A novel therapeutic approach to Prion Diseases

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Challenges of anti-prion therapeutics

- **Blood-brain barrier**
- **Absence of pre-clinical diagnosis**
- **Structure of the prion?**
- **Mechanism of conversion the prion protein?**
- **Prion strain selection and mutation**
  -> a moving target?
Conversion of the prion protein into its pathogenic counterpart

Seeding model

Normal prion protein

Pathogenic prion protein
Reduced amounts of prion protein delay prion disease
Prion protein is dispensable for the host

Normal development and behaviour of mice lacking the neuronal cell-surface PrP protein


129/Ola Mice Carrying a Null Mutation in PrP that Abolishes mRNA Production Are Developmentally Normal

J. C. Manson,*,1 A. R. Clarke,2 M. L. Hooper,2 L. Aitchison,1 I. McConnell,1 and J. Hope1
Therapeutic approach to reduce cellular prion protein
High Throughput screening approach for reducing prion protein

Detection of PrP at the cell surface: immunofluorescence

Anti-prion protein monoclonal antibody

The Scripps Florida
ultra high throughput screening platform
High Throughput screening approach for reducing prion protein

FRET-Enabled High Throughput Assay (FEHTA)

Z’>0.5
Pilot screen, US Drug collection (1280 compounds)

Summary of compounds reducing cell surface prion protein by more than 50%

DMSO (purple) : no drug control
Pilot screen, US Drug collection (1280 compounds)

Summary of compounds exhibiting ≤ 10% toxicity
Pilot screen, US Drug collection (1280 compounds)

Summary of selected compounds

DMSO (purple) : no drug control

Selected compounds (<10% toxicity, activity in secondary assays)

★ **Tacrolimus** : immunosuppressant

★ **Astemizole** : anti-allergy drug
Pilot screen, US Drug collection (1280 compounds)

Confirmatory assays

IF Prion protein labeling

Control

C2151

Treated cells (duplicate)

PrP KO cells

Untreated cells

C2151

Flow cytometry
Efficacy of PrP suppressing compounds in cell culture

Scrapie prion-infected neuroblastoma cells: Western blot to display pathogenic prion protein

9 days post-infection

No rebound effect

18 days (6 days w/o Treatment)
Mode of action: Tacrolimus reduces prion protein inside and outside the cell

Protein

Transcript

Drugs used at prion inhibitory dose (PID)
Mode of Action: Astemizole induces ‘autophagy’ (self-eating)

Drugs used at prion inhibitory dose (PID)
Astemizole prolongs the survival time of prion-infected mice

Scrapie prion-infected mice (*intracerebral*)
Astemizole treatment (*intraperitoneal, day 20 to 50 post-infection*)
Perspectives

**Astemizole**  $\rightarrow$  Further explore therapeutic efficacy

**PrP-FEHTA methodology**  $\rightarrow$
- NIH-funded screen
- Development of new anti-prion drugs
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