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β-cyclodextrin decreases the MCO-induced aggregation rate of Prion Proteins

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ESRF
The European Synchrotron

- **Prion diseases**: Transmissible Spongiform Encephalopathies (TSEs)

- Group of fatal neurodegenerative disorders

Human

Creutzfeldt-Jakob Disease (CJD)	One case/million population/year
Gerstmann-Sträussler-Scheinker Syndrom (GSS)	Rare 1 to 100/100 million
Fatal Familial Insomnia (FFI)	Affects less than 200,000 people

Animal

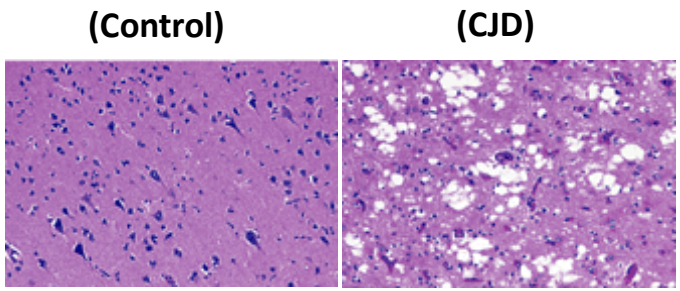
Scrapie (Sheep & Goats)	1732 UK
Bovine Songiform Encephalopathies (BSE) or Mad Cow Disease (Cattle)	1986 UK

- **Prion diseases are characterized by:**

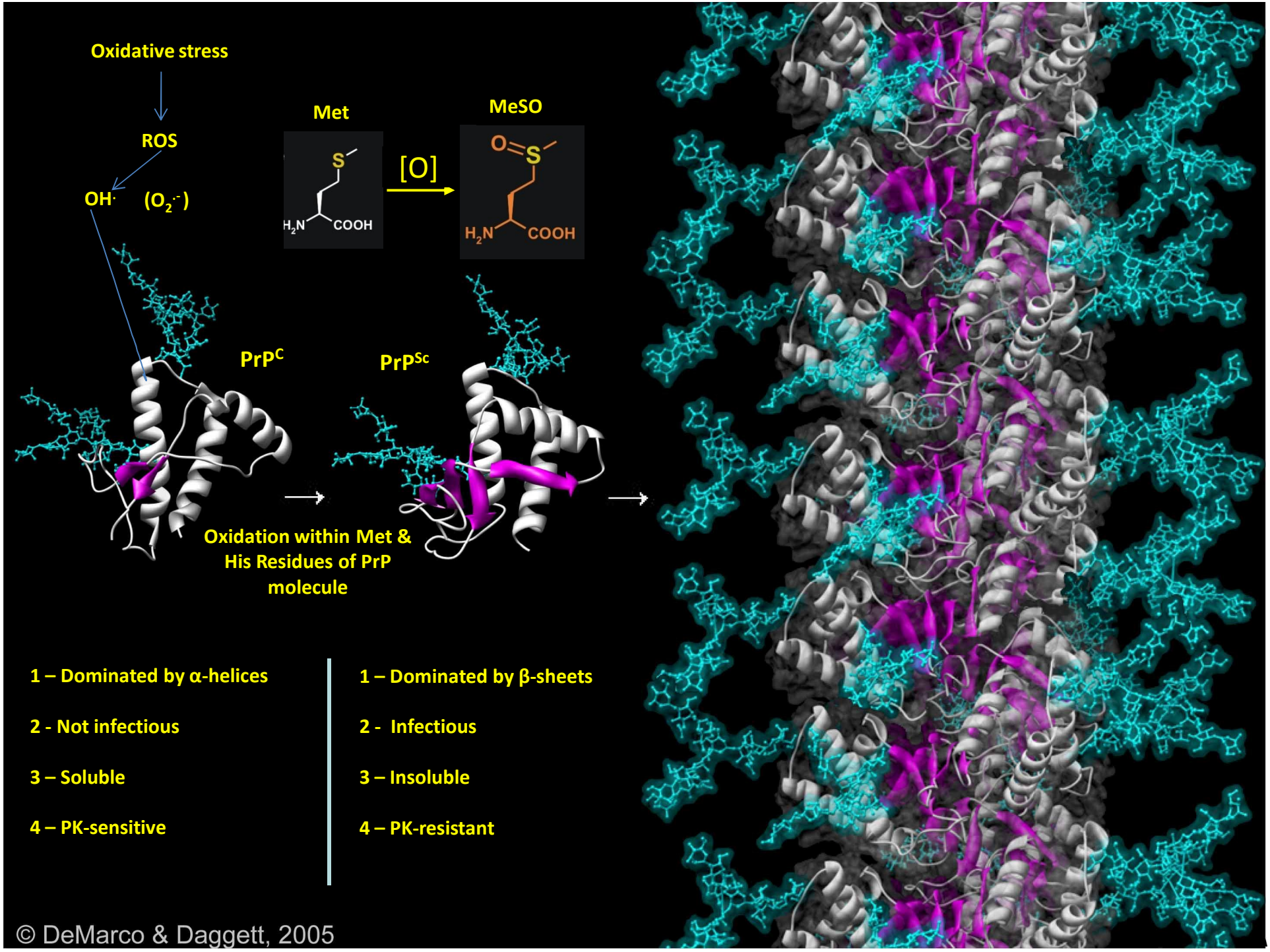
- An extended asymptomatic period (long incubation period)
- Short disease course ending with death

- Infectious: Feeding on scrapie-contaminated materials
- Familial: Mutation in the PRNP gene
- Sporadic: Occurs spontaneously without any apparent cause

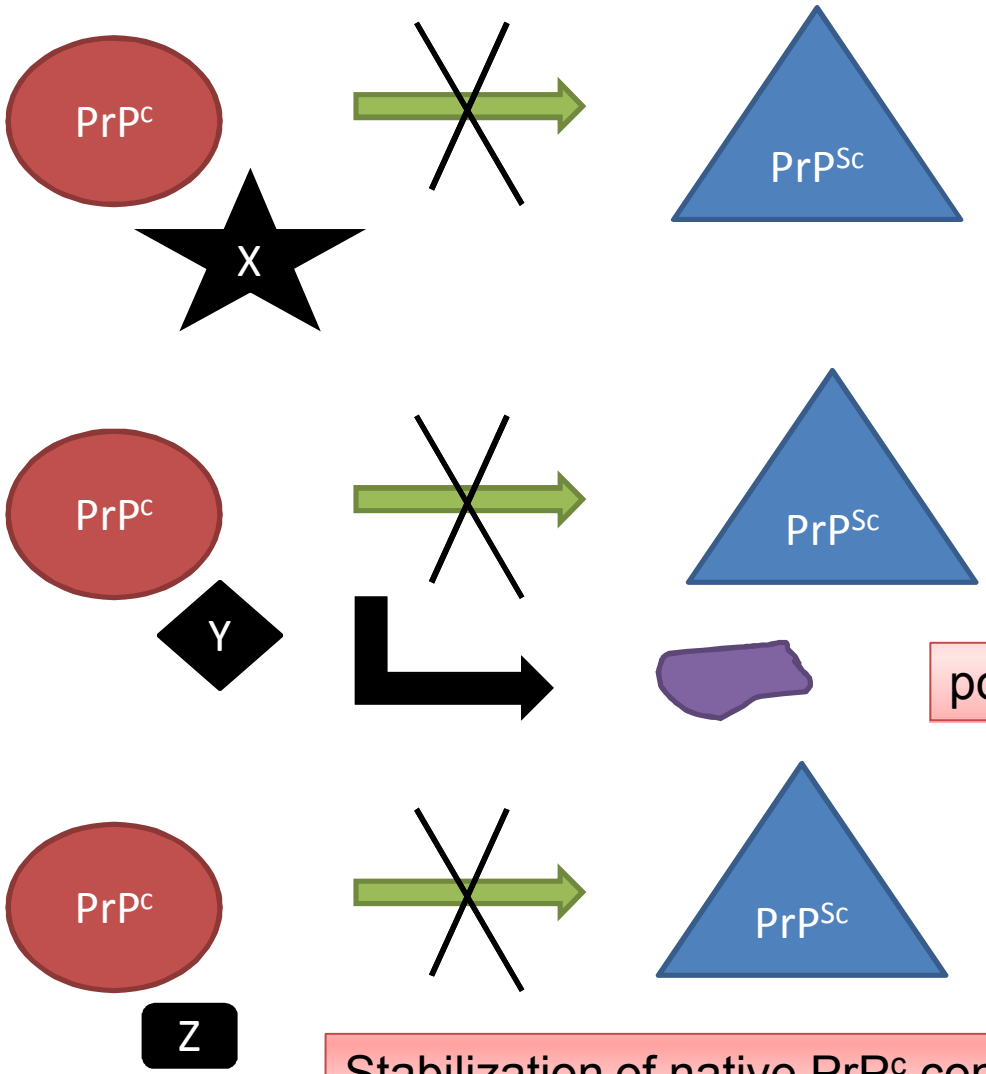
- **Histopathological features:**
- Spongiform degeneration of brain
- Neuronal vacuolation
- Astrocytic gliosis



Adriano *et al.*, 2001



- At present, there is no effective therapy to treat prion diseases



X = Congo red, quinacrine, chloropromazine , and several polyanionic glycans like dextran and pentosan sulfate

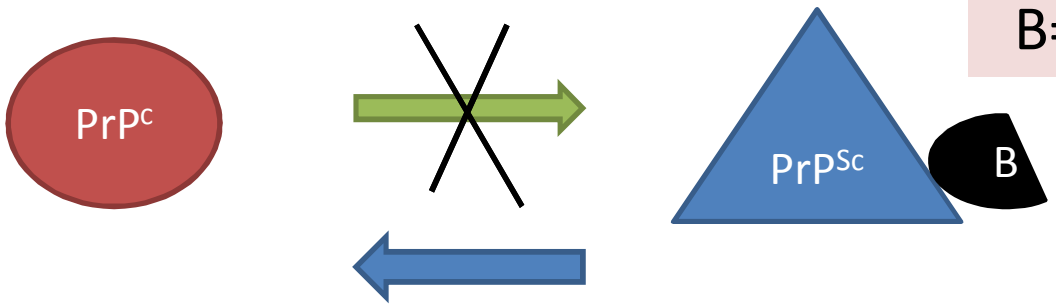
Y = : Suramin

posttranslational misfolding of PrP^{C}

Z = Chemical chaperones (glycerol, DMSO, and TMAO)

Stabilization of native PrP^{c} conformation (chemical chaperones)

- Monoclonal antibodies



B= β- sheet breaker peptides

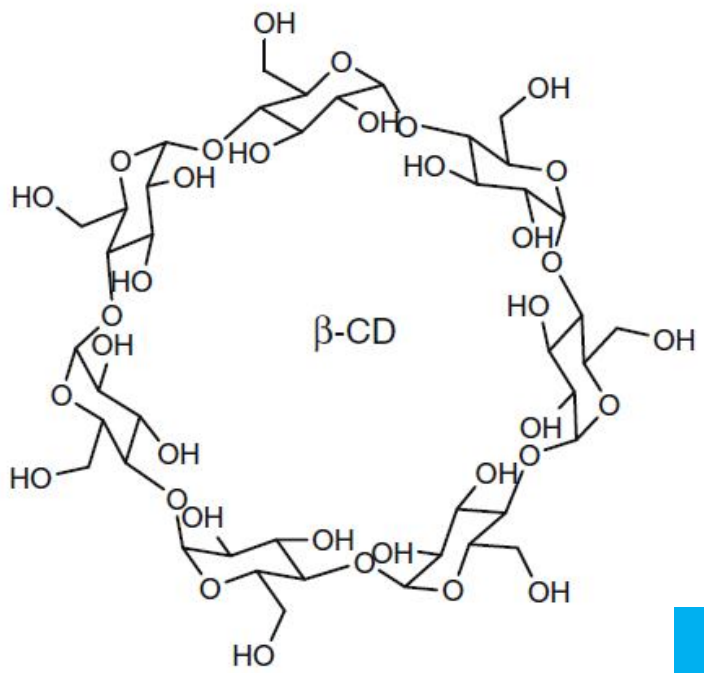
Obstacles in the treatment of TSEs by anti-prion compounds

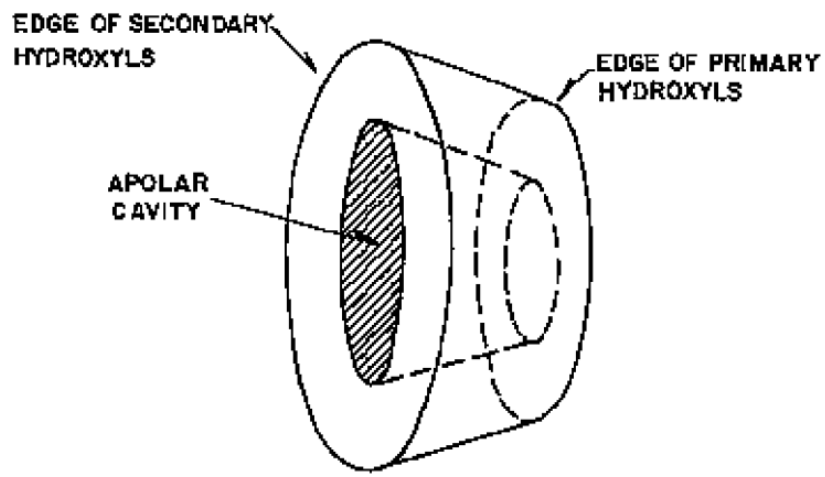
- Low ability to cross the blood brain barrier (BBB)

- Don't exhibit any therapeutic effect when administered after the appearance of neurologic signs into animal model

The development of optimized and effective therapies against TSEs is urgently needed

Important to identify compounds with therapeutic activity against TSEs





β- cyclodextrin

- Clear the PrP^{Sc} isoform from ScN2a cell cultures
- Inhibits the toxic effect of β-amyloid peptide (residues 1-40) in cell culture
- Pass the BBB up to 4mM
- Stable against human enzymes
- Does not elicit an immune response

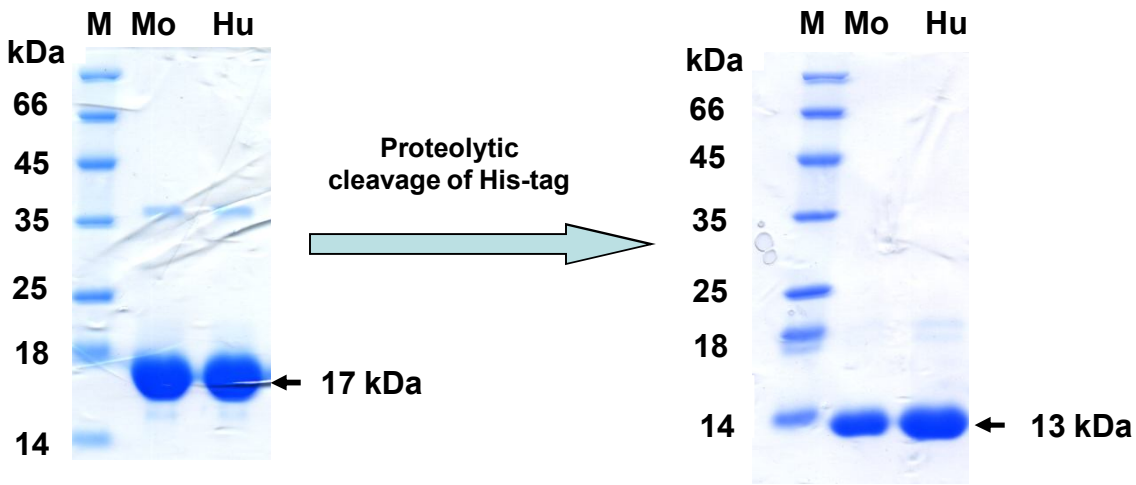
Marguerite *et al.*, 2007

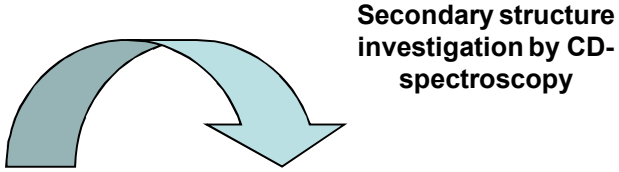
QUESTIONS TO BE ANSWERED

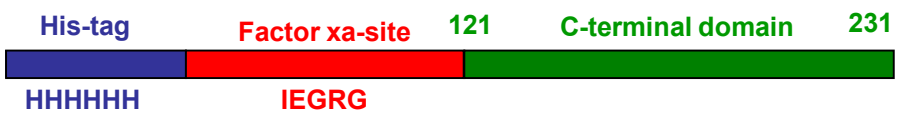
1- Does β-CD influence the *in vitro oxidative* aggregation of PrPs?

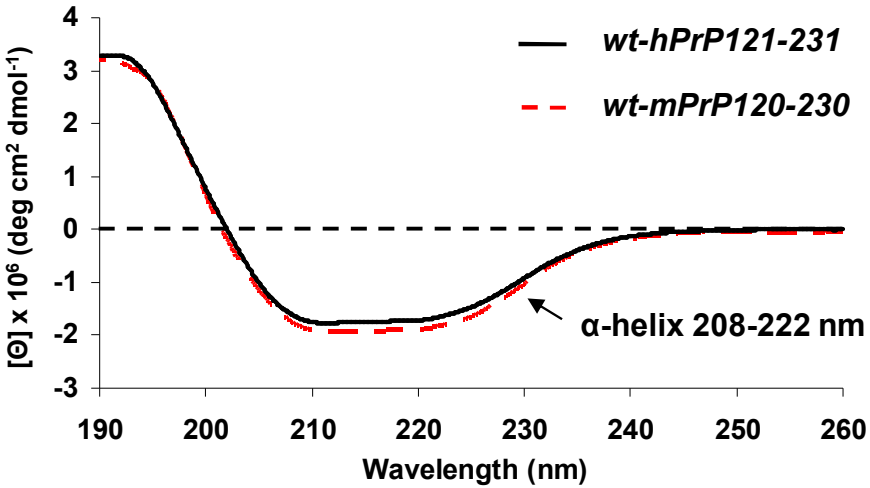
2- Does β-CD bind to recombinant PrPs?

Recombinant expression and purification of mouse (mPrP120-230) and human (hPrP121-231) prion proteins

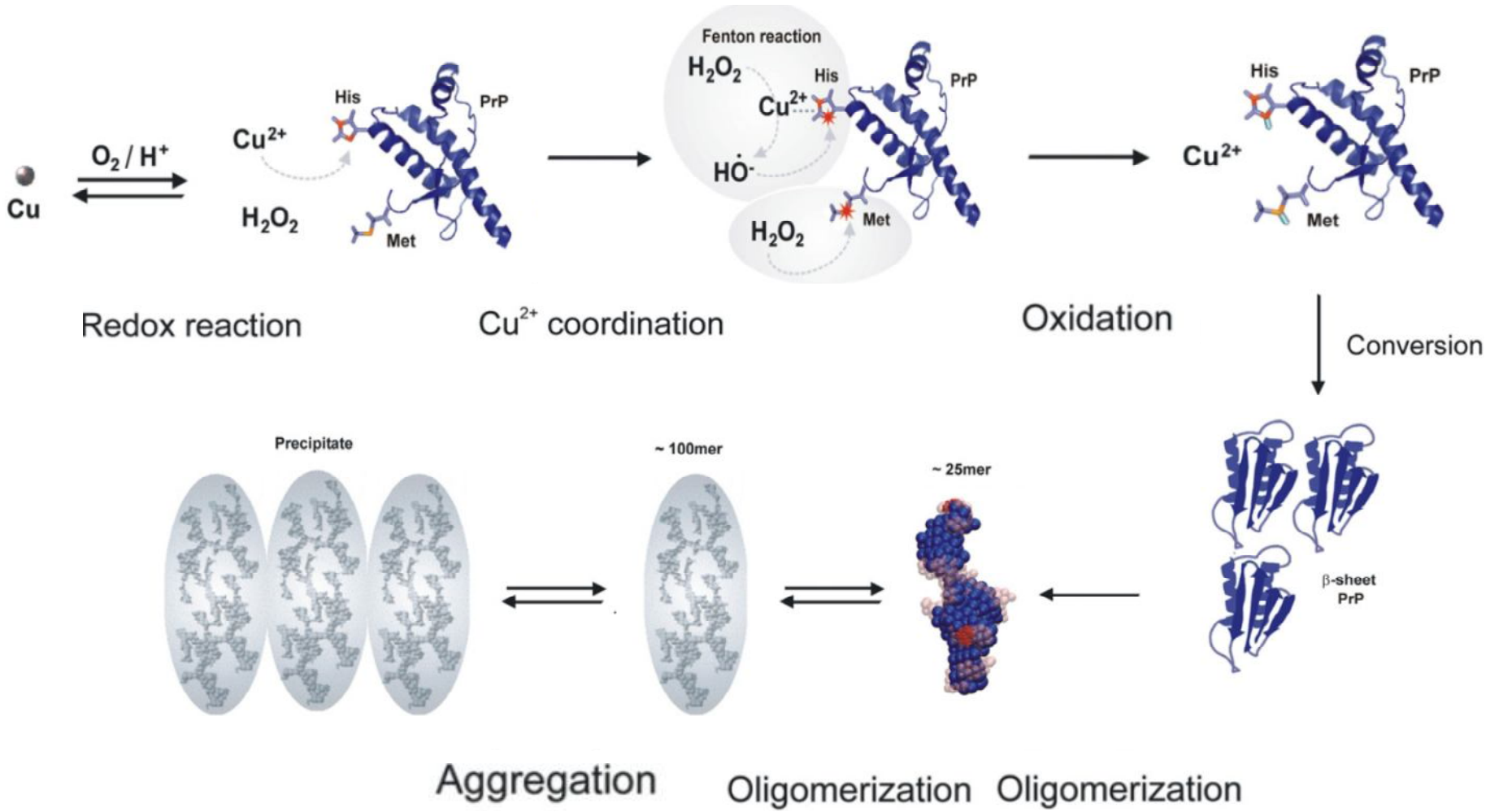






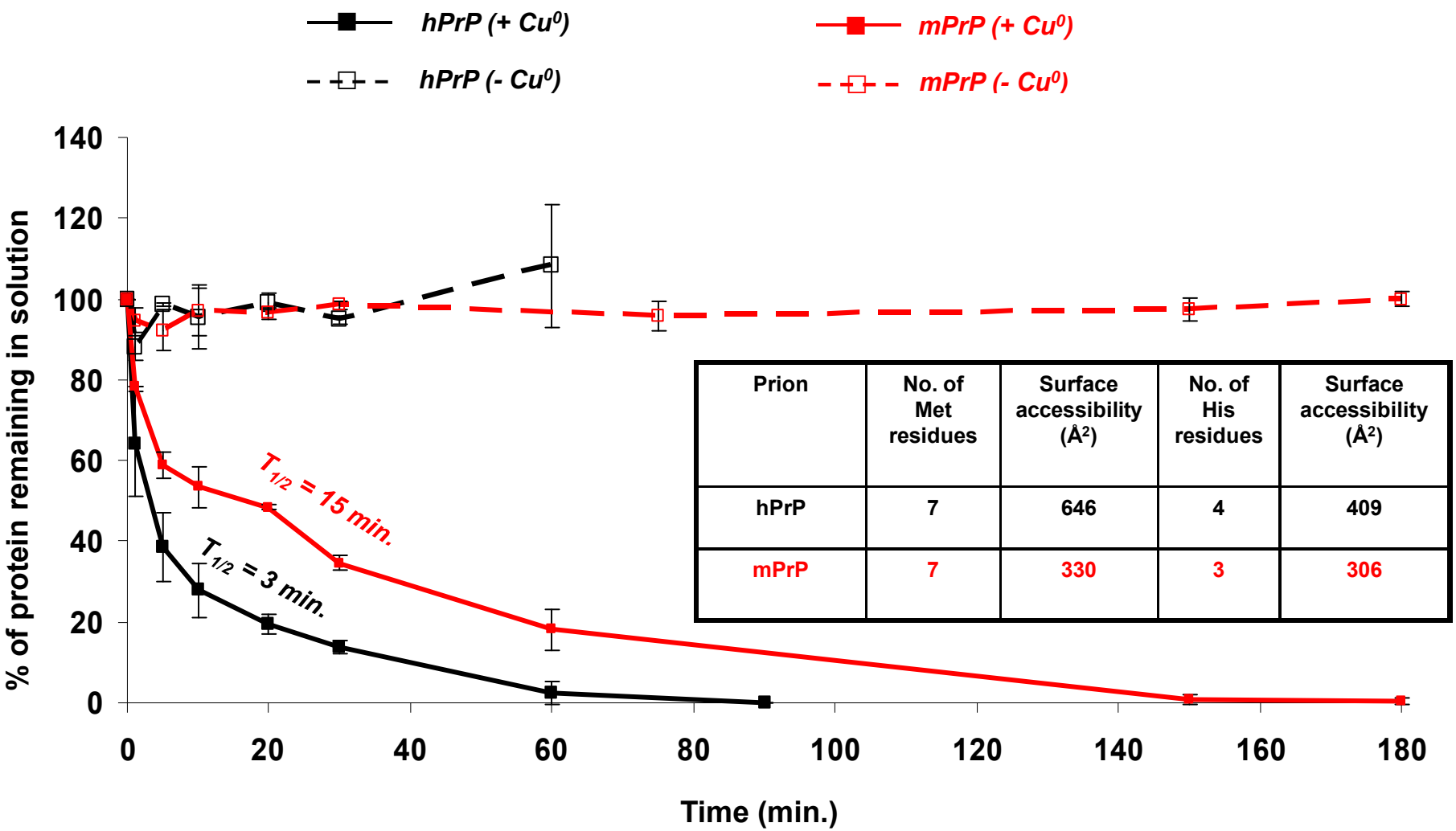


Oxidative-induced aggregation of prion proteins by metal catalyzed oxidation (MCO)



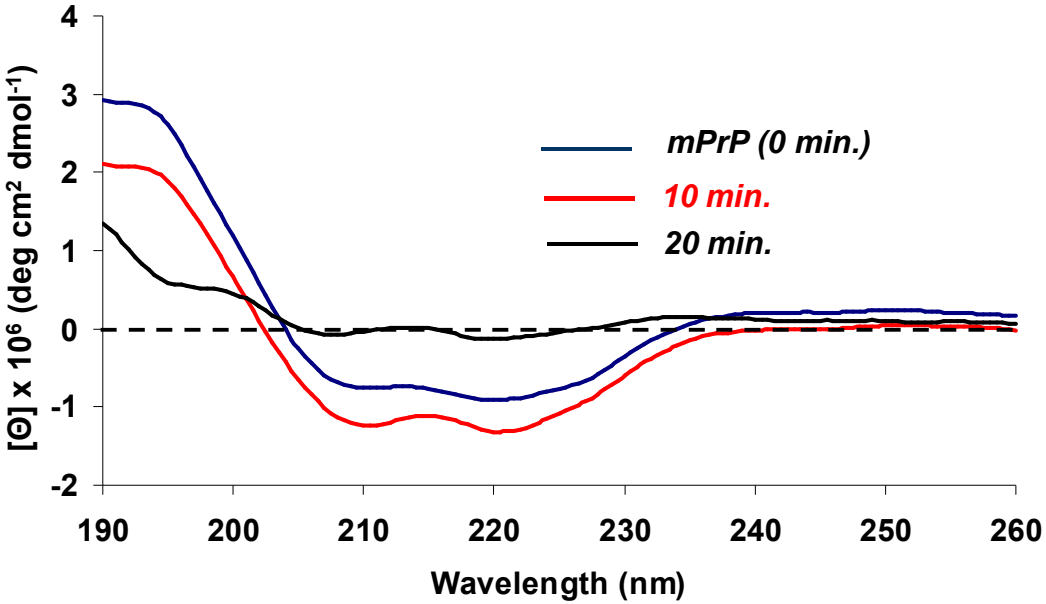
Redecke *et al.*, 2007

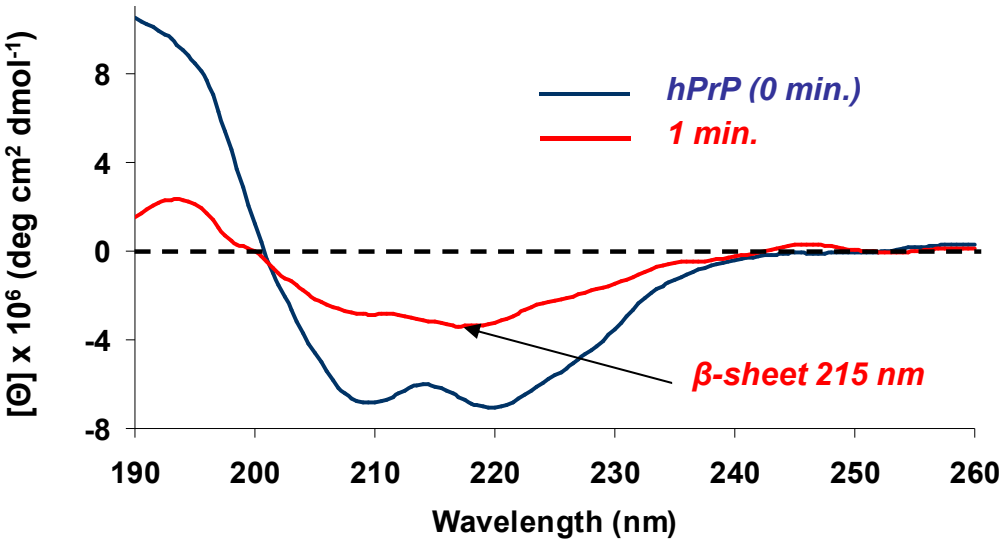
In vitro oxidative aggregation of the C-terminal domains mPrP and hPrP induced by MCO



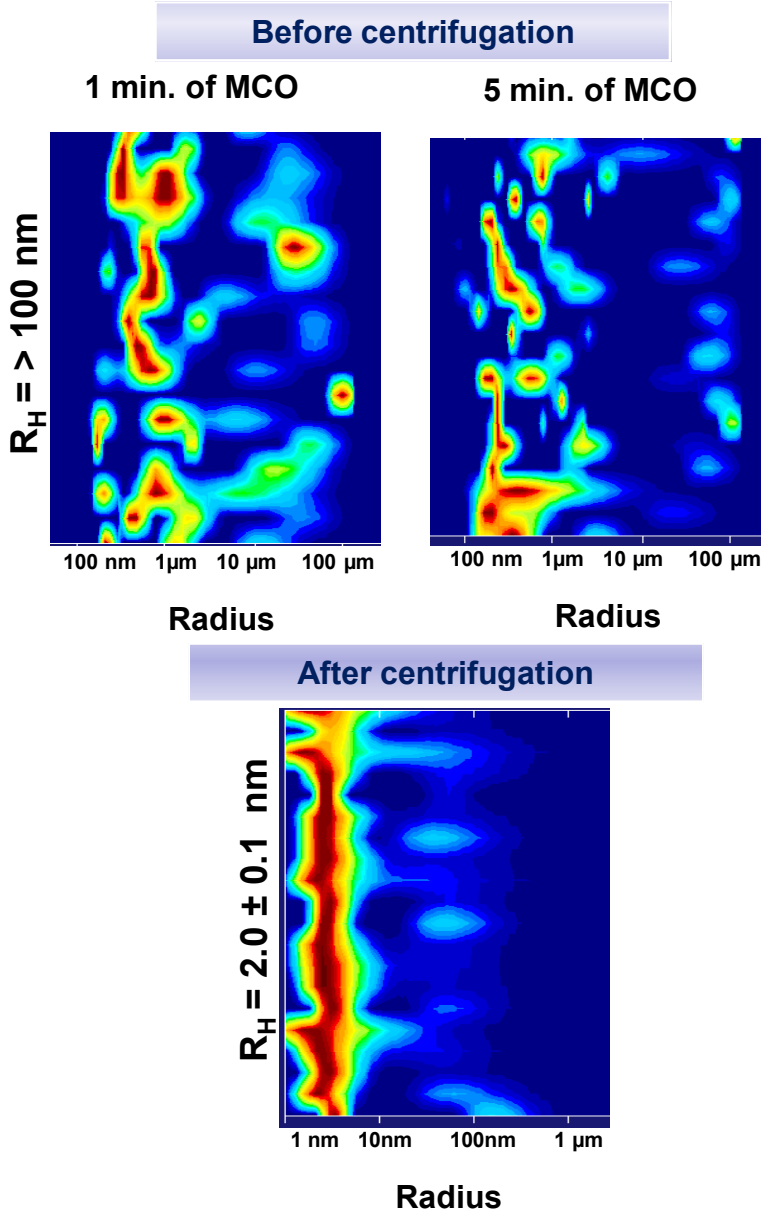
Prion	No. of Met residues	Surface accessibility (Å²)	No. of His residues	Surface accessibility (Å²)
hPrP	7	646	4	409
mPrP	7	330	3	306

Secondary structure changes of mPrP and hPrP on the pathway of MCO

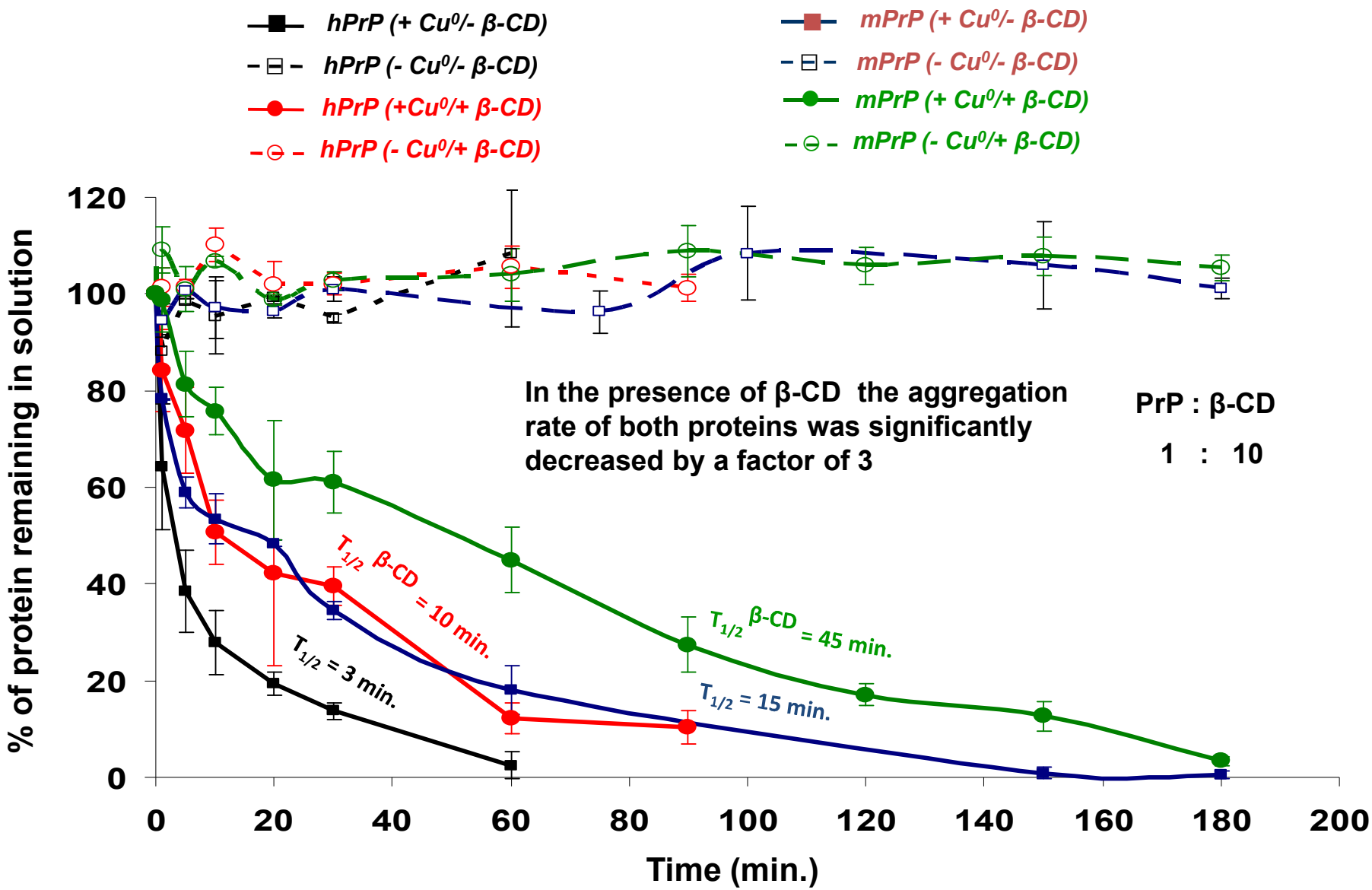




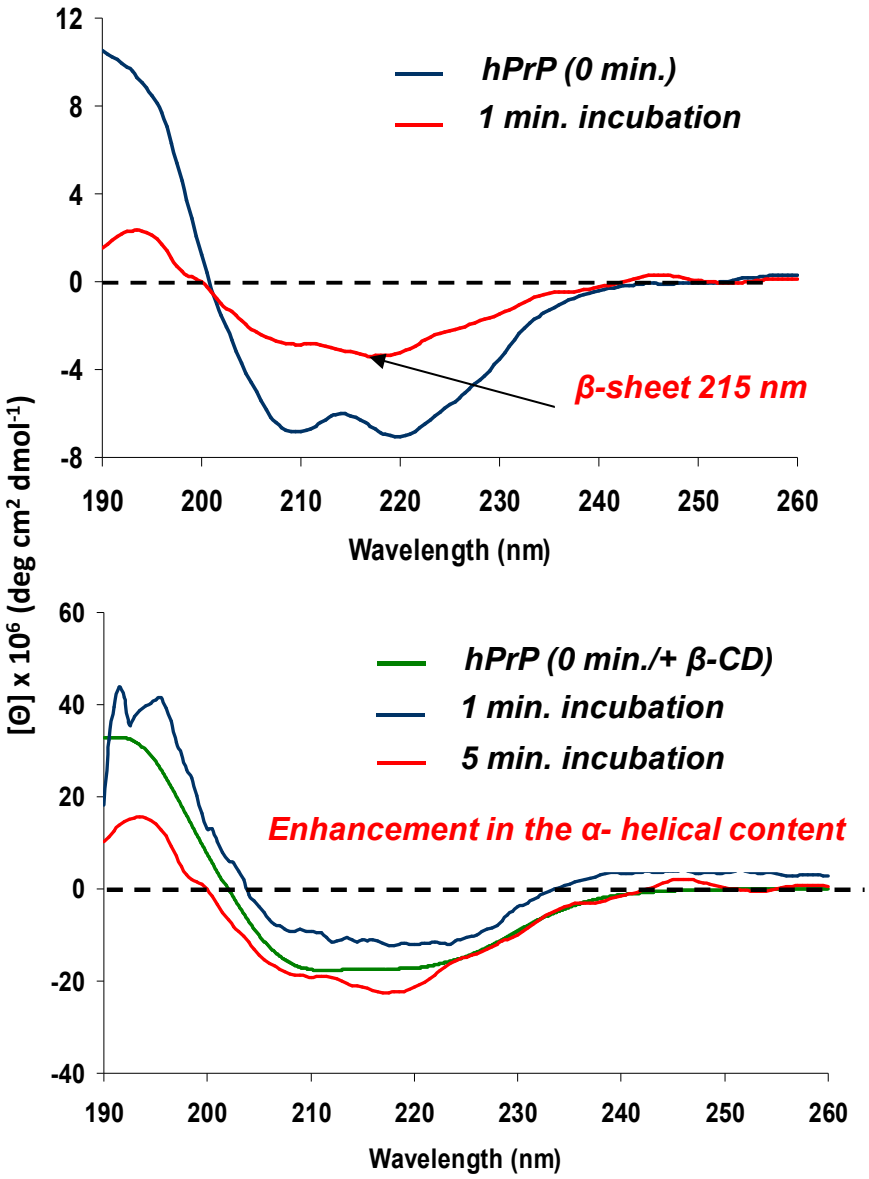
Dynamic light scattering (DLS) of hPrP

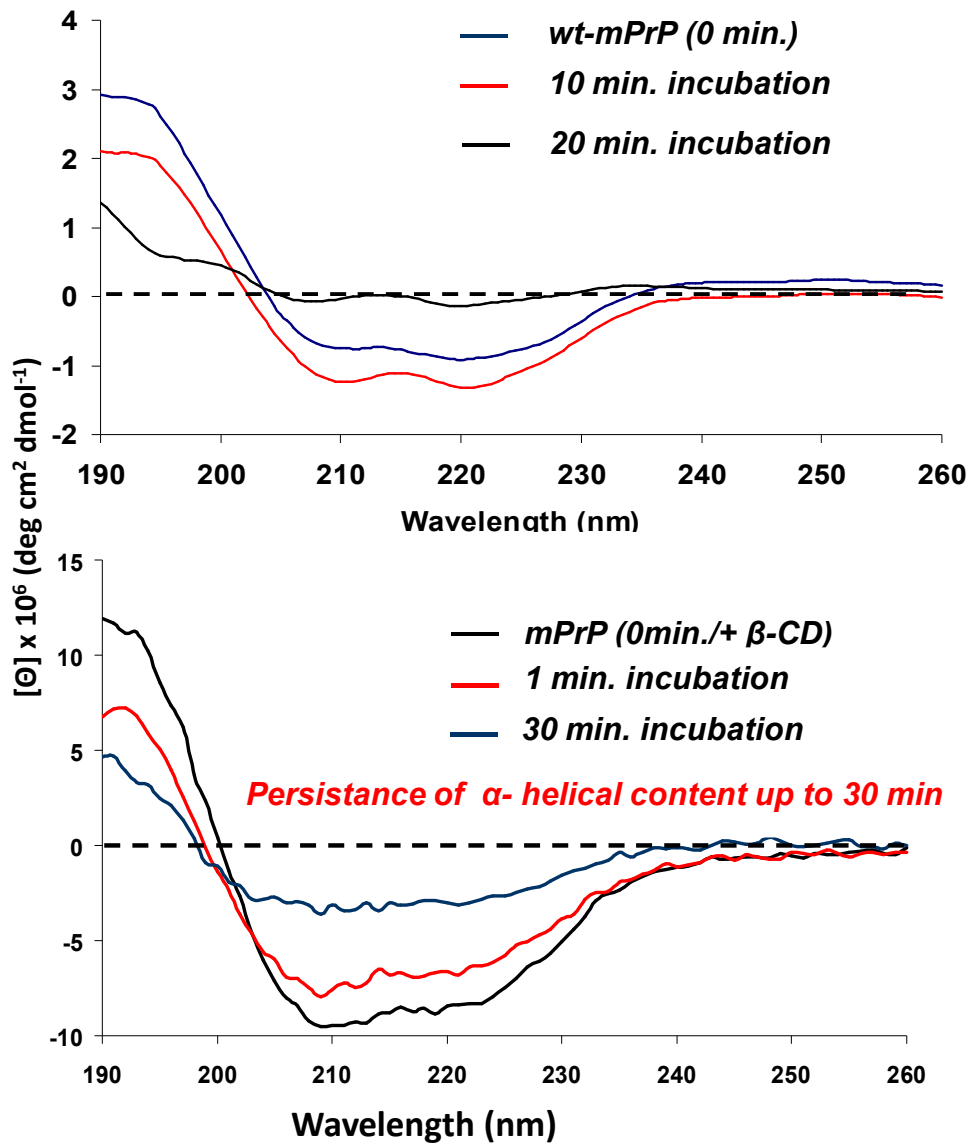


Effect of β-CD on the oxidative aggregation of hPrP and mPrP induced by MCO

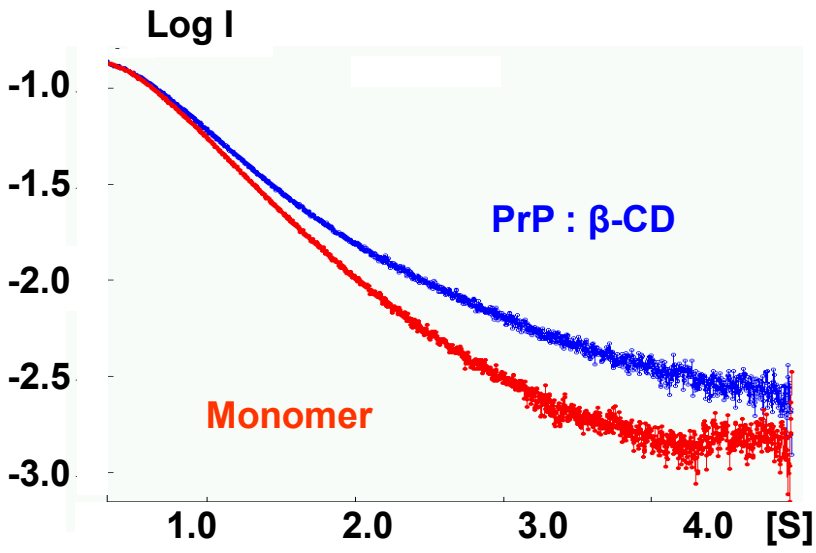


Secondary structural changes of hPrP and mPrP on the pathway of MCO in the presence of β-CD





SAXS analysis of mPrP and hPrP in the presence and absence of β-CD

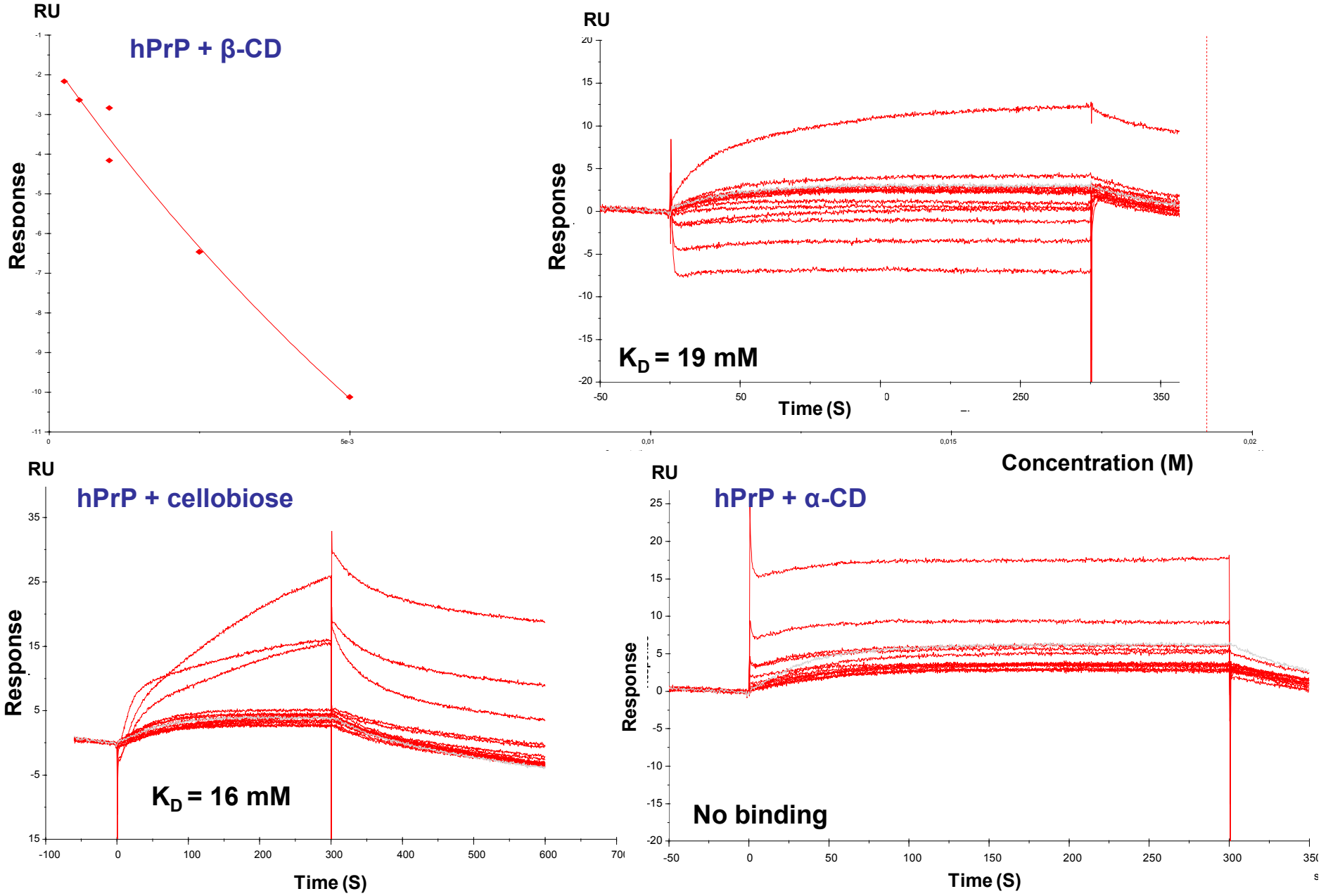


PrP : β-CD

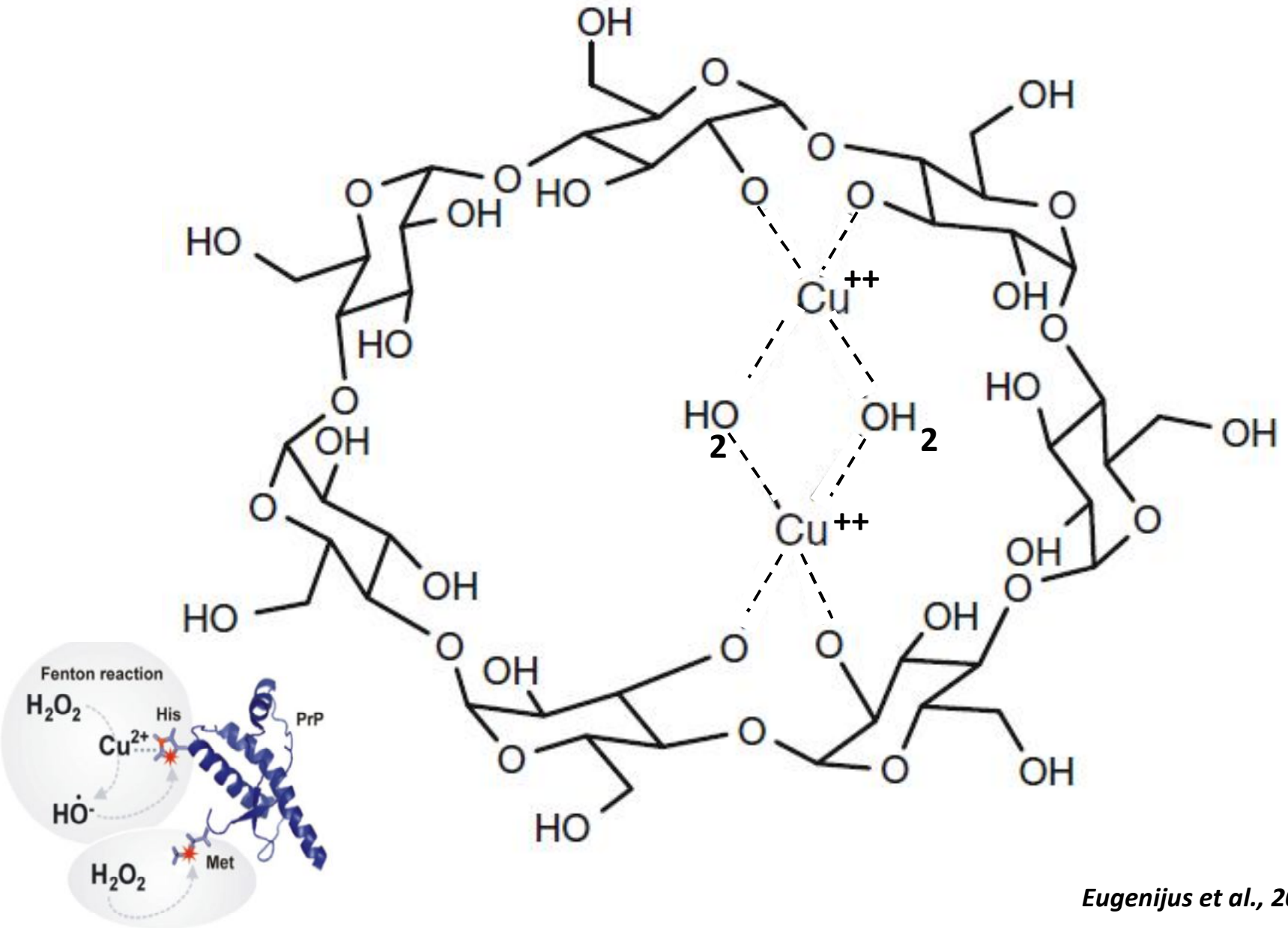
1 : 10

Protein	R_g (nm)
mPrP	1.83 ± 0.02
mPrP (+ β-CD)	1.66 ± 0.01
hPrP	1.80 ± 0.02
hPrP (+ β-CD)	1.66 ± 0.03

Determination of the binding affinity of β-CD to hPrP by surface plasmon resonance (SPR)



Chelation of Cu^{2+} ions by β-CD



Eugenijus et al., 2009

Summary and Outlook

- Oxidative stress plays a central role in the α→β structural conversion of PrP via oxidative modification of the surface exposed Met and His residues
- β-CD decreases the MCO-induced aggregation rate of PrPs by complexation of copper ions in the redox active state
- Copper has been reported to facilitate the refolding of the partially denatured infectious PrP^{Sc} isoform and its chelation alters the protease cleavage pattern of PrP^{Sc} isoform (McKenzie *et al*., 1998 and Wadsworth *et al*., 1999)

Summary and Outlook

- Therefore, clearence of copper by β-CD from scrapie infected brain can cause subsequent prolongation of the incubation time of the prion disease
- The rsults provide a new insight to develop a lead structres against prion diseases and the other associated protein conformational disorders

Aknowledgement

- Christian Betzel
- Lars Redecke
- Dirk Rehders

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THANK YOU