Self-assembly of peptides into fibrillar deposits is the hallmark of human amyloid disorders such as type 2 diabetes mellitus and Alzheimer’s disease. Amyloid formation is promoted by polyelectrolytes and other physiological factors in the biological environment. Specifically, highly sulfated linear polysaccharides, glycosaminoglycans (GAGs), associate with extracellular amyloid deposits in vivo. We are using solid-state NMR (SSNMR) and other biophysical techniques to define the fibre-GAG interface and the effect of GAGs on the fibre assembly mechanism.

Amyloid beta peptide (Abeta) forms typical amyloid fibres which are amenable to structural studies. Abeta fibres with 2-fold and 3-fold symmetric morphologies (Petkova et al. 2005, Science 307:262) were grown using seeds from the Tycko group. Fibres align upon stirring using a Couette cell to give a small linear dichroism (LD) signal. In the presence of the sulphated GAG heparin, a large LD signal is observed in the amide region and 3-fold symmetric fibres show additional signals due to aromatic-aromatic interactions. GAG binding assays assessed using heparinase cleavage showed more heparin was bound by fibres with 3-fold symmetric morphology than 2-fold. Areas of $^{13}$C chemical shift perturbation within Abeta fibres upon heparin addition have been identified. Detection of through space proton-proton contacts is being used to define the heparin binding site of Abeta fibres. Docking of hexasaccharide onto 3-fold symmetric fibres suggests a structural model for the complex.