**Center for Biomolecular Structure and Dynamics - Research**

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**Project Title:** Structural and physiologic consequences of native post-translational modifications of the prion protein: a mechanism for toxicity

**Project Abstract:**
Prion diseases are “protein-only” fatal neurodegenerative diseases associated with the massive structural transformation of the normally soluble, GPI-anchored prion protein monomer (PrPsen for protease sensitive) into an aggregated, insoluble protein high in beta sheet content (PrPres for protease resistant). There is considerable debate regarding the actual cause of neuronal death; current thinking is that PrPres may propagate the disease but not be the actual toxic agent. Recent *in vivo* studies suggest that uncontrolled cation flux (a gain of function for PrPsen) is in part the cause of cell death, at least for some mutations that cause familial disease. We hypothesize that the observed ion current is directly related to conformational changes in PrPsen. The structural changes may induce ion flux by modulating the behavior of normal ion channels, but we believe that PrPsen forms pores by at least partially integrating into the membrane. We propose to investigate this hypothesis by using NMR and CD to compare wild type GPI-anchored PrPsen in bicelles with a mutant ΔCR, which has been shown to induce cation flux. Previous NMR crystallographic studies of PrPsen, while numerous, were done on protein that lacked glycosylation, the GPI anchor, and lipid, and thus membrane-induced structural changes would not have been evident.