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Mini Review

In silico designing of Targeted Protein Degraders

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Abstract

Targeted protein degradation is projected as a radical therapeutic strategy in developing small molecule drugs. However, rational designing of such chemical entities is challenging and various CADD approaches are being explored across the globe to generate novel degraders. This brief review portrays some of the notable in silico molecular modeling techniques employed to date in degrader designing, including one of our proprietary algorithms (ALMOND) which demonstrated significant predictive ability across different target classes.

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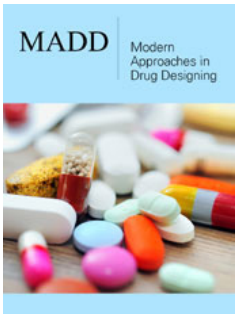

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Introduction

Targeted protein degradation as a therapeutic approach has seen phenomenal development and huge investments in recent years [1]. Proteolysis - targeting chimeras (PROTACs) and associated molecules that induce targeted protein degradation are of great value mainly because of potential advantages over conventional target occupancy-driven inhibitors with respect to dosing, safety, efficacy, selectivity and ability to modulate 'undruggable' targets [2]. These heterobifunctional small molecules harbor three chemical features: a moiety binding to the target protein, another one binding to E3 ubiquitin ligase and a linker for conjugating these two elements [3]. Apart from PROTACs, there are also certain non-chimeric small molecule protein-dimerizers called Molecular Glues, which also bind ubiquitin E3 ligases and recruit proteins for degradation, similar to PROTACs bringing about targeted protein degradation [4].

Clinical effectiveness of molecular glues is well-known [5] and quite a few PROTAC molecules have also recently shown adequate safety profile, therapeutic window and anti-cancer activity in the clinical setting [6]. However, the know-how of chemical matter designing is still maturing and the rational design approaches for degrader-based molecules are currently being probed [2]. These chemical entities can be modelled along with their target proteins as a tri-component binding system that can display cooperativity because of specific ligand-induced molecular recognition. In the beginning, most drug design techniques in this field relied on binary target engagement, partly due to limited structural data on ternary complexes. However, recent co-crystal structures of several PROTACs in ternary complex highlight the importance of protein–protein interactions and intramolecular contacts to the mode of action of this class of compounds [4]. These discoveries have opened the door to a new direction for structure-guided drug designing. This short perspective underscores some of the thought-provoking and noteworthy in silico structure-guided predictive algorithms explored so far for modeling and designing of such chemical entities.

One of the earliest known structure-guided PROTAC modeling algorithm is the PPIT (Protein-Protein Interaction Inducing Technology) methodology of Arvinas. The technique involves homology modeling coupled with molecular dynamics simulation that eventually aids in de novo warhead and linker designing [7]. Pérez-Benito et al. [8] described a molecular modeling tool that connects different pharmacophore signals via the shortest pathway along the receptors vdW surface and then computes scores for prioritization of new bivalent ligand designs. This tool could evaluate preferred linker lengths for different systems. Pfizer delineated a ternary complex based restrained and exhaustive conformer sampling technique which was used for designing BTK degraders of varying linker lengths [9]. The models generated rationally elucidated simultaneous engagement of BTK and CRBN by PROTACs,

which eventually leads to BTK ubiquitination and degradation. Dana-Farber, Harvard Medical School and Novartis reported application of a molecular docking tool named Rosetta [10,11] for generating virtual models of degrader induced ternary complexes. Using this tool, they demonstrated modest reproducibility of the crystallographic binding conformation of a BRD4 degrader in complex with target protein and CRBN. The model also provided a rational direction for optimization of linker length and attachment position (exit vector). Very recently, Bai N et al. [12] also reported implementation of the same tool for generating models of ternary complexes. In addition, they demonstrated that the generated models can be translated to rational prediction of degradation potency as well as selectivity. A 3D linker designing methodology from Oxford Protein Informatics Group, Exscientia, Ltd and the University of Cambridge [13] highlighted a structure-guided fragment or partial structure linking approach. The technique considers two fragments or fractional structures and thereafter designs a bifunctional molecule incorporating both. The whole process is protein-context-dependent and considers relative distance and orientation between the partial structures. Chemical Computing Group published some clustering and conformer sampling-based approaches for modeling ternary complexes and demonstrated that the techniques could reliably reproduce known crystallographic ternary complex structures [14,15]. Another fascinating methodology proposed by Weizmann Institute of Science employs sampling of both protein–protein interaction as well as degrader molecule conformational spaces. Using this methodology, they could demonstrate near-native prediction of crystallographic binding modes and ternary complex conformations. The technique is known as PRosettaC [16]. Even though some of these techniques could predict the conformation of ternary complexes with modest to good accuracy, there are only limited validation data available in the public domain to comprehend the extent to which these predictive models or tools can reliably predict secondary outcomes like ubiquitination and protein degradation. We recently developed a computing algorithm, ALMOND (ALgorithm for MOdeling Neosubstrate Degraders) [17] that employs both protein-protein as well as small molecule-protein docking simulations along with exhaustive conformational sampling and scoring. An outline of the same is depicted in Figure 1. Using this approach, we could demonstrate prediction of target degradation potency, as well as isoform selectivity in an epigenetic target class (SMARCA2/4) with over 80% accuracy. Good predictive accuracy has been observed in few other target classes, as well as BET bromodomains and kinases. Nevertheless, this technique is currently limited to designing degraders with very short or no linkers and further developments are ongoing to address the gaps.

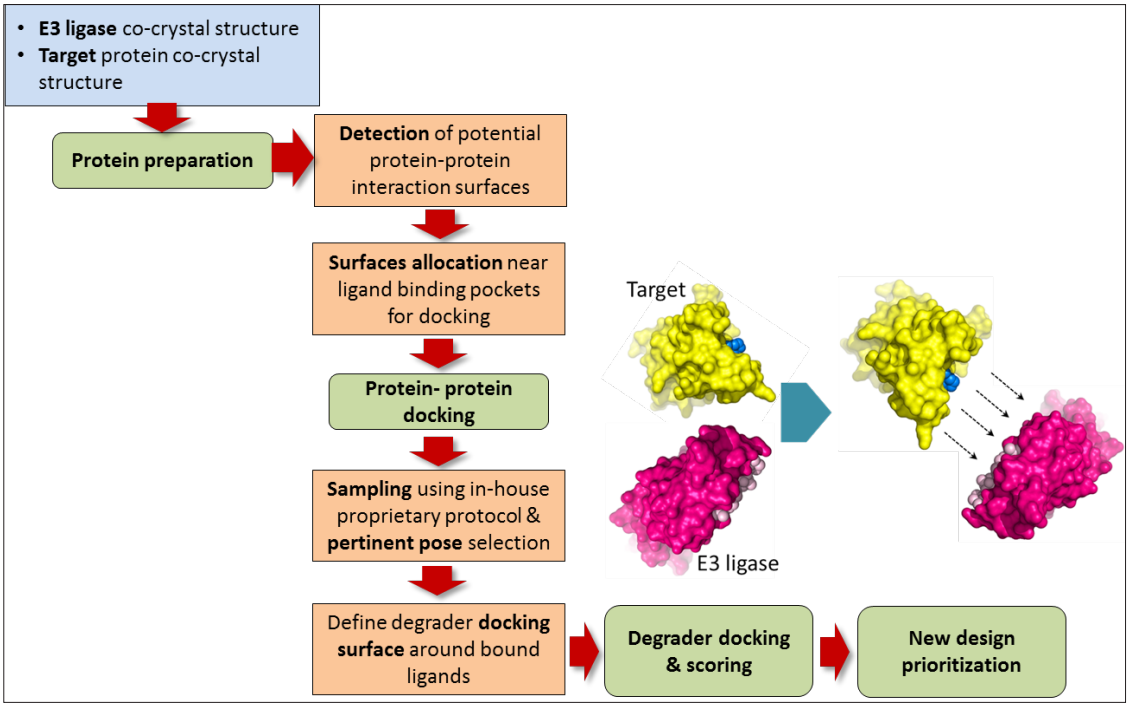

Figure 1: Schematic illustration of ALMOND algorithm.

In summary, targeted protein degradation has evolved as a trailblazing technique for knocking down different classes of proteins. Despite a number of distinct advantages over traditional target inhibitors, rational designing of such class of compound remains a significant challenge as of date. The authors believe advances in in silico and structural modeling techniques will play vital roles in the near future to gain finer comprehension of the structural biology and dynamics of degrader ternary complexes and will be essential to address the current gaps in knowledge associated with such chemical matter design.

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