PROTACs [1]

PROTACs

Proteolysis-Targeting Chimeras (PROTACs) are heterobifunctional molecules capable of inducing protein-targeted degradation via the recruitment of the ubiquitin–proteosome system (UPS) PROTACs are made of three moieties: a warhead or protein of interest (POI) ligand, an E3 ubiquitin (E3) ligase-recruiting ligand and a linker connecting the two components.
The ability of PROTACs to exploit the primary intracellular degradation pathway in eukaryotic cells derives from the simultaneous engaging of the E3 ligase and the POI. This results in the formation of a stable ternary complex mediating the polyubiquitination of the POI, later degraded by the 26S proteasome.
PROTACs (also referred to as degraders) have emerged as a promising and innovative tool in the drug discovery landscape. In fact, their event-driven mode of action considerably increases the druggable portion of the proteome, overcoming one of the major limitations of small-molecule receptor inhibitors. Unlike small-molecule inhibitors, degraders target proteins with no known active sites or deep binding pockets, including scaffold proteins, protein complexes and transcription factors. Among the most remarkable advantages of degraders, the long-lasting efficacy and the sub-stoichiometric mode of action (referred to as protein knockdown) should be mentioned. Moreover, degraders seem to be a good therapeutic approach to overcome acquired resistance in cancer treatment.

Links
[1] http://www.cassmedchem.unito.it/en/node/5