# Natural Prion Structure is Very Different from the Structure of Recombinant Prion Protein Amyloid

The mammalian prion protein (PrP) folds into an alternative conformation $PrP^{Sc}$ to form the infectious entity responsible for human Creutzfeldt-Jakob disease, bovine spongiform encephalopathy (mad cow disease), scrapie in sheep, and several other mammalian CNS disorders[1]. The mis-folded protein is the sole component of the infectious prion. Prions can form amyloids, characterized by the formation of long unbranched protein filaments, distinct staining properties, and a structure of β-strands approximately at right-angles to the filament axis. This cross-β structure is indicated by meridional intensity at about 4.75 Å resolution in fiber diffraction patterns. Although this characteristic diffraction feature has been seen in many amyloids, until now it has not been observed for prions.

Amyloids have been implicated in more than forty diseases, including neurodegenerative diseases such as Alzheimer's, Parkinson's, and Creutzfeldt-Jakob diseases, as well as type II diabetes and other non-neurological amyloidoses. There is increasing evidence that the propagation of amyloid protein mis-folding, essentially a process of infection without any requirement for a nucleic acid in the infecting material, is in principle the same in functionally non-infectious diseases like Alzheimer's as it is in overtly infectious prion diseases such as scrapie and mad cow disease.

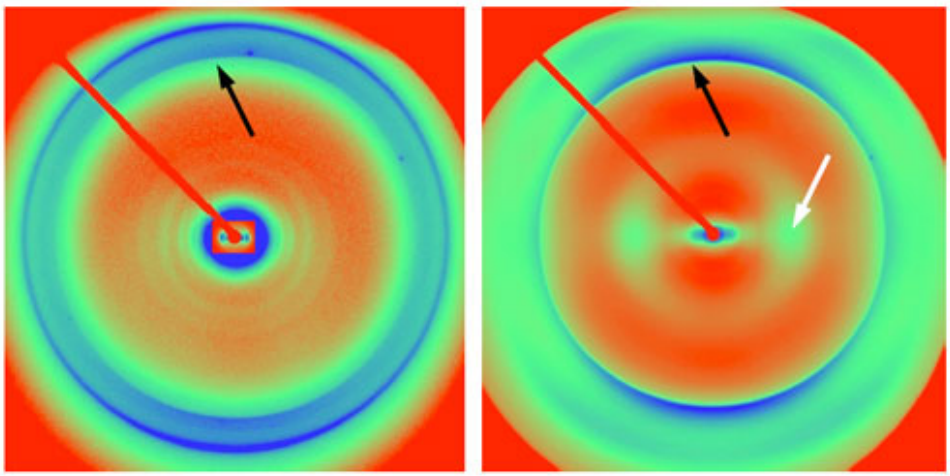

**Figure 1.** X-ray diffraction patterns from (left) brain-derived Syrian hamster PrP 27–30 and (right) recombinant mouse PrP (89–230). The recombinant hamster diffraction pattern is very similar to the mouse pattern. Black arrows indicate cross-β meridional diffraction at close to 4.8 Å resolution; white arrow indicates broad equatorial diffraction at about 10.5 Å resolution, seen in recombinant diffraction patterns, but not in patterns from brain-derived prions.

Diffraction data (Fig. 1) were obtained from fibers of hamster and mouse brain-derived PrP 27–30, a proteolysed form of $PrP^{Sc}$ that retains full infectivity and about 65% of the prion protein. Diffraction from many amyloids, and particularly from prions, is extremely weak because of both the amyloid structure and the high degree of disorder often found in biological amyloids. Interpretable diffraction required

elaborate purification protocols from hamster and mouse brains, carefully controlled conditions for fiber formation[2], and the exceptionally clean and intense beam from SSRL Biological Small-Angle X-ray Scattering Beamline 4-2. Additional data were obtained from the BioCARS beamline at the APS at Argonne National Laboratory. The equatorial diffraction patterns from brain-derived prions were characteristic of cylindrical structures, consistent with a β-helical structure such as has been proposed from electron microscopic and protein folding considerations[3]. Weak meridional diffraction in some patterns indicated an axial repeat of 19.2 Å, the repeat expected from a four-stranded β-sheet, again supporting the proposed β-helical structure.

Diffraction data were also obtained from fibers of recombinant mouse and hamster PrP amyloid (Fig. 1). Although the recombinant amyloids have been found to be infectious[4], a remarkable achievement in itself, the infectivity is much less than that of natural brain-derived prions. The recombinant diffraction patterns were markedly different from those of brain-derived prions. They were characterized by strong equatorial intensity at approximately 10.5 Å, absent from brain-derived prions, and indicating the presence of stacked β-sheets. Diffraction patterns calculated from the β-helical structure and a model stacked β-sheet structure[5] strongly resembled the observed diffraction patterns for the brain-derived prions and recombinant PrP amyloid respectively (Fig. 2).

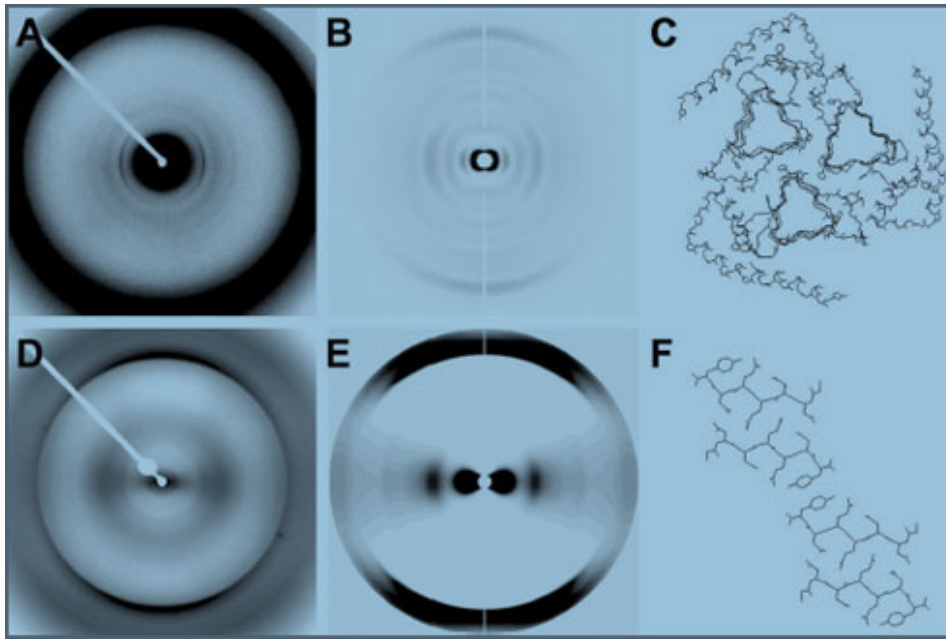


**Figure 2**. Observed and calculated diffraction patterns for β-helical and stacked-sheet models. (*A*) Experimental diffraction pattern from hamster PrP 27–30. (*B*) Calculated diffraction from a β-helical model. (*C*) Model used to calculate data in *B*. (*D*) Experimental diffraction pattern from recombinant PrP amyloid. (*E*) Calculated diffraction from a stacked-sheet model. (*F*) Model used to calculate data.

Diffraction from synthetic prions recovered from transgenic mice inoculated with the recombinant PrP amyloid strongly resembled diffraction from naturally occurring prions. A number of hypotheses might explain these observations. It may be that

only a small fraction of recombinant PrP amyloid has a replication-competent conformation. Alternatively, the recombinant amyloid may have to undergo a conformational maturation to acquire replication competency, or inhibitory forms of recombinant amyloid may interfere with replication during the initial transmission.

**Primary Citation**

Holger Wille, Wen Bian, Michele McDonald, Amy Kendall, David W. Colby, Lillian Bloch, Julian Ollesch, Alexander L. Borovinskiy, Fred E. Cohen, Stanley B. Prusiner, and Gerald Stubbs (2009) Natural and synthetic prion structure from X-ray fiber diffraction. *Proc. Natl. Acad. Sci. USA* **106**, 16990–95.

**References**


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This work was supported in part by grants from the National Institutes of Health (NS064, AG010770, and AG02132), the Fairchild Foundation, and the G. Harold and Leila Y. Mathers Foundation. DWC was supported in part by a Jane Coffin Childs postdoctoral fellowship.



SSRL is primarily supported by the DOE Offices of Basic Energy Sciences and Biological and Environmental Research, with additional support from the National Institutes of Health, National Center for Research Resources, Biomedical Technology Program, and the National Institute of General Medical Sciences.