BBSRC-funded PhD at the University of Bath, UK: Conformational dynamics of the immune regulator STING

Are you fascinated by the way that proteins can change shape? Do you want to find out how this can be affected by drug binding? Do you want an interdisciplinary PhD on a cancer immunotherapy drug target with an industrial placement at the global pharmaceutical company MSD? Then apply for this BBSRC-funded PhD at the University of Bath, UK: Conformational dynamics of the immune regulator STING. Informal enquiries welcome to c.a.dodson@bath.ac.uk. **This studentship is funded for EU / International / UK students and all suitably qualified applicants (biological or physical science background) are very welcome to apply.**

Protein conformational dynamics – and the way in which these are influenced by small molecule ligands – are increasingly thought to underpin the mechanism of many biological processes. The protein STING (stimulator of interferon genes) regulates the interferon-mediated antiviral response and is activated by 2',3'-cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) in response to cytosolic DNA. STING is also activated by the presence of some pathogenic bacteria. Upon activation, bound cGAMP is sequestered from bulk solution within the STING dimer interface by closure of a 20-residue lid region, coupled to larger-scale conformational change. There is currently much commercial interest in the development of STING agonists for use in anti-cancer immunotherapy, however the underlying biophysical behaviour of STING (timescale and drivers of conformational change) remains poorly understood.

This project will address this gap by developing a fluorescence assay to report on STING conformational change in solution. We will characterise STING conformation in the presence and absence of small molecule ligands and determine the timescale of conformational change. We will probe conformational heterogeneity by performing experiments at the single molecule level and will carry out modelling to relate protein conformation and dynamics to ligand residence time. Our experimental equipment can capture events on timescales ranging from nanosecond to hours.

The project will be supervised by Dr Charlotte Dodson at University of Bath (lead academic supervisor), Dr Katie Chapman at MSD (Merck Sharp Dohme; industrial supervisor) and Prof Jean van den Elsen (University of Bath; second academic supervisor). It is suitable for students with a biological or physical science background who are interested in the physical behaviour of proteins and drug-target interactions. As part of the PhD, you will undertake a 6 month placement in the MSD laboratories at the Francis Crick Institute in London.

Closing date for applications: 7th December 2020