**Understanding PROTACS (PROteolysis TArgeting Chimeras) in Disease Treatment**

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PROTACS (PROteolysis TArgeting Chimeras) are a new chemical modality for the treatment of disease (cancer, immune disorders, neurodegenerative diseases etc.) and have different biology compared to other drug approaches. PROTACS are unsymmetrical bifunctional molecules that connect a ‘Protein of interest (POI)’ ligand via a linker to an E3 ligase ligand allowing binding to the POI and subsequent degradation of the protein by the proteasome (see figure 1)1. As the degradation induced by PROTACs is a catalytic process they may work at low doses and possess several advantages over conventional small molecules; most notably allowing targeting of proteins that were previously considered “undruggable” due to lack of a functional binding domain. Very little is known regarding the physical properties of these novel large molecular weight, flexible and often poorly soluble compounds. This project will study the crystallisability, stabilization of amorphous forms, formation of crystalline/amorphous salts and coamorphous systems, and formulation approaches to deliver a formulated PROTACS product. Aggregation in solution is also a highlighted problem; therefore, understanding the role non-covalent interactions have on crystal packing and aggregation properties will be important. This project is multidisciplinary and will involve computational work, chemical biology, formulation and work on real PROTACS at AstraZeneca’s Macclesfield site.

The project is led by formulations expert Dr. James McCabe at AstraZenca in collaboration with Prof. Jon Steed who has many years’ experience of novel crystal growth strategies, interrogation of crystal structures and understanding of non-covalent interactions and their impact on solution/solid state behavior. Prof. Mark Wilson at Durham has experience in molecular dynamics and multiscale simulations of soft matter systems and Dr Clare Mahon is experienced in aggregation properties of large molecules such as polymers in biological applications.