Bioprocessing Technology Institute
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Quantitative approaches in studying protein aggregation

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Host: Dr Ian Walsh

Seminar Abstract

Protein aggregation is a ubiquitous phenomenon in which peptides and proteins convert from their native, soluble state into intractable aggregated structures. This behaviour can manifest pathologically in a range of human disorders, while also posing as a critical challenge in biopharmaceutical processes. In order to study the molecular mechanisms of self-assembly, we have used the combination of a chemical-kinetics experimental assay and theoretical analysis to interpret the macroscopic experimental observables in terms of microscopic fundamental rate-determining steps in self-assembly reactions. Using the example of the amyloid-β peptide (Aβ) whose aggregation is a hallmark in Alzheimer's Disease, we demonstrate the quantitative modulation of its aggregation process through the presence of different biological factors including cholesterol-rich lipid membranes, metal ions, and proteins with chaperoning functions. From there, we further develop a drug discovery strategy, known as "Structure-Kinetic Activity Relationship" (SKAR), which relates the chemical structure of a small molecule inhibitor to its potency in reducing the rate of formation of specific pathogenic species in the aggregation process. Altogether, our work has presented new opportunities in uncovering the fundamental complexities pertaining to self-assembly reactions. In particular, we will discuss how such methods can potentially be adapted as well to solve issues in biotherapeutic manufacturing processes, such as glycoprotein therapeutics, through the development of new analytical tools and workflows, including methods like hydrogen deuterium exchange mass spectrometry (HDX-MS) and capillary electrophoresis (CE).

About the Speaker

Sean received his BSc in Chemistry from University College London in 2014, and an MPhil in Chemistry from the University of Cambridge in 2015. He continued to do a PhD in Biophysics at the University of Cambridge, studying mechanisms of protein aggregation through a combination of chemical-kinetics based experimental assays coupled with theoretical analysis. After obtaining his PhD in 2019, he joined a biotechnology startup based in the UK working on the development and characterisation of antibodies, and subsequently managing a team of scientists to develop antibody-based assays for diagnostic and therapeutic purposes in protein misfolding diseases. His research interest focuses on developing approaches in understanding and controlling self-assembly reactions to preserve stability and functionality of biotherapeutic molecules. At BTI, Sean has joined the GlycoAnalytics team to explore new methods and workflows in the characterisation of biologics, such as charge-variant analysis and glycoprofiling.

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