Experiences of circular dichroism spectroscopy in the study of self-assembling proteins

David Middleton, Department of Chemistry, Lancaster University

Around 30 human diseases and disorders are associated with protein self-assembly into insoluble, β-sheet rich amyloid fibrils that accumulate as plaque-like deposits in extracellular spaces. The fibril load can compromise organ function in some cases, but it is thought that soluble, cytotoxic oligomers that precede the nucleation of fibril growth are the common source of pathogenicity. An array of physical methods is needed to understand the factors that drive protein self-assembly at the molecular and atomic level and circular dichroism (CD) spectroscopy plays an important role in this regard. This presentation will give an overview of our recent experiences of bench-top and synchrotron radiation CD applied to amyloid systems, and highlight some of the problems encountered when studying proteins as they undergo self-polymerisation. Examples will be given showing how CD, when combined with NMR and other biophysical techniques, has enhanced our understanding of the medin amyloid polypeptide associated with amyloid lining the aorta, and apolipoprotein A-I amyloid associated with atherosclerosis. Finally, it will be shown that CD reveals the intriguing possibility that naturally occurring polysaccharides can catalyse the formation of amyloid by proteins and peptides that are not normally prone to self-assembly. In all cases, CD is a convenient and versatile tool for following the structural changes that accompany the assembly process from monomer to oligomer to fibril.