Designing chemical probes for DCAF1 using match maker™

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Abstract

DCAF1 has been identified as a putative antiviral host target as well as a potential target to enable the proteasome-mediated degradation of therapeutic targets. It has a complex domain architecture, which contains a WD40 repeat (WDR) domain. The WDR domain is one of the most abundant protein-protein interactions (PPIs) domains in the human proteome. Given the significant role that PPIs play in many cellular processes and diseases there has been renewed interest in exploring WDR domain proteins, including DCAF1. Acting through the WDR domain, DCAF1 recruits substrate proteins to the CUL4A-RBX1-DDB1-DCAF1 E3 ubiquitin ligase complex for subsequent proteasomal degradation, which is the key process we aimed to modulate or exploit using small molecule probes. To discover novel DCAF1 probes, the interaction profiles of approximately 3 million commercially available compounds with ~8,500 proteins, including DCAF1, were rapidly predicted using Cyclica's MatchMaker technology. Briefly, MatchMaker is a deep learning approach capable of assessing small molecule-protein interactions across the proteome. MatchMaker predictions informed the nomination of compounds based not only on predicted binding for DCAF1, but also on the lack of interaction with undesirable off-targets. Using MatchMaker predictions, alongside traditional CADD tools, we predicted and tested experimentally multiple hits for DCAF1, one of which, CYCA-117-70 was subsequently co-crystallized and deposited as the first co-crystal structure of DCAF1 in the PDB [PDB ID: 7SSE 3].

Biography

Julie received her BSc(Hons) in Chemistry from University College Cork in 2004, then began her career as a Senior QC Analyst at Pfizer. She subsequently worked for an electrochemical start-up "Anzode" in New Zealand and as an analytical chemist for Colorcon before moving into investment banking, where she used her experience managing projects to perform Execution Management at CIBC for 5 years. Julie then returned to science, obtaining an MSc in Drug Design from University College London, where she earned the Dean's Prize for her dissertation on repositioning drugs to treat malaria. She became a member of the OICR Drug Discovery team in 2017, working as a computational chemist, specifically virtual screening, providing structural insights to binding, generating homology models of proteins as well as database management for various projects. Julie has been working as a Senior Scientist on the Drug Discovery team at Cyclica since August, 2020, where she applies Cyclica's technology to drug discovery projects. Today's talk will provide an overview of Cyclica's MatchMaker technology and how Julie used Matchmaker to design a novel inhibitor for DCAF1, resulting in the first co-crystal structure of DCAF1 with a ligand to be deposited in the PDB.

References

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