

# Investigation of Prion Repeat Domains: Metal Binding, Coordination, and Selectivity.

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In the past several decades, considerable time and resources have been devoted to the study of mammalian prion proteins due to their role in transmissible spongiform encephalopathy (TSE) diseases such as “Mad Cow” disease in cattle, chronic wasting disease in deer, and Creutzfeldt-Jakob disease in humans. Despite the wealth of information on the mechanism of these diseases (the misfolding of the native protein) and the affinity and coordination of metal ions to the N-terminal octarepeat motifs, the role of metal coordination in both the native and disease forms is still being debated. Additionally, there is conflicting evidence on whether the avian prion protein is a metal chelator. (Interestingly, despite having a comparable protein, there is no known corresponding prion disease for birds.) For these reasons, we have designed a series of small peptides based on both the avian and mammalian repeat domains to investigate the metal binding affinity, coordination, specificity and reactivity.

The first peptide, P7, was designed to isolate and stabilize the octarepeat sequence (PHGGGWGQ) of mammalian prion within the context of the known and robust protein fold of *engrailed* homeodomain. This 28-mer peptide was remarkable because it not only maintained the overall structure of the parent motifs, but it also bound Cu(II) ions selectively, in the same coordination environment and with similar affinity as the parent octarepeat motif. Additionally, several other peptides based on the mammalian octarepeat are currently being investigated.

In order to investigate the possible binding site of the avian prion protein, two repeat units of the hexarepeat were used in the design of H2. Intriguingly, the peptide bound only one metal ion per the two repeats, indicating directionality and definition of the binding site. It also was found to have selectivity for Cu(II) ions and with an affinity in the  $\mu\text{M}$  range. Unlike the P7, H2 was found to have a measurable affinity for Zn(II) ion.