Prion Disease 102:

More Prion Research Basics

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CJD Foundation Family Conference

July 19th, 2024

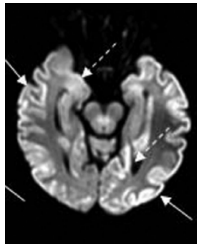
Prion Diseases of Animals and Humans

Animal Prion Diseases

Bovine Spongiform Encephalopathy (BSE) “Mad Cow Disease”

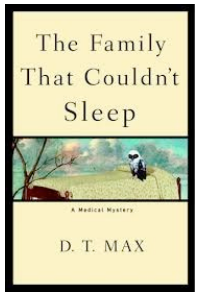
Chronic Wasting Disease (CWD) (deer, elk, and moose)

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

Interesting Properties of Prion Diseases

- Only type of disease that can manifest in three distinct ways:
  - Sporadically (spontaneously): sporadic CJD, VPSPr
  - Genetically: familial CJD, GSS, FFI
  - Via an infectious route: BSE, scrapie, CWD, vCJD, iatrogenic CJD, kuru

- Certain animal prion diseases can be transmitted naturally from animal to animal
  - CWD
  - Scrapie

- Prions are very ”sticky” and notoriously hard to inactivate/destroy

Dr. Jason Bartz
“Detection of residual prions from decontaminated medical and laboratory surfaces”

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
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Prion Protein (PrP) Sequence

```
MANLGCWMLVLFVATWSDLGLCKKRPKPGGWNTGGSRYPGQGSPGGNRYPPQGGGGWGQP
HGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQGGGTHSQWNKPSKPKTNMKHMAGAAAAGA
VVGGLGGYMLGSAMSRPIIHFGSDYEDRYYRENMHRYPNQVYYRPMDEYSNQNNFVHDCV
NITIKQHTVTTTTKGENFTETDVKMMERVVEQMCITQYERESQAYYQRGSSMVLFSSPPV
ILLISFLIFLIVG
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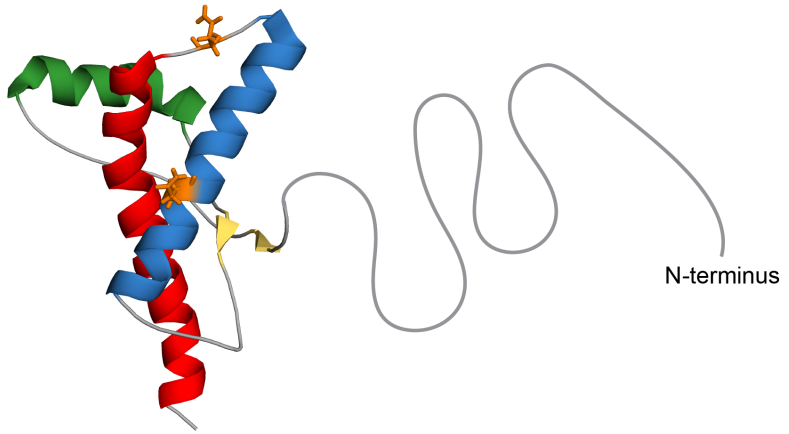
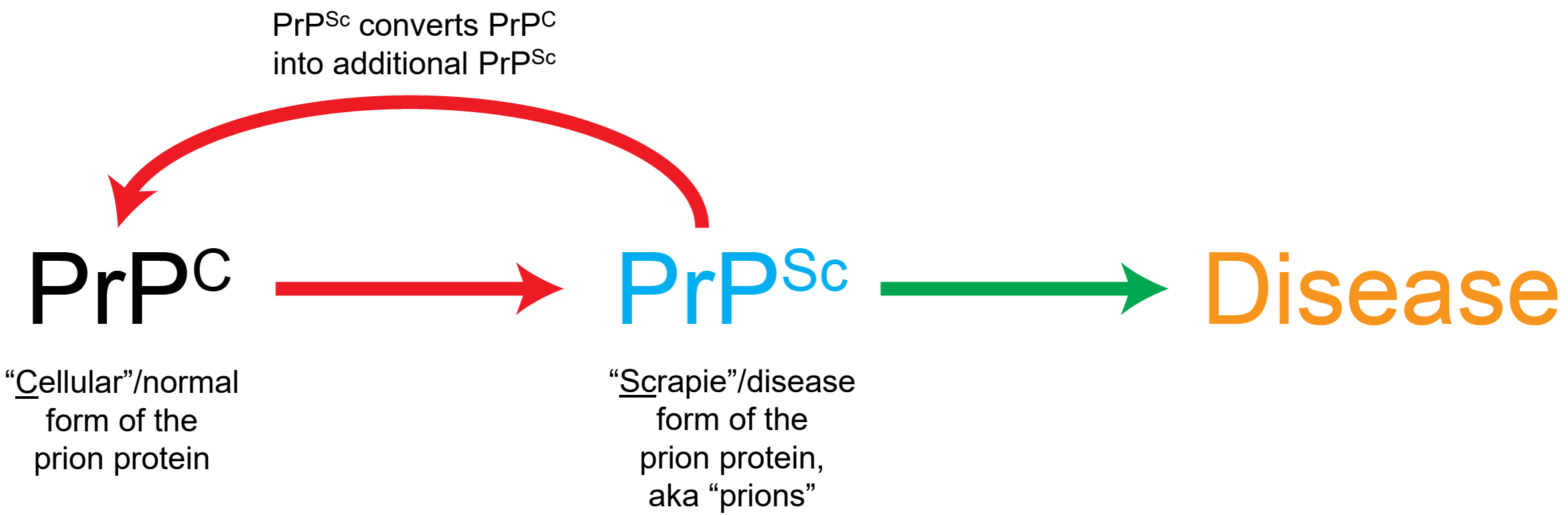
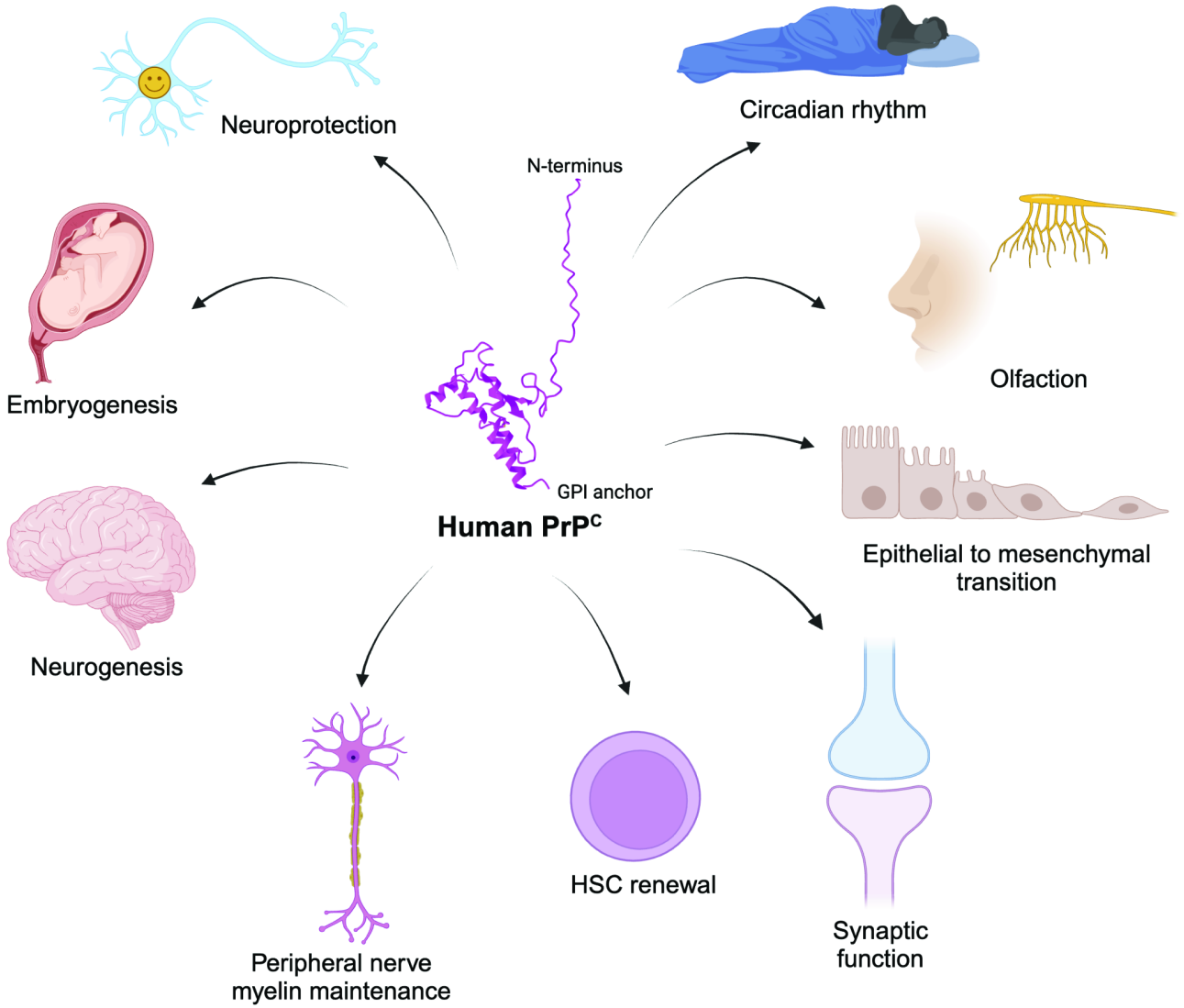


Prion Disease in a Nutshell



What is the Function of PrP^C?



Dr. Victoria Lawson

"Risk of cancer from reduced expression of PrP^C: implications for prion disease treatment"

What is a Prion?

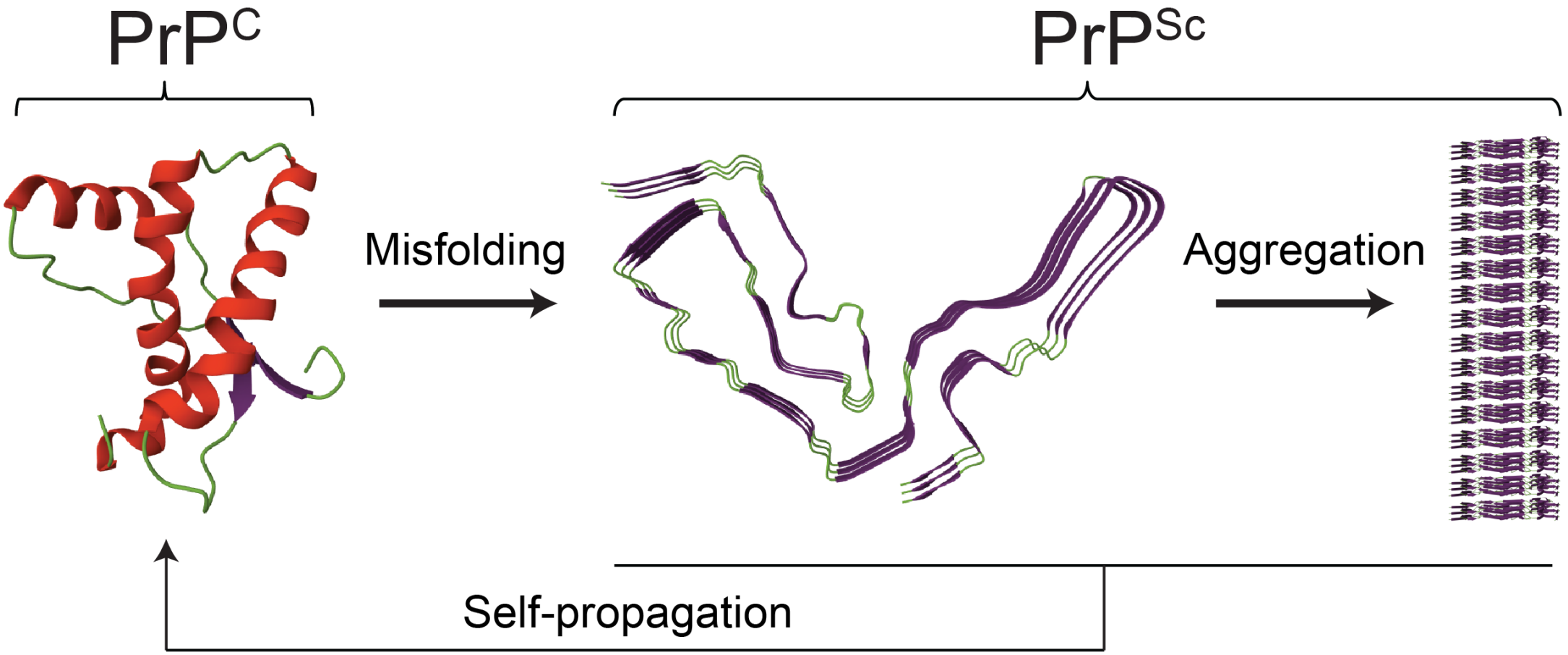
PrP^{C}

Normal protein movements

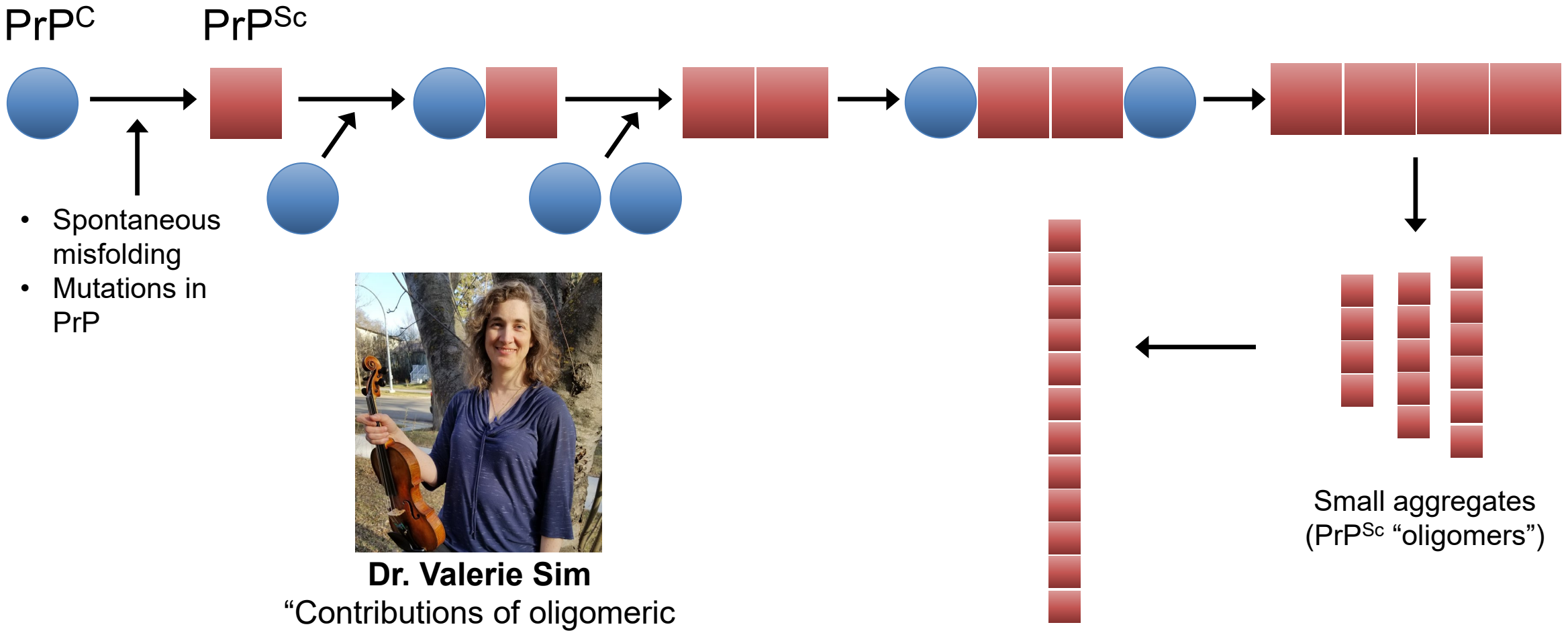
PrP^{Sc}

Conversion into a dangerous shape

Prion Replication and Propagation



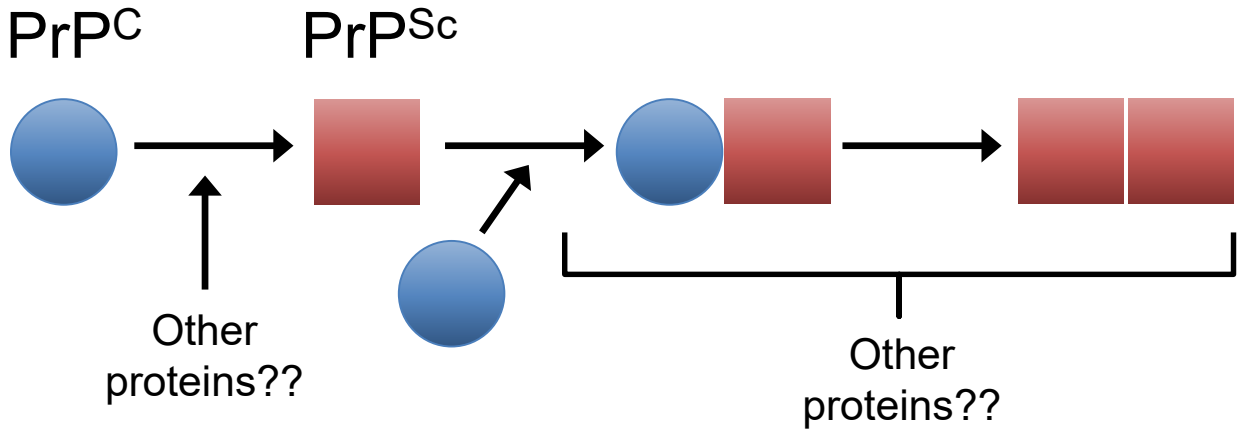
Prion Replication and Propagation



Dr. Valerie Sim

"Contributions of oligomeric prion populations to phenotypic variability in VPSPr versus silent prions"

Is PrP a “Lone Wolf” in Prion Disease



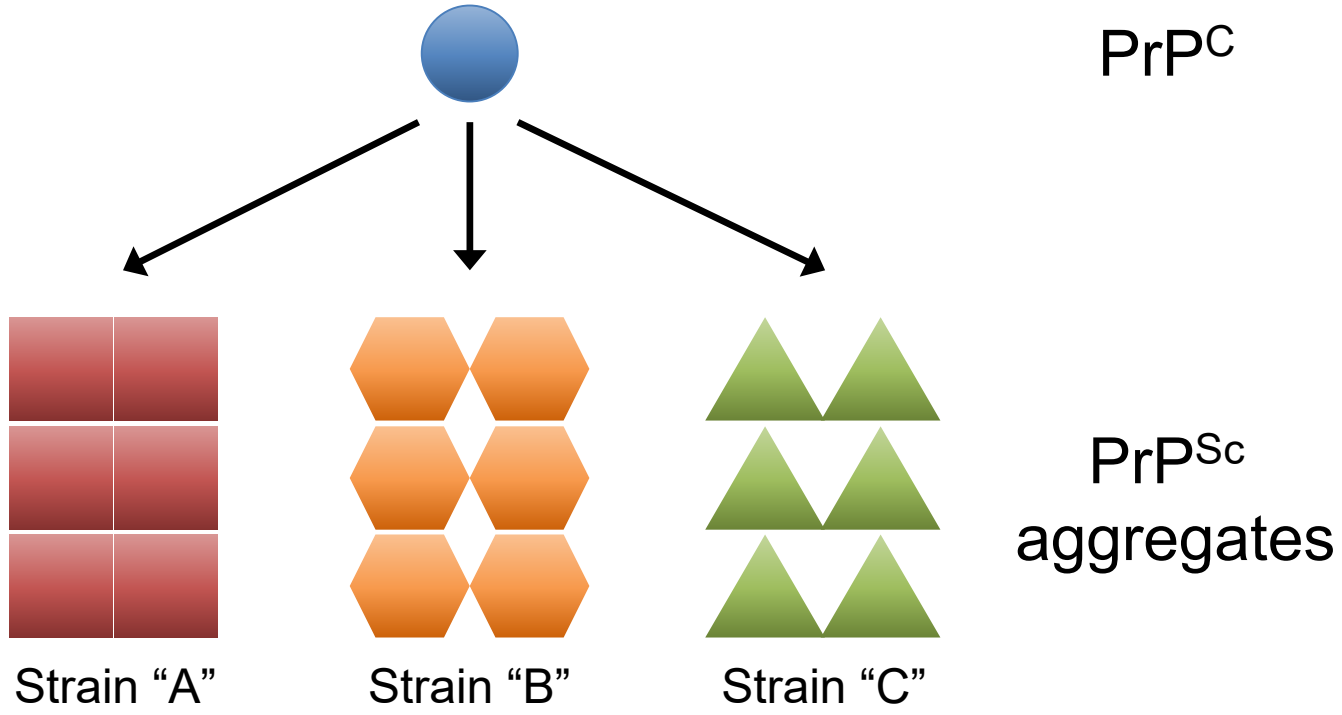
Dr. Robert Mercer
“Identification of PrP^Sc interaction partners and characterization of their role in prion propagation”

Dr. Thomas Cunningham
“Generation of humanized STX6 overexpression mice to study prion disease genetic risk”

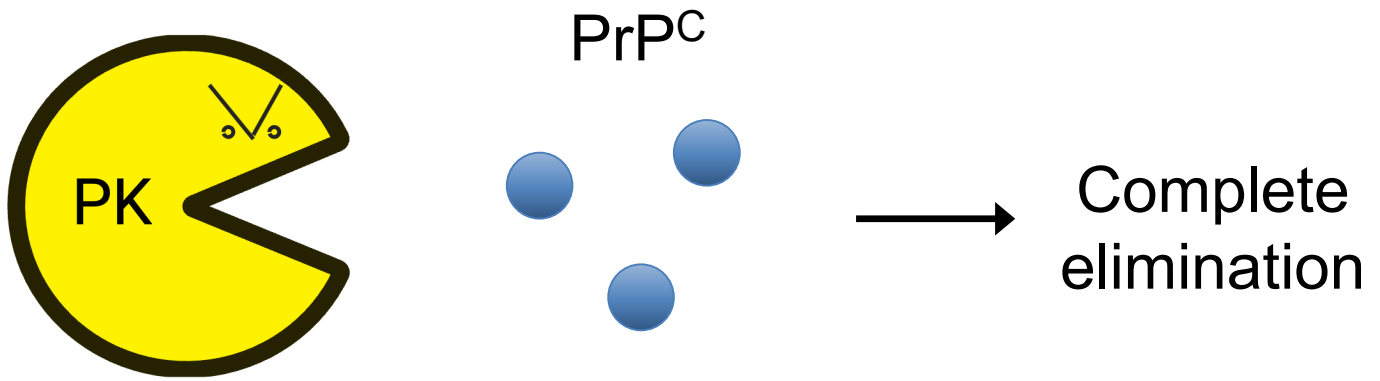
Prion Strains

- 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

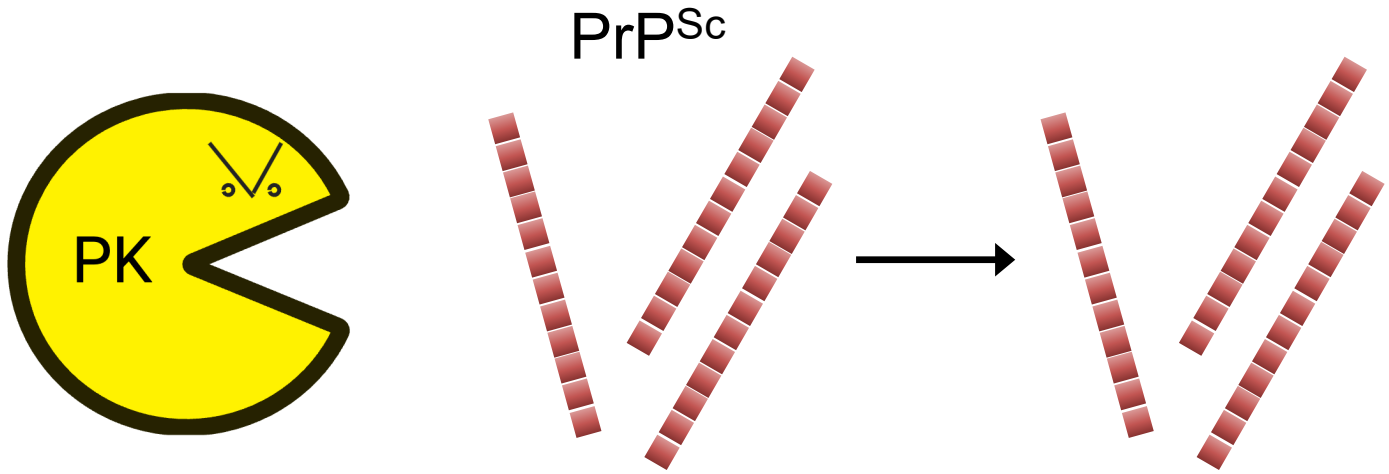
- Prion strains represent distinct structures of protein aggregates



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

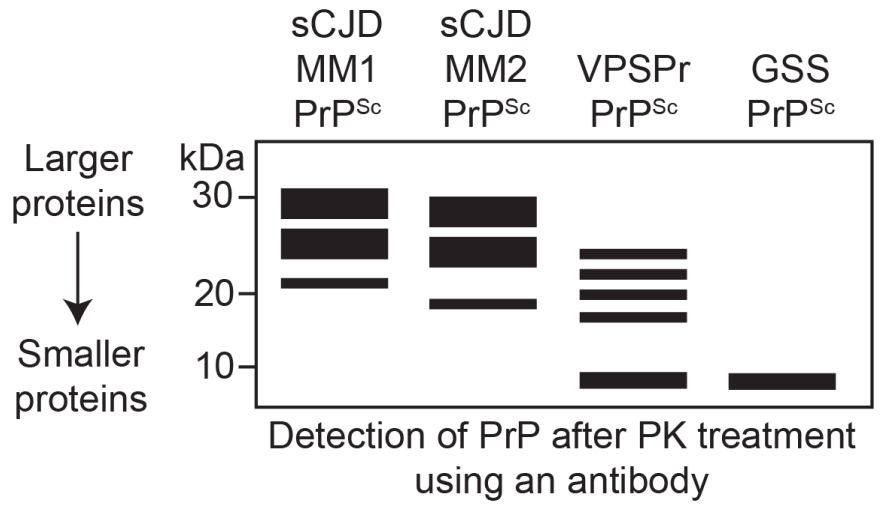


PK = Proteinase K



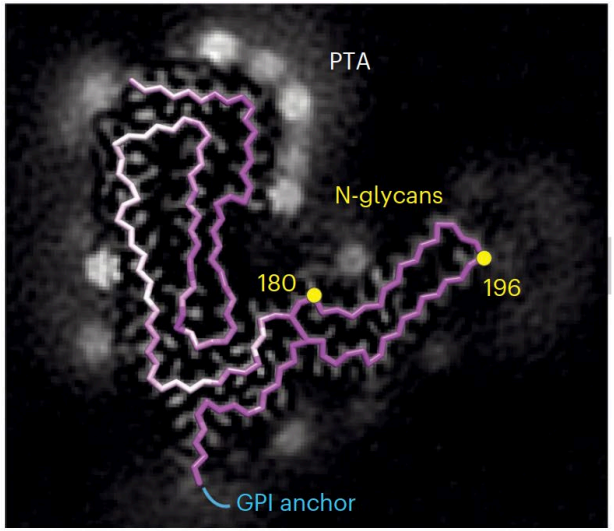
PrP^{Sc} is resistant to degradation by PK!

Delineation of Prion Strains

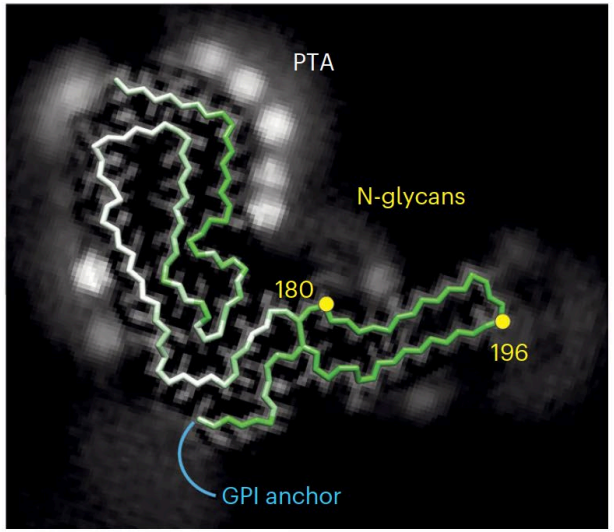


Detection of PrP after PK treatment using an antibody

ME7 mouse prion strain



RML mouse prion strain



Manka *et al.*, *Nature Chemical Biology*, 2023

Dr. Qiuye Li

"High-resolution structural determination of MM1 and MM2 sCJD prions"

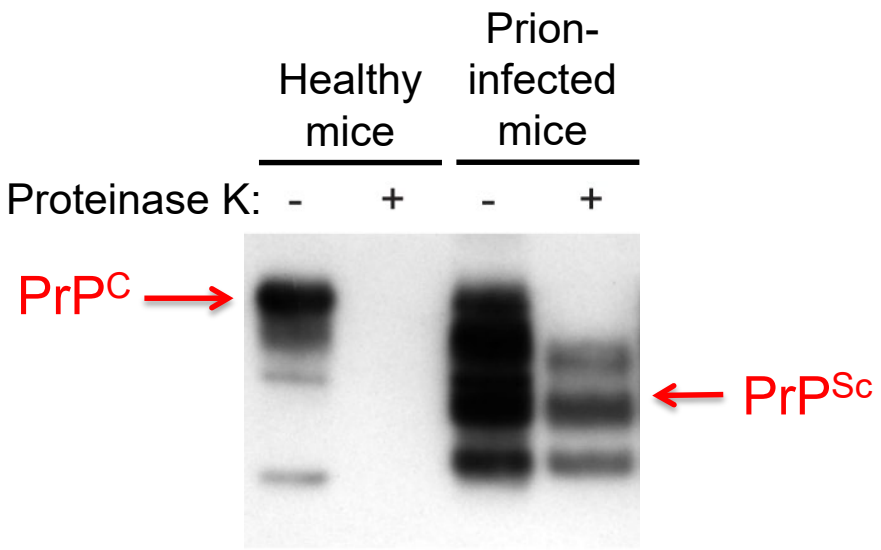
Prions Are Infectious Proteins

Inoculate mouse prions intracerebrally

Mice

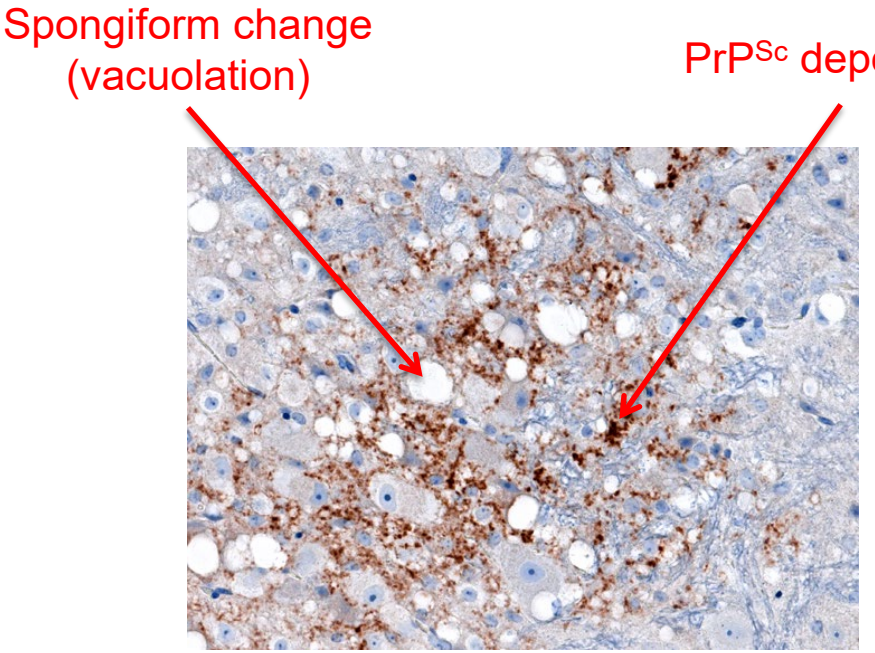
Inoculate hamster prions intracerebrally

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

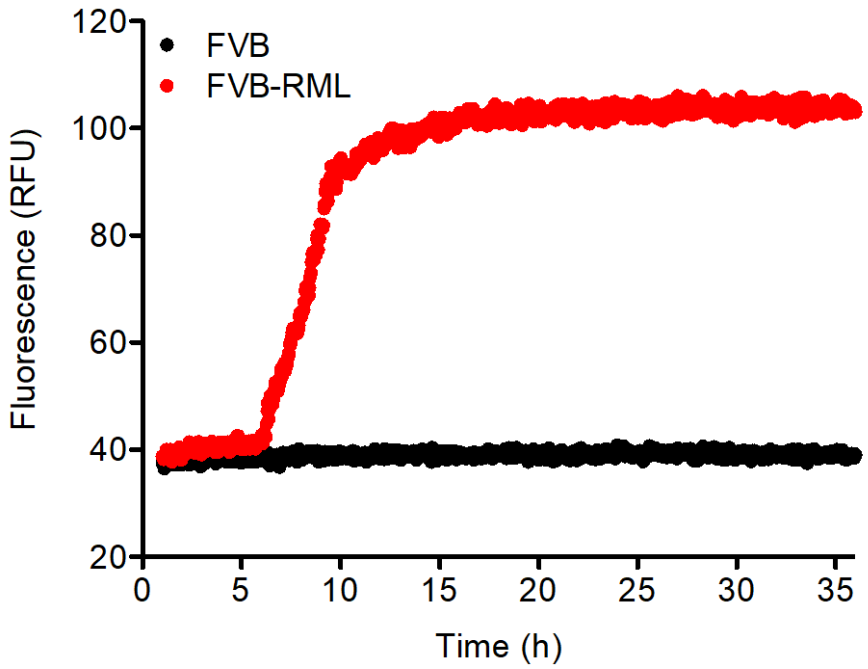
Horses

Dogs

Highly prion-susceptible Species

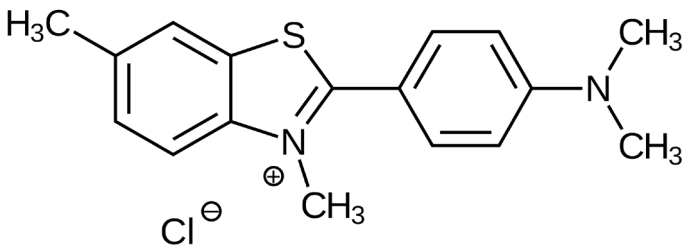
Bank voles

In Vitro Prion Detection Using RT-QuIC



Prion-infected mouse brain

Healthy mouse brain



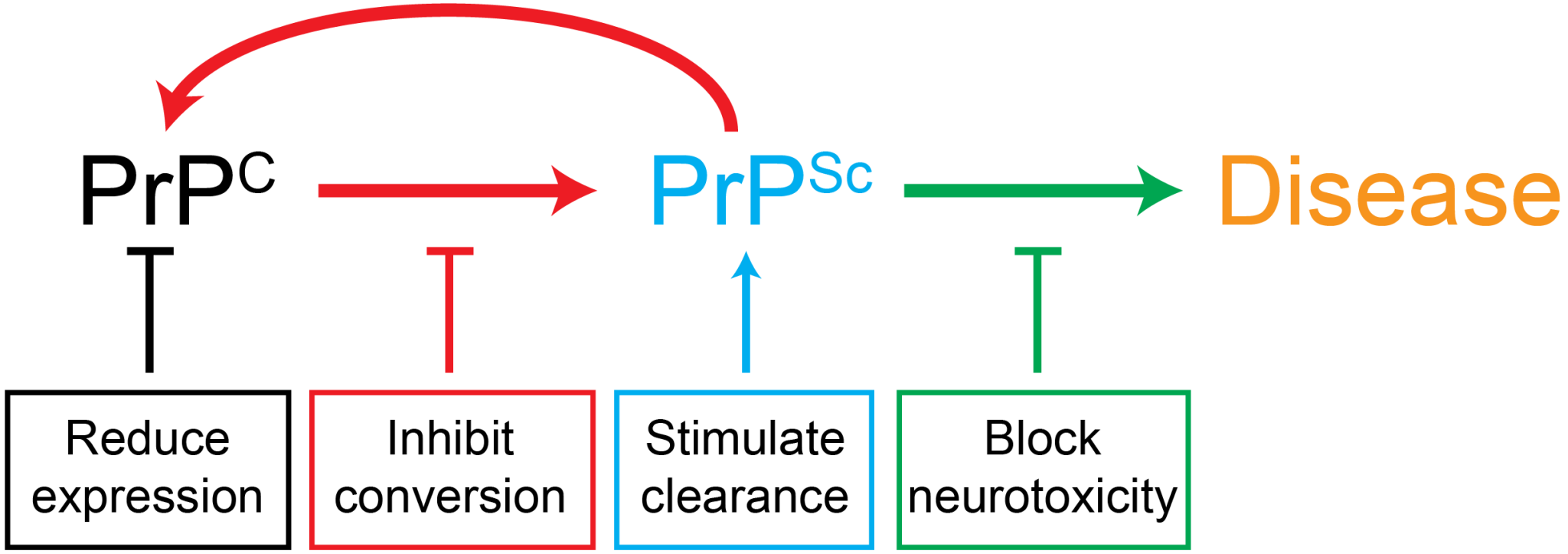
Thioflavin T: Becomes fluorescent when bound to protein aggregates

- 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

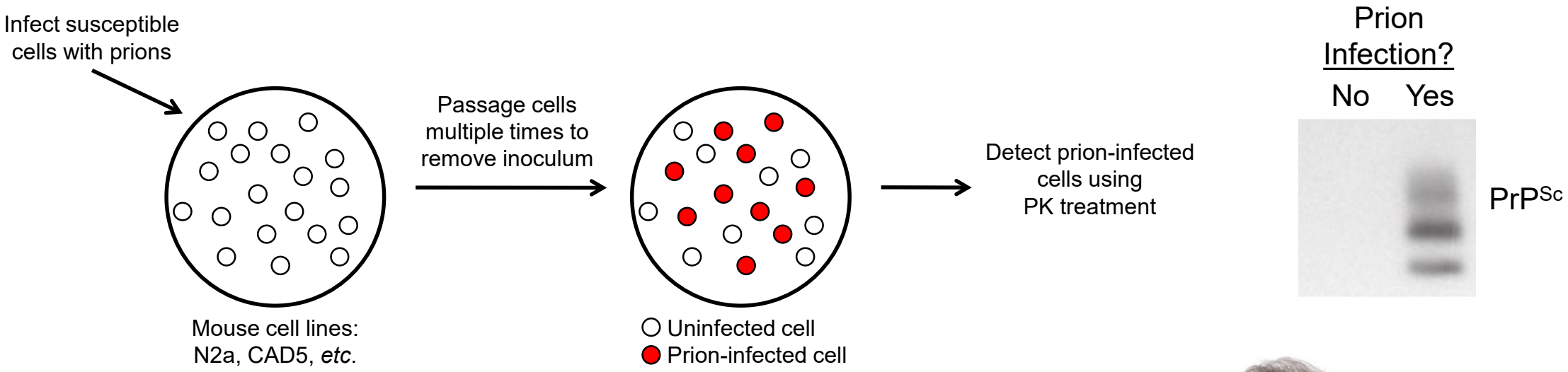
- RT-QuIC is extremely sensitive: it can detect minute quantities of prions in the CSF, nasal brushings, and skin from sporadic CJD patients

Dr. Sarah Vascellari
"Development of blood and urine diagnostic tests for human prion diseases using RT-QuIC"

The Search for Prion Disease Therapeutics



Replication of Prions in Cultured Cells



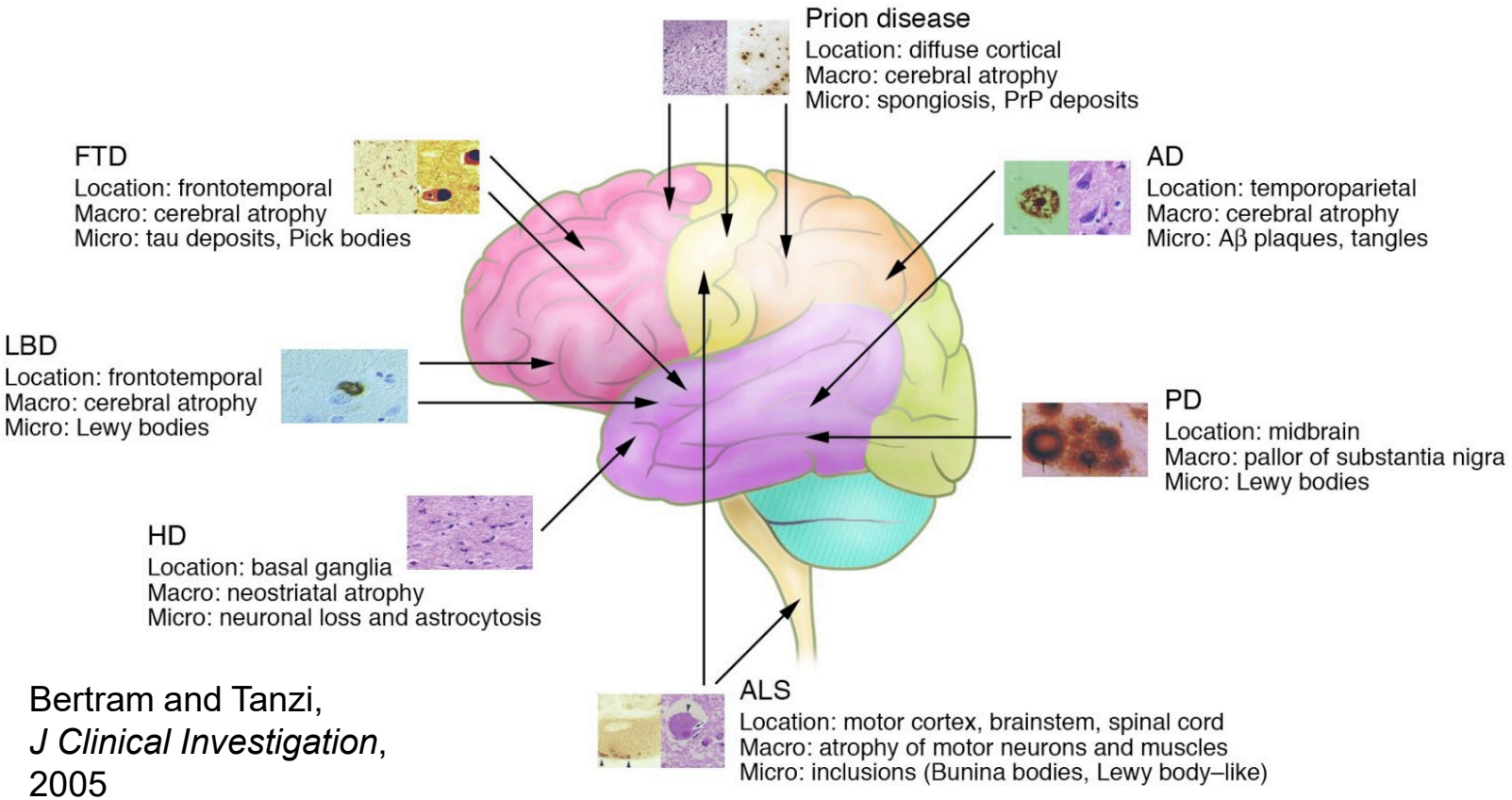
- Prion-infected cells are very useful for:
  - Studying the biology of PrP^{Sc}
  - Identifying anti-prion drugs

- Unfortunately, only a very limited number of prion strains (mostly mouse strains) can be replicated in cultured cells

Dr. Parmjit Jat

"Elucidating the factors required for propagating human CJD prions"

Neurodegenerative Diseases



Bertram and Tanzi,
J Clinical Investigation,
2005

- Common themes in neurodegenerative diseases:
  - Loss of neurons in the brain or peripheral nervous system
  - Protein misfolding and aggregation
  - Protein co-pathologies

Dr. Ignazio Cali
"Detection of abnormal prion protein in patients with non-prion disease dementia"

Propagation of the “Prion Principle”

Examples

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

Applications

- RT-QuIC tests 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??