Prion Disease 103:

Even More Prion Research Basics

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CJD Foundation Family Conference

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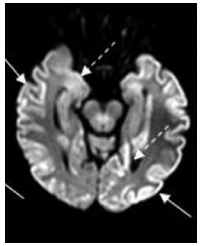
Prion Diseases of Animals and Humans

Animal Prion Diseases

Bovine Spongiform Encephalopathy (BSE) “Mad Cow Disease”

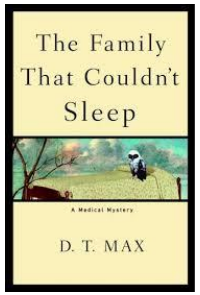
Chronic Wasting Disease (CWD) (deer, elk, and moose)

Scrapie (sheep and goats)



Human Prion Diseases

<u>Sporadic</u>
Creutzfeldt-Jakob Disease (CJD)
Variably Protease-Sensitive Prionopathy (VPSPr)



<u>Genetic</u>
Fatal Familial Insomnia (FFI)
Gerstmann-Sträussler-Scheinker disease (GSS)
Familial CJD (fCJD)

<u>Infectious/Acquired</u>
Kuru
Variant CJD
Iatrogenic CJD

A Quick Biology Review

DNA (genes) —Transcription→ RNA —Translation→ Protein

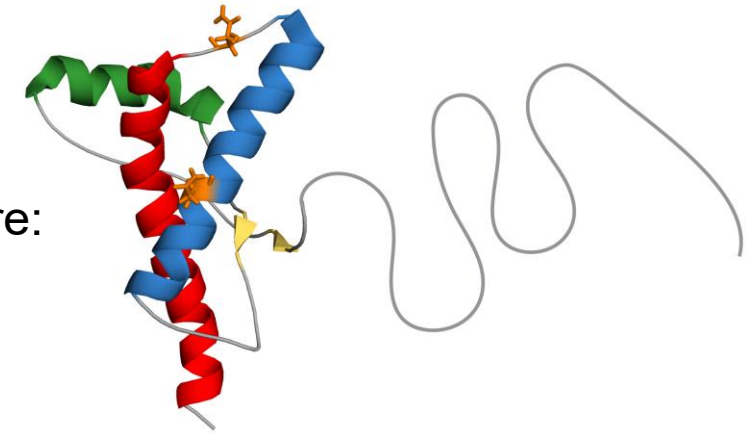
Prion (*PRNP*) Gene Sequence

```
ATGGCGAACCTTGGCTGCTGGATGCTGGTTCTCTTTGTGGCCACATGGAGTGACCTGGGC
CTCTGCAAGAAGCGCCCGAAGCCTGGAGGATGGAACACTGGGGGCAGCCGATACCCGGGG
CAGGGCAGCCCTGGAGGCAACCGCTACCCACCTCAGGGCGGTGGTGGCTGGGGGCAGCCT
CATGGTGGTGGCTGGGGGCAGCCTCATGGTGGTGGCTGGGGGCAGCCCCATGGTGGTGGC
TGGGGACAGCCTCATGGTGGTGGCTGGGGTCAAGGAGGTGGCACCCACAGTCAGTGGAAC
AAGCCGAGTAAGCCAAAAACCAACATGAAGCACATGGCTGGTGCTGCAGCAGCTGGGGCA
GTGGTGGGGGGCCTTGGCGGCTACATGCTGGGAAGTGCCATGAGCAGGCCCATCATACAT
TTCGGCAGTGACTATGAGGACCGTTACTATCGTGAAAACATGCACCGTTACCCCAACCAA
GTGTACTACAGGCCCATGGATGAGTACAGCAACCAGAACAACTTTGTGCACGACTGCGTC
AATATCACAATCAAGCAGCACACGGTCACCACAACCACCAAGGGGGAGAACTTCACCGAG
ACCGACGTTAAGATGATGGAGCGCGTGGTTGAGCAGATGTGTATCACCCAGTACGAGAGG
GAATCTCAGGCCTATTACCAGAGAGGATCGAGCATGGTCCTCTTCTCCTCTCCACCTGTG
ATCCTCCTGATCTCTTTCCTCATCTTCCTGATAGTGGGATGA
```

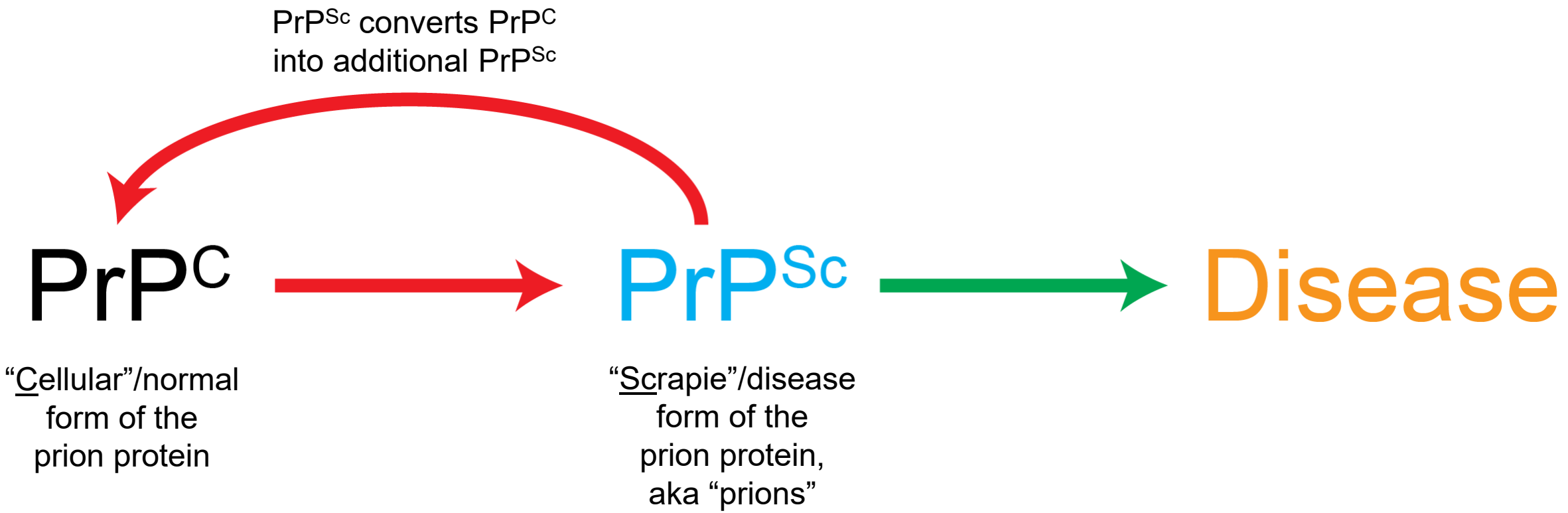
Prion Protein (PrP) Sequence

```
MANLGCWMLVLFVATWSDLGLCKKRPKPGGWNTGGSRYPGQGSPGGNRYPPQGGGGWGQP
HGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQGGGTHSQWNKPSKPKTNMKHMAGAAAAGA
VVGGLGGYMLGSAMSRPIIHFGSDYEDRYYRENMHRYPNQVYYRPMDEYSNQNNFVHDCV
NITIKQHTVTTTTKGENFTETDVKMMERVVEQMCITQYERESQAYYQRGSSMVLFSSPPV
ILLISFLIFLIVG
```

PrP^{C} Structure:



Prion Disease in a Nutshell



What is a Prion?

PrP^{C}

Normal protein movements

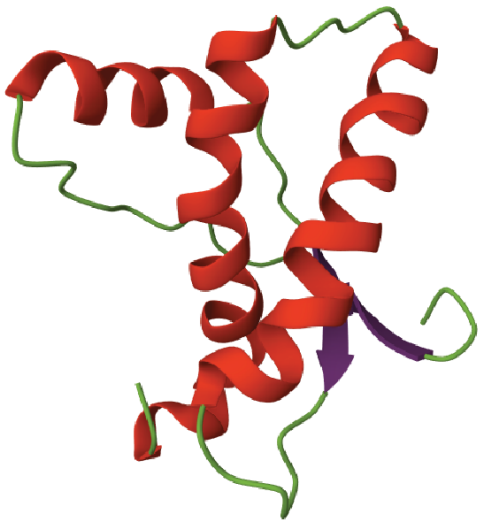
PrP^{Sc}

Conversion into a dangerous shape

Prion Replication and Propagation

- Spontaneous misfolding
- Mutations in PrP
- Pre-existing PrP^{Sc}

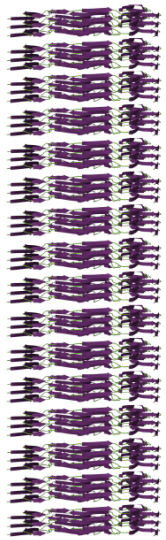
PrP^{C}



Misfolding

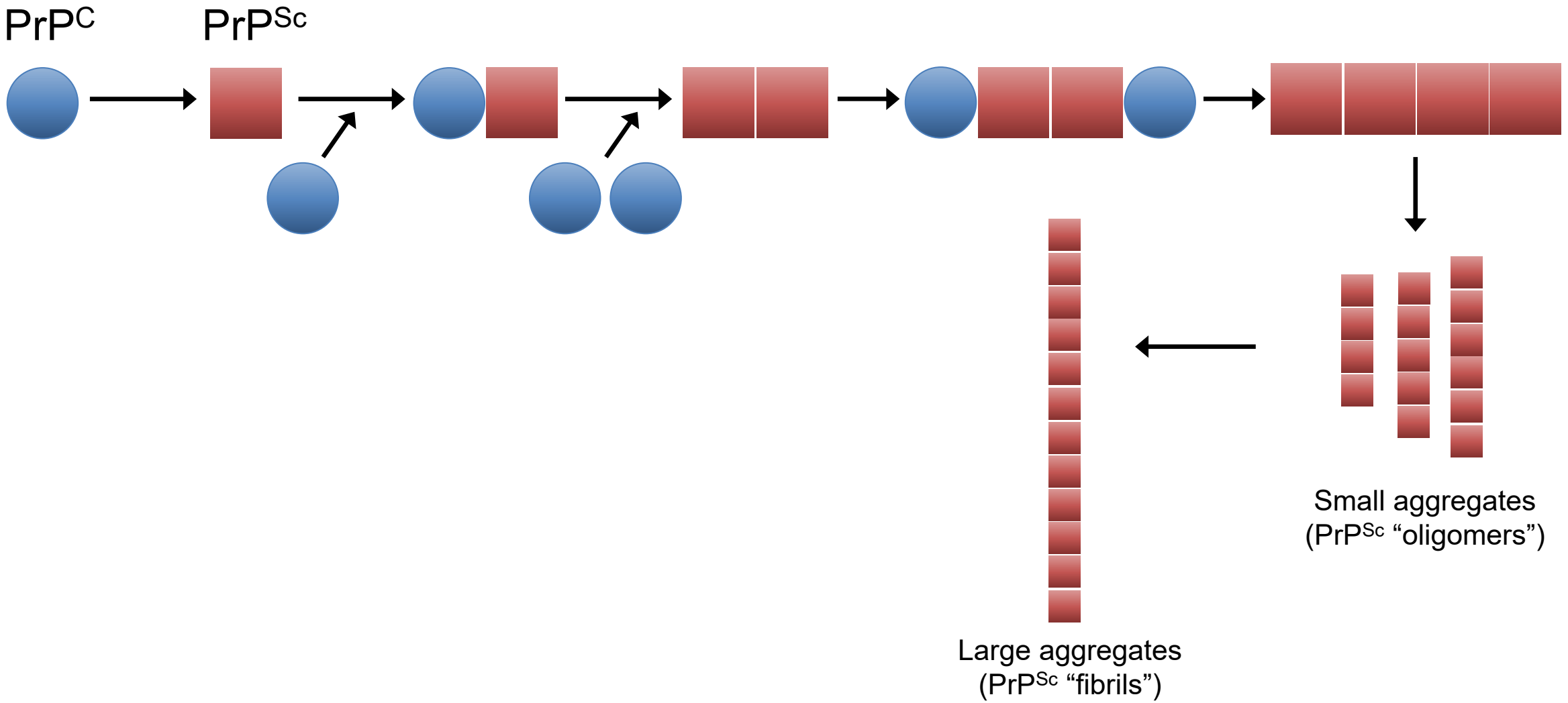
PrP^{Sc}

Aggregation



Self-propagation

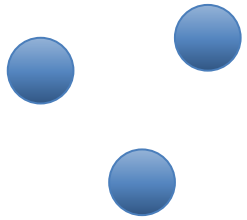
Prion Replication and Propagation



How do Researchers Distinguish Between PrP^{C} and PrP^{Sc}?

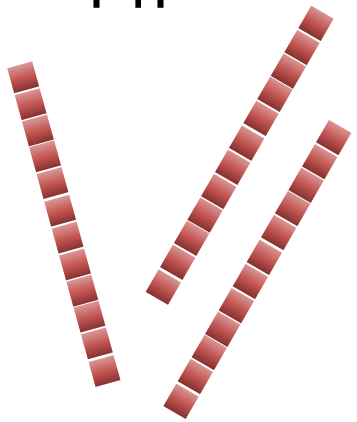
PK = Proteinase K

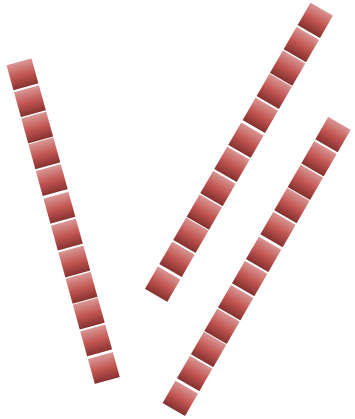
PrP^{C}



Complete elimination

PrP^{Sc}





PrP^{Sc} is resistant to degradation by PK!

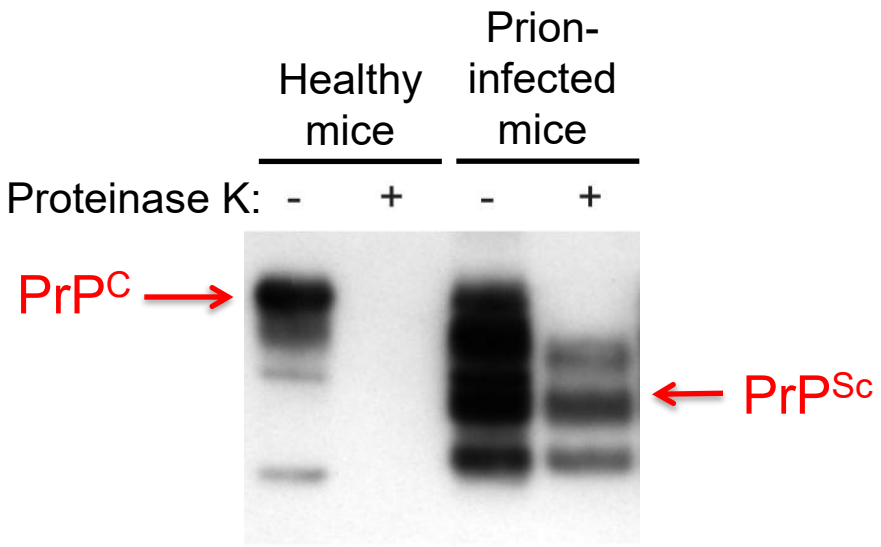
Prions Are Infectious Proteins

Inoculate mouse prions intracerebrally

Mice

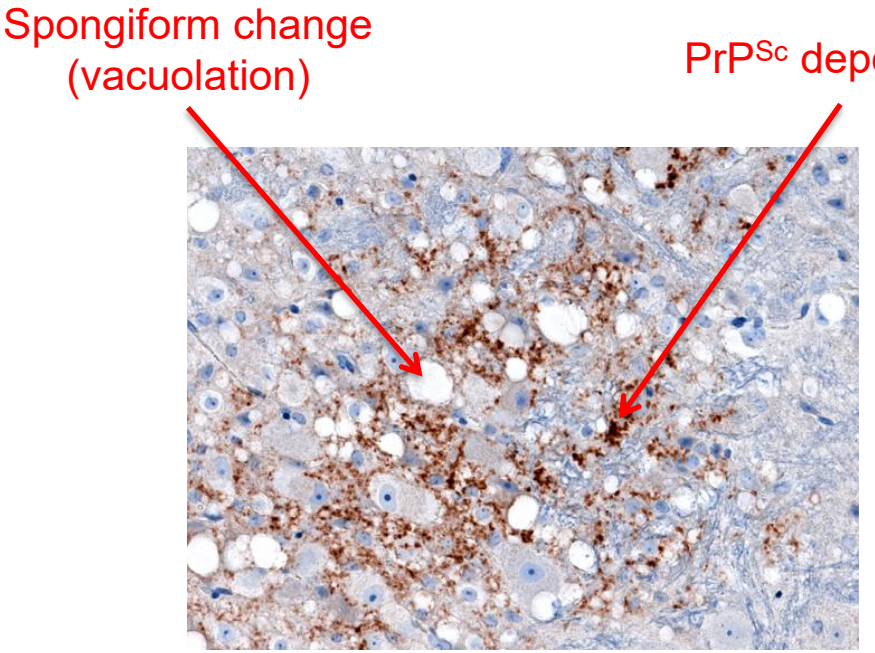
Inoculate hamster prions intracerebrally

Hamsters



Incubation periods

- Mouse prions: ~120-150 days
- Hamster prions: ~70-80 days



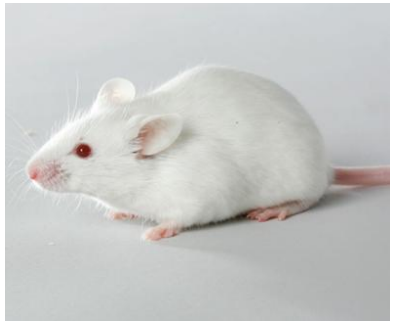
Prion Replication and the Species Barrier

Hamster prions

Human prions

Deer prions

Sheep prions



Mice

Poor Transmission
(Low transmission rates,
long incubation periods)

"Species Barrier"

Prion-resistant species

Horses

Dogs

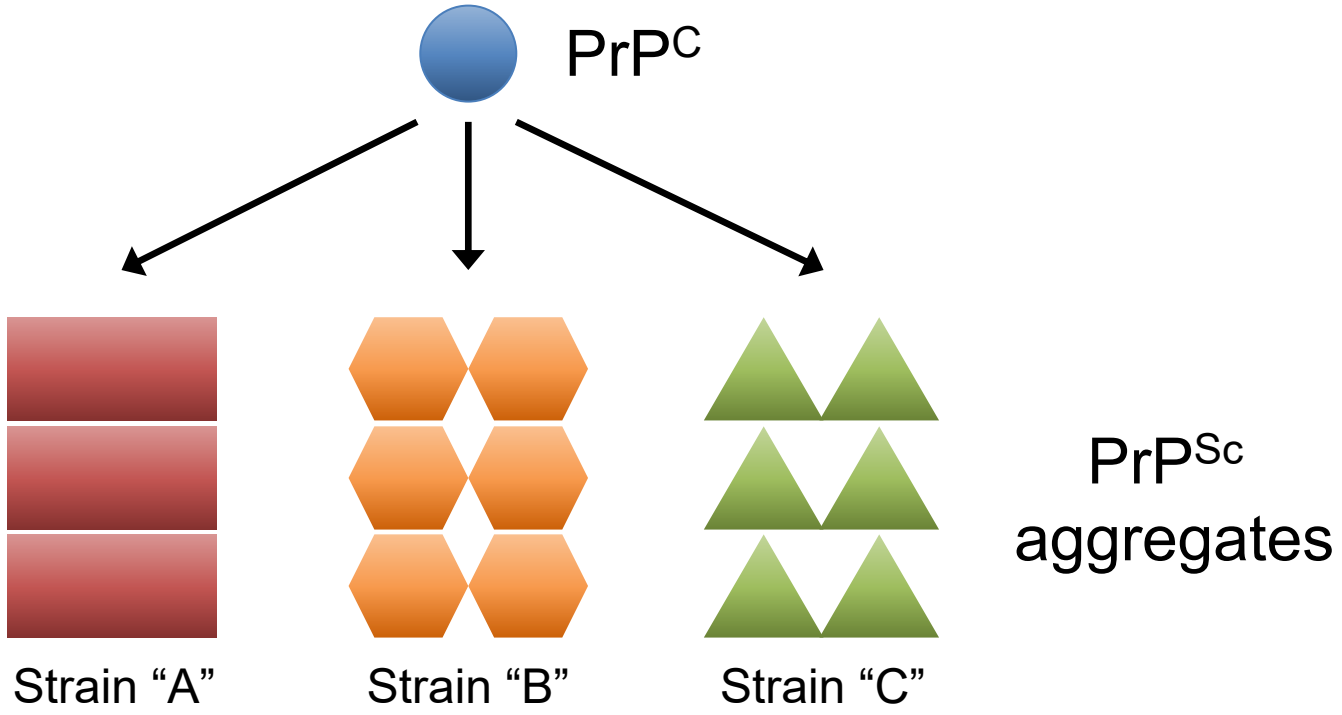
Highly prion-susceptible Species

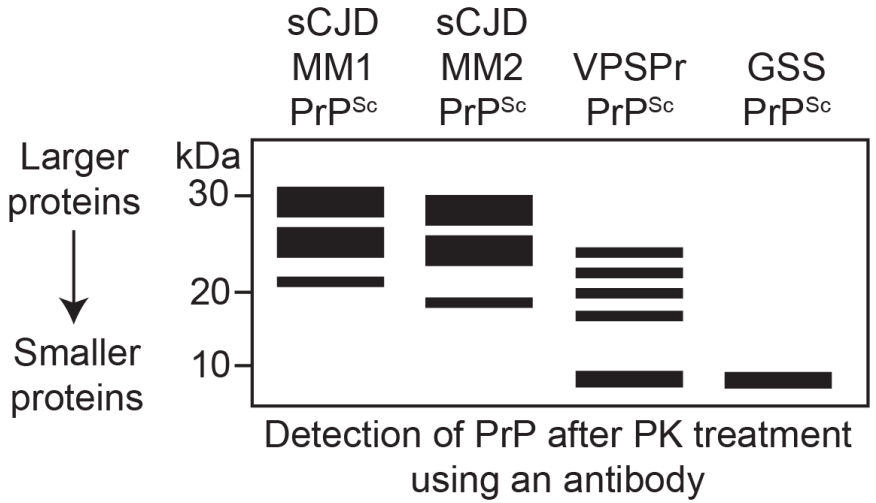
Bank voles

Prion Strains

- Clinical and pathological variability in the prion diseases (both in laboratory animals and humans) can be explained by the existence of distinct “strains” of prions

- Prion strains represent distinct structures of protein aggregates

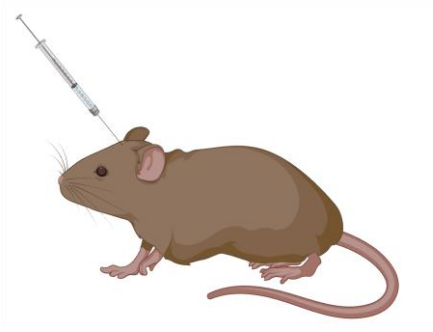




Prion Models:
Infectious vs. Spontaneous Prion Disease

Infectious Prion Disease

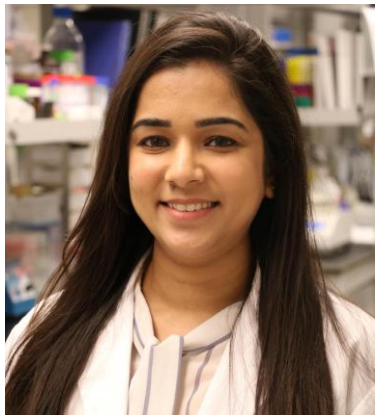
Inoculate with prions



- Prion disease initiated by the injection of pre-formed PrP^{Sc}
- ~99% of prion disease studies in mice
- ~1% of human prion disease cases

Spontaneous Prion Disease

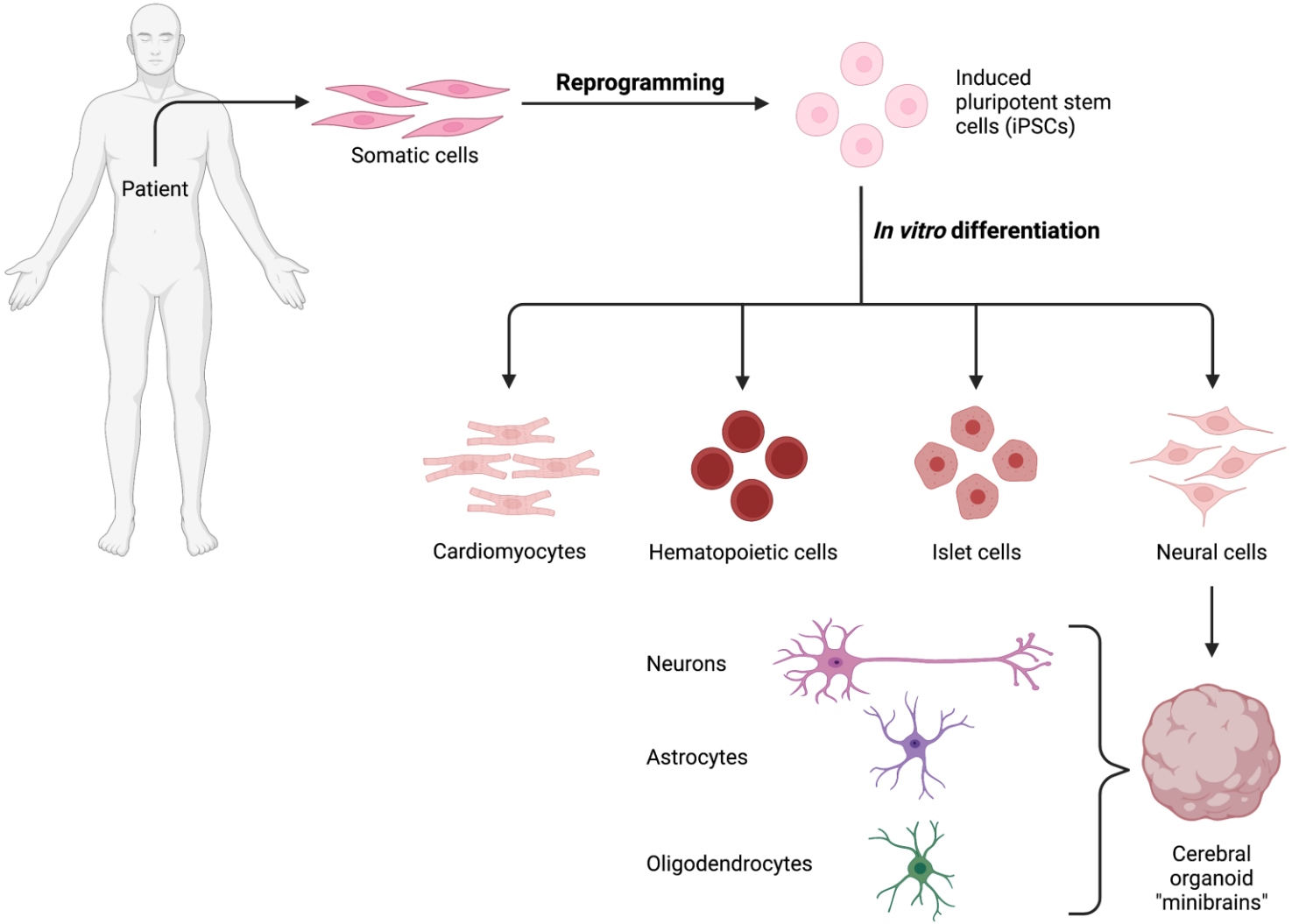
- Prion disease initiated by the spontaneous formation of PrP^{Sc}
- ~1% of prion disease studies in mice
- ~99% of human prion disease cases



Dr. Surabhi Mehra

"Understanding the molecular mechanism of spontaneous prion emergence in knock-in mouse models"

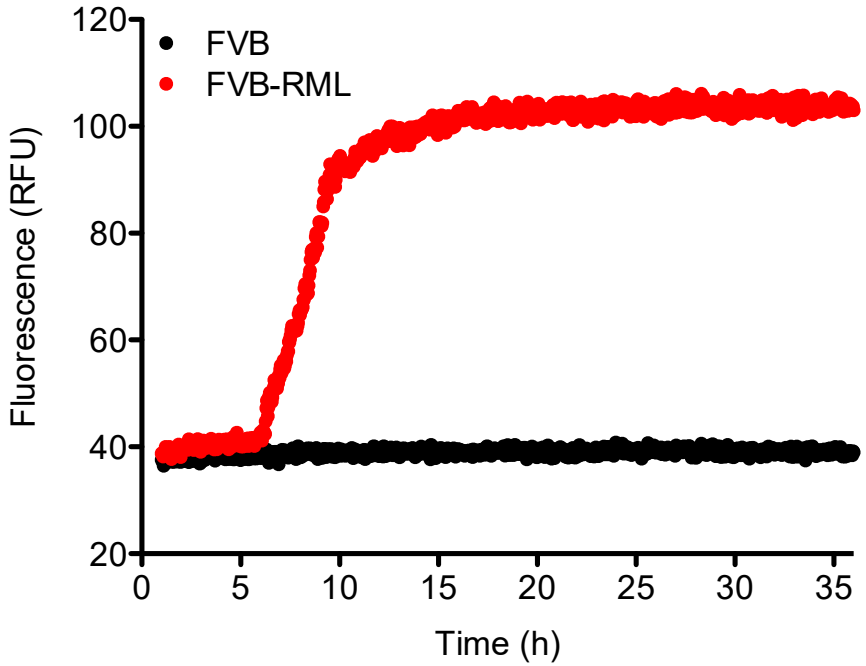
Generation of Cerebral Organoids for Studying Human Prions



Dr. Arielle Hay

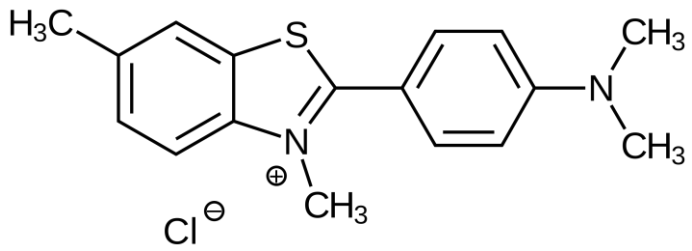
"Generating cerebral organoids from donors with sporadic Creutzfeldt-Jakob Disease"

In Vitro Prion Detection Using RT-QuIC



Prion-infected mouse brain

Healthy mouse brain

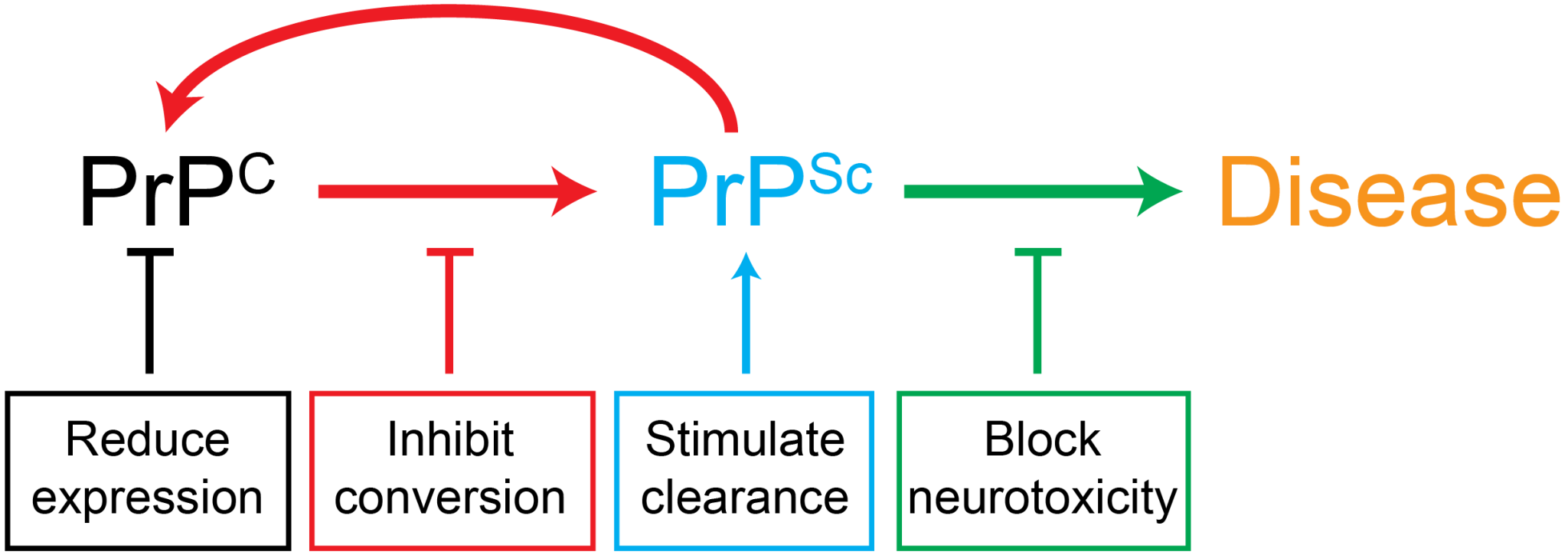


Thioflavin T: Becomes fluorescent when bound to protein aggregates

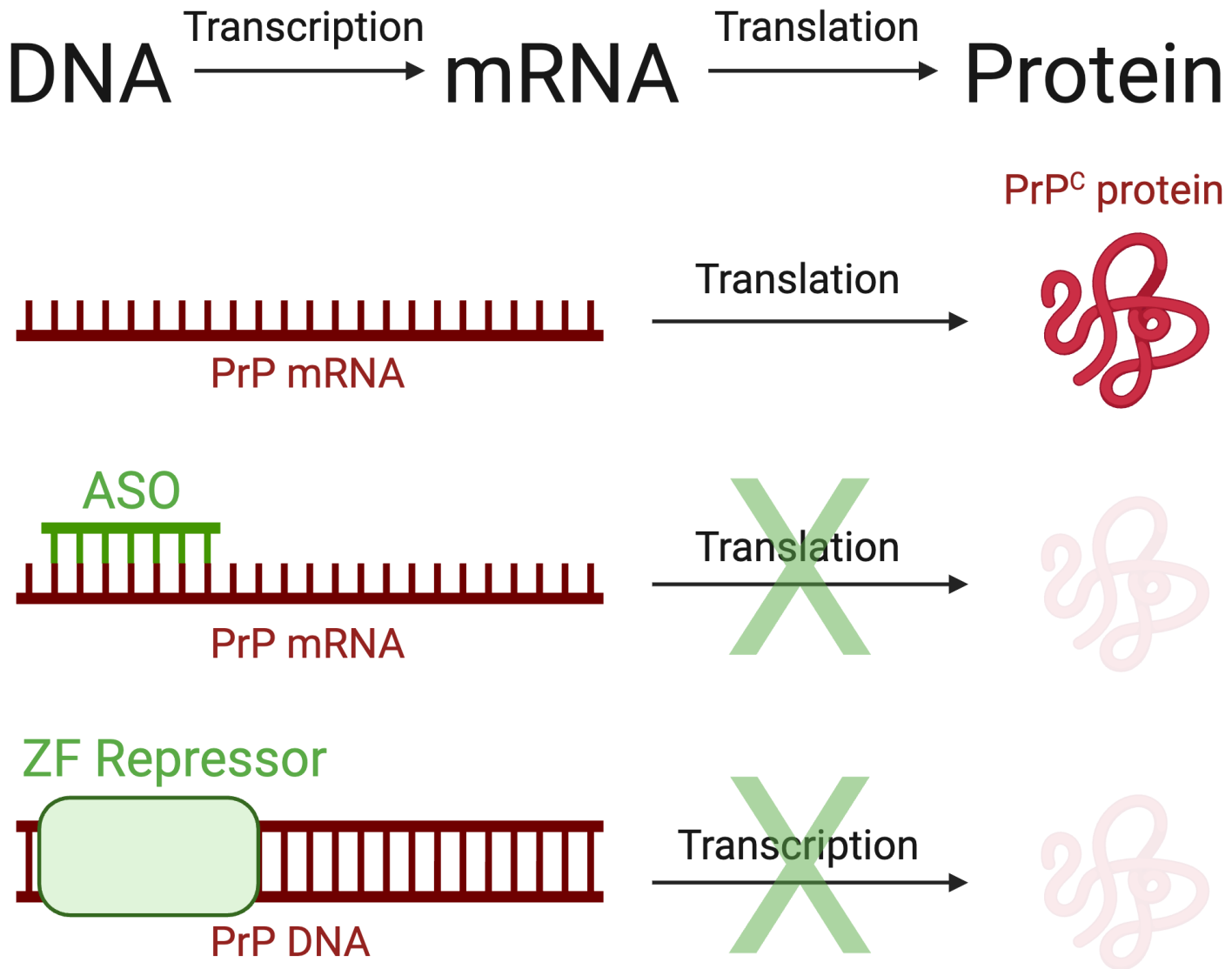
- Addition of PrP^{Sc} to recombinant PrP^{C} and incubation at 37°C with shaking results in the production of PrP aggregates that can be detected using Thioflavin T fluorescence
- RT-QuIC is extremely sensitive: it can detect minute quantities of prions in the CSF, nasal brushings, and skin from sporadic CJD patients

Dr. Matthias Schmitz
"Validation of a non-invasive diagnostic test for prion diseases using tear fluid"

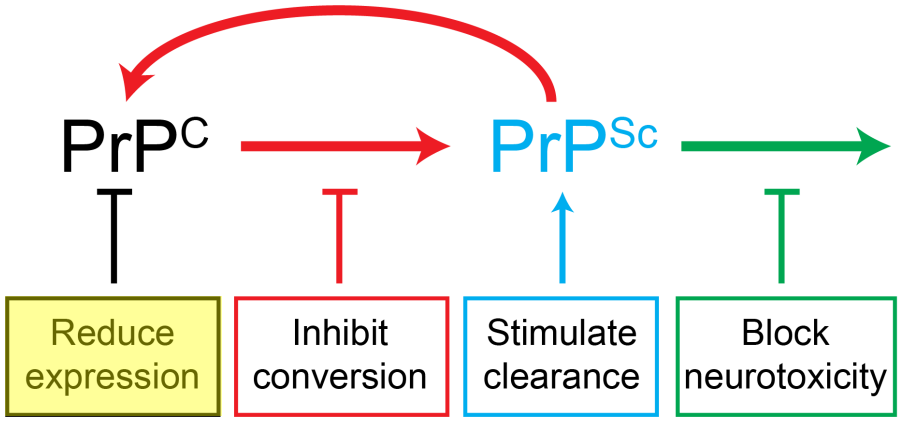
The Search for Prion Disease Therapeutics



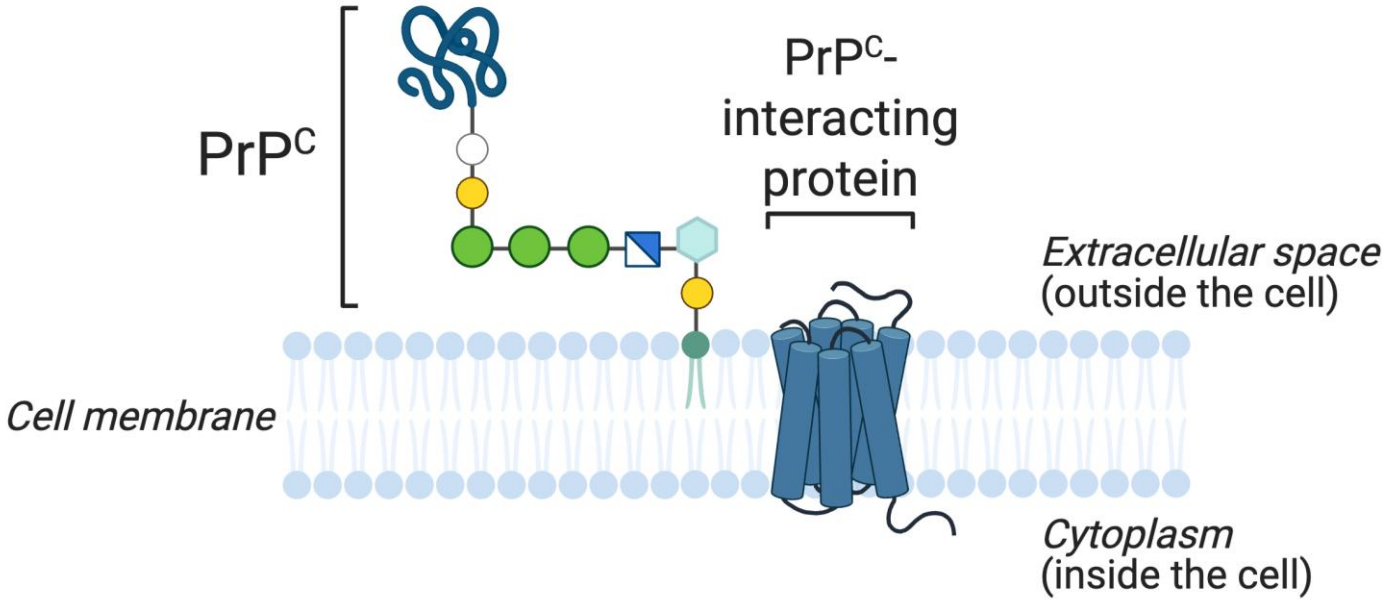
Strategies for Reducing PrP^C Levels



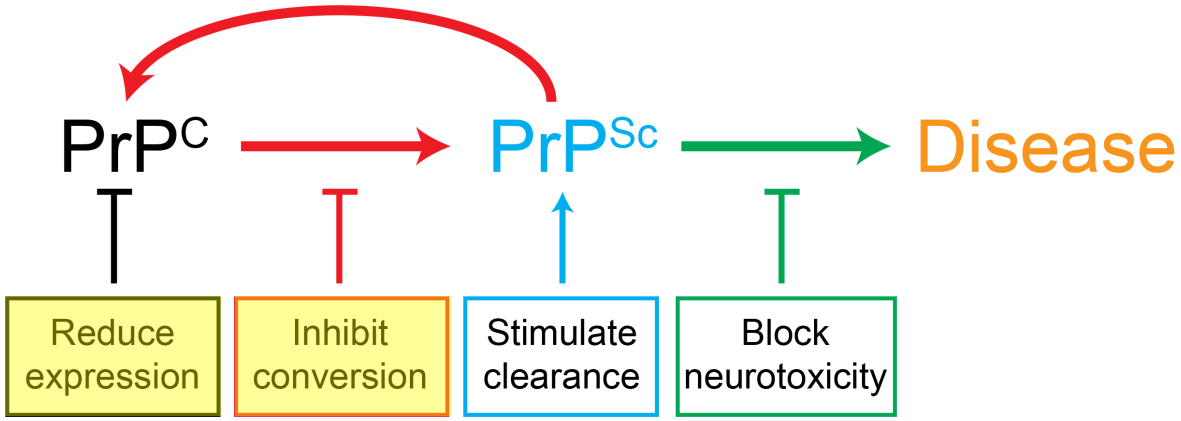
The Search for Prion Disease Therapeutics



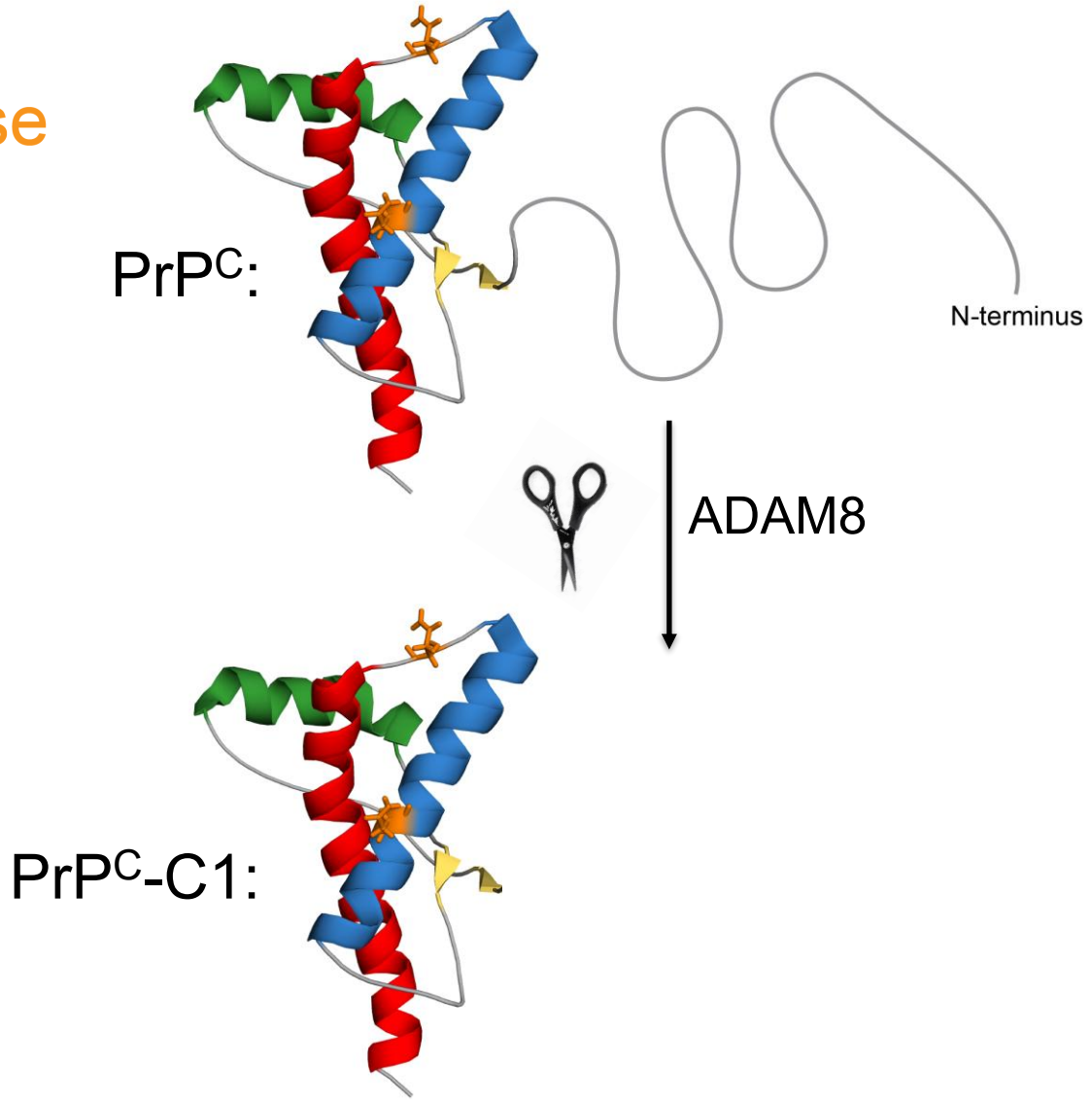
Dr. Gerold Schmitt-Ulms
"Bridging the pre-clinical gap for a small brain-penetrant molecule that reduces PrP^C levels"



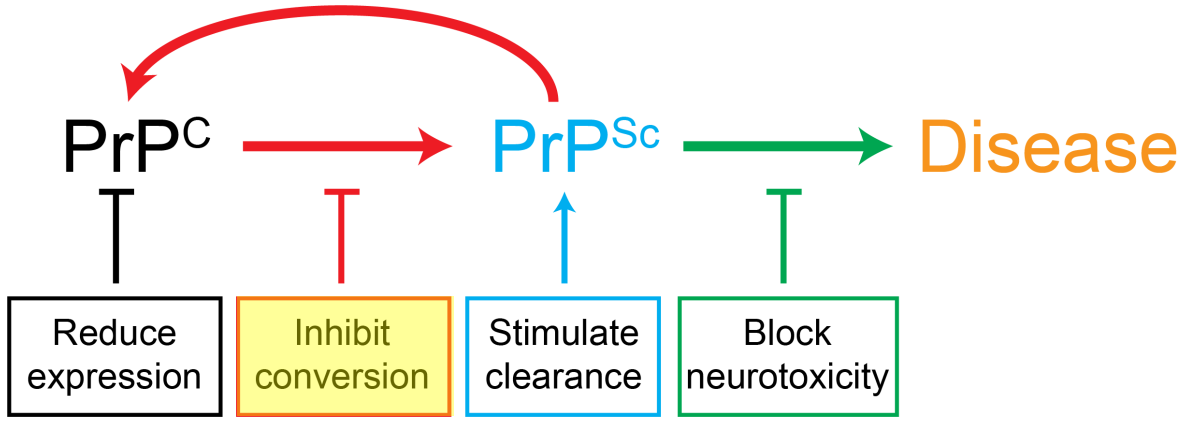
The Search for Prion Disease Therapeutics



Dr. Qingzhong Kong
"Development of ADAM8-based Gene Therapy for CJD"

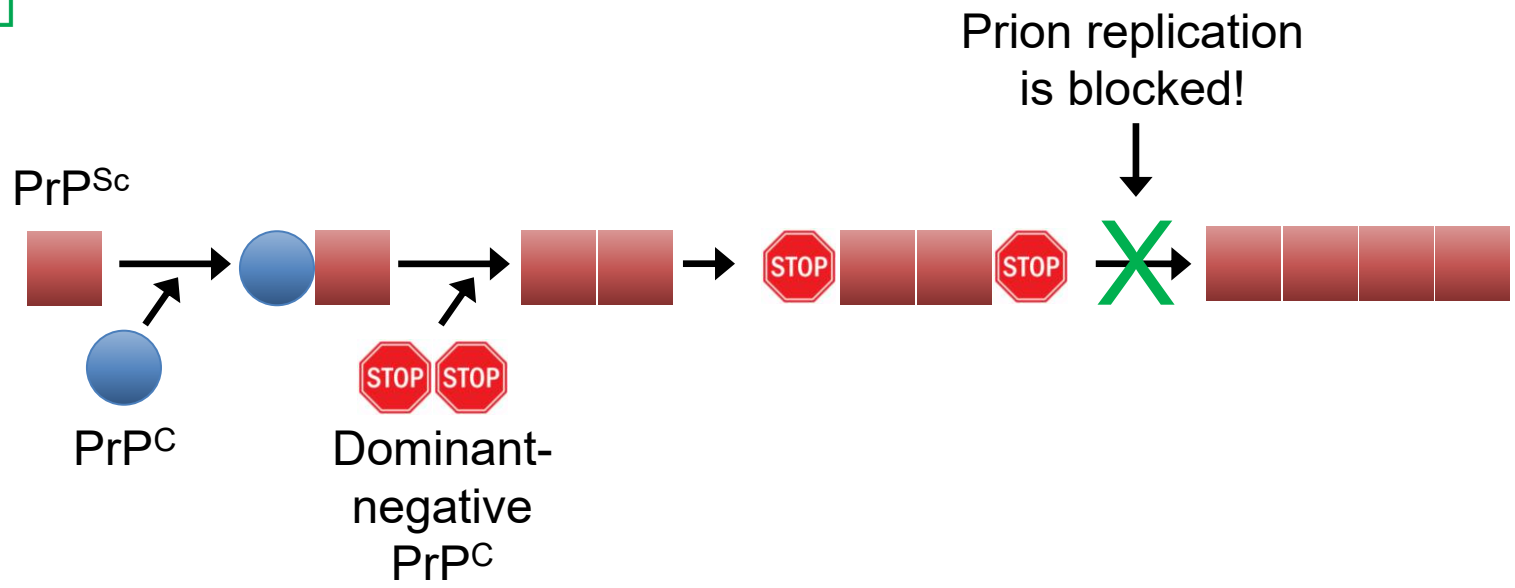


The Search for Prion Disease Therapeutics

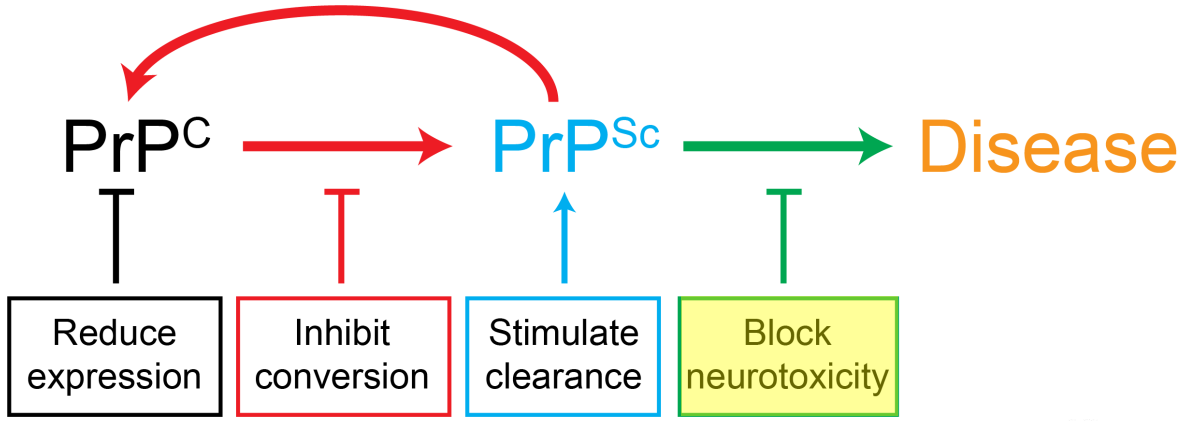


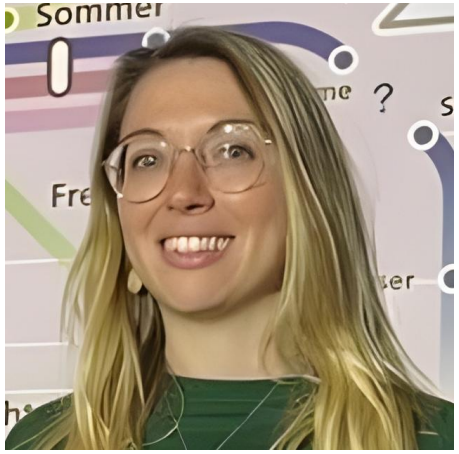
Dr. Joaquin Castilla

"Exploring the efficacy of dominant negative protein-based gene therapy for different prion diseases"



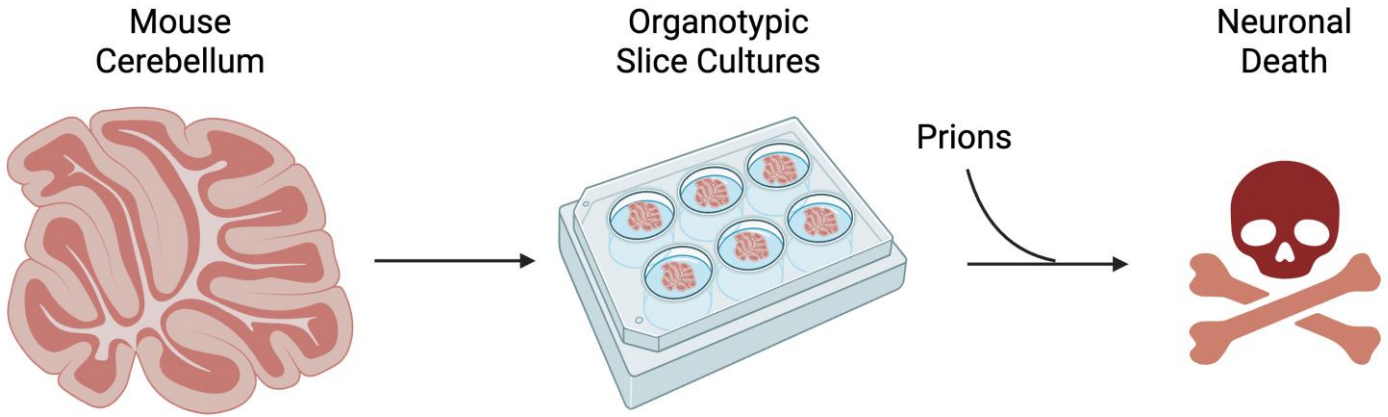
The Search for Prion Disease Therapeutics





Dr. Elena De Cecco

"Investigation of Glycoprotein Nonmetastatic Melanoma protein B (GPNMB) as potential therapeutic target in Prion Diseases"



Propagation of the “Prion Principle”

Examples

- α-Synuclein (Parkinson’s disease)
- Aβ (Alzheimer’s disease)
- Tau (Alzheimer’s disease, frontotemporal dementia, CTE)
- TDP-43 (ALS)

Applications

- SAA/RT-QuIC for Alzheimer’s and Parkinson’s disease
- Animal models for studying the ”prion-like” propagation of protein aggregates
- Protein aggregate strains as an explanation for disease heterogeneity

Fundamental prion disease research can lead to major advances in our ability to understand, diagnose, and treat other human neurodegenerative diseases!

ANY QUESTIONS??