Contribution of oligomeric prion populations to phenotypic heterogeneity in variably protease-sensitive prionopathy (VPSPr) versus silent prions

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CENTRE FOR PRIONS
AND PROTEIN FOLDING DISEASES
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The origin of prions

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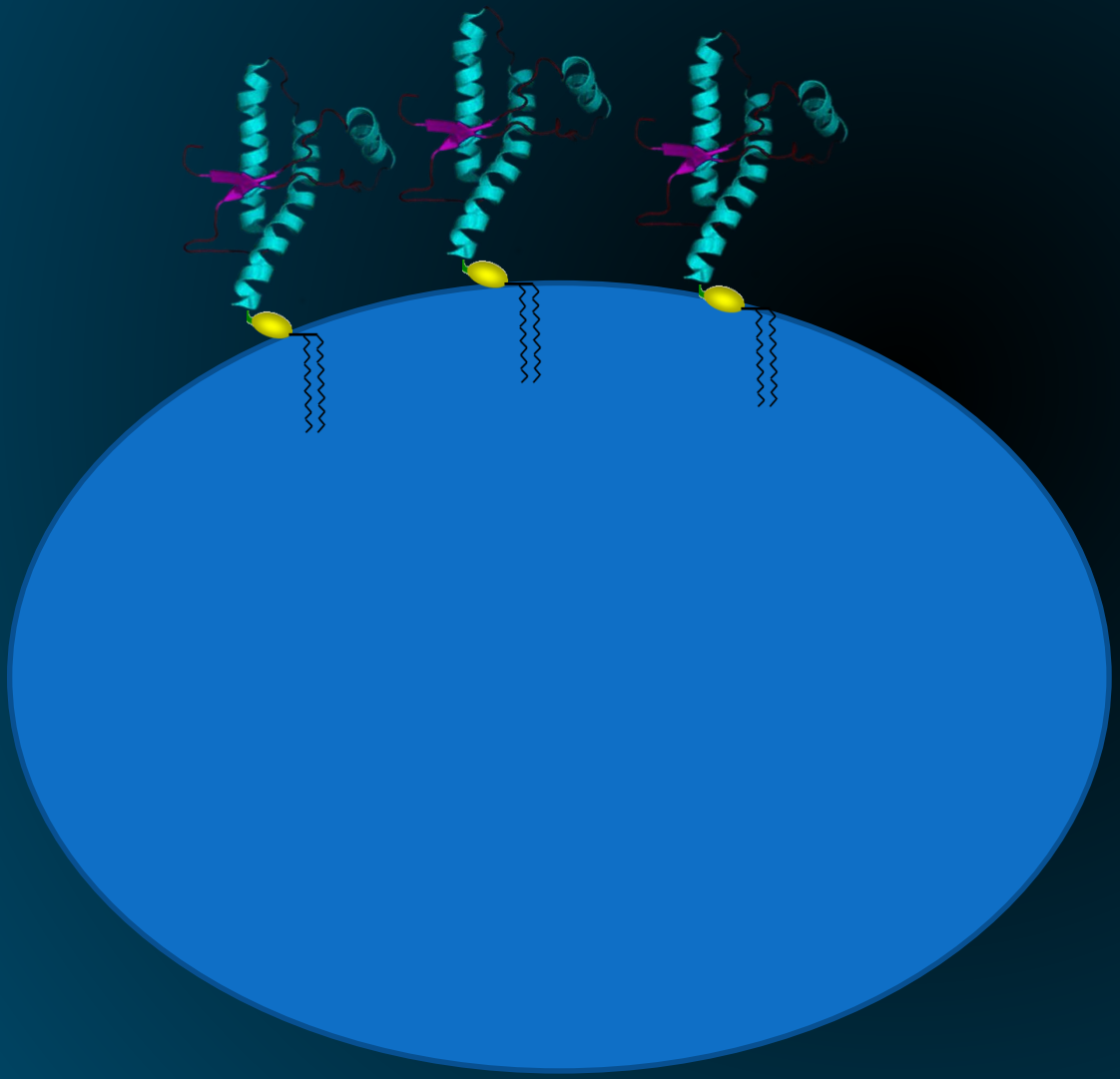
Spontaneous

Unlucky

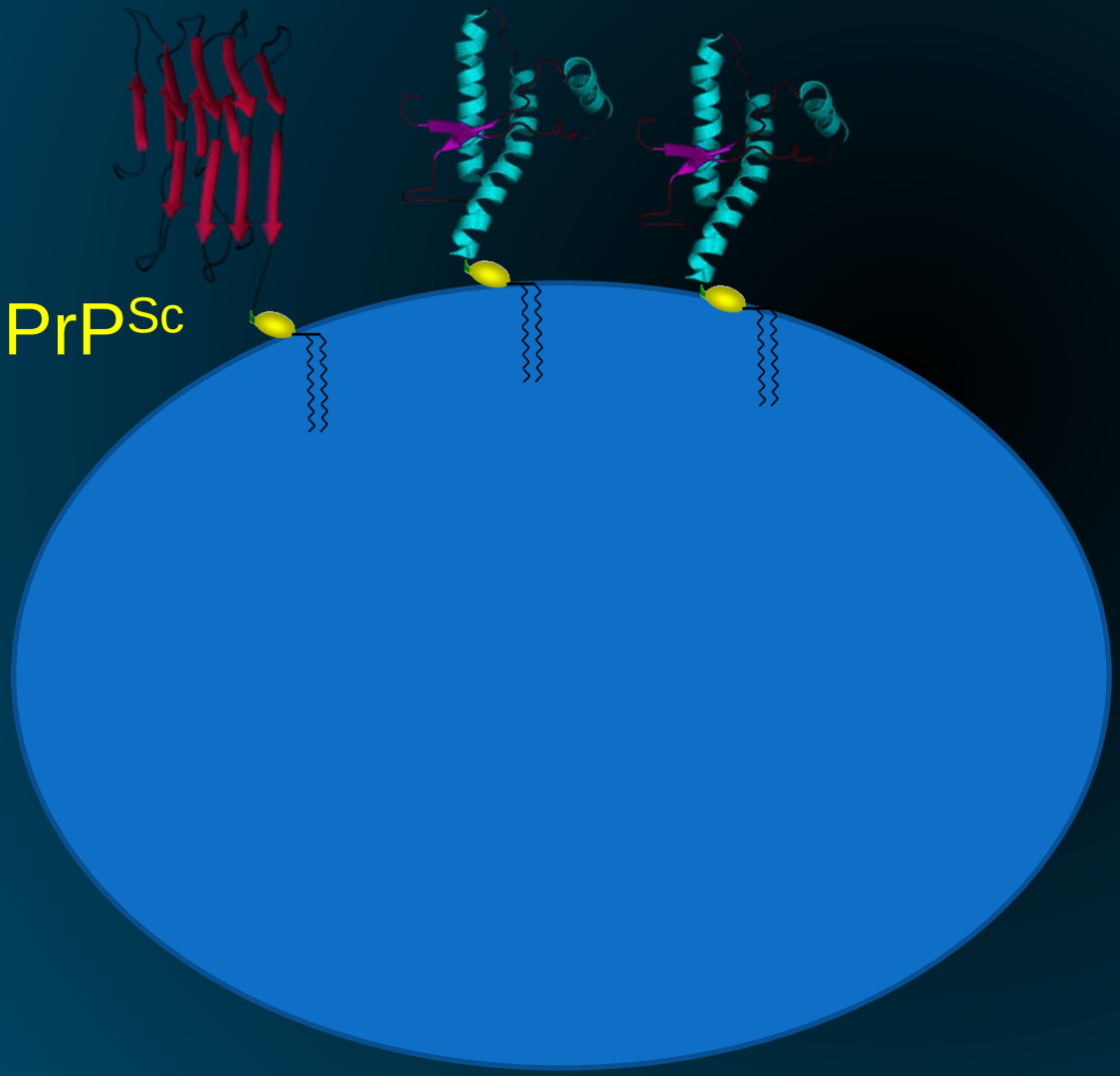
1 in a million

The prion life cycle…

Cellular prion protein (PrP^C)



1. Conversion



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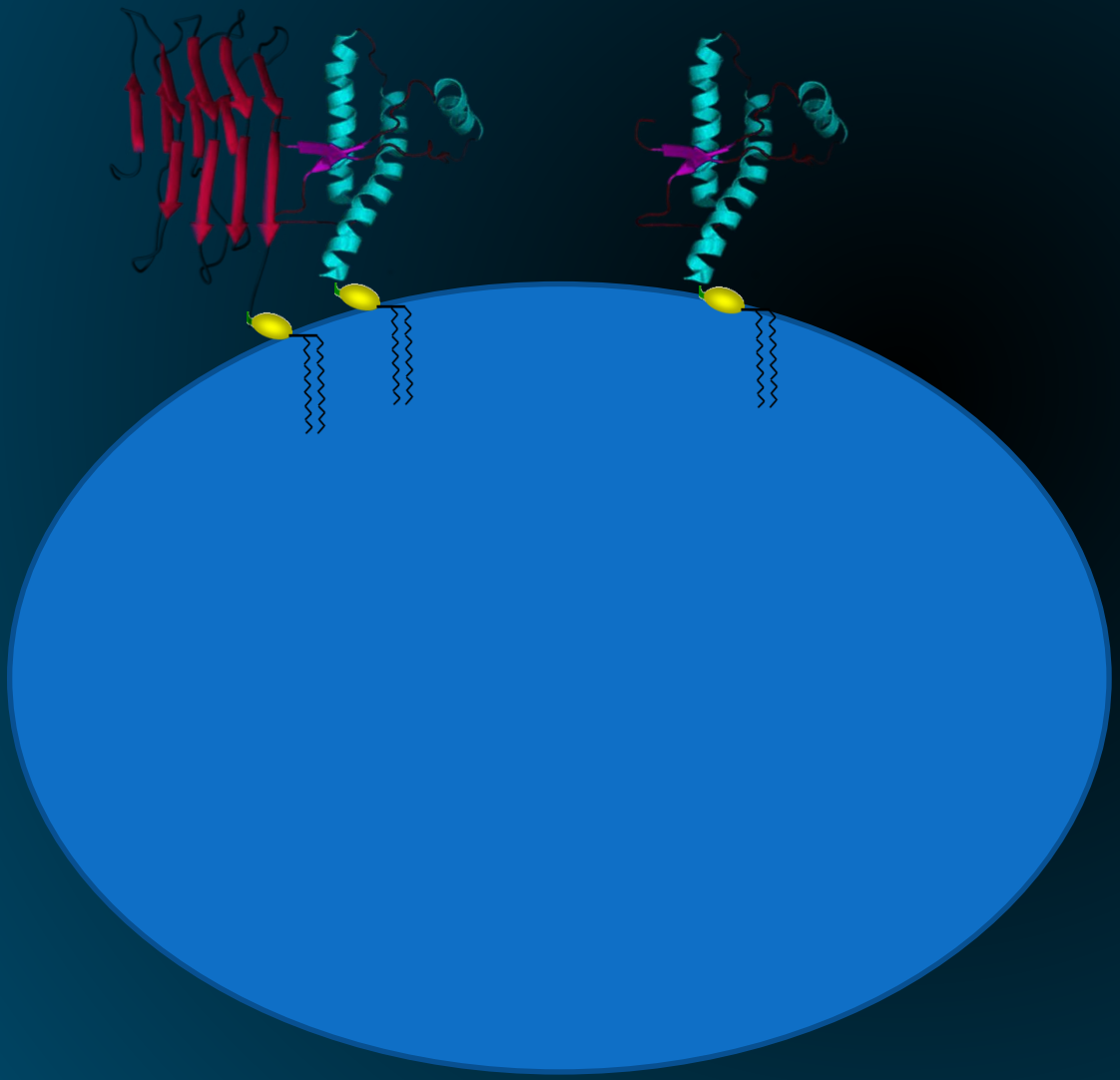

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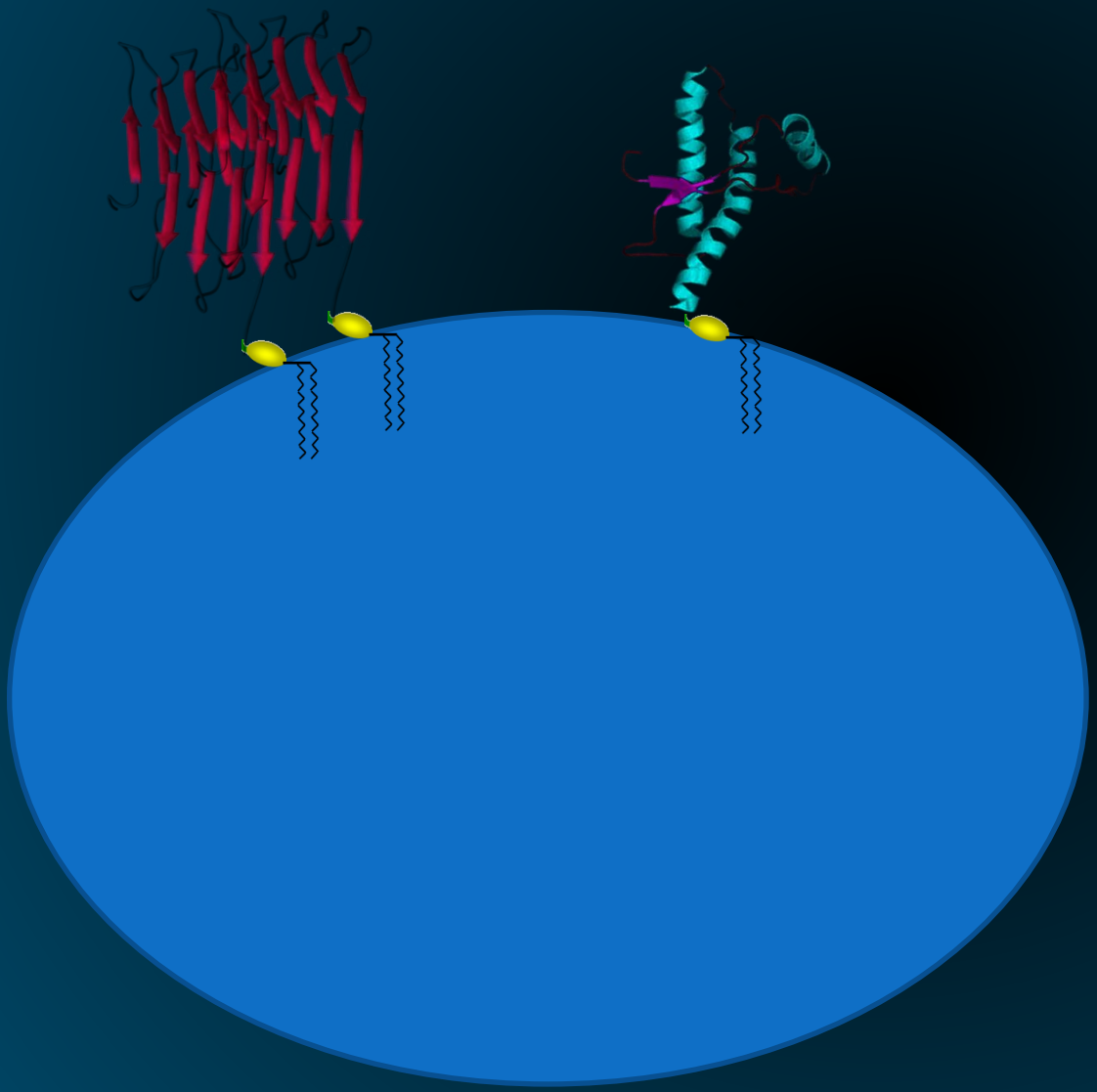

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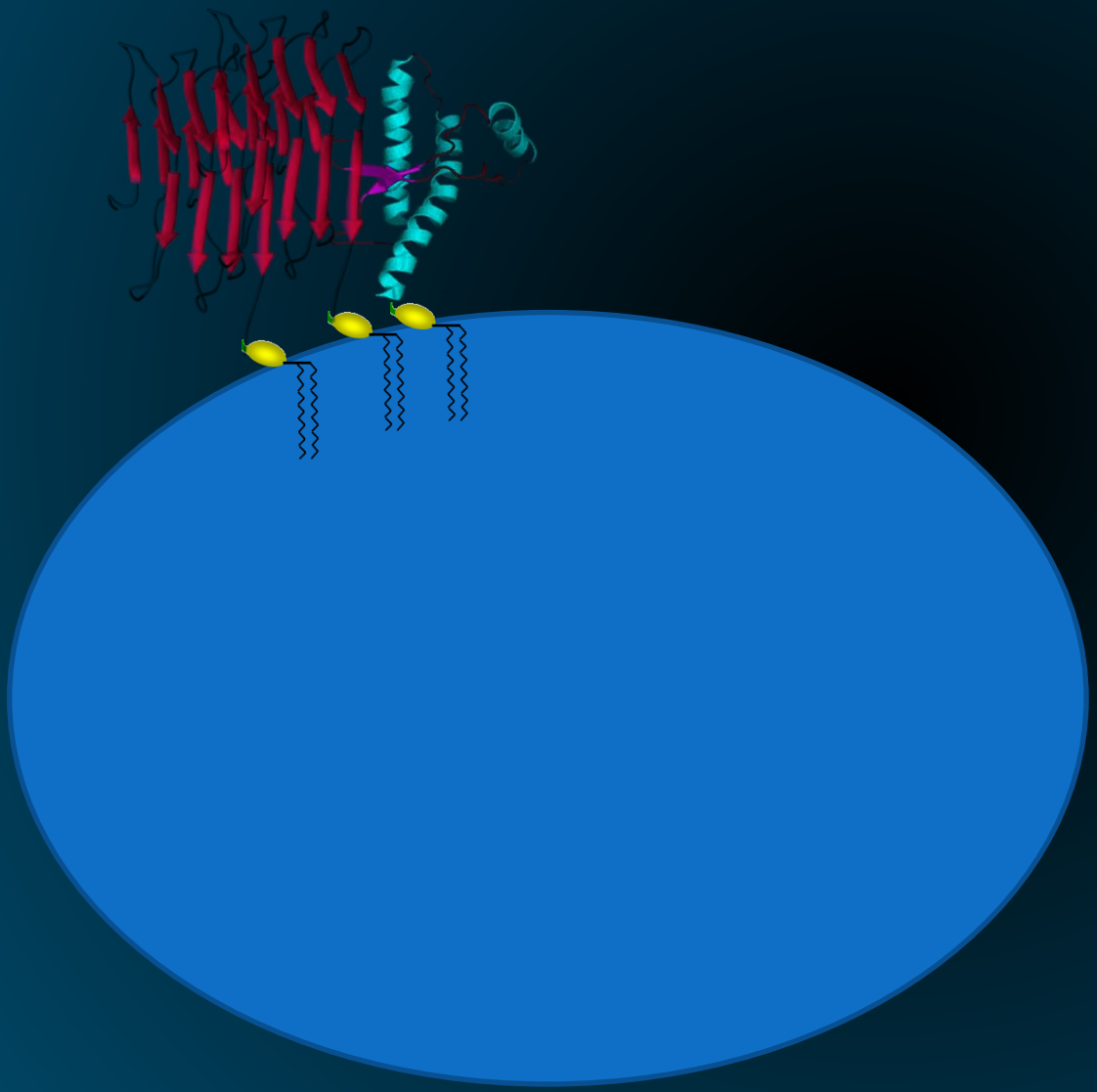
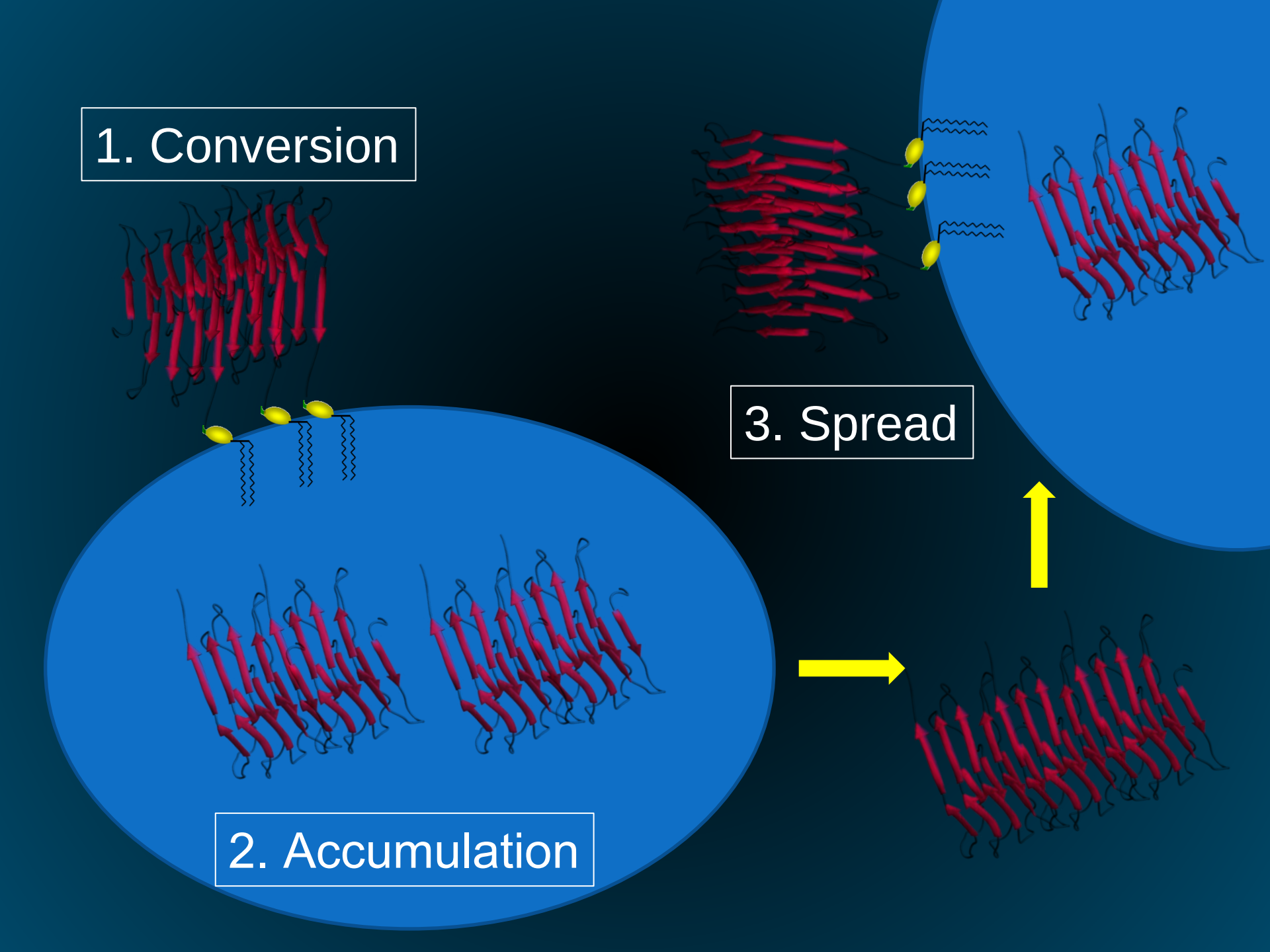
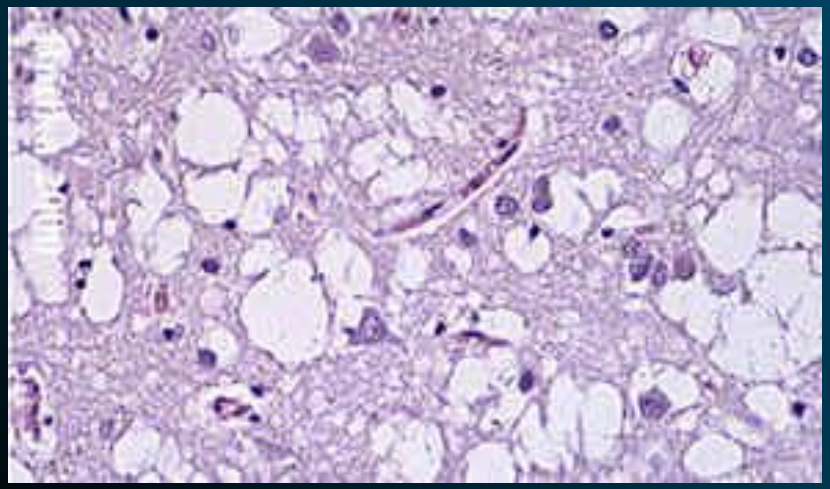



1. Conversion
3. Spread
2. Accumulation

Pathology (end stage)

- Spongiform change
- Neuronal loss
- Astrocytosis



Hematoxylin and eosin stain. © H. Budka 2000

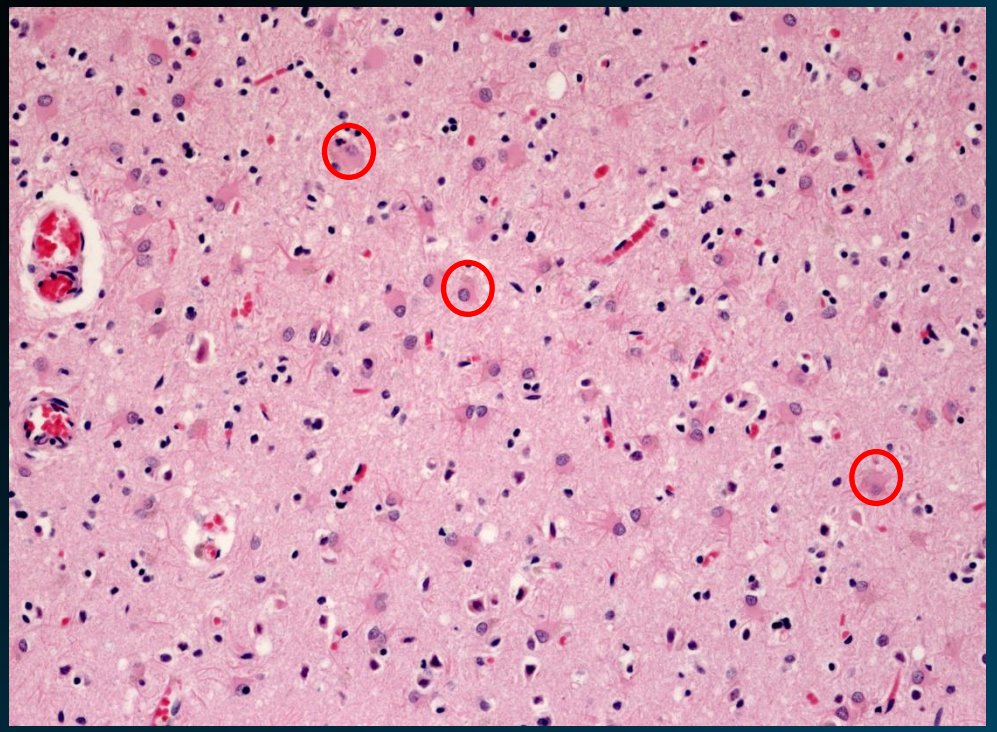
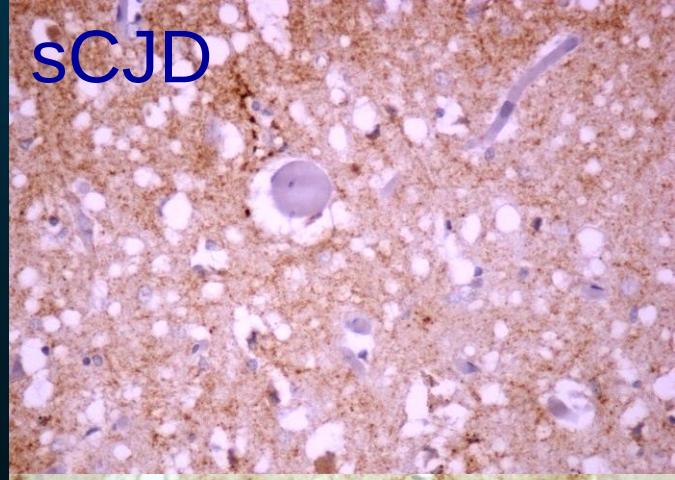
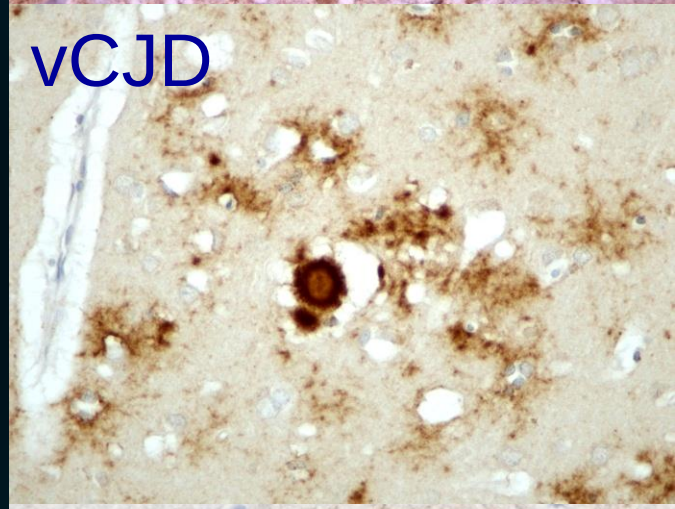


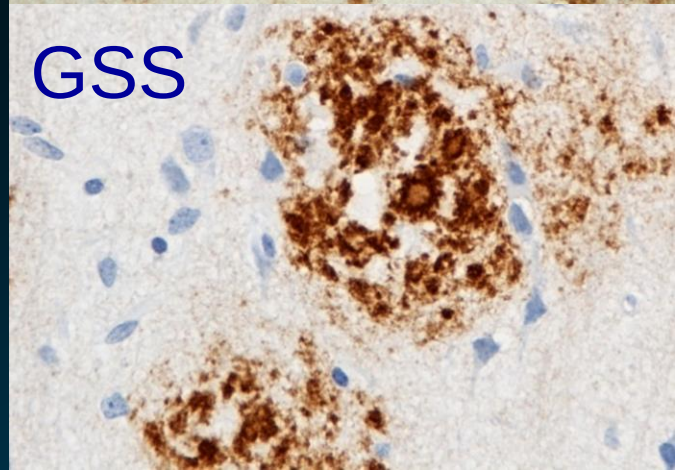
Image courtesy of J. Joseph

Pathology (end stage)

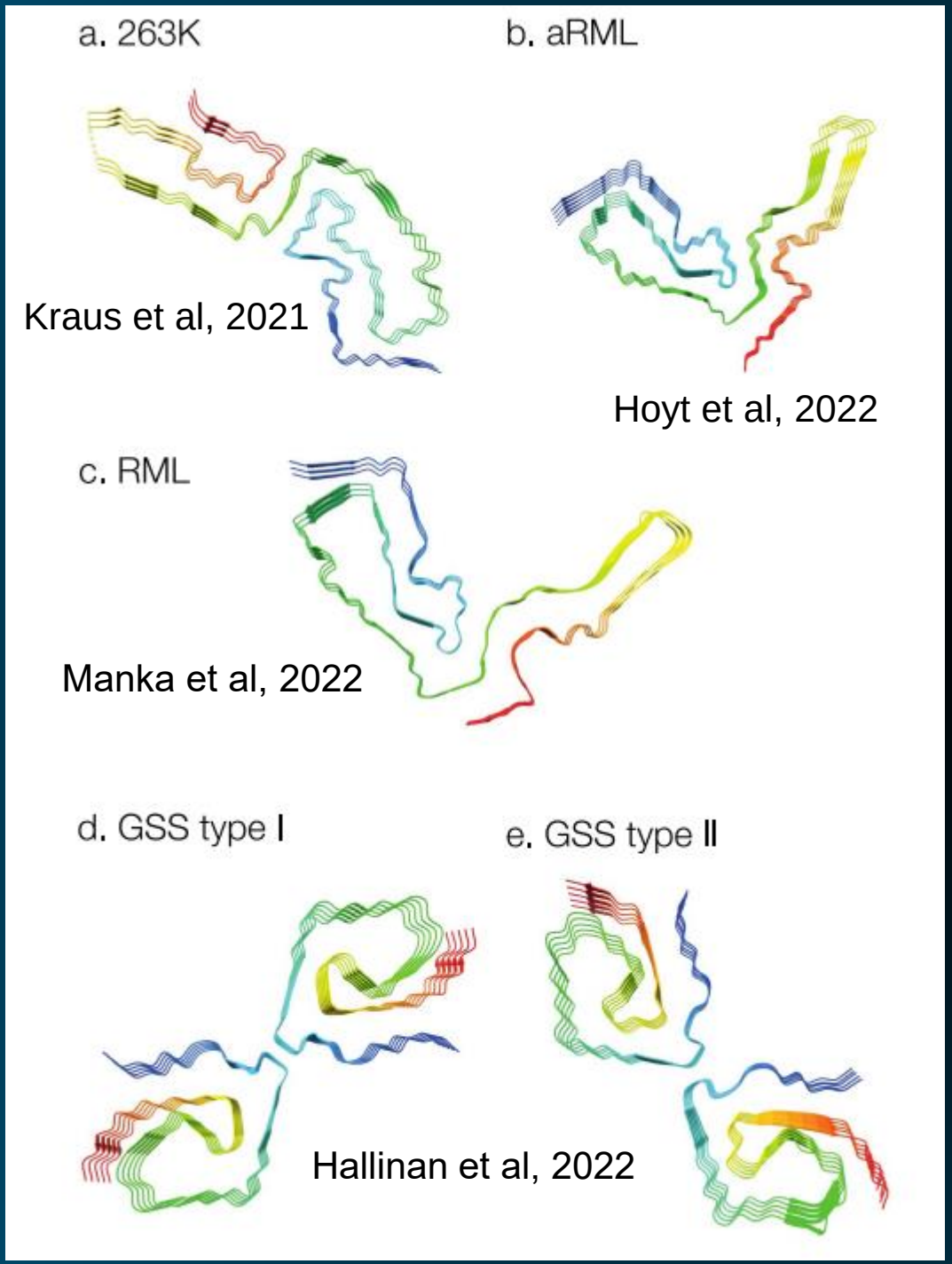
- Spongiform change
- Neuronal loss
- Astrocytosis
- Accumulation of PrP^{res} (strain dependent)







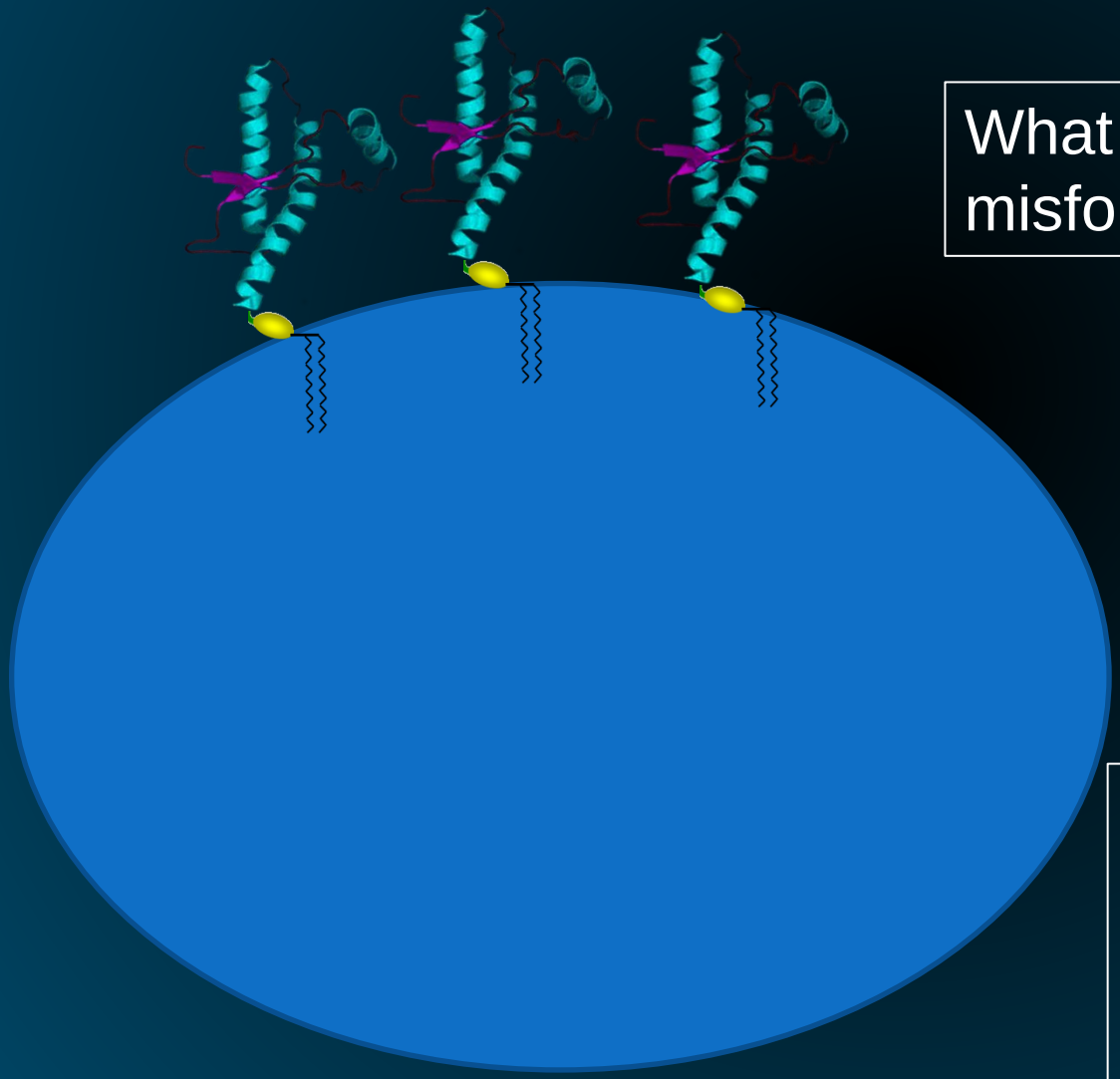
Images courtesy of G. Jansen



Shape matters

Figure from Fleming, Masters Thesis 2023

But how does it all start?



What does the first misfolding event look like?

Do all misfolding events generate prions that cause disease?

What determines whether a misfolding event will generate disease-causing prions?

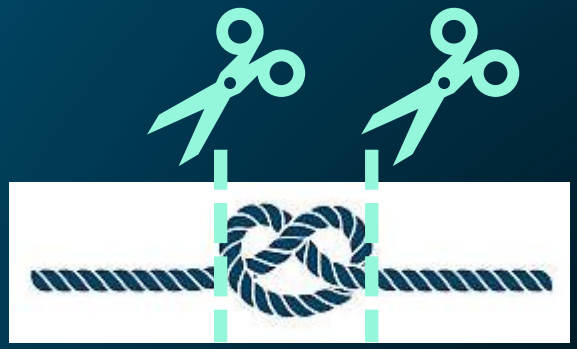
Silent prions

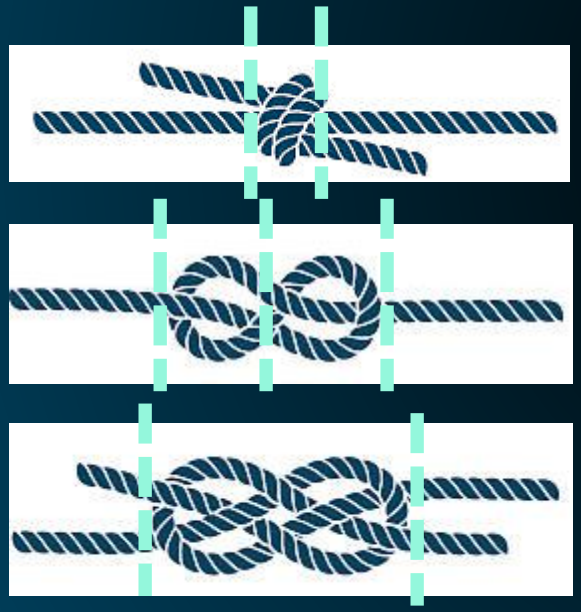
- In normal brain, there are trace amounts of misfolded PrP
  - Yuan et al., 2006; Zou et al., 2011
- These “silent prions” don’t cause disease
- What is it about their structure that renders them harmless?

We compared the size, shape and stability of these silent prions to more infectious prions in order to understand why one lies dormant while the other causes devastating disease.

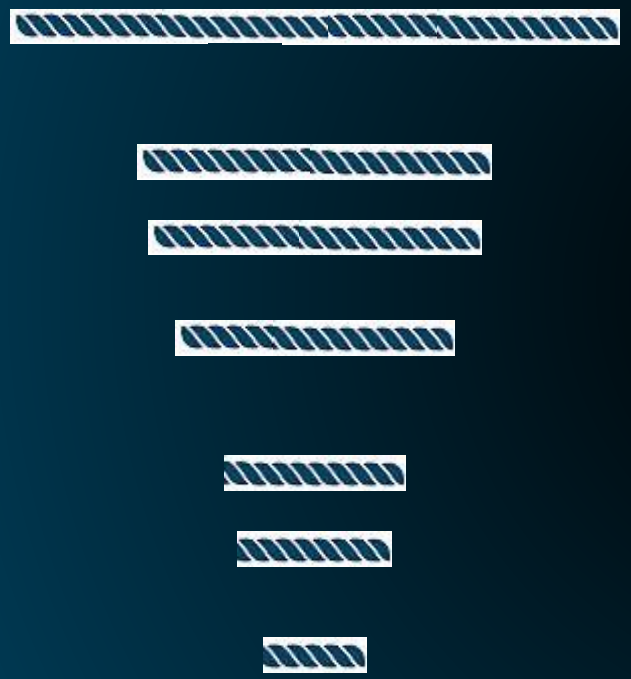
Fragment analysis

- When prions misfold, parts of them can no longer be cleaved by enzymes.

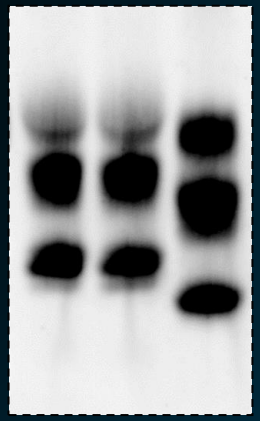




Separating fragments

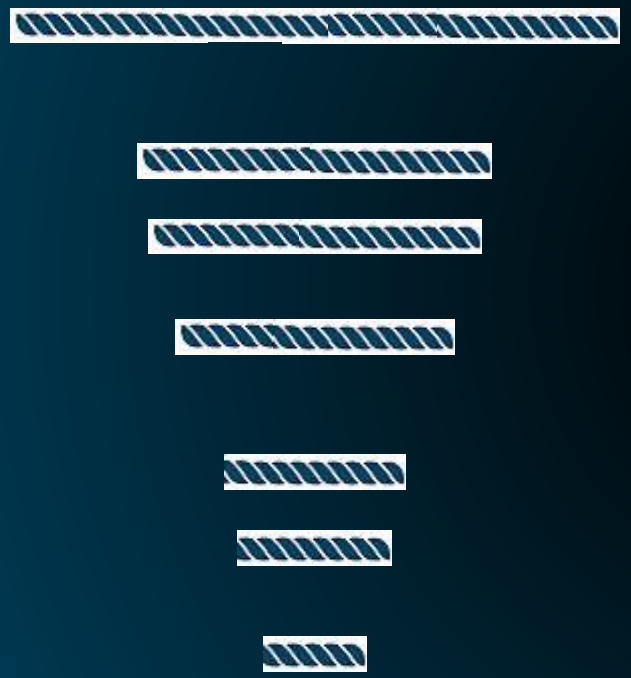


PrP^{Sc} on western blot after PK digestion

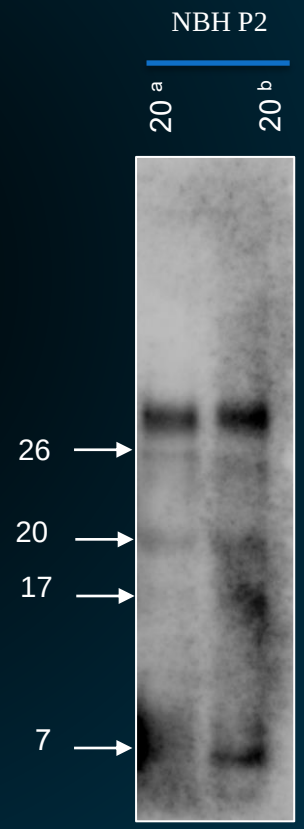


Common subtypes
MM1, MV1, MM2

Separating fragments

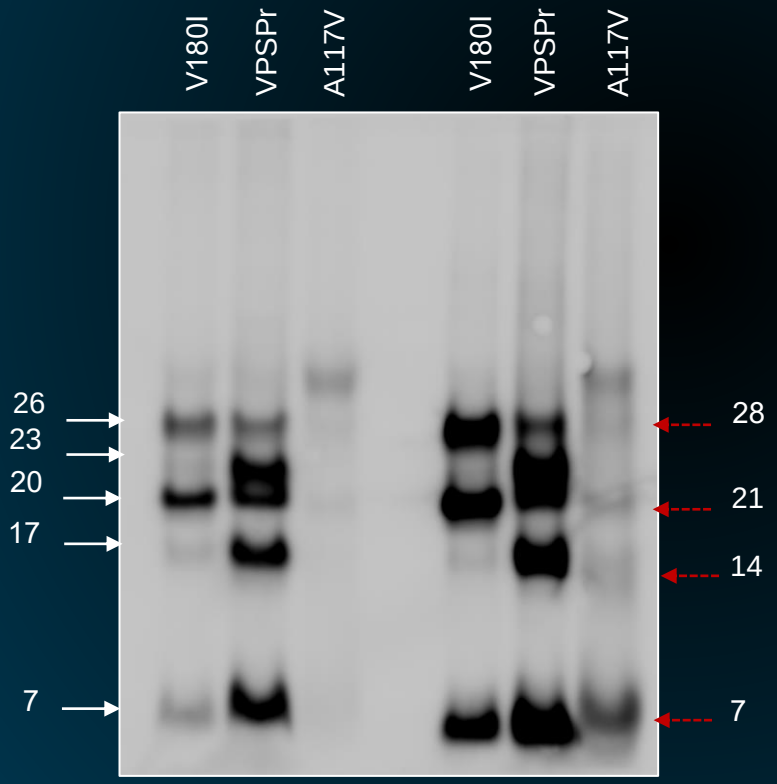


Silent prions



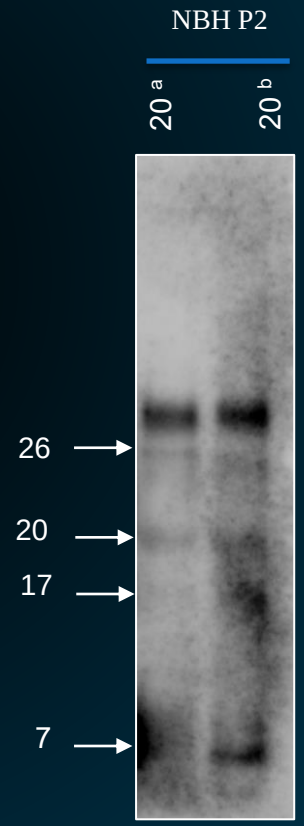
Separating fragments

Disease-causing prions



To-2; 1:10K

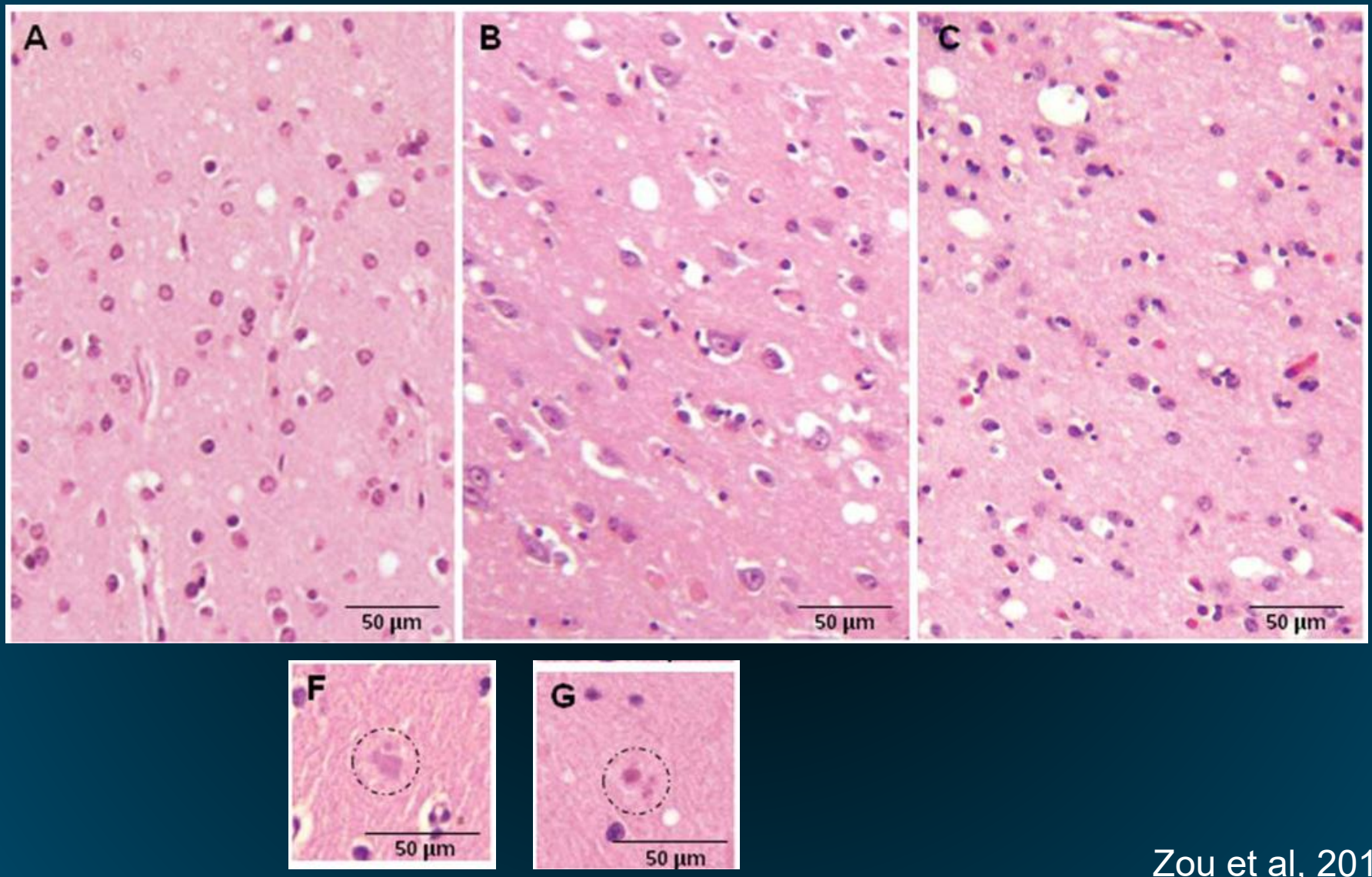
Silent prions



Disease-causing prions that have fragment overlap with silent prions

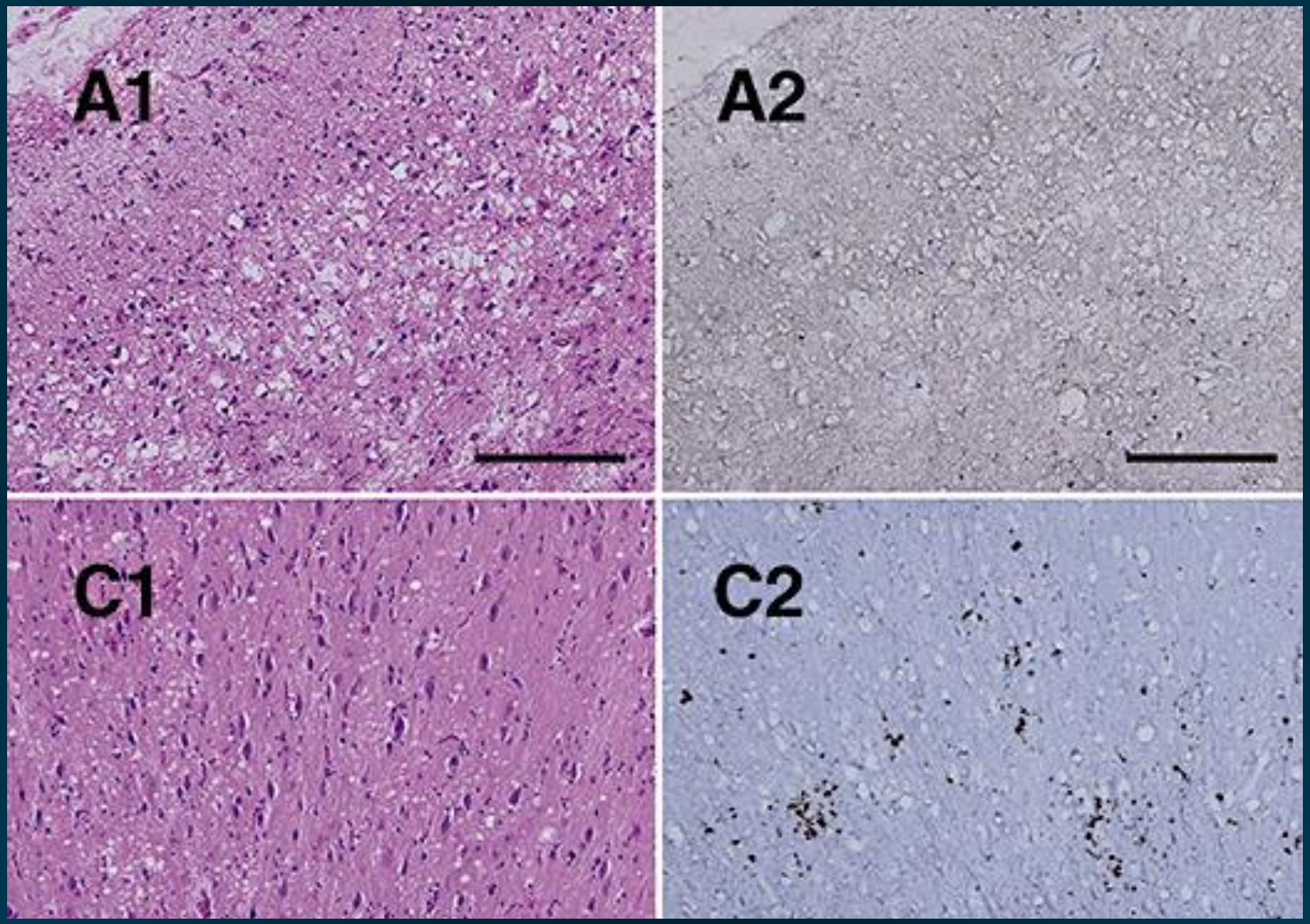
- Variably protease sensitive prionopathy (VPSPr)
  - Zou et al, 2010
  - spontaneous disease; rare (1/100 million)
  - older onset, slower disease course
- Genetic CJD: V180I
  - genetic, 1% risk
  - older onset, slower disease course
- Genetic CJD: A117V
  - genetic, 100% penetrance
  - young onset, slower disease course

VPSPr



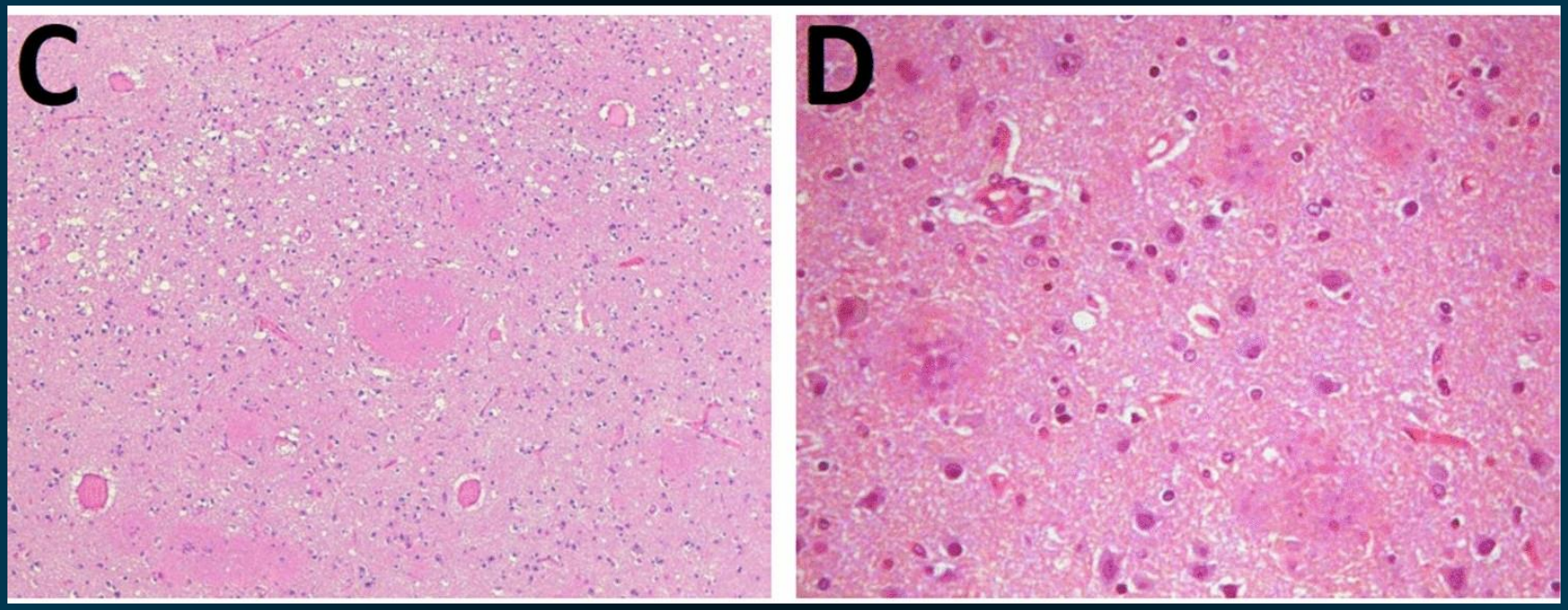
Zou et al, 2010

V180I



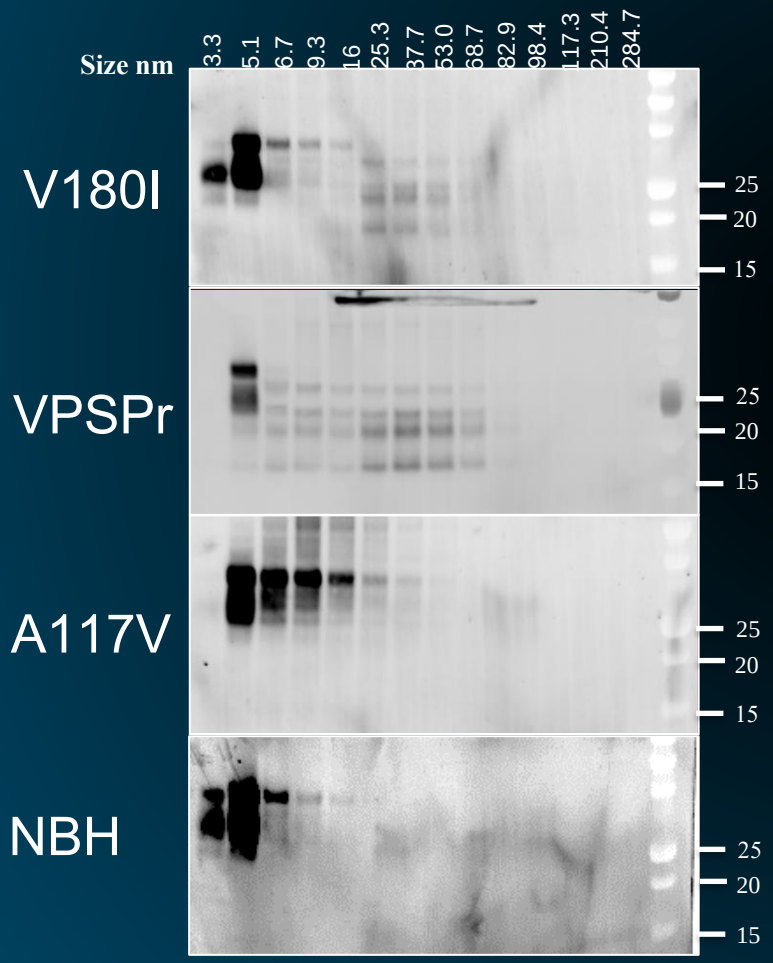
Iwasaki et al., 2011

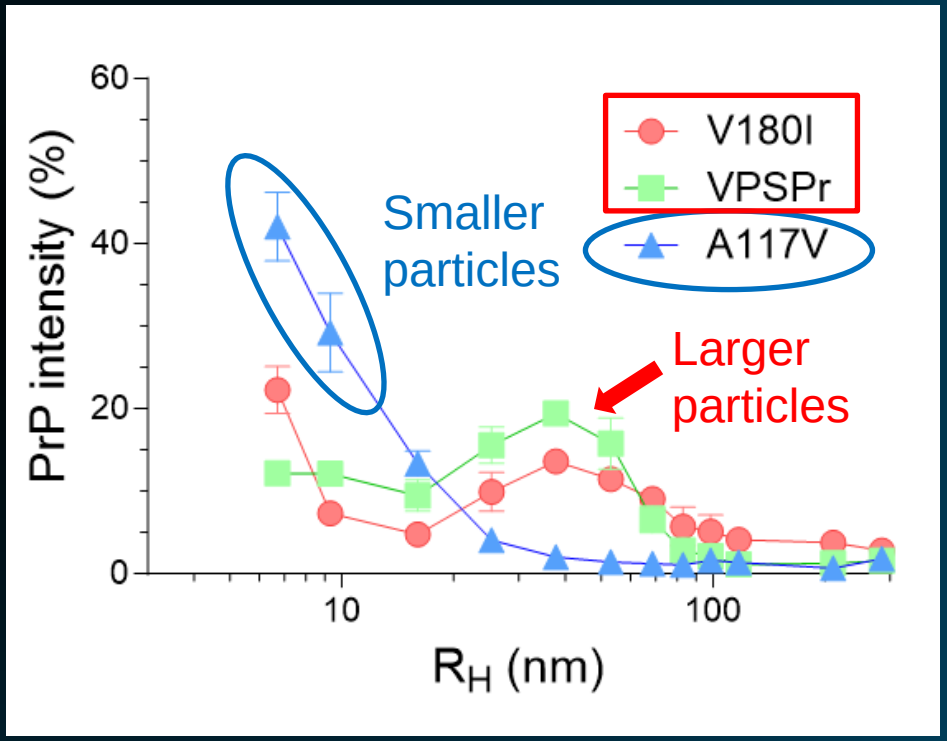
A117V



Erana et al. 2022

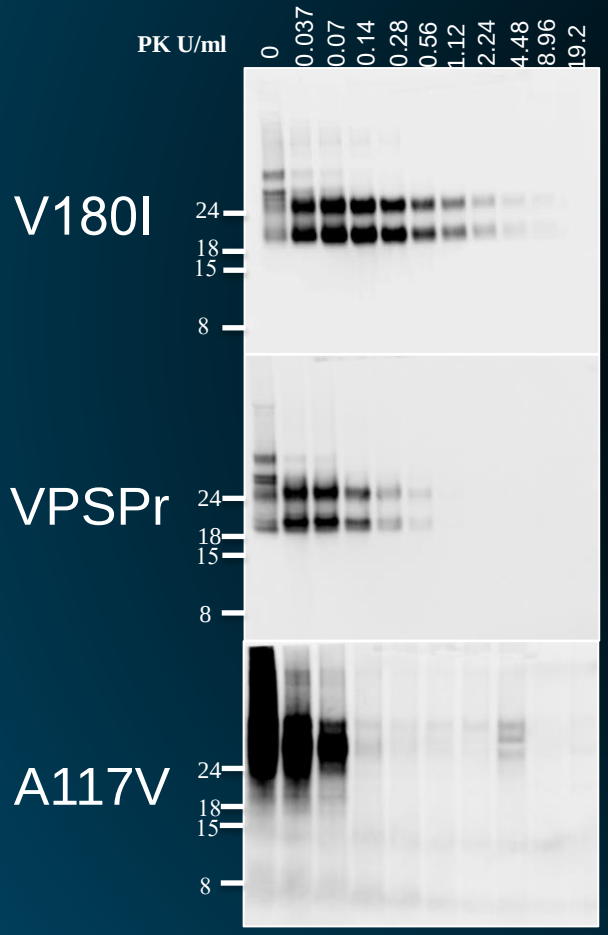
Size distribution analysis by Asymmetric flow field flow fractionation (AF4)



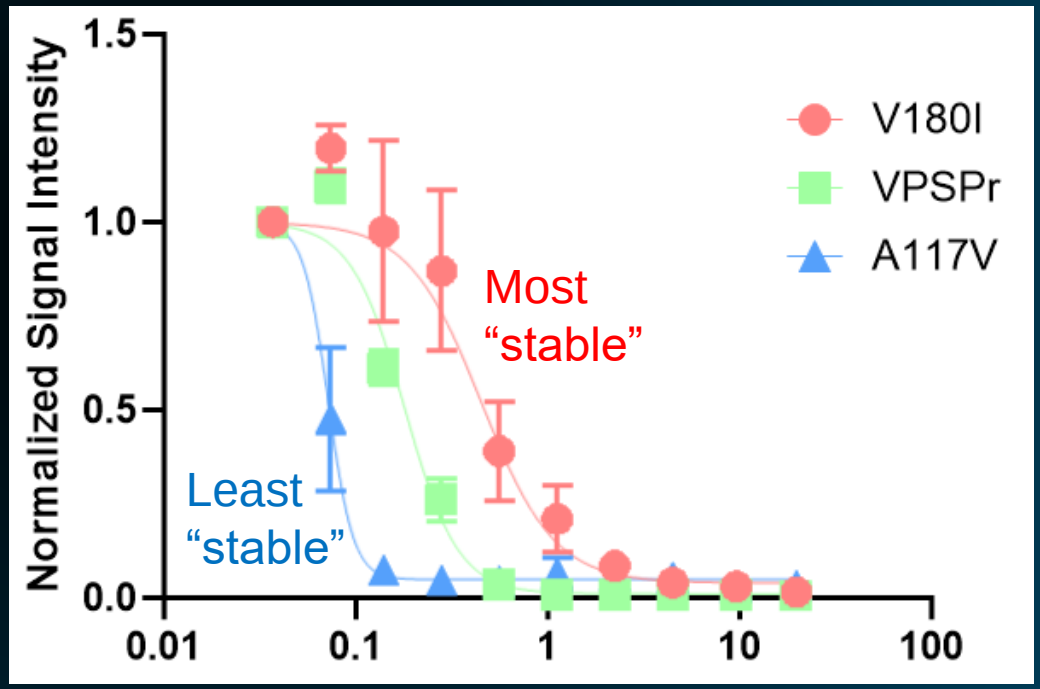


N=3 for each subtype
N=1 for control negative for prion disease

Resistance to increasing concentrations of proteinase

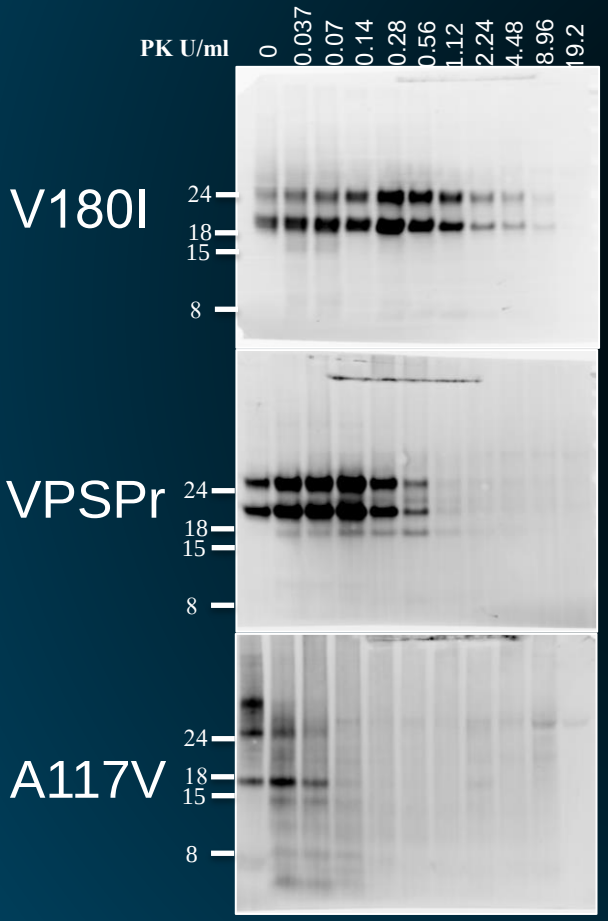


3F4

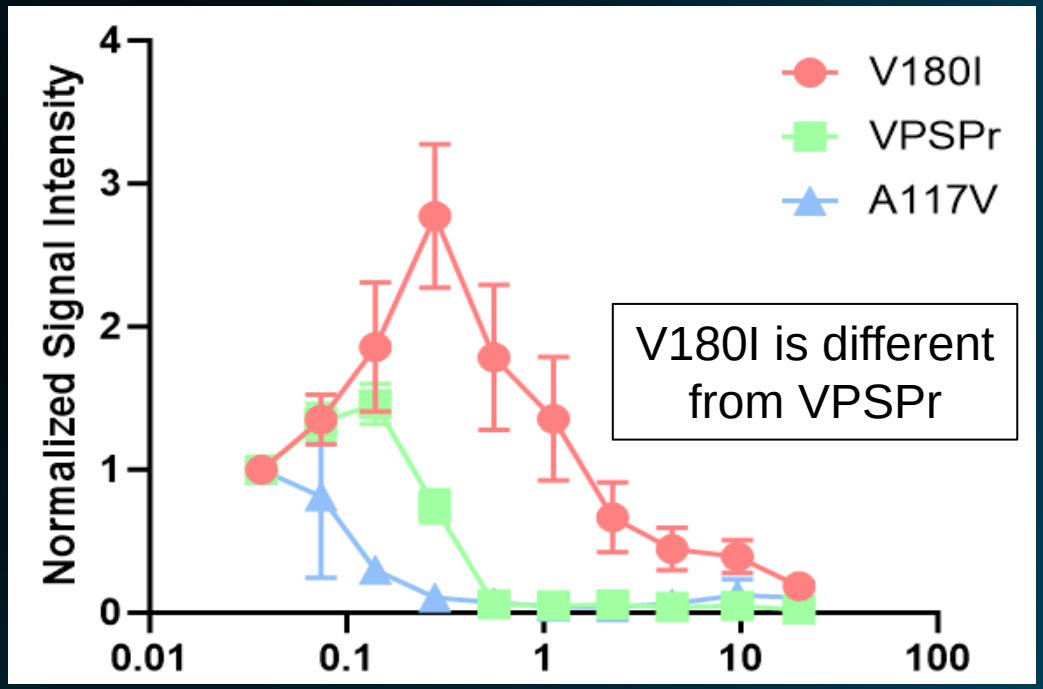


N=3 for each subtype

Resistance to increasing concentrations of proteinase



To-2



N=3 for each subtype

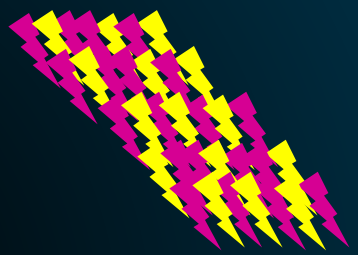
Origin of prions?

Silent prions
No disease
Low amounts
Small
Unstable

A117V mutation
100% risk

Younger onset
Slow disease
Small, Unstable

VPSPr
1/100 million risk



Older onset
Slow disease
Larger
Less stable

V180I mutation
1% risk

Older onset
Slow disease
Larger
More stable

Normal PrP^{C}

Unstable PrP

Unstable PrP^{Sc}

Stable PrP^{Sc}

Next steps: acquire large amounts of normal brain to increase yield of silent prions for further comparisons

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Lab contributors 2023:

- Satish Nemani
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- Grant Norman
- Hailey Pineau
- Marcus Pehar
- Tolani Brimmo
- Milan Shah
- Maddy Charlton

Collaborators:

- Jeff Joseph, University of Calgary
- Brian Appleby, Case Western Reserve

https://sites.ualberta.ca/~vsim/
Includes links to TedX talk 2017

@PrionGirl on Twitter (X)

Patient and family donors

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GenomeAlberta

AlzheimerSociety ALBERTA AND NORTHWEST TERRITORIES

CJD FOUNDATION

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Supporting Families Affected by Prion Disease