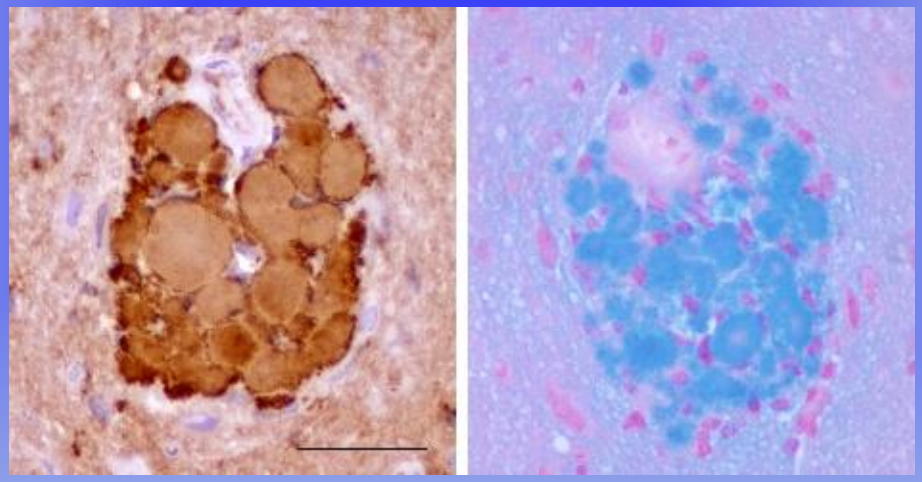
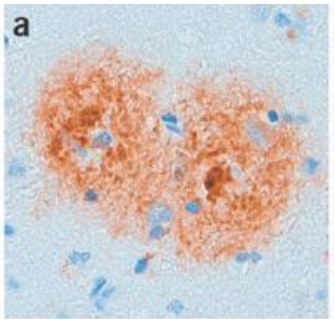
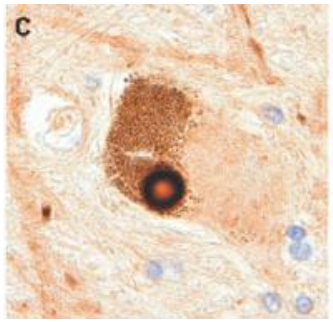
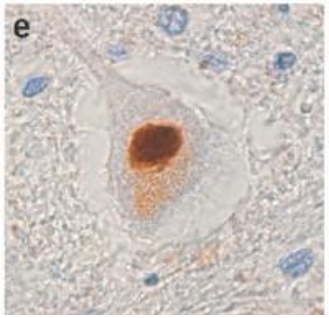
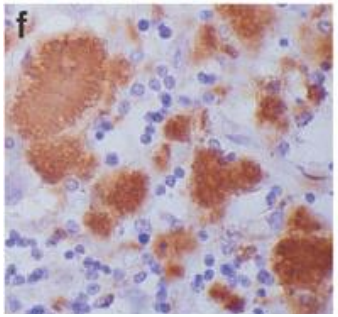
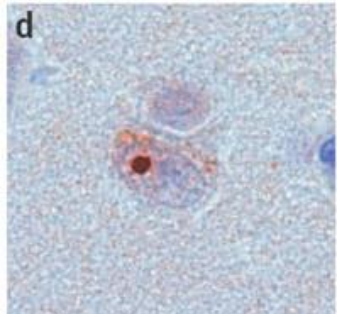
# Mechanisms of Selective Cell Vulnerability in Human Prion Disease



Christina Sigurdson
*Department of Pathology*
*UC San Diego*

*13th Annual CJD Foundation Family Conference*
*July 10-13, 2015*

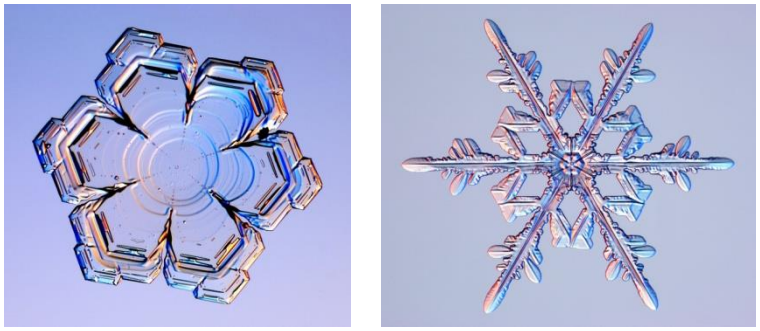
# Protein misfolding and aggregation is a common feature of neurodegeneration

| Alzheimer | Parkinson | Amyotrophic lateral sclerosis | Creutzfeldt-Jakob | Huntington |
|---|---|---|---|---|
|  |  |  |  |  |
| **Amyloid-β plaques** cortex | **α-synuclein** substantia nigra | **Ubiquitin inclusions** spinal cord | **$PrP^{Sc}$ plaques** cerebellum | **Poly-Q inclusions** striatum |

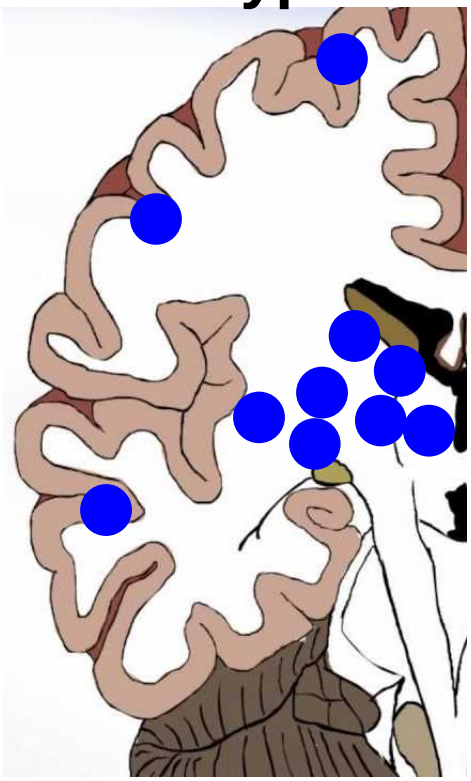
*Modified from Forman et al, Nature Medicine, 2006*

# Prion conformational subtypes: Distinct disease phenotypes occurring in patients

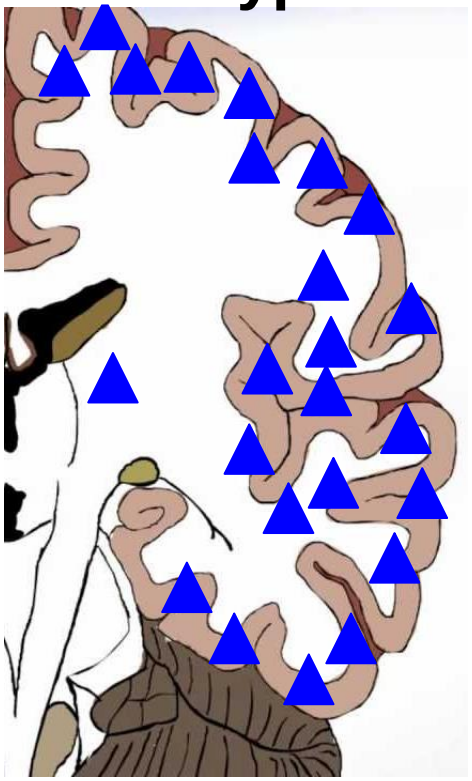
**distinct conformations**



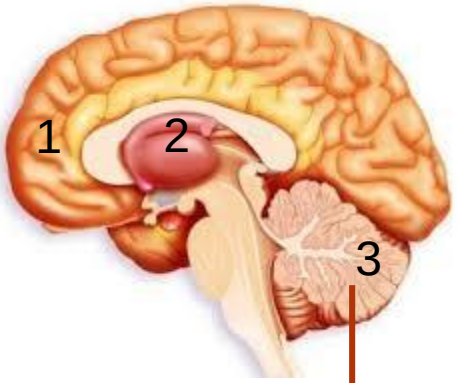
**Subtype 1**



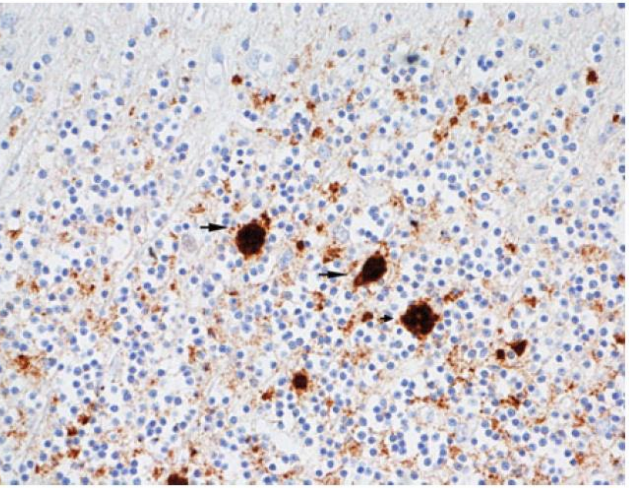
**Subtype 2**



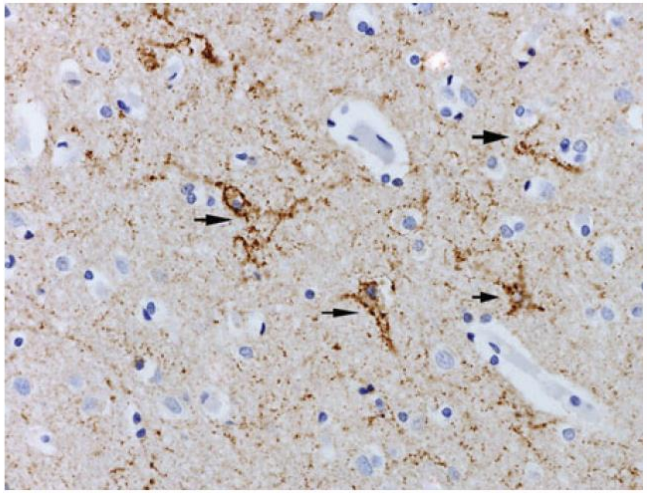
# Human prion disease: prion plaques vary in morphology and cells targeted



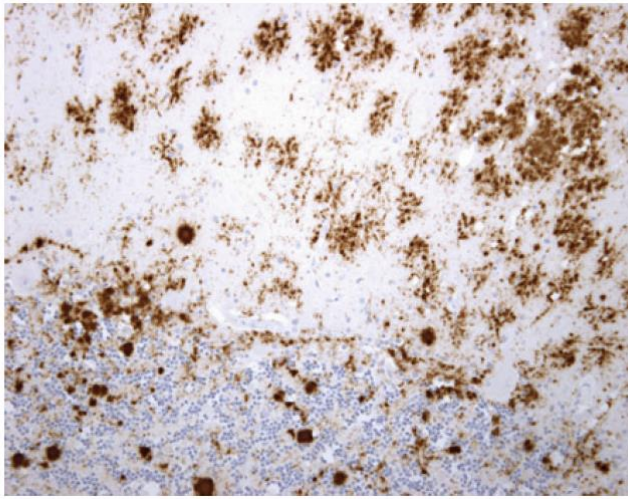

Sporadic CJD
Plaque deposits



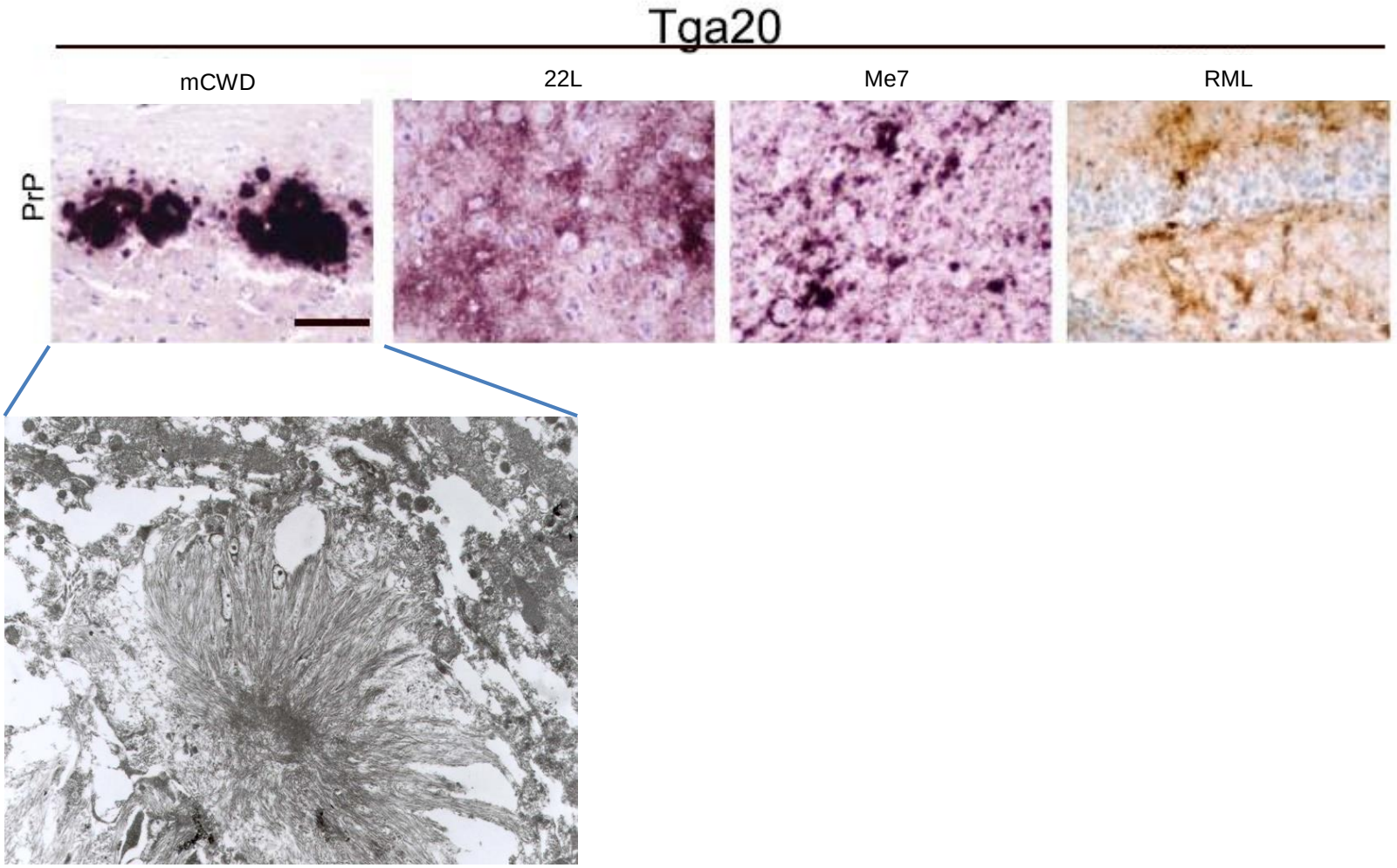
Perineuronal deposits



vCJD
Plaques



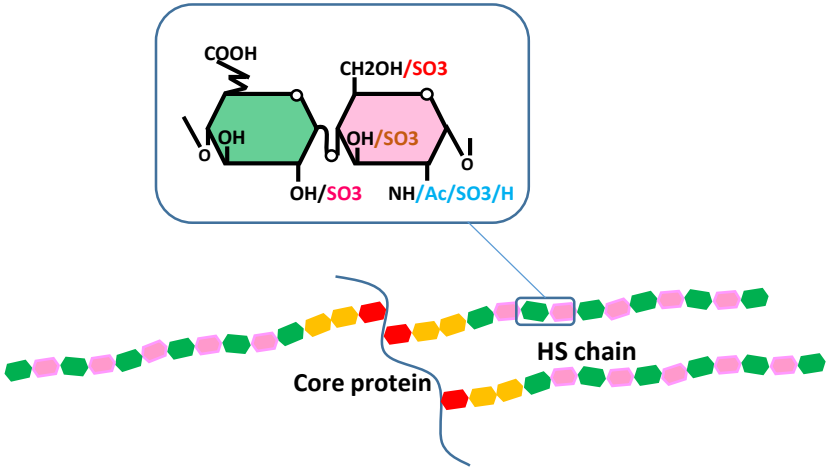
# Prion protein aggregates vary by morphology and cells targeted in mice



**What mechanism underlies the selective cell vulnerability in prion disease?**

# Heparan sulfate proteoglycans and prion pathogenesis

- **Diverse glycoproteins on cell surfaces and in the extracellular matrix**
- **Promotes the internalization of $PrP^{C}$ and propagation of $PrP^{Sc}$**
- **Prolongs prion disease in scrapie-infected rodents**



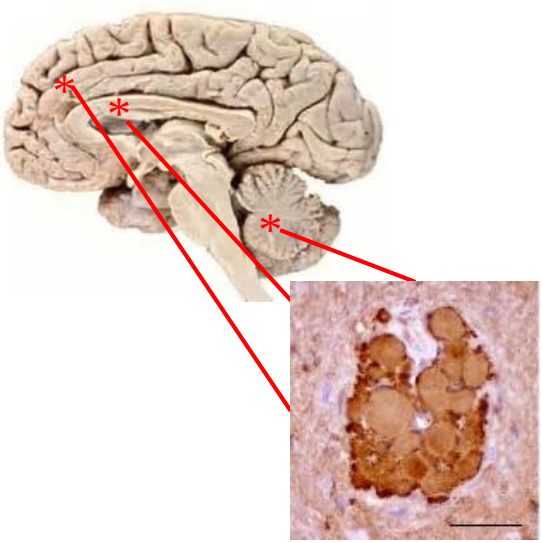
## Hypothesis:

**$PrP^{Sc}$ interaction with heparan sulfate proteoglycans is a major determinant underlying prion cell tropism**

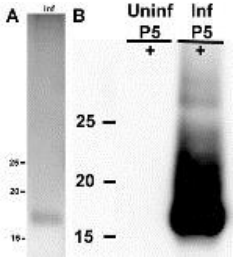
# Defining the HS molecules associated with the most common human CJD subtypes

1) Purify $PrP^{Sc}$ from 3 brain regions

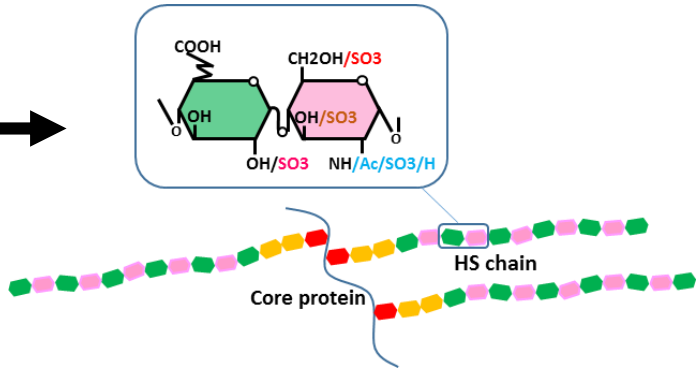
**Prion-infected brain**



purification

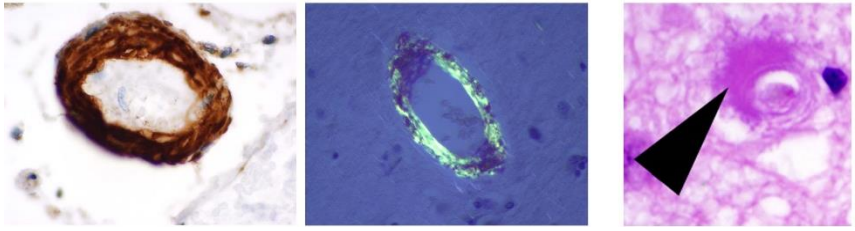



2) Identify the $PrP^{Sc}$ bound heparan sulfate by liquid chromatography-mass spectrometry (LC/MS)

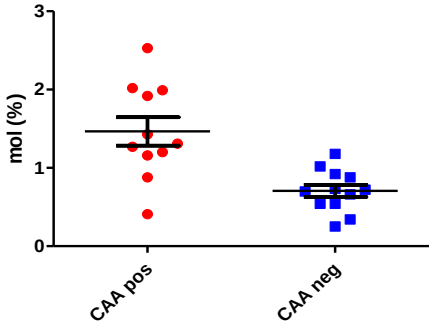



*Quantify N-$SO_3$, 2-O-$SO_3$, 6-O-$SO_3$ groups and N-acetylated, N-sulfated and N-unsubstituted glucosamine residues*

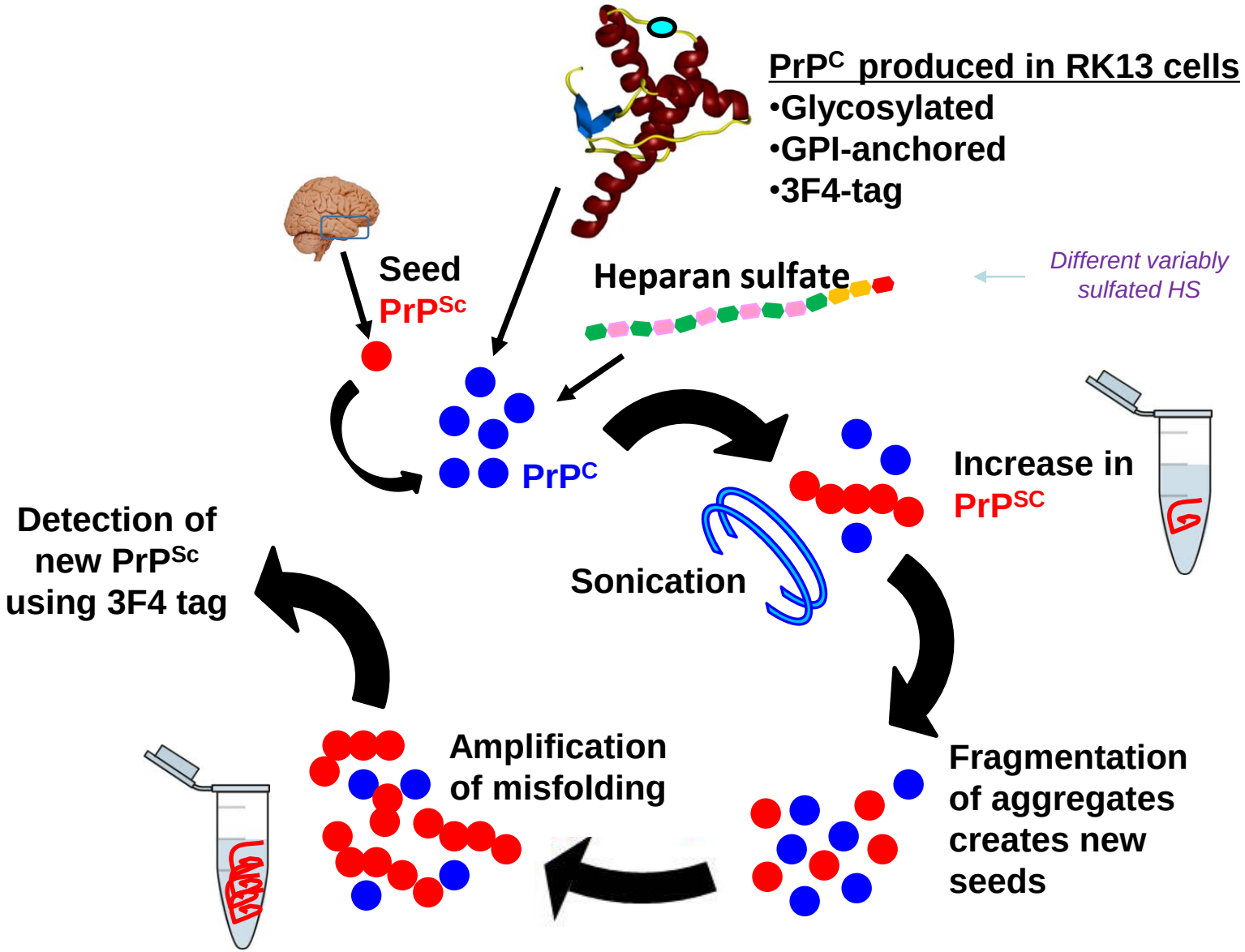
Amyloid β: cerebral amyloid angiopathy (CAA)



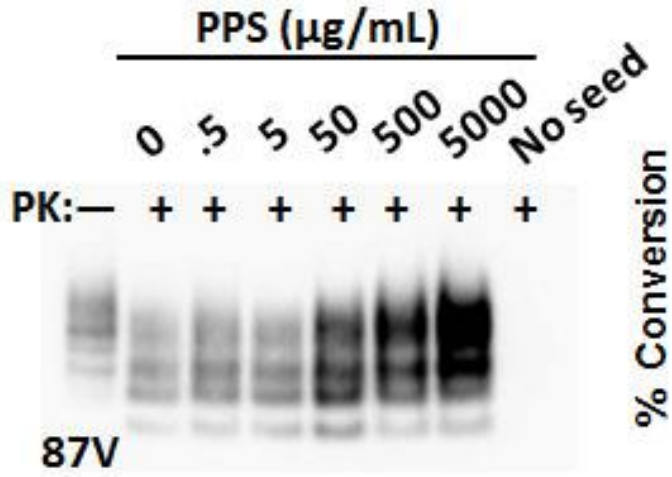
IHC Congo red HE

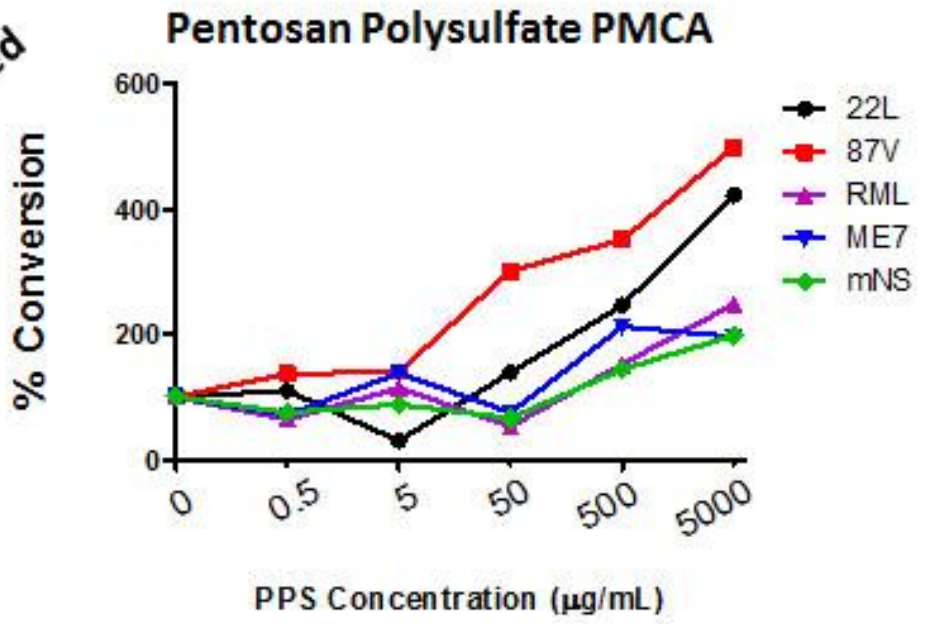


# How does the sulfation of HS molecules impact prion replication?

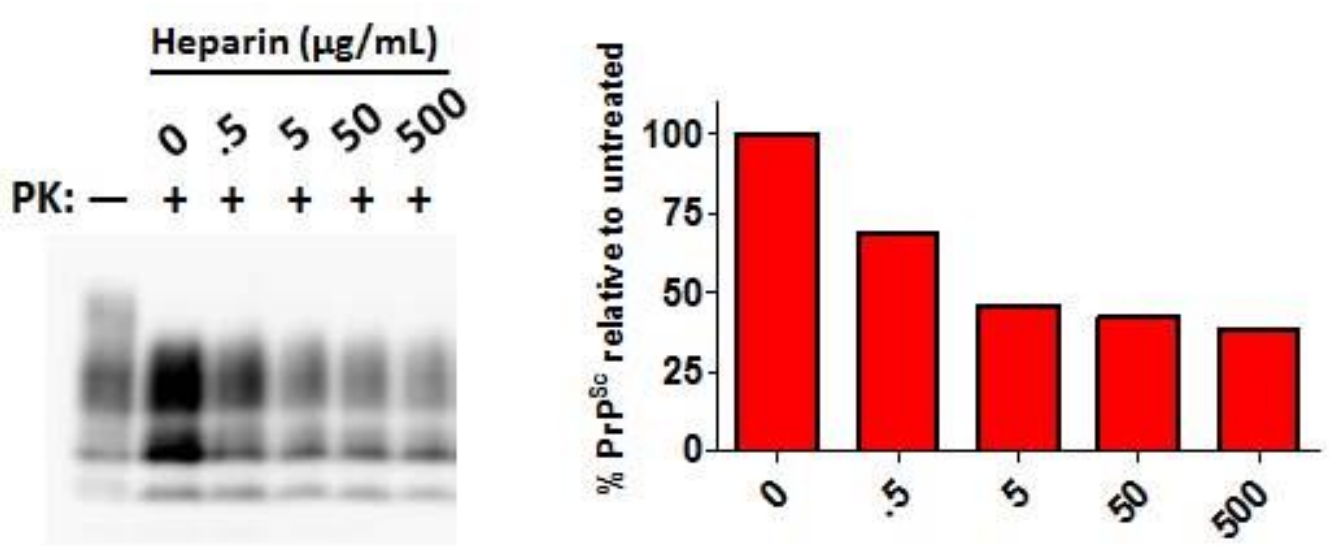


# Heparin and pentosan polysulfate enhance prion conversion in a dose-dependent manner



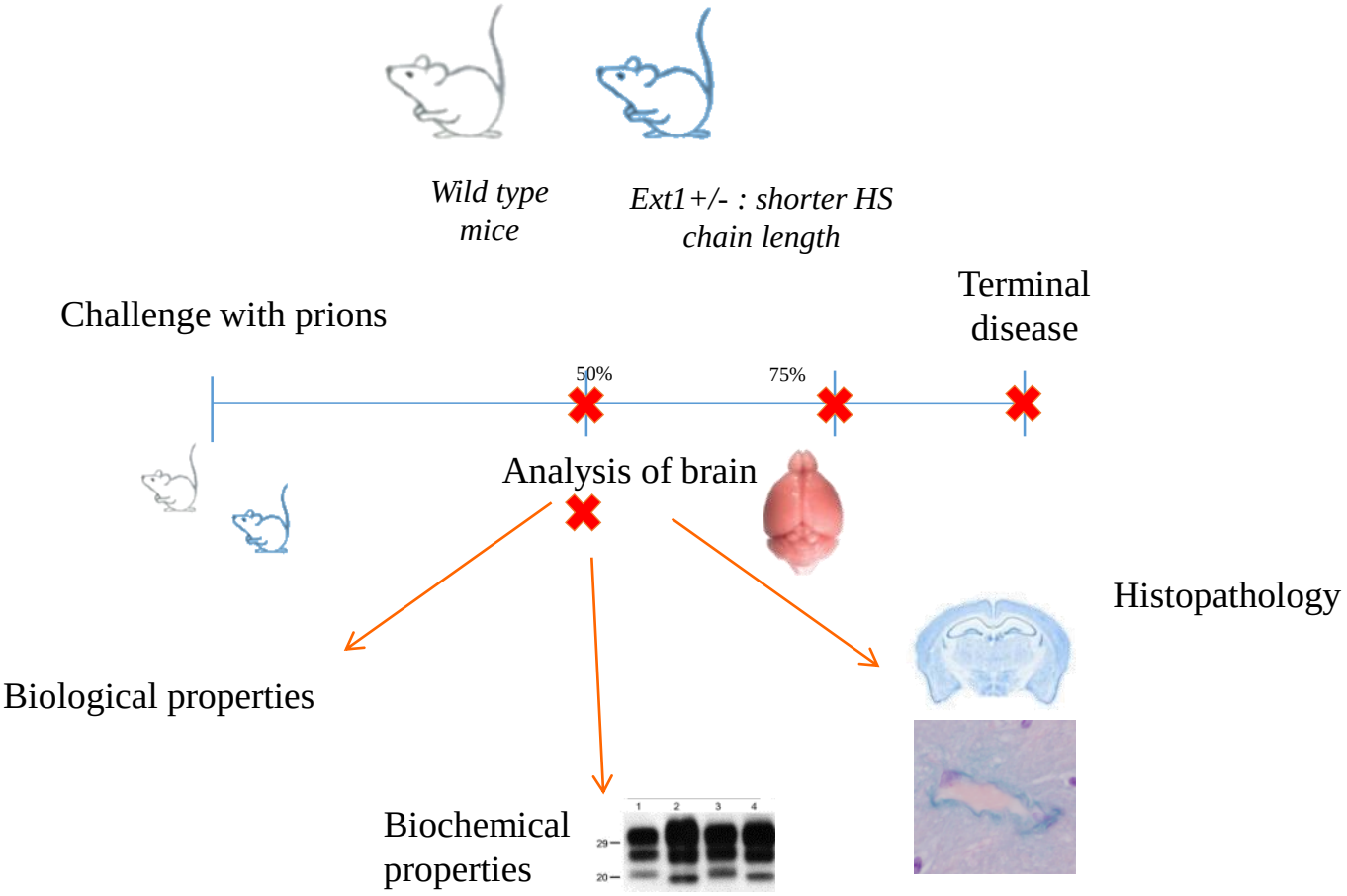



# Heparin and PPS lead to a decrease $PrP^{Sc}$ levels in persistently prion-infected cells




*Demonstrates the paradoxical effect of HS – in cell lysate amplification versus in live cells and in vivo*

# The impact of sulfation of HS chains on prion disease progression




*Ongoing……*

# Conclusions

- $PrP^{Sc}$ purified for mass spectrometry analysis to identify the heparan sulfate bound to $PrP^{Sc}$
- Pentosan polysulfate promotes $PrP^{Sc}$ formation in vitro in the PMCA assay
- Heparin and pentosan polysulfate decrease $PrP^{Sc}$ levels in prion-infected cells in culture

# *Acknowledgements*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