of residues[a]	Native structure of protein or peptide[b]
Nonneuropathic systemic amyloidoses			
AL amyloidosis[c]	Immunoglobulin light chains or fragments	~90[f]	All-β, Ig like
AA amyloidosis[c]	Fragments of serum amyloid A protein	76–104[f]	All-α, unknown fold
Familial Mediterranean fever[c]	Fragments of serum amyloid A protein	76–104[f]	All-α, unknown fold
Senile systemic amyloidosis[c]	Wild-type transthyretin	127	All-β, prealbumin like
Familial amyloidotic polyneuropathy[d]	Mutants of transthyretin	127	All-β, prealbumin like
Hemodialysis-related amyloidosis[c]	β2-microglobulin	99	All-β, Ig like
ApoAI amyloidosis[d]	N-terminal fragments of apolipoprotein AI	80–93[f]	Natively unfolded
ApoAII amyloidosis[d]	N-terminal fragment of apolipoprotein AII	98[i]	Unknown
ApoAIV amyloidosis[c]	N-terminal fragment of apolipoprotein AIV	~70	Unknown
Finnish hereditary amyloidosis[d]	Fragments of gelsolin mutants	71	Natively unfolded
Lysozyme amyloidosis[d]	Mutants of lysozyme	130	α+β, lysozyme fold
Fibrinogen amyloidosis[d]	Variants of fibrinogen α-chain	27–81[f]	Unknown
Icelandic hereditary cerebral amyloid angiopathy[d]	Mutant of cystatin C	120	α+β, cystatin like

Malalties Conformacionals en humans

Disease	Aggregating protein or peptide	Number of residues[a]	Native structure of protein or peptide[b]
Nonneuropathic localized diseases			
Type II diabetes[c]	Amylin, also called islet amyloid polypeptide (IAPP)	37	Natively unfolded
Medullary carcinoma of the thyroid[c]	Calcitonin	32	Natively unfolded
Atrial amyloidosis[c]	Atrial natriuretic factor	28	Natively unfolded
Hereditary cerebral haemorrhage with amyloidosis[d]	Mutants of amyloid β peptide	40 or 42[f]	Natively unfolded
Pituitary prolactinoma	Prolactin	199	All-α, 4-helical cytokines
Injection-localized amyloidosis[c]	Insulin	21 + 30[j]	All-α, insulin like
Aortic medial amyloidosis[c]	Medin	50[k]	Unknown
Hereditary lattice corneal dystrophy[d]	Mainly C-terminal fragments of kerato-epithelin	50–200[f]	Unknown
Corneal amylodosis associated with trichiasis[c]	Lactoferrin	692	α+β, periplasmic-binding protein like II
Cataract[c]	γ-Crystallins	Variable	All-β, γ-crystallin like
Calcifying epithelial odontogenic tumors[c]	Unknown	~46	Unknown
Pulmonary alveolar proteinosis[d]	Lung surfactant protein C	35	Unknown
Inclusion-body myositis[c]	Amyloid β peptide	40 or 42[f]	Natively unfolded
Cutaneous lichen amyloidosis[c]	Keratins	Variable	Unknown

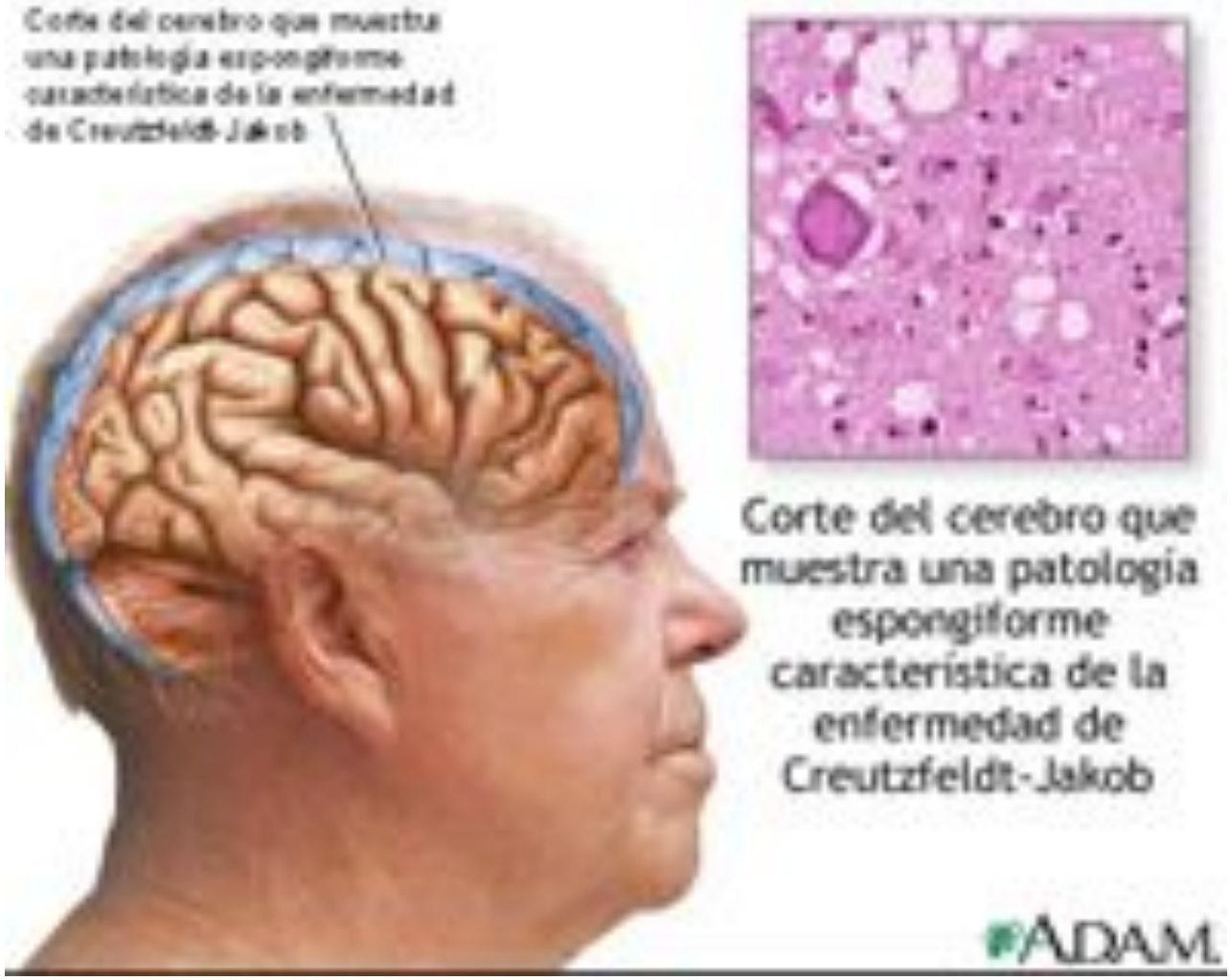
Malalties Conformacionals en humans

TABLE 1. PREVALENCE OF NEURODEGENERATIVE DISEASES IN THE UNITED STATES IN 2000.

DISEASE	NO. OF CASES	NO. PER 100,000 POPULATION*
Prion disease	400	<1
Alzheimer's disease	4,000,000	1450
Parkinson's disease	1,000,000	360
Frontotemporal dementia	40,000	14
Pick's disease	5,000	2
Progressive supranuclear palsy	15,000	5
Amyotrophic lateral sclerosis	20,000	7
Huntington's disease	30,000	11
Spinocerebellar ataxias	12,000	4

*Data are based on a population of approximately 275 million in 2000.

Causa de les malalties neurodegeneratives primàries

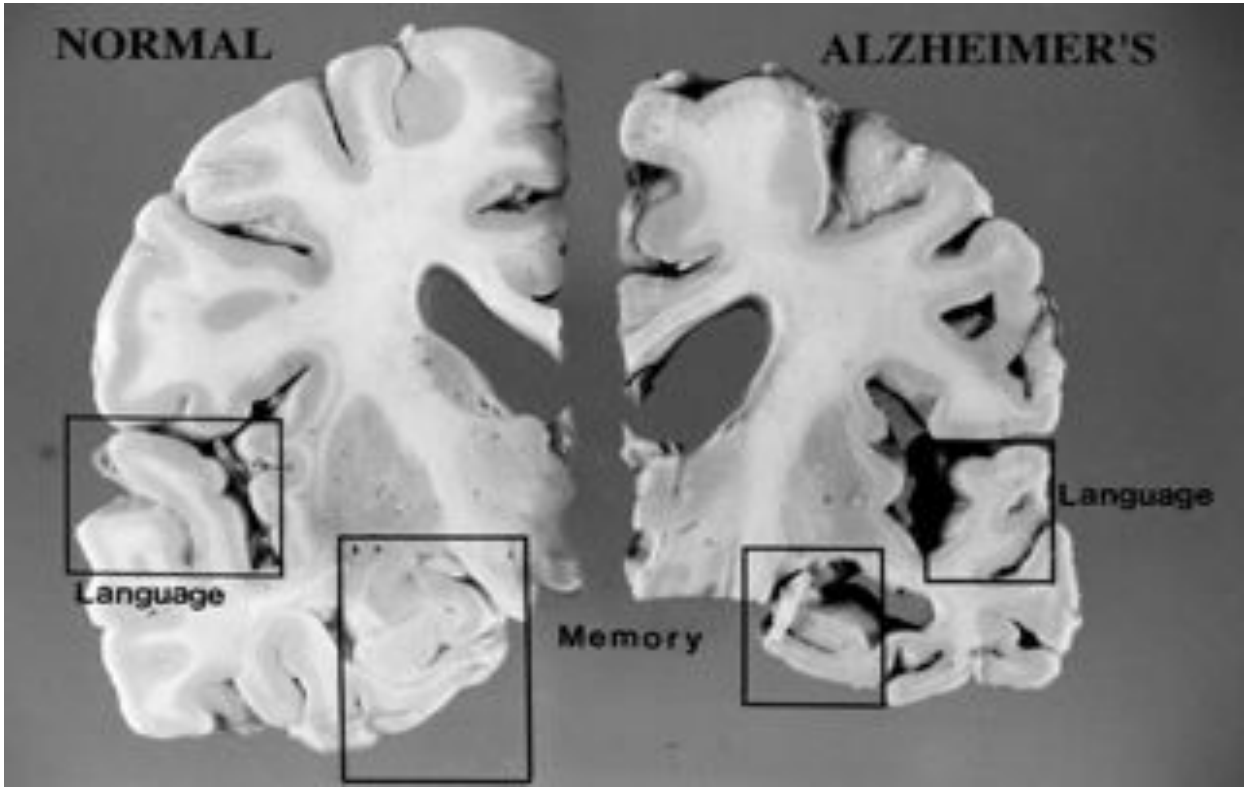


Malaltia d'Alzheimer

Característiques de la malaltia d'Alzheimer

Pèrdua progressiva de neurones en determinades regions del cervell

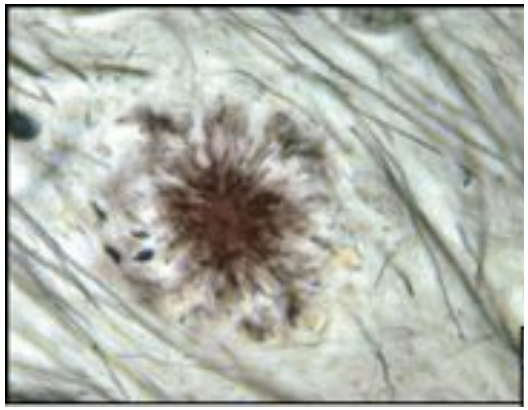
- Lòbuls temporals medials: Memòria
- Regions de Broca y de Wernicke: Llenguatge



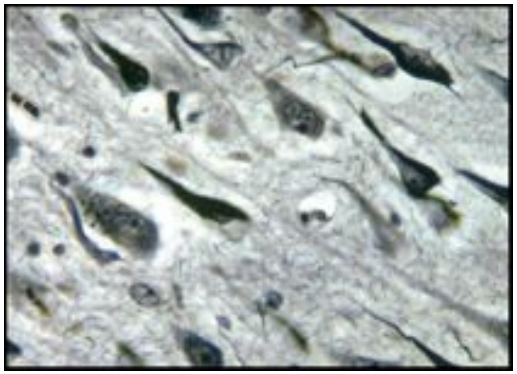
Característiques de la malaltia d'Alzheimer

Característiques anòmales del cervell de malalts de Alzheimer

Entramats neurofibrilars

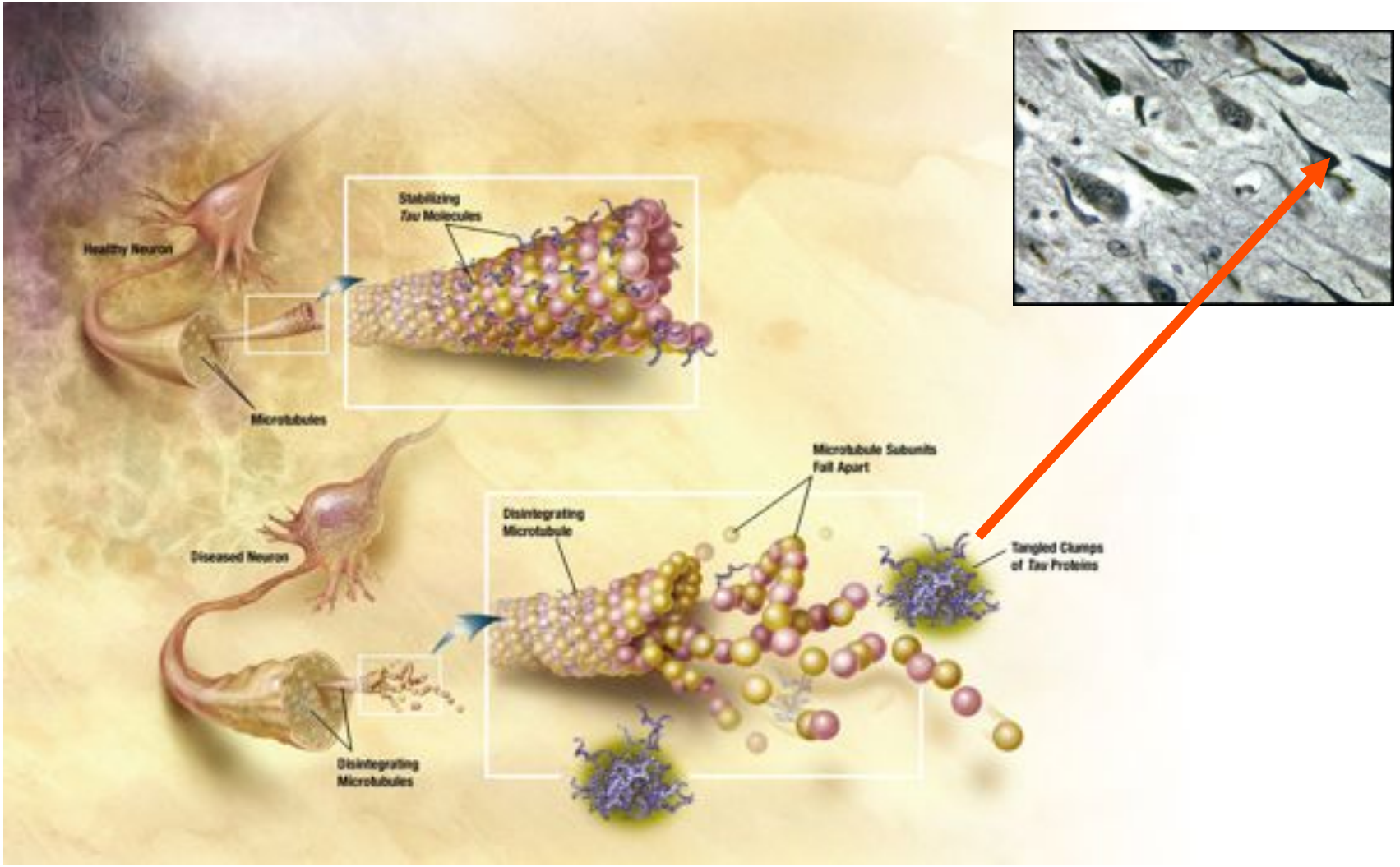


Plaques senils



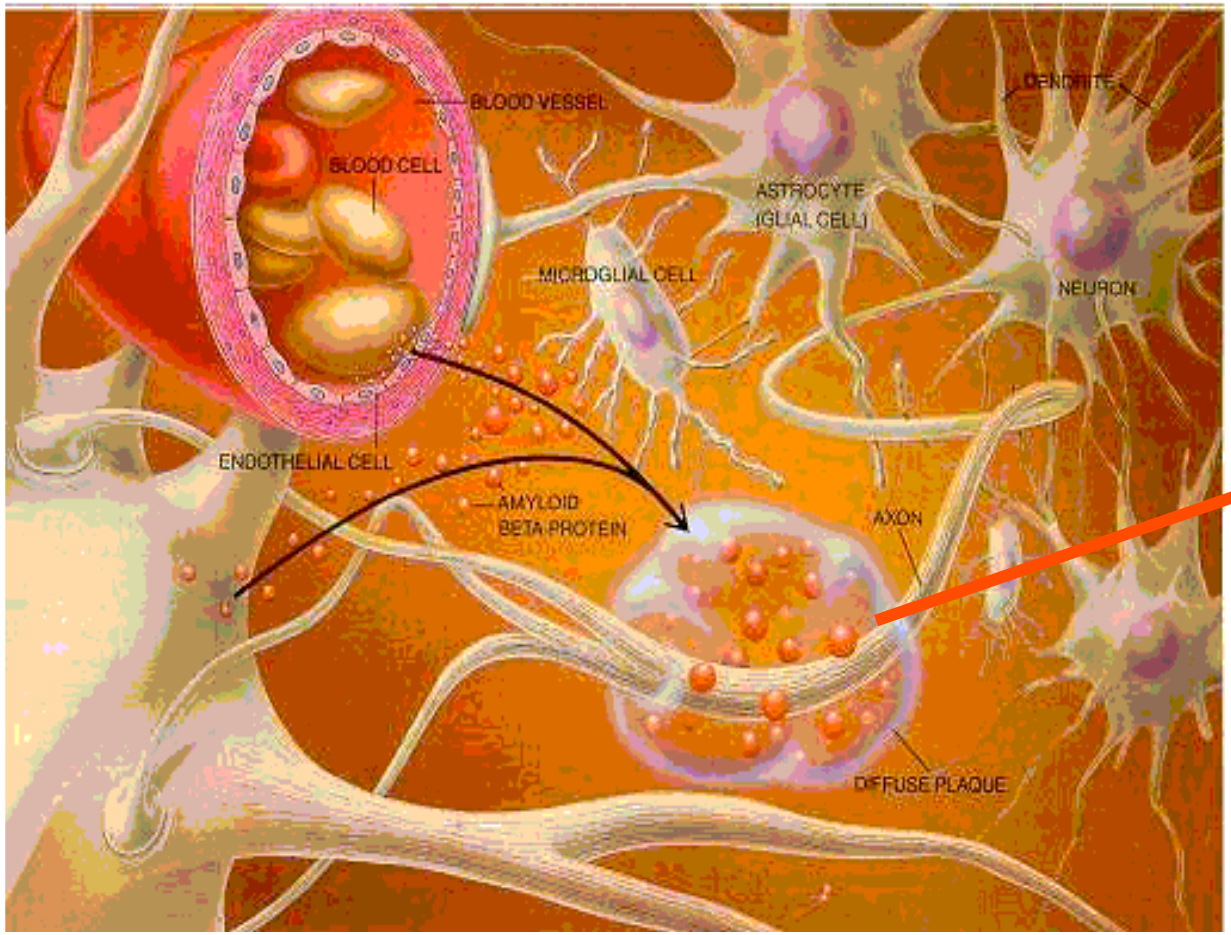
Característiques de la malaltia d'Alzheimer

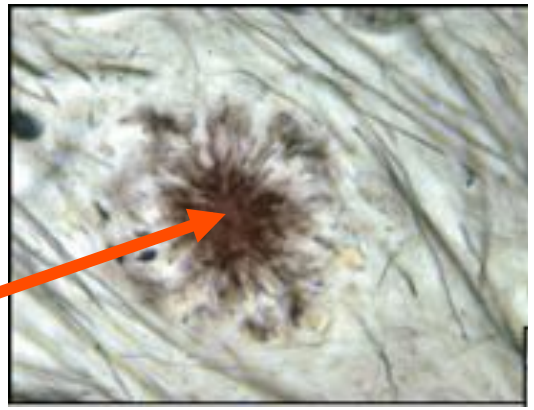
Entramats neurofibrilars



Característiques de la malaltia d'Alzheimer

Plaques senils o amiloides

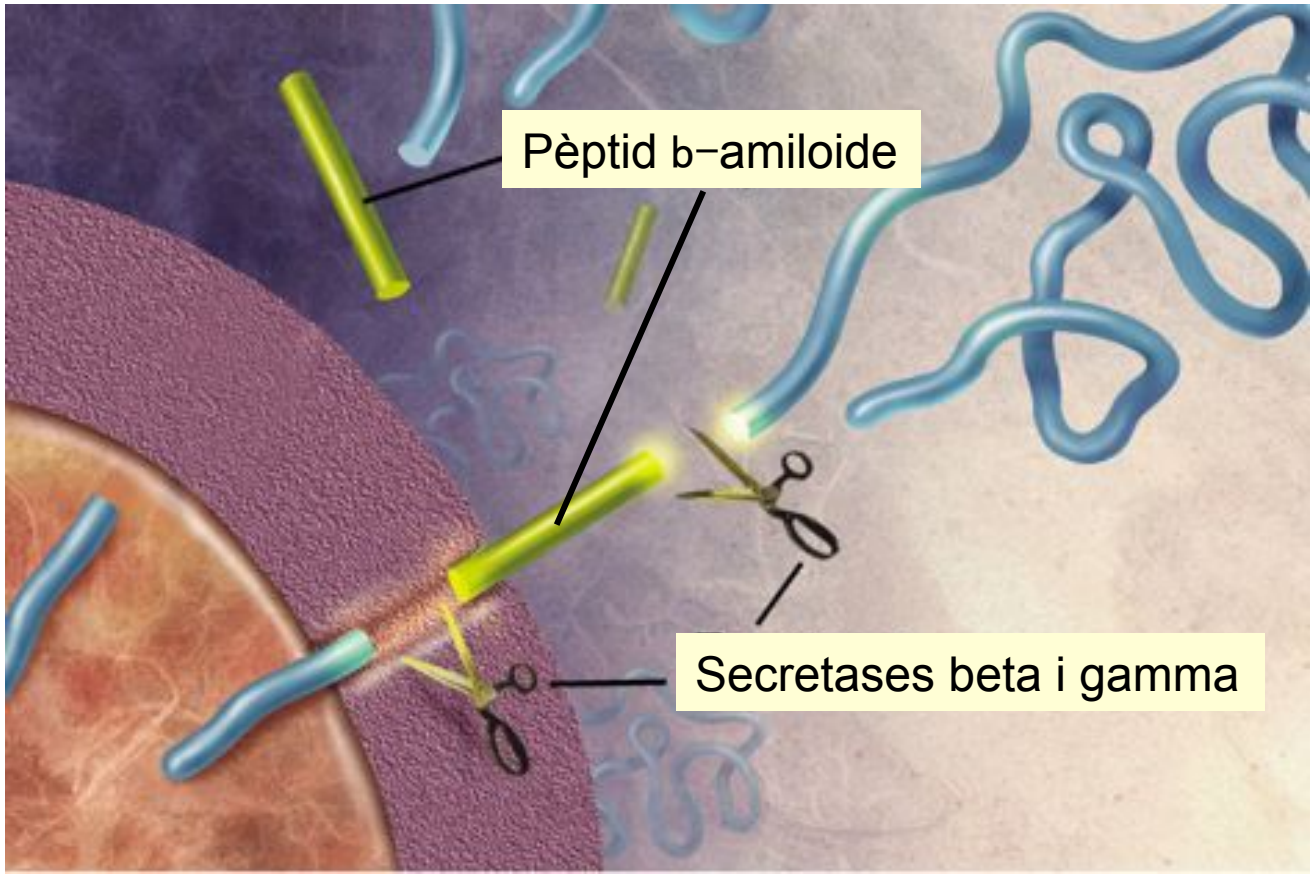




Característiques de la malaltia d'Alzheimer

APP → Pèptid soluble

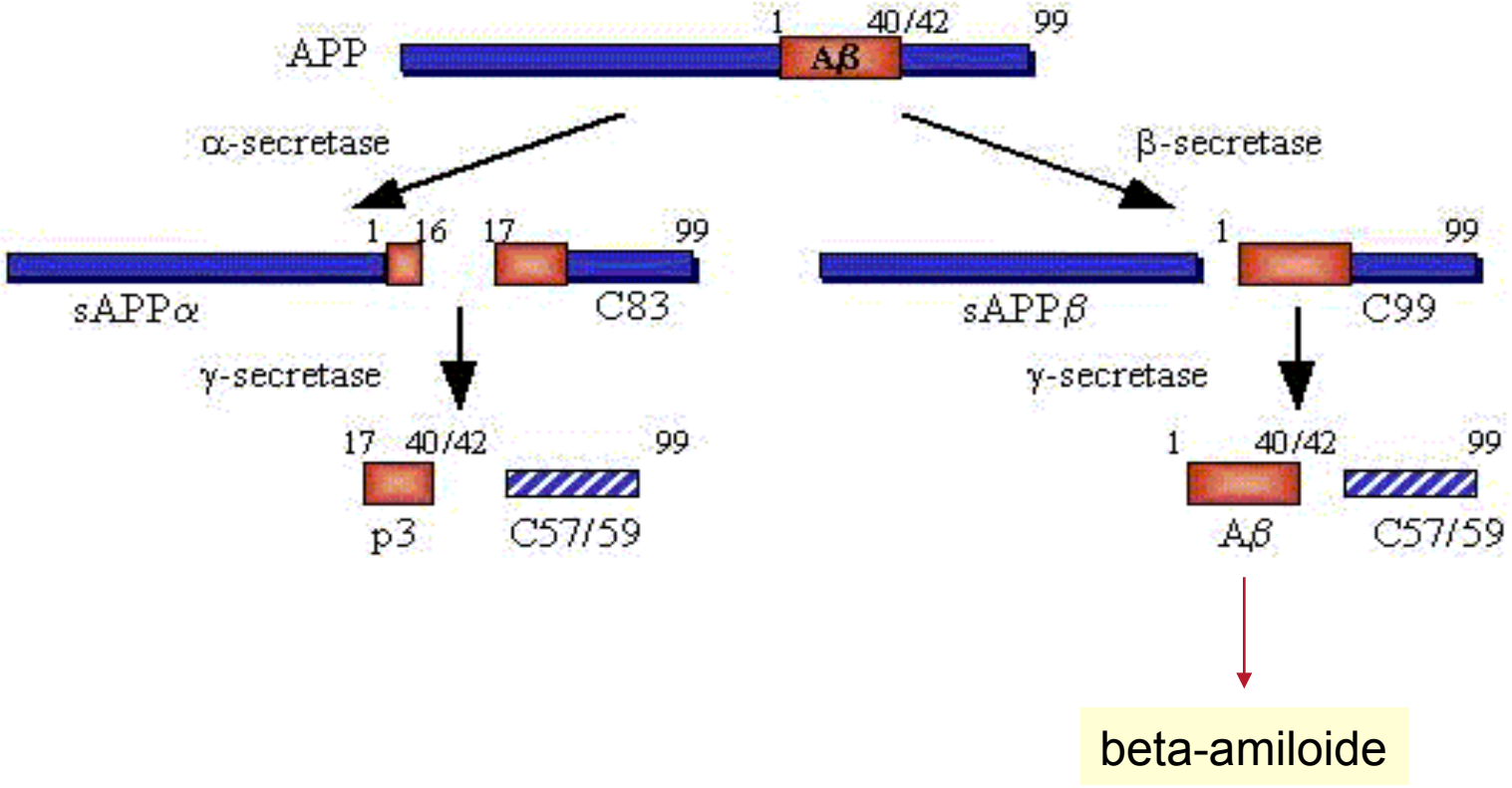
secretases



Característiques de la malaltia d'Alzheimer

APP → Beta-amiloide

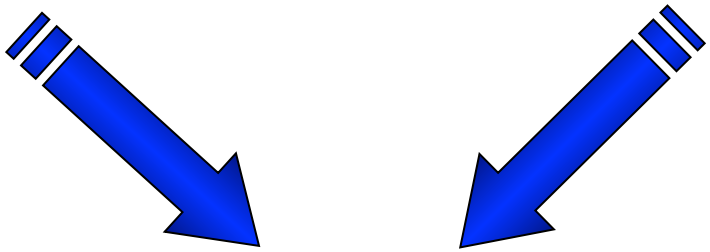
Ruptura proteolítica



Característiques de la malaltia d'Alzheimer

~~¿Entramats neurofibrilars de proteïna tau ?~~

~~¿Formació de Fibres del pèptid beta-amiloide? (Plaques senils)~~



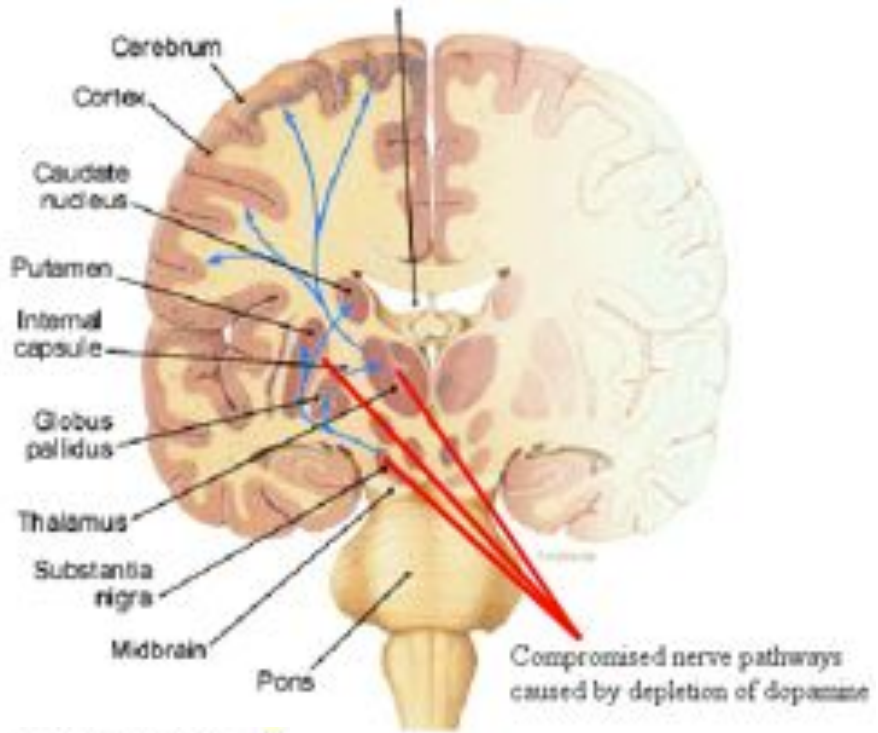
Formació d'estructures oligomèriques

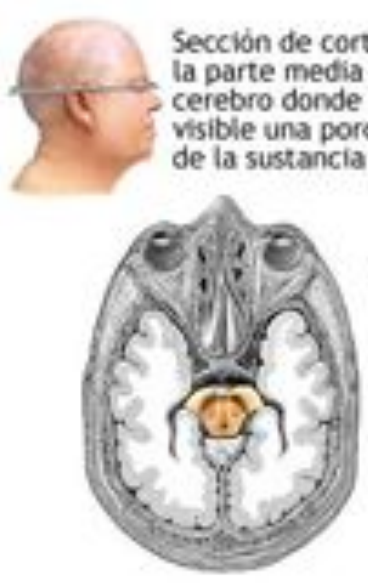
*Estudis realitzats en animals transgènics, in-vivo, ex-vivo i in-vitro

Malaltia de Parkinson

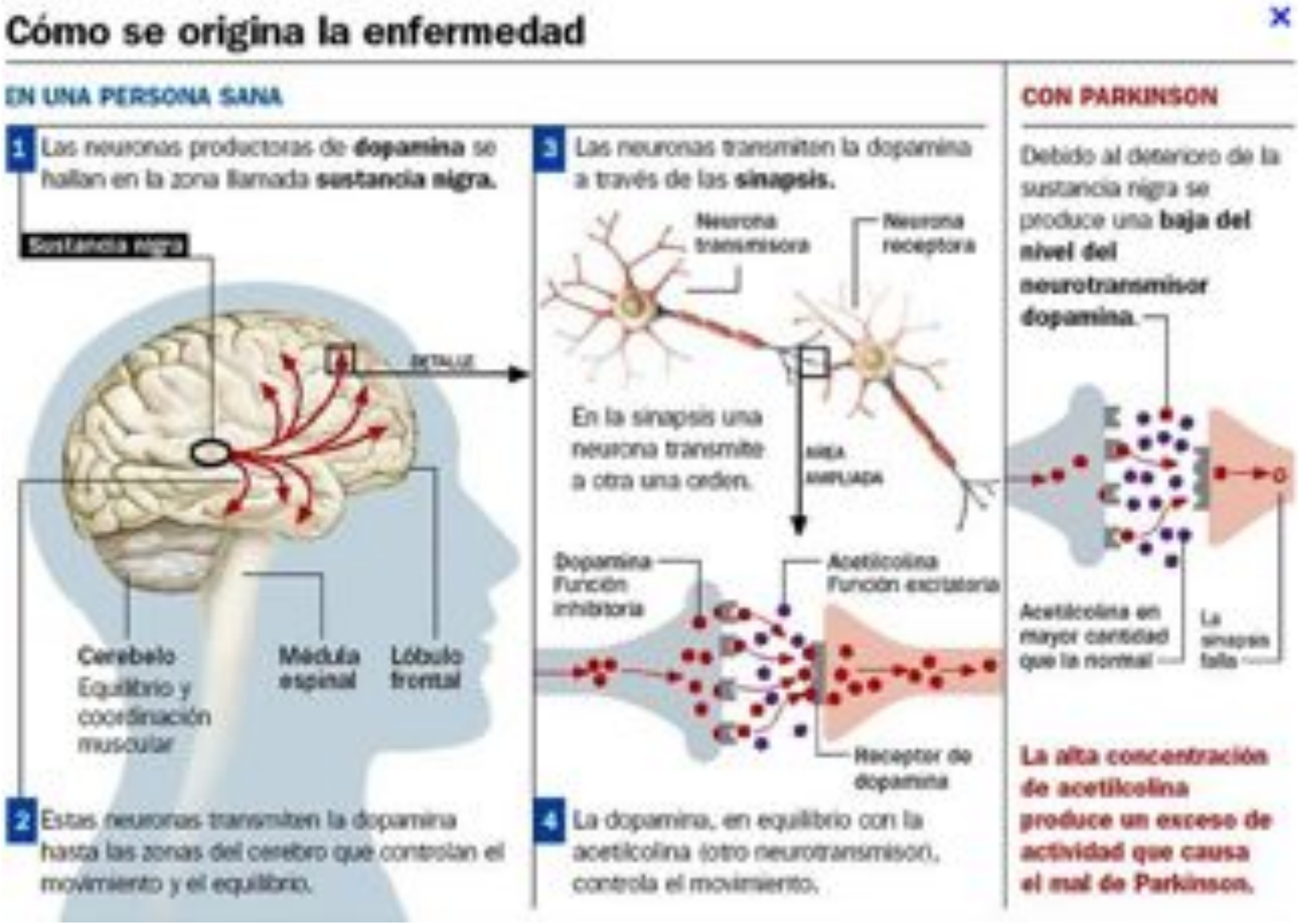
(Sinucleinopaties)

Agregació de l'alfa sinucleïna





Agregació de l'alfa sinucleïna



Agregació de l'alfa sinucleïna

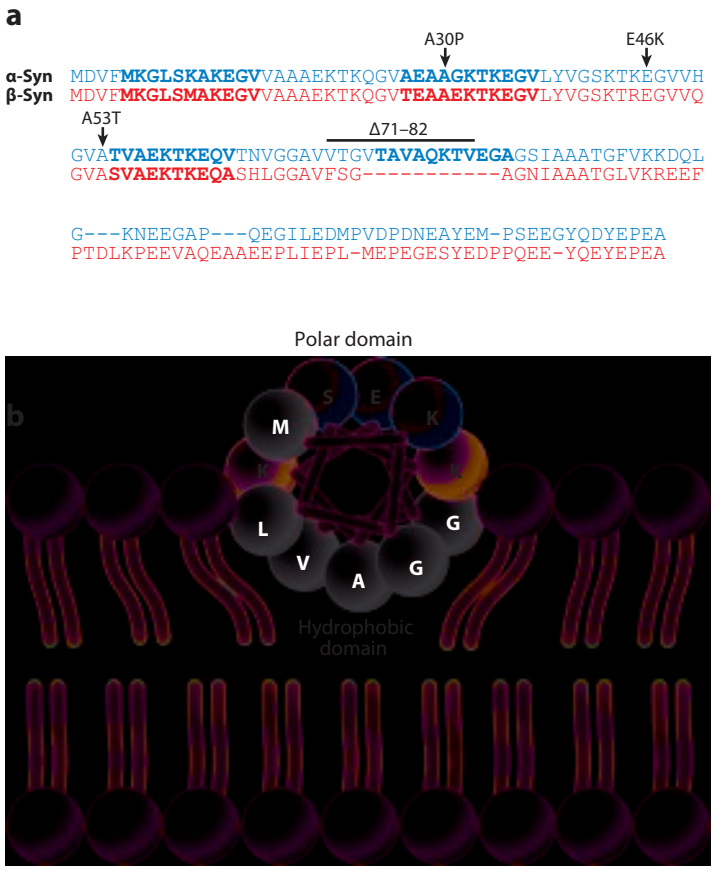


Figure 2

α-Synuclein (α-syn) and β-syn (*red* and *blue*, respectively) are highly homologous. (*a*) The highly conserved, imperfect repeats that form A2-type amphipathic α-helices are in bold. The hydrophobic core (Δ71–82), which is required for α-syn fibrillization in vitro and toxicity in vivo, is indicated by the horizontal line. This hydrophobic domain is absent in β-syn. Arrows identify the location of the point mutations associated with familial Parkinson's disease. (*b*) An axial view of α-syn residues when displayed on an Edmundson helix wheel. Polar residues (i.e., S, E, and K) face the hydrophilic environment of the cytosol, whereas hydrophophic residues are buried in the acyl chains of the phospholipid bilayer. Positively charged lysine residues (K) separate the polar and hydrophobic domains and interact directly with the anionic surface of the phospholipid bilayer.

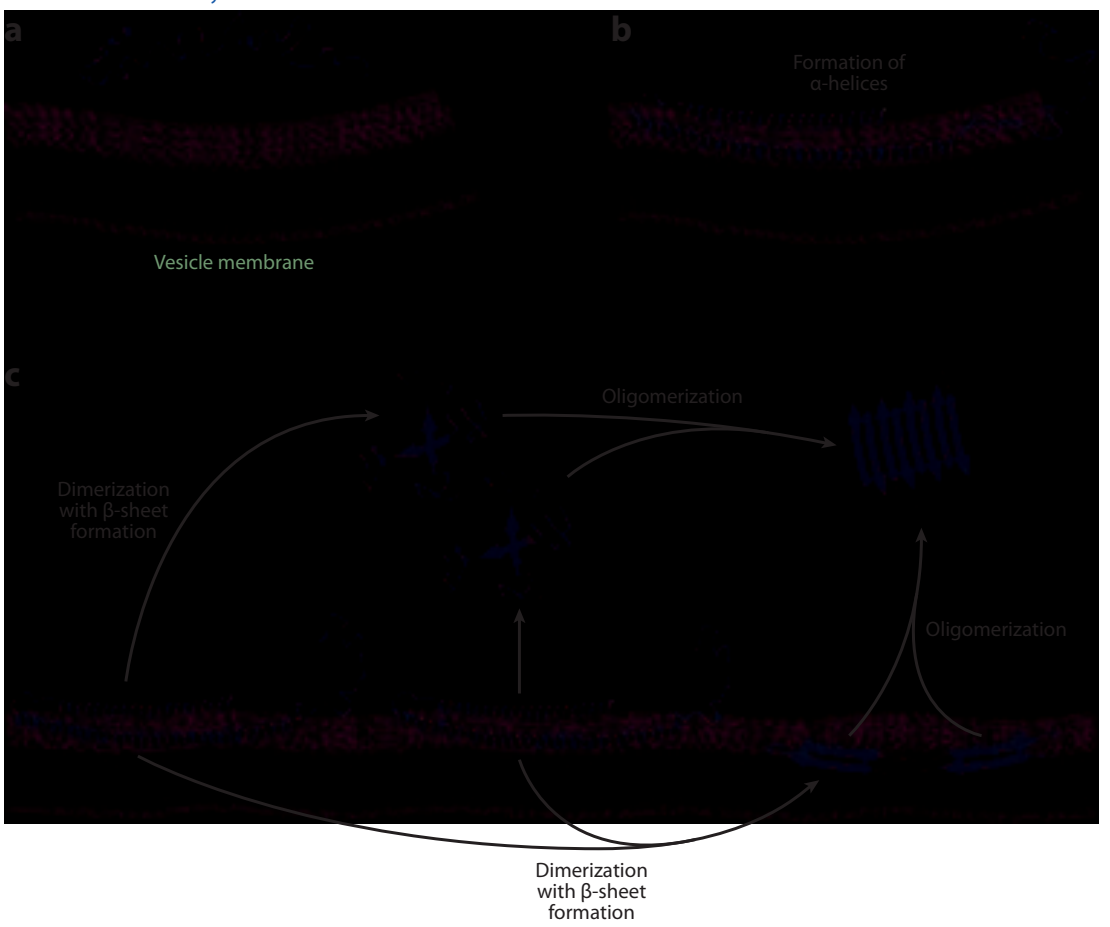


Figure 4

α-Synuclein (α-syn) requires lipid interactions to form dimers, oligomers, and mature amyloid fibrils. (*a*) In solution, α-syn is natively unfolded. (*b*) In the presence of vesicle membranes containing anionic phospholipids, the N terminus of α-syn forms two α-helices that allow it to associate with the surface of the membrane. (*c*) Stabilization of α-syn's membrane interactions (through the A53T or E46K mutations) or increased α-syn concentration (through genetic multiplication) facilitates the formation of α-syn dimers on the membrane surface or in the cytoplasm. Through dimerization, α-syn adopts a β-sheet secondary structure that, through association with α-syn monomers or other dimers, leads to oligomer formation. These oligomers seed fibril formation and deposit as amyloid within Lewy bodies and Lewy neurites.

Agregació de l'alfa sinucleïna i formació Cossos de Lewis

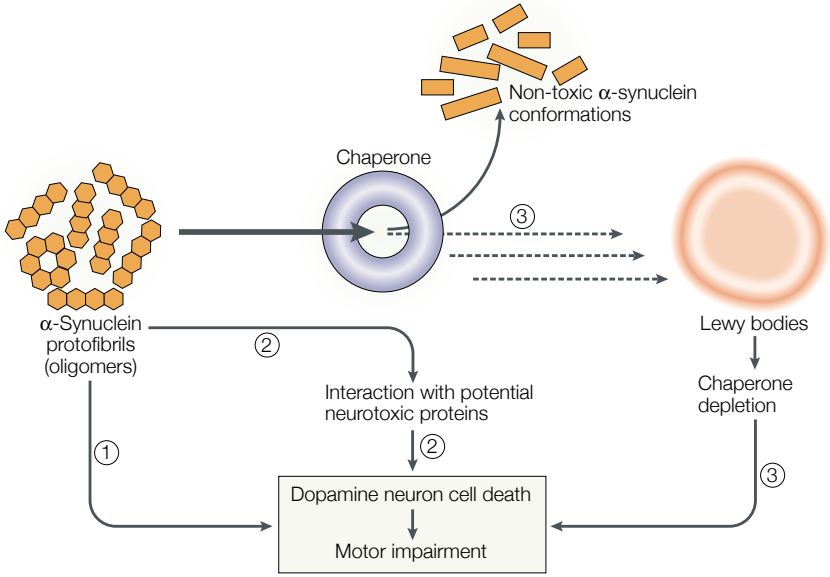


Figure 3 | **Relationship between chaperone molecules and α-synuclein toxicity.** It has been proposed that chaperones might alter the conformation of highly toxic protofibrils or oligomers — the intermediates of fibril formation — and reduce their neurotoxicity through changes in protein structure (1). By modulating the structure of α-synuclein, chaperones inhibit their interaction with other neurotoxic proteins that would activate cell death pathways (2). In the synucleinopathies, chaperone molecules become sequestered in Lewy bodies and Lewy neurites, leading to chaperone depletion, which might be directly responsible for cell death (3) (REF. 71).

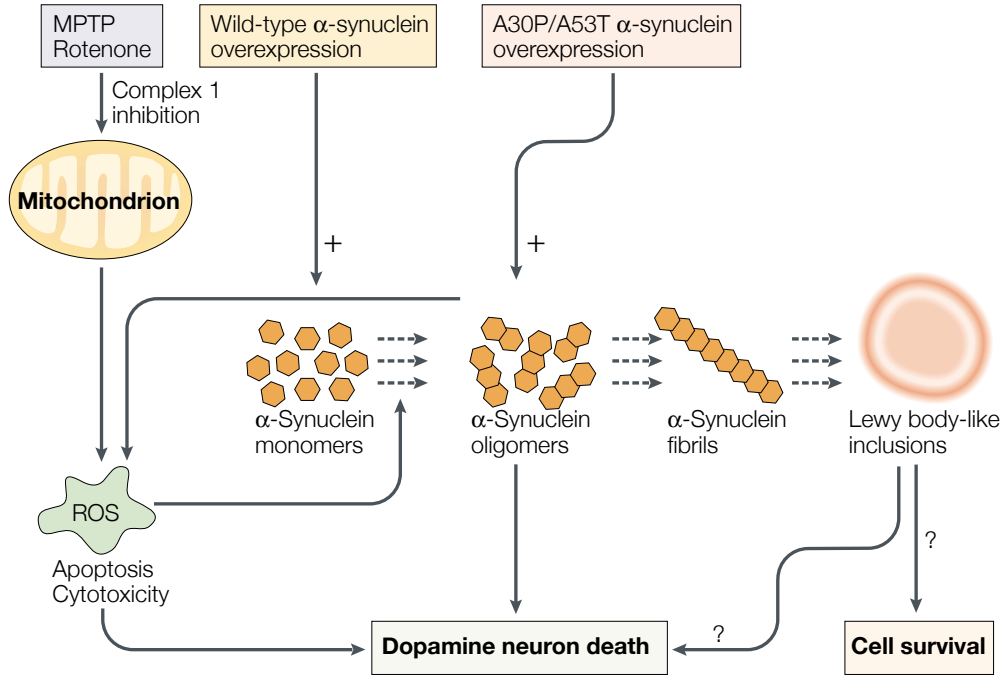


Figure 4 | **Generation of animal models of the synucleinopathies.** Animal models of the synucleinopathies have been created using neurotoxins (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or rotenone) or by overexpressing α-synuclein. In both cases, α-synuclein accumulates in the cells, leading to formation of protofibrils, fibrils, and occasional inclusion bodies. Overexpression of A30P or A53T α-synuclein results in an increased concentration of α-synuclein oligomers. Overexpression of wild-type α-synuclein leads to an increased concentration of α-synuclein monomers, which then undergo oligomerization and form fibrils. When inhibitors of mitochondrial complex I such as MPTP and rotenone are used, radical oxidative species (ROS) are formed, and apoptotic or cytotoxic cascades are activated, ultimately leading to death of dopamine neurons. The ROS also induce α-synuclein aggregation and protofibril formation[29,30]. The protofibrils can then lead to further ROS production[31,32], generating a feedforward process that could potentiate neuronal degeneration.

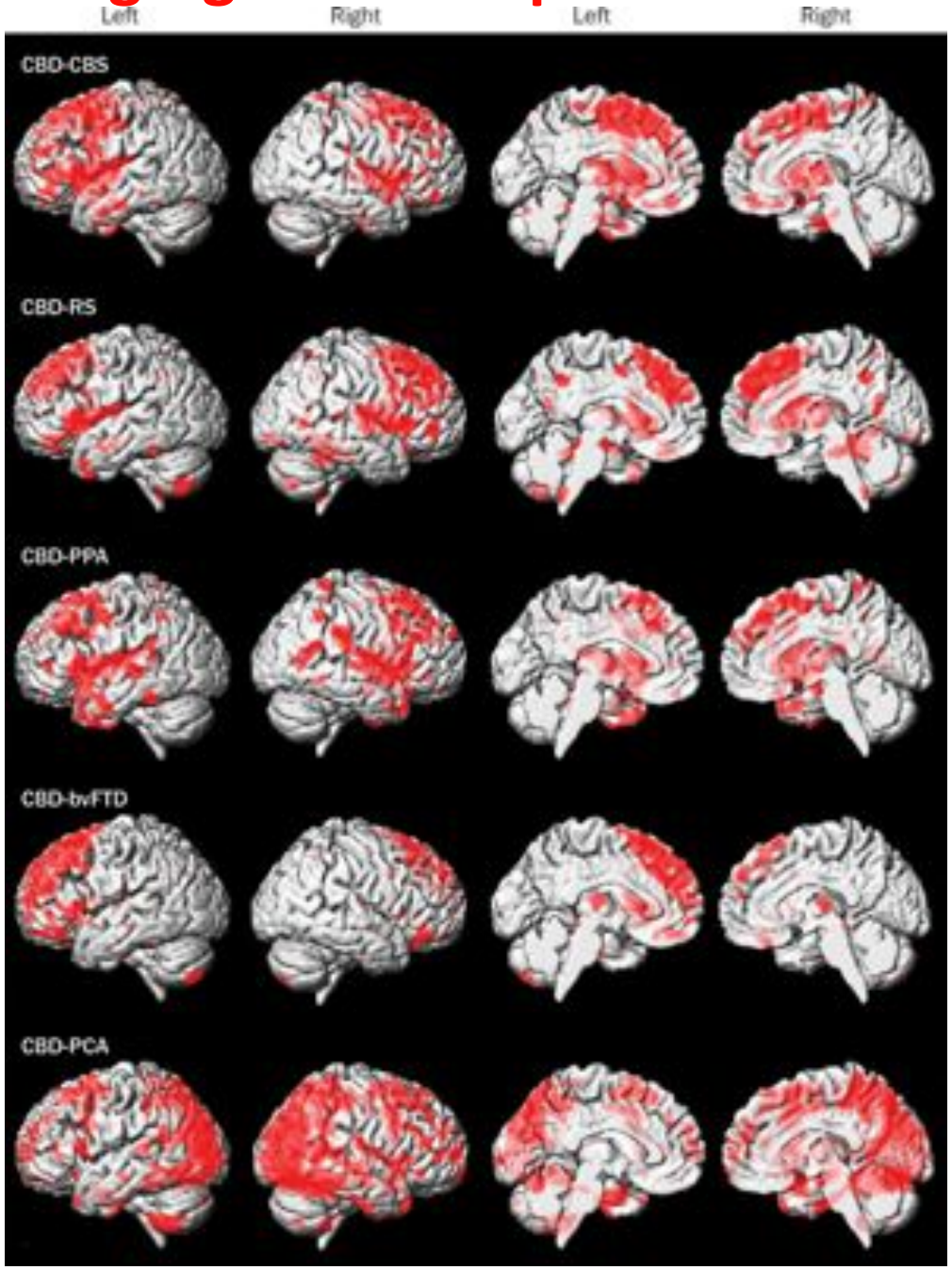
Demència Frontotemporal

(Tautopaties)

Agregació de la proteïna Tau

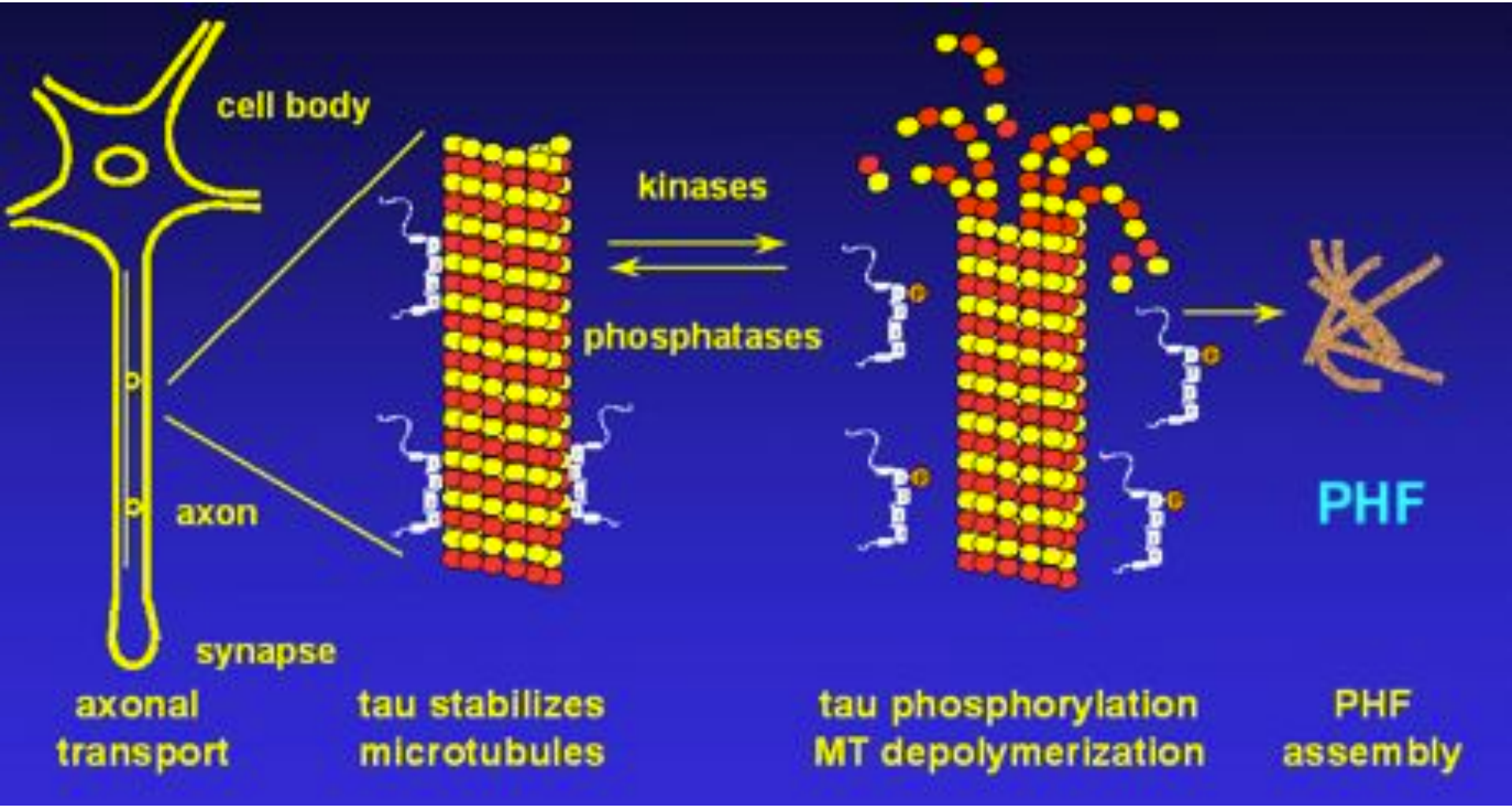
Proteinopathies (aberrant aggregation)			
Disease	Protein	Pathological finding	Protein conformation
Prion diseases	PrP^{Sc}	PrP amyloid plaques	β-sheet
Alzheimer's disease	Aβ	Aβ amyloid plaques	β-sheet
	Tau	Paired helical filaments in neurofibrillary tangles	β-sheet + α-helix
Parkinson's disease	α-synuclein	Lewy bodies	β-sheet + α-helix
Frontotemporal dementia	Tau	Straight filaments and paired helical filaments	—
Pick's disease	Tau	Pick bodies	—
Progressive supranuclear palsy	Tau	Straight filaments is neurfibrillary tangles	—
Amyotrophic lateral sclerosis	Neurofilament	Neural aggregates	—
Huntington's disease	Huntingtin	Nuclear inclusions	β-sheet
Spinocerebellar ataxia			
Type 1	Ataxin 1	Nuclear inclusions	β-sheet
Type 2	Ataxin 2	Cytoplasmic inclusions	β-sheet
Machado-Joseph disease	Ataxin 3	Nuclear inclusions	β-sheet

Agregació de la proteïna Tau

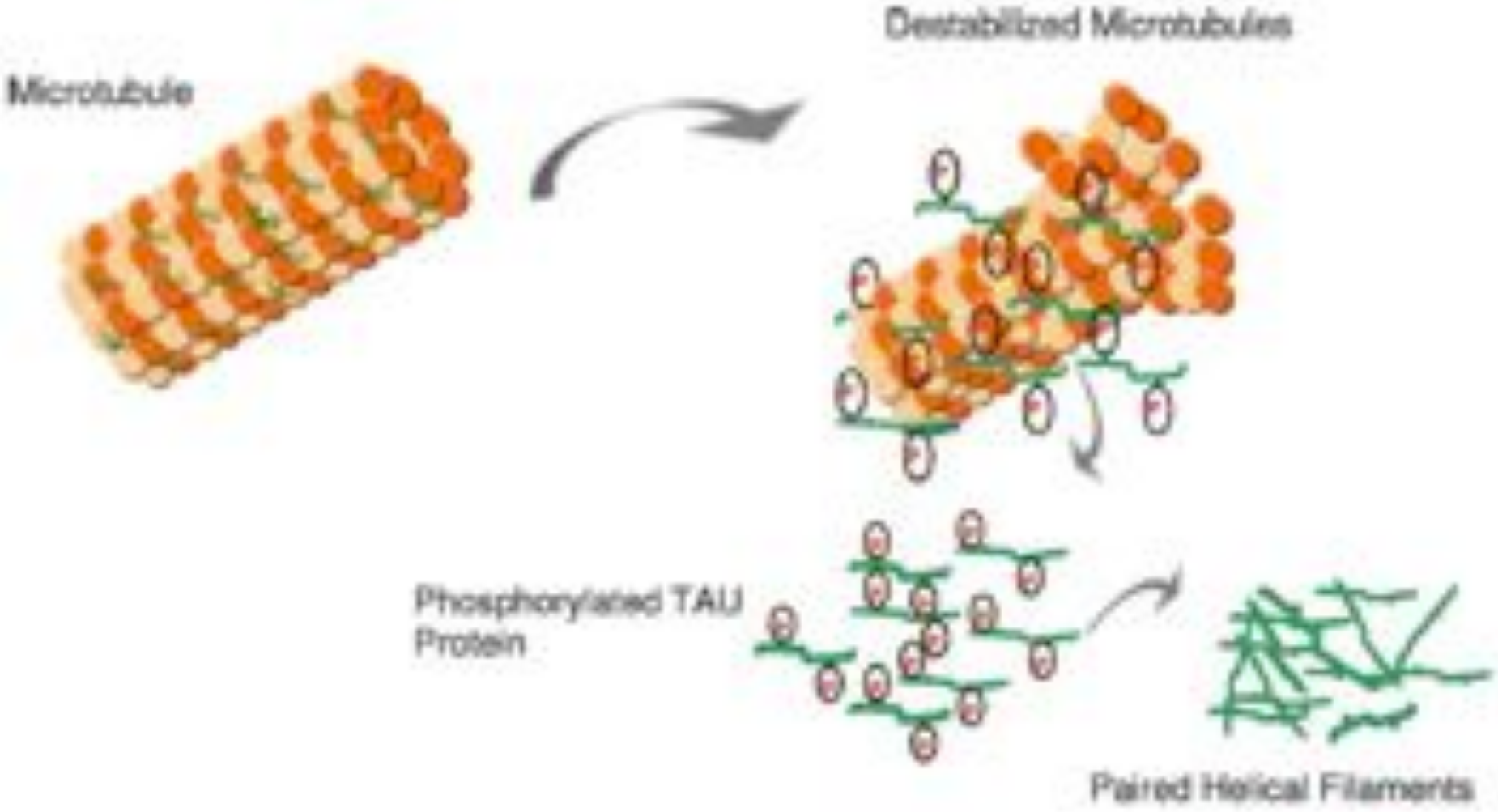


Kouri, N. *et al.* (2011) Corticobasal degeneration: a pathologically distinct 4R tauopathy

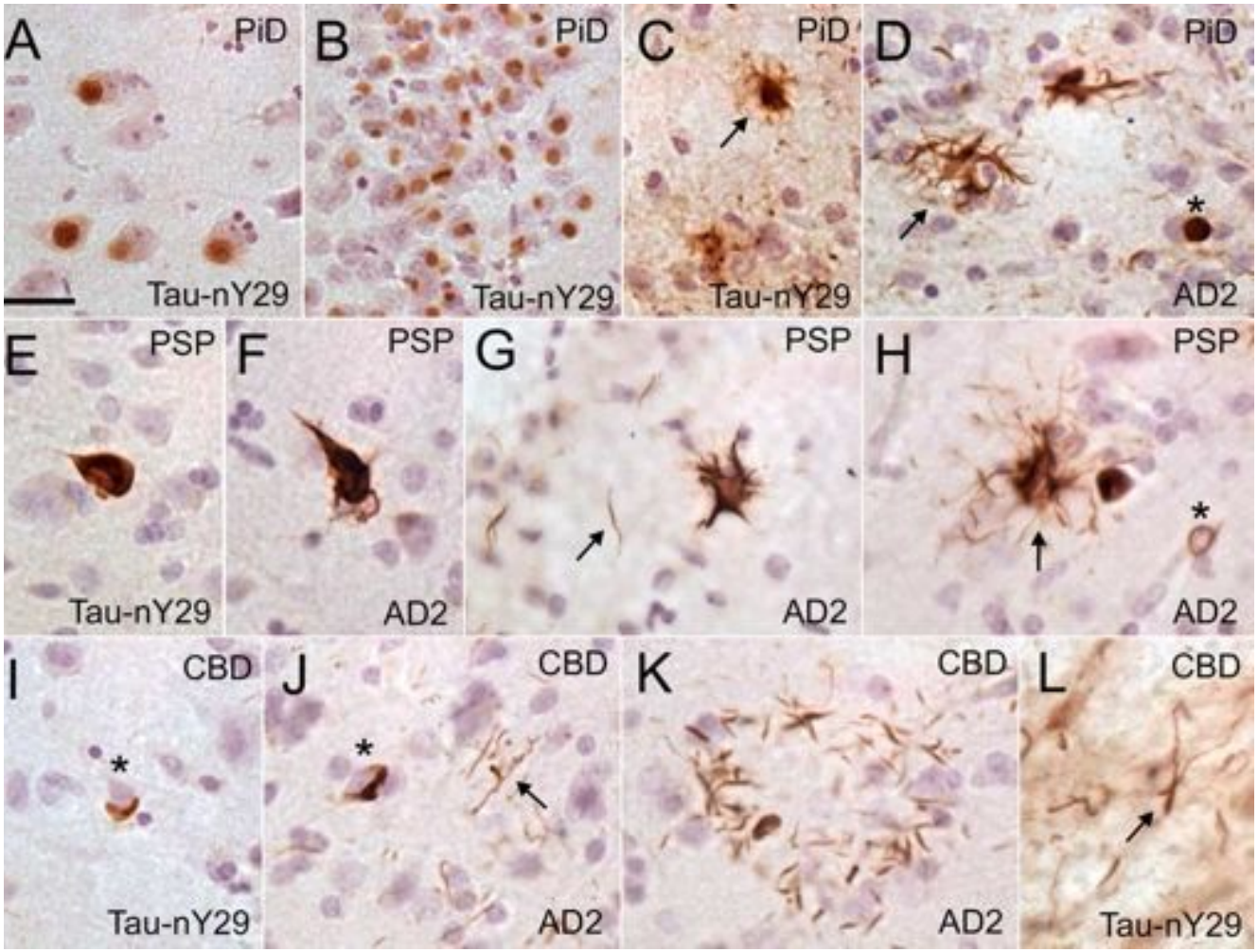
Agregació de la proteïna Tau



Agregació de la proteïna Tau



Agregació de la proteïna Tau

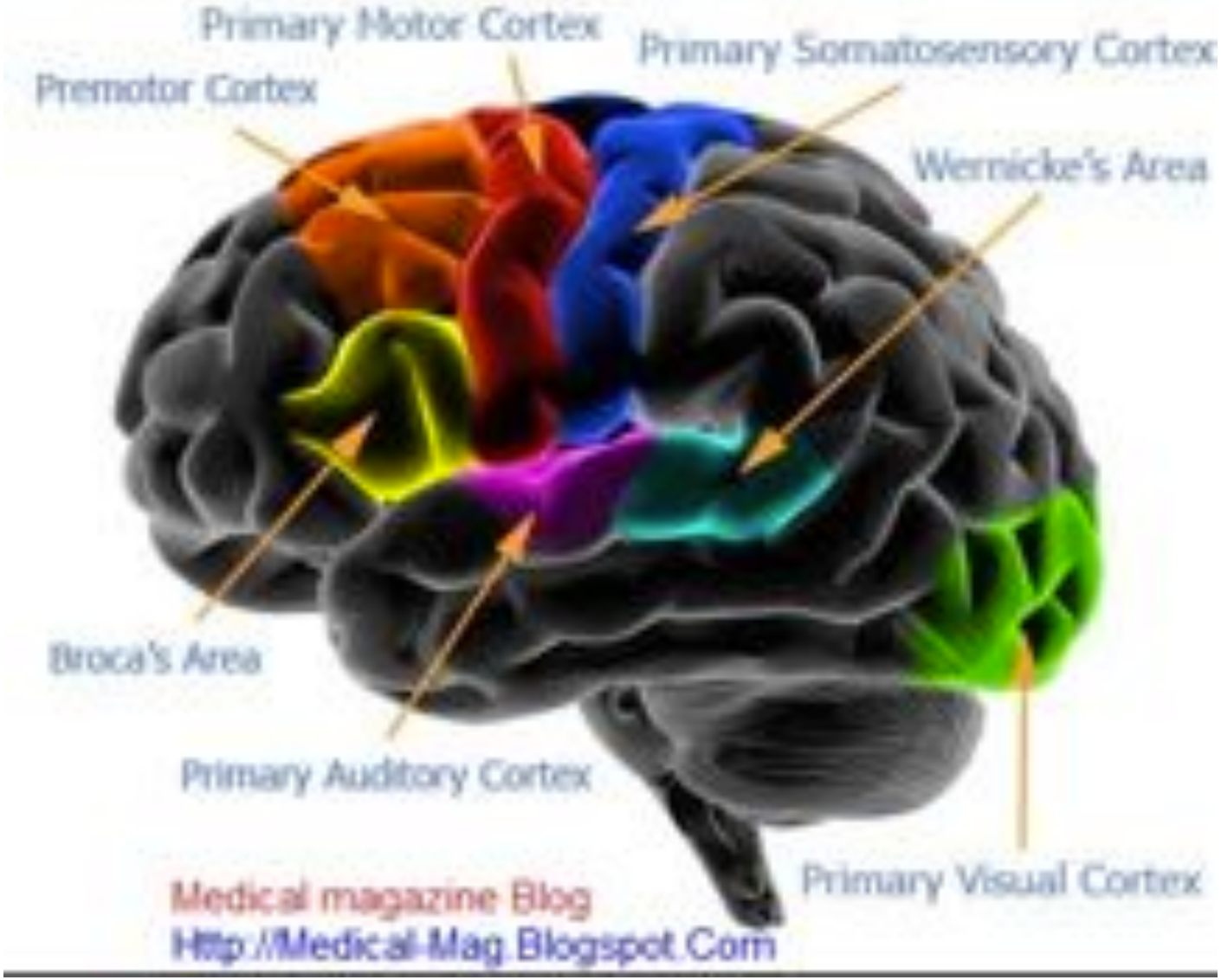


gure 6. Tau-nY29 differentially labels the fibrillar tau inclusions of non-AD tauopathies. In PiD cases, Tau-nY29 stains numerous Pick body inclusions in the frontal cortex (***A***) and granular cell yer of the dentate gyrus (***B***). ***C***, Ramified astroglia (arrow) also exhibit robust labeling with Tau-nY29. ***D***, The AD2 antibody, which serves as a positive control for tau pathology in the non-AD uopathies, labels both the ramified astroglia (arrow) and Pick bodies (asterisk). ***E***, ***F***, In PSP, Tau-nY29 detects globose NFTs in the frontal cortex. Notably, the glial pathology of PSP, including thorny troglia (***G***), tufted astroglia (***H***, arrow), and coiled bodies (***H***, asterisk), lacks Tau-nY29 reactivity. Moreover, Tau-nY29 exhibits little-to-no staining of neuritic threads (***G***, arrow) in the gray matter the frontal cortex. The perinuclear inclusions of CBD are highly reactive toward both the Tau-nY29 (***I***, asterisk) and AD2 (***J***, asterisk) antibodies. However, the neuritic thread-like processes (***J***, arrow) d astroglial plaques within the frontal cortex (***K***) lack significant Tau-nY29 staining. ***L***, Dense Tau-nY29-positive threads (arrow) were observed in the pons of CBD cases. Scale bar, 25 μm.

Malaltia de Huntington

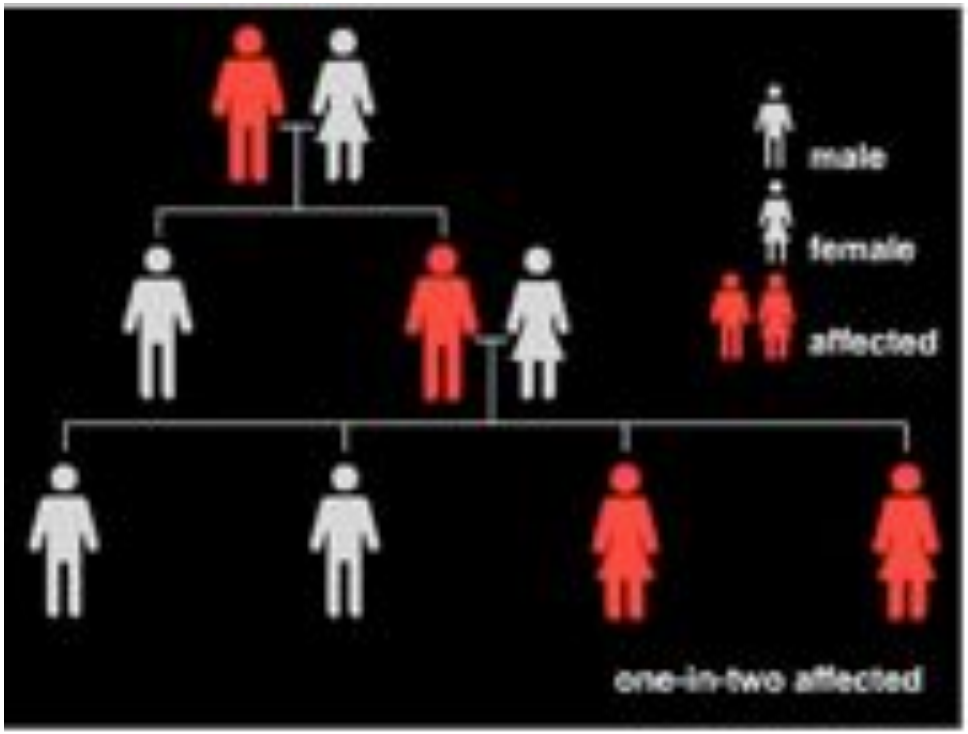
(poliQpaties)

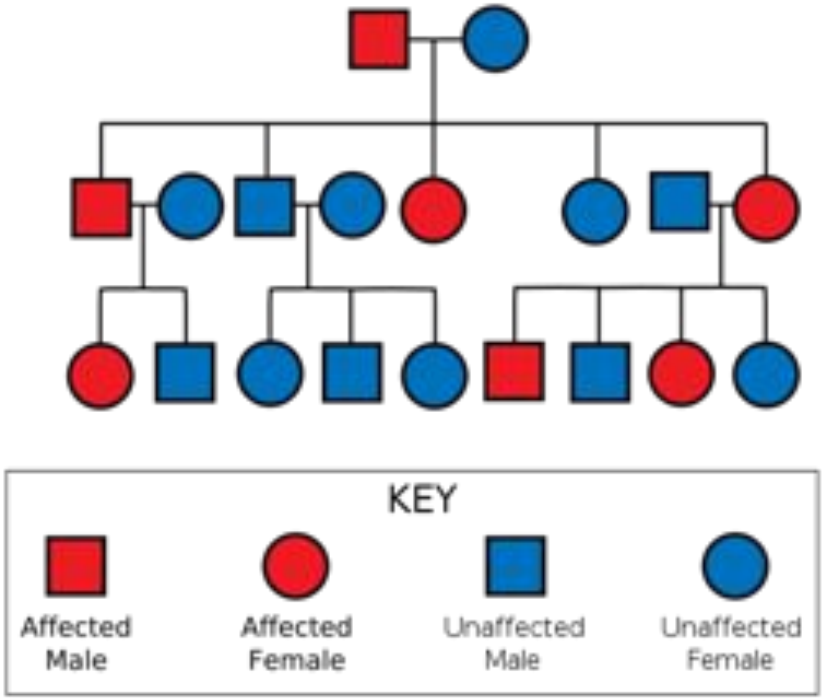
Afectació


Primary Motor Cortex
Primary Somatosensory Cortex
Premotor Cortex
Wernicke's Area
Broca's Area
Primary Auditory Cortex
Primary Visual Cortex
Medical magazine Blog
Http://Medical-Mag.Blogspot.Com

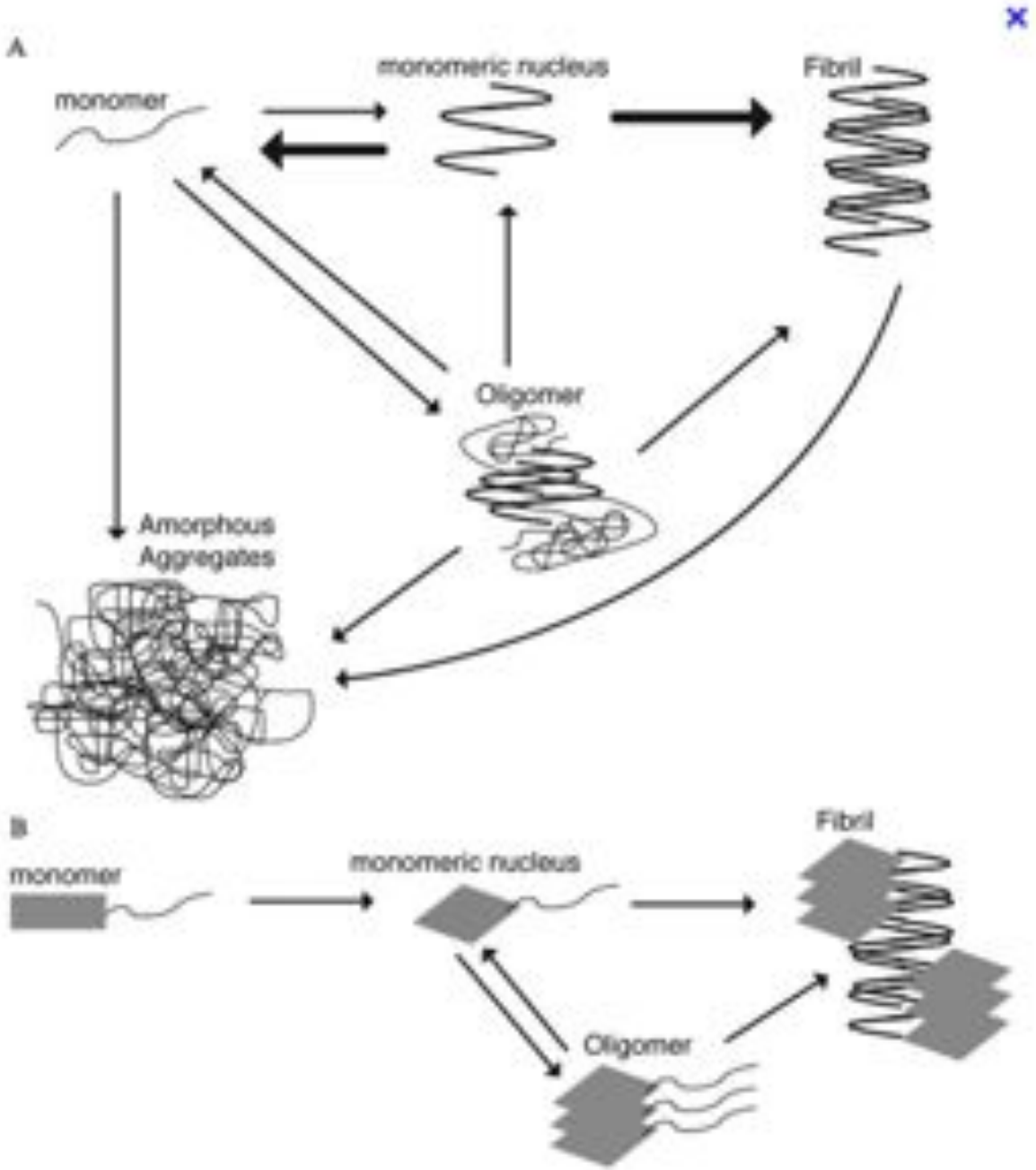

Huntington's Disease Affects the Brain's Basal Ganglia
Basal Ganglia

Genètica: Autosòmica dominant

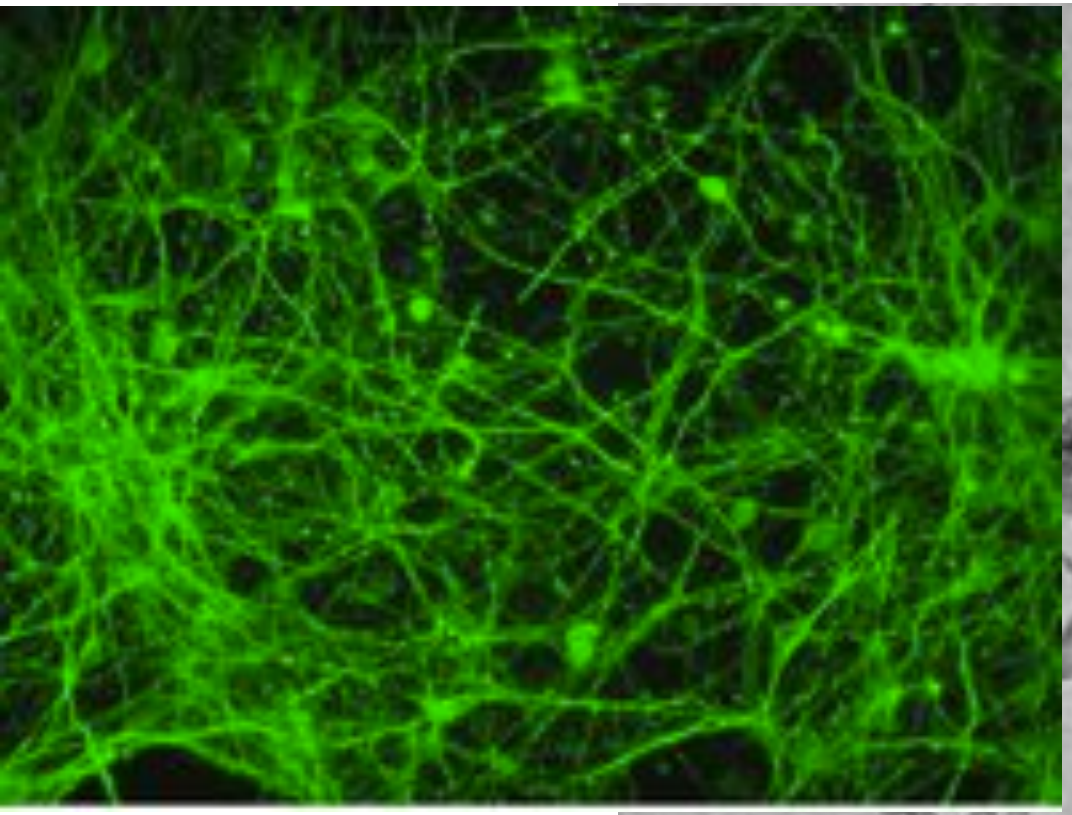


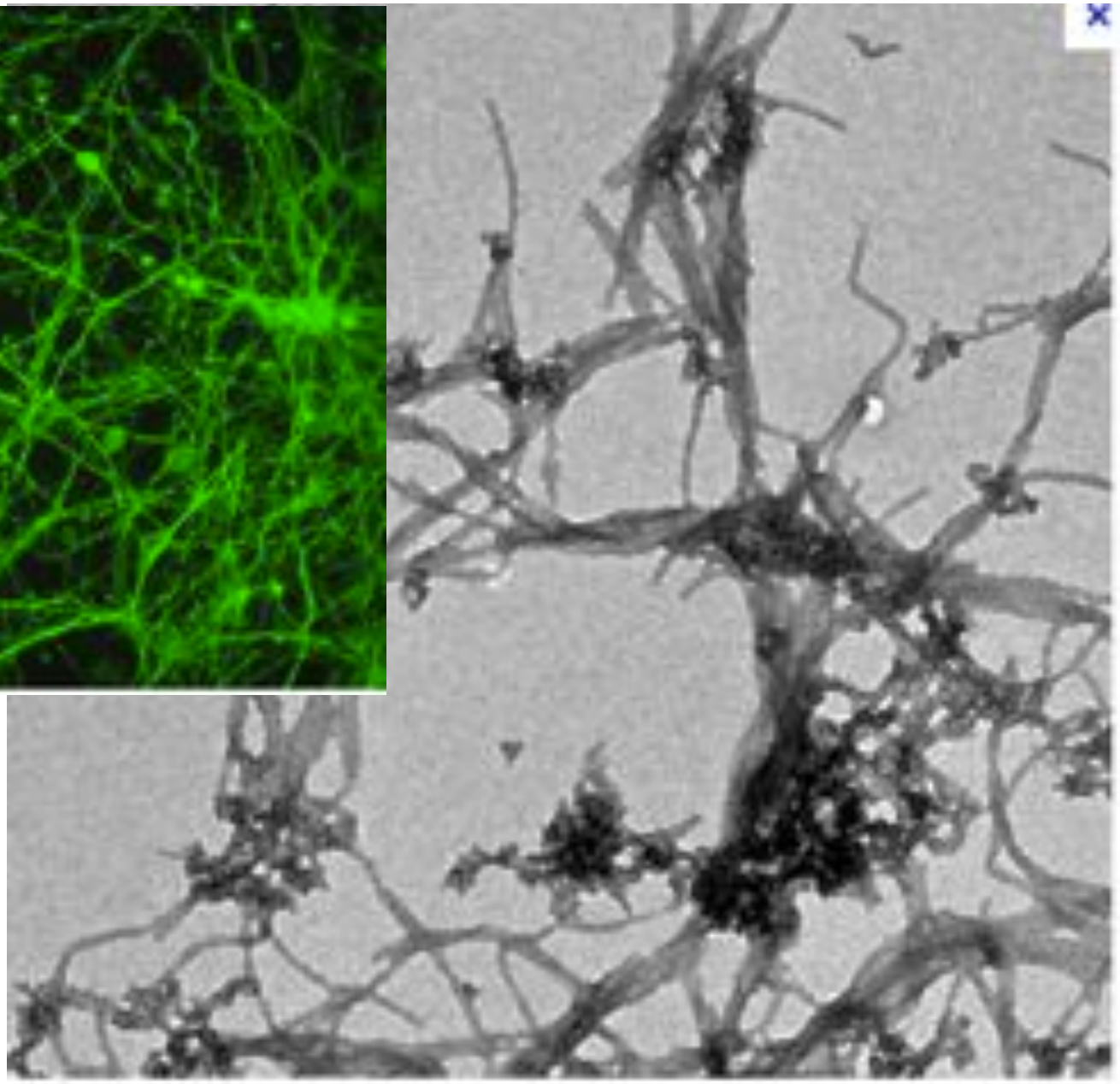


Agregació de la huntingtina



Agregació de la huntingtina

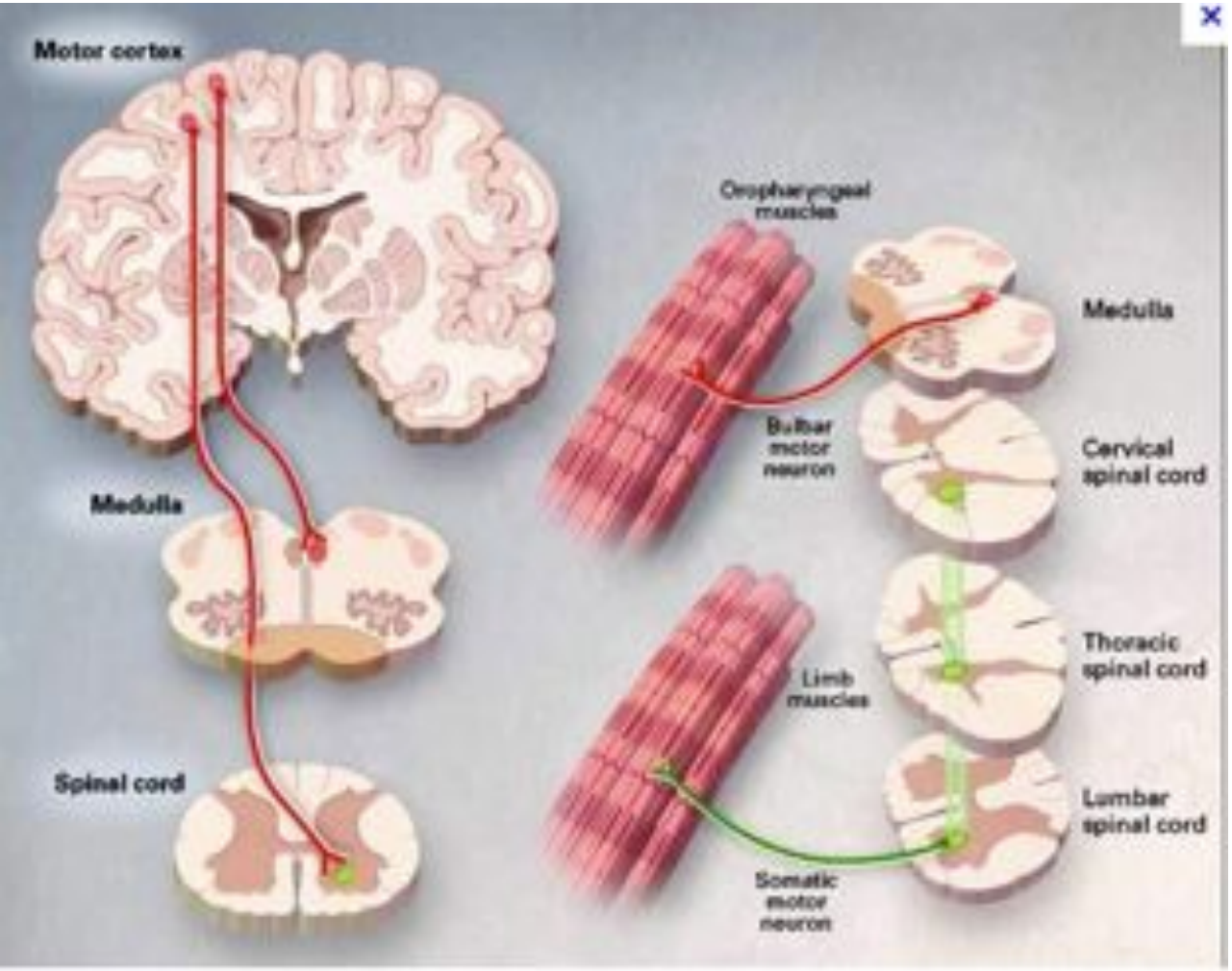




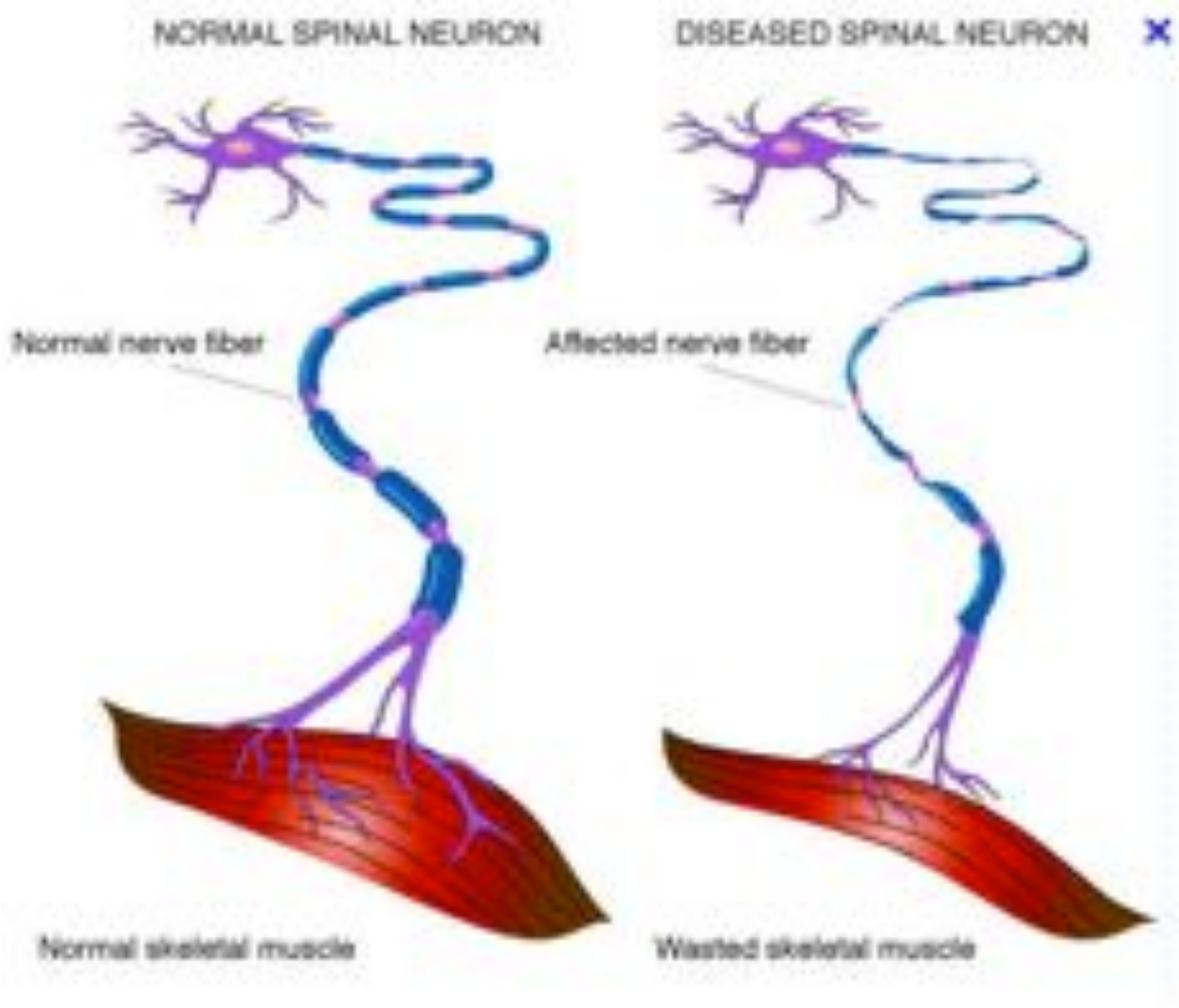
Esclerosi Lateral Amiotròfica

(Superoxid dismutasopatia)

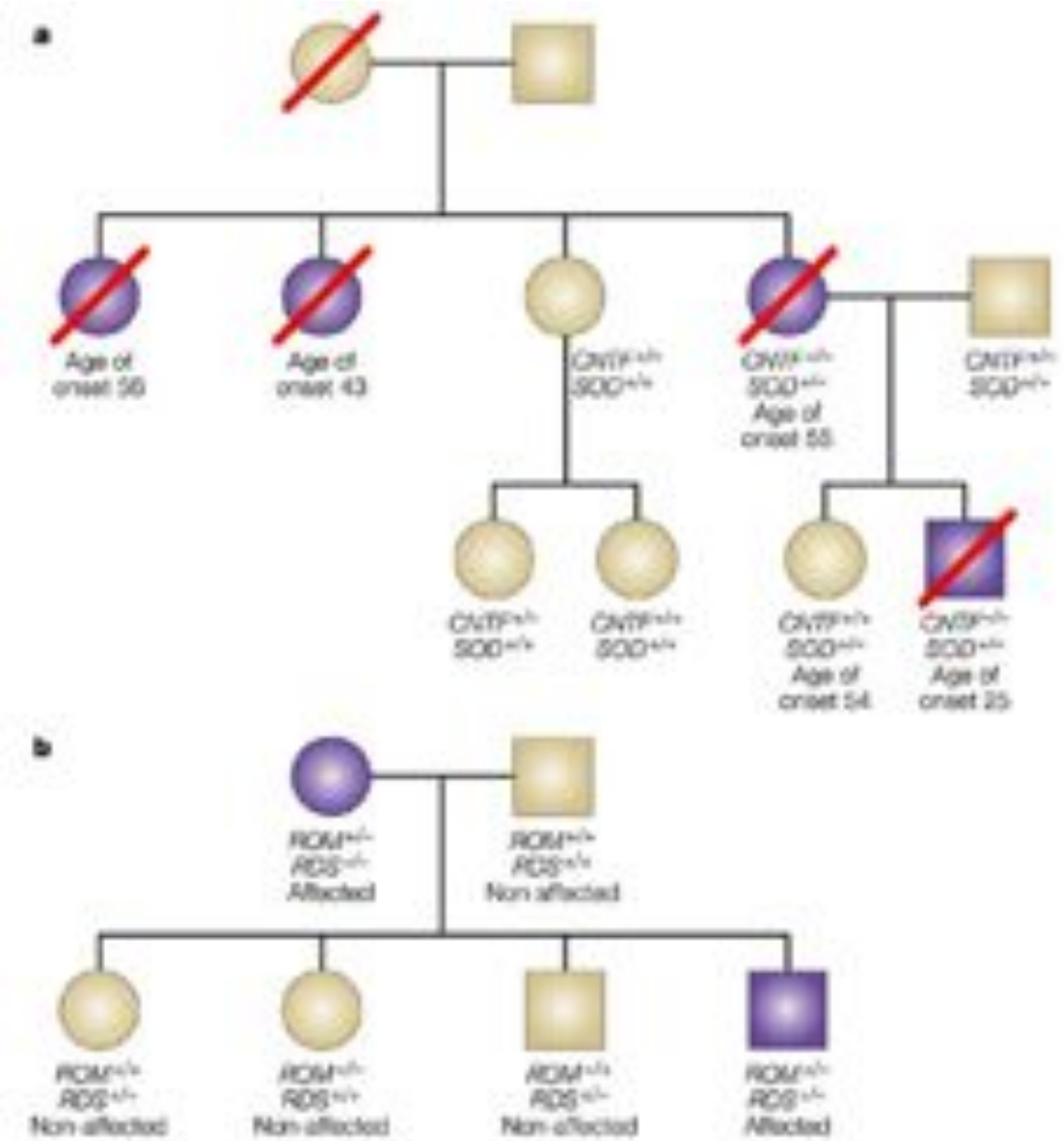
Esclerosi Lateral Amiotròfica - ALS



Esclerosi Lateral Amiotròfica - ALS

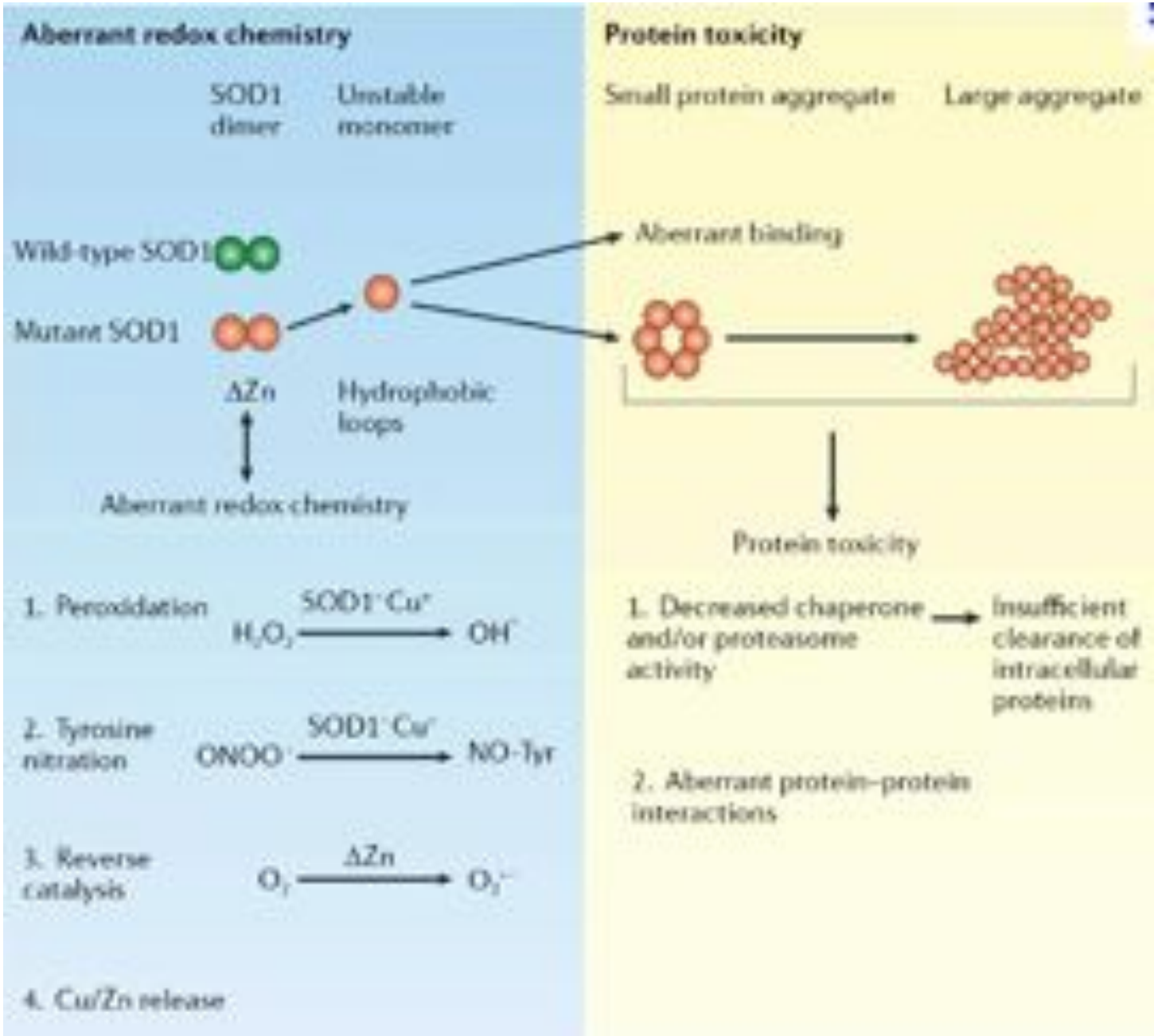


Esclerosi Lateral Amiotròfica - ALS



Nature Reviews | Genetics

Superoxid dismutasa – SOD1



Encefalopaties espongiformes

(Proteïna Prió)

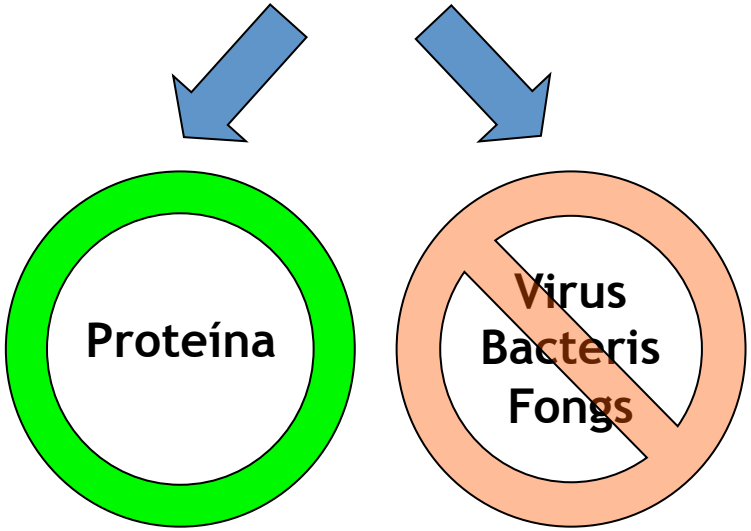
Prió com agent infecciós

Stanley Prusiner

Prió: El suposat «virus lent» (1974)

No detecció de àcid nuclèic

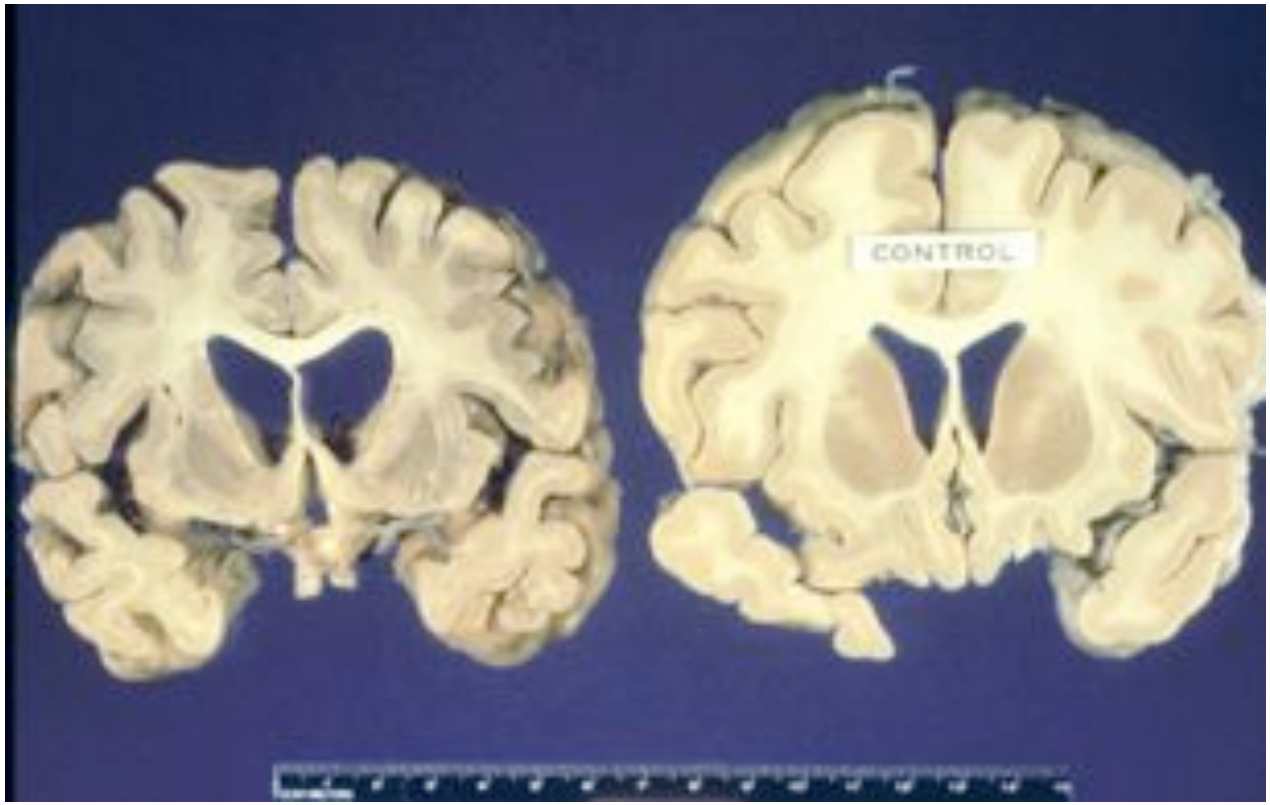
Definició de prion com nou agent infecciós (1982)



Premi Nobel de medicina en 1997

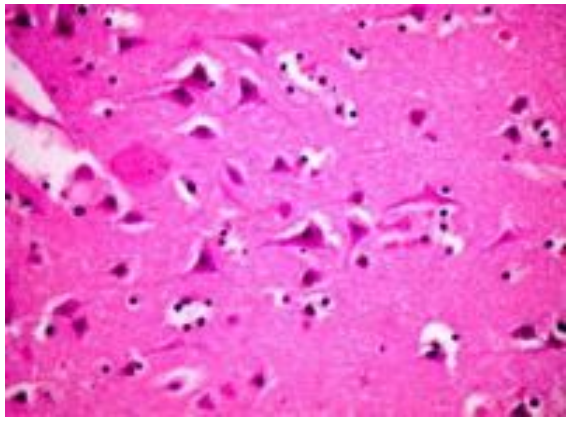
Malaltia de Creutzfeldt-Jakob: Característiques

- Encefalopatia: Acumulació d'agregats proteics en forma de cossos d'inclusió
- Epidemiologia 1980-1990s.
- Causa: espontània o associada al consum de carn contaminada, instrumental quirúrgic, transplantaments d'òrgans, teràpies hormonals i vacunacions...

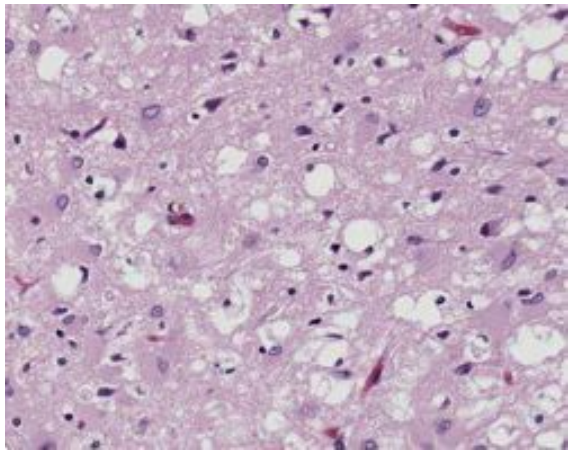


Malaltia de Creutzfeldt-Jakob: Característiques

Degeneració del sistema nerviós central, pèrdua de la coordinació, insomni i demència.



L'aparició d'esta simptomatologia està associada a l'increment de neurotoxicitat, stress cel·lular i mort cel·lular, i neurodegeneració.



Malaltia de Creutzfeldt-Jakob: Proteïna PrP

PrP^{C} → PrP^{SC}

Diposits infecciosos al cervell

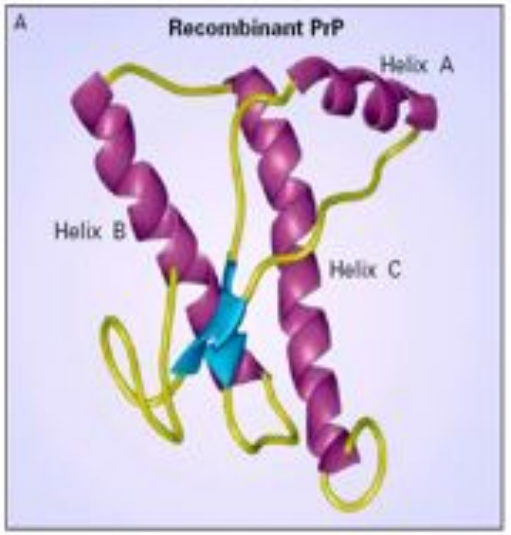
↓

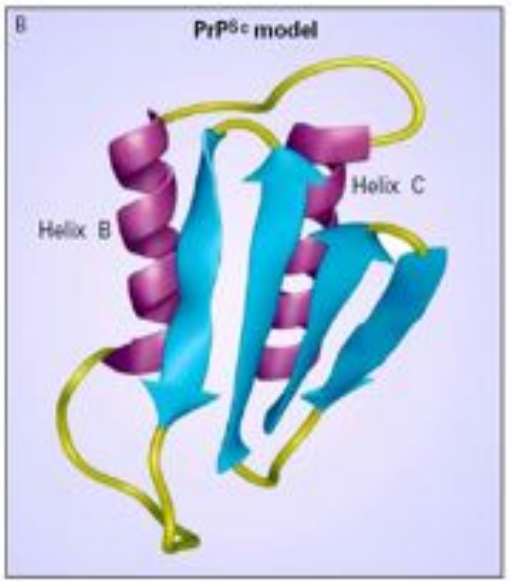
PrP acumulada

Material infecciós protèic

Prion : « small ***pro***teinaceous ***in***fectious particles »

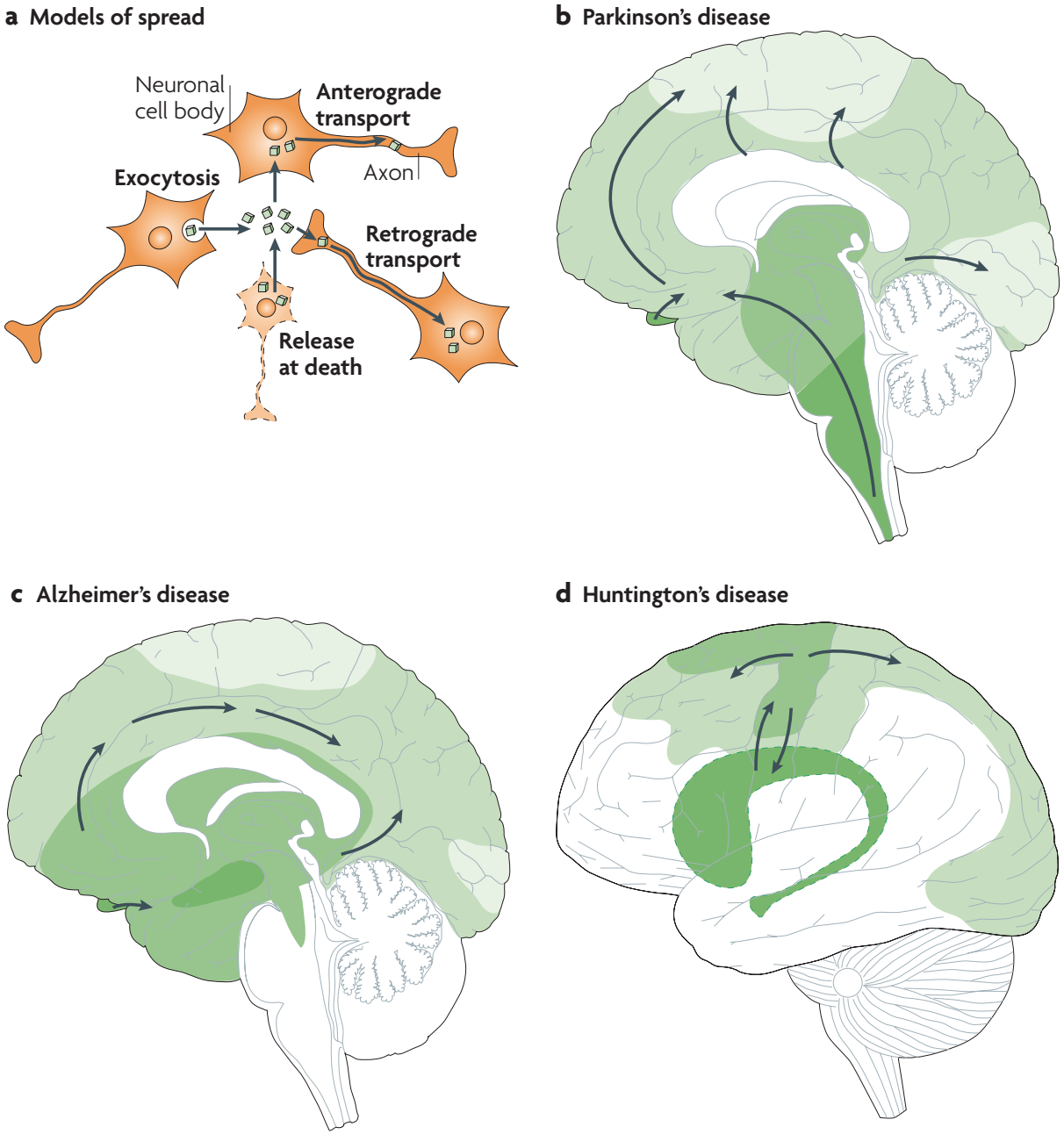
(Prusiner, 1982)





Hipòtesis « protein-only »

Malaltia de Creutzfeldt-Jakob: Bases de l'agregació

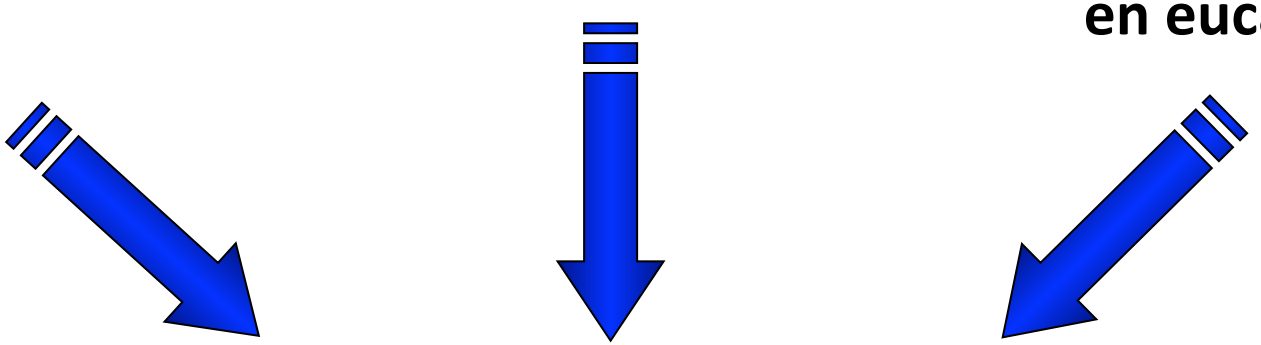


Intervenció en malalties conformacional

Estudis *in vitro*

Estudis *in vivo* en procariota

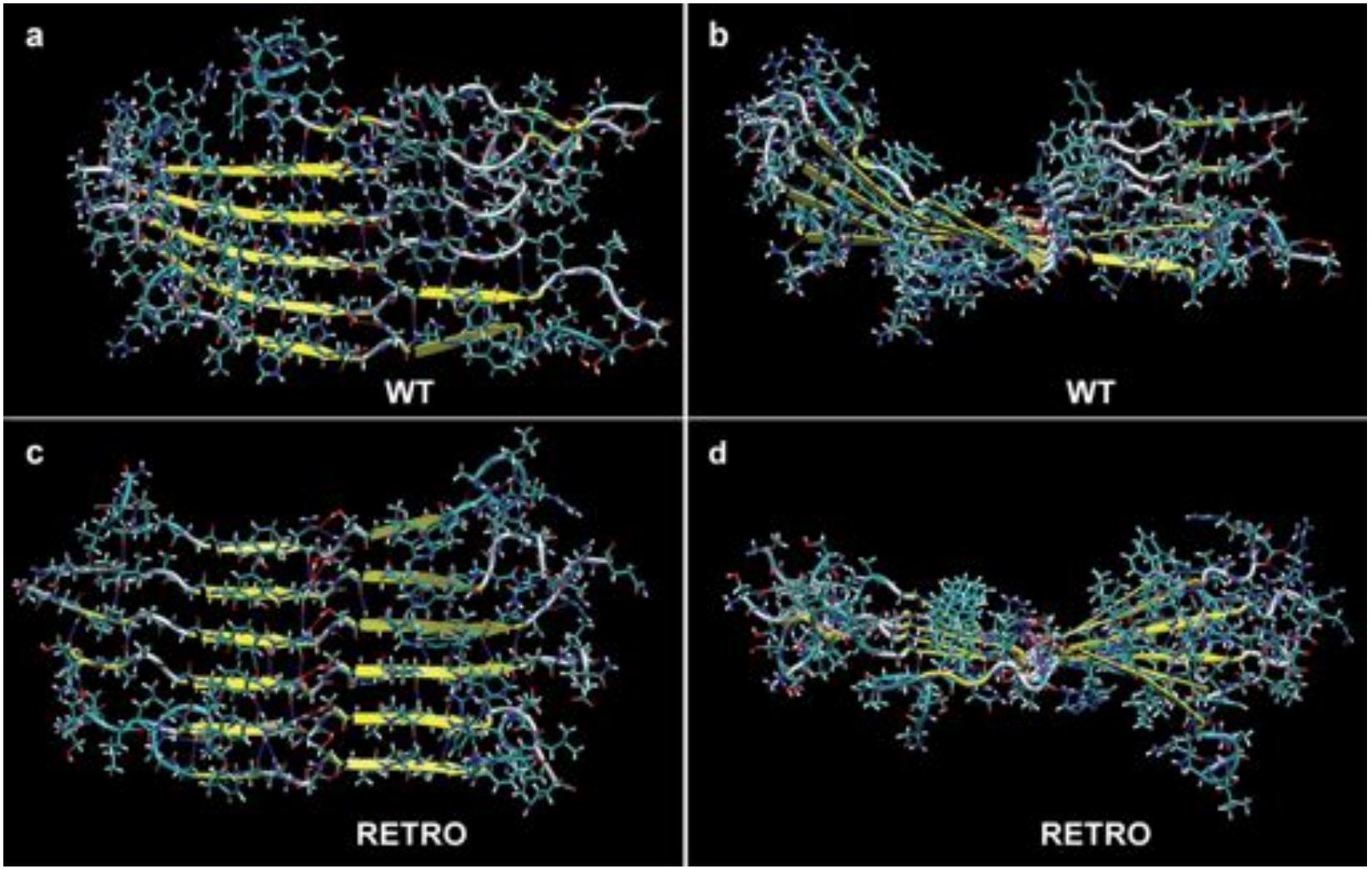
Estudis *in vivo* en eucariota



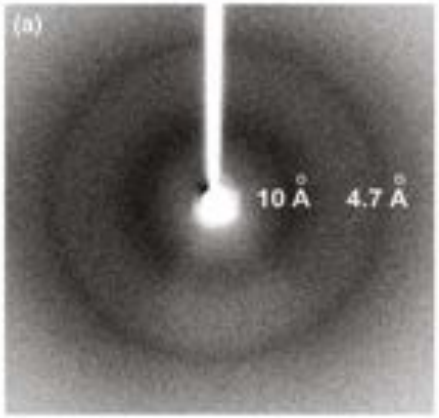
- **Estudis de predicció (Bioinformàtica i modelització)**
- **Estudis estructurals (Estructura – activitat)**
- **Screening de inhibidors**

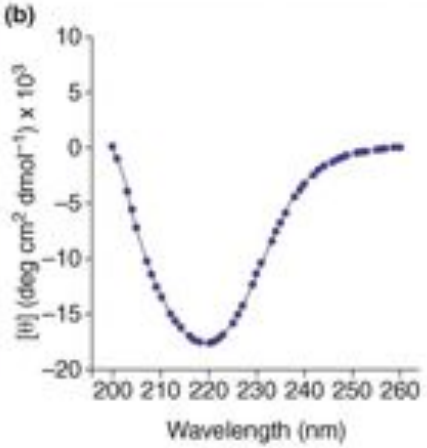
Estudis *in vitro*

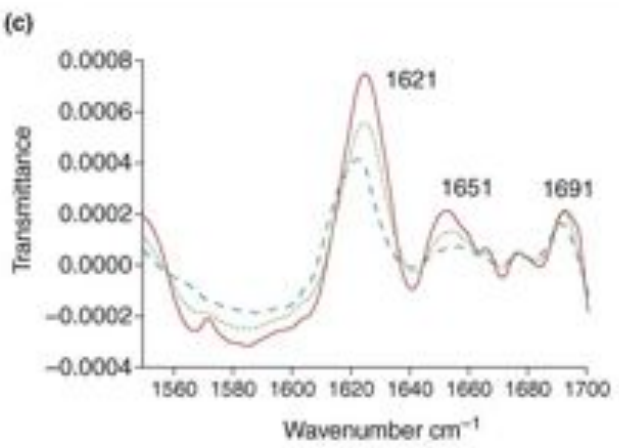
Dinàmica molecular

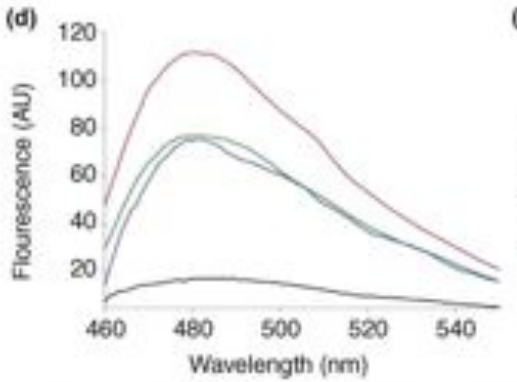


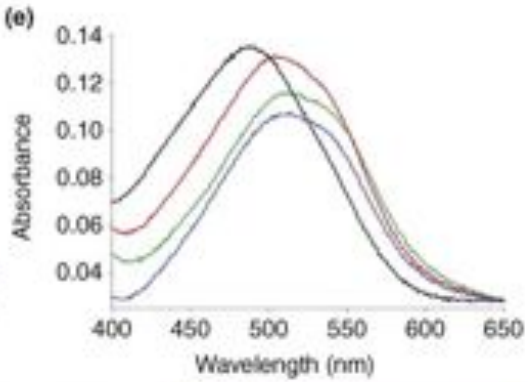
Estudis *in vitro*

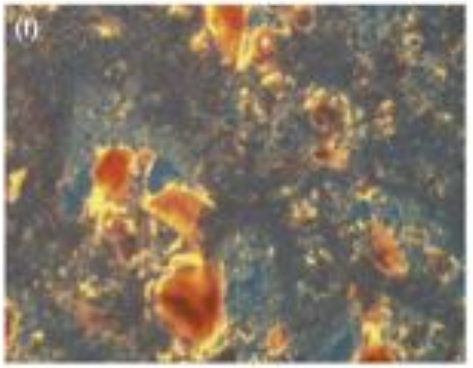


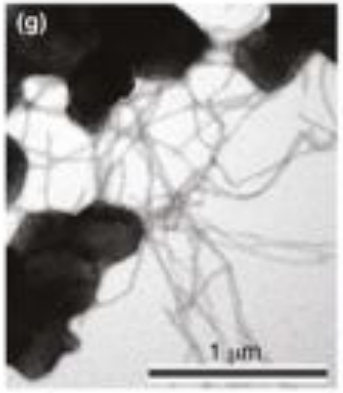


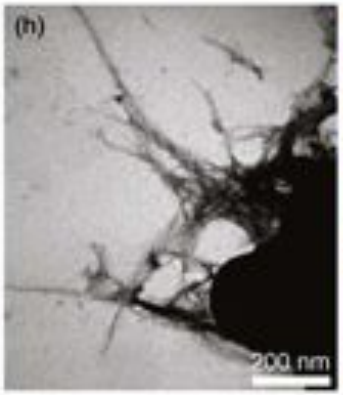


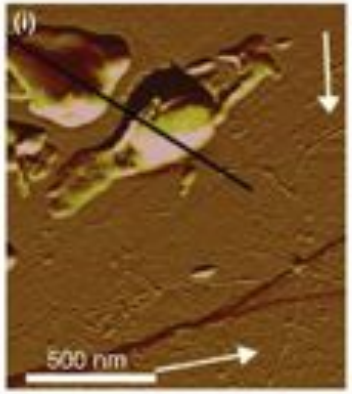


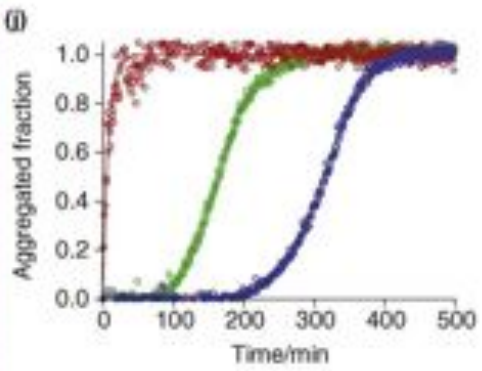






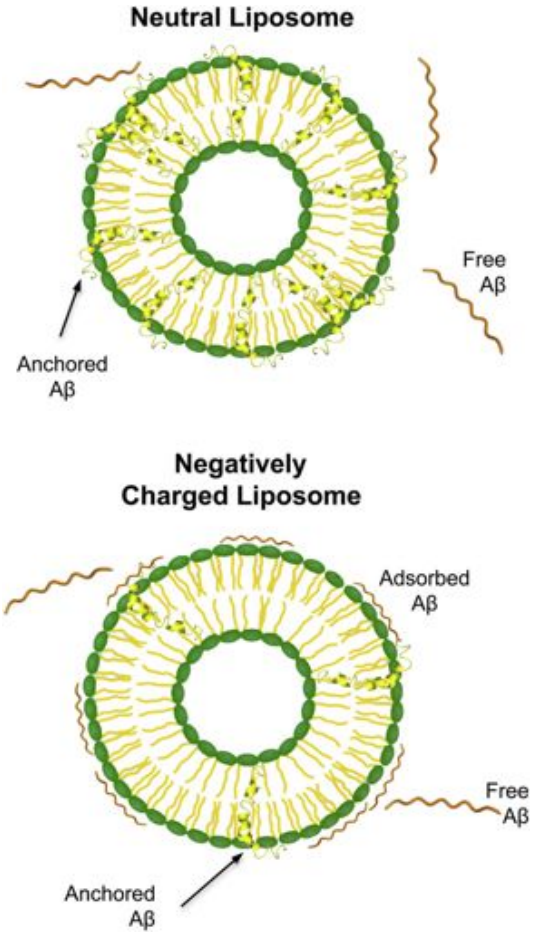






Estudis *in vitro – in vivo*

Interaccions membrana – proteina:
Formació de porus, disrupció de membranes i mort cel·lular



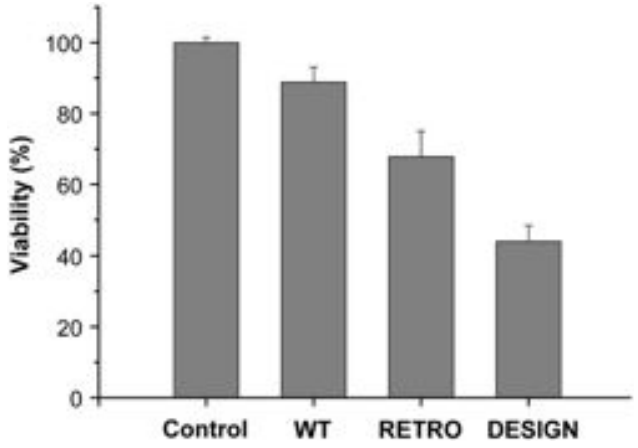
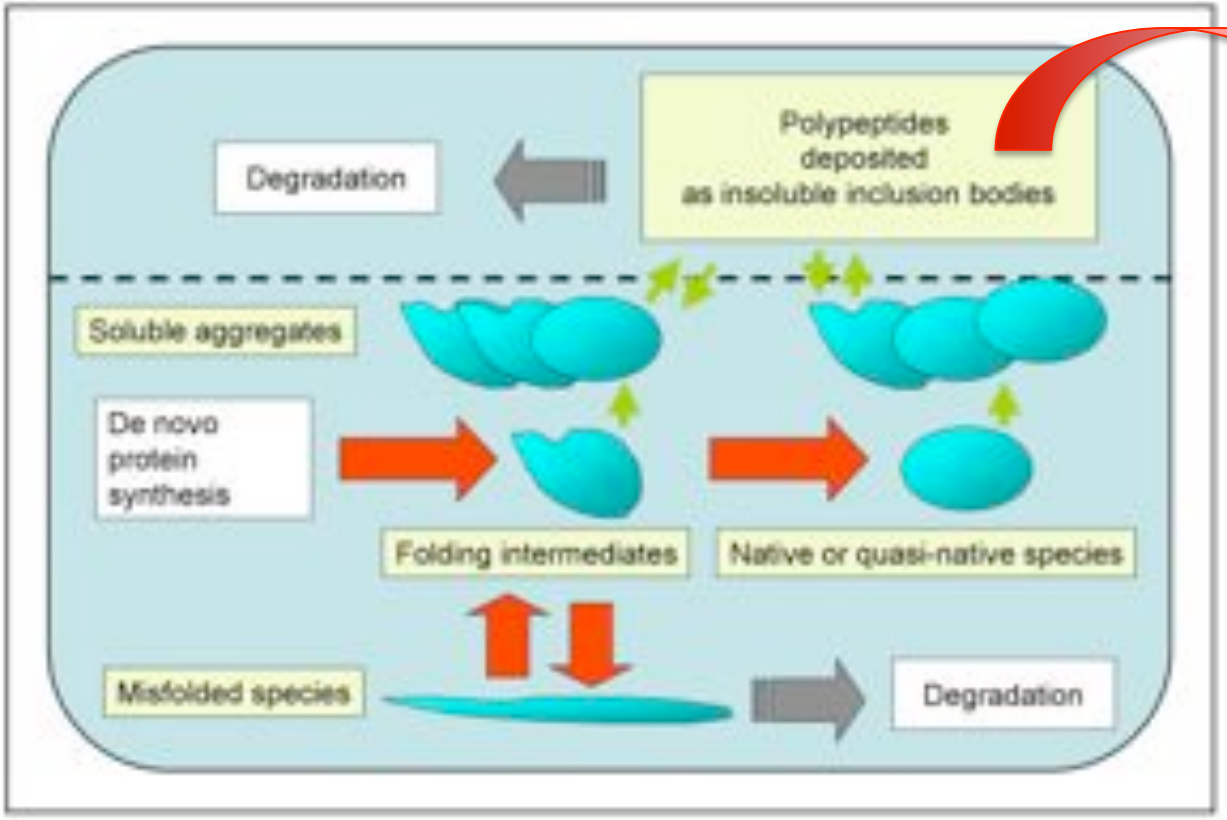


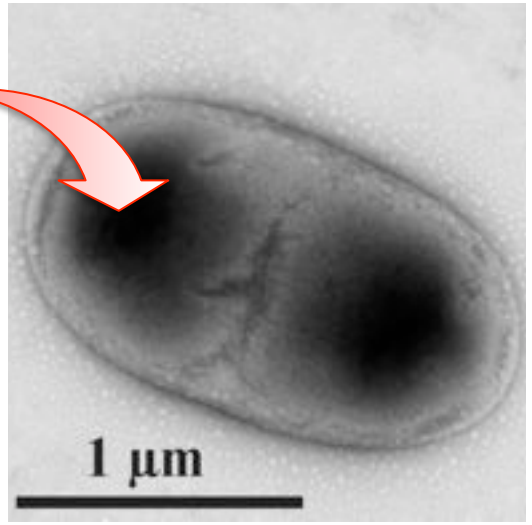
Fig. 9. Viability analysis of SH-SY5Y cells exposed to WT, RETRO, and DESIGN amyloid fibrils for 48 h. Error bars indicate ± SE ($n = 6$). One hundred percent cell viability was assigned to control samples corresponding to cells incubated in peptide free DMEM.

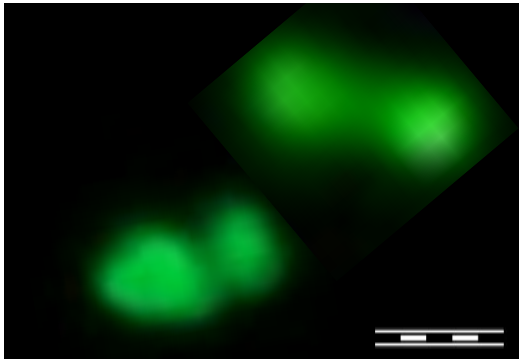
Membranes artificials

Línies cel·lulars

Estudis *in vivo* en procariota

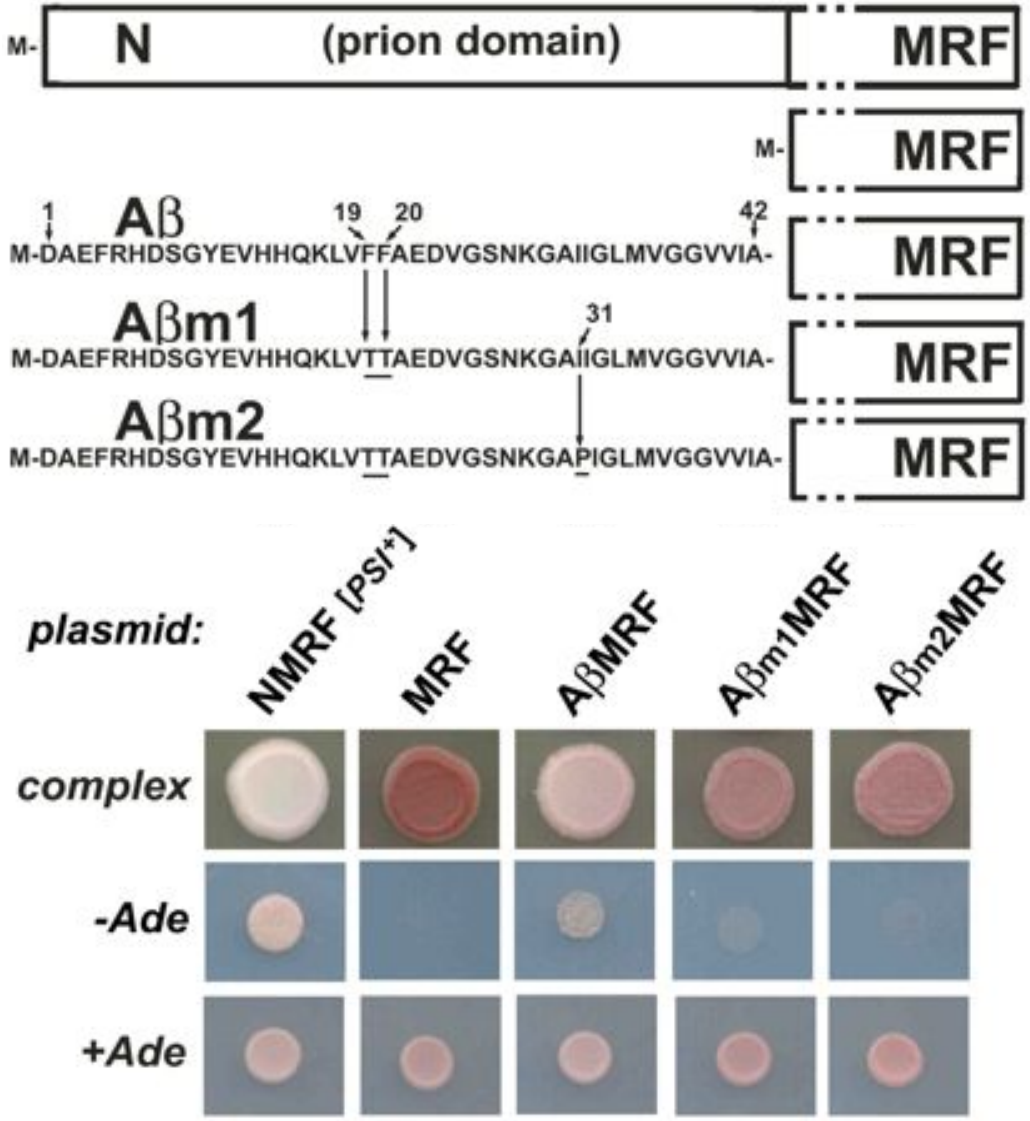






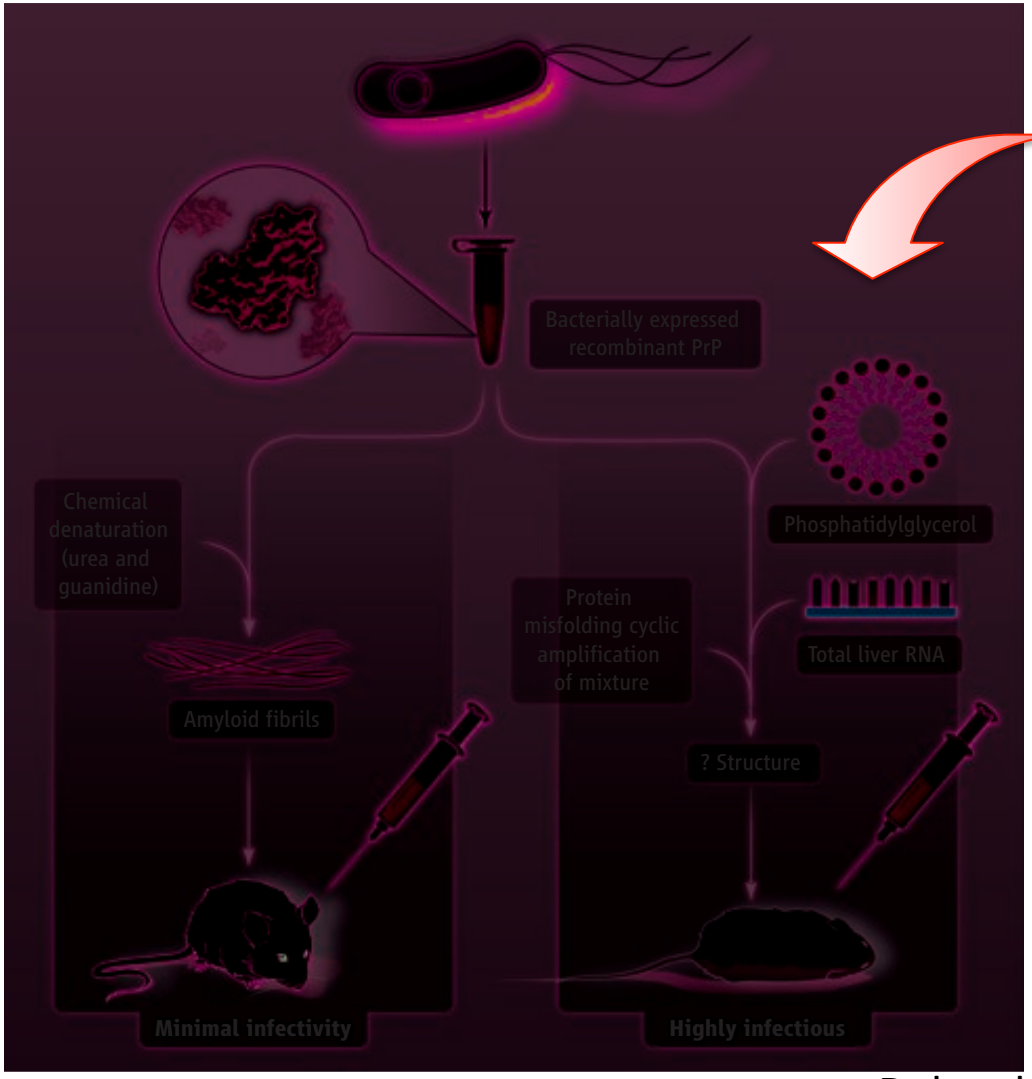
Estudis *in vivo* en eucariota

Estudis *in vivo* en llevat

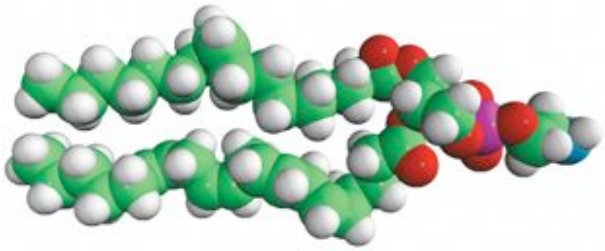


Estudis *in vivo* en eucariota

Estudis *in vivo* en animals trangènics



Phosphatidylethanolamine (PE)



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