NUS National University of Singapore

Department of Biological Sciences
Faculty of Science

SEMINAR

Thurs, 22 Aug 2019 | 11.30am | DBS Conference Room 1

Hosted by A/Prof Pakorn Kanchanawong, MBI

Dynamic-liquid conformations in disease pathology and transmission

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Many proteins that perform important biological functions are completely or partially disordered under native conditions. These so-called intrinsically disordered proteins (IDPs) do not adopt a well-defined three-dimensional structure in isolation, but instead populate a heterogeneous ensemble of rapidly interconverting conformational states. Recognition of the natural abundance and functional importance of IDPs, is in fact changing our current understanding of protein science. The field has only recently come to acknowledge that disease-relevant IDPs have properties of protein misfolding disorders, with evidence of the spreading of pathogenic proteins within the central nervous system. Many of these IDPs are found associated with cellular membranes, in both their normal and disease conformations suggesting that these protein-membrane interactions may play a key role in the pathogenesis of these diseases. However, a large gap remains in our ability to quantitatively recapitulate the functional complexity of cells through the reconstruction of partial cellular functions in vitro from purified or engineered parts. To accomplish this goal, we use interdisciplinary approaches combining single molecule biophysics and computational methods and develop tools for unprecedent quantitative assessment of our observables. Here two IDP systems will be discussed; islet amyloid polypeptide and □-synuclein, proteins associated with type II diabetes and Parkinson's disease, respectively. With their exceptional spatio-temporal heterogeneity and high conformational flexibility, IDPs represent complex systems that act at the edge of chaos and are specifically tunable by various means. Our aim is to obtain fundamental insight into kinetic and structural transitions associated with these proteins to reveal their intracellular gains of function. Addressing common characteristics of such systems including their dynamic nature and multivalency, we further question how these properties and their propensity to form liquid-liquid droplets may be relevant to their function and disease progression and transmission.

Artwork by Ann Nee, DBS, NUS