# UNDERSTANDING THE MOLECULAR MECHANISM OF SPONTANEOUS PRION EMERGENCE IN KNOCK-IN MOUSE MODELS

Surabhi Mehra, PhD

Postdoctoral Fellow, Watts Lab

Tanz CRND, University of Toronto, CA

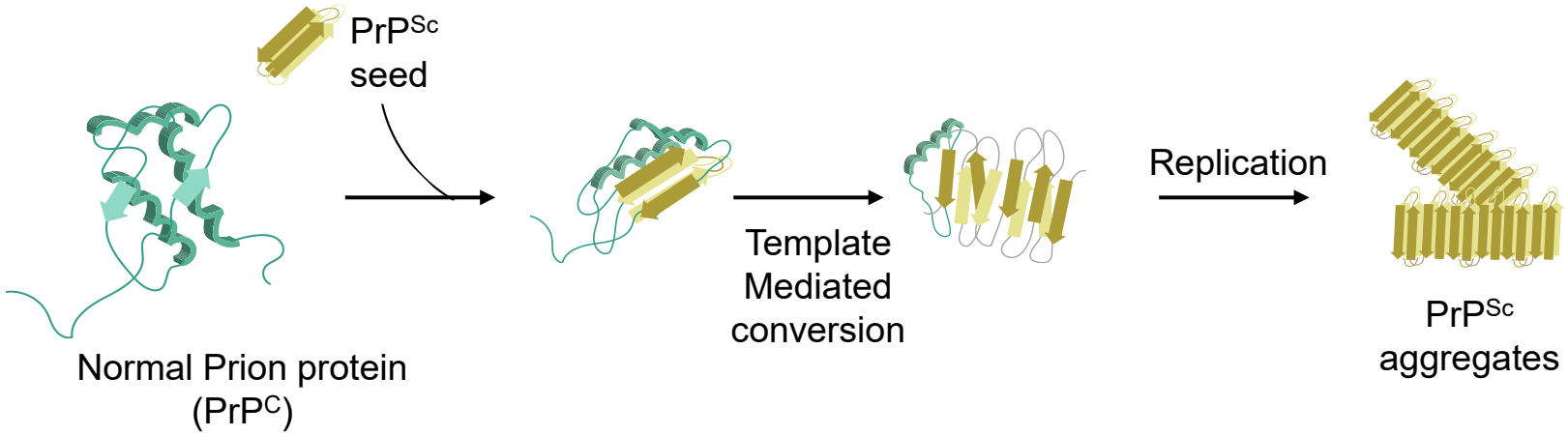
CREUTZFELDT-JAKOB DISEASE FOUNDATION, INC.

*Supporting Families Affected by Prion Disease*

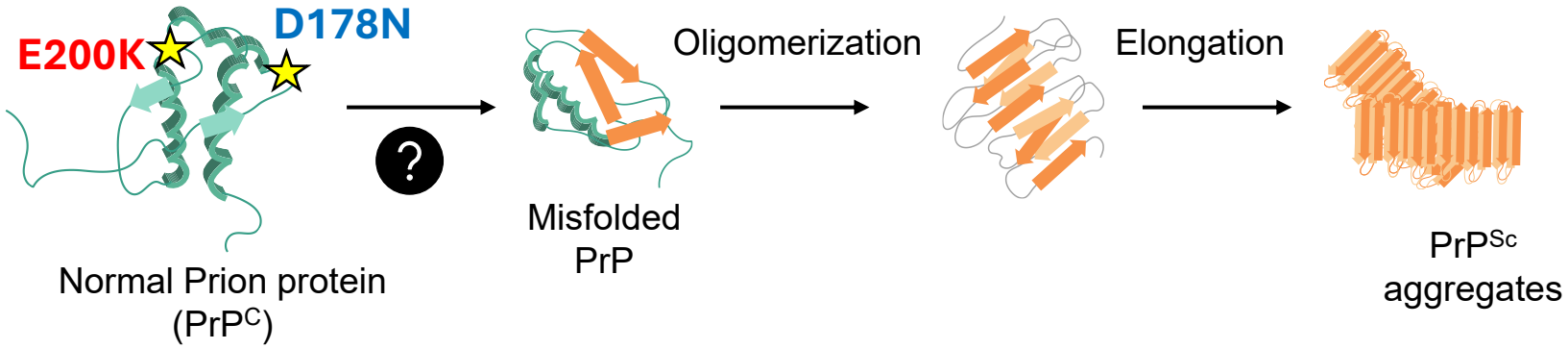
# *Prion diseases: rarely infectious, mostly spontaneous*

Prion disease are rare, fatal and incurable brain disorders caused by
PRIONS-**P**rotease **R**esistant **I**nfectious **O**rgan-specific **N**eurotoxic **S**elf-replicating proteins

**Classical Model**
(*Based on infection with pre-formed prions*
*<1% of human cases*
*e.g., Kuru*)




**Spontaneous onset**
*(Most human cases*
*>99 %*
*e.g., sCJD, fCJD, FFI)*




*How prion disease begins without infection*, and how we can model and ultimately intervene in this process early?

# *Knocking in bank vole PrP: unlocking spontaneous prion disease*

Human, mouse, hamster, elk, sheep, deer prions

Wild-type/ transgenic Bank-voles

Sick

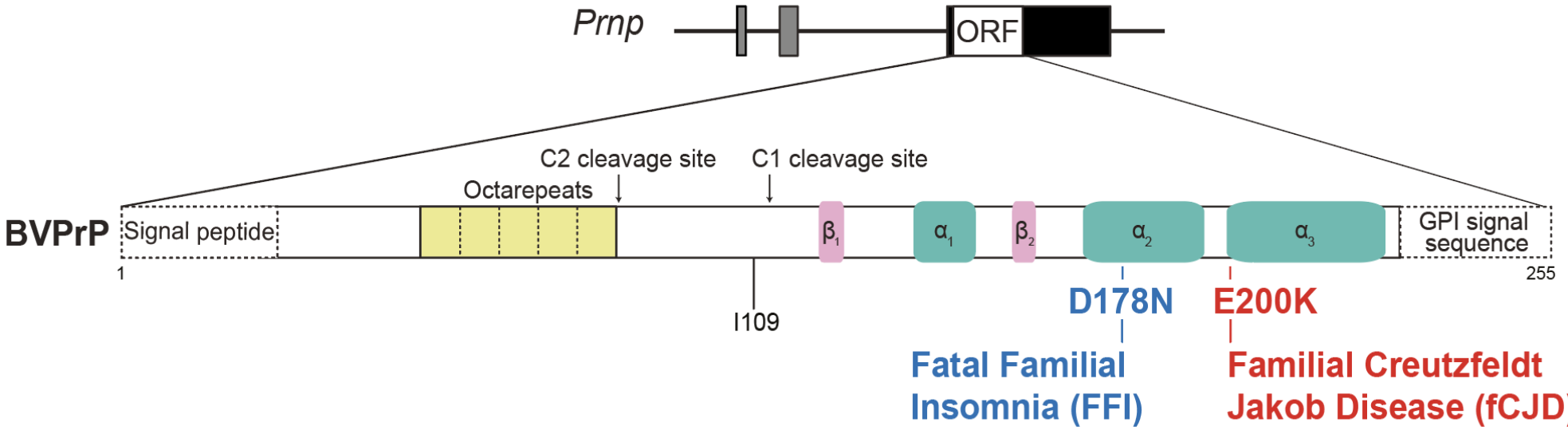
**‘No Species Barrier”**

**“High susceptibility to diverse prion types”**

---

kiBVI$^{WT}$
kiBVI$^{E200K}$
kiBVI$^{D178N}$

Knockin mouse models






In collaboration with Walker Jackson

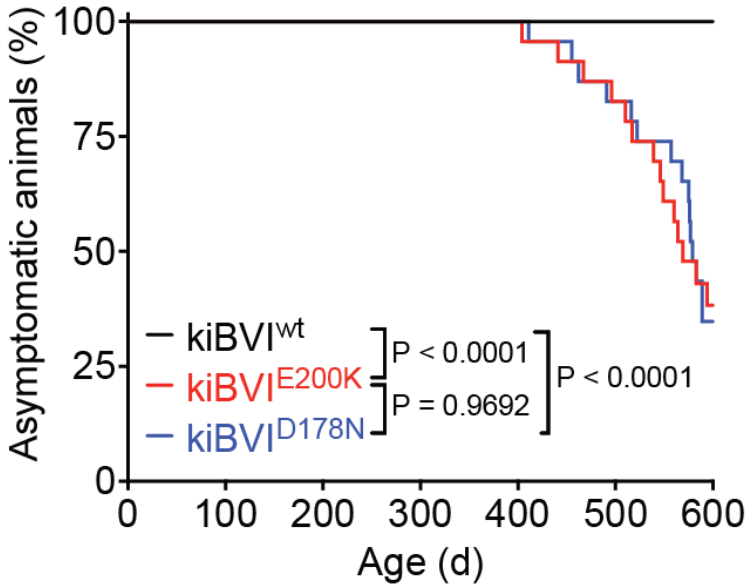
# *Knockin bank vole PrP mice develop spontaneous prion disease*

Mutant bank vole PrP knock-in mice (E200K or D178N)

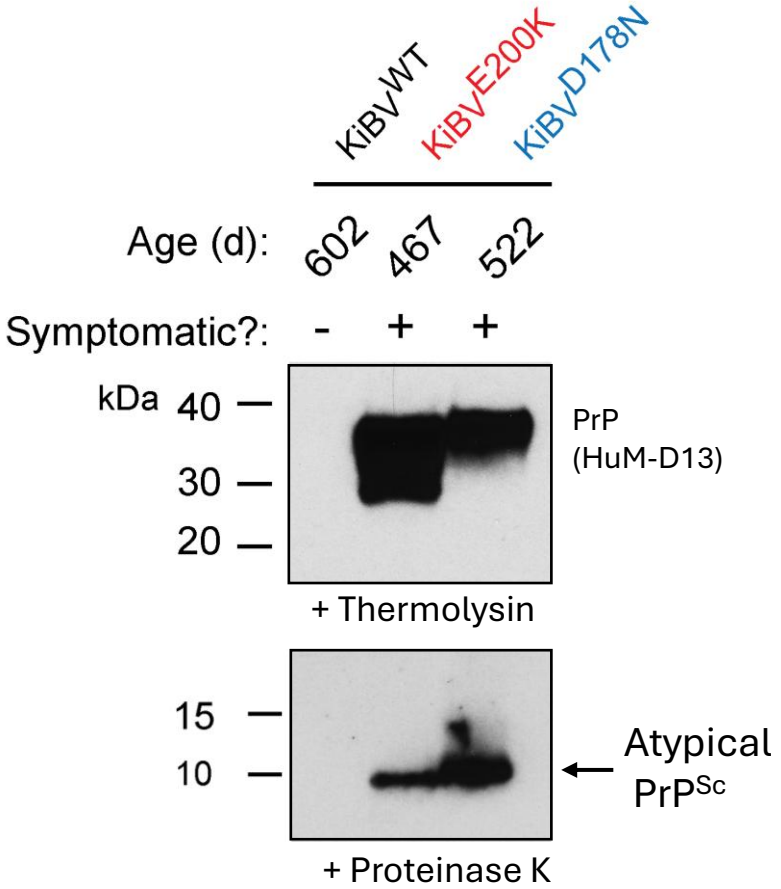
~400-500 days

Neurological illness

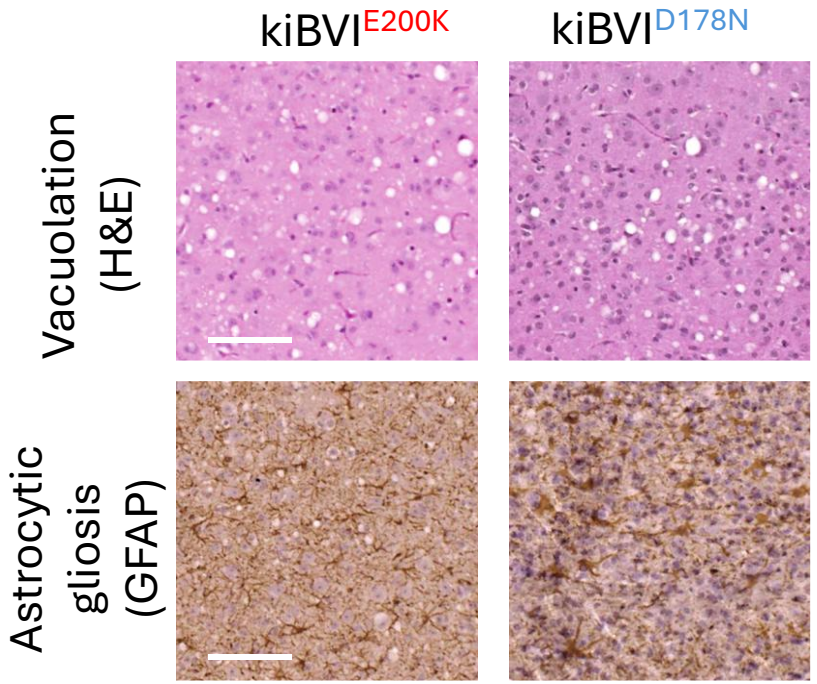
**Symptoms** : Kyphosis, tremor, Bradykinesia, weight loss, ataxia, limb abnormalities, dermatitis




Spontaneously Sick




Atypical prions




Prion disease pathology



Mehra et al., *Journal of Clinical Investigation*, 2024

# *Generation of heterozygous knock-in mice*

**knockin mice**

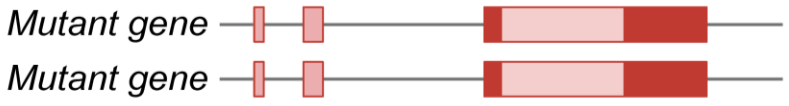
Homozygous

**Human**

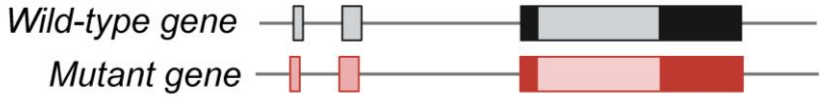
~ 99 % cases- Heterozygous

**knockin mice-Hets**

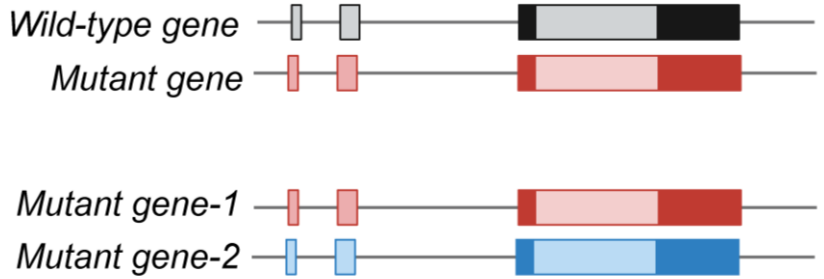
Heterozygous




Prion disease




fCJD, FFI




Mehra et al., *JCI*, 2024

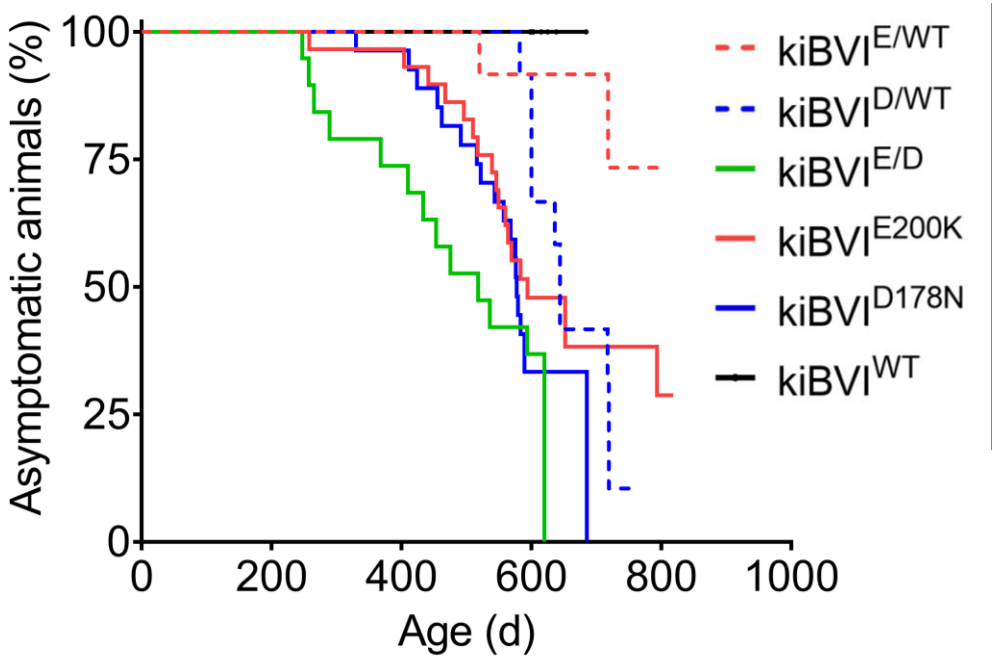
# *Impact of gene dosage on disease progression and prion accumulation*

**knockin mice-Hets**

kiBVI$^{E200K/WT}$

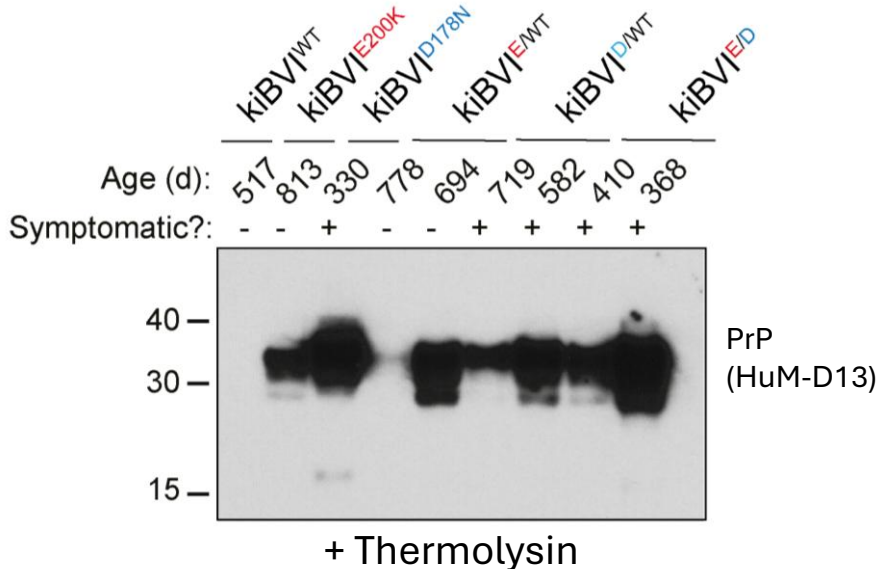
kiBVI$^{D178N/WT}$

kiBVI$^{E200K/D178N}$

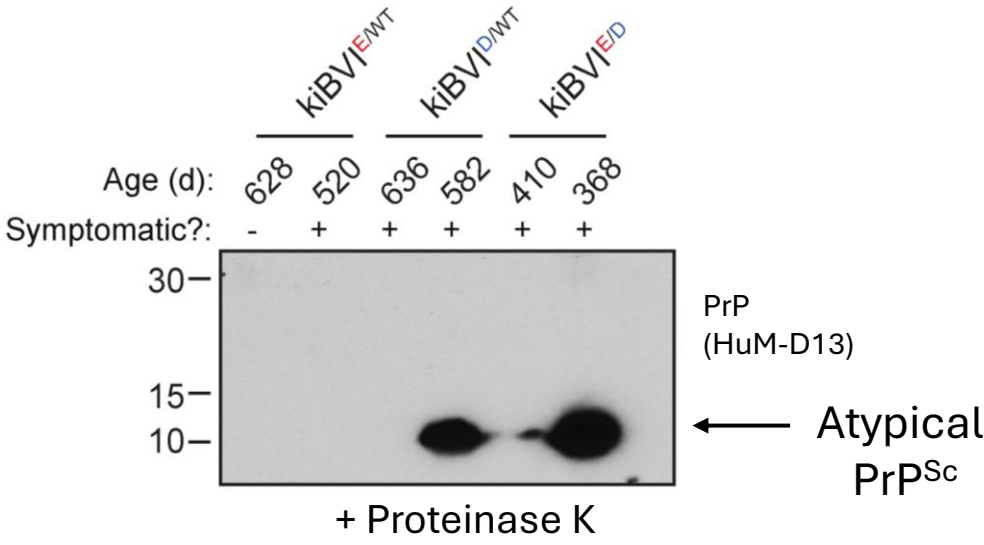



**Symptoms** : Kyphosis, tremor, Bradykinesia, weight loss, ataxia, limb abnormalities, dermatitis

Spontaneously Sick



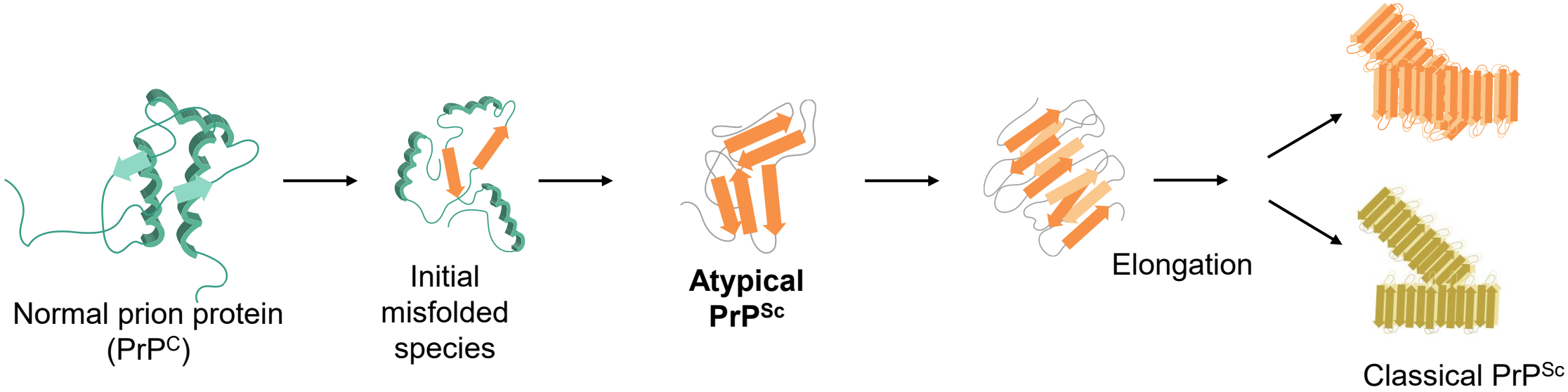

+ Thermolysin

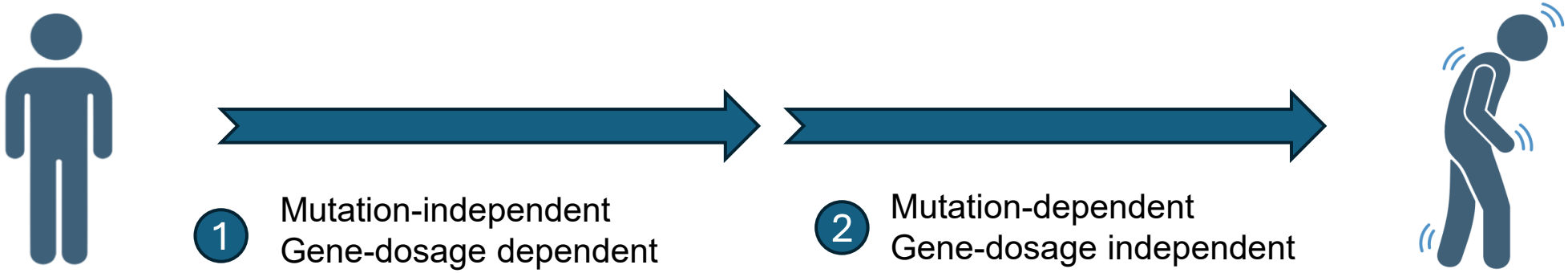



+ Proteinase K

Atypical Prions

# *Two-step mechanism of spontaneous misfolding*




This two-step model helps explain why people with genetic mutations — even though they carry them from birth — typically don't develop symptoms until much later in life.

# Summary

**Spontaneous Illness in Mice with CJD and FFI Mutations**
Knock-in mice carrying human CJD and FFI-related mutations (D178N and E200K) developed neurological disease on their own, without any exposure to infectious prions.

**Common Prion Formation Across Mutations**
Early formation of prion strains in CJD/FFI may occur regardless of the specific mutation involved.

**Gene Dosage Matters**
The amount of misfolding-prone prion protein plays a bigger role in triggering disease than the mutation type alone. It also suggests that people with two copies of a mutation may be at greater risk.

# Future goals

**Understand how different genetic mutations cause prion proteins to misfold in specific ways** — and what makes them turn toxic.

**Figure out if the early, atypical forms of misfolded prions can change into the more harmful, classical ones** that are typically seen in full-blown disease.

**Explore possible treatments** that could either stop the misfolding process early on or block the classical prion versions from forming altogether.

**For any questions, feel free to reach out at**

surabhi.mehra@utoronto.ca

www.linkedin.com/in/surabhi-mehra-phd11

**Want to learn more? Scan the QR code to read the full article.**

Mehra et al., *Journal of Clinical Investigations* 2024

# Acknowledgements

## Watts Lab

- **Joel C. Watts**
- **Erica Stuart**
- Genki Amano
- Raphaella So
- Nicholas Silver
- Leo Li
- Christopher Situ
- Jason Ye
- Mark Metri

## Tanz CRND

- Jennifer K. Griffin

**Past Members**

- **Matthew Bourkas**
- **Hamza Arshad**
- Alison Mao
- Lella Erceg

## Collaborators

- Walker S. Jackson
- Stephanie A. Booth
- Surachai Supattapone

UNIVERSITY OF TORONTO

CIHR IRSC

CJD FOUNDATION

CREUTZFELDT-JAKOB DISEASE FOUNDATION, INC.

*Supporting Families Affected by Prion Disease*

**The Tom Stivison Memorial Research Grant**

**Contributed by: Sandra (Cookie) Stivison**

**The Sherry Maxwell Fabian Memorial Grant**

**Contributed by: Tom Fabian**

**The Harvey L. Hall Memorial Grant**

**Contributed by: Lavonne C. Hall**

**The Robert Vitanza Memorial Grant**

**Contributed by: Michael Vitanza**

**The Lynda Morris Memorial Grant**

**Contributed by: David Morris and Family**