

**P010** Deconvoluting the copper<sup>2+</sup> binding modes of full-length prion protein

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The prion protein (PrP) is a cell-surface Cu<sup>2+</sup> binding glyco-protein which when misfolded is responsible for a number of transmissible spongiform encephalopathies. Full-length PrP(23-231) and constructs in which the octarepeat region has been removed, or His95 and His110 is replaced by alanine residues, have been used to elucidate the order and mode of Cu<sup>2+</sup> coordination to PrP(23-231). We have built on our understanding of the appearance of visible CD spectra and EPR for various PrP fragments to characterise Cu<sup>2+</sup> coordination to full-length PrP. At physiological pH, Cu<sup>2+</sup> initially binds to full-length PrP in the amyloidogenic region between the octarepeats and the structured domain at His95 and His110. Only subsequent Cu<sup>2+</sup> ions bind to single histidine residues within the octarepeat region. Ni<sup>2+</sup> ions are used to further probe metal binding and, like Cu<sup>2+</sup>, Ni<sup>2+</sup> will bind individually to His95 and His110, involving preceding main-chain amides. Competitive chelators are used to determine the affinity of the first mole equivalent of Cu<sup>2+</sup> bound to full-length PrP; this approach places the affinity in the nano-Molar range. The affinity and number of Cu<sup>2+</sup> binding sites support the suggestion that PrP could act as a sacrificial quencher of free radicals generated by copper redox cycling.