Highly Synergistic Combination Therapy for Prion Diseases

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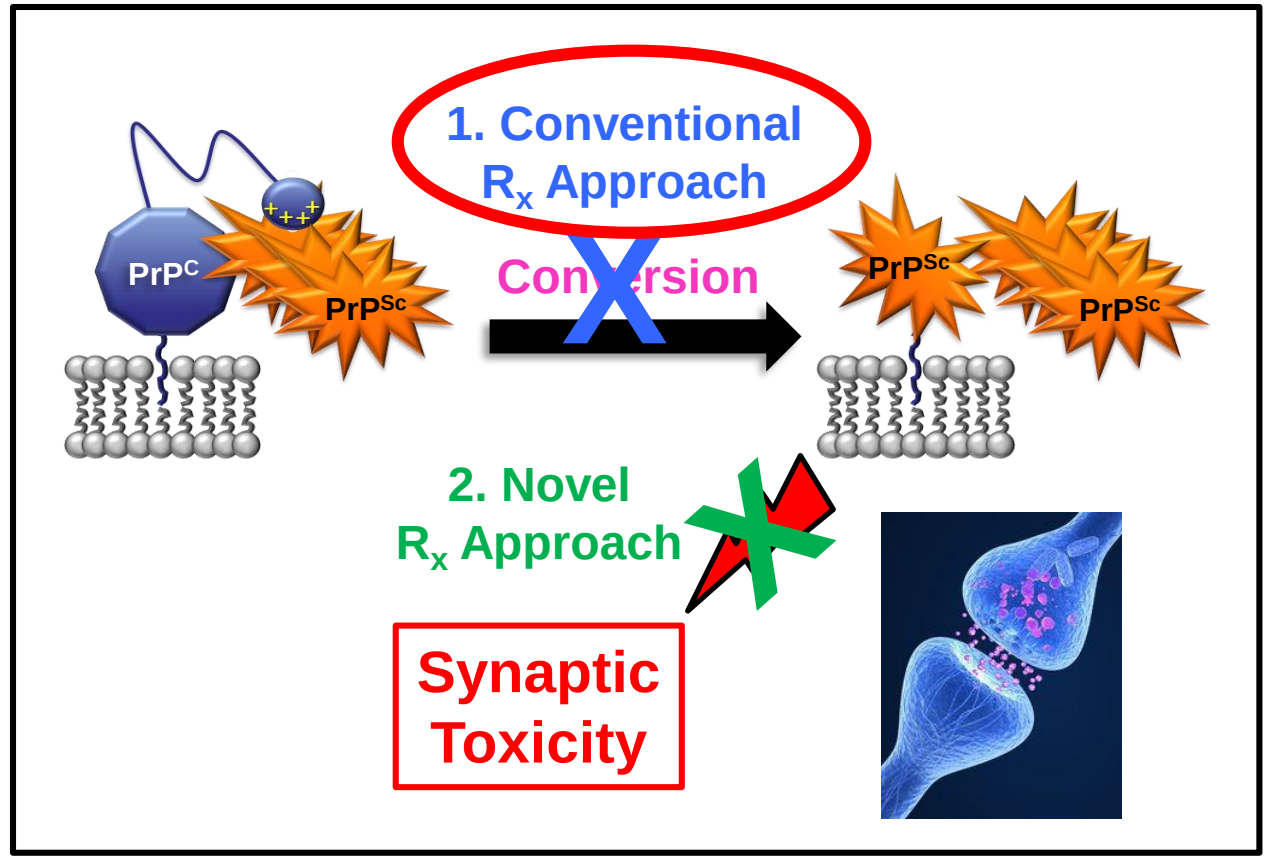
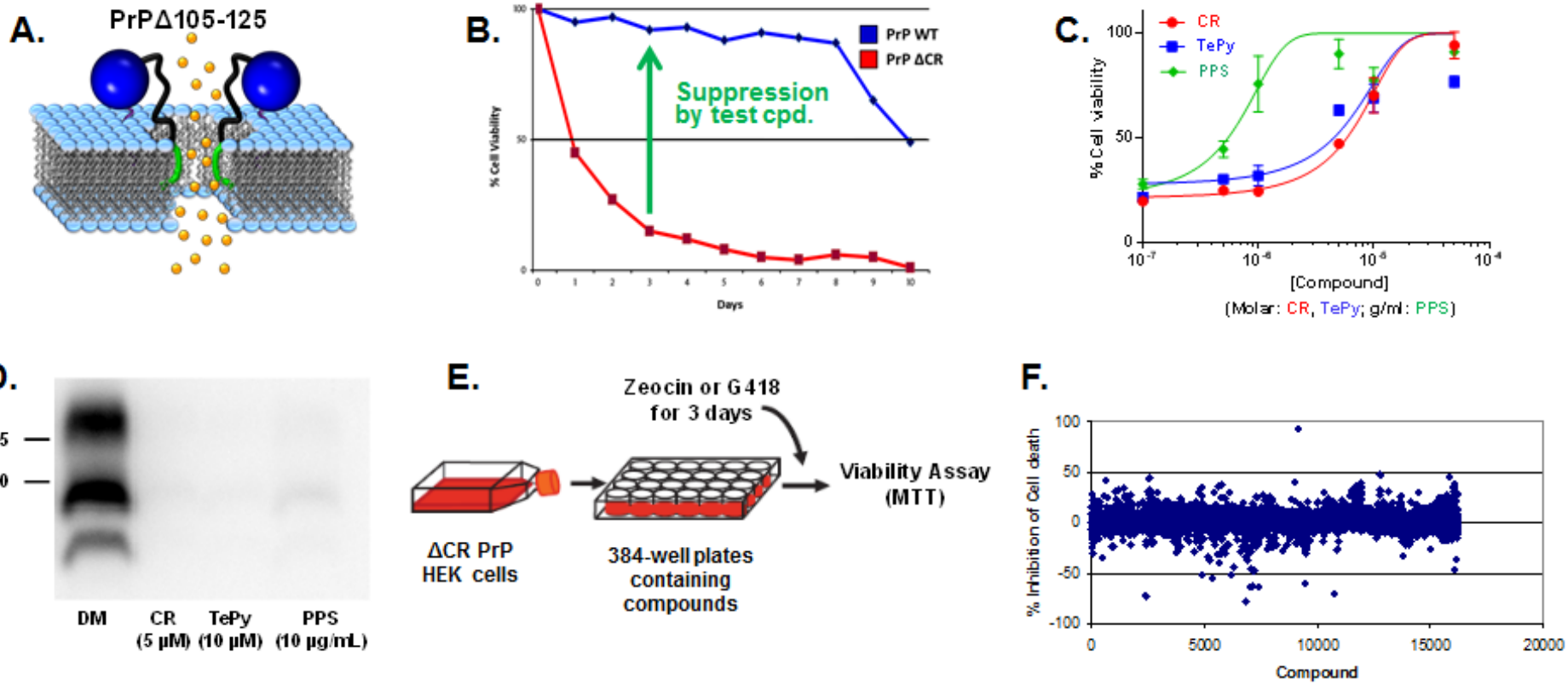
A two-pronged therapy:
Block prion propagation and toxicity

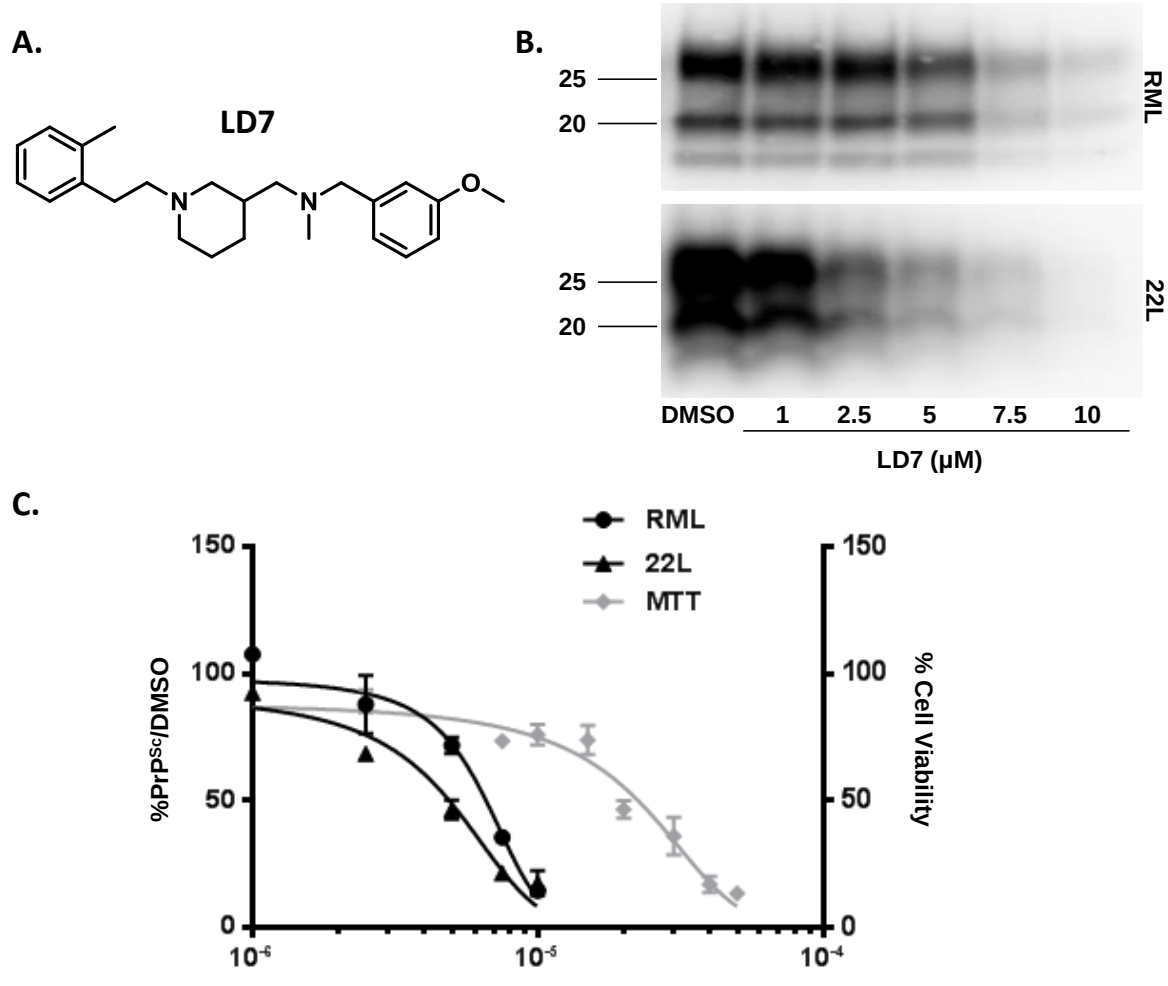


Halt or even reverse ongoing neuronal damage

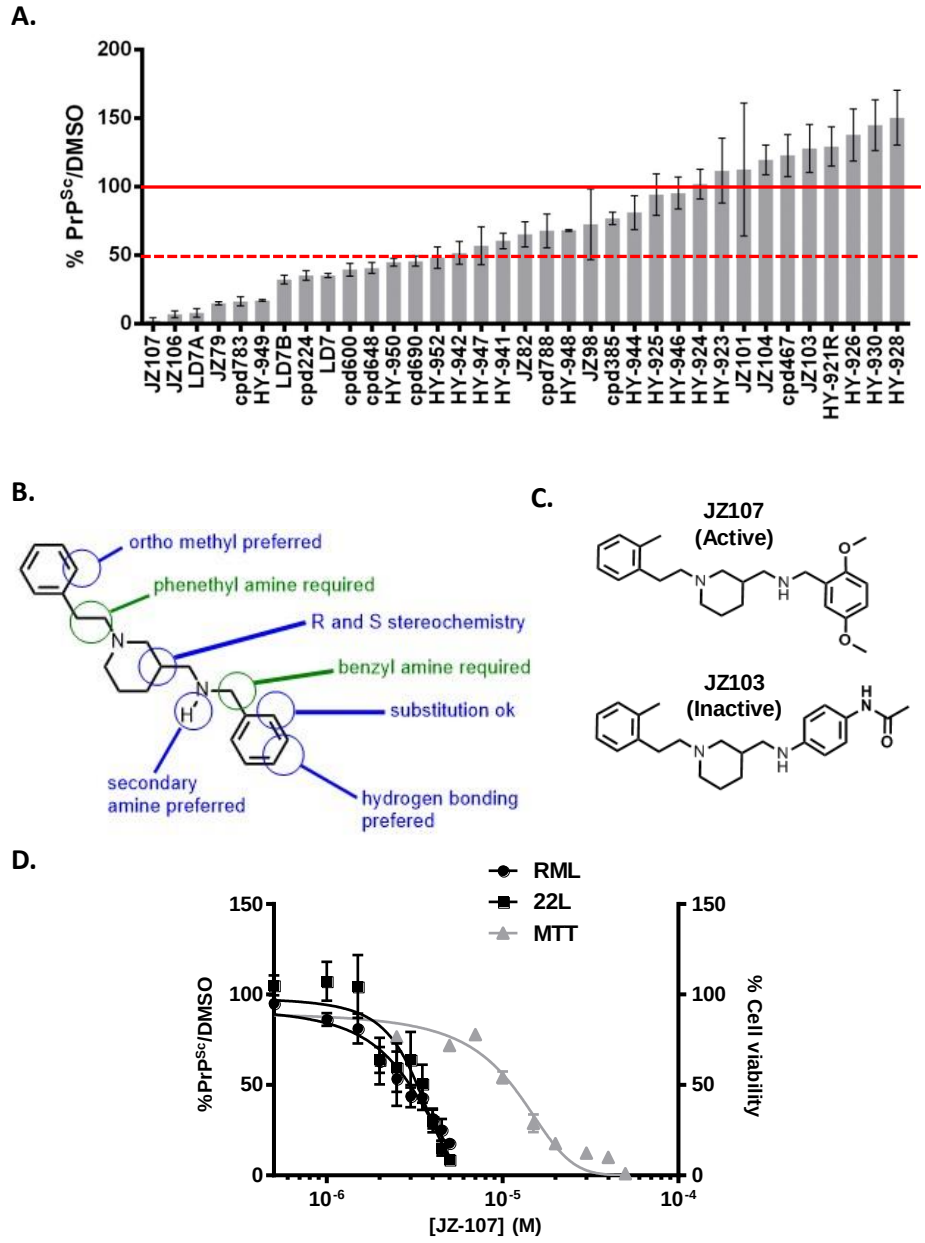
Perform a “drug screen” to identify active compounds (we used an special version)



We found an active compound, which inhibits prion accumulation in cells



We improved the compound: more potent, less toxic

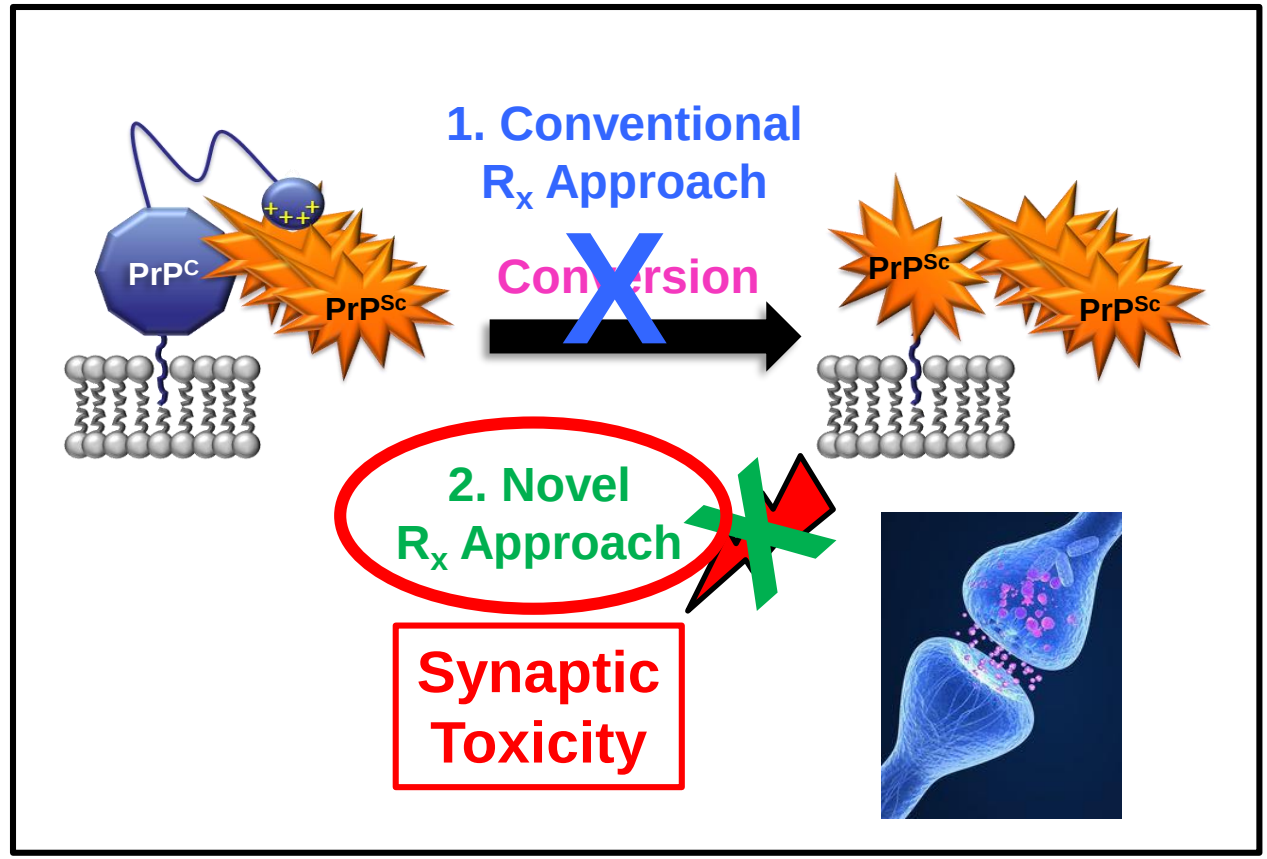


Further drug development (ongoing)

- **Identify the "target" of the drug: what does it bind to?**
- **Find other drugs that bind to the same target, but offer other advantages (e.g., already used in humans for other diseases)**
- **Test these for their ability to block prion accumulation in cells**

Now we have some promising molecules that block step #1: prion propagation (accumulation of PrP^{Sc})

A two-pronged therapy:
Block prion propagation and toxicity

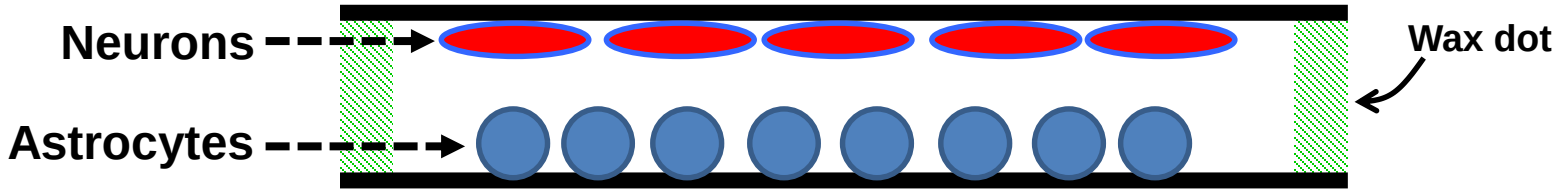


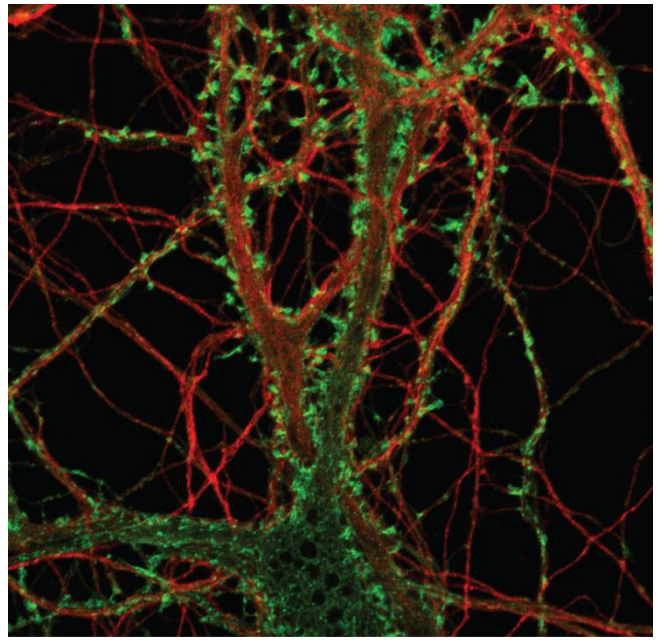
Halt or even reverse ongoing neuronal damage

We need a cell culture system to study prion neurotoxicity:

- **Analyze cellular/molecular mechanisms**
- **Assay/characterize different toxic species**
- **Test therapeutic compounds**

Cell Culture System:
Mouse hippocampal neurons



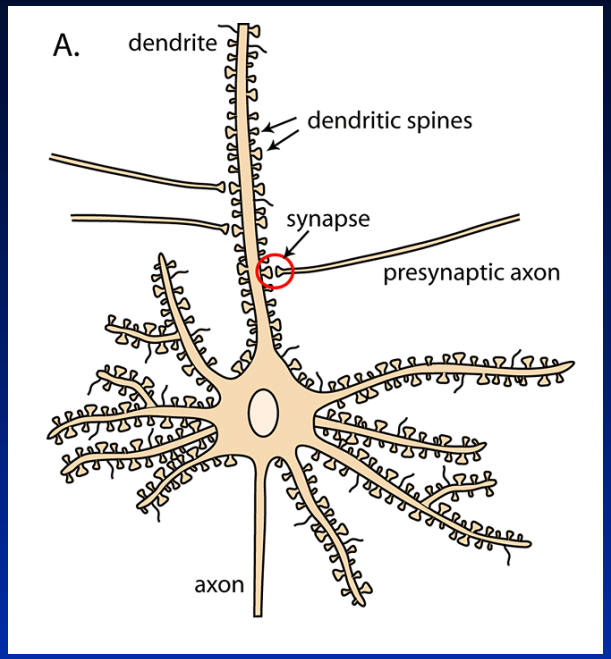


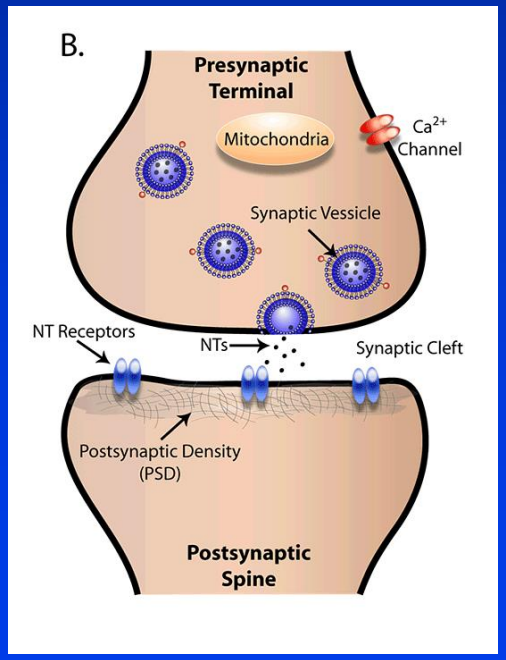
Green: Fl-Phalloidin (F-actin in spines)
Red: anti-tubulin (dendrites, axons)

Cheng Fang
PLoS Pathogens, 2016
(cover photo)

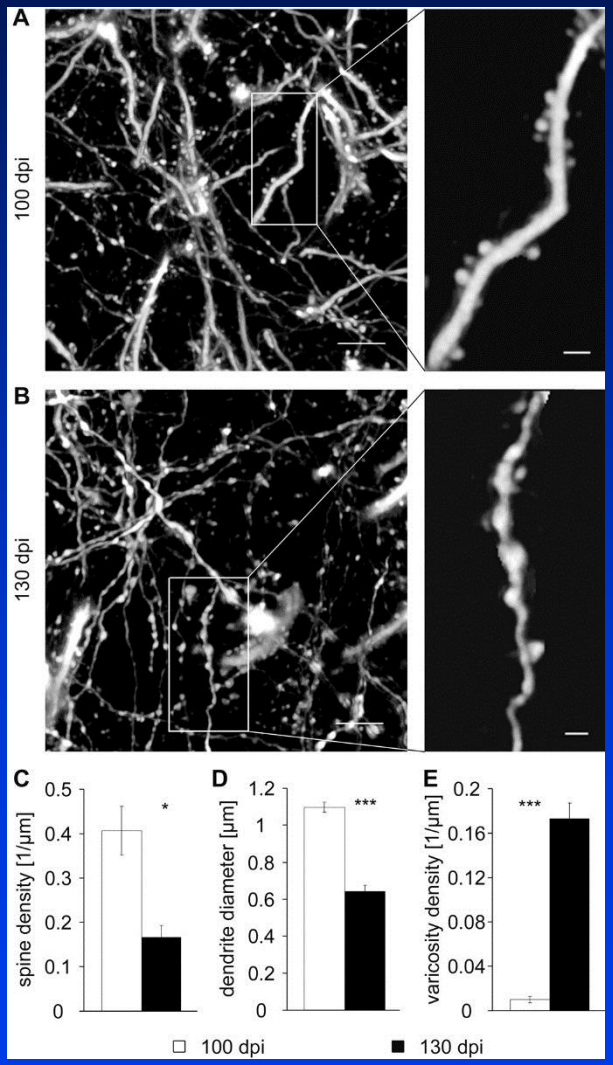
Culture for 3 weeks: mature axons and dendrites (with spines)

Dendritic spines: Sites of physiological synaptic modulation (learning/memory) & neuropathology



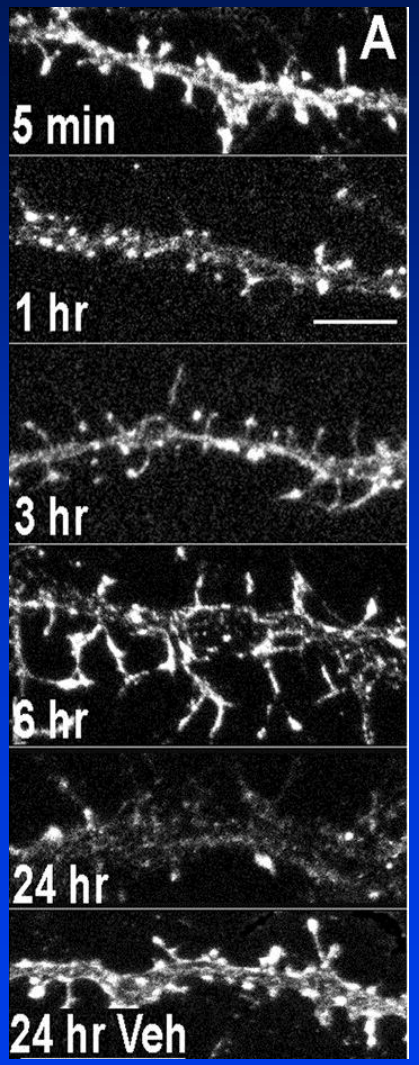


Prion Diseases



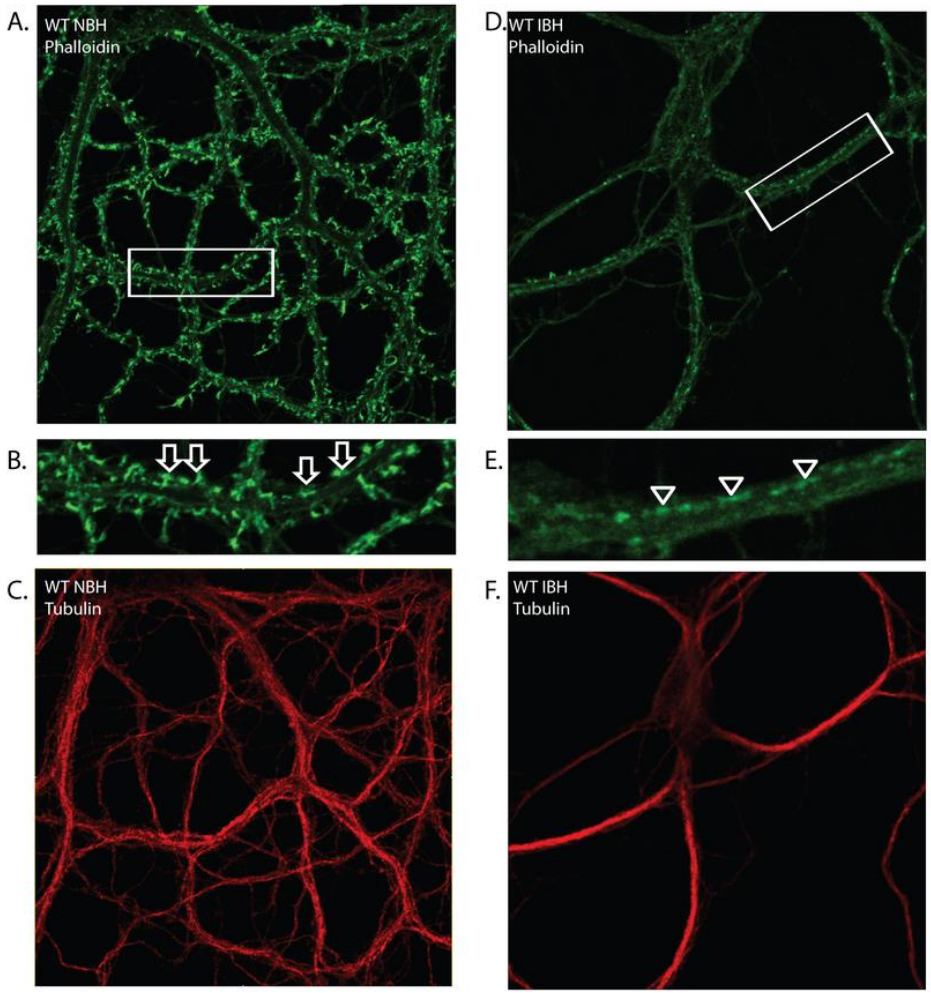
Fuhrmann et al. , *J. Neurosci*. (2007)

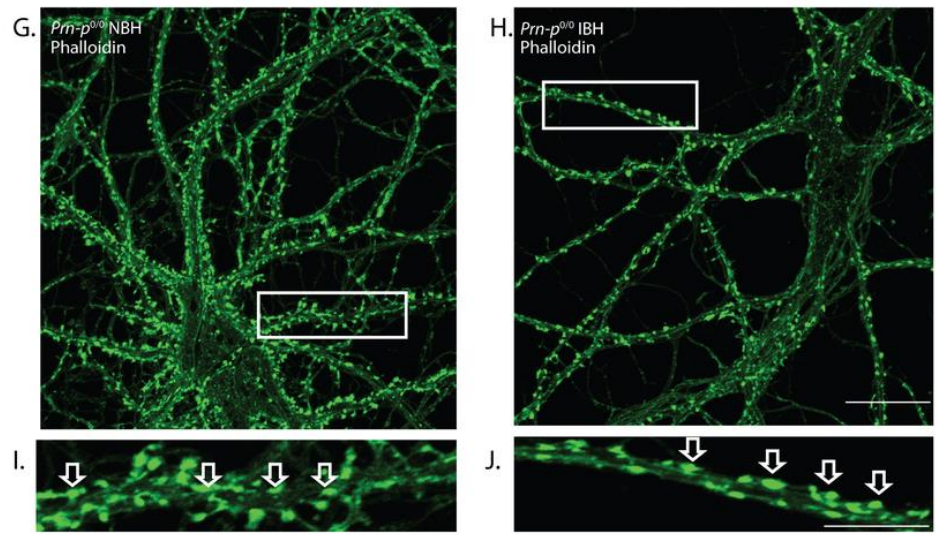
Alzheimer's (Aβ)

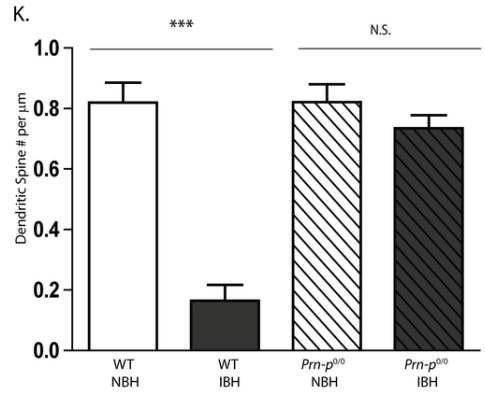


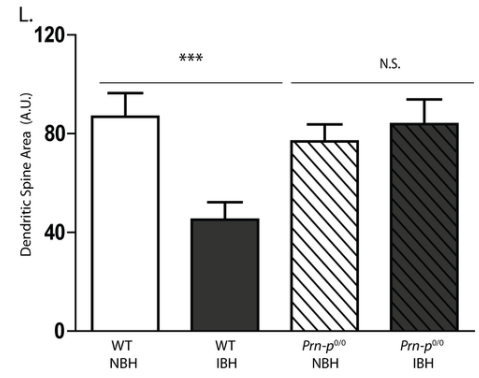
Lacor et al., *J. Neurosci*. (2007)

Prions cause collapse of dendritic spines: impaired neuronal function





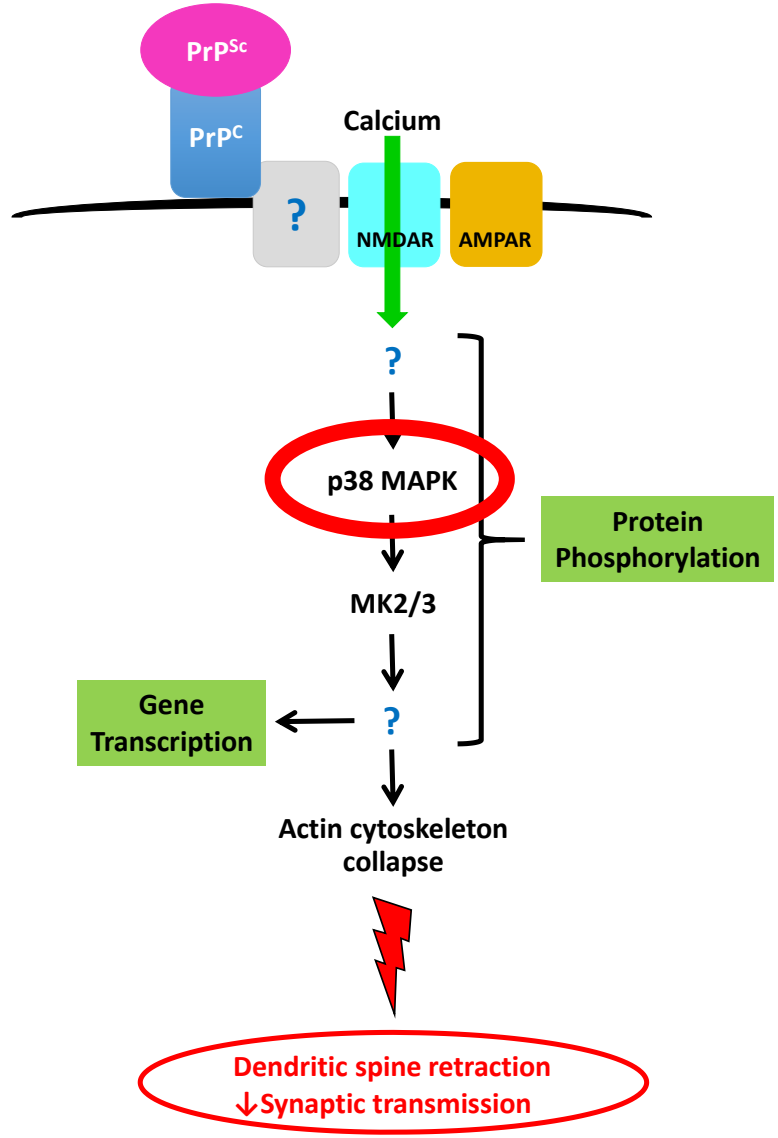




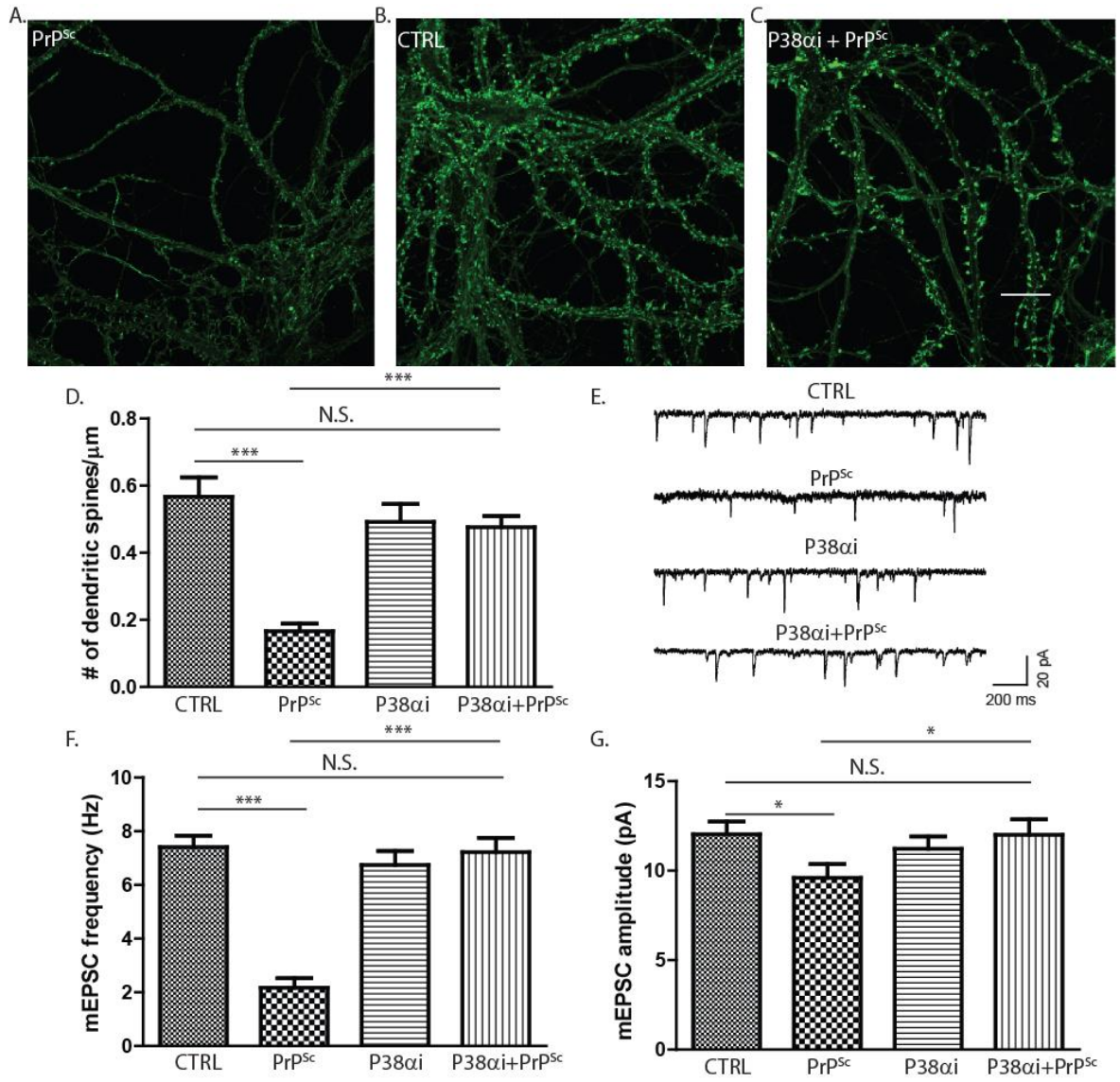
- **Dependent on PrP^C expression**
- **Flattening/retraction of spines**
- **Before degeneration of shafts**

Fang et al., *PLoS Path*. (2016)

A cellular pathway for prion synaptic toxicity



p38 MAPK inhibitors reverse prion damage to synapses!



Our Plan

Combine two kinds of drugs*:

1. PrP^{Sc} propagation inhibitor

2. p38 MAPK inhibitor

***Select drugs that have been used previously in humans (neurological, inflamm. diseases)**

Feed these drugs to mice w/ a prion disease. Measure:

1. Clinical features (survival)

2. Neuropathology

3. Biochemistry

Does this drug combination slow or prevent prion disease in mice?

If so, maybe this therapy can be moved rapidly into humans

Summary

- We have identified a new class of compounds that inhibit the accumulation of prions in cells, and have identified improved versions of these compounds.
- We have worked out a cellular pathway responsible for the neurotoxic effects of prions, and have identified compounds that block specific steps in this pathway.
- We are now testing clinically relevant examples of these two categories of compounds in mouse models of prion disease.
- We hope our studies will result in a highly synergistic combination therapy for prion diseases that may be directly translatable into human patients.

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