Development of PROTACs for targeted protein degradation

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Proteolysis Targeting Chimeras (PROTACs) are heterobifunctional molecules that facilitate degradation of targeted proteins in the cell via the ubiquitin proteasome system. The catalytic mechanism offers a novel means to inhibit protein activity, while protein degradation offers a means to inhibit proteins with scaffold or other structural functions. PROTAC molecules are comprised of a ligand for the protein of interest, and a ligand for an E3 ligase (typically VHL or Cereblon) bound together by a linker. The molecule facilitates the recruitment of an E3 ligase to the protein of interest, enabling the formation of a ternary complex, which allows the E3 ligase to polyubiquitinate the protein of interest on lysine residues. This causes the protein to be recognised by cellular machinery resulting in its targeting to the proteasome for degradation. The ligand for the target protein as well as the linker and E3 ligase ligand are key in determining the ability of this complex to form.

We have synthesised multiple PROTACs that are effective at knocking-down two proteins of interest, utilising VHL or Cereblon. By using commercially available proteasome inhibitors we have verified that degradation occurs through the proteasome. Experiments have shown that degradation is concentration and time dependent, beginning at around 4 hours with maximal effects observed by 24-48hrs. For one target we have observed a ‘hook’ effect, whereby the PROTAC becomes saturating at higher concentrations, allowing the compound to exclusively bind to either the E3 ligase or the protein of interest. This saturation effect results in only partial protein degradation being observed, with greatest degradation at lower concentrations (0.625μM).

These findings present PROTACs as a potential future therapeutic that could be used to degrade a wide range of proteins, previously deemed ‘undruggable’. These molecules could therefore be applied to a variety of disease areas.