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Perspective

Perspective on Targeted Protein Degradation strategy by PROTAC Technology

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The targeted protein degradation- proteolysis targeting chimeras (PROTAC) technology is an attractive strategy to evaluate the fast biology and changes in a target protein, and its degradation [1]. The PROTAC- a hetero bi functional small molecule, one end contains a ligand of protein of interest (POI) and other end E3 ligase ligand attached through a linker, there by formation of a ternary complex resulted in ubiquitination of E3 ligase and ultimately tagging target proteins (POI) that then are recognized by the proteasome for degradation [2]. PROTAC technology uses event driven process and catalytic mode of action, which is different than traditionally occupancy driven pathway and attracting from academia to industry.

Figure 1: Targeted protein degradation of PROTAC technology.

The unique PROTAC technology have proven a tool to investigate the biological functions of proteins in a post translational level and found many discoveries such as TRIM24 dependency in AML cell lines [3], BCR-ABL independency on CML stem cells [4] and a critical role of BRD9 (subunit of BAF) in synovial sarcoma [5]. we also used this strategy to evaluate the post translational functions of CBP/P300 protein in the cell [6]. In this study we developed a potent and selective PROTAC dCBP-1 that induce a degradation of CBP/P300 proteins in the multiple myeloma cancer cell lines. Using the series of experiments, we showed the degradation is selective over other proteins and the mechanism is dependent on ternary complex formation, followed by ubiquitination, and proteasomal degradation. This compound is exceptionally potent at killing multiple myeloma cells and ablates oncogenic enhancer activity driving MYC expression.

The PROTAC technology proven to be successful and willbe having very bright future in the drug discovery and development process.

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