Treatment with a Non-Toxic, Self-Replicating Anti-Prion

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Outline

- Prion replication.
  - Brain cell environment.
  - Misfolding of the cellular prion protein (PrP\textsuperscript{C}) into PrP\textsuperscript{Sc}.
- Modeling prion disease.
  - Phases of prion infection.
- Non-pathogenic prions.
  - Synthetic prions.
- Anti-prion concept.
  - Competition between pathogenic and non-pathogenic prions.
- Summary, conclusions, and future directions.
Prion Replication: Misfolding of the Cellular Prion Protein (PrP<sup>C</sup>)

Modeling Prion Disease: Clinical Phenotype

Common Models

PrPSc Titer

Time After Exposure

Infectivity Phase

Toxic Phase

Percent Survival

Time After Exposure

Asymptomatic

Symptomatic
Exposure to pathogenic prions.

- Toxicity and clinical onset.
- Tendency to be rapid and aggressive.
Do Non-Pathogenic Prions (Anti-Prions) with Therapeutic Potential Exist?

- Exposure to nonpathogenic, nontoxic anti-prions.
  - Accumulation without disease.
  - Tendency to replicate slowly.
Synthetic Prions: Promising Anti-Prion Candidates

- Recapitulating PrP misfolding in the laboratory.
  - Highly pathogenic and infectious conformations are rare.
  - Some self-replicate *in vitro* and *in vivo* without clinical onset.

Wang et al., 2010 Science; Makarava et al., 2010 Acta Neuropathol
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Anti-Prion Concept

- Simultaneous replication of pathogenic prions and anti-prions.
- Competition will reduce the amount of toxic prions, lower brain damage, and delay disease.
Anti-Prions Competing with Pathogenic Prions

USAIN BOLT’S MAX. SPEED
27.7 MPH

AVERAGE HUMAN WALKING
3 MPH

SOURCES: Illinois State University ISU ReD: Research and eData; Atlas Obscura; Live Science; Atkins Bookshelf
Efficiency Dependent on Treatment Timing

Disease Progression

Birth

Onset

Prion

Anti-Prion Treatments

A. Post-Exposure Treatment

B. Simultaneous Treatment

C. Prophylactic Treatment

A

B

C

0 60 80 100 120

0 60 80 100

0 60 80 100 120 140 160 180 200

Percent Survival

Time

0 20 40 60 80

Control

AP: t = +63 d

AP: t = 0

AP: t = -63 d

Efficiency Dependent on Treatment Timing
Prophylactic anti-prion treatment reduced infectivity by ~99%.
Anti-Prions Inhibit Pathogenic PrP<sub>Sc</sub> Replication

- PrP<sub>Sc</sub> deposition was low, but detectable, in the brains of anti-prion treated asymptomatic animals.
Summary and Conclusions

- A non-toxic, self-replicating anti-prion was generated from full-length recombinant PrP\textsuperscript{C}.
  - Mild PrP\textsuperscript{Sc} deposition observed > 400 dpi.
  - No clinical signs (> 600 dpi).

- The anti-prion significantly inhibited pathogenic prions in hamsters.
  - Simultaneous and prophylactic treatment.
  - Efficiency was dependent on time and the pathogenic prion dose.

- After anti-prion treatment, PrP\textsuperscript{Sc} accumulation was significantly lower, and disease was occasionally prevented.
  - Prion infectivity was reduced by approximately 2 logs.

**Conclusion:** Prion replication can be separated from toxicity, thus providing a novel target for therapeutic intervention.
Future Directions

- Define the underlying mechanism for the anti-prions.
  - Competition for PrP^C substrate, host response to prophylactic treatment, etc.

- Determine whether anti-prions are applicable to diverse prion diseases of different species.
  - Utilize established transgenic mouse models.

- Attempt to obtain more potent anti-prions.
  - Do non-pathogenic prions that replicate faster exist?
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