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Targeted Protein Degradation: Mechanisms, Therapeutic Applications, Challenges, and Future Directions

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Abstract: Targeted Protein Degradation (TPD) has emerged as a transformational therapeutic technique for removing disease-causing proteins by utilising the cell's natural degradation systems, such as the ubiquitin-proteasome and lysosomal pathways. Unlike conventional inhibitors, TPD can target previously "undruggable" proteins, such as transcription factors and scaffolding proteins. Key modalities include proteolysis-targeting chimaeras (PROTACs), molecular glues, and lysosome-directed techniques like LYTACs and AUTACs. TPD has shown tremendous potential in oncology, neurological disorders, and immune-mediated diseases, with clinical candidates such as ARV-471 displaying good efficacy. TPD has several advantages, including catalytic activity, increased selectivity, and the ability to overcome drug resistance. However, issues persist in terms of oral bioavailability, off-target effects, and E3 ligase diversity. Emerging technologies like as artificial intelligence-driven design, novel delivery systems, and extended E3 ligase discoveries are propelling innovation in the field. As clinical results mount, TPD is set to transform drug research and treatment approaches for a wide spectrum of disorders.

Keywords: *Targeted Protein Degradation (TPD), PROTACs, Molecular Glues.*

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I. INTRODUCTION

Targeted Protein Degradation (TPD) is a novel therapeutic technique that eliminates disease causing proteins by utilising the cell's natural protein disposal systems rather than just inhibiting their function [1, 2]. Unlike conventional inhibitors, which occupy a binding site to impede function, TPD agents guide the target protein to cellular degradation machinery—most often the ubiquitin-proteasome system or the lysosome—where it is permanently eliminated from the cell [3,4]. TPD creates new therapeutic prospects by allowing the targeting of scaffolding proteins, transcription factors, and other "undruggable" proteins that do not have accessible catalytic sites for traditional medicines [5, 6].

II. MECHANISMS & MAIN MODALITIES

A. PROTACs (Proteolysis-Targeting Chimeras)

PROTACs are tiny, bifunctional molecules made up of two linked ligands: one that binds to the protein of interest (POI) and the other that activates an E3 ubiquitin ligase [7,8]. By combining these two proteins, PROTACs cause the development of a ternary complex (POI PROTAC-E3), which facilitates POI ubiquitination and transports it to the proteasome for destruction [9]. Importantly, this mechanism is catalytic, which means that a single PROTAC molecule can cause the destruction of many POI molecules. The potency and selectivity of a PROTAC are mostly determined by the ternary complex's shape and stability, rather than its binary binding affinities [10, 11]. A successful PROTAC design typically includes three critical elements: (a) a ligand for the POI, (b) a ligand for a recruited E3 ligase such as CRBN, VHL, MDM2, or IAPs, and (c) a linker that allows for effective ternary complex formation [12-15].

B. Molecular Glues

Molecular glues are tiny monovalent molecules that facilitate or stabilise direct contacts between an E3 ligase and a target protein [16]. Unlike PROTACs, they do not require a bifunctional design or linker and are frequently identified by

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phenotypic screening or chance findings in medicinal chemistry [17]. A well-known example is the class of thalidomide analogues, which reprogram the cereblon (CRBN) E3 ligase to promote the degradation of novel neosubstrates [18,19]. Molecular glues are frequently extremely selective and easier to optimise as tiny compounds; nonetheless, their discovery and rational design are less predictable than PROTACs [20-22].

C. Lysosome-Directed Strategies (LYTACs, AUTACs, ATTEC, AUTOTAC)

While PROTACs and molecular glues rely primarily on the ubiquitin-proteasome system, lysosome-directed methods offer an alternate method for degrading extracellular, membrane associated, or aggregated proteins [23]. LYTACs (lysosome-targeting chimeras) bind cell surface proteins and route them to endocytic receptors, which transport the cargo to lysosomes for destruction [24]. Instead, AUTACs and ATTECs use the autophagy apparatus to selectively degrade intracellular protein aggregates and organelles [25,26], whilst AUTOTACs take this notion a step further by employing autophagy-targeting receptors to accomplish more targeted degradation [27-29]. Collectively, these lysosome-based techniques increase TPD's breadth, allowing it to treat proteinopathies and membrane targets that proteasome-based strategies cannot reach [30–33].

III. APPLICATIONS ACROSS DISEASE AREAS

A. Oncology

Oncology is the most active field of TPD development, as many cancer-causing proteins are transcription factors or scaffolding proteins that are difficult to target with traditional inhibitors [12, 34]. PROTAC degraders have been developed to target hormone receptors such as ER and AR, kinases, and anti-apoptotic proteins such as BCL-xL, with several of them currently in advanced preclinical and clinical phases [13,35,36]. One such example is ARV-471 (vepdegestrant), an ER-targeting PROTAC that has advanced to late-stage clinical studies for ER-positive breast cancer [42,43].

B. Neurodegeneration

The buildup of misfolded or aggregated proteins is a common pathogenic feature in neurodegenerative illnesses such as Alzheimer's, Parkinson's, and Huntington's [23, 31]. To eradicate tau, huntingtin, and α-synuclein aggregates, researchers are exploring lysosome targeting degraders and autophagy-based techniques [32, 33, 46]. While these techniques appear promising, effective central nervous system (CNS) administration and neuronal toxicity reduction remain substantial hurdles [29, 31].

C. Immune, Inflammatory, and Other Conditions

Beyond cancer and neurodegeneration, TPD is also emerging as a strategy to regulate immune signaling pathways and degrade extracellular cytokines or receptors [27,44]. LYTACs and related modalities have shown potential in modulating autoimmune and inflammatory diseases by selectively removing pathogenic extracellular proteins [45,47]. Owing to their modularity and adaptability, TPD technologies are expected to have applications well beyond oncology and CNS disorders, extending into a broad range of therapeutic areas [35,48].

IV. ADVANTAGES OF DEGRADATION OVER INHIBITION

Targeted protein degradation has various advantages over standard inhibition techniques. First, it provides access to proteins that were previously thought to be "undruggable," such as transcription factors and scaffolding proteins that lack enzymatic active sites [1,5,16]. Second, degraders function via a catalytic mechanism, which means that a single molecule can cause the elimination of several copies of the target protein, potentially lowering the required therapeutic dose [9,10]. Finally, because TPD completely destroys the protein rather than only inhibiting its function, it has a different resistance profile when compared to traditional inhibitors, potentially circumventing some drug resistance mechanisms [44, 49].

V. KEY CHALLENGES AND LIMITATIONS

Despite their promise, targeted protein degraders face several important challenges. A major concern lies in their physicochemical properties—PROTACs, in particular, are often large and highly polar, which limits oral bioavailability and complicates drug-like behavior [11,41]. Selectivity is another issue, as inappropriate recruitment of E3 ligases can lead to unintended degradation of non-target proteins, raising the risk of off-target effects [15,18,19]. The field is also constrained by the limited number of E3 ligases currently exploited for drug development, with only a handful such as CRBN, VHL, MDM2, and IAPs being widely used; expanding this toolbox remains a critical priority [45]. Finally, pharmacokinetic challenges persist, including ensuring compound stability, reducing rapid metabolism, and achieving effective penetration into hard-to-reach tissues such as the brain and solid tumors [29,41].

VI. CLINICAL LANDSCAPE AND TRANSLATIONAL MILESTONES

The clinical translation of targeted protein degradation is already underway, with several degraders advancing through trials. Among the most notable are ER-targeting PROTACs such as ARV-471, which has shown encouraging results in phase 2/3 studies [42]. These early oncology programs provide critical proof-of-concept, demonstrating that degrader drugs can achieve clinical efficacy and tolerability [22,36,43]. In parallel, strong momentum from academic–industry collaborations and sustained venture funding is fueling rapid growth of the pipeline, supporting both the optimization of existing modalities and the exploration of next generation approaches [35,50].

VII. ENABLING TECHNOLOGIES AND FUTURE DIRECTIONS

The continued advancement of targeted protein degradation relies heavily on enabling technologies that address current limitations and expand therapeutic potential.

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One priority is the expansion of the E3 ligase toolbox. Structure-guided methods and high-throughput screening are being leveraged to discover novel ligases that could enable tissue- or context specific degradation, thereby improving selectivity and safety [45]. Delivery innovations are another critical area. Advances in medicinal chemistry, rational linker design, and the use of nanoparticle-based carriers are helping to overcome pharmacokinetic hurdles, improving both oral bioavailability and tissue penetration [36,41]. Artificial intelligence and computational modeling are also playing an increasingly important role. Machine learning approaches are being applied to predict ternary complex geometry, optimize linker properties, and guide rational degrader design with greater efficiency [37,38]. Finally, future clinical success will depend on integrating degraders into broader therapeutic strategies. Combination regimens with kinase inhibitors, immunotherapies, or radiotherapies are under active investigation, offering potential synergy and improved outcomes [49]. Equally important will be the development of biomarker assays to monitor degradation efficiency and pathway modulation, which will be essential for implementing precision medicine approaches [50,51].

VIII. CONCLUDING PERSPECTIVE

Targeted protein breakdown has emerged as a major paradigm shift in drug discovery, providing a fundamentally new approach to eliminating disease-causing proteins [1,2]. PROTACs, molecular glues, and lysosome-directed degraders have effectively progressed from theoretical concept to clinical proof-of-principle [22, 36]. Although hurdles persist, such as pharmacokinetics, selectivity, and safety, continuous advancements in medicinal chemistry, computational design, and delivery platforms are rapidly tackling these issues [37,41,45]. The optimistic clinical success of degraders like ARV-471 highlights their potential to become cornerstone treatments in modern pharmacology, paving the way for a new generation of medications with transformative effects [42,43,49].

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