Prion diseases are fatal, transmissible neurodegenerative diseases such as Mad Cow Disease and Creutzfeldt-Jakob Disease (CJD) in humans. CJD often has decades-long incubation periods and cannot be effectively diagnosed while in incubation. Brain sections of post-mortem CJD patients (lower) exhibit sponge-like holes compared to healthy brain sections (upper). There are currently no cures for prion diseases and prions are resistant to common methods of sterilization.

### Abstract

Fatal prion diseases, such as Creutzfeldt-Jakob disease in humans, are associated with the conversion of the normally folded mammalian PrP protein to a misfolded prion form that aggregates. Understanding how prions behave has been greatly facilitated by the study of prions in Saccharomyces cerevisiae, or baker’s yeast. In yeast, the translation release factor, Sup35, misfolds to form the [PSI+] prion. Although the Sup35 protein has a significantly different primary sequence from PrP, its prion form behaves similarly to human prions. The N-terminus of Sup35 is Q/N-rich and responsible for prion formation. Determining the structure of this region has proven difficult since the N-terminus forms aggregates instead of the ordered crystals required for structural studies. However, a small seven amino acid sequence (GNNQQNY) from Sup35’s N-terminus was crystallized by Nelson et al. (2005). We have constructed a 3D physical model of GNNQQNY as part of the MSOE SMART Teams program using 3D printing technology. GNNQQNY’s structure suggests that multiple prion molecules assemble into strong fibrous aggregates through tightly structured interlocking parallel beta sheets called a cross-beta spine. The structure of GNNQQNY suggests a potential model of how human prions assemble, which could potentially help in developing therapies that prevent aggregation.

### Summary

The [PSI+] yeast prion can be used as a model of mammalian prion behavior. Understanding aggregation of the GNNQQNY sequence may lead to possible therapies for human prion diseases.

### GNNQQNY Aggregate Structure

The Q/N rich N-terminus of Sup35, which is responsible for [PSI+] formation, cannot form crystals. Nelson et al. were able to crystallize 7 amino acids (GNNQQNY) from the prion domain. GNNQQNY binds in interlocking antiparallel units, which form a stack held together by hydrogen bonds (left).

### Sup35, [PSI+], and Related Research

The translational release factor, Sup35, can misfold to form the [PSI+] prion. Fusing the Green Fluorescent Protein (GFP) to Sup35 allows tracking within the cell. [PSI+] appearance is enhanced by increasing the levels of Sup35-GFP in the cell. Before prion induction, Sup35-GFP is spread evenly (1. left panel). During initial stages of prion formation, Sup35 forms intermediate ring and line structures (1. center) that eventually turn into fluorescent dots (1. right) that indicate [PSI+] aggregates.

When researchers induce [PSI+] formation in cells lacking a cell polarity gene, BEM1 (2.), the intermediate ring stages (2. center) appear normally, but cells do not become [PSI+]. Therefore, bem1 deletion mutants inhibit [PSI+] prion formation.