The Role of Animal Models in Identifying and Testing Treatments

Joel Watts, PhD

Assistant Professor

Tanz Centre for Research in Neurodegenerative Diseases

Department of Biochemistry, University of Toronto

joel.watts@utoronto.ca

CJD Foundation 2016 Conference

July 9th, 2016

Tanz Centre for Research in Neurodegenerative Diseases

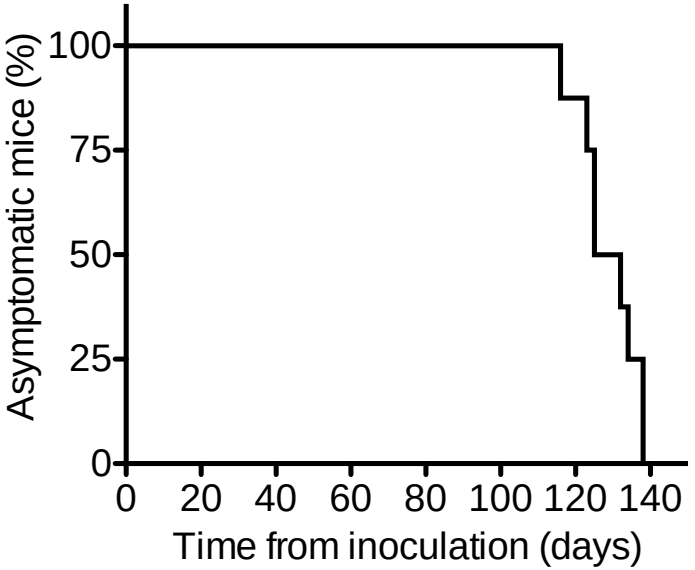
Biochemistry
UNIVERSITY OF TORONTO

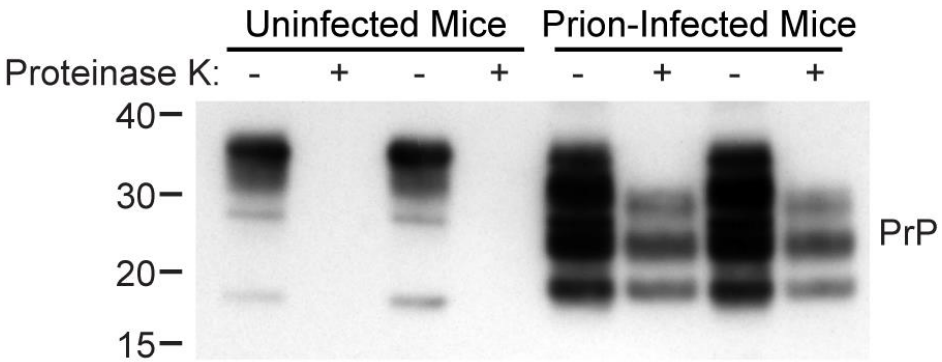
Why Use Mice to Study Prion Disease?

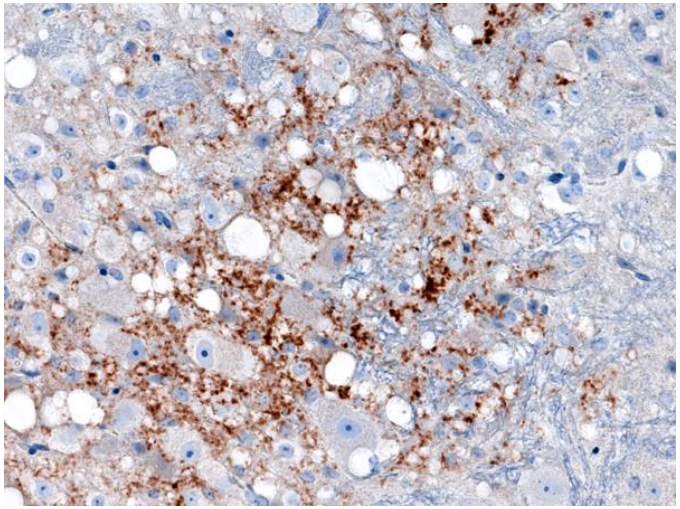
- Lack of appropriate cultured cell model
  - Currently, CJD prions cannot be replicated in cultured cells
- Complexity of the brain is not easily mimicked using cultured cells
  - Multiple cell types
  - Non-dividing cells
- Certain features of prion disease cannot be studied using cell or other *in vitro* models
  - Neuroinvasion
  - Prion neurotoxicity
- Translational considerations when designing therapeutics
  - Blood-brain-barrier
  - Metabolism of compounds

Transmission of Prion Disease to Mice

Intracerebral inoculation of prions







PrP^C is Required for Prion Disease

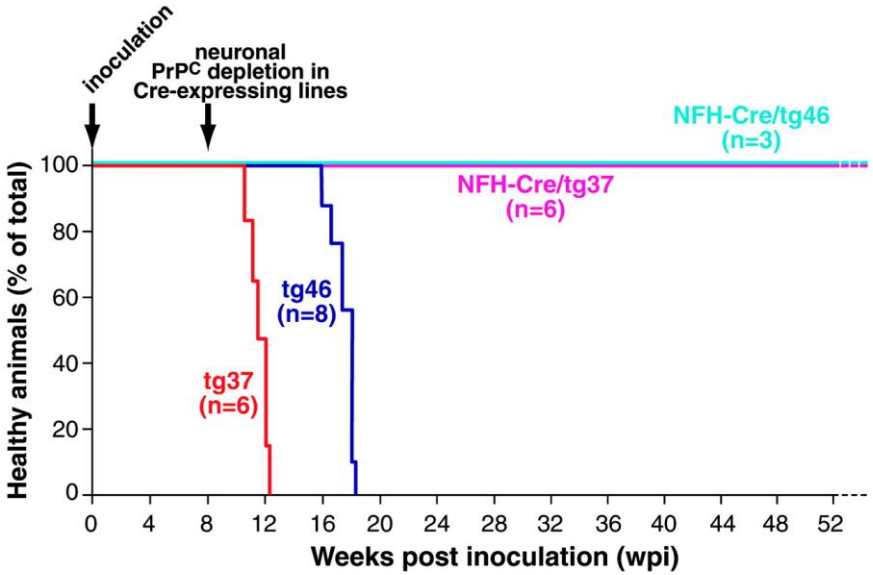
$PrP^C \rightarrow PrP^{Sc} \rightarrow$ Disease

Intracerebral inoculation of prions

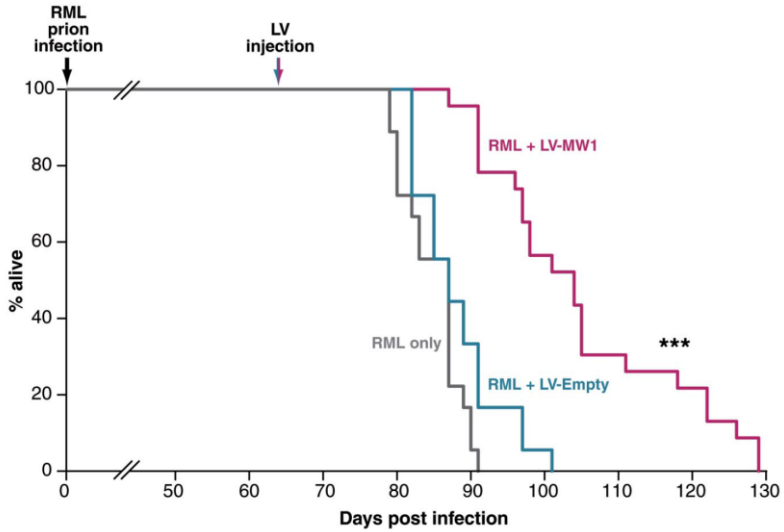
PrP knockout mice

→ No prion disease!!

Büeler *et al*., *Cell*, 1993

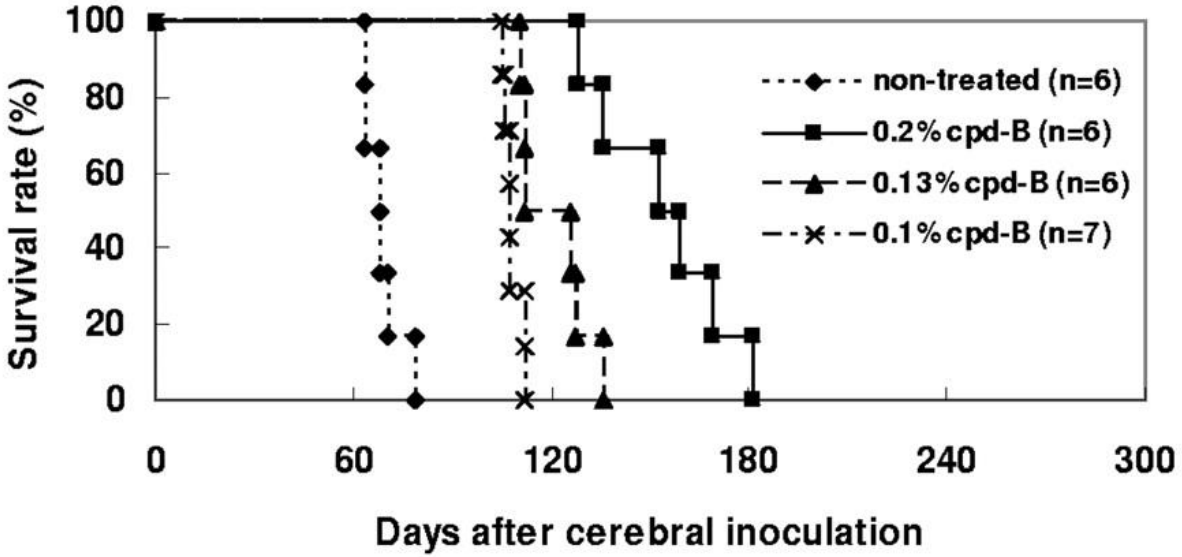


Mallucci *et al*., *Science*, 2003



White *et al*., *PNAS*, 2008

Small Molecules Extend the Lifespan of Prion-Infected Mice



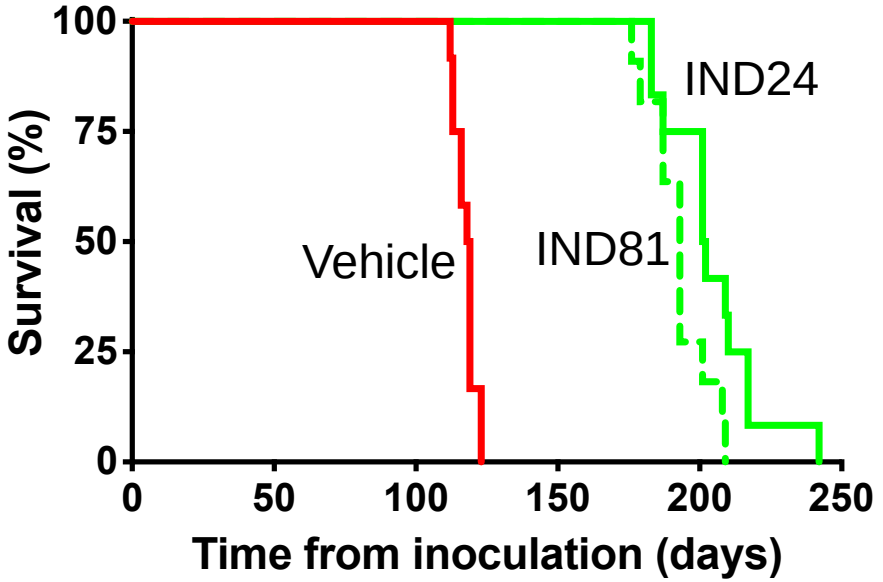
Kawasaki *et al*., *J Virol,* 2007

- Other effective anti-prion small molecules:
  - anle138b
  - Polythiophenes
  - 2-aminothiazoles (i.e. IND24)

IND24 and IND81 Greatly Extend the Lifespan of Prion-Infected Mice

Inoculate mouse prions intracerebrally

Non-transgenic



Berry *et al*., *PNAS*, 2013

- IND24-treated mice eventually died of prion disease, but their survival time was almost doubled compared to vehicle-treated mice

IND24 Greatly Extends the Lifespan of Prion-Infected Mice

Day Treatment Started	Mean Incubation Period (days)
Untreated	118
1 day post-inoculation	204
34 days post-inoculation	202
61 days post-inoculation	221
90 days post-inoculation	118
14 days prior to inoculation	452

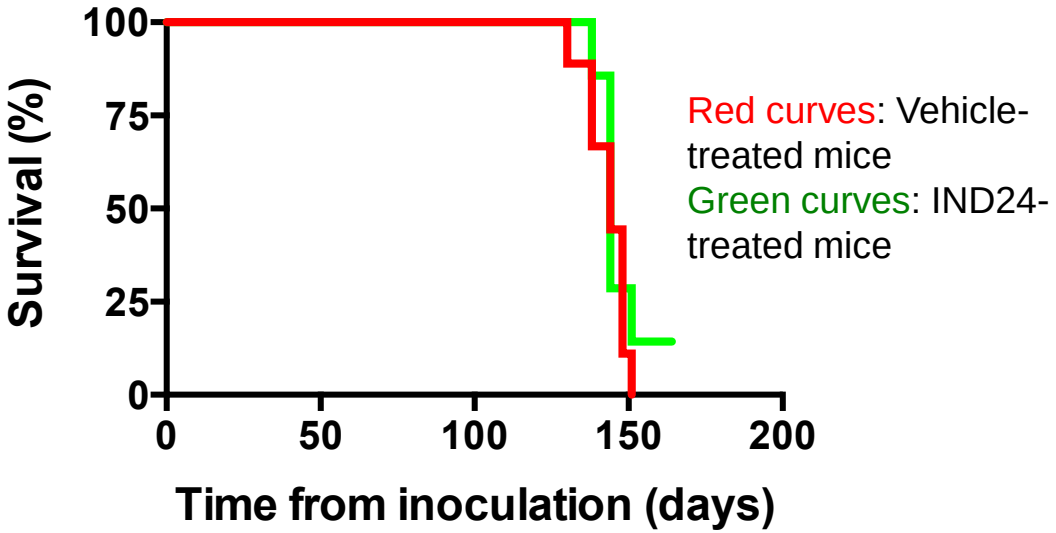
Giles *et al*., *JPET*, 2015

- *Conclusion*: Prion disease therapeutics are most effective when administered early on during the disease course

But…IND24 Does Not Extend the Lifespan of Mice Infected with Human Prions

Inoculate with sCJD prions

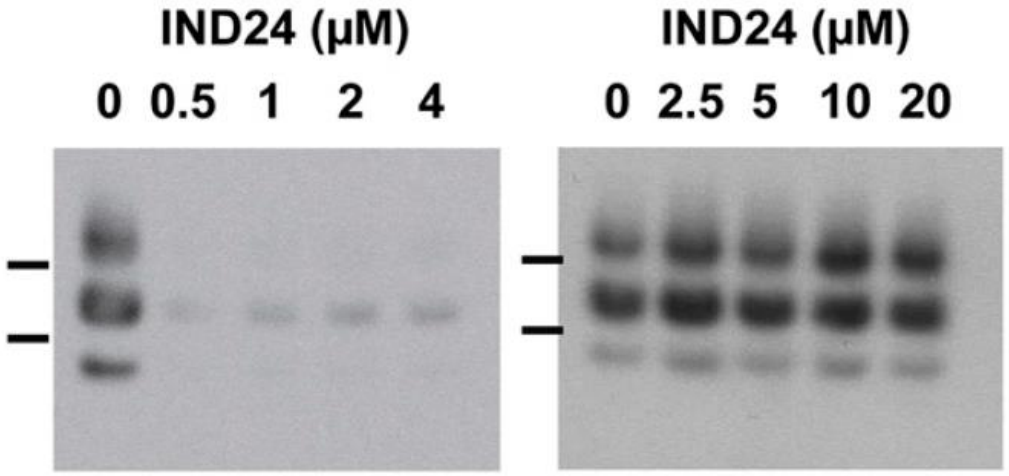
Tg(Human PrP)



Berry *et al*., *PNAS*, 2013

- *Conclusion*: The efficacy of anti-prion compounds is prion-strain specific

Persistent IND24 Treatment Gives Rise to Drug-Resistant Prions



Vehicle-treated mice IND24-treated mice

Berry *et al*., *PNAS*, 2013

- Prions from mice treated with vehicle (control) are sensitive to IND24
- But…the prions from mice treated with IND24 are now resistant to IND24!
- *Conclusion*: Like bacterial and viral pathogens, prions can evolve!

Mouse 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

Attempts to Generate Tg Mouse Models of Inherited Human Prion Diseases

Tg(Mutant MoPrP)
Tg(Mutant HuPrP)

Mutations: P102L (GSS), D178N (fCJD/FFI), E200K (fCJD), Octa14 (GSS)

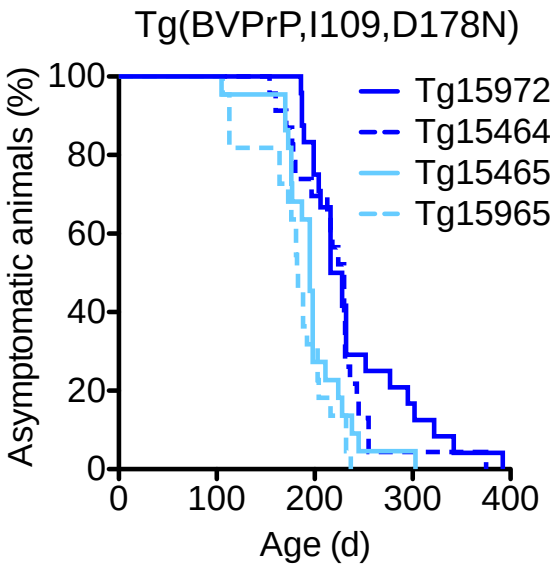
→

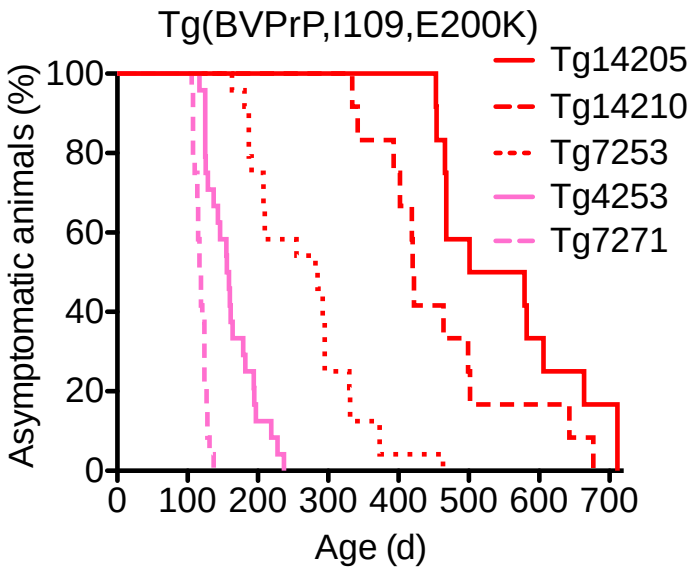
Neurological Disease (sometimes)
-Not transmissible
-No PK-resistant PrP
-Atypical neuropathology

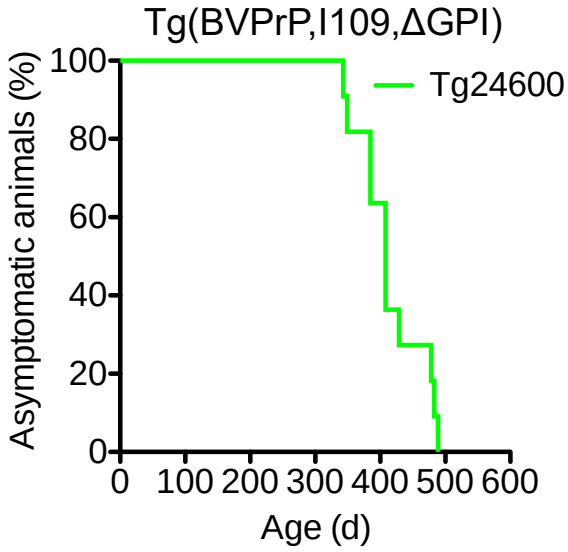
Criteria for an authentic mouse model of spontaneous prion disease:

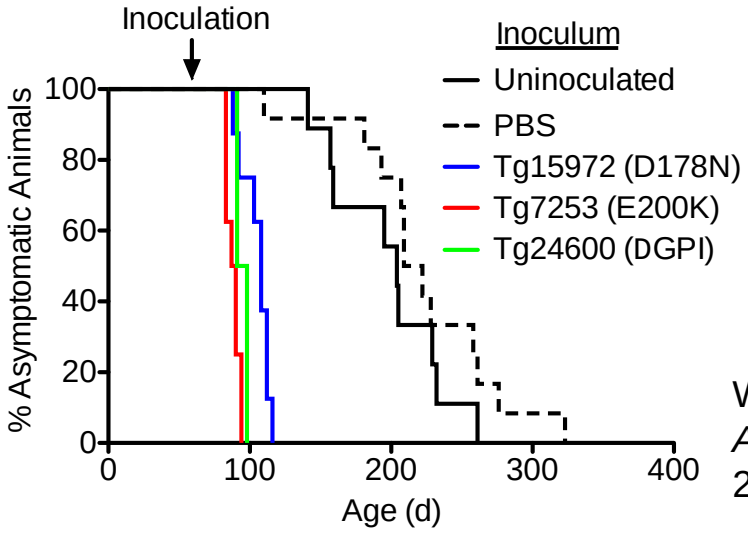
1. Develops spontaneous signs of neurological illness
2. The brains of spontaneously sick animals exhibit prion disease-specific neuropathology
3. The brains of spontaneously sick animals contain PK-resistant PrP species
4. The disease is transmissible

Tg Mice Expressing Mutant BVPrP Develop a Spontaneous, Transmissible Disease



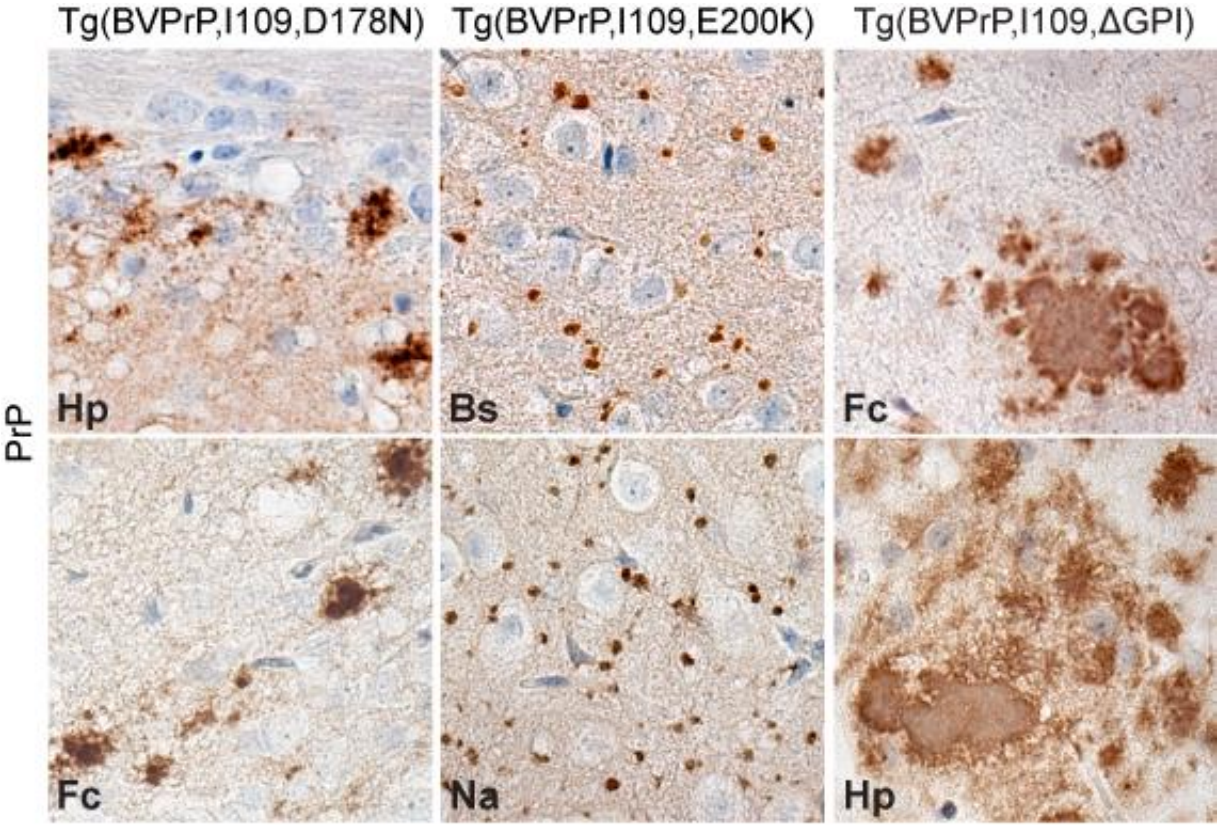






Watts *et al.*, *Acta Neuropathologica*, 2016

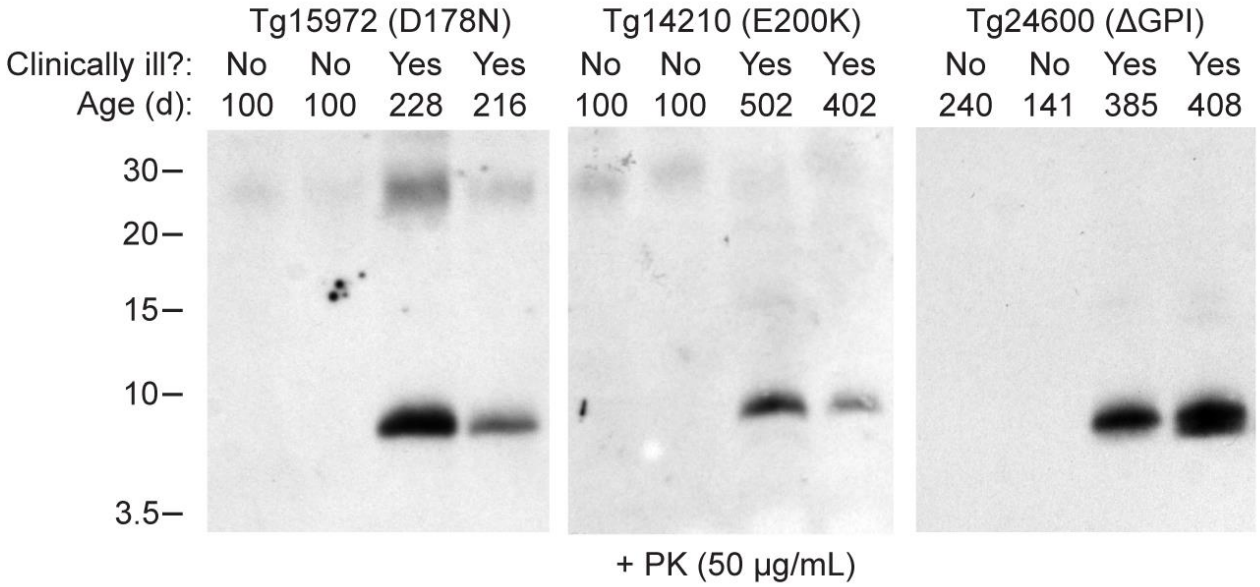
Prion Disease Neuropathology in Spontaneously Sick Mutant BVPrP Tg Mice

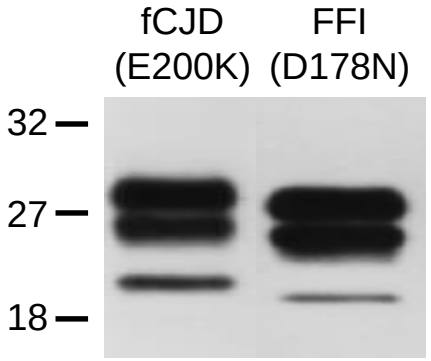


- *Conclusion*: Each mutation specifies the formation of distinct PrP^{Sc} aggregates

Watts *et al*., *Acta Neuropathologica*, 2016

PK-Resistant PrP in Spontaneously Sick Mutant BVPrP Tg Mice

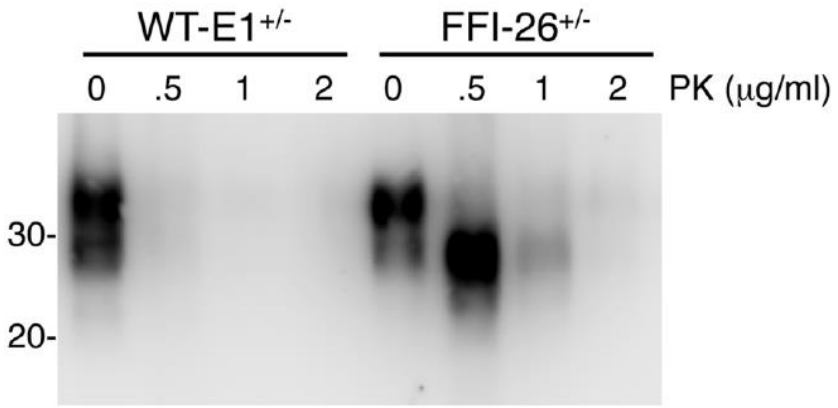




Telling *et al*., *Science*, 1996

Watts *et al*., *Acta Neuropathologica*, 2016

PrP^{Sc}-Independent Disease Pathogenesis in Tg(FFI) Mice



- Tg(FFI) mice develop spontaneous disease, but highly PK-resistant PrP is not observed in the brain
- The disease is non-transmissible
- However, the mice develop FFI-like sleep abnormalities
- PrP^{Sc} may not always be necessary for disease pathogenesis!

Bouybayoune *et al*., *PLoS Pathogens*, 2015

Acknowledgements

Stan Prusiner

Kurt Giles

UCSF

Jan Stöhr
David Berry
Smita Patel
Marta Gavidia
Sumita Bhardwaj
Joanne Lee
Ana Serban
Steve DeArmond
Abby Oehler
The entire Hunter's Point animal facility

University of Toronto

Erica Stuart
Matthew Bourkas
Hamza Arshad
Heather Lau
Angus Lau
Alejandro Ruiz Riquelme

Gerold Schmitt-Ulms
Mohadeseh Mehrabian

Istituto Superiore di Sanità

Romolo Nonno

Funding

NSERC CRSNG
CIHR IRSC
Creutzfeldt-Jakob Disease Foundation, Inc.
INNOVATION.CA
CANADA FOUNDATION FOR INNOVATION | FONDATION CANADIENNE POUR L'INNOVATION
Alzheimer Society CANADA

Talk Overview

- Mice injected with prions exhibit all the characteristics of human prion diseases
- Mouse studies have revealed that the prion protein (PrP) is an excellent therapeutic target
- Several molecules have been identified that extend the lifespan of mice infected with mouse prions
- As of yet, no molecule has been identified that is capable of extending the lifespan of mice infected with human prions
- Progress has been made towards the development of a mouse model of spontaneous prion disease, but challenges remain