A Multi-Targeted Approach to Therapy for Prion Disease

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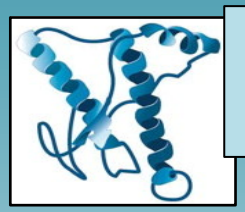
Objectives


Review the Process of Prion Disease
Identify the Targets
Failures and Successes

Prion Disease is aTwo-Step Process



PrP^{C}

Spontaneous Conversion
(85-90%)

PrP^{Mut}

PRNP mutation
(~10-15%)

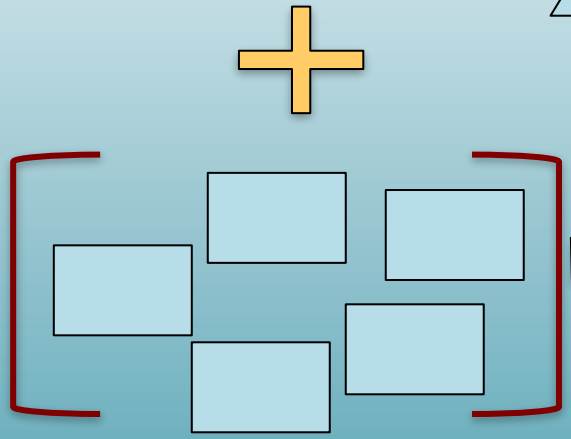
PrP^{Sc} +

PrP^{Sc}

Exposure
(zoonotic and iatrogenic)
(<1%)

Generation

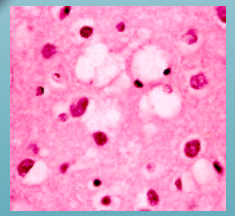
Propagation

PrP^{C} → PrP^{Sc} PrP^{Sc} + 

PrP^{Sc} accumulation

Clinical Symptoms

Resident neuronal PrP^{C} in brain is the substrate for conversion by PrP^{Sc}



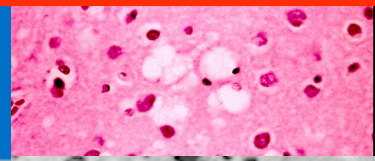
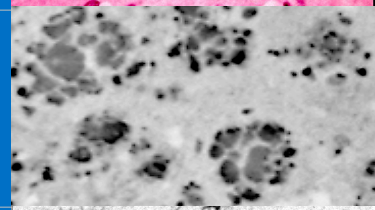
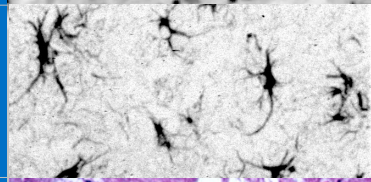
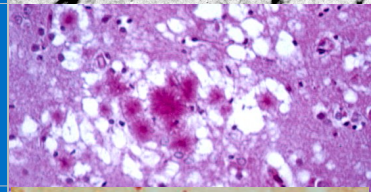
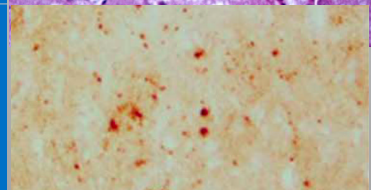
Spongiform Degeneration

PrP^{Sc}

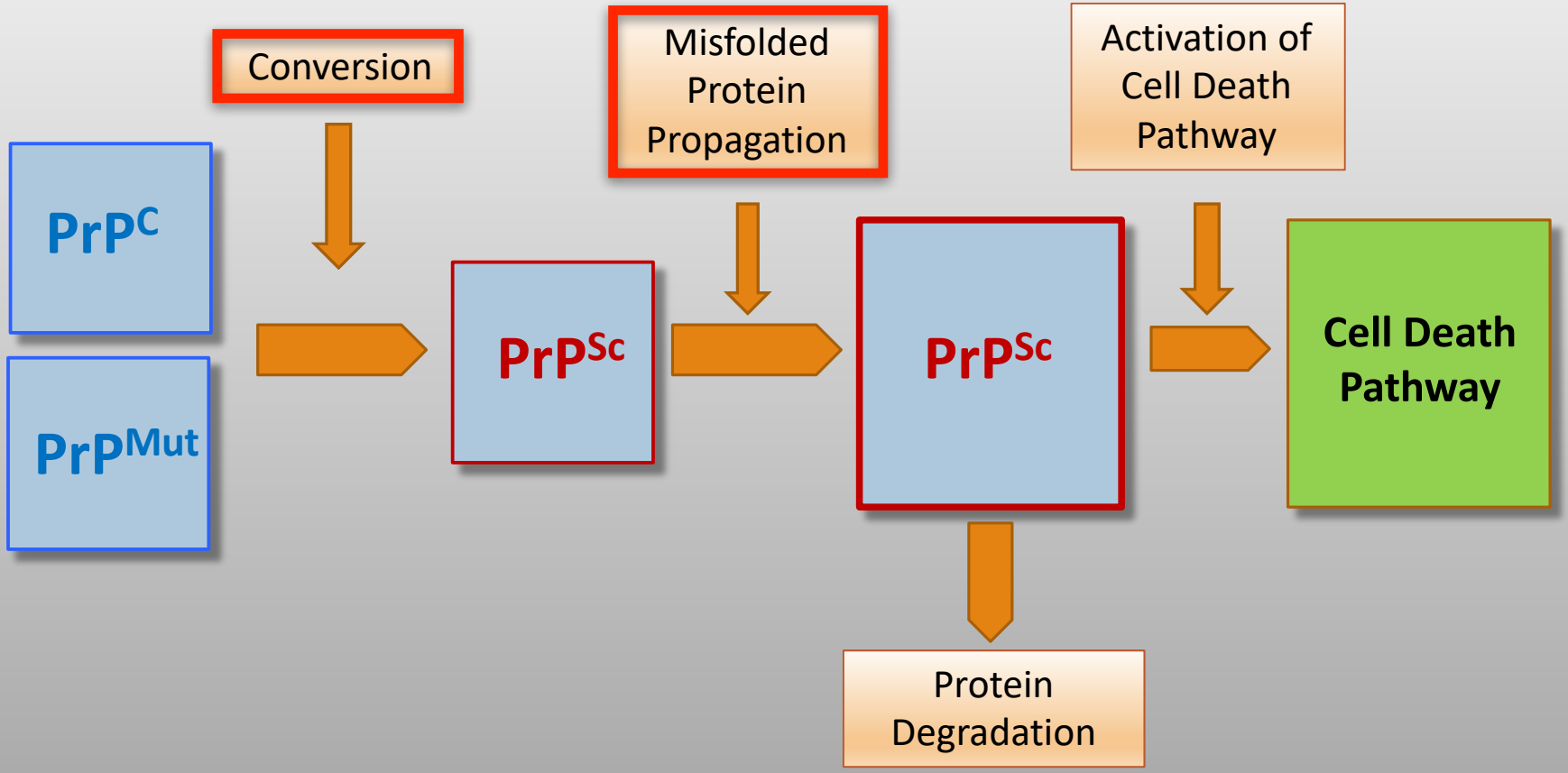
- +

Proteinase K

Major Prion Disease Subtypes

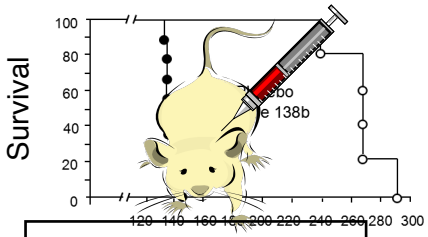
Disease	Age at Onset	Features	Course	Histopathology	
Creutzfeldt-Jakob Disease (CJD) [sporadic/genetic/iatrogenic]	~60-70	Dementia, ataxia, myoclonus	4-6 mo.	Spongiform Degeneration	
Gerstmann-Straussler-Scheinker (GSS) [ONLY genetic]	~30-50s	Ataxia onset, late dementia	3-7 yrs.	Multicentric PrP amyloid plaques w/ limited spongiform degeneration	
Fatal Insomnia (FI) [sporadic/genetic]	~35-55	Insomnia, autonomic dysfunction (tachycardia, hypertension, lacrimation) then dementia and ataxia	1- 2 yr.	Thalamic neuronal dropout and gliosis	
Variant CJD (vCJD) [acquired]	~16-35	Psychiatric onset (depression, apathy), pain syndrome, then ataxia, dementia	~1 yr.	"Florid" (flower-like) PrP plaques surrounded by spongy degeneration	
Variably Protease-Sensitive Prionopathy (VPSPr) [sporadic]	~70s	Psychiatric symptoms, aphasia, dementia, frontal features, parkinsonism, ataxia	~2 yr.	Plaque-like accumulations of PrP	

Potential Targets for PrD Therapy

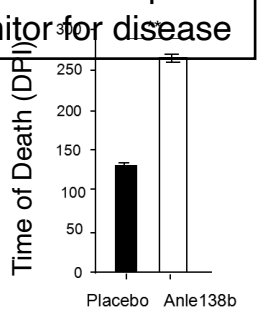


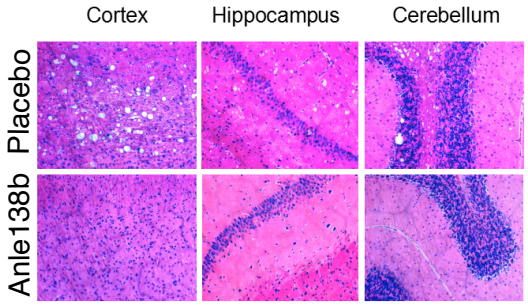
Anle138b Delays Death In a Transmissible but not Genetic Model of Prion Disease

Transmissible Model

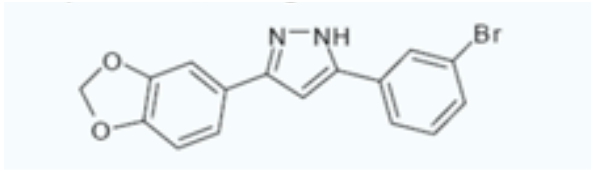


Inoculate with prions
Monitor for disease





140 d post inoculation

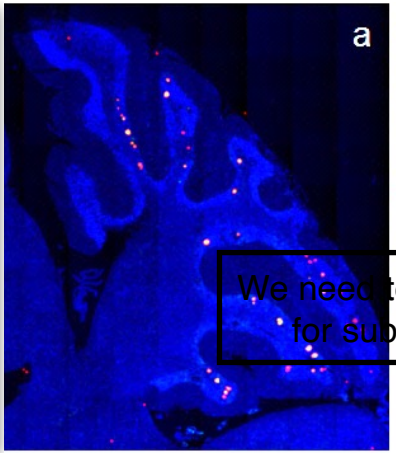


Diphenyl-pyrazole (DPP)
Oligomer Modulator
(Breaks-up aggregating proteins)
University of Munich

Tested in two models of prion disease

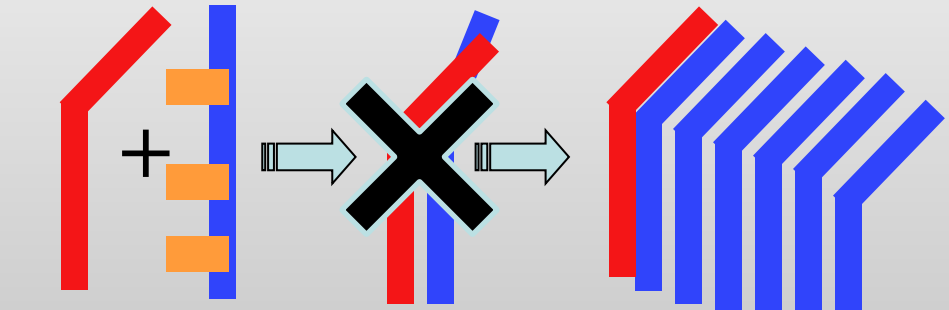
Genetic Model

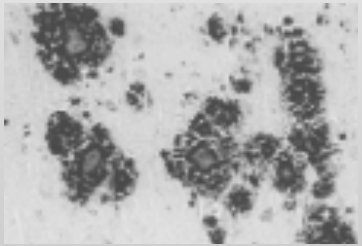
Mouse produces prions
Monitor for spontaneous disease



We need to account for subtypes!

Propagation of Prions Requires A Specific Interaction Between PrP^{Sc} and PrP^{C}

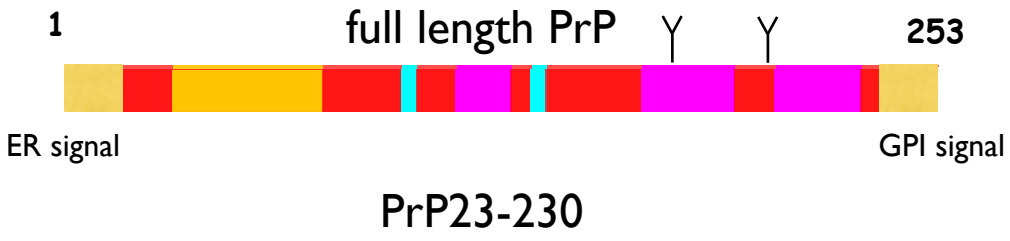




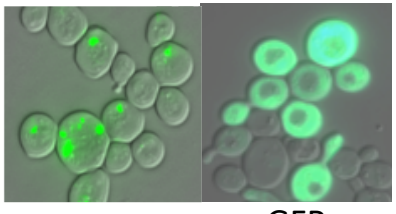
PrP amyloid

- How do PrP^{Sc} and PrP^{C} interact to propagate?
- Can we identify sites of importance that could be targeted to slow or prevent disease?

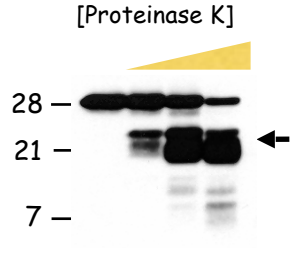
Interfering with Prion Propagation



Yeast



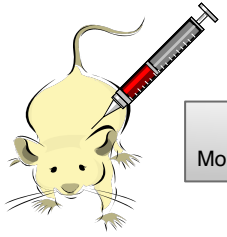
PrP-GFP GFP



?

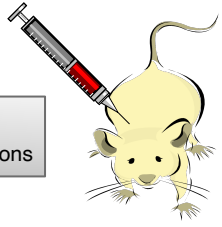
Tg(PrPΔ112-119) mice Appear Resistant to Prion Disease

Tg(PrP$^{\Delta 112\text{-}119}$/PrP$^{-/-}$)



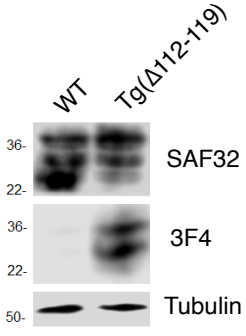
Tg(PrP$^{+/-}$)

RML
Mouse prions



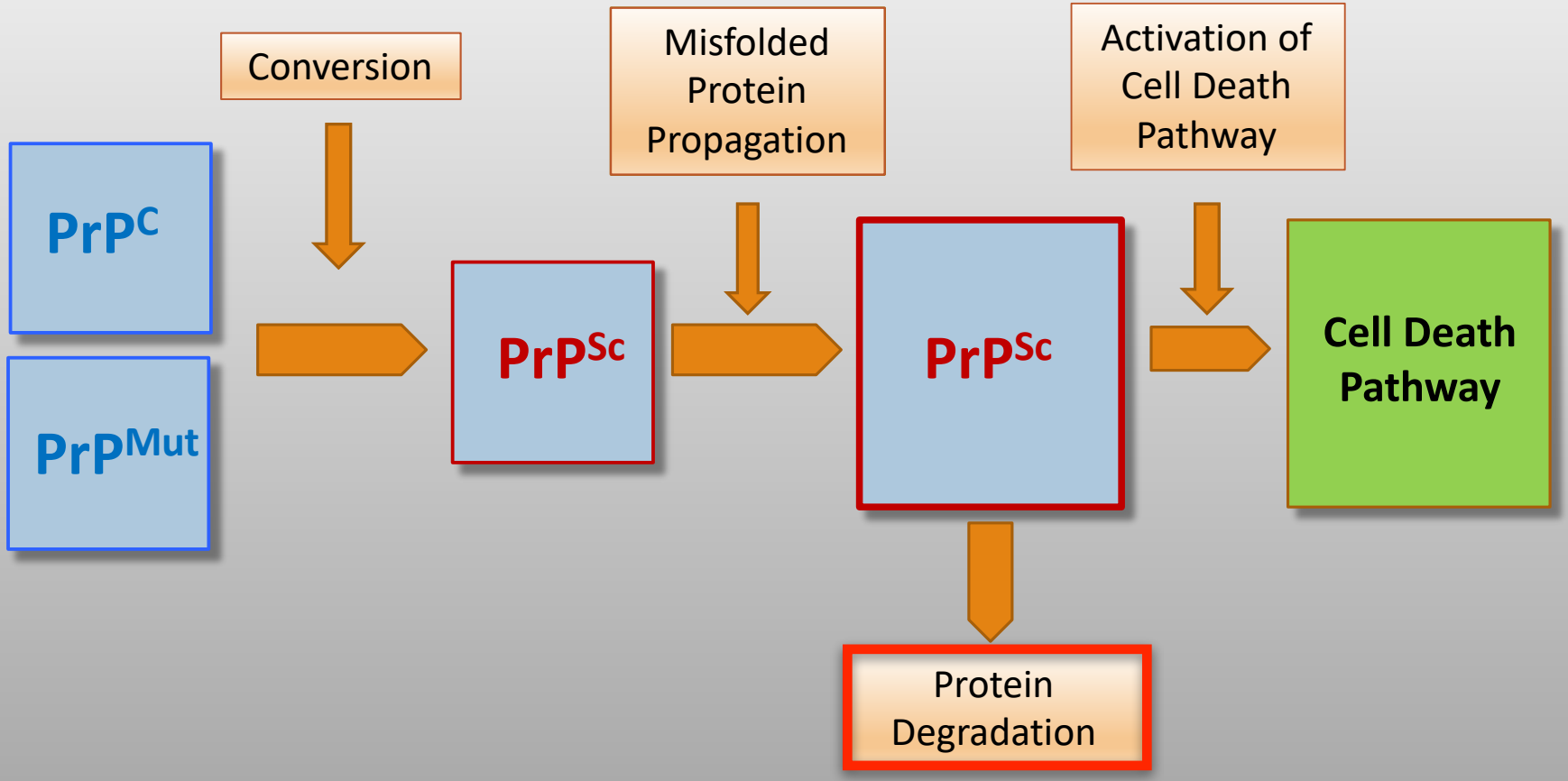
Tg(PrP$^{\Delta 112\text{-}119}$)

More To Come!

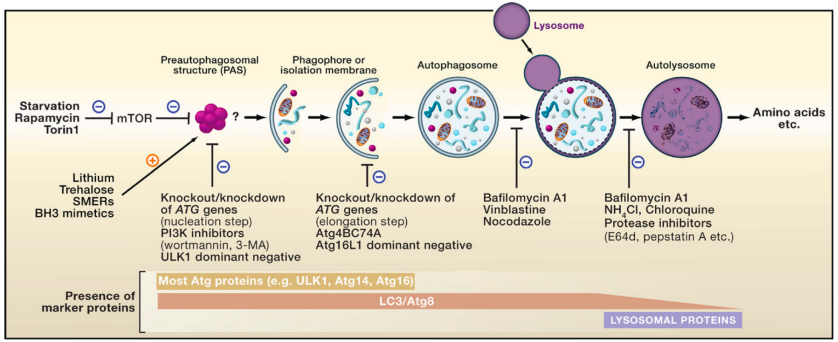


No spontaneous disease
> 800 d (n = 20)

Potential Targets for PrD Therapy



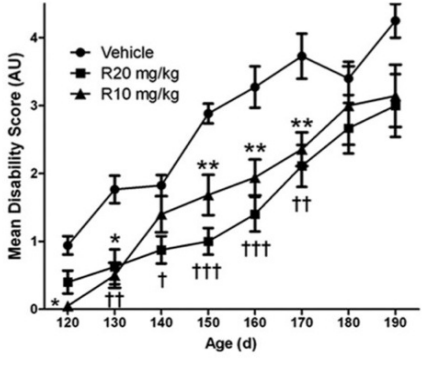
Enhancing Autophagy with Rapamycin Delays Onset of Prion Disease in Tg(GSS) mice



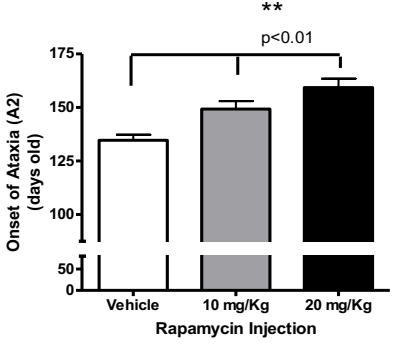
Modified from Ravikumar et al, JCS (2009).

Rapamycin treatment -10 or 20 mg/kg i.p. M-W-F starting at 4 weeks

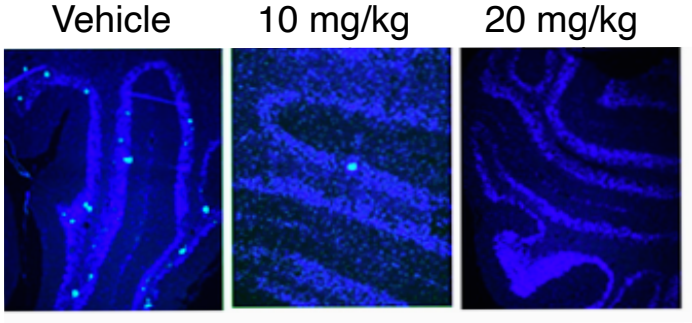
Disability Reduced

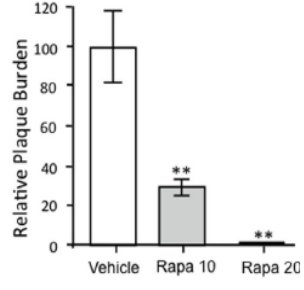


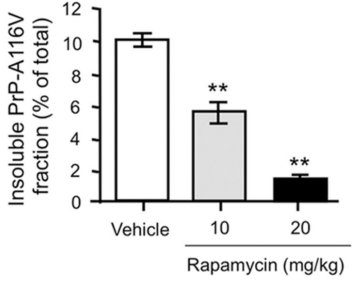
Onset Delayed



PrP Plaque Reduction



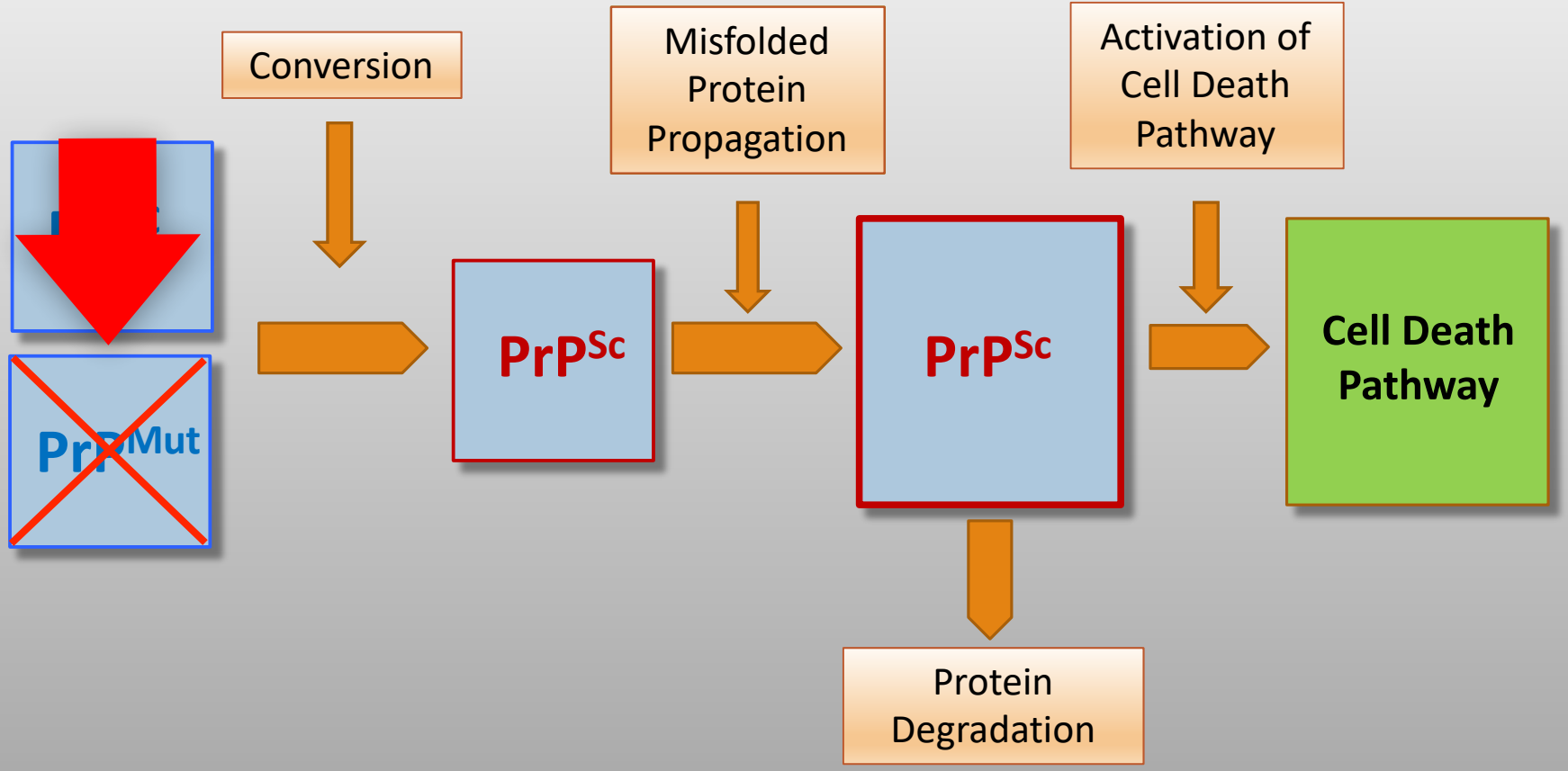




Average age of onset:

- Vehicle: ~ 134 d
- 10 mg/Kg: ~ 149 d (10% delay, ** p<0.01)
- 20 mg/Kg: ~ 159 d (18% delay, ** p<0.01)

Potential Targets for PrD Therapy

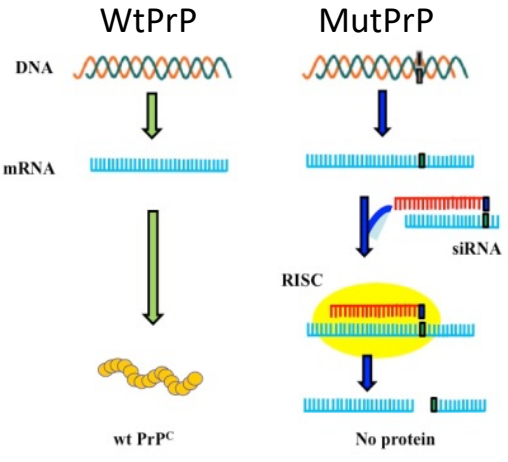


Targeting Genetic Prion Disease

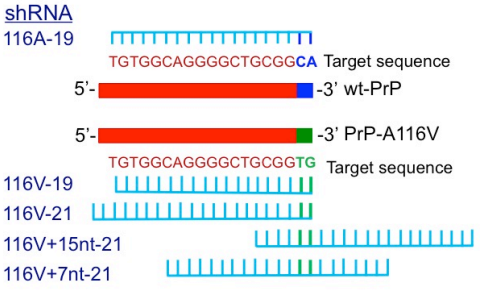
Advantages:

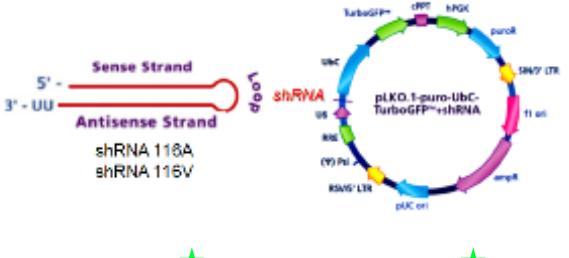
- Carriers can be identified early
- Therapy can be initiated long before disease development
- Prevent initiation of disease
- Autosomal dominant diseases - target only mutated allele

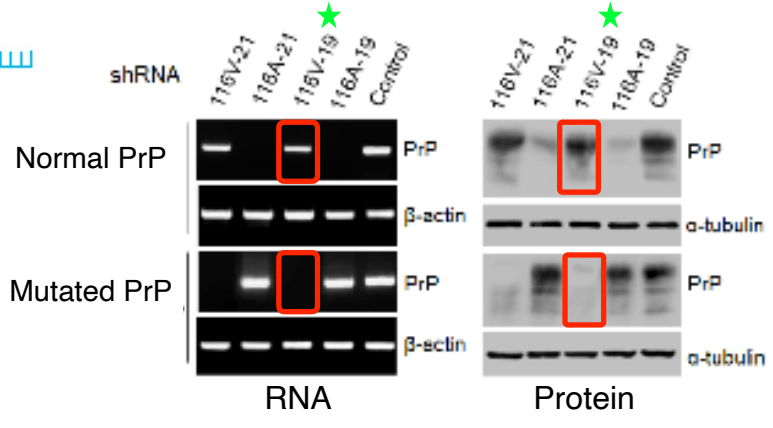
Allele-Specific
RNA interference



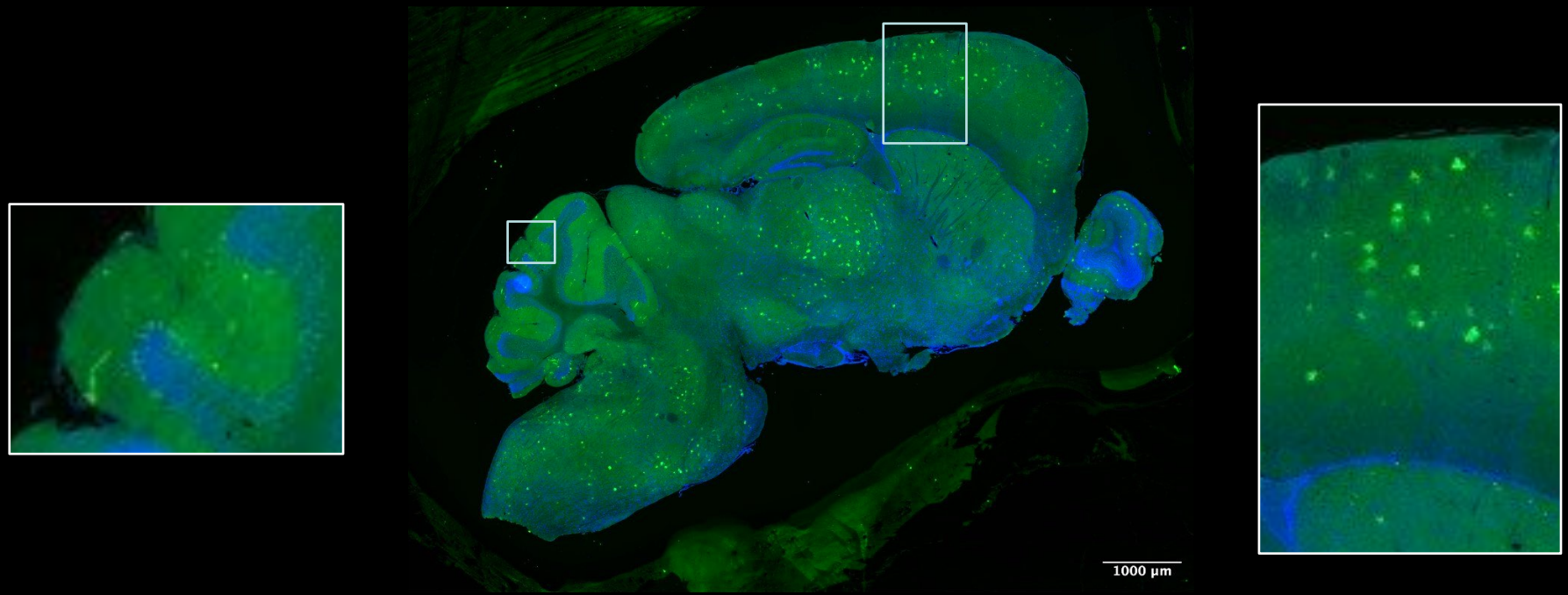
Targeted sequences prepared
and tested for efficiency







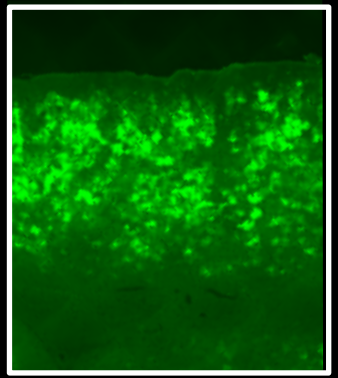
AAV9 Delivery of Allele-Specific shRNA-A116V

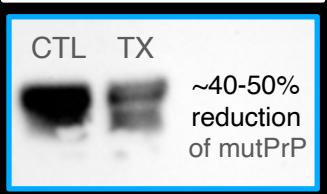


Stained brain section from a 36d old TgGSS mouse after tail vein-injection of AAV9-U6-PrPshRNA-A116V-CMV-GFP at 33d. GFP-tagged AAV9 is green and cell bodies are in blue (DAPI)

AAVPHP.eB-GFP Delivery of Allele-Specific shRNA-A116V

AND NOW WE WAIT.....





Stained brain section of TgGSS mouse after retro-orbital sinus injection of AAVPHP.eB-U6-PrPshRNA-A116V-CMV-GFP at 3 weeks.

Final Thought

- **There are many options and possibilities to change the course of prion disease…!**
- **I'm confident it will get done**

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