Structural studies of cell signalling adaptor protein STimulator of INterferon Genes (STING) in complex with small molecule inhibitors

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Stimulator of interferon genes, also known as STING, is a key facilitator of innate immunity. It is a membrane signalling protein and functions as a small homodimer of 80 kDa. When the monomers come together to form the dimer, the C-terminal region of each monomer forms a butterfly-shaped ligand binding site [1].

STING senses pathogen or damage-associated molecular patterns (PAMPs and DAMPs), which are conserved molecular motifs secreted upon pathogen infection or by stressed, damaged or cancerous cells. A broad range of dsDNA and cyclic dinucleotides are responsible for STING activation triggering a downstream cascade of signalling events that lead to the production of interferons [2, 3]. Given its role in the first line of cell defense, STING is very important in the context of disease. Its activation has been linked with pathogen neutralisation and cancer immunotherapies. On the other hand, prolonged stimulation of the STING pathway has been associated with hyperinflammation, autoimmune diseases and the detrimental effects observed in traumatic brain injury [2, 4]. Dampening that pathway might be beneficial in many cases. Unfortunately, few STING inhibitors have reached the pre-clinical stage, but none made it to clinical trials [5, 6].

Our research aims to shed light on the molecular mechanisms of STING inhibition by providing structural insights into inhibitor-STING complexes. Currently, there are only structures of STING with activators, but none with inhibitors. We will explore druggable pockets located in full-length human STING with a series of inhibitors that have been previously reported in the literature but lack structural validation. We will use direct binding assays and cryo-electron microscopy to confirm binding and guide structure-based drug design. Progress has been made towards the expression, purification and characterisation of human STING and I will report advances in cryo-EM experiments and direct binding assays, exploring how STING interacts with the selected inhibitors.

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