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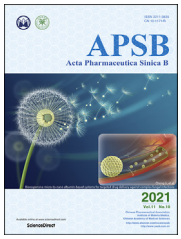

COMMENTARY

# Commentary: PROTACs make undruggable targets druggable: Challenge and opportunity

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Proteostasis (protein homeostasis) ensures precise adjustment of cellular demand to proteins in the stress conditions, which is essential in the maintenance of health environment inside cells and is indispensable for the life of organisms[1]. There are two major intracellular degradation systems for the cytosol proteins, the ubiquitin-proteasome system (UPS) and the autophagy-lysosomal system[2]. The key process of protein degradation is to recognize and extract the defective proteins from cellular organelles. During eukaryotic evolution, endoplasmic reticulum (ER)-associated protein degradation (ERAD) pathway has emerged for degradation of ER-resident proteins tightly regulated by the ubiquitin-dependent pathways[3]. In addition, degradation of defective proteins in mitochondria is also regulated by similar ubiquitin-dependent systems termed as mitochondria-associated degradation (MAD)[3]. Within mitochondria, there are also protein quality control machineries for different mitochondrial sub-compartments, including molecular chaperones and $AAA^+$ proteases for transporting, folding, unfolding, and degradation of proteins[4]. Precise control of the degradation process is an ideal strategy in the treatment of a variety of diseases, such as cancer, autoimmune diseases, neurodegenerative disorders, and aging, etc. PROTACs (PROteolysis TArgeting Chimeras), which were developed by Craig Crews and colleagues[5], have brought great hopes for making "undruggable targets" druggable in the potential new therapeutic strategy. PROTACs are referred to the synthetic heterobifunctional molecules, which contain a ligand for the target protein, a linker that recruits an E3 ubiquitin ligase for ubiquitination-mediated and proteasome-dependent protein degradation[6,7]. This class of molecules represents a new strategy for drug development, which is covered in a recent review article titled "Targeted protein degraders crowd into the clinic" at the journal of *Nature Reviews Drug Discovery* by Asher Mullard[8]. The article highlights the advantages of PROTACs in minimizing off-target-effect, first-in-class openings, cell selectivity, and low-molecular weight molecular glue. Indeed, the PROTACs-based drugs appear to have several desirable advantages compared to conventional.

## 1. To slow down drug resistance and reduce degrader target risk

The androgen receptor (AR) is a well-known target in the treatment of prostate cancer with the clinical efficacy demonstrated by AR

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antagonism. However, drug resistance to the anti-AR drugs has been an obstacle due to overexpression of AR protein in response to the treatment. To overcome the drug resistance, Arvinas Therapeutics, the pioneer company using PROTACs in drug development, has developed the first PROTACs-based drugs (ARV-110) with an initial clinical trial in 2019, and now is in the phase II trial. ARV-110 is an AR degrader, which is effective at a low dose for sufficient degradation of AR. The degradation occurs is fast enough to take care of AR-resistance. There are more than 15 synthesized degraders being considered for clinic trials by the end of 2021. The degrader toolbox grows rapidly[9,10], in which a PROTACs-tracking database suggests that there are more than 1600 heterobifunctional degraders for above 100 mammalian proteins. Increased number of large pharmaceutical companies have been participating in the competition in the development of druggable degraders.

In reduction of off-target effects, an example of PROTACs degrader is ibrutinib, a first-in-class inhibitor of Bruton tyrosine kinase (BTK) for treatment of patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) initially approved in 2013. By now, ibrutinib has been approved for application to various blood cancers. Ibrutinib acts through binding to BTK to inhibit the kinase in interaction with the substrate protein. The off-target effects have been the weaknesses of the medicine. To take care of the issue, PROTACs has been used in the development of two new BTK inhibitors (NX-2127 and NX-5948). NX-2127 is now in the phase I clinical trial and NX-5948 will be on the way to the clinic later this year.

## 2. To benefit the development of first-in-class drugs

Unlike the small molecular inhibitors that only block the active site of the target proteins, the degraders have the ability to destruct the proteins with multiple functions, which is one of the key selling points for PROTACs-based drugs. For example, when the catalytic activity of a kinase is blocked by inhibitors, the other activities of the kinase protein may remain to down-regulate the drug activity. In contrast, the degraders may offer great opportunities to resolve the issue by removal of the proteins (such as kinases) to inactivate both kinase and non-kinase activities. KT-474 is the degrader of IRAK4, a kinase that enables inflammatory signaling of both IL-1 family receptor and Toll-like receptor (TLR). PROTACs-based drug, KT-474, is the only one by now outside the oncology field in the phase I clinical trial for the autoimmune diseases including Alzheimer's disease (AD) and Huntington's disease. KT-474 may transform the current therapies to patients with the two diseases.

## 3. To improve the target selectivity

PROTACs can also improve cell selectivity to reduce toxicity. There are more than 600 known E3 ubiquitin ligases in the human proteome[8], and their protein expression levels are quite different in cells. Precise control of the ligase activity would benefit the degrader in the target selectivity, especially eliminating the protein targets usually undruggable by the current technology. Navitoclax is an inhibitor of BCL-XL, which is a potential anti-cancer drug that can be used either alone or in combination with other agents in the treatment of small cell lung cancer and acute lymphocytic leukemia. In addition, it can enhance the therapeutic effect of other chemotherapeutic agents[11]. Navitoclax has entered phase I and phase II clinical trials. However, navitoclax treatment leads to a reduction in platelet count. BCL-XL degrader DT2216 (navitoclax fused to a VHL-recruiting warhead), which was developed by Dialectic Therapeutics. Guangrong Zheng and Daohong Zhou, the co-founders of Dialectic Therapeutics, reported that DT2216 was less toxic to the platelets, while being much more effective at killing tumor cells than navitoclax[12]. DT2216 may have a good opportunity to be a safe and effective first-in-class anticancer agent targeting BCL-XL and is now in the phase I trial.

## 4. Glue degraders to render PROTACs a super-degrader

Unlike the heterobifunctional degraders that capture their targets through ligand−protein interactions, glue degraders capture their targets by modulating protein−protein interfaces to gain power in destroying the targets. However, it seems impossible for the heterobifunctional degraders. DKY709, targeting Helios, is now in the phase I trial for advanced solid tumors, as monotherapy and in combination with anti-PD1 PDR001.

GTPases are usually hard to be targeted. BMS developed a glue degrader CC-90009, which can lead to a maximized degradation of GTPase GSPT1 with a minimized toxicity through reducing degradation of Ikaros, Aiolos and other neosubstrates.

## 5. Future perspectives

The degrader toolbox is still growing, but most of them are based on the UPS system. To generate a complete line of the degraders, instead of just hijacking the E3 ligases, the finding of degrader targets for ER (ERAD) and mitochondria proteins (MAD) as well as the other organelles is still a challenge right now.

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