SCIENCES FONDAMENTALES ET BIOMÉDICALES
Sciences
Université Paris Cité

Therapeutic target for Alzheimer's disease and Prions: contribution of the 1C11 neuronal cell line

September, 25 2025

Dr. Mathéa PIETRI
Team « Signaling and Neurodegenerative Diseases »
CNRS UMR7654 / École polytechnique

Structural Biology of the Cell

Mad cow disease= example of prion diseases

Mad cow crisis (1988-2003):

GB : 185 000 cases of mad cow

France : 1000 cases of mad cow

Transmissible Spongiform Encephalopathies (TSE)
= class of neurodegenerative disorder

HUMAN

- Infectious
- Rare (2/1,000,000)
- Fatal
- No treatment

Fatal Familial Insomnia

KURU

Creutzfeldt-Jakob Disease And variant

Gertsmann-Sträussler-Scheinker Disease

Interspecies Transmission

PRIONS

BSE (cow)

Chronic Wasting Disease (Cervids)

Scrapie (sheep)

Transmissible mink Encephalopathy

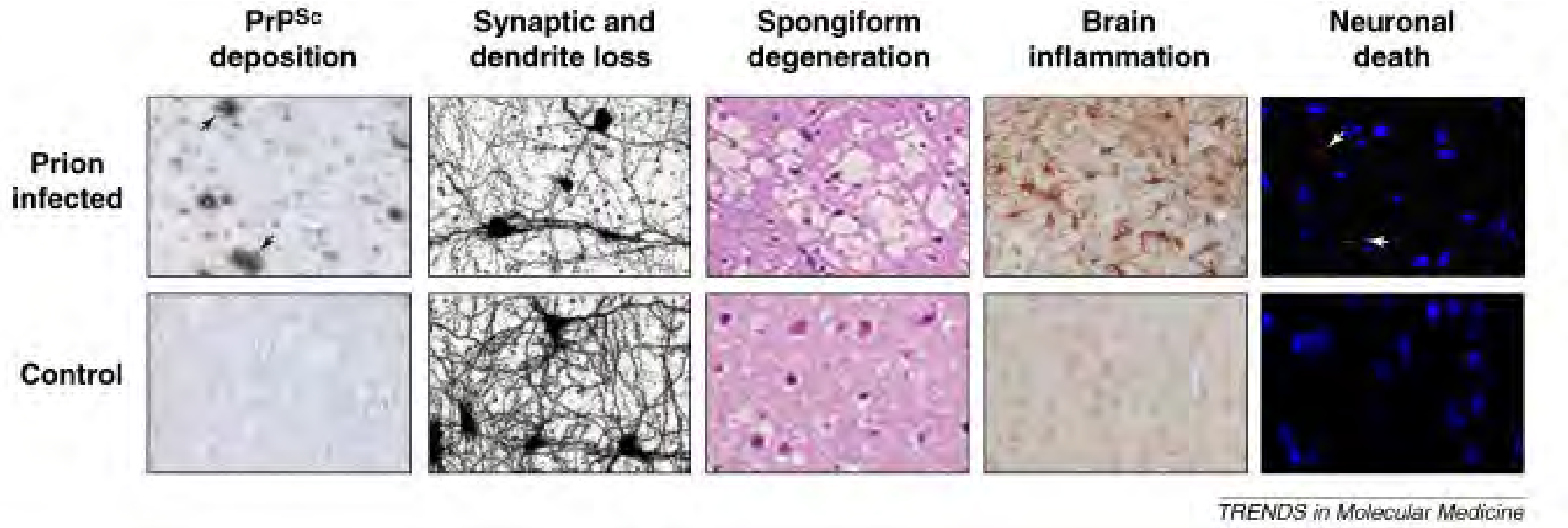
ANIMAL

Features of TSEs

- ✓ TRANSMISSIBLE**:** (naturally e.g. mad cow or experimentally)
- ✓ SPONGIFORM: Vacuoles
- ✓ ENCEPHALOPATHY : Neuronal death (apoptosis) => brain atrophy

+

- ✓ Amyloid plaques: Protein misfolding and aggregation
- ✓ Astrogliosis = activation of glial cells (as a cause or a consequence of inflammation)



=> **CJD SYMPTOMS**: long asymptomatic period (up to 50 years); fulminant cognitive and motor declines

(Soto et Satani, 2011)

Amyloid plaques :
a common feature of Prion and Alzheimer's diseases.

Prion disease: intracellular and extracellular accumulation of amyloid aggregates positive to prion protein staining
= plaques similar to those characteristic of **Alzheimer's Disease**

Alzheimer's | Creutzfeldt-Jakob's

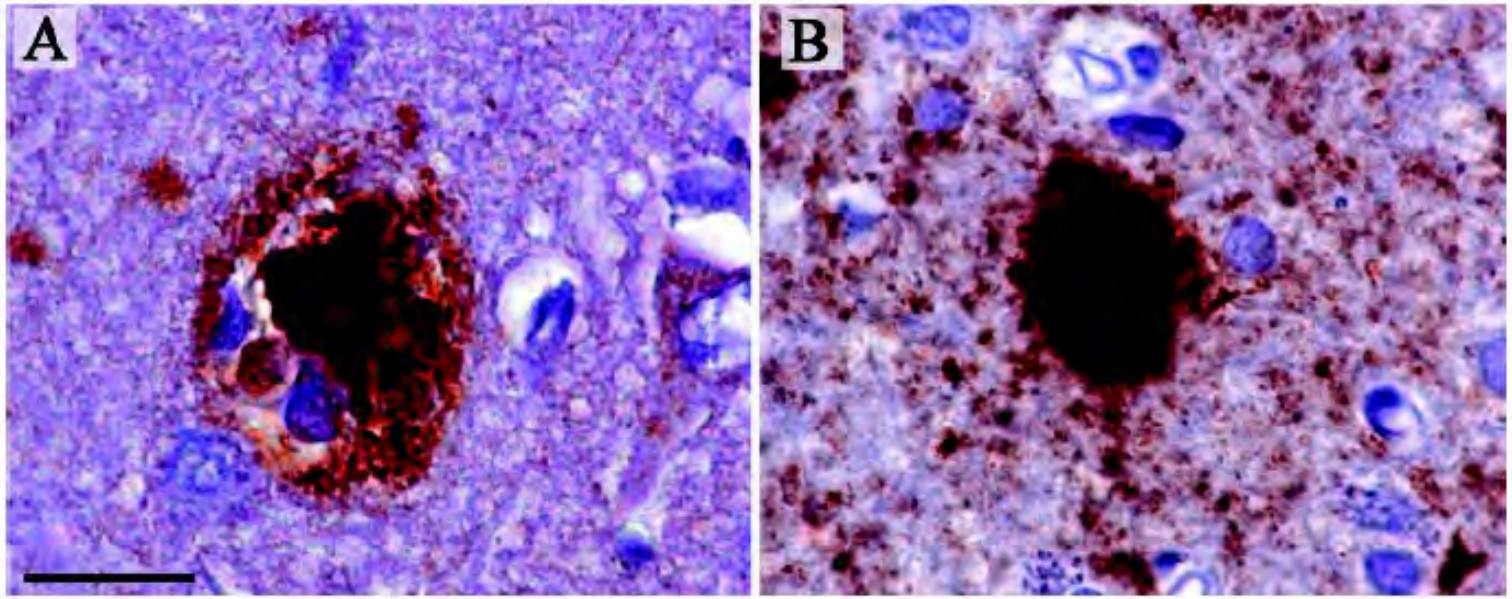


Fig. 1. Both Alzheimer's and prion diseases are characterized by the deposition of pathological proteins in the brain, often in the form of plaques. The brown color is indicative of immunostained cortical deposits of the Aβ peptide and of the PrP^{Sc} protein in brains of patients suffering from Alzheimer's disease (**A**) and Creutzfeldt-Jakob disease (**B**), respectively. Scale bar: 20 μm.

Aguzzi A, Haass C. Science. 2003 Oct 31;302(5646):814-8. Review.

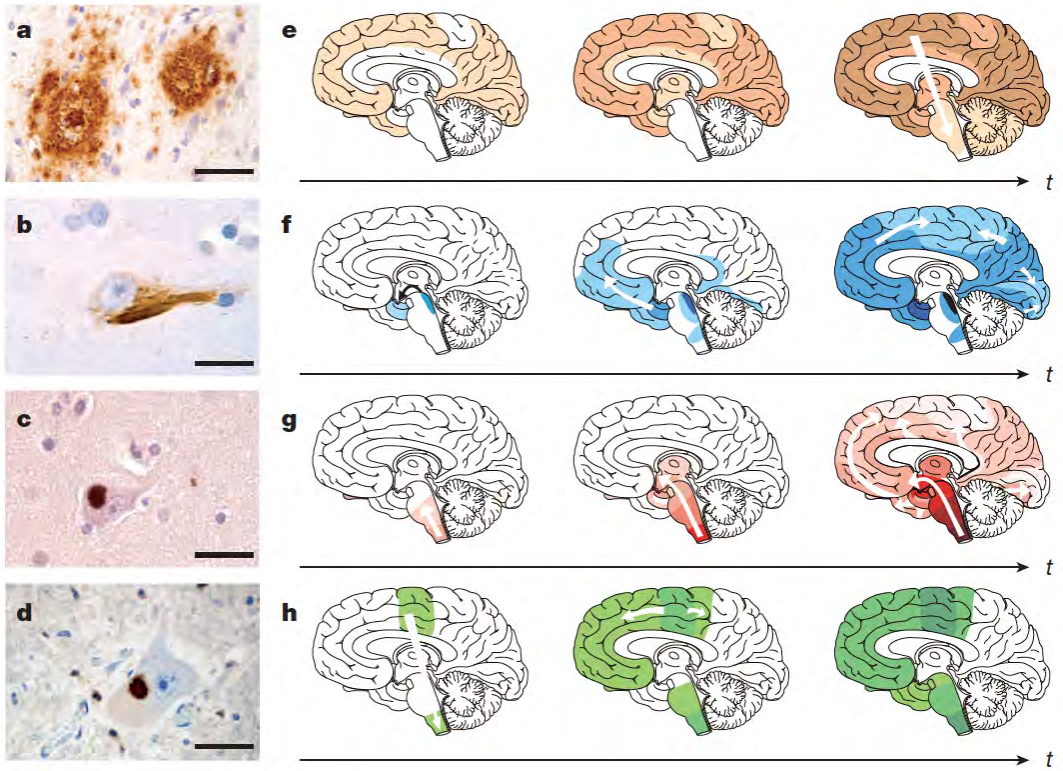
TSEs share common features with other neurodegenerative diseases

Neuronal cell death, Age-related diseases, Aggregation of misfolded proteins
= proteopathies = amyloid-based neurodegenerative diseases.

Alzheimer
- Plaque senile ← Aβ
- NFT ← Tau

Parkinson — α-synuclein

Amyotrophic Lateral sclerosis — TDP-43

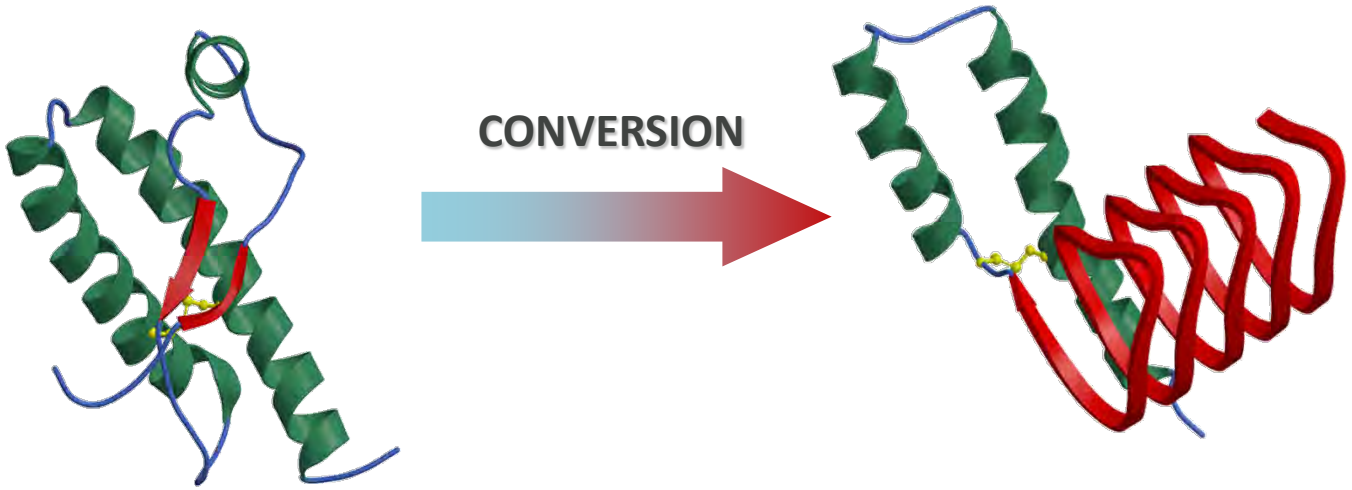


Jucker M. Nature,2013

BUT: location and pattern of protein aggregation ≠
Prion diseases are the sole infectious neurodegenerative disease

What is the agent causing prion diseases?
Prion concept

- **Prusiner** dropped a dogma of biology:
  one protein can be infectious => Proteinacenous Infectious particle



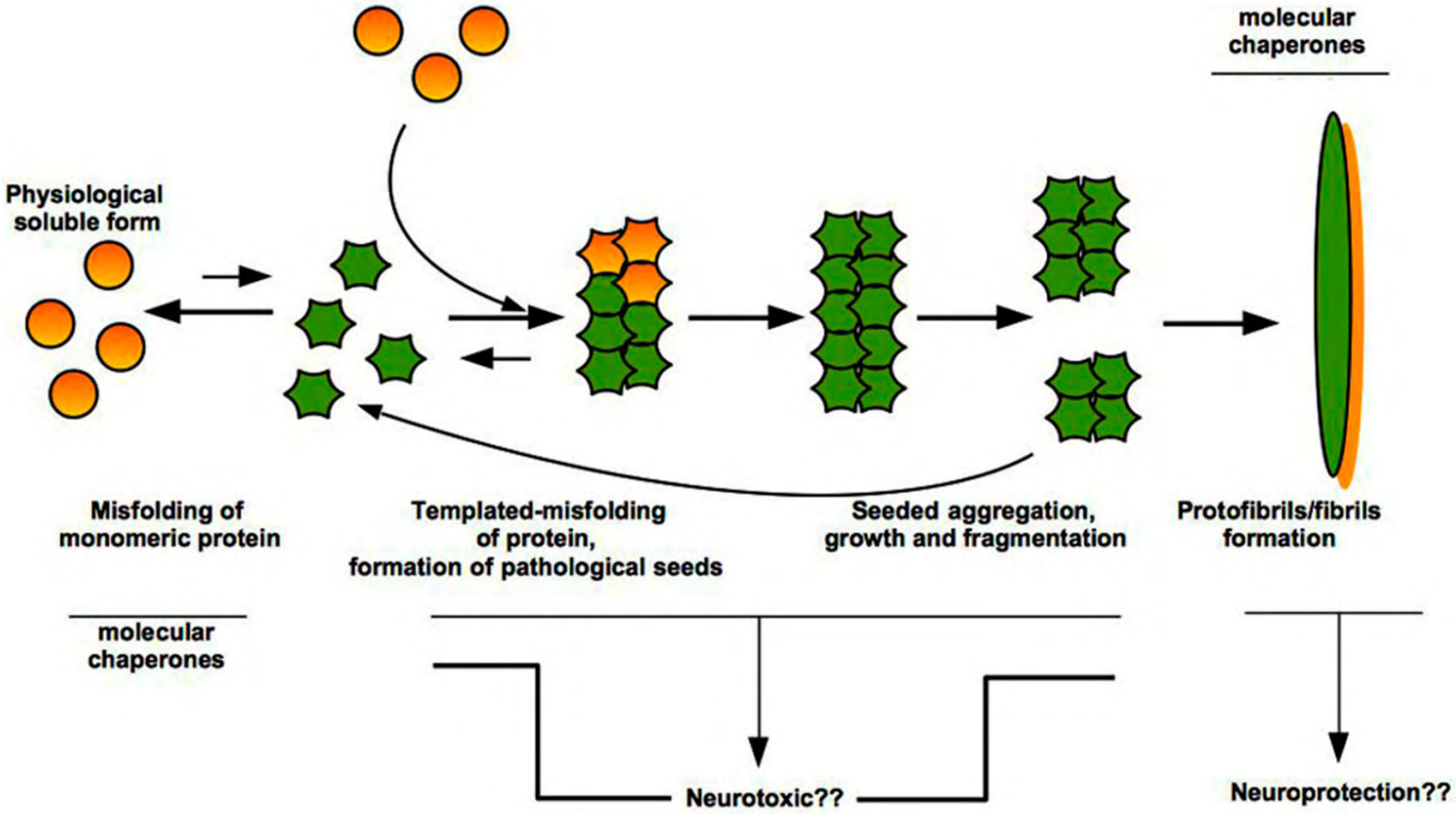
Cellular prion protein
(PrP^{C})

Scrapie prion protein
(PrP^{Sc})

- ✓ Normal protein of the host
- ✓ Ubiquitous protein

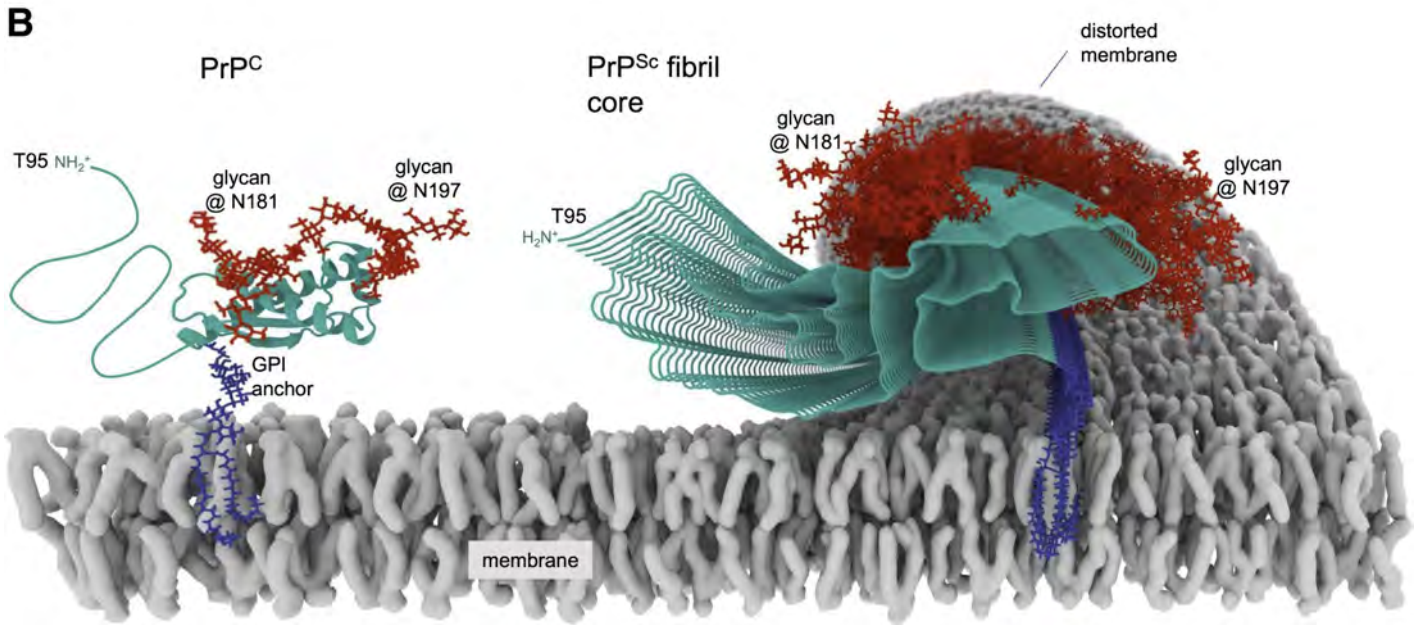
- ✓ Main component of Prions
- ✓ Only in TSE-afflicted brains

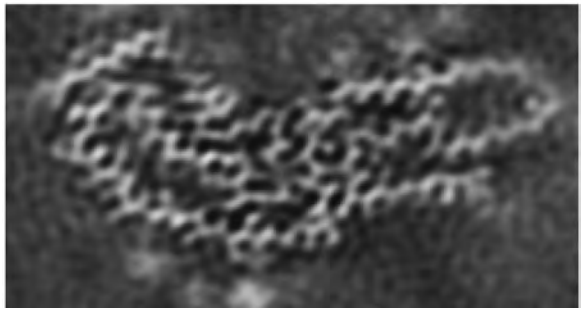
How prions propagate?
Nucleation polymerization model for PrP^{C} → PrP^{Sc} conversion.



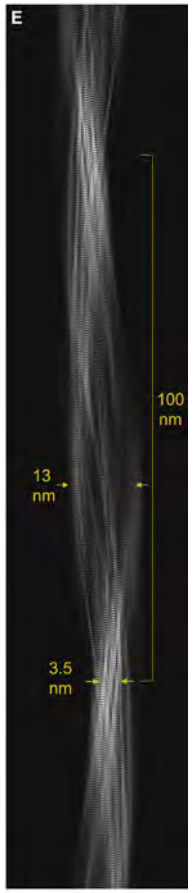
=> Prion-like proteins: Aβ, Tau, α-synuclein…

How prions propagate?
Models for PrP^{C} → PrP^{Sc} conversion.





Projection of density map of fibril cross-section derived from single-particle cryo-EM analysis

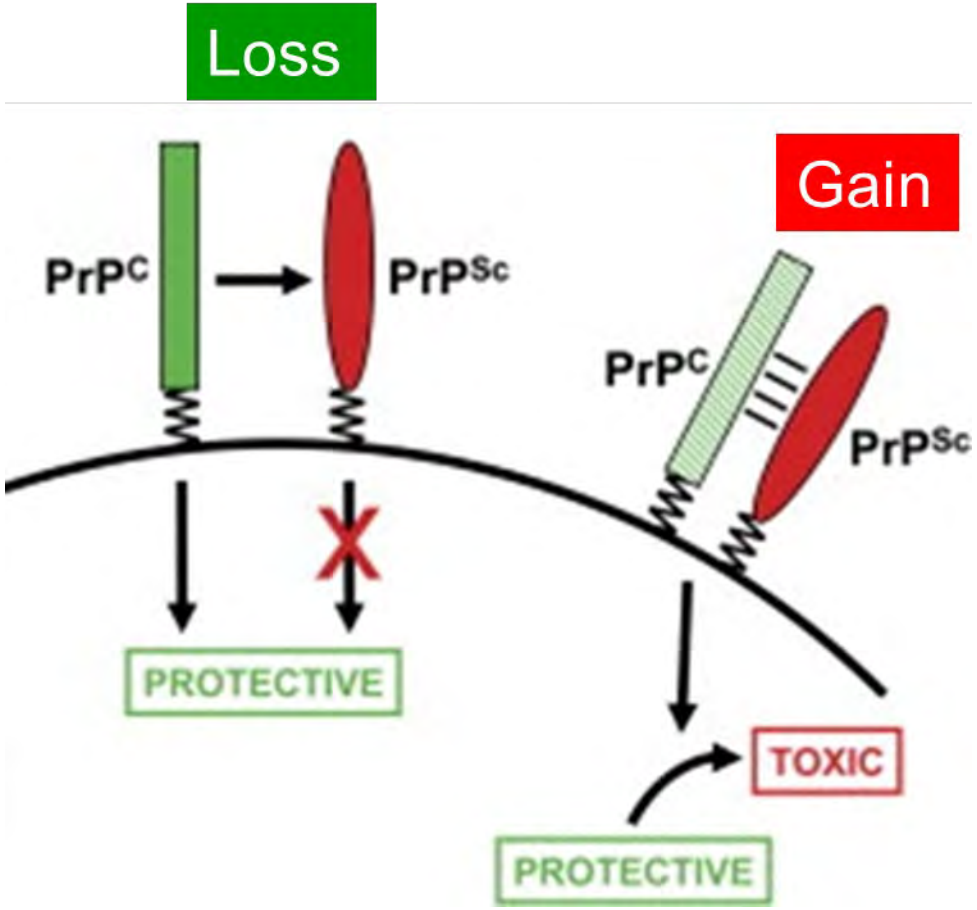


Projection of the fibril density map

*High-resolution structure and strain comparison of infectious mammalian **prions**.*
Kraus A, et al. Mol Cell. 2021 doi: 10.1016/j.molcel.2021.08.011.

Why prion-infected neurons die?
Corruption of PrP^C functions

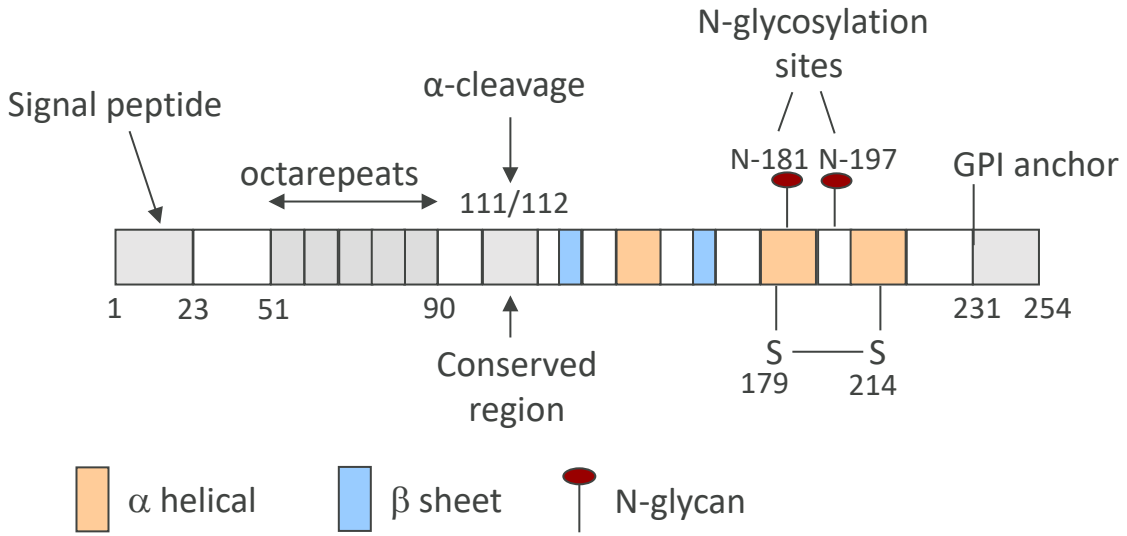
- PrP KO mice are resistant to infection by pathogenic prions

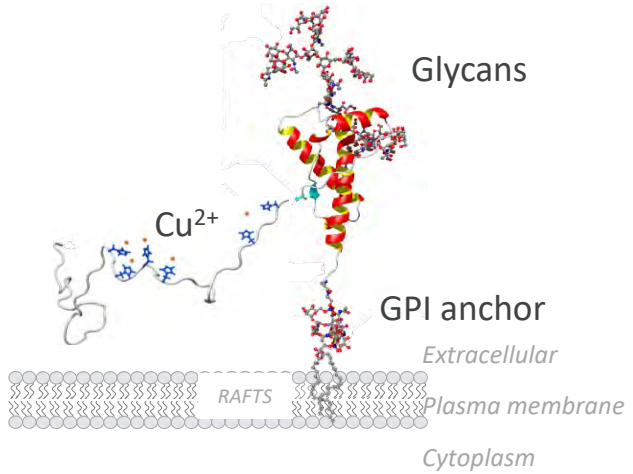


=> understand the PrP^C function in neurons to decipher the mechanisms of prions neurotoxicity!

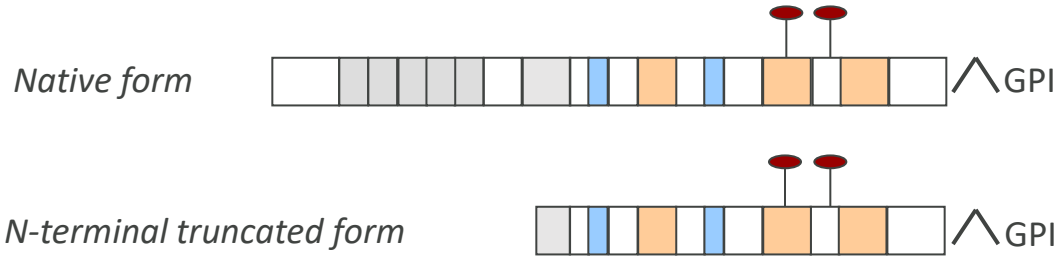
Cellular Prion Protein

- Primary structure and post-translational modifications.

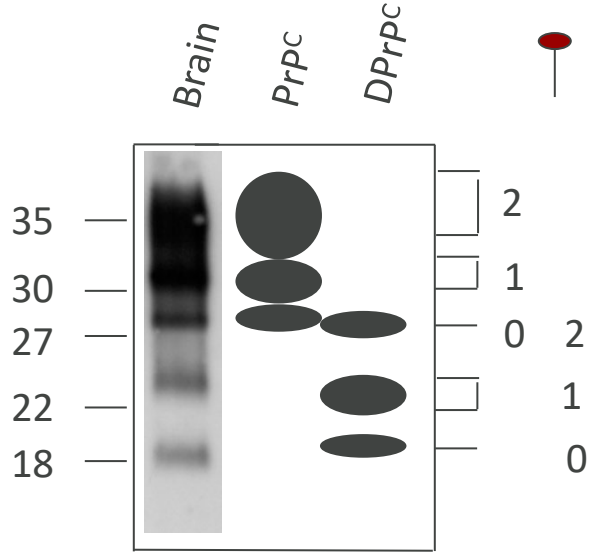




- Glycosylation and binding to metals



✓ α-Cleavage



=> Not one PrP^C but various isoforms

Physiologic role of Cellular Prion protein

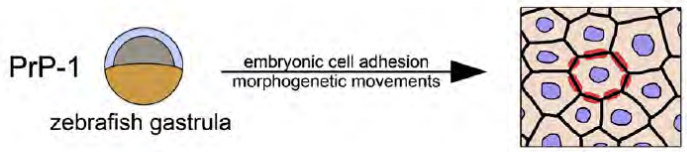
$PrP^{-/-}$ models:

- **souris**

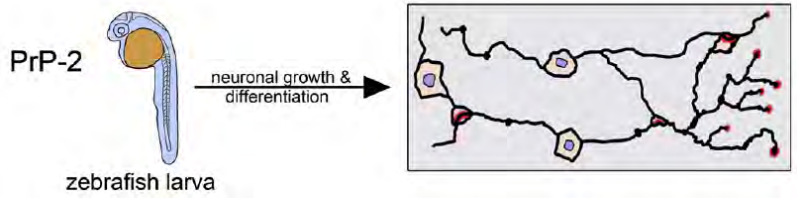
Viables & normal CNS development

=> No obvious function for PrP^C

- **Zebra Fish**

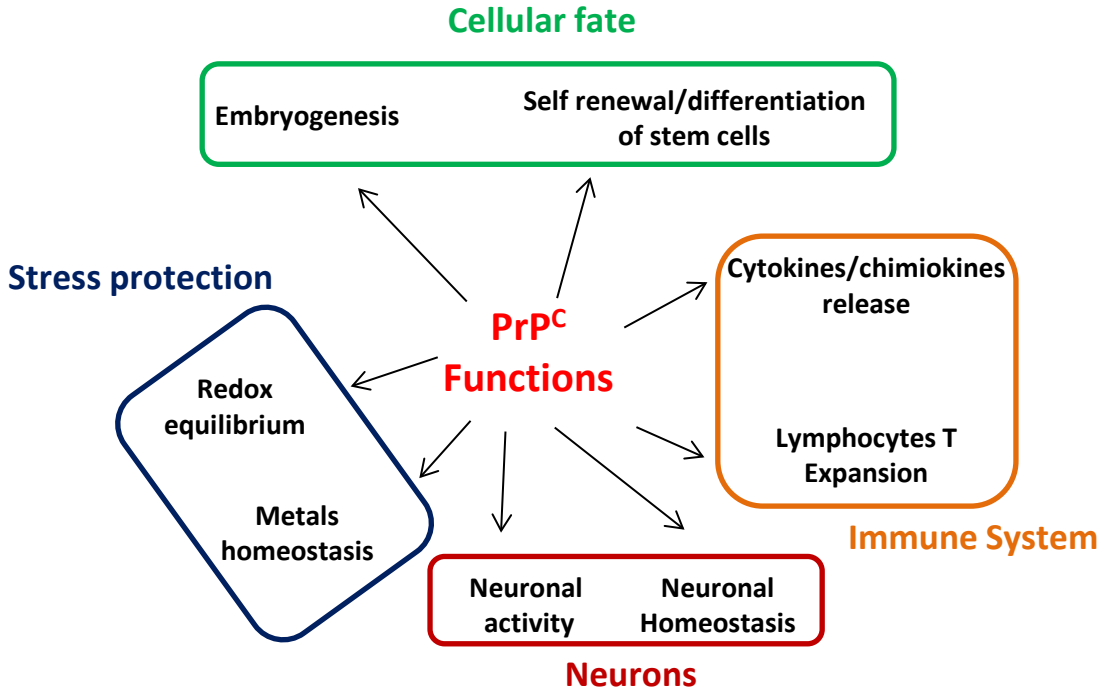


Ubiquitous role



Neurospecific role

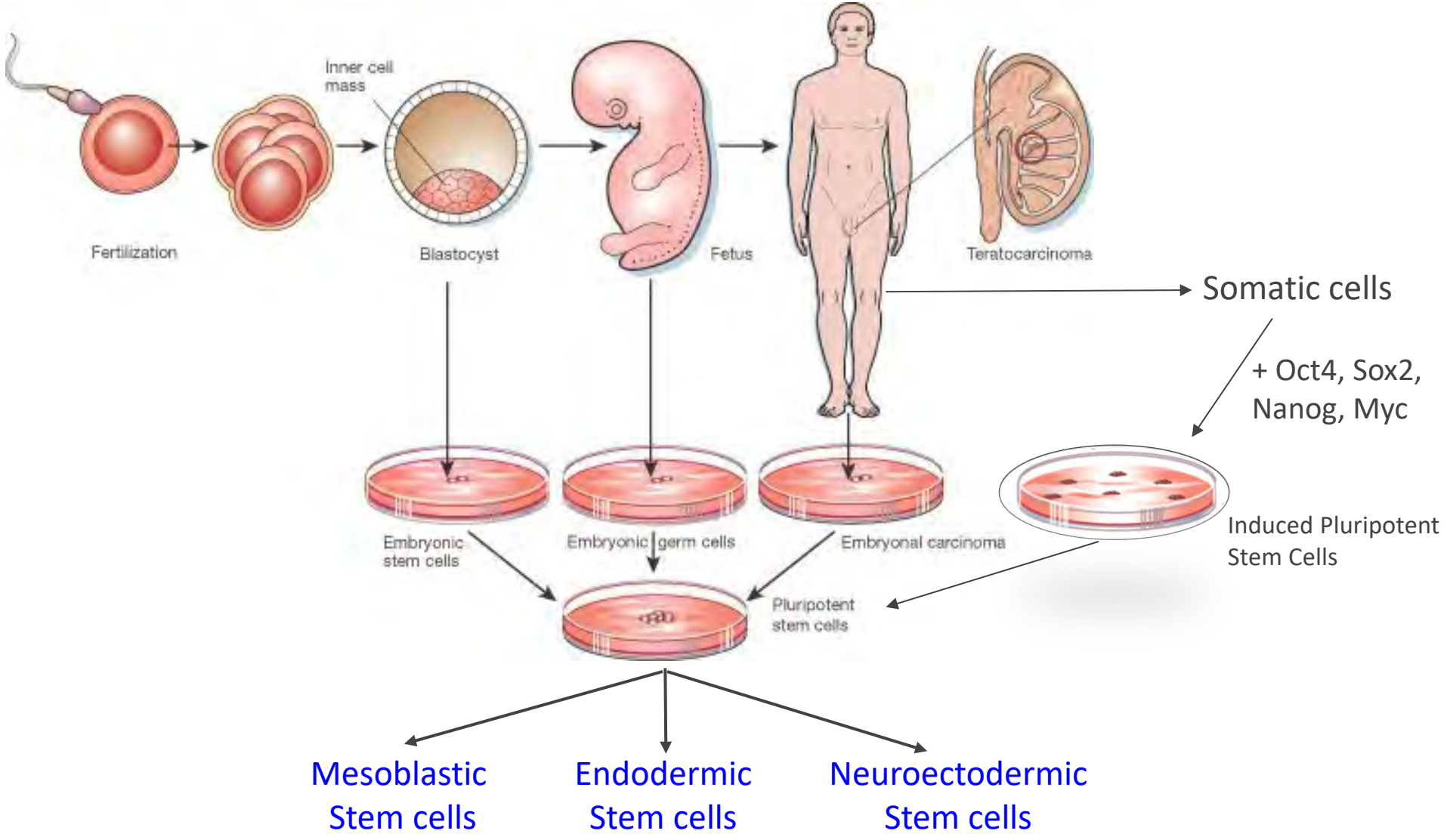
Málaga-Trillo 2011; Leighton 2018



⇒ No obvious function for PrP^C ! Protective role?

⇒ **Hyp: PrP^C is so important for neuronal cell homeostasis that mechanisms compensate lack of PrP^C**

Pluripotent stem cells: ES/EG/EC/iPS

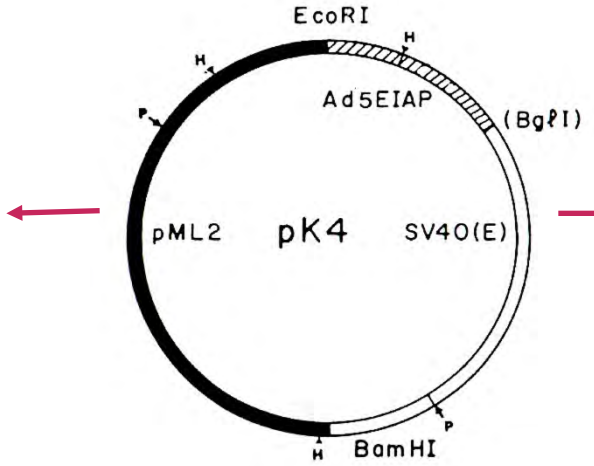


Cell populations obtained after ES/EC/iPS differentiation are heterogeneous and stop dividing

➔ difficult to clone and select cell lines having properties of lineage precursor cells.

Strategy to select lineage precursor cells

pK4 pluripotent cell lines EC



pK4 transgenic mice

Induction of differentiation

3 germ layers derivatives
Differentiated cells + immature cells

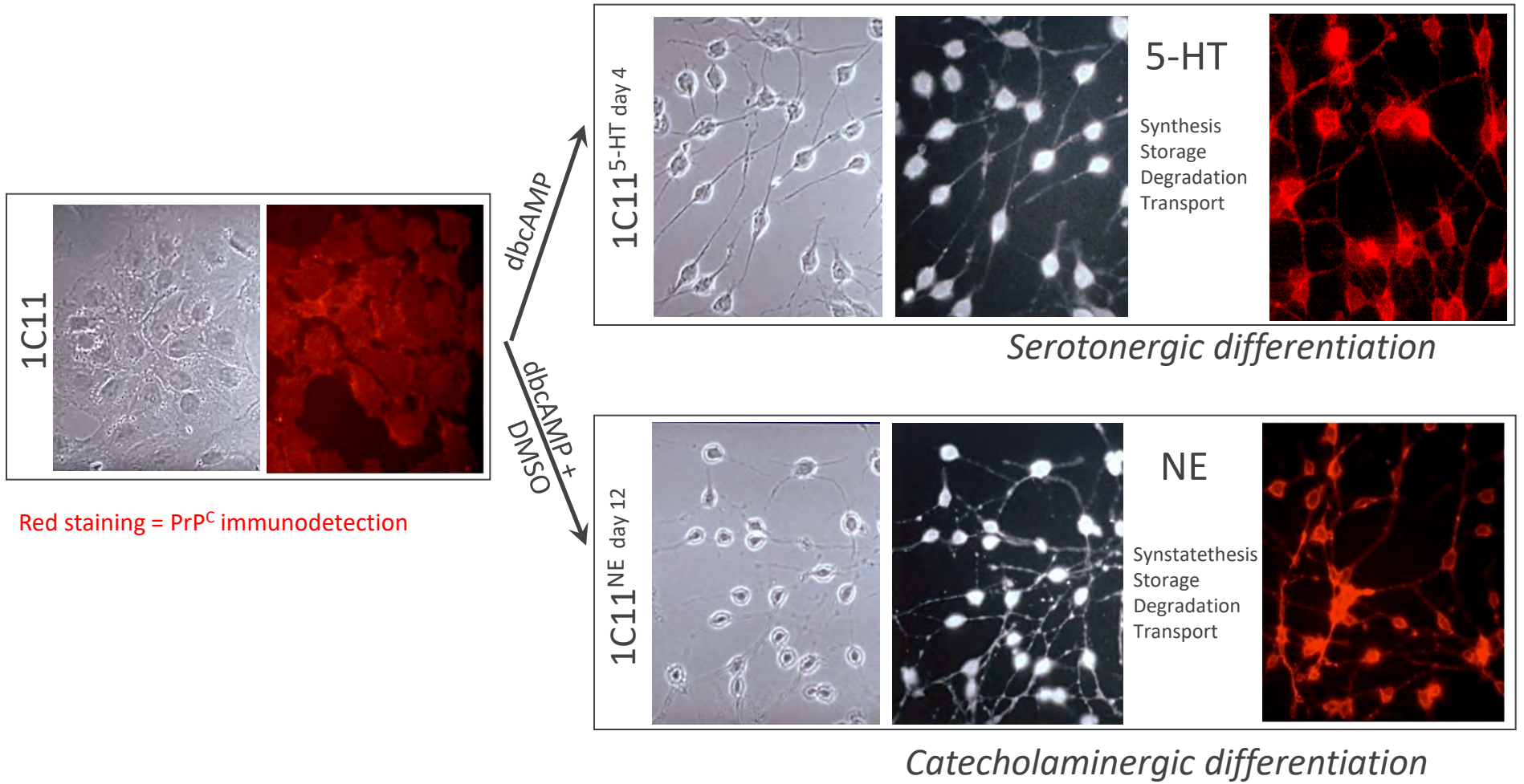
Cloning and Selection :
-loss of EC/ES cell markers
-Ability to differentiate at high frequency towards alternative fates along a given lineage

1C11 neuroectodermic cell line
C1 mesodermic cell line

Salivary gland cell lines
Renal cell lines

DENTAL Pulp stem cell lines
(ED18 molar of Tg embryos)

The 1C11 neuroectodermal cell line



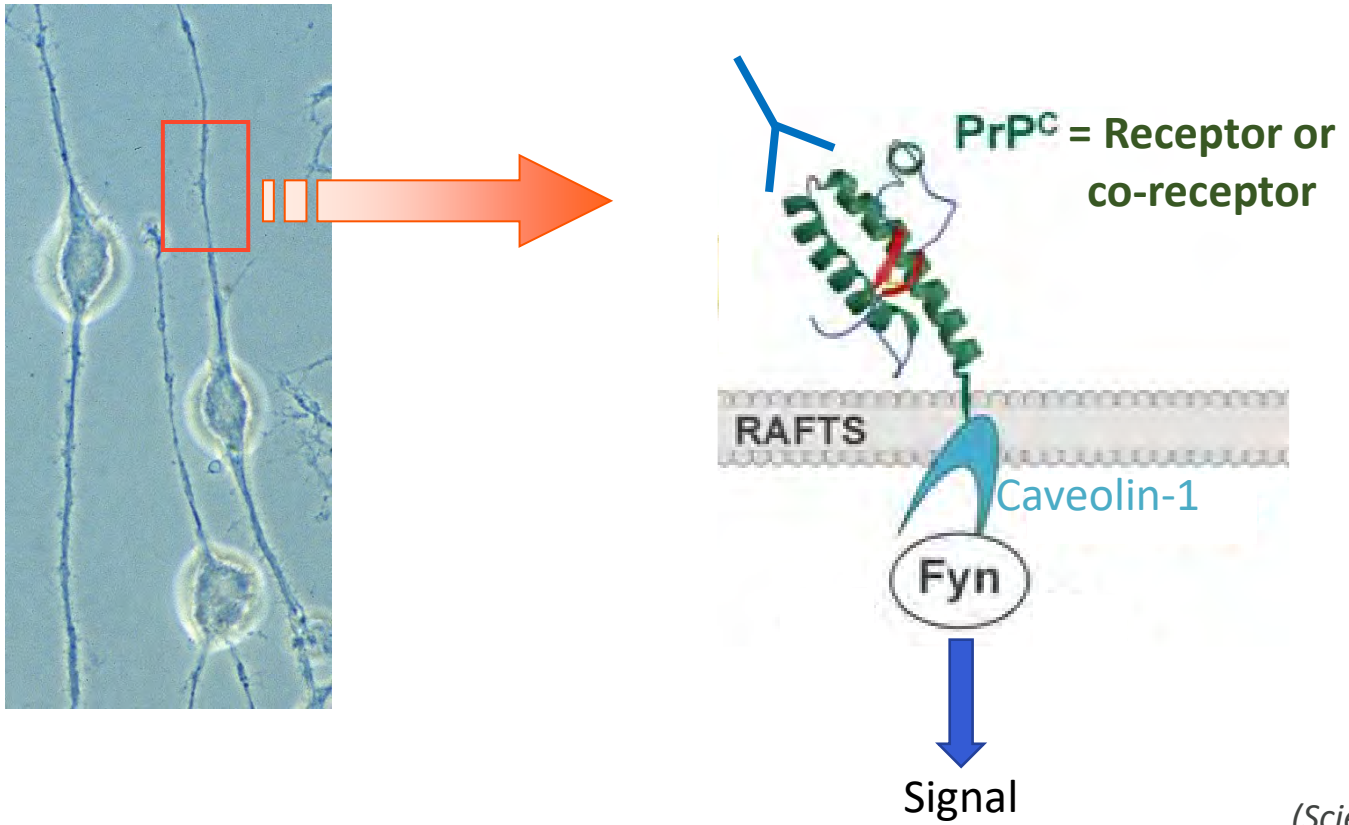
Red staining = PrP^C immunodetection

=>3 different differentiation states, 100% differentiation

=> Expressed all PrP^C isoforms whatever differentiated state!

Signaling function of PrP^C
Proof of concept

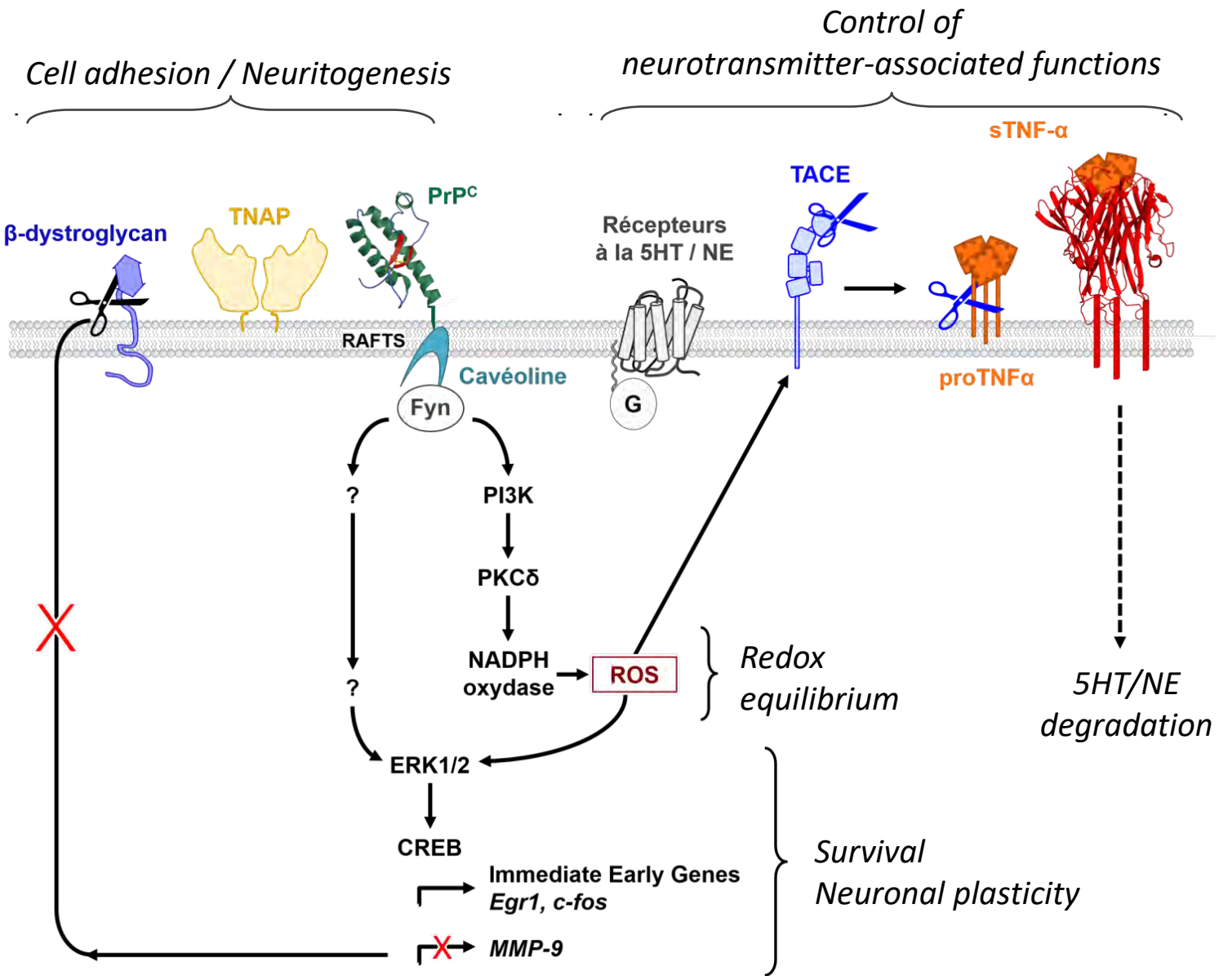
- Experimental strategy: cross linking using antbodies to mimic a natural ligand.



(Science, 2000)

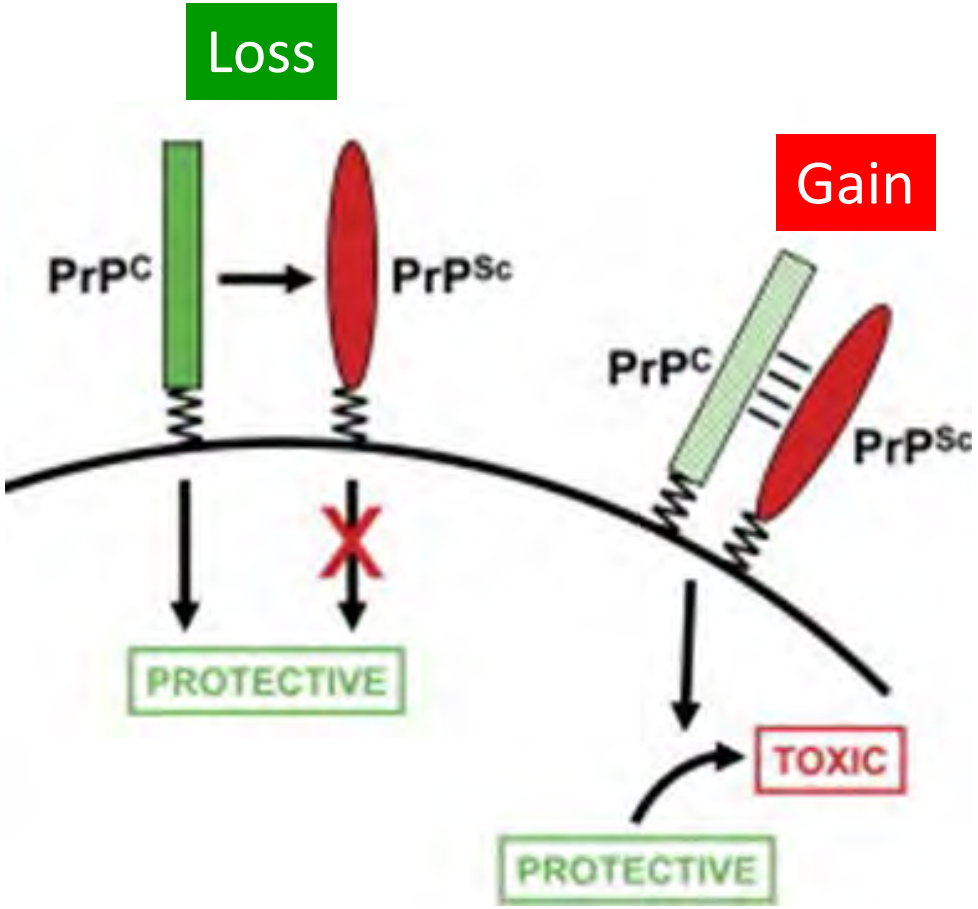
=> PrP^C-Caveolin1-Fyn Tyrosine kinase : Neurospecific signaling platform recruited only in neurites.

The multifaceted function of PrP^C in a neuronal context



Schneider et al. , Front. In Biosc., 2011

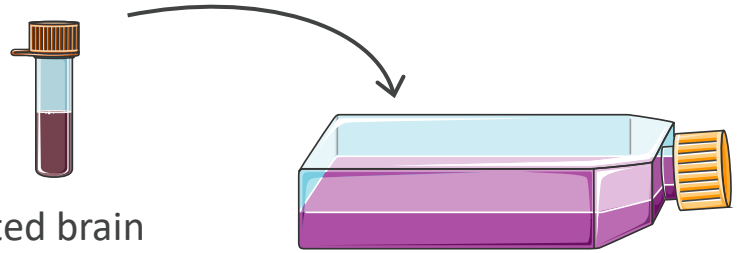
What is the impact of PrP^{Sc} on function of PrP^{C}? Loss / Gain?



(Harris et al, 2006)

What is the impact of PrP^{Sc} on function of PrP^{C}? Infection of 1C11 cell line

- The 1C11 cell line is chronically infected by several prion strains

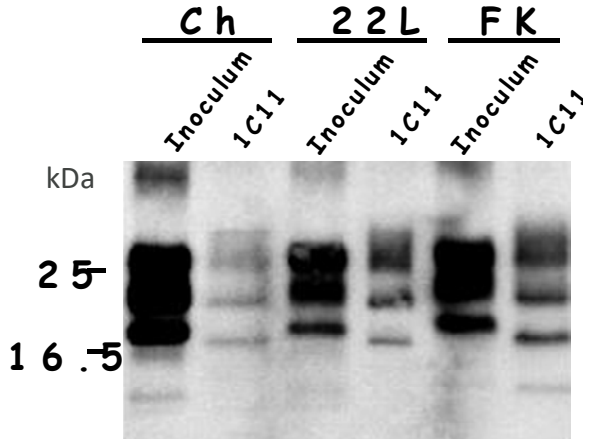


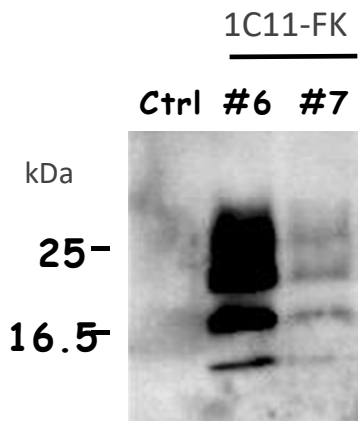
Infected brain homogenates (Chandler, 22l or FK)

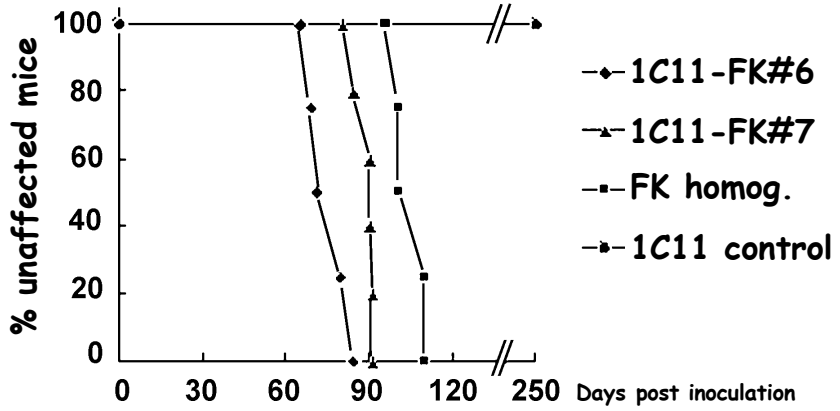
1C11 cells

1 passage → subcloning →

- PrP^{Sc} detection
- Bioassay



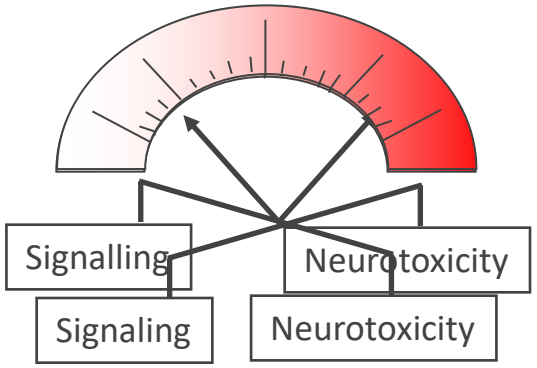




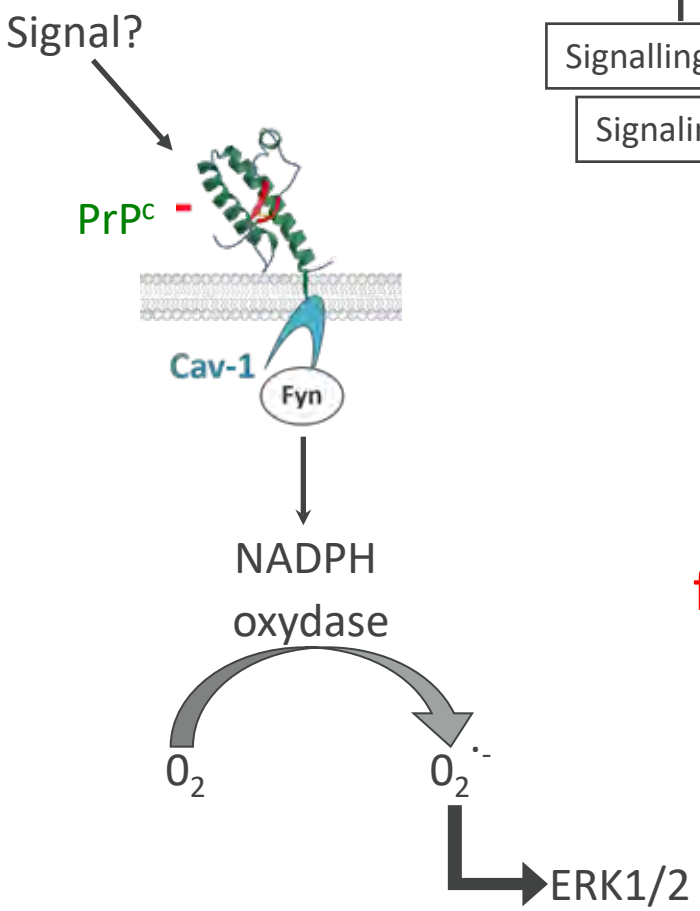
(Mouillet-Richard S et al., JBC, 2008)

=> In prion-infected 1C11 cells: gain of function of the PrP^{C}-NOX coupling!!!

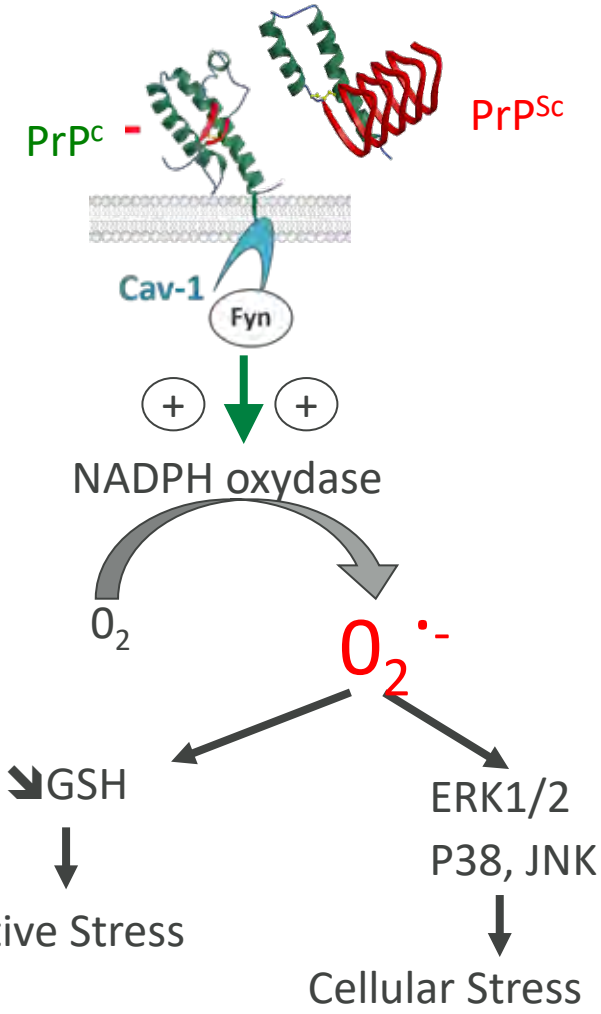
From signaling …



…to neurotoxicity



= Gain of function



Fine tuning of redox equilibrium

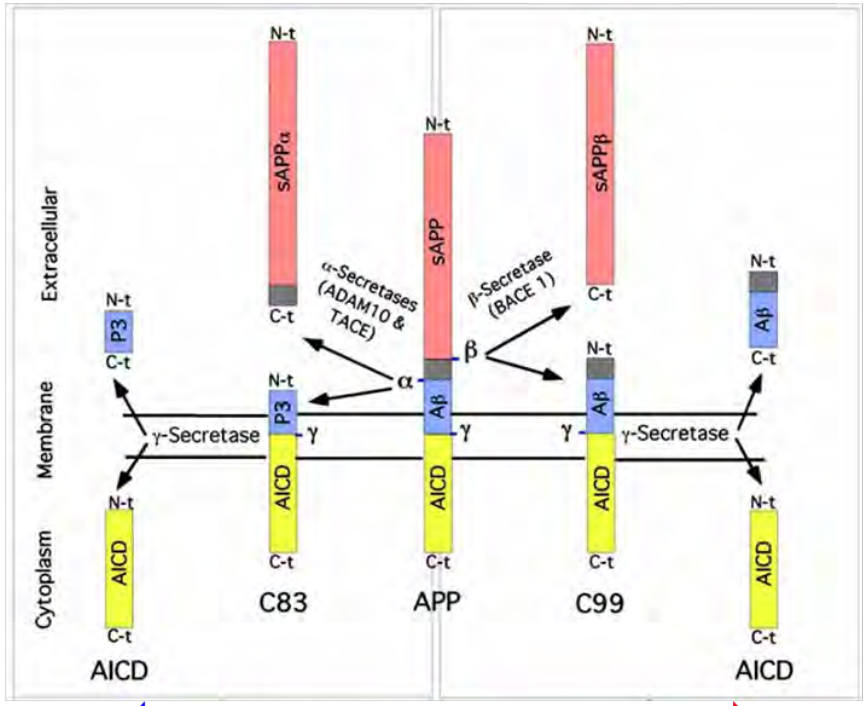
=> Neuronal homeostasis

Lost of neuronal homeostasis

=> Neuronal death

Prion disease and Alzheimer's disease: same fight?

- In AD, neuronal cell death is induced by Aβ peptides
- Aβ peptides are produced by cleavages of Amyloid Precursor Protein (APP)



↗ sAPPα

neuroprotective

P3 — Non-Toxic pathway — TACE/γ-secretase

Toxic pathway — BACE/γ-secretase — Aβ

↗ $A\beta_{40/42}$

neurotoxic

Prion disease and Alzheimer's disease: same fight?

nature Vol 457|26 February 2009|doi:10.1038/nature07761

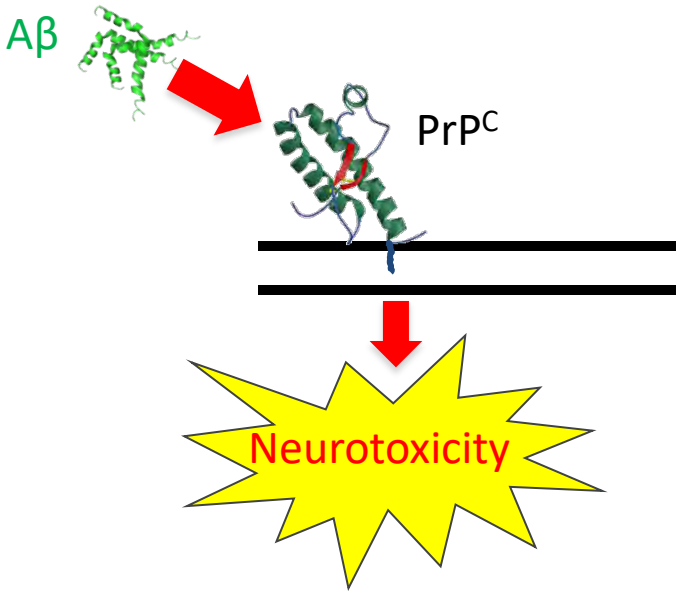
LETTERS

Cellular prion protein mediates impairment of synaptic plasticity by amyloid-β oligomers

Juha Laurén[1], David A. Gimbel[1], Haakon B. Nygaard[1], John W. Gilbert[1] & Stephen M. Strittmatter[1]

- ✓ Aβ peptides bind to PrP^C with high affinity.
- ✓ PrP^C could relay neurotoxicity of Aβ peptides !

=> MECHANISMS??

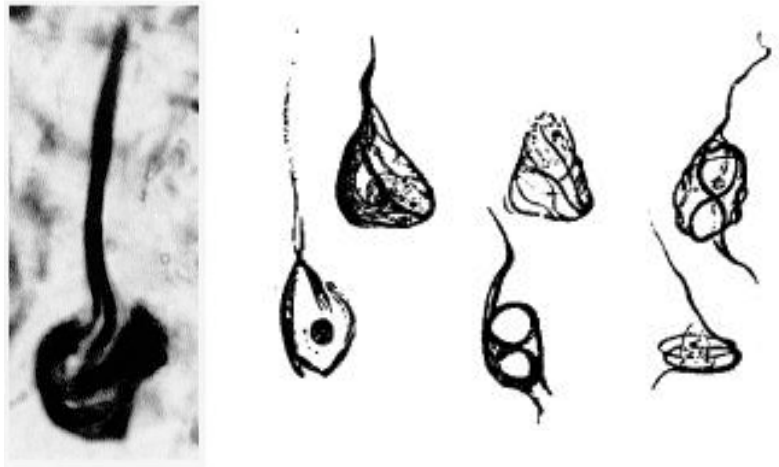


Alzheimer's disease
Discovery

- **Auguste D**, a 51-year-old woman : shown progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence.

- At necropsy, there were plaques, neurofibrillary tangles, and arteriosclerotic changes.

Alois Alzheimer
(1864-1915)



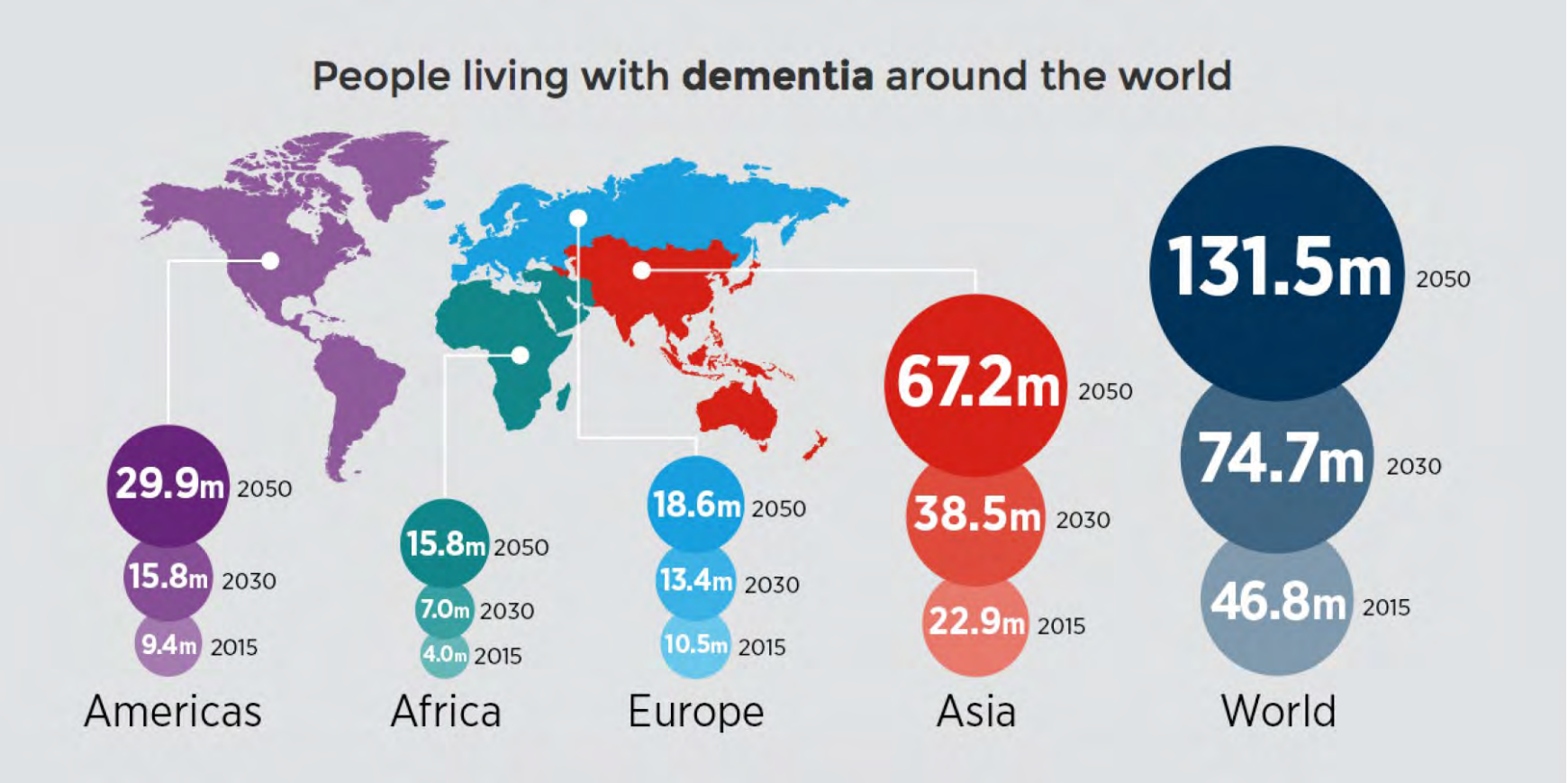
Bielkhowsky's stain section from Auguste Deter's brain (left) neurofibrillary tangles drawn by Alois Alzheimer (right)

First description of tangle and plaque pathology
by Alois Alzheimer (1901)

Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. 1907 Jan ; 64:146-8.

Alzheimer's disease (AD)
Epidemiology

- ✓ AD is the most common form of dementia accounting for >60% of all the cases.
  - In France: ~1M in 2019; +225 000 /year
  - Word: 35.6M in 2019; +7.7M /year



World Alzheimer Report 2015

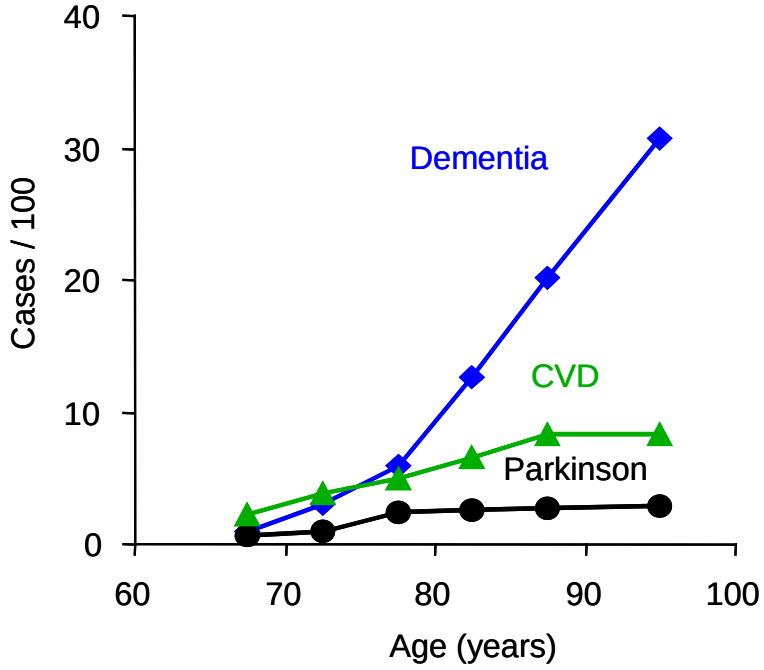
Alzheimer's disease (AD)
Epidemiology

✓ Most of the cases of AD *ARE SPORADIC*.

The prevalence of inherited forms of AD is <1%

✓ Risk factors for sporadic AD:

- aging
- head injuries
- hormonal changes
- vascular diseases
- inflammation
- ApoE e4 allele polymorphism
- exposure to pollutants : nanoparticulate matter; pesticides; metals (Al^{+++},Cu^{++} and Zn^{++})

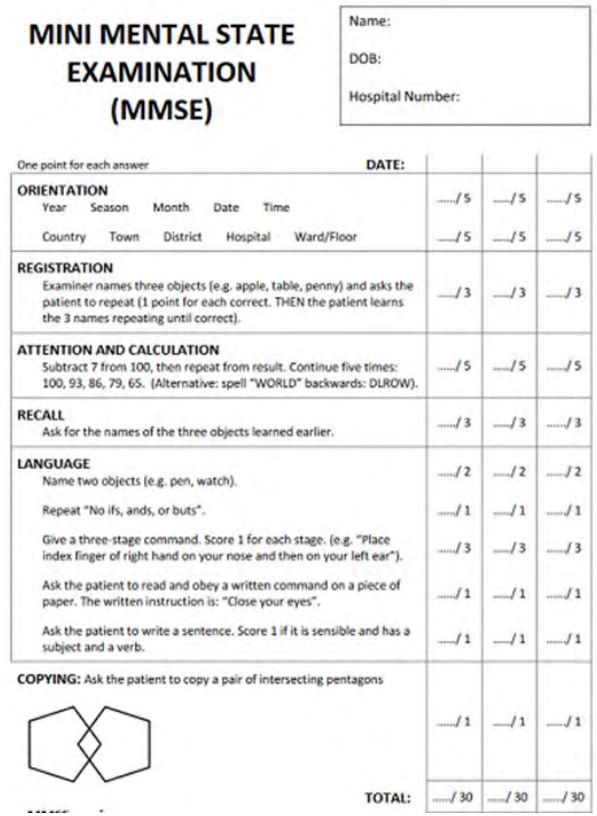


ApoE polymorphism and disease risk (alzdiscovery.org/)

Genotype	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
Disease Risk	40% less likely	40% less likely	2.6 times more likely	Average risk	3.2 times more likely	14.9 times more likely

Alzheimer's disease (AD)
Symptoms

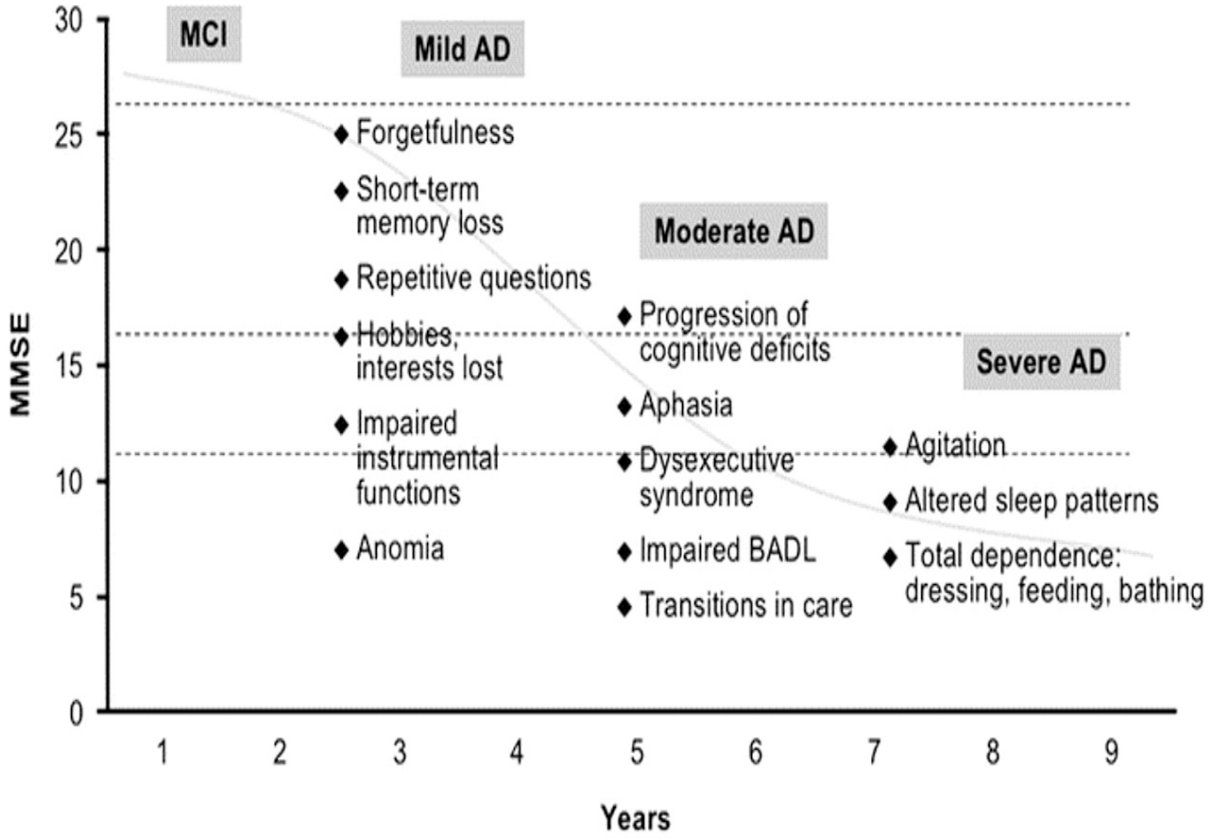
- AD is a progressive neurodegenerative disorder affecting the elderly population. Once it starts, it progresses with aging.



MINI MENTAL STATE EXAMINATION (MMSE)

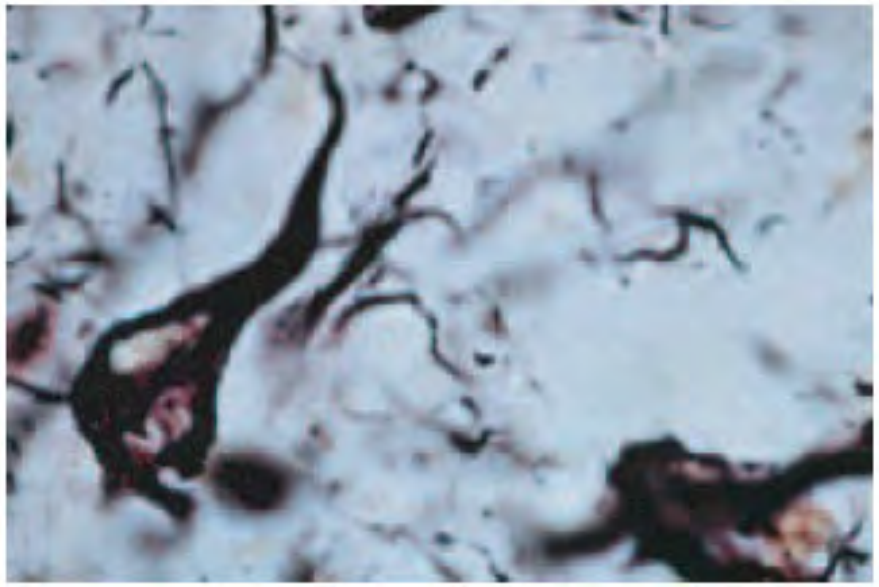
Name:
DOB:
Hospital Number:

One point for each answer	DATE:		
ORIENTATION Year Season Month Date Time	...../5	...../5	...../5
Country Town District Hospital Ward/Floor	...../5	...../5	...../5
REGISTRATION Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct).	...../3	...../3	...../3
ATTENTION AND CALCULATION Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 65. (Alternative: spell "WORLD" backwards: DLROW).	...../5	...../5	...../5
RECALL Ask for the names of the three objects learned earlier.	...../3	...../3	...../3
LANGUAGE Name two objects (e.g. pen, watch).	...../2	...../2	...../2
Repeat "No ifs, ands, or buts".	...../1	...../1	...../1
Give a three-stage command. Score 1 for each stage. (e.g. "Place index finger of right hand on your nose and then on your left ear").	...../3	...../3	...../3
Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes".	...../1	...../1	...../1
Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb.	...../1	...../1	...../1
COPYING: Ask the patient to copy a pair of intersecting pentagons	...../1	...../1	...../1
TOTAL:	...../30	...../30	...../30



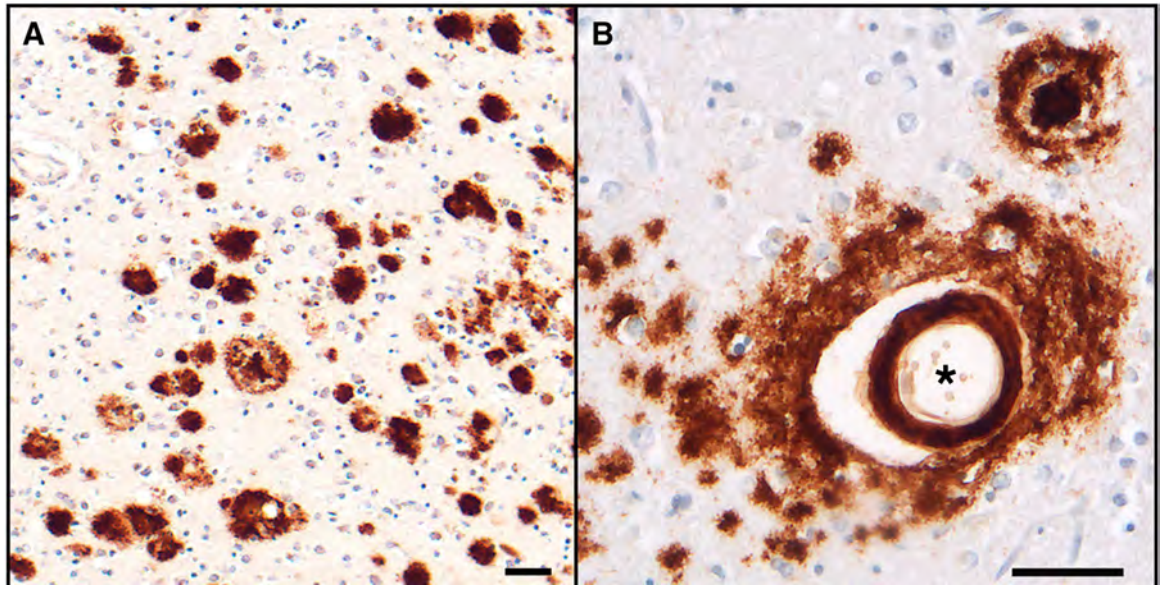
Alzheimer's disease (AD)
Histopathological hallmarks

- It is characterized by the presence of lesions both at an **extracellular** level (the **β-amyloid plaques),** and at an **intracellular** levels (the **Neurofibrillary tangles, NFT**).



Neurofibrillary tangles

- hyperphosphorylated protein tau



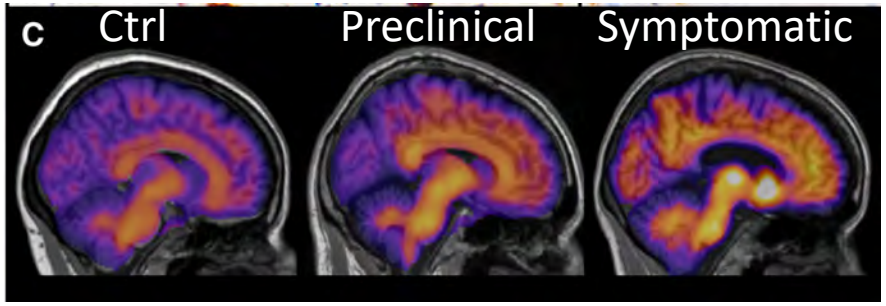
Amyloid plaques (A) and Cerebral β-Amyloid Angiopathy (CAA, B *)

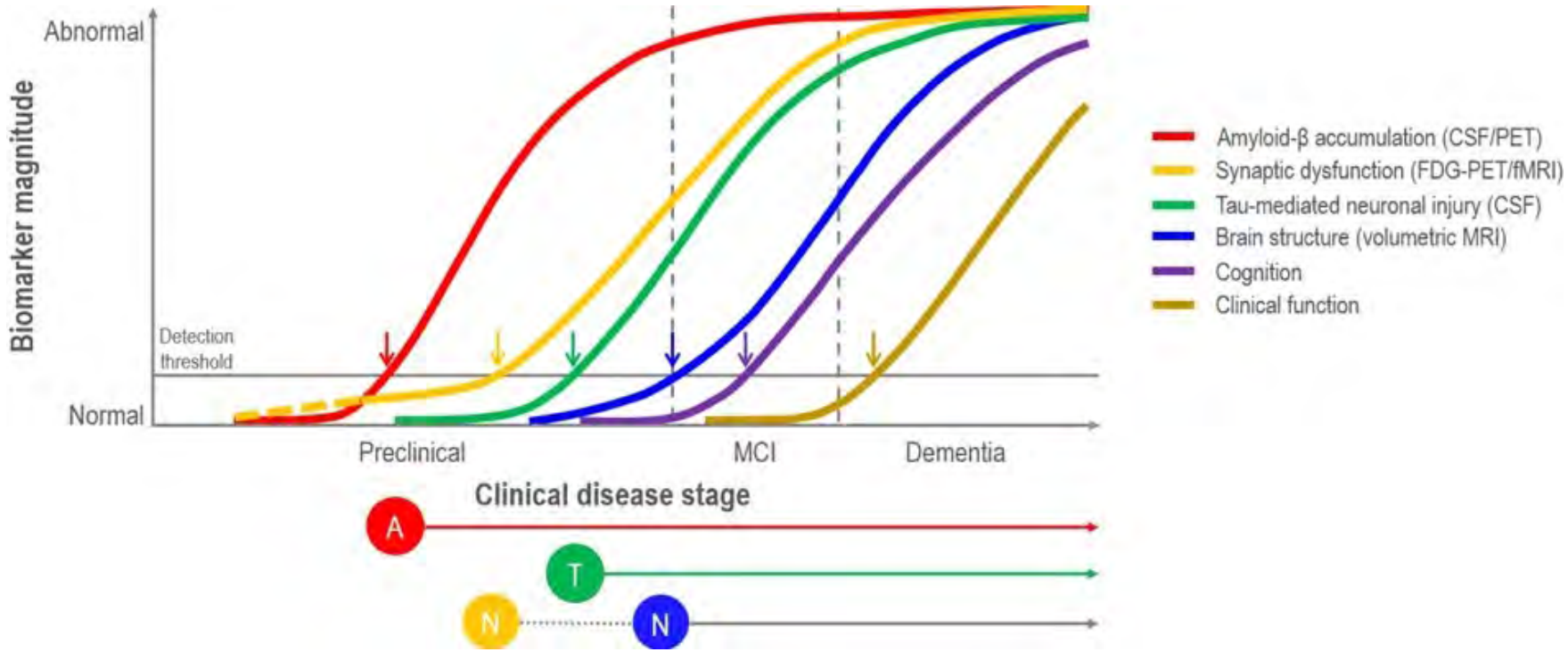
- protein β-amyloid (Aβ) fibrils

M. Jucker, et al. Alzheimer's disease: From immunotherapy to immunoprevention, Cell, 2023

Alzheimer’s disease (AD)
Dynamic biomarkers

Aβ-PET images with Pittsburgh compound tracer in familial AD

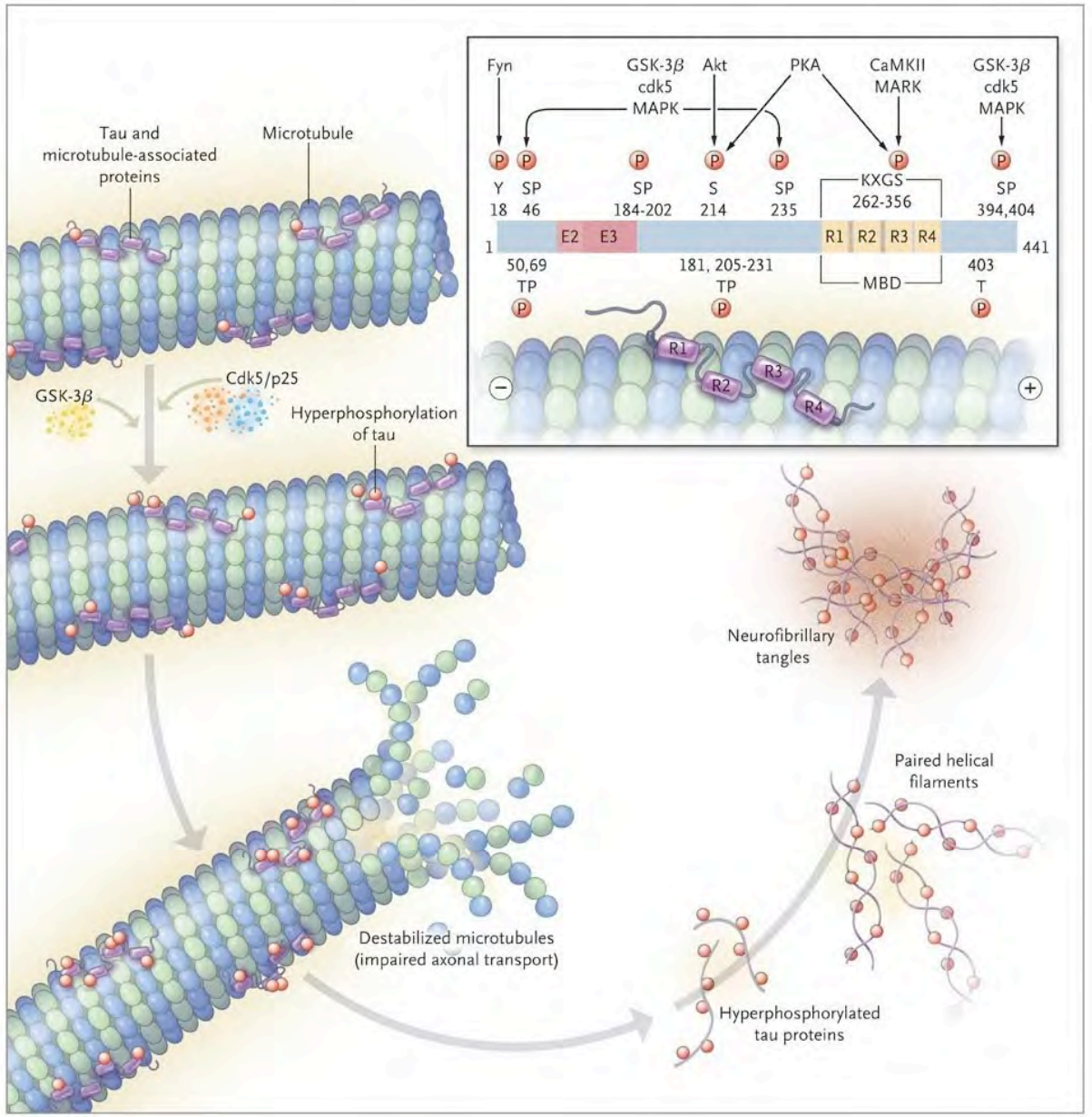




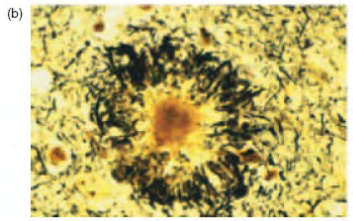
M. Jucker, et al. Alzheimer's disease: From immunotherapy to immunoprevention, Cell, 2023

Alzheimer's disease (AD)
Formation of NFTs

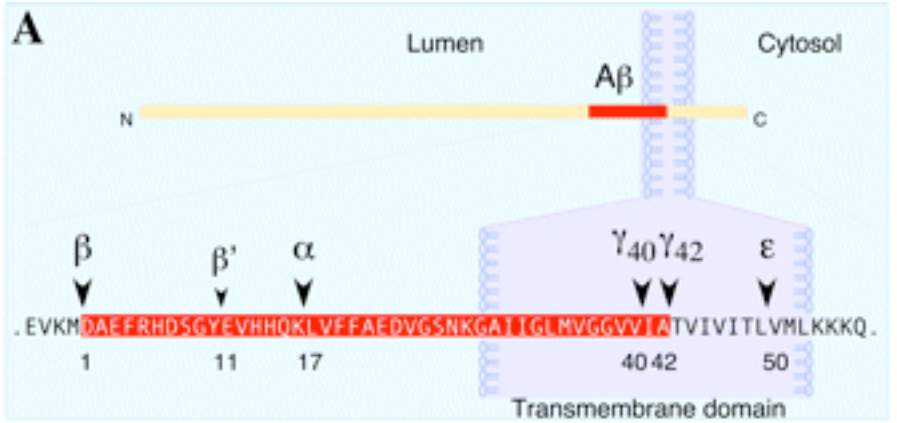
Tau based neurofibrillary tangle

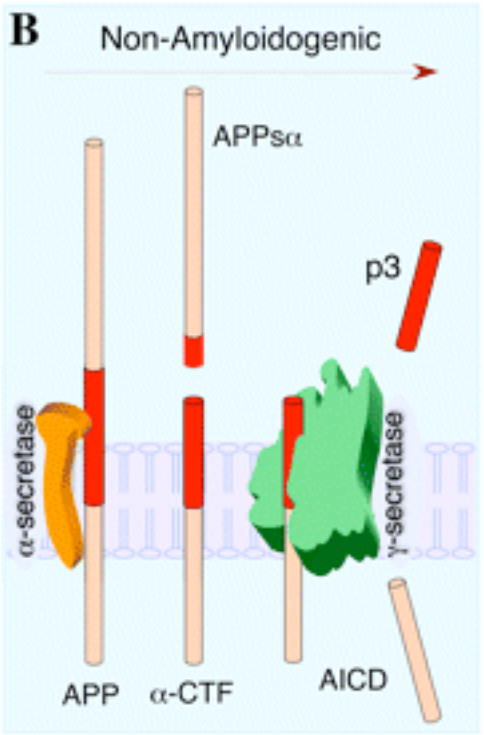


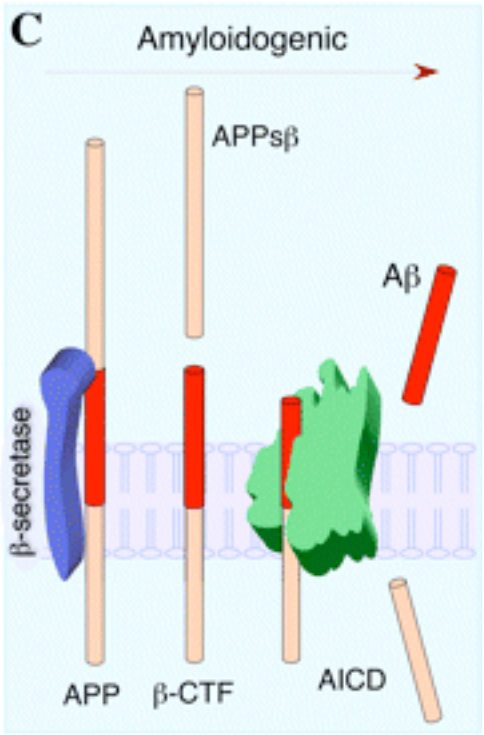
Alzheimer’s disease (AD)
Origin of β-amyloid plaques: APP processing



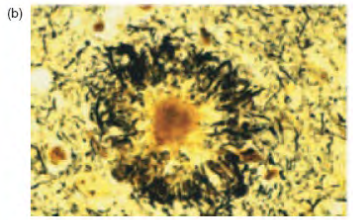
Amyloid based Neuritic plaque



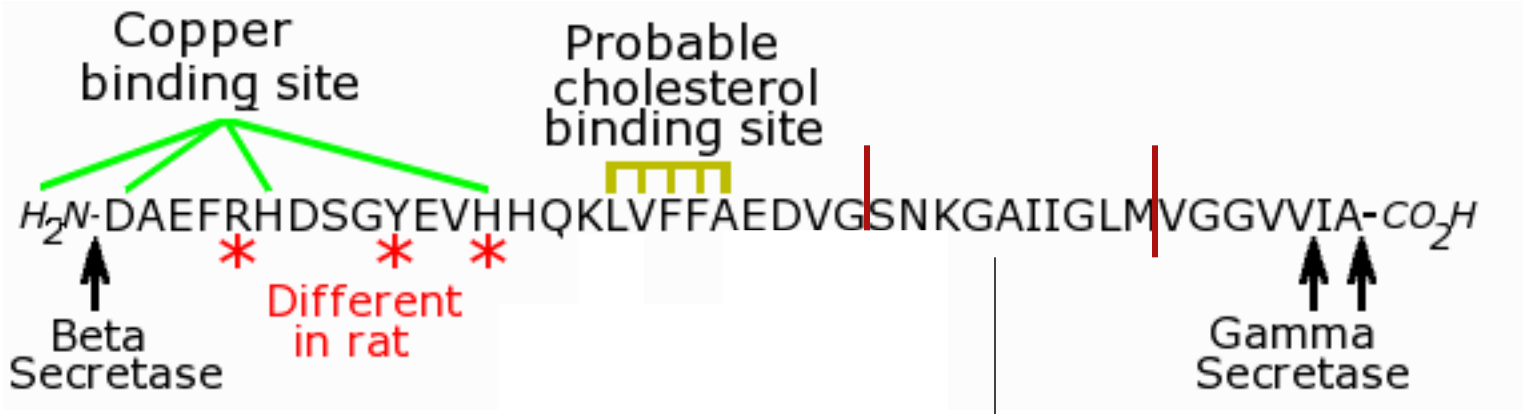




Alzheimer's disease (AD)
Structure of β-amyloid peptide

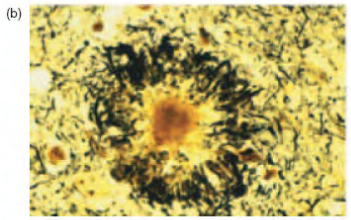


Amyloid based Neuritic plaque

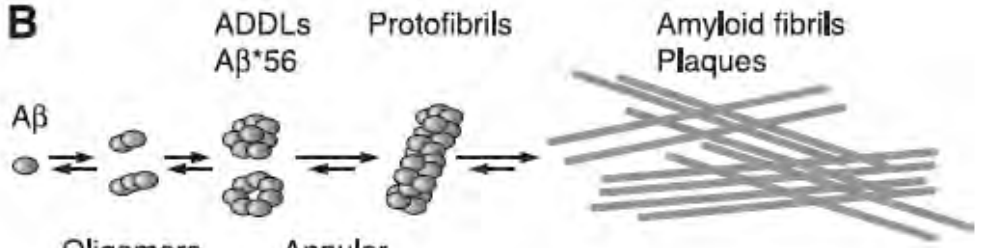


25-35, the most critical region for the change of conformation from a-sheet to b-sheet

Alzheimer's disease (AD)
β-amyloid peptide aggregation

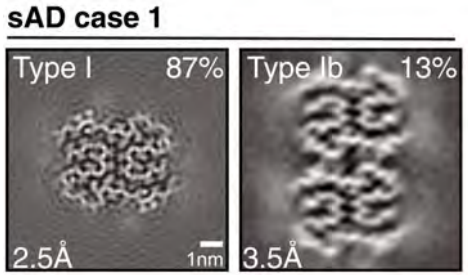


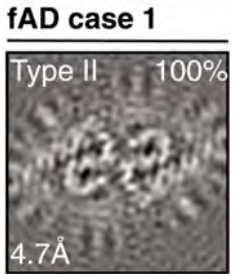
Amyloid based Neuritic plaque

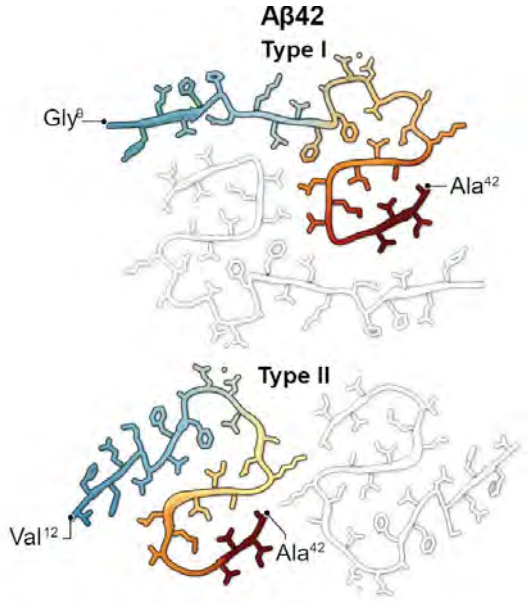


Physiol Rev 90: 465–494, 2010;

Murine Aβ peptides do not aggregate!





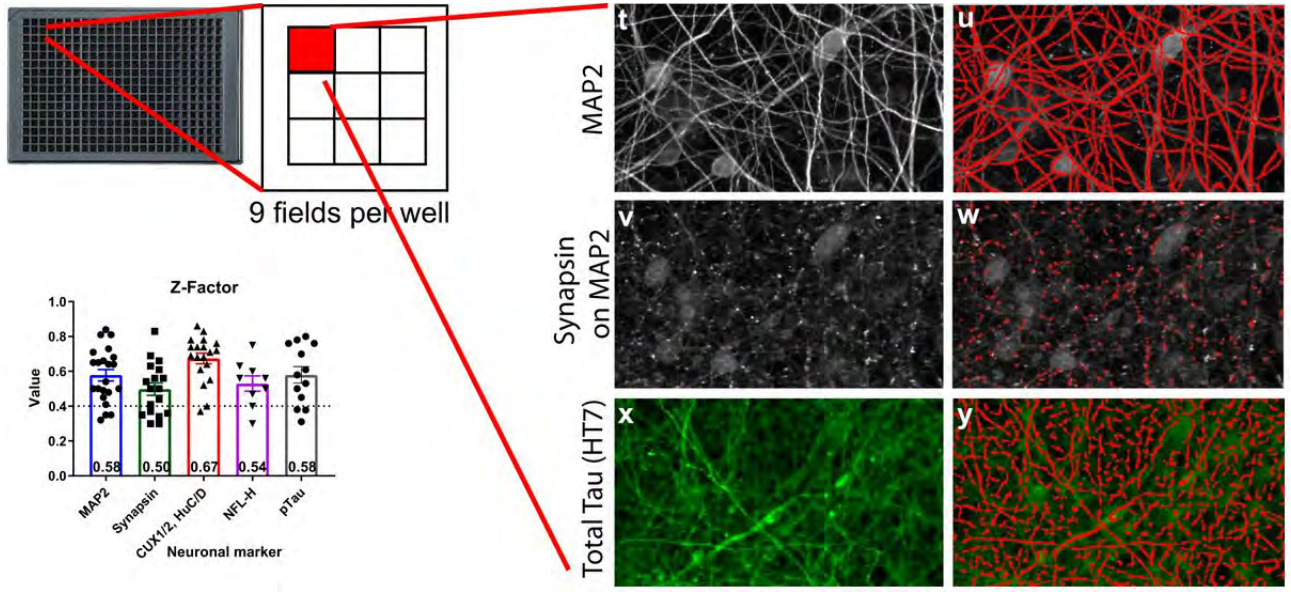


Cryo-EM–derived structures of fibrils formed from Aβ42 from human brain tissue reveal different « strains » associated with distinct neurodegenerative diseases.

Yang Yang et al, Science , 2022. DOI: 10.1126/science.abm7285

Alzheimer's disease (AD)
β-amyloid peptide/Tau toxicities

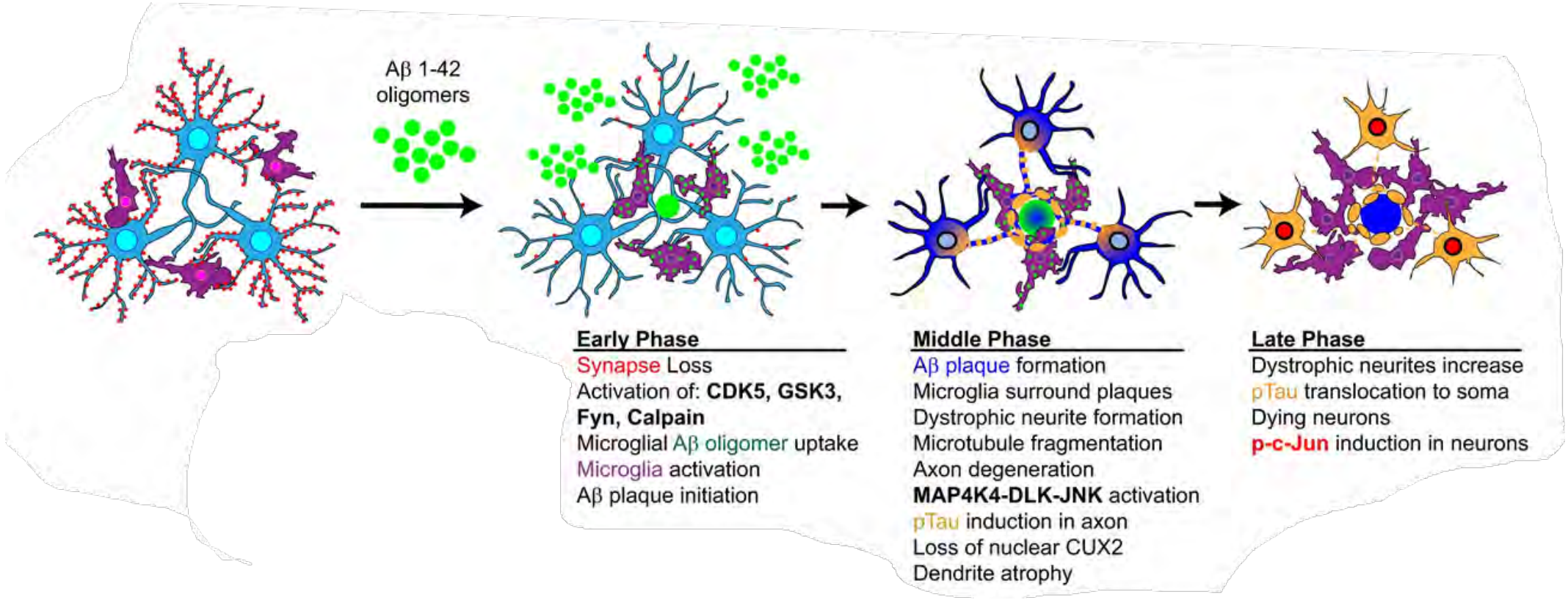
A high-throughput, automated human iPSC-derived neuron differentiation and culturing platform = a new model of AD



Mature culture (12 weeks) => image analysis

Alzheimer's disease (AD)
β-amyloid peptide/Tau toxicities

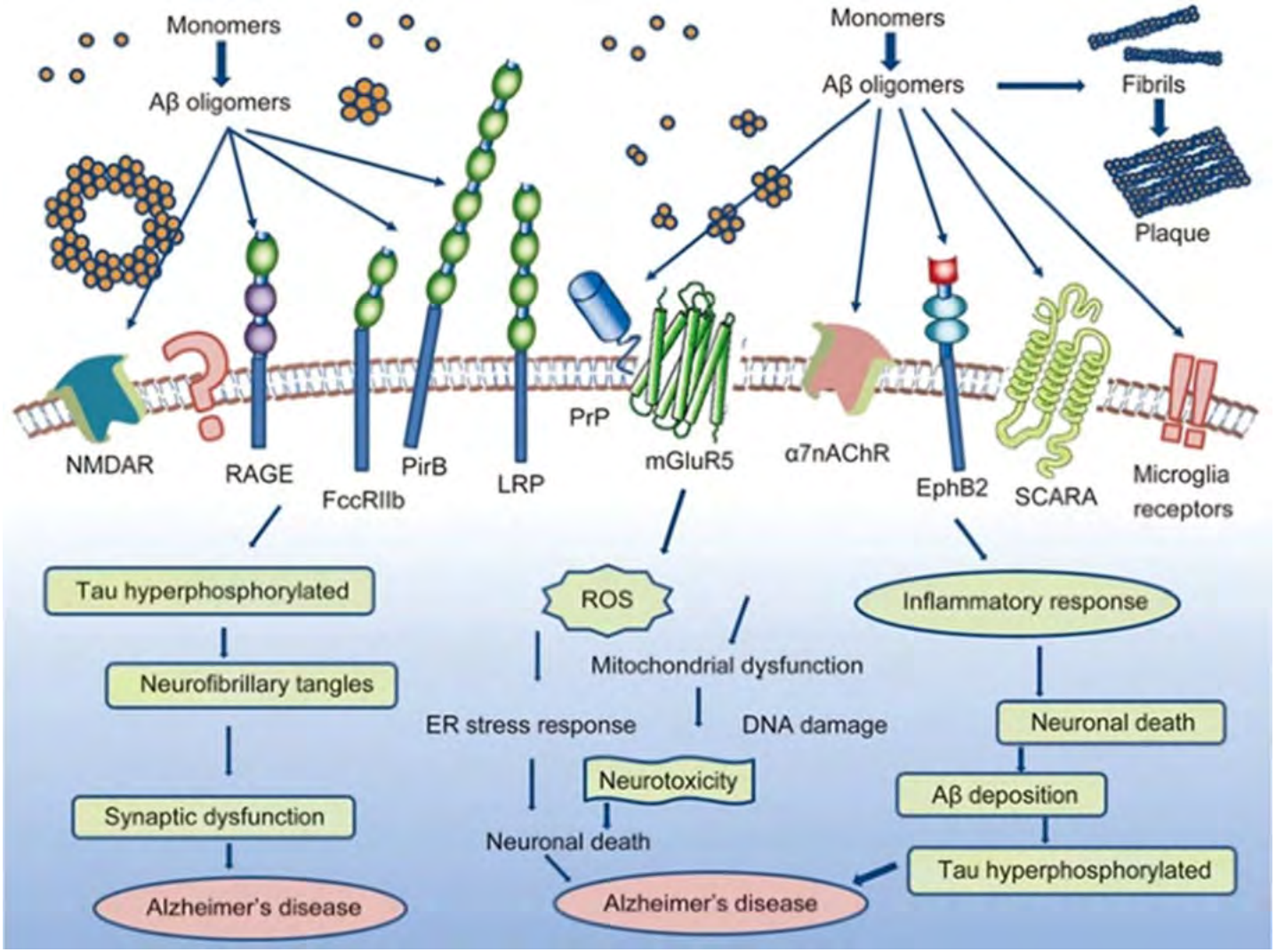
- Amyloid-β and tau: interaction for toxicity
  => Role of microglia



Aβ and microglial activation are two independent processes that, when they converge, lead to tau pathology

*Bassil, R., et al. Improved modeling of human AD with an automated culturing platform for iPSC neurons, astrocytes and microglia. Nat Commun **12,** 5220 (2021)*

Alzheimer's disease (AD)
Amyloid cascade hypothesis



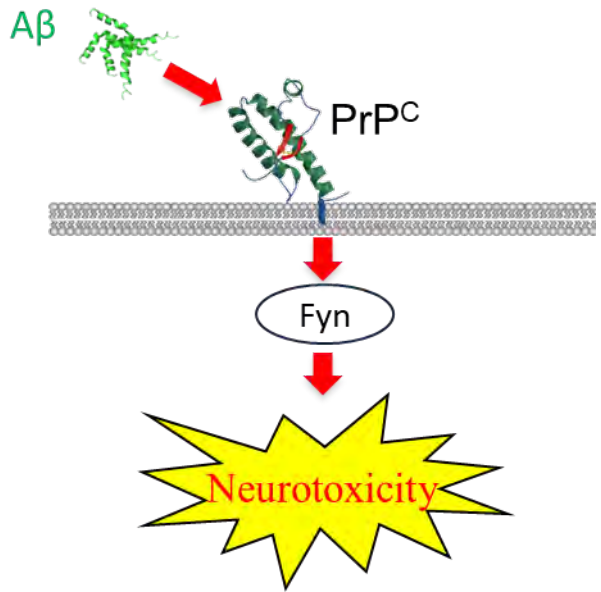
Do Prion and Alzheimer's diseases share common neurodegenerative mechanisms?

nature neuroscience

Alzheimer amyloid-β oligomer bound to postsynaptic prion protein activates Fyn to impair neurons

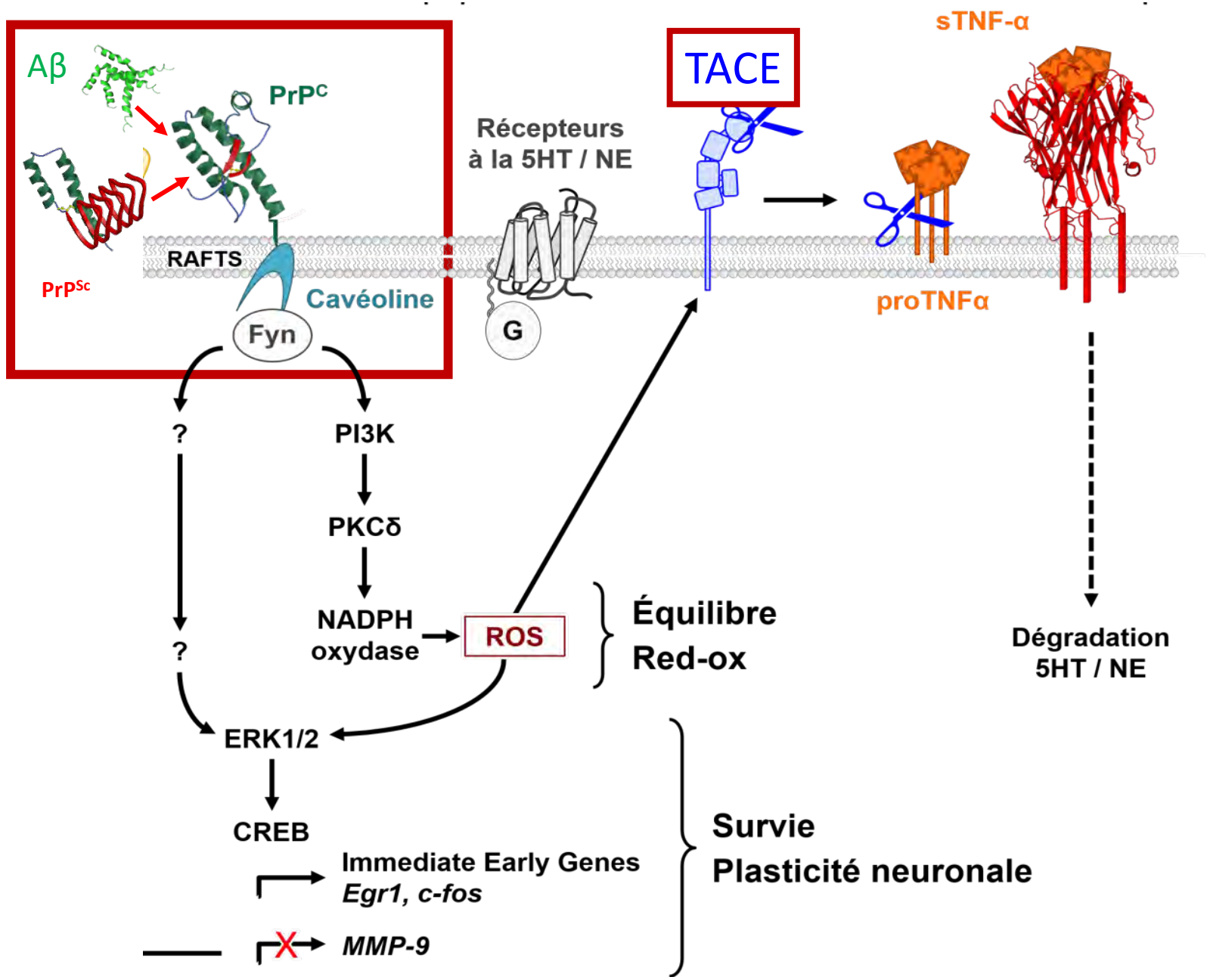
Ji Won Um[1], Haakon B Nygaard[1], Jacqueline K Heiss[1], Mikhail A Kostylev[1], Massimiliano Stagi[1], Alexander Vortmeyer[2], Thomas Wisniewski[3], Erik C Gunther[1] & Stephen M Strittmatter[1]

Amyloid-beta (Aβ) oligomers are thought to trigger Alzheimer's disease pathophysiology. Cellular prion protein (PrP^C) selectively binds oligomeric Aβ and can mediate Alzheimer's disease–related phenotypes. We examined the specificity, distribution and signaling of Aβ-PrP^C complexes, seeking to understand how they might alter the function of NMDA receptors (NMDARs) in neurons. PrP^C is enriched in postsynaptic densities, and Aβ-PrP^C interaction leads to Fyn kinase activation. Soluble Aβ assemblies derived from the brains of individuals with Alzheimer's disease interacted with PrP^C to activate Fyn. Aβ engagement of PrP^C-Fyn signaling yielded phosphorylation of the NR2B subunit of NMDARs, which was coupled to an initial increase and then a loss of surface NMDARs. Aβ-induced dendritic spine loss and lactate dehydrogenase release required both PrP^C and Fyn, and human familial Alzheimer's disease transgene–induced convulsive seizures did not occur in mice lacking PrP^C. These results delineate an Aβ oligomer signal transduction pathway that requires PrP^C and Fyn to alter synaptic function, with deleterious consequences in Alzheimer's disease.

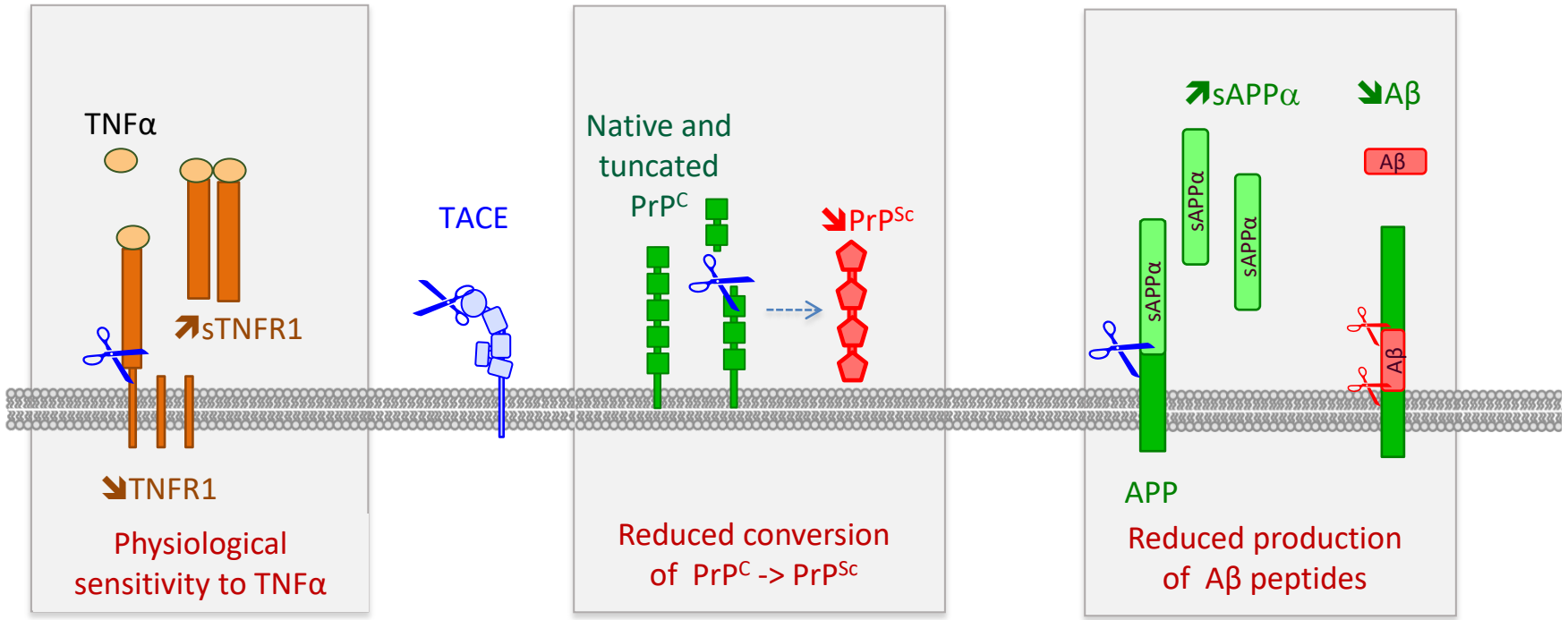


Nature neuroscience, 2012

Prion and Alzheimer's disease: Same fight?



TACE physiological functions



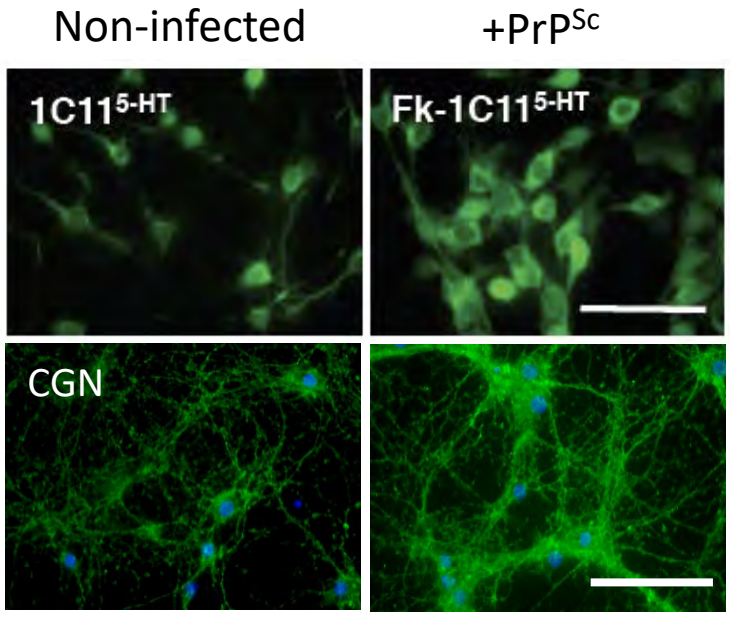
TACE deregulation => prion / Alzheimer's diseases ?

Little was known about TACE regulation

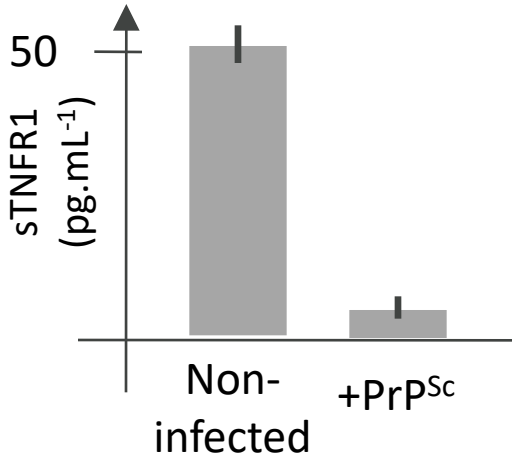
Prion infection triggers TNFR1 under-shedding and hypersensitizes cells to TNFα toxicity

↗ cell surface level of TNFR1

↘ sTNFR1 in cell culture medium



CGN = Cerebellar Granule Neuron

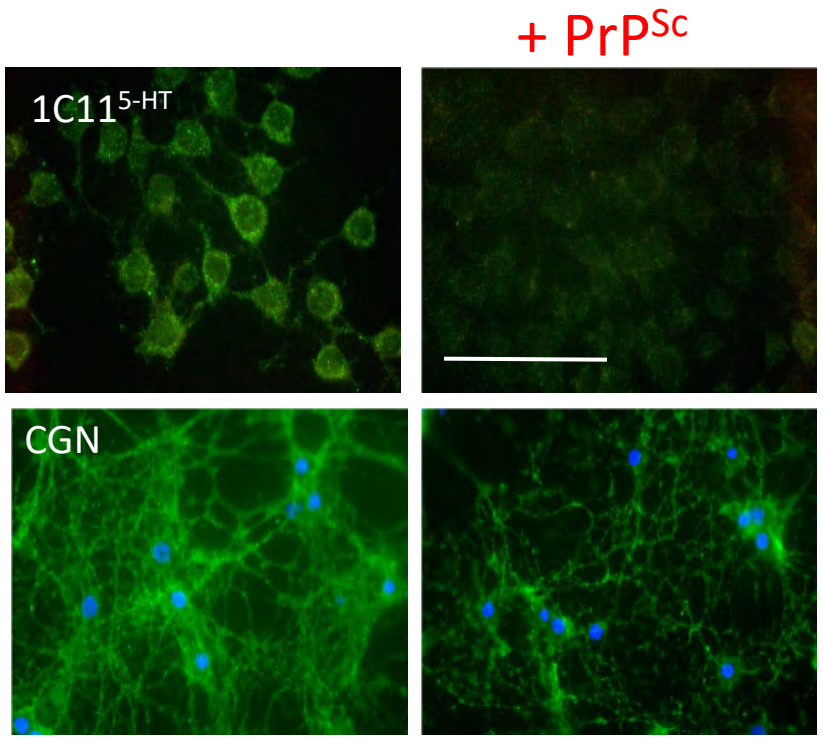


↗ sensitivity of infected neurons to TNFα

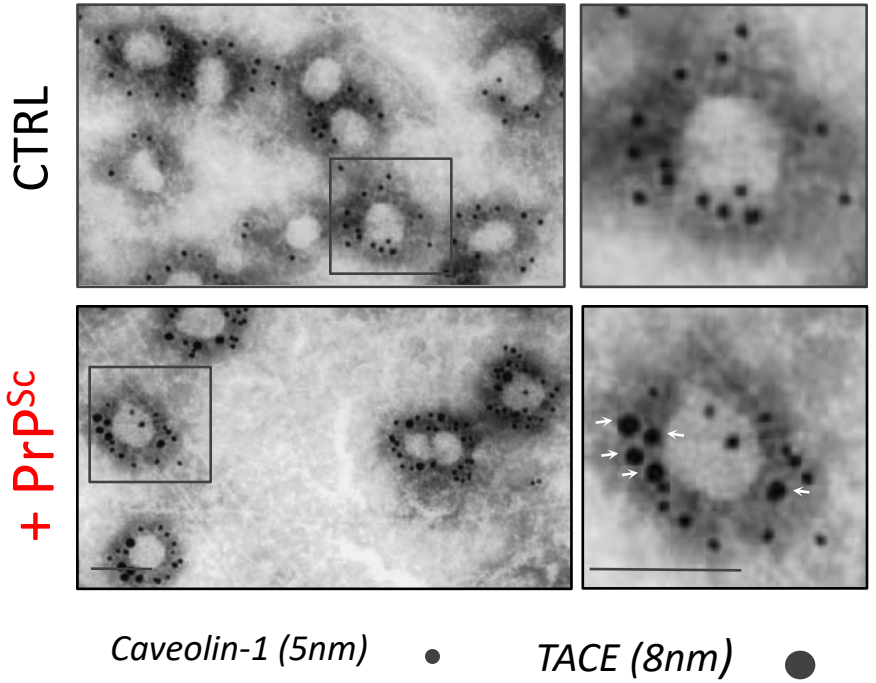
Defect of TACE shedding activity in prion-infected neurons ?

TACE internalization in prion-infected cells

↘ TACE at the plasma membrane

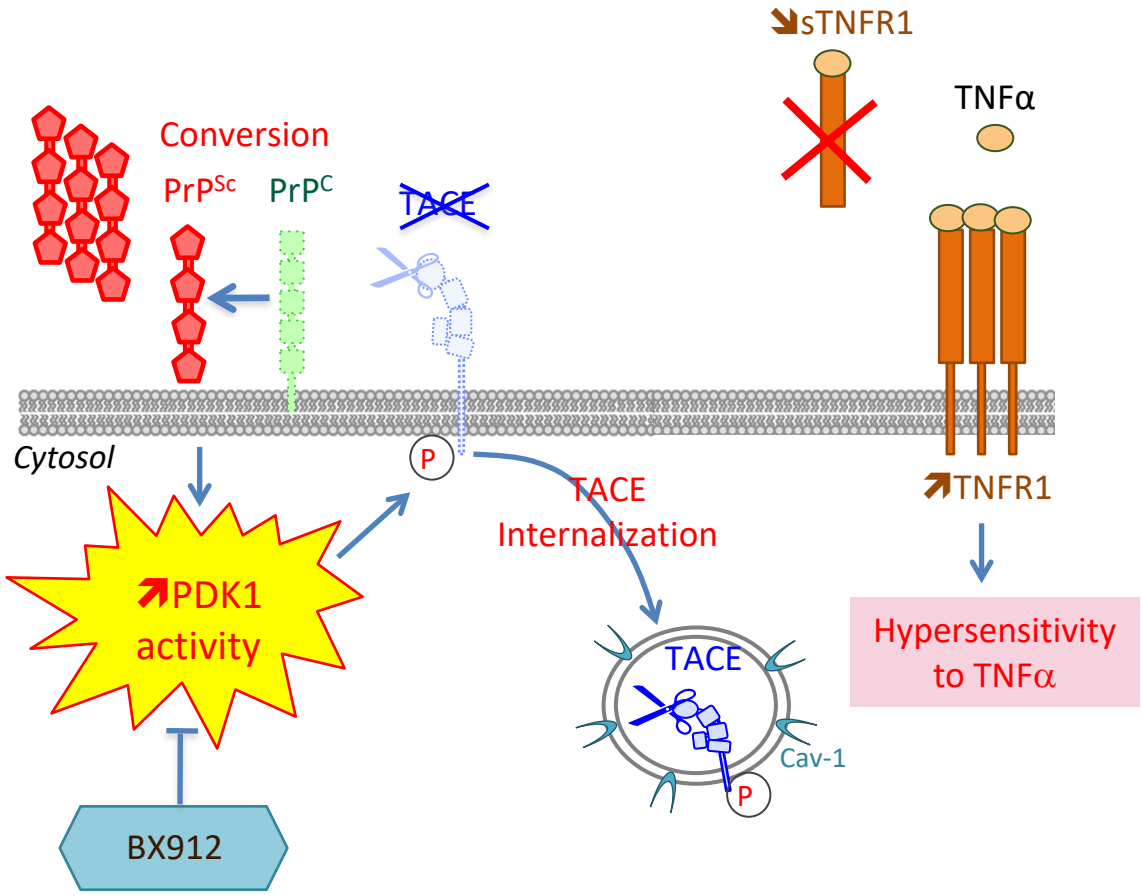


TACE is associated with caveolae in infected cells



Coll J.M. Launay/ Hoffmann LaRoche

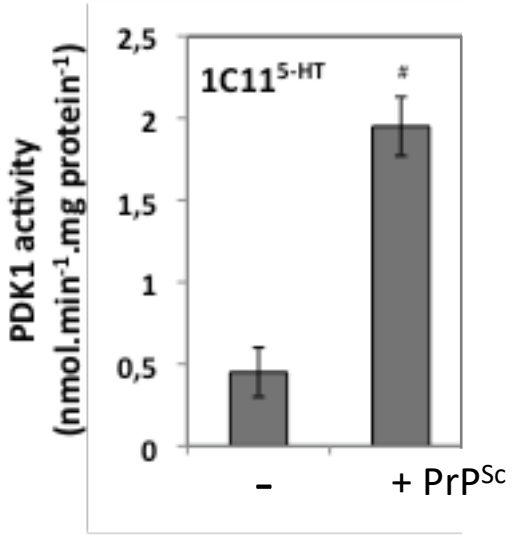
TACE internalization depends on PDK1 overactivity in prion-infected cells



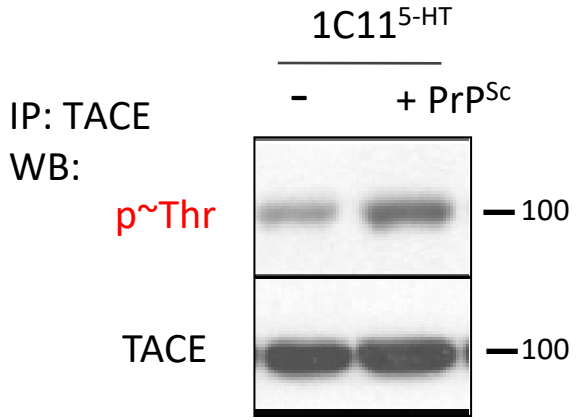
Antagonizing PDK1 activity to rescue TACE shedding activity at the plasma membrane?

PDK1 = 3-phosphoinositide-dependent kinase 1

PDK1 activity



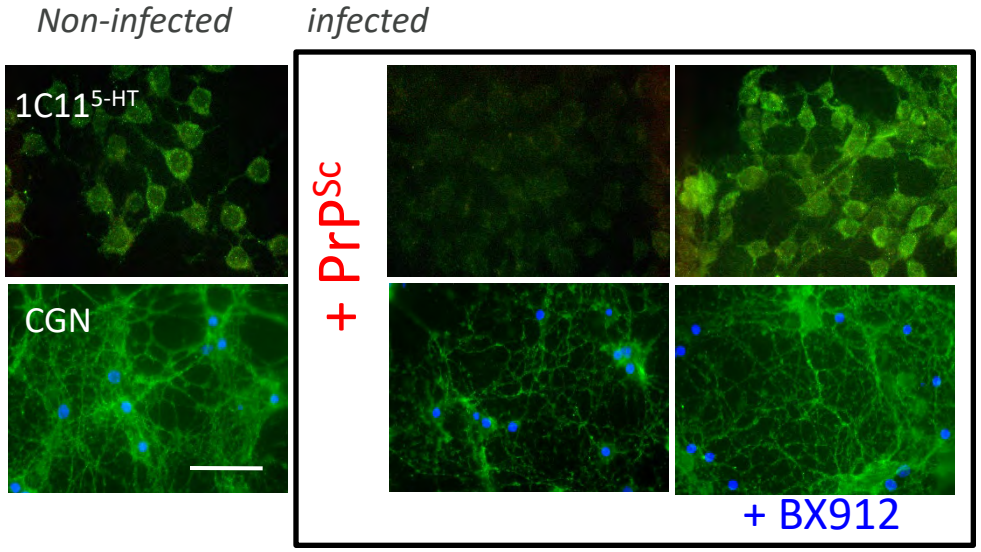
phospho-TACE



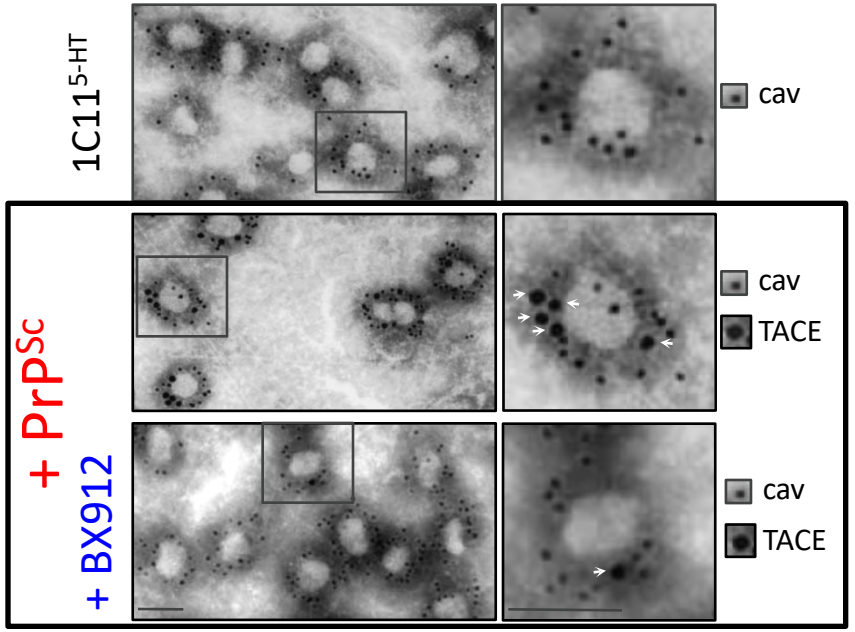
Nature Medicine, 2013

PDK1 inhibition relocates TACE from caveolae to the plasma membrane

Cell surface Immunostaining of TACE

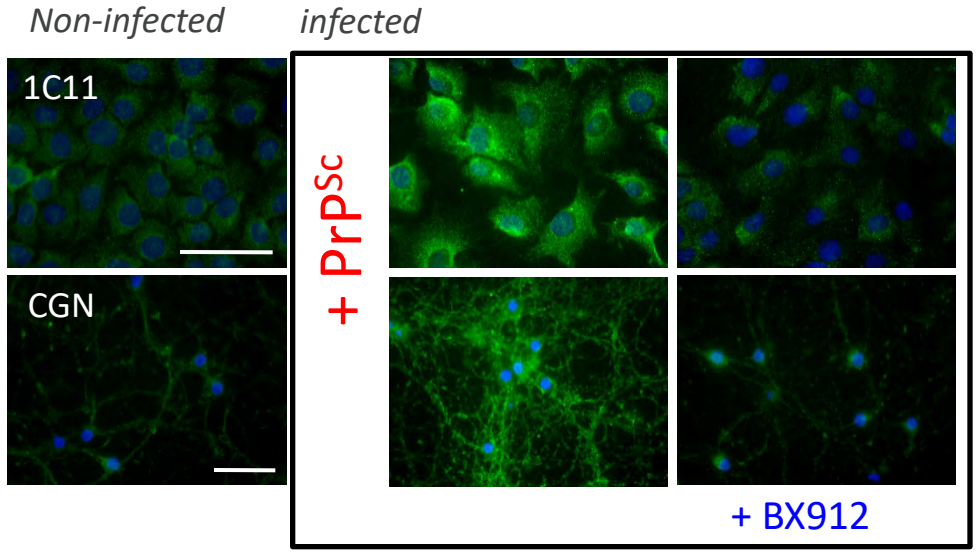


Immunogold electron microscopy

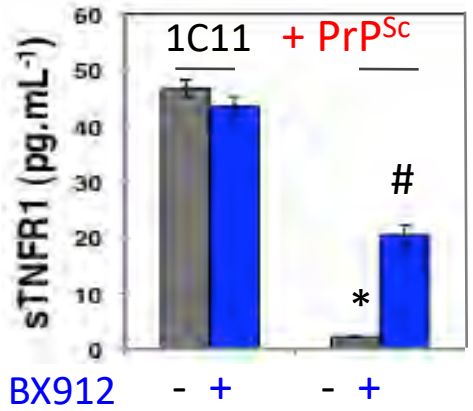


PDK1 inhibition restores TACE shedding activity at the plasma membrane

TNFR1



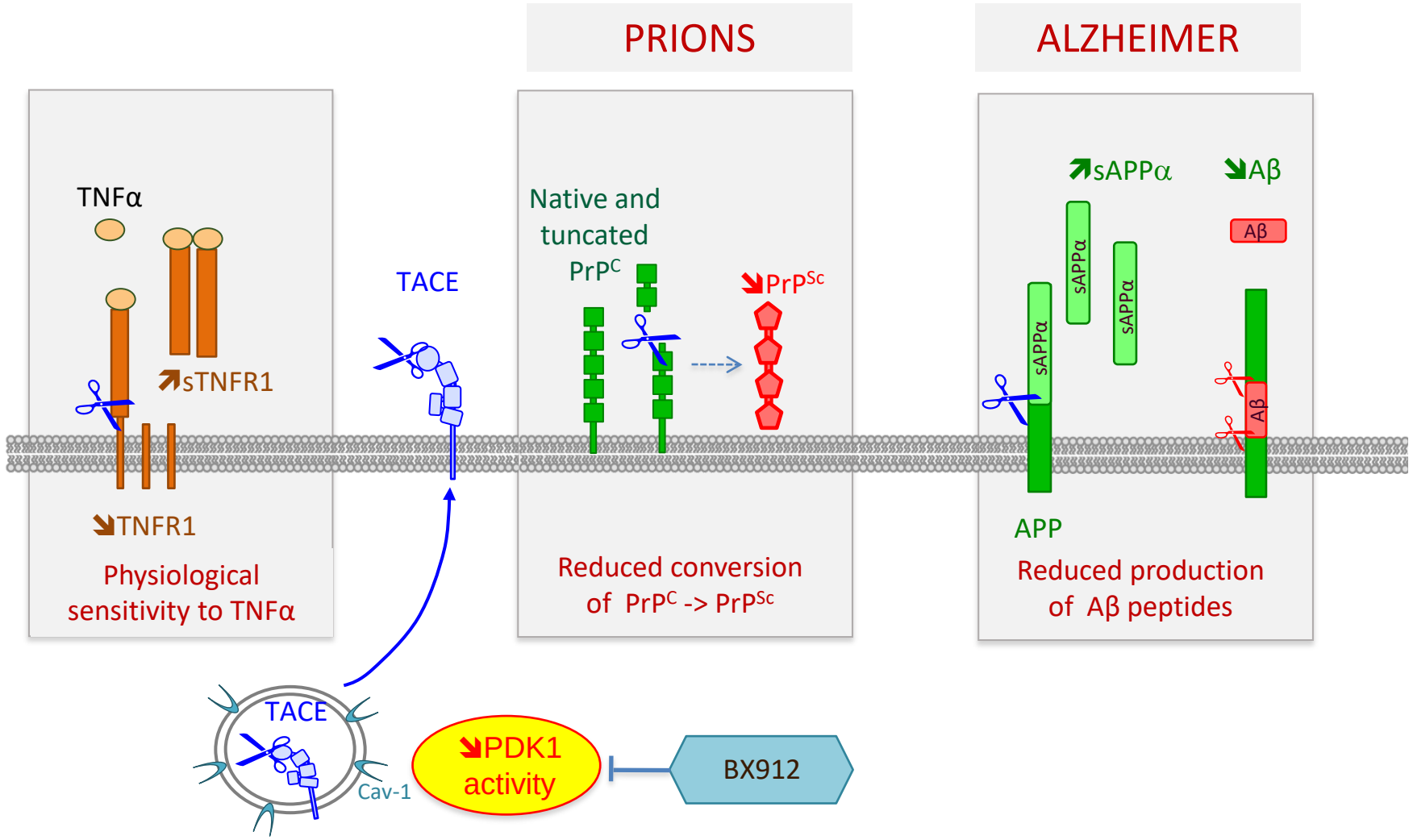
sTNFR1



BX912 rescues the shedding of TNFR1 by TACE

=> Desensitization of prion-infected cells from TNFα toxicity

PDK1 as a therapeutic target against prion and Alzheimer's diseases?

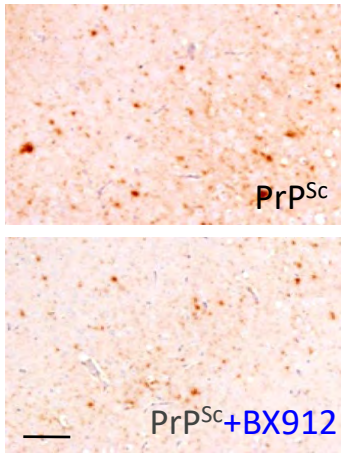


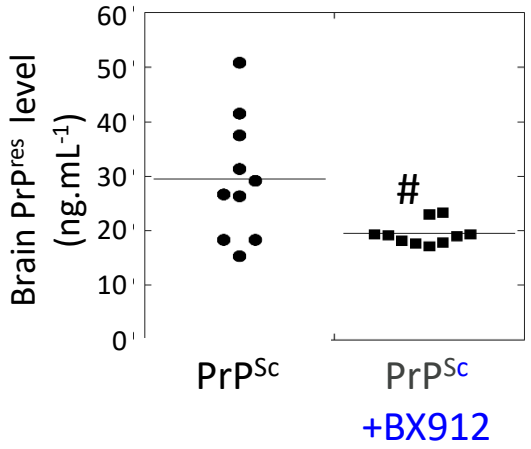
Thus relocated TACE would have 3 beneficial effects in neurodegenerative diseases

Inhibiting PDK1 activity with BX912 in prion-infected mice…

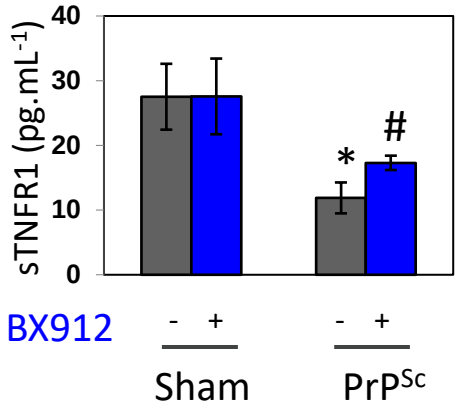
↘brain PrP^{Sc}

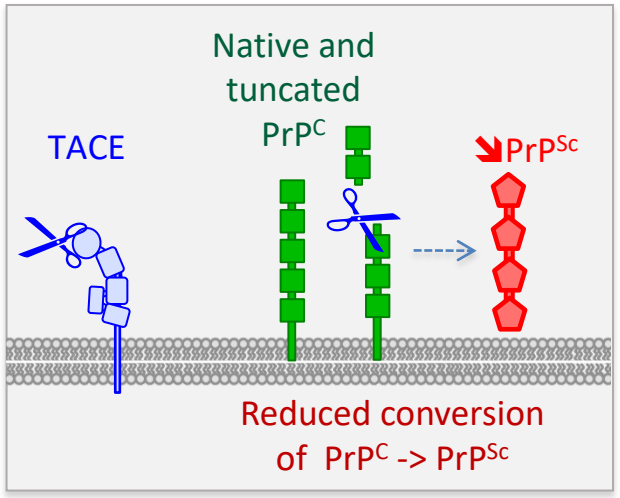
PrP^{Sc} deposition



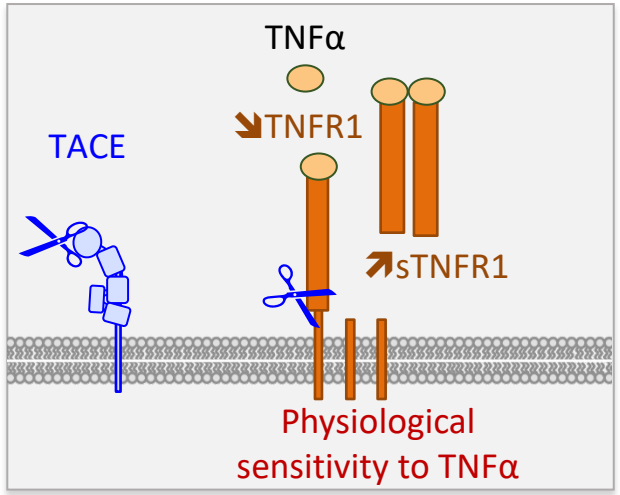


↗ sTNFR1 in CSF





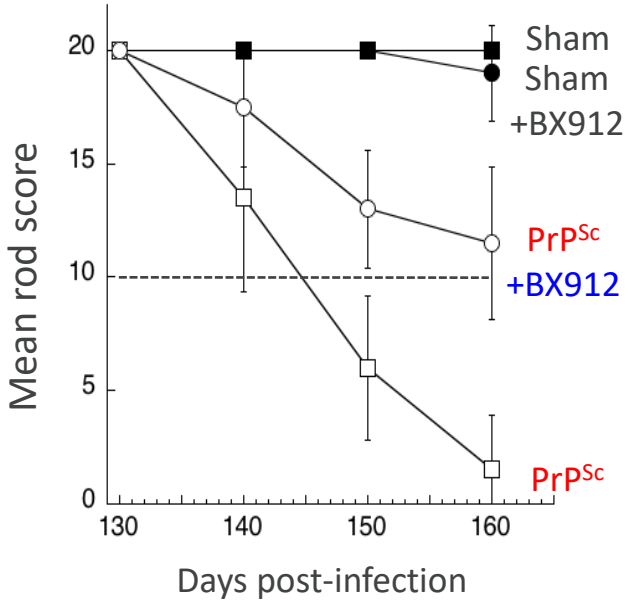
Same effect upon PDK1 silencing with siRNA



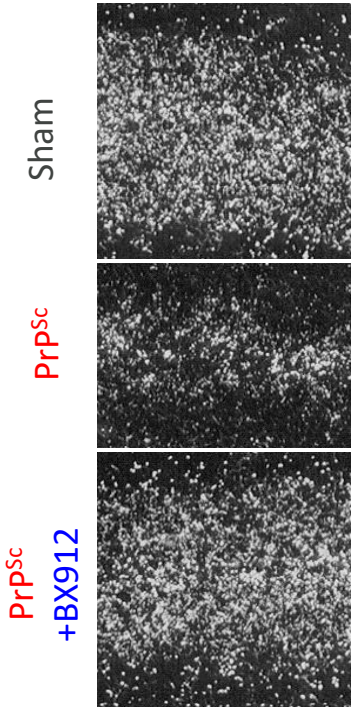
Coll. J.M. Launay/ Hoffmann LaRoche

Inhibiting PDK1 activity with BX912 in prion-infected mice…

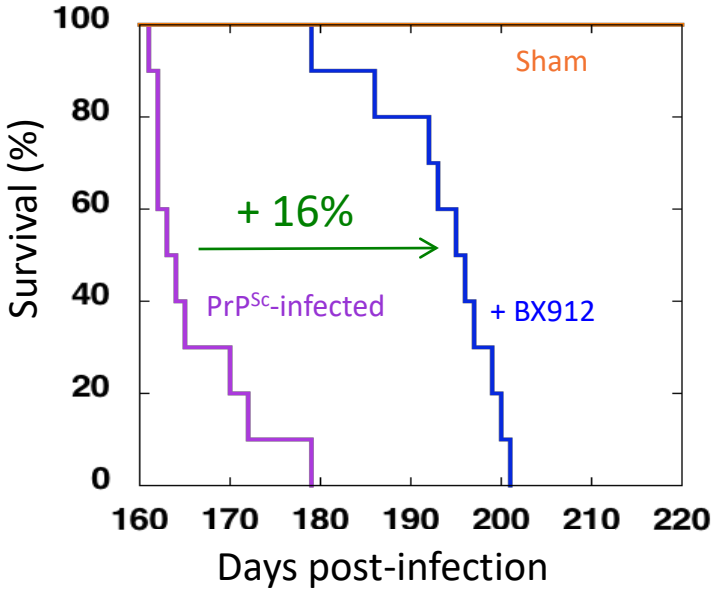
↘ motor deficits



↘ neurodegeneration in the IGL



↗ survival time

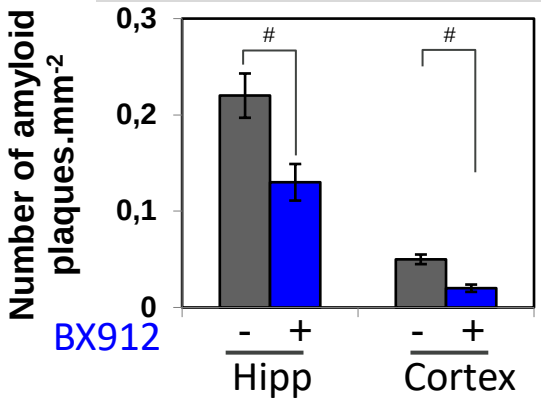


Coll. J.M. Launay/ Hoffmann LaRoche

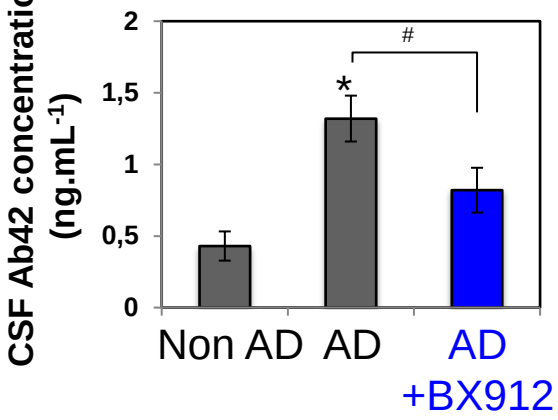
One drug for both prion and Alzheimer’s diseases ?

Inhibiting PDK1 activity with BX912 in Alzheimer's mouse models (Tg2576, 3xTg-AD, 5xTg-AD)…

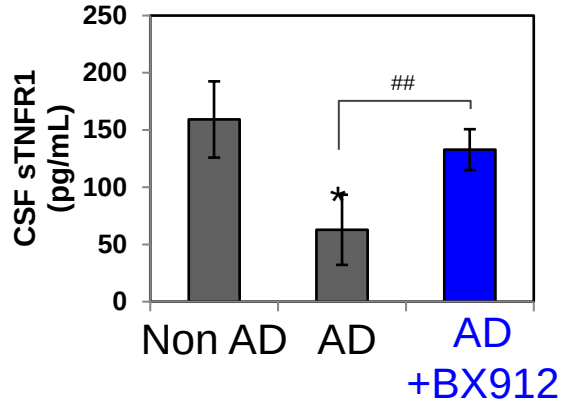
↘ amyloid plaques

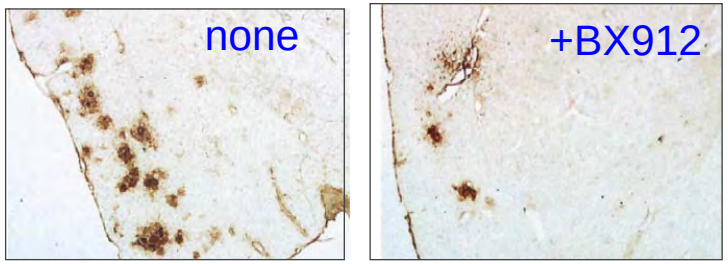


↘ Aβ in CSF

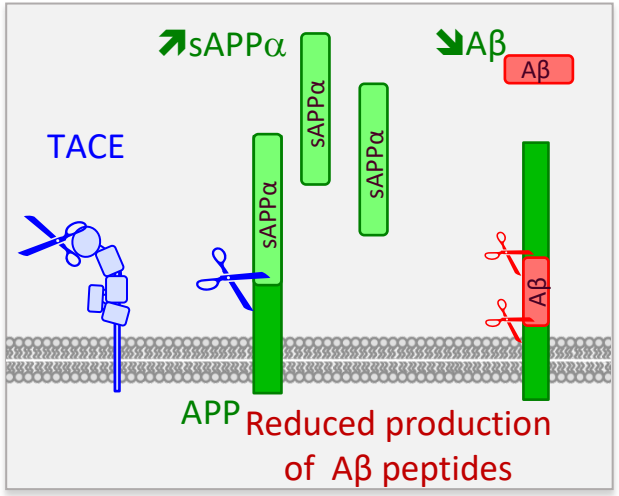


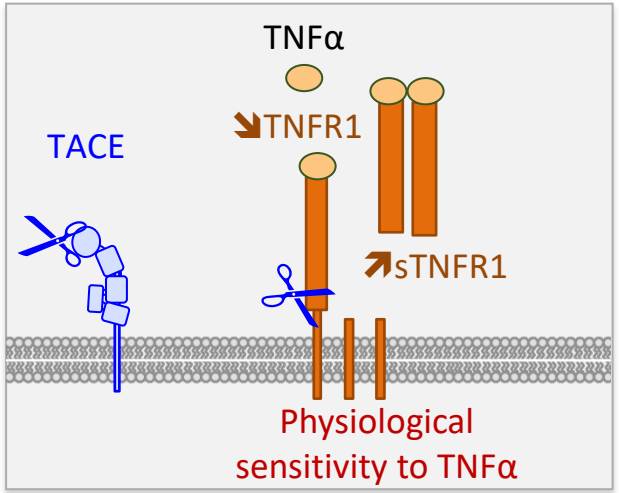
↗ sTNFR1 in CSF





Cortex slices
Thioflavin S staining of amyloid plaques



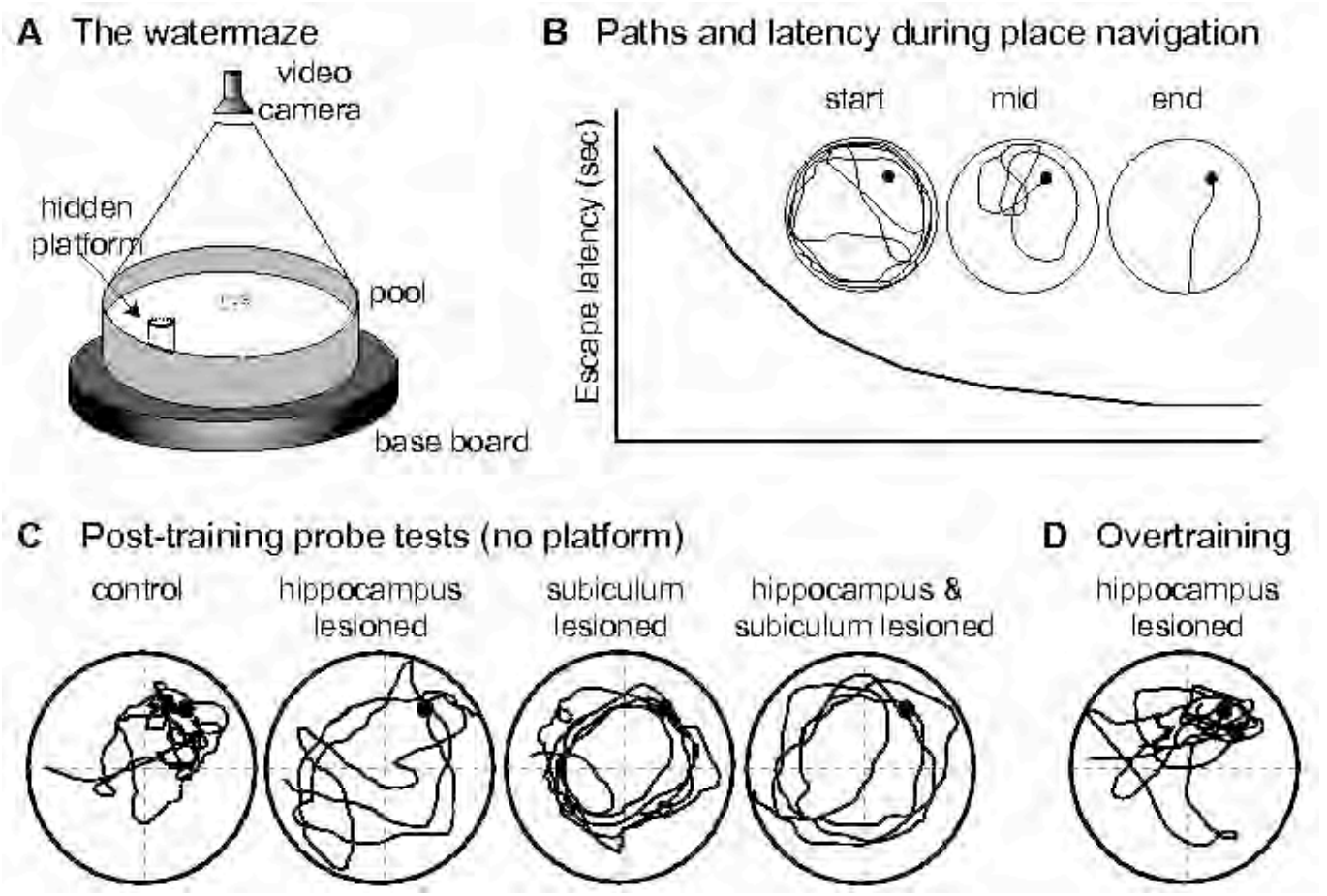


Coll. J.M. Launay/ Hoffmann LaRoche

How to test behavioral benefit of PDK1 inhibition in AD mice?

- Morris water maze test: behavioral test of memory/cognitive function

2 m diameter watermaze at the University of Edinburgh



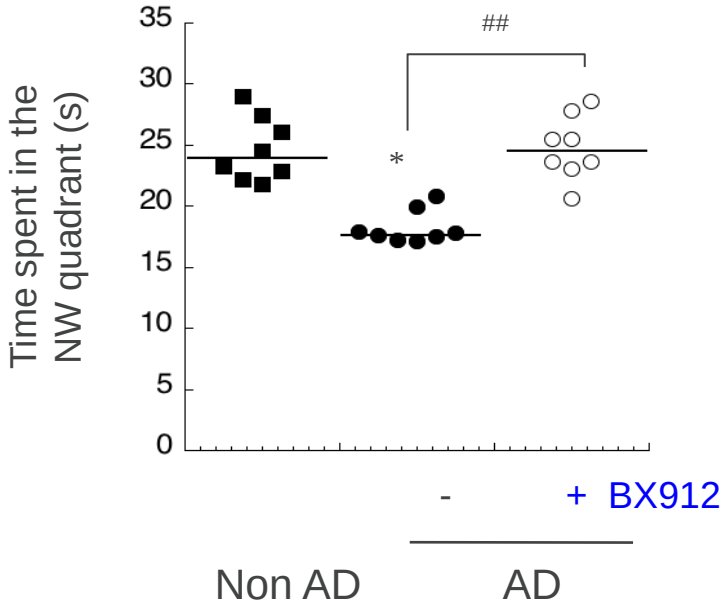
How to test behavioral benefit of PDK1 inhibition in AD mice?

- Nesting construction test: behavioral test of social/affialiative function

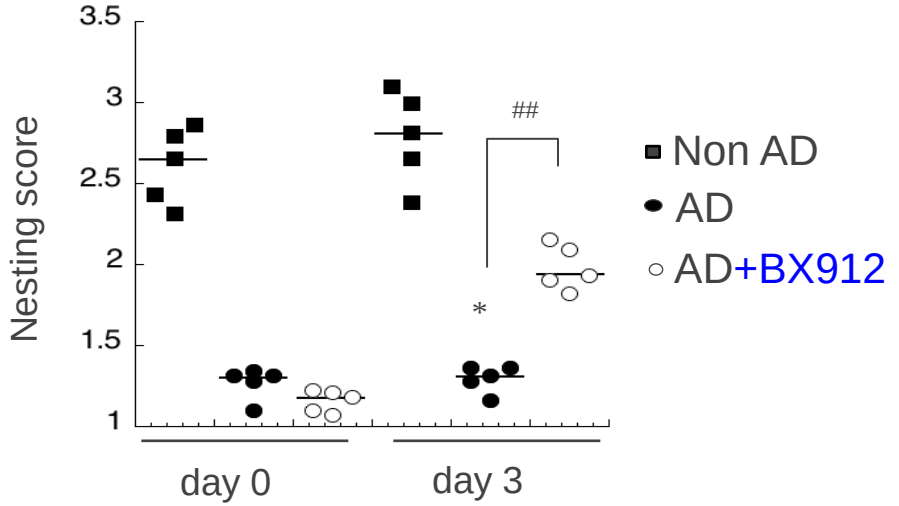
Inhibiting PDK1 activity with BX912 in Alzheimer's mouse models (Tg2576, 3xTg-AD, 5xTg-AD)…

↘ memory and cognitive impairments

Morris Water Maze

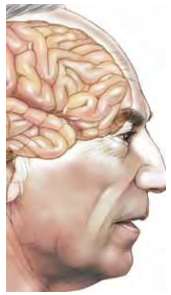


Nesting



Coll. J.M. Launay/ Hoffmann LaRoche

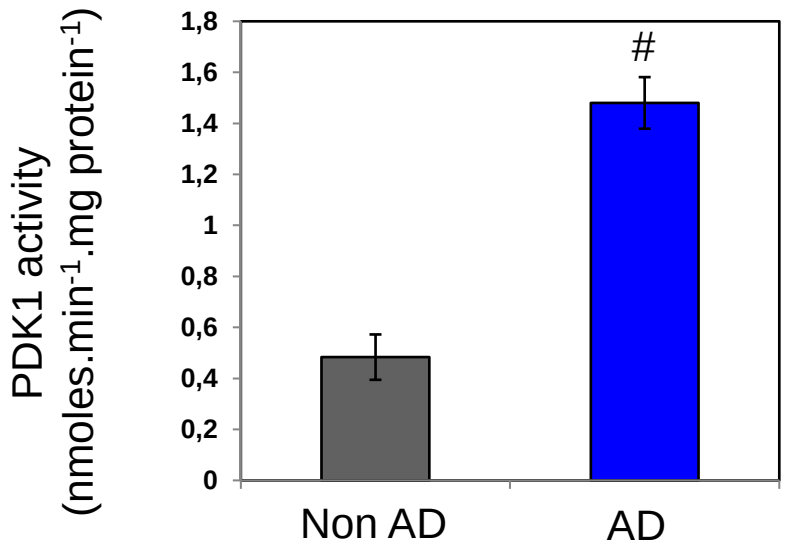
➔PDK1 inhibition alleviates both prion and Alzheimer's diseases in mice



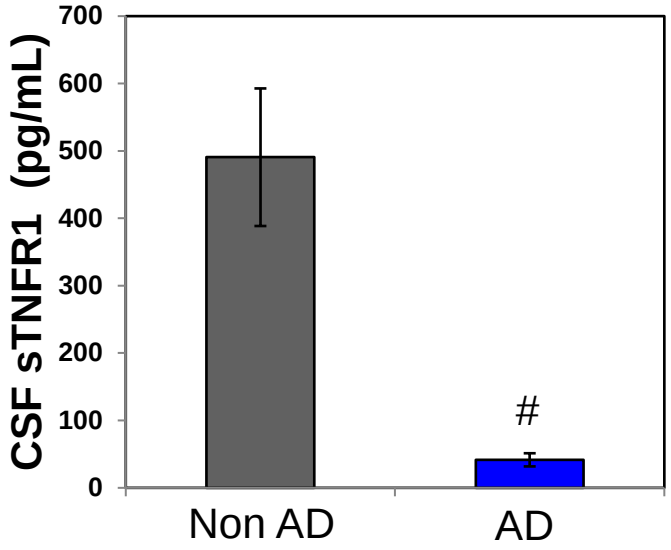
PDK1: a therapeutic target for AD patients ?

6 AD patients

↗ PDK1 activity in human AD brain



↘ sTNFR1 in CSF of AD patients

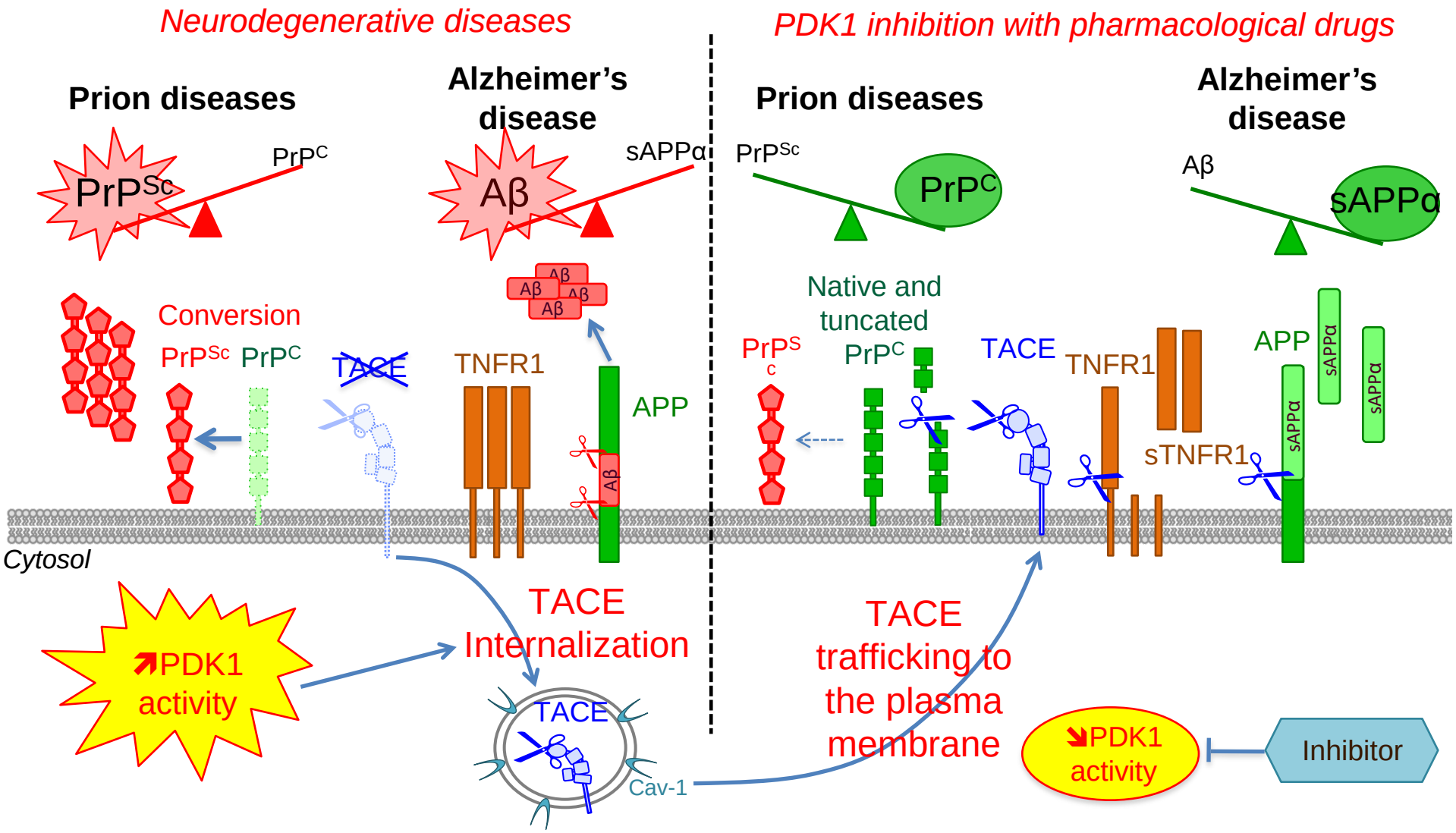


TACE internalization

Defect of TACE shedding activity
(Readout sTNFR1)

Coll. J.M. Launay/ Hoffmann LaRoche

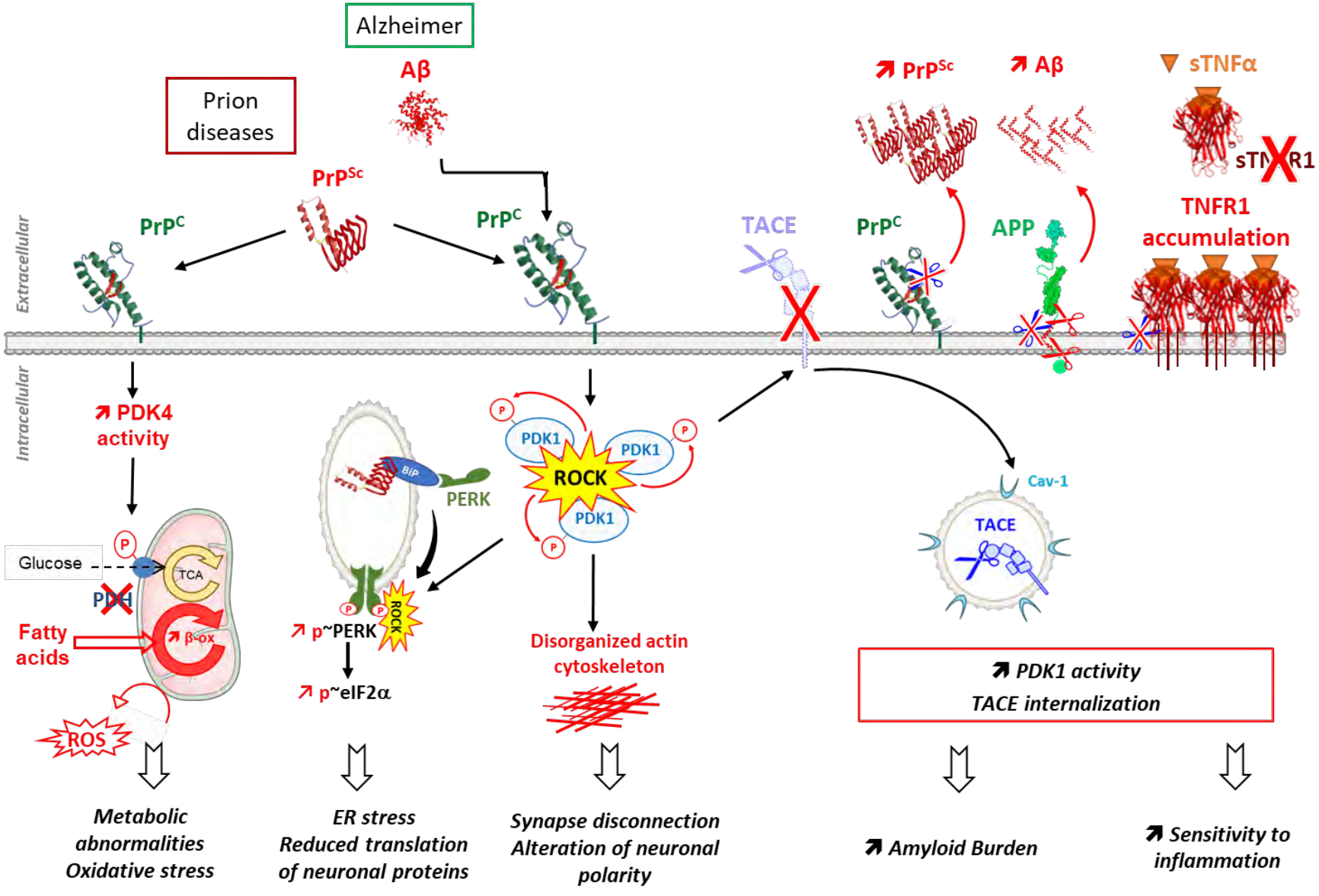
Summary



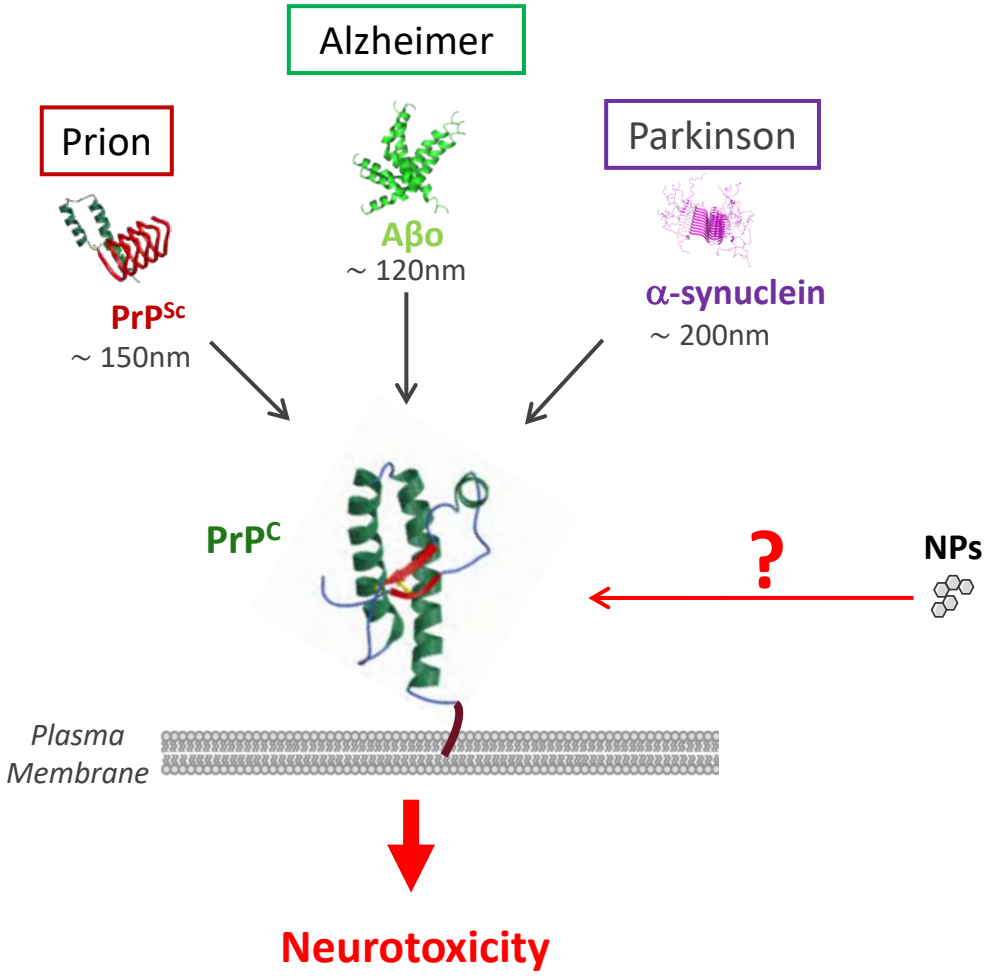
Prion and Alzheimer's diseases share common neurodegenerative mechanisms
PDK1: therapeutic target for both diseases

Nature Medicine, 2013

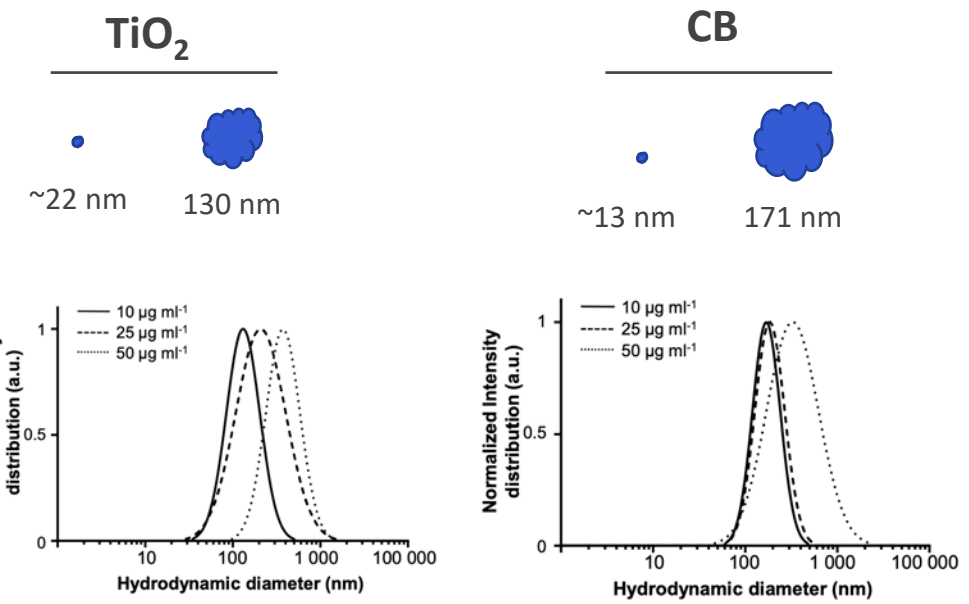
Common neurodegenerative mechanisms, common therapeutic targets



The PrP^C : a neuronal receptor that relays amyloid neurotoxicity



- *Hydrodynamic diameter (nm) of TiO_2 and CB NPs measured by DLS in DMEM/F12 at 37 °C*

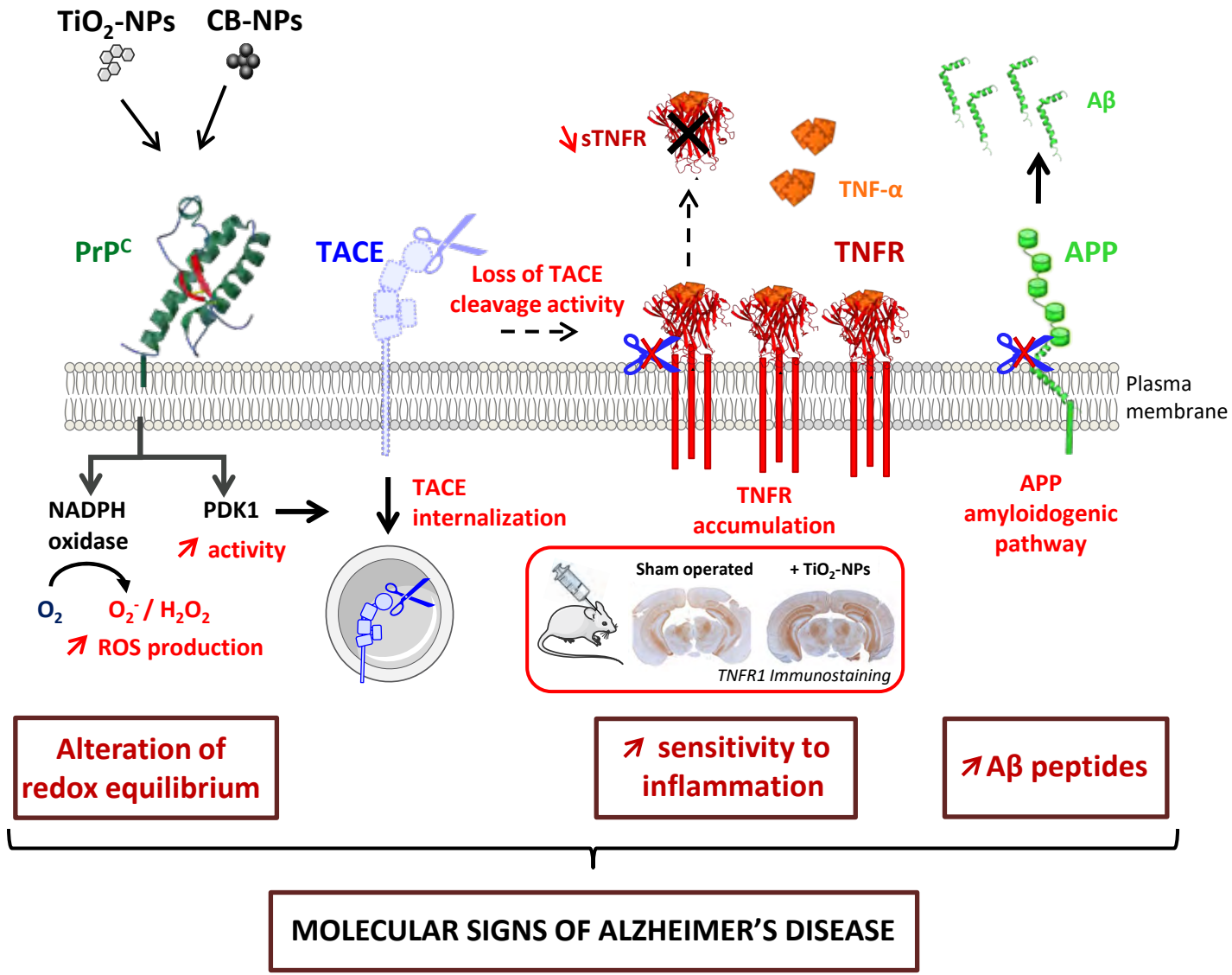


Diameter of TiO_2/CB NPs aggregates in biological fluids similar to amyloïd diameters

PrP^C : a neuronal receptor that relays the neurotoxicity of nanoparticle aggregates?

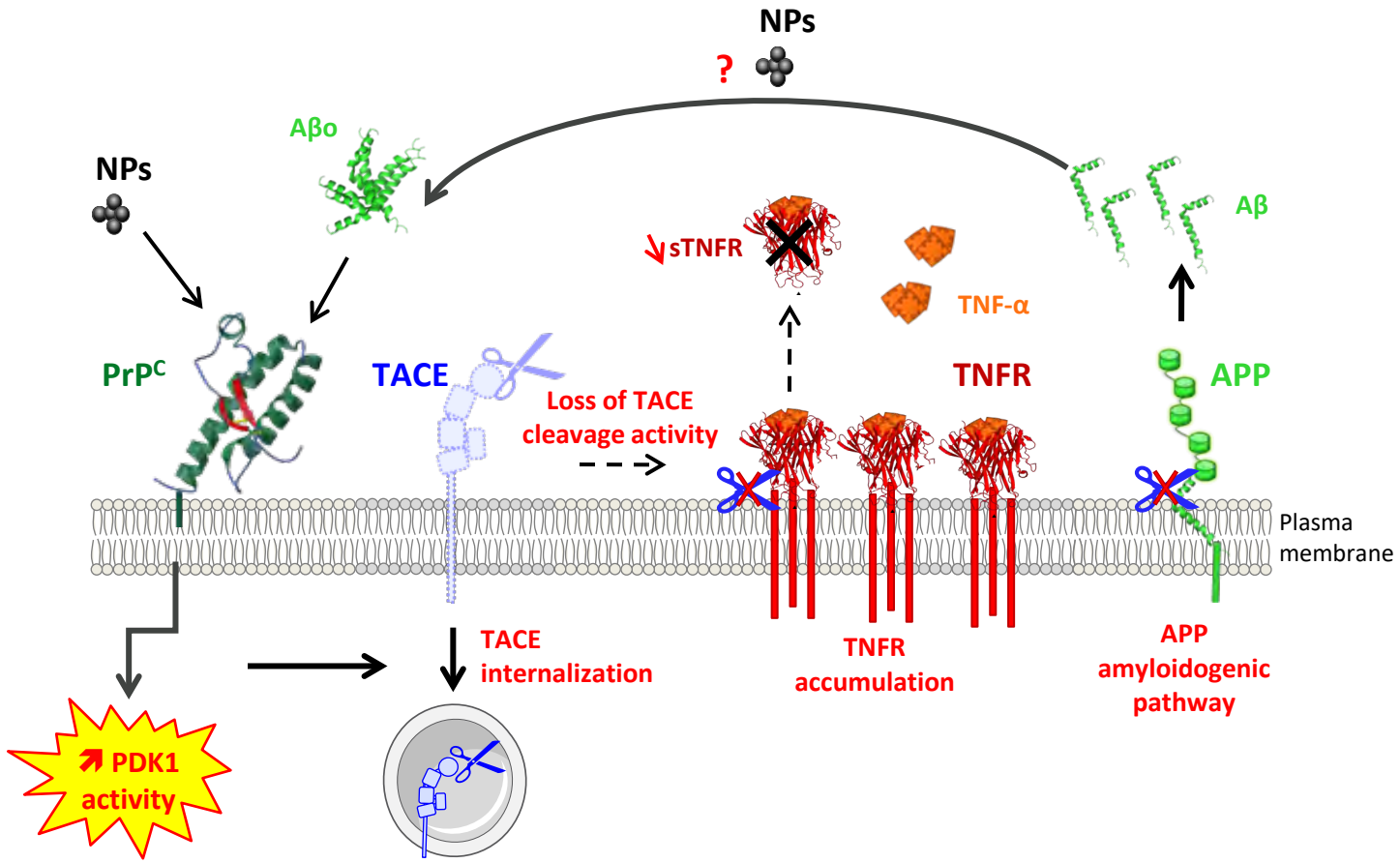
Laurén et al., 2009; Aulić et al., 2017

Role of Environmental NPs in the onset of AD



Ribeiro et al., Particle and Fibre Toxicology (2022)

Role of Environmental NPs in AD progression?



Perspectives:

1. NPs only initiate vicious circle supporting by PrP^C/PDK1/TACE pathocascade => **AD onset**
2. NPs influence Aβ peptide assembly in neurotoxic species accelerating vicious circle => **AD onset & progression**

TAKE HOME MESSAGE

- **1C11 cell line** = A stem cell background to tackle basic and clinical challenges relating to neuronal response to antidepressants/ prion - induced neurodegeneration/ neurotoxicity

- Pathological conditions emerge from **deregulation of signaling cascade** normally dedicated to homeostasis

- Importance of **spatio-temporal distribution** of signaling effectors

- Prion and Alzheimer's disease share **common mechanism** of neurodegenerescence : deregulation of PrP^C signaling function

- **Role of nanopollutants in the emergence of AD**

TEAM « SIGNALING AND NEURODEGENERATIVE DISEASES»
B. SCHNEIDER
CNRS UMRS1124

Structural Biology of the Cell

Team Members:

Benoît SCHNEIDER (DR CNRS)

Anne BAUDRY (CR INSERM)

Mathéa PIETRI (MCU U. Paris)

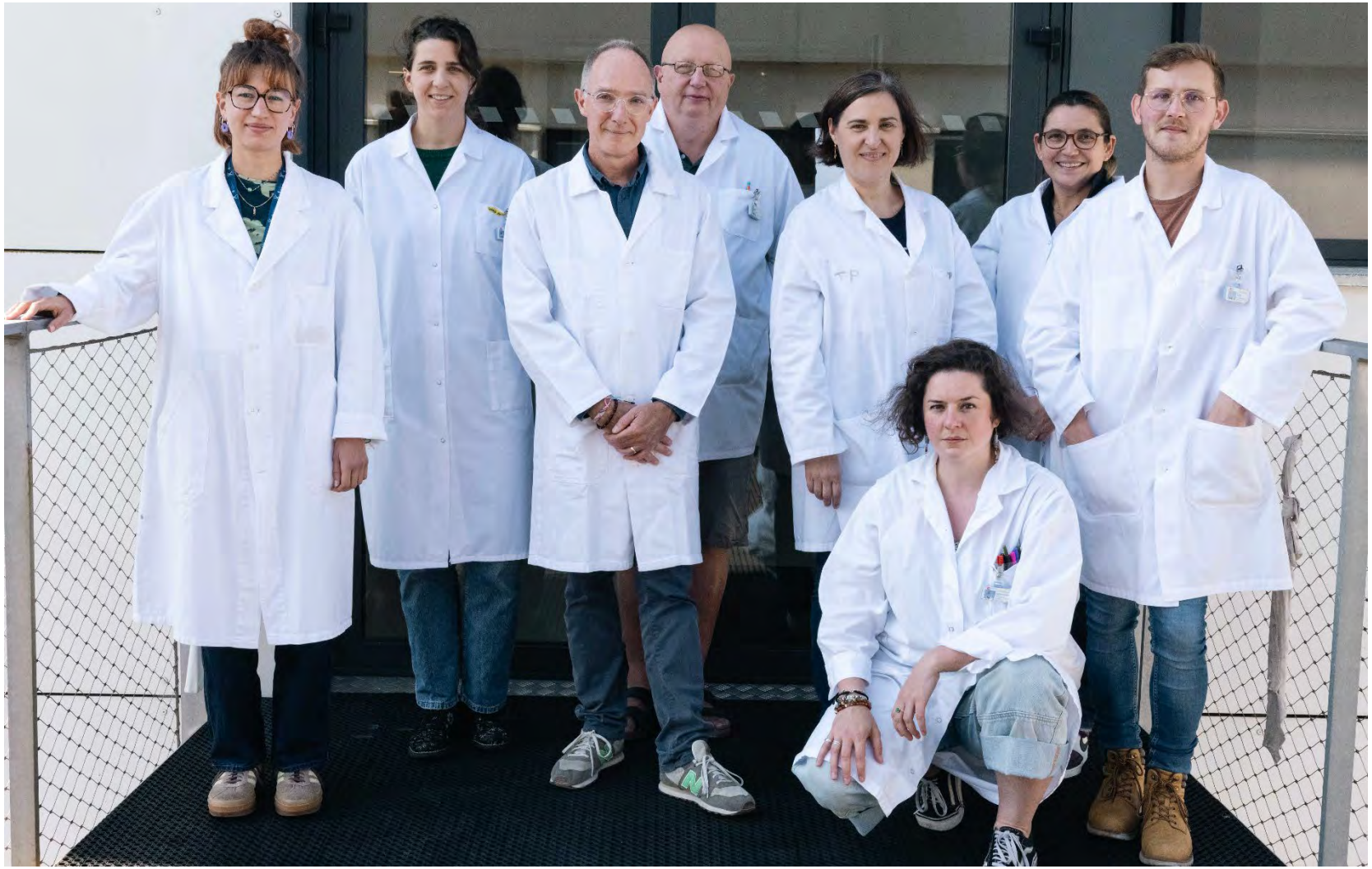
Aurélie ALLEAUME-BUTAUX (IR INSERM)

Marc DAUPLAIS (IR CNRS)

Flavien PICARD (Post-Doc)

Clara BIANCHI (PhD)

Florence ROUSSEL (PhD)

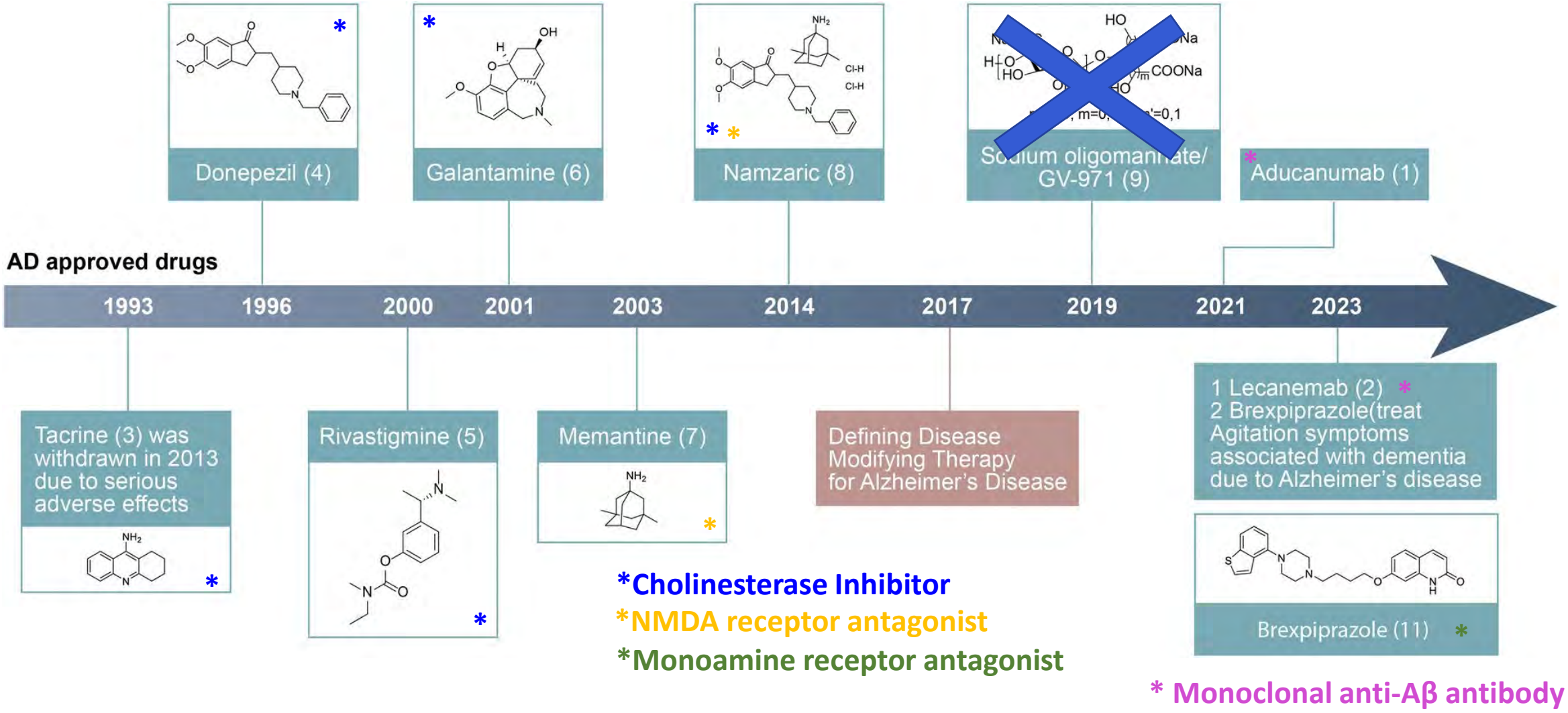


cnrs

ÉCOLE POLYTECHNIQUE

IP PARIS

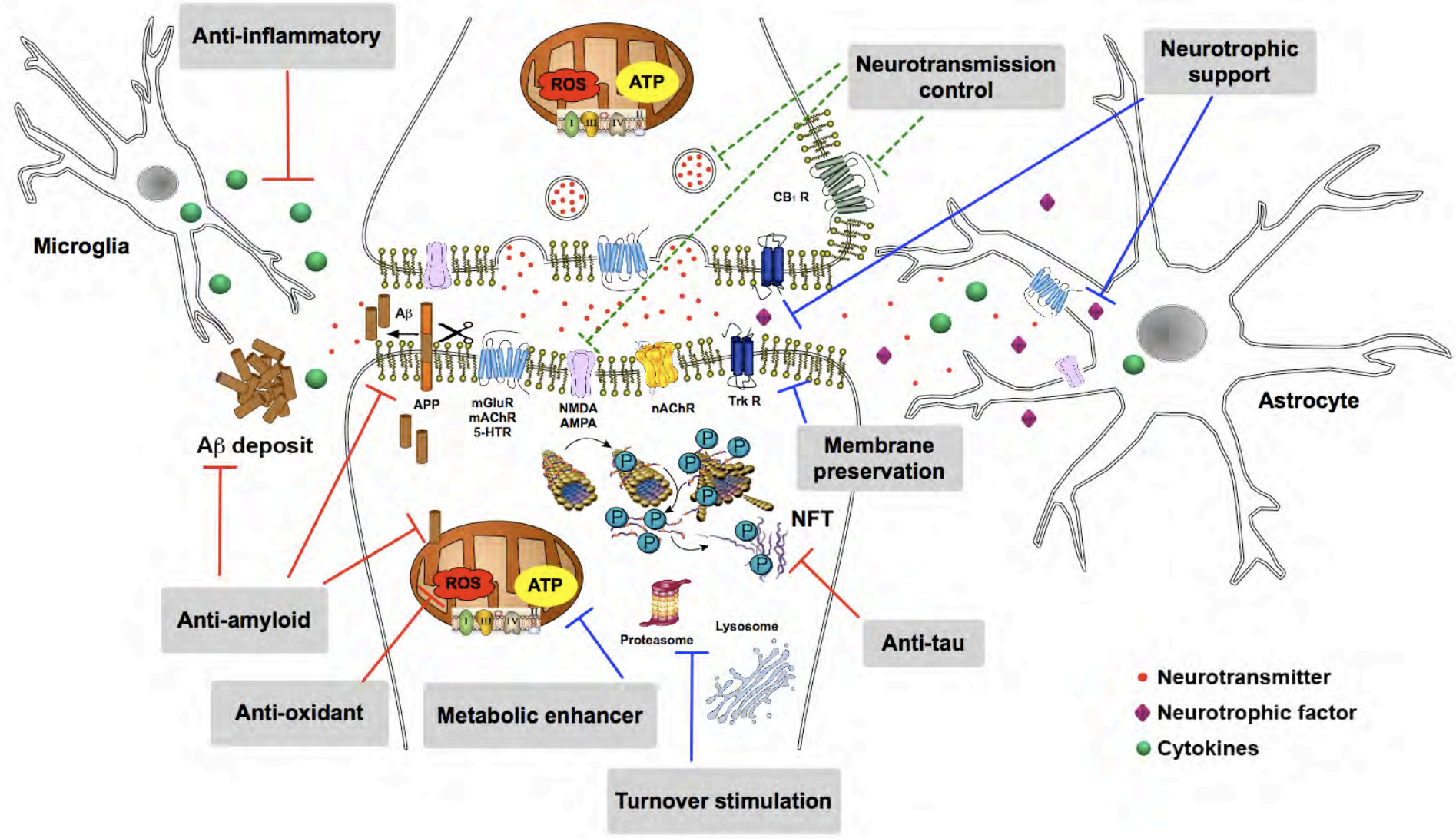
PDK1 place in current therapeutic strategy for AD



Treatments restricted to symptomatic treatment and common side effects (vomiting, muscles weakness,...)

First Disease Modifying drug

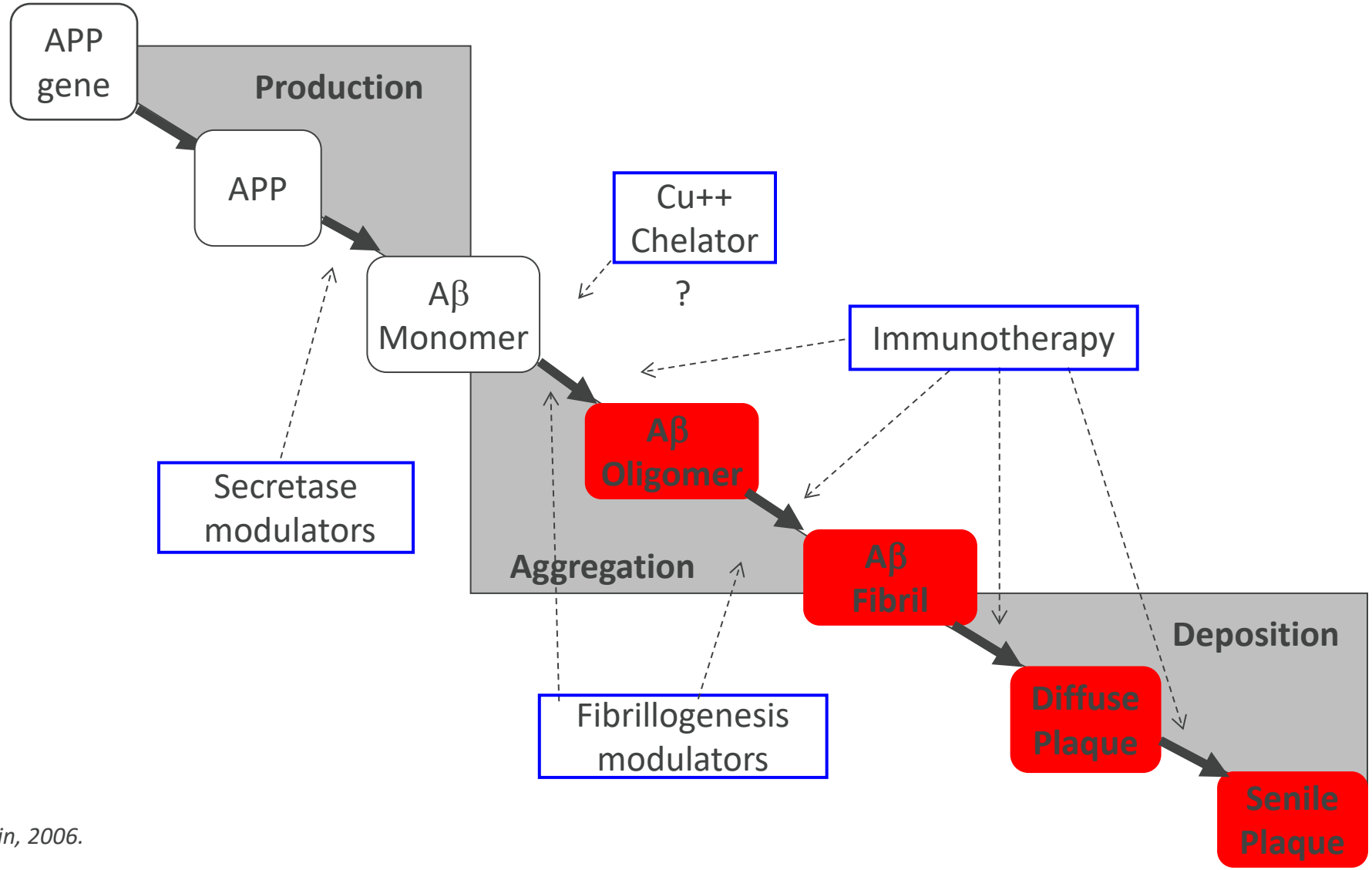
PDK1 place in current therapeutic strategies for AD



Ester Aso and Isidre Ferrer (2013).

PDK1 place in current therapeutic strategies for AD

β-Amyloid–related disease-modifying strategies



Relkin, 2006.

PDK1 place in current therapeutic strategy for AD Secretase pathway

❑ Current experimental strategy => treat as early as possible

✪ Early diagnosis IMPOSSIBLE

- Beta secretase (“BACE1”) inhibitors
  - Most attractive theoretically?
  - Prior agents have failed: did not cross blood-brain-barrier
  - Several agents in/approaching

- Gamma secretase inhibitors
  - Various agents have shown the desired biological effect
  - 2 in phase II-III trials now (Lilly, BMS) => stopped due to side effects (Notch pathway)

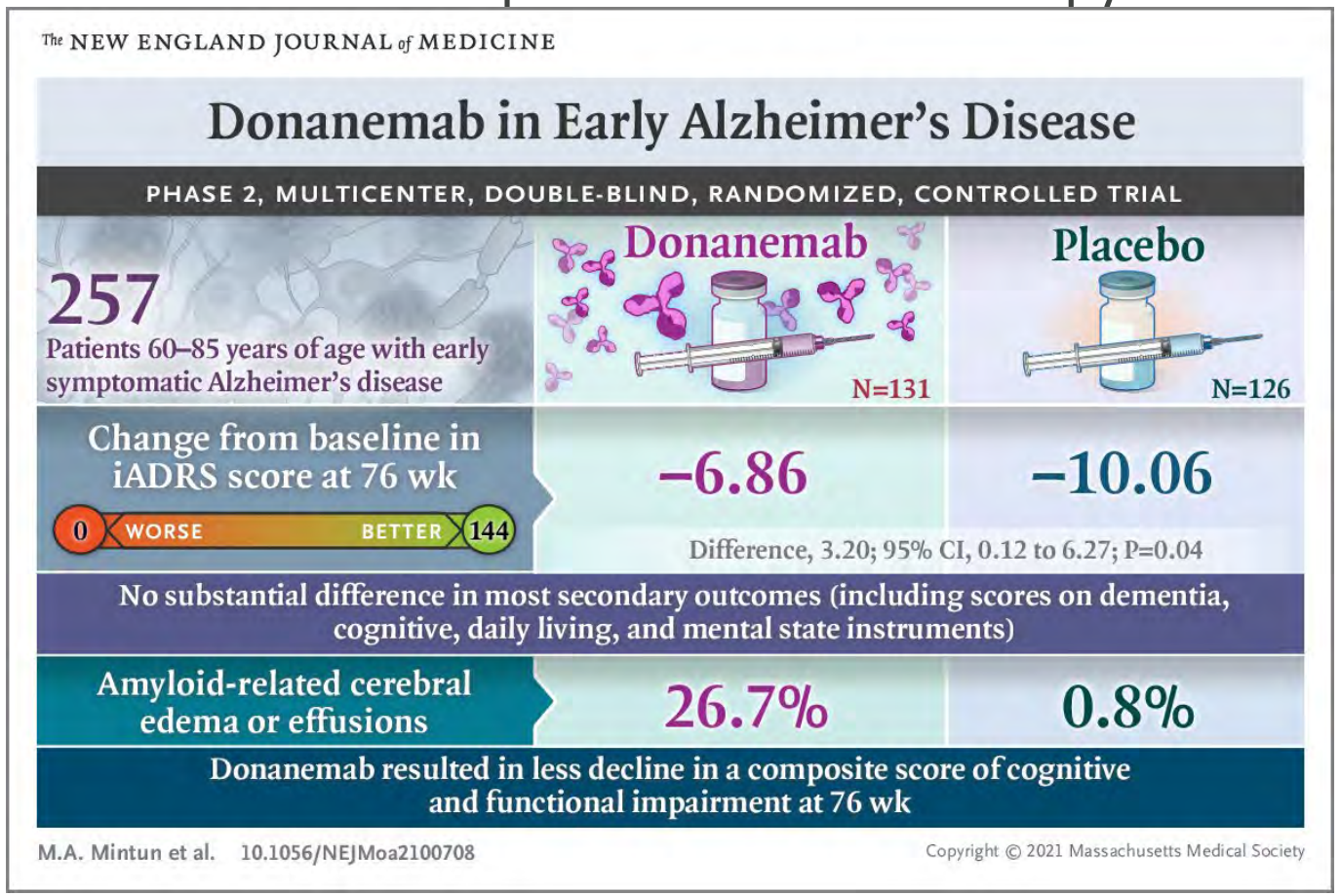
- Tarenflurbil (“Flurizan”), a putative gamma secretase modulator, failed to show benefit in phase III trial

PDK1 inhibition: could be given in late stages of AD

✪ Toxicity of PDK1 inhibitors currently available!!!

PDK1 place in current therapeutic strategy for AD

New hope from Immunotherapy?



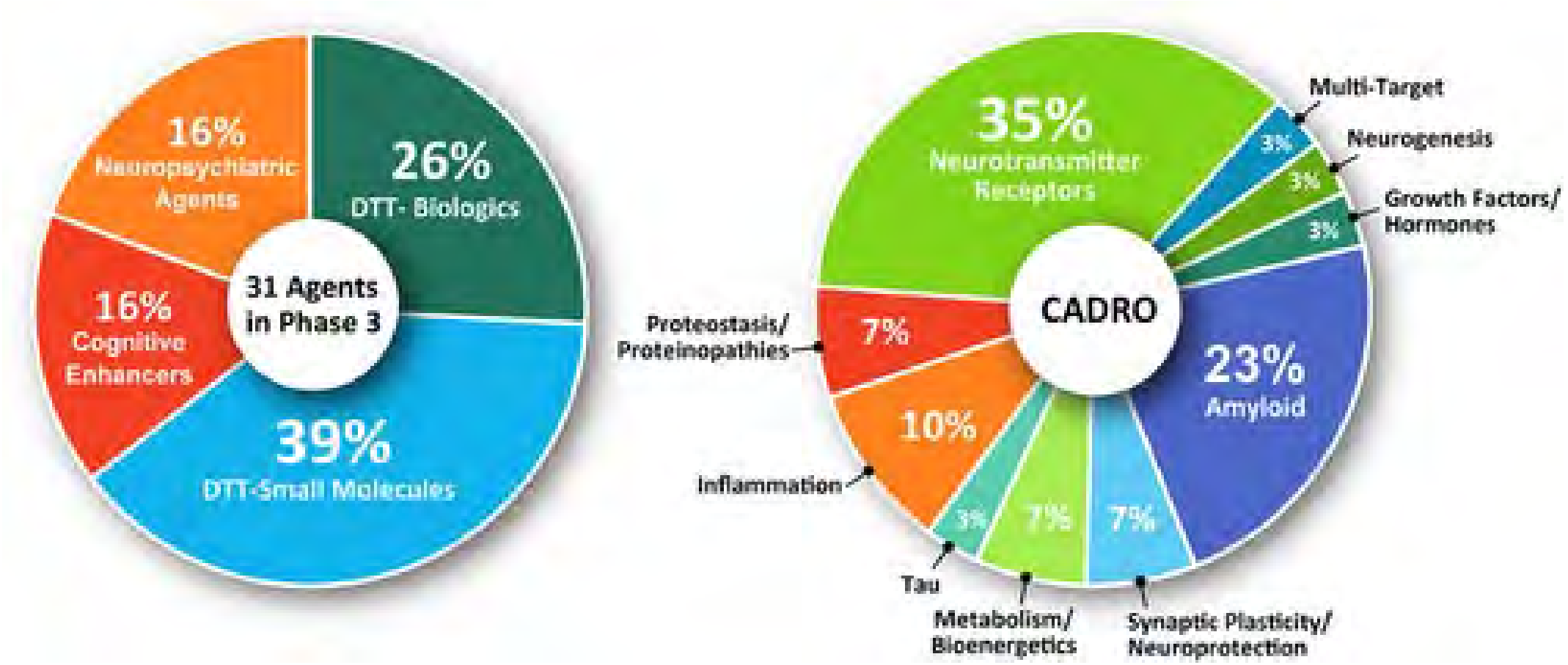
Donanemab (Lilly), Lecanemab (Biogen & Eisai), Aducanumab (Biogen & NeuroImmune) => decrease of Aβ deposition (up to 87%) accompanied by decreased pTau in CSF but not NFL (Neurodegeneration marker)

+ Amyloid-related imaging abnormalities (ARIAs) => brain microhemorrhages

+ Clinical trials phase IV until 2026 before FDA approval (Aducanumab)

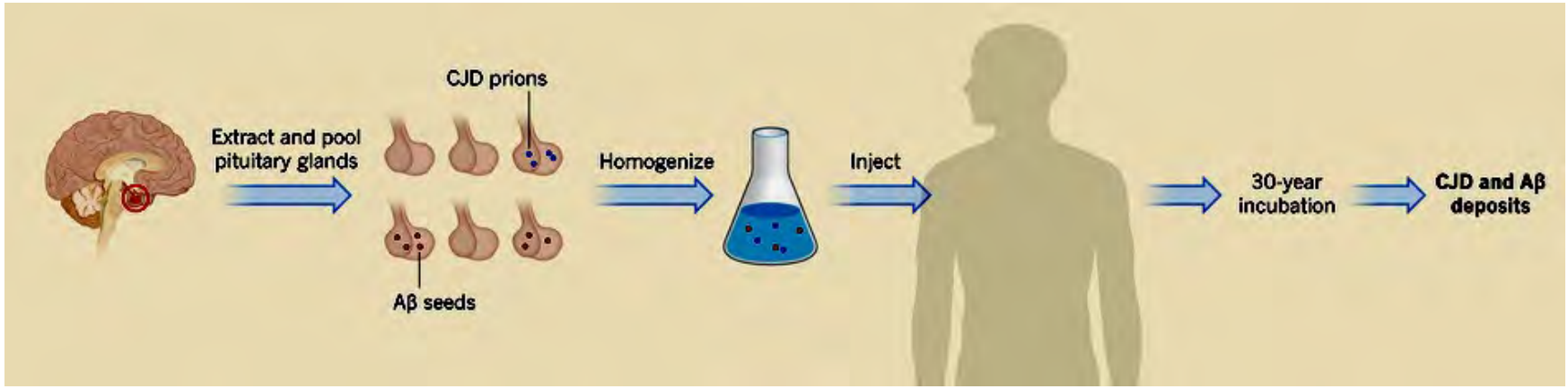
PDK1 place in current therapeutic strategy for AD (2025)

Alzheimer’s Drug Development pipeline (Phase III)



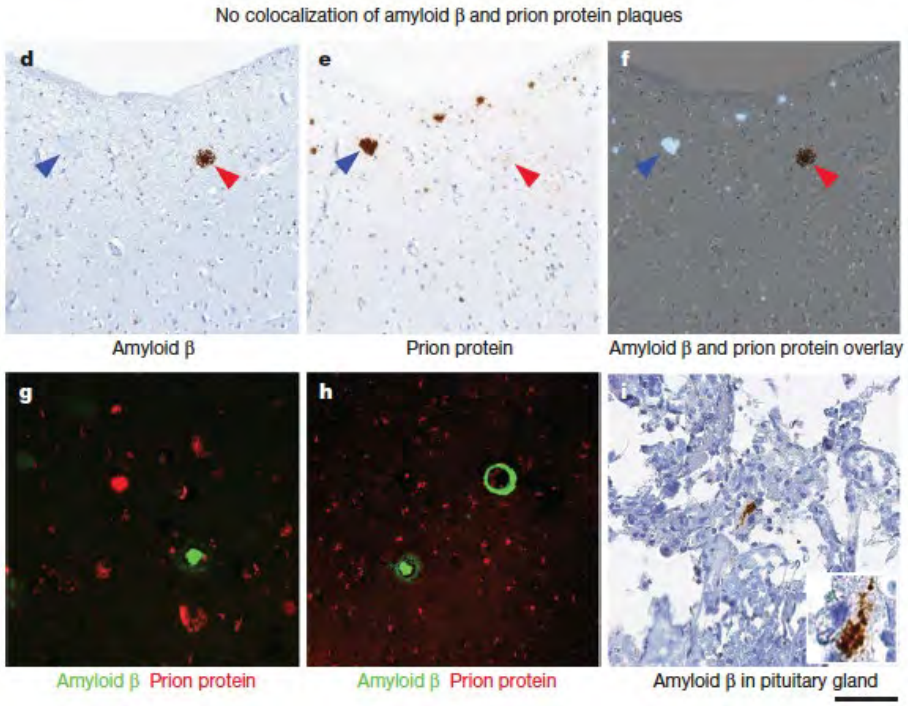
Common Alzheimer's Disease Research Ontology (CADRO)

Aβ transmitted?



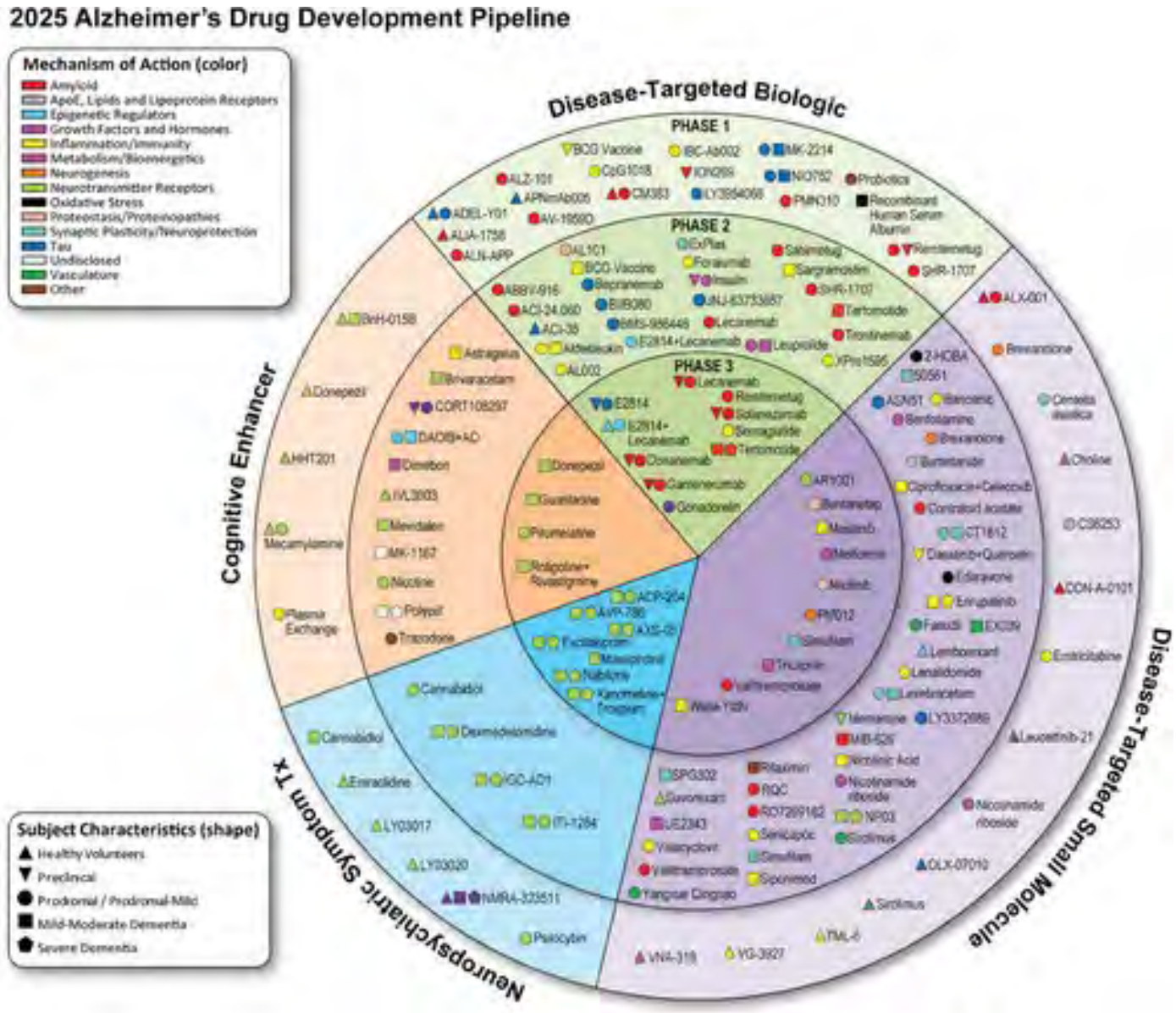
Before 1985, some people treated with cadaver-derived human growth hormone (c-hGH) developped after 30 years a iatrogenic CJD .
These people also had Aβ deposits in the brain, suggestive of incipient Alzheimer's disease.

Hyp: cadaver-derived human growth hormone also contains Aβ seeds => AD transmitted?



PDK1 place in current therapeutic strategy for AD

Alzheimer's Drug Development pipeline



BME PARIS
BioMedical Engineering
MASTER'S PROGRAM