Modelling Self-Assembling Peptides with Anti-Cancer Drug Delivery and Imaging Properties

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Self-assembling peptides exploit the chemical side chain diversity in the 20 proteogenic amino acids to tune their interactions with water and with each other. These peptides can be designed in a segmental fashion, with segments for hydrophobic interactions (rich in Phe and Tyr) such as π-π stacking, enzyme cleavable sequence (rich in Gly and Pro) and polar domains (enriched in charged residues). The ability to design such peptide amphiphiles relies on the efficient multiscale modelling of the process of self-assembly.

By using combination of coarse-grained approaches and atomistic molecular dynamics simulations, we can provide insights into the role of each residue in these systems designed to be packages for anti-cancer drugs which due to their hydrophobicity and poor solubility, show little cellular uptake otherwise. Coarse-grained MD simulations, allow for comparison of sequence variants especially in terms of solvent-exposure of charged groups, which show excellent agreement with experimentally measured zeta potentials and critical aggregation concentrations. Atomistic modelling also provides insights into linker sequence dependent conformations that aid in rationalization of circular dichroism and infrared spectra.

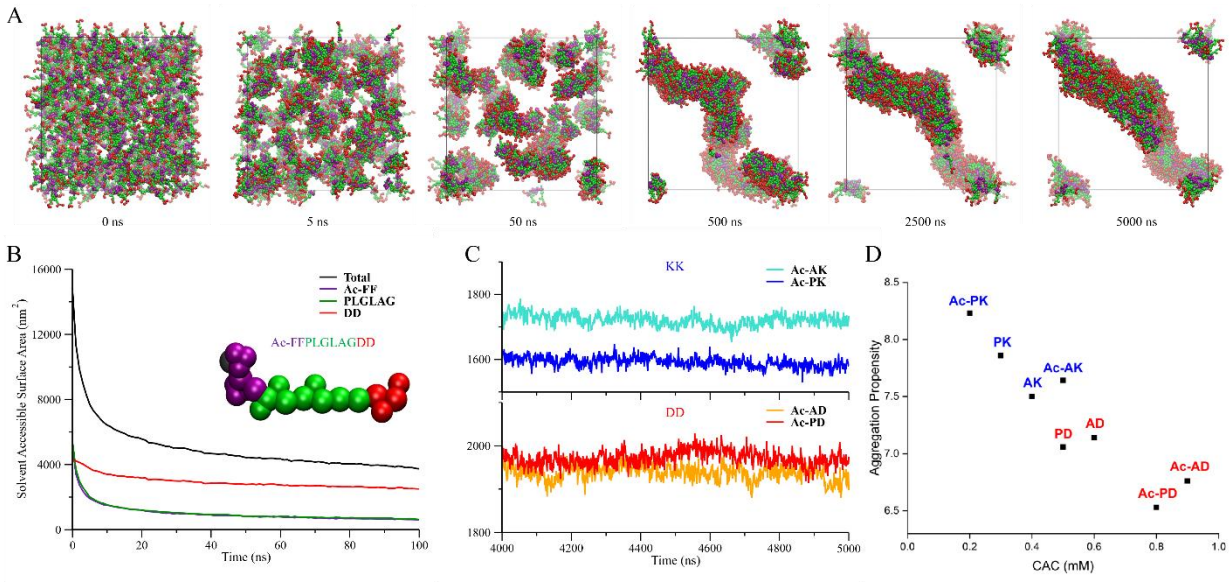

Figure 1 (A) Shows the Coarse-Grained MD trajectory of the self-assembly of a designed peptide amphiphile whose sequence is shown in (B) with changes in the Solvent Accessible Surface Area (SASA) of each color coded peptide segment showing the key role of the hydrophobic sequestration. (C) SASAs of the charged domains of these amphiphiles across single amino acid variants of these peptides. (D) Correlation between experimentally determined Critical Aggregation Concentration (CAC) and Aggregation Propensity = $SASA_{initial}/SASA_{final}$.