P-2.165

Optimising Pipelines for in Silico Protac Screening

William Midgley [1], Fabio Montisci [2], Bojana Popovic [2], Ehmke Pohl [1]

[1] Durham University, Durham, United Kingdom

[2] Cambridge Crystallographic Data Centre, Cambridge, United Kingdom

PROTACs (Proteolysis Targeting Chimeras) are molecules which use the body's protein degradation system to remove unwanted proteins. They bind an E3 ligase with the "anchor" end and the protein of interest (POI) with the "warhead" end with a linker joining the two, bringing the POI close to the ligase. The ligase then ubiquitinates the POI, flagging it to be degraded by a proteasome. Although research is limited, linker design is essential to functional PROTAC development. Linker length, content, and attachment point can affect binding affinity and selectivity. Therefore, this project aims to develop computational methods to help direct PROTAC linker design by improving protein dynamics predictions.

We use the Cambridge Crystallographic Data Centre's (CCDC) Genetic Optimisation for Ligand Docking (GOLD) software for visualising and ranking PROTAC binding interactions with the POI and ligase. Docking poses are scored using methods which use a variety of metrics to determine docking ability. The CCDC's PROTAC Conformer Generator is used along with molecular dynamics simulations in order to produce high throughput PROTAC efficacy prediction in order to develop better pipelines for PROTAC design.

We will also use in vitro techniques to determine binding affinities of PROTACs to E3 Ligases and POI to corroborate the in silico results. Preliminary results will be presented.