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Review Paper

Targeted Protein Degradation (PROTACs & Molecular Glues): Mechanisms and Therapeutic Potential

Pradnya Kumbhar*, Akshay Nemade, Dr. Sandeep Waghulde

LSHGCT'S Gahlot Institute of pharmacy, Koparkhairane, Navi Mumbai, Maharashtra, India- 400709, UP, India

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ABSTRACT

Targeted protein degradation (TPD) has emerged as a transformative therapeutic strategy that overcomes the limitations of traditional occupancy-driven pharmacology. Unlike conventional small-molecule inhibitors that temporarily block protein function, TPD eliminates disease-causing proteins by harnessing the endogenous ubiquitin–proteasome system (UPS). Among TPD approaches, Proteolysis Targeting Chimeras (PROTACs) and molecular glues represent the most advanced and promising modalities. PROTACs and molecular glues have demonstrated significant therapeutic potential in oncology, neurodegenerative disorders, inflammatory diseases, and infectious conditions, with several candidates currently undergoing clinical evaluation. Despite promising progress, challenges such as pharmacokinetic limitations, off-target effects, and optimization of drug-like properties remain. This review provides a comprehensive overview of the molecular mechanisms underlying PROTACs and molecular glues, their design principles, therapeutic applications, and recent advances. Additionally, current challenges and future perspectives are discussed, highlighting the potential of targeted protein degradation as a next-generation paradigm in drug discovery and precision medicine.

INTRODUCTION

Traditional inhibition-based drug approach

Traditional drug discovery has primarily relied on occupancy-driven pharmacology, where small-molecule drugs bind to a specific site on a target protein and inhibit its function without removing the protein from the cell. These inhibitors typically interact with active sites, such as enzyme catalytic pockets or receptor binding domains, to block biological activity and produce therapeutic effects. This approach has been highly successful and led to the development of numerous approved drugs for cancer, cardiovascular diseases, and infectious disorders. However, these drugs require

***Corresponding Author:** Pradnya Kumbhar
Address: *Department of Pharmaceutical Quality assurance, LSHGCT'S Gahlot Institute of pharmacy, Koparkhairane, Navi Mumbai, Maharashtra, India- 400709*
Email : pradnyakumbhar000@gmail.com
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continuous target engagement and sufficient drug concentration to maintain inhibition, which limits their effectiveness in some cases.

In addition, conventional small-molecule inhibitors usually function through reversible binding, meaning that protein function can resume once the drug dissociates, necessitating repeated dosing to maintain therapeutic efficacy.

Limitations of conventional small-molecule inhibitors:

1. Inability to target "undruggable" proteins
2. Requirement for continuous drug exposure
3. Development of drug resistance
4. Incomplete functional suppression
5. Limited therapeutic scope

Concept of Targeted Protein Degradation

Targeted protein degradation (TPD) is an emerging therapeutic strategy that utilizes the cell's natural protein disposal machinery, particularly the ubiquitin–proteasome system, to selectively eliminate disease-causing proteins rather than merely inhibiting their function.

Advantages over traditional therapeutics

1. Complete removal of target proteins
2. Ability to target undruggable proteins
3. Catalytic mechanism of action
4. Overcoming drug resistance
5. Expanded therapeutic applications

Ubiquitin–Proteasome System (UPS): Basic Mechanism

The ubiquitin–proteasome system (UPS) is the primary intracellular pathway responsible for selective degradation of short-lived, damaged, or misfolded proteins in eukaryotic cells. It plays a critical role in regulating numerous cellular processes including cell cycle progression, signal transduction, transcription, and apoptosis.

UPS-mediated degradation occurs through a highly coordinated enzymatic cascade involving ubiquitin, ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), ubiquitin ligases (E3), and the 26S proteasome complex.

Components of UPS

1. Ubiquitin
2. E1: Ubiquitin-Activating Enzyme
3. E2: Ubiquitin-Conjugating Enzyme
4. E3: Ubiquitin Ligase
5. Proteasome

Mechanism of Protein Degradation via UPS

Step 1: Activation: Ubiquitin is activated by the E1 enzyme using ATP.

Step 2: Conjugation: Activated ubiquitin is transferred to an E2 enzyme.

Step 3: Ligation: E3 ligase transfers ubiquitin from E2 to the target protein, forming polyubiquitin chains.

Step 4: Recognition: The polyubiquitinated protein is recognized by the 26S proteasome.

Step 5: Degradation: The proteasome unfolds and degrades the protein into peptides. This cascade ensures selective and regulated degradation of proteins.

PROTACs (Proteolysis Targeting Chimeras)

PROTACs are heterobifunctional small molecules that simultaneously bind a target protein and an E3 ubiquitin ligase, inducing selective degradation via the ubiquitin–proteasome system.

Mechanism of Action of PROTACs:

Step 1: Cellular Entry of PROTAC

After administration, the PROTAC molecule enters the cell through passive diffusion or active transport.

- Once inside the cell, it remains intact and functional.
- Its bifunctional nature allows simultaneous interaction with two proteins.

Step 2: Binding of PROTAC to Target Protein

The target-binding ligand part of PROTAC binds specifically to the target protein.

- This interaction is similar to traditional inhibitor binding.
- However, PROTAC does not inhibit function but prepares protein for degradation.

Example targets:

- BRD4
- Androgen receptor
- Estrogen receptor

Step 3: Recruitment of E3 Ubiquitin Ligase

The other end of the PROTAC binds to an E3 ubiquitin ligase such as:

- CRBN (Cereblon)
- VHL (Von Hippel-Lindau)
- MDM2

This forms a bridge between:
Target protein – PROTAC – E3 ligase

Step 4: Formation of Ternary Complex

A stable ternary complex is formed:
Target Protein – PROTAC – E3 Ligase
This is the most critical step.
Functions:

- Brings target protein close to E3 ligase
- Enables ubiquitination

This step determines degradation efficiency.

Step 5: Ubiquitination of Target Protein

E3 ligase transfers ubiquitin molecules to the target protein.
Process:

- E1 activates ubiquitin
- E2 carries ubiquitin
- E3 transfers ubiquitin to target protein

Polyubiquitin chain is formed.
This acts as degradation signal.

Step 6: Recognition by 26S Proteasome

The polyubiquitinated target protein is recognized by the 26S proteasome.
Proteasome functions:

- Recognizes ubiquitin tag
- Unfolds protein
- Degrades into peptides

Step 7: Proteasomal Degradation of Target Protein

The target protein is completely degraded into:

- Peptides
- Amino acids

This removes the disease-causing protein.

Step 8: Release and Recycling of PROTAC (Catalytic Action)

After degradation:
PROTAC molecule is released unchanged.
It can bind another target protein and repeat process.

This makes PROTAC:

- Catalytic
- Highly efficient
- Effective at low dose.

Molecular Glues

Molecular glues are small molecules that induce or stabilize protein–protein interactions between a target protein and an E3 ubiquitin ligase, leading to ubiquitination and proteasomal degradation of the target protein.

Mechanism of Action of Molecular Glues:

Molecular glue enters cell
↓
Binds E3 ligase
↓
Recruits target protein
↓
Stabilizes interaction
↓
Ubiquitination
↓
Proteasomal degradation

Flow Chart number. 01

Design and Development Strategies of PROTACs and Molecular Glues:

The rational design and development of targeted protein degraders such as PROTACs and molecular glues require careful consideration of multiple factors, including target protein selection, E3 ligase selection, linker design, and computational optimization. These strategies ensure efficient degradation, selectivity, and favorable pharmacokinetic properties.

Strategy	Purpose
Target selection	Disease relevance
E3 ligase selection	Ubiquitination
Linker optimization	Complex stability
Structure-based design	Improve binding
Computational methods	Optimize design

Table number. 01

Therapeutic Applications:

Targeted protein degradation technologies such as PROTACs and molecular glues have shown significant therapeutic potential in cancer, neurodegenerative, infectious, and inflammatory diseases by selectively degrading disease-causing proteins rather than inhibiting them.

- Cancer:
  Cancer is the most extensively studied therapeutic area for PROTACs and molecular glues because many oncogenic proteins are difficult to inhibit but can be degraded.
- Breast Cancer:
  Breast cancer is often driven by estrogen receptor (ER) signaling. PROTACs targeting ER have shown promising results.
- Leukemia:
  Molecular glues such as immunomodulatory drugs (IMiDs) degrade transcription factors involved in leukemia.
- Prostate Cancer
  Prostate cancer depends on androgen receptor (AR).
  PROTACs targeting AR have shown excellent therapeutic potential.
- Neurodegenerative Diseases
  Neurodegenerative diseases involve accumulation of toxic proteins.
  PROTACs can remove these proteins.
- Alzheimer's Disease
  Key target proteins: Tau protein, Beta-amyloid.
  PROTACs degrade Tau protein.
  Benefits: Reduce neurotoxicity.
- Parkinson’s Disease
  Key target protein: Alpha-synuclein
  PROTACs can degrade alpha-synuclein.
- Inflammatory Diseases
  Inflammatory diseases involve overexpression of inflammatory proteins.
  PROTACs degrade inflammatory mediators.
  Targets: NF-κB, JAK kinases

Applications: Rheumatoid arthritis, Autoimmune diseases.

Clinical Trials and Marketed Products

Drug	Type	Target	Disease	Clinical status
ARV-110	PROTAC	Androgen receptor	Prostate cancer	Clinical trial
ARV-471	PROTAC	Estrogen receptor	Breast cancer	Clinical trial
Lenalidomide	Molecular glue	CRBN substrates	Multiple myeloma	Approved
Thalidomide	Molecular glue	CRBN substrates	Multiple myeloma	Approved

Table number. 02

CONCLUSION

Targeted protein degradation (TPD), particularly through PROTACs and molecular glues, represents a transformative advancement in modern drug discovery. Unlike traditional small-molecule inhibitors that require continuous occupancy of active sites, PROTACs and molecular glues eliminate disease-causing proteins by harnessing the ubiquitin–proteasome system, offering a catalytic and event-driven mechanism of action. This approach enables degradation rather than inhibition, resulting in prolonged pharmacological effects and the potential to target proteins previously considered undruggable. In modern drug discovery, targeted protein degradation is now recognized as a powerful therapeutic modality with applications across cancer, neurodegenerative disorders, infectious diseases, and inflammatory conditions. Several PROTACs are currently in clinical trials, and molecular glue drugs have already achieved regulatory approval, demonstrating the clinical feasibility of this strategy.

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