Highly Synergistic Combination Therapy for Prion Diseases

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A two-pronged therapy: Block prion propagation and toxicity

1. Conventional $R_x$ Approach
2. Novel $R_x$ Approach

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

A. 

B. 

C. 

D. 

% PrP^Sc/DMSO

% Cell viability

Ortho methyl preferred
Phenethyl amine required
R and S stereochemistry
Benzyl amine required
Substitution ok
Secondary amine preferred
Hydrogen bonding preferred

JZ107 (Active)

JZ103 (Inactive)

RML
22L
MTT

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\textsubscript{Sc})
A two-pronged therapy: Block prion propagation and toxicity

1. Conventional Rx Approach
   - Conversion
   - Halt or even reverse ongoing neuronal damage

2. Novel Rx Approach
   - Synaptic 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

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

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

Cheng Fang

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

Prion Diseases

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

Alzheimer's (Aβ)

Prions cause collapse of dendritic spines: impaired neuronal function

- Dependent on PrPc expression
- Flattening/retraction of spines
- Before degeneration of shafts

Fang et al., *PLoS Path.* (2016)
A cellular pathway for prion synaptic toxicity

PrP<sub>Sc</sub> → Calcium → p38 MAPK → MK2/3 → Protein Phosphorylation → Gene Transcription → Actin cytoskeleton collapse → Dendritic spine retraction ↓ Synaptic transmission
p38 MAPK inhibitors reverse prion damage to synapses!
Our Plan

Combine two kinds of drugs*:  
1. \textit{PrP}^{\text{Sc}} \text{ 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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