



Prion diseases: *In vitro* conversion assay and applications

The Challenge: Several neurodegenerative disorders including, 1) bovine spongiform encephalopathy in cows (“mad cow disease”), 2) scrapie in sheep and 3) Cruzfeldt Jacob disease in humans, are all caused by the misfolding and aggregation of the normal form of the prion protein (PrP^C) into infectious, amyloid form (PrP^{Sc}). PrP^{Sc} accumulates as amyloid plaques in the central nervous system, including the brain, and is toxic to neurons. The prion diseases are 100% lethal; no anti-prion therapeutics or ante-mortem diagnostics are currently available. Inventing a technology for producing the disease-related, amyloid form of PrP *in vitro* would be valuable for studying the basic mechanism of prion disease and for a variety of commercial applications.

UMBI Solution: A UMBI scientist has developed a simple, one-step protocol for generating a disease-related amyloid form of the prion protein *in vitro* using full-length recombinant PrP^C. While not infectious, the amyloid form of the prion protein produced *in vitro* mimics all physical features of the authentic, infectious PrP^{Sc}. The current invention opens new opportunities for a number of applications including, 1) modeling of prion conversion *in vitro*, 2) utilizing amyloid form as an immunogen for generating PrP^{Sc}-specific antibodies, 3) screening of anti-prion drugs using an *in vitro* conversion assay, and 4) developing anti-prion therapeutic strategies that involve active immunization with recombinant amyloid.

Commercial Applications:

- Drug development: automated *in vitro* high-throughput method for screening potential anti-prion drugs and inhibitors.
- Generation of PrP^{Sc}-specific antibodies.
- Development of active immunization.

Advantages:

- Recombinant amyloid mimics PrP^{Sc} conformation, while not infectious.
- The invention has been reduced to practice in semi-automated *in vitro* assay for screening of prion inhibitors.

Stage of Development: Preclinical

Patent Status: Pending US and PCT applications

Licensing Potential: UMBI is seeking exclusive or non-exclusive licensees to all or part of this technology. The UMBI inventor would welcome the opportunity to collaborate with any licensee to further refine this invention or extend its capabilities.

Inventor & UMBI Reference: Baskakov, 04-011

Relevant Selected Publications:

1. Bocharova, O.V., Breydo, L., Parfenov, A, Salnikov, V.V., Baskakov, I.V. 2005 *In vitro* conversion of full-length mammalian prion protein produces amyloid form with physical properties of PrP^{Sc}. *J. Mol. Biol.* v.346, p 645-659.
2. Breydo, L., Bocharova, O.V., Baskakov, I.V. 2005 Semi-Automated cell free conversion of prion protein: applications for high throughput screening of potential anti-prion drugs, *Analytical Biochemistry*, v.339, p. 165-1733.
3. Novitskaia, V., Makarava, M., Bellon A., Bocharova, O.V., Bronstein, I. Williamson, A., Baskakov, I.V. 2006 Probing the conformation of the prion protein within a single amyloid fibrils using a novel immunoconformational assay, *J.Biol.Chem.* V. 281, p. 15536-15545.
4. Anderson, M., Bocharova, O.V., Makarava, N., Breydo, L., Salnikov, V.V, Baskakov, I.V. 2006 High Polymorphism and Ultrastructural Organization of Prion Protein Amyloid Fibrils: An Insight from High Resolution Atomic Force Microscopy, *J.Mol.Biol.* V. 358, p. 580-596.
5. Makarava, M., Baskakov I.V. 2008 The same primary structure of the prion protein yields two distinct self-propagating states. *J.Biol.Chem.* in press.

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