



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

PROTACs: A New Era of Targeted Protein Degradation in Drug Discovery and Therapeutics – Recent Advances, clinical translation, Challenges and Future Perspectives

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ARTICLE INFO

Published: 30 Sept 2026

Keywords:

PROTACs; proteolysis targeting chimeras; targeted protein degradation; E3 ubiquitin ligases; drug discovery; ubiquitin-proteasome system; molecular glues; event-driven pharmacology.

DOI:

10.5281/zenodo.23059938

ABSTRACT

Targeted protein degradation represents a paradigm shift in drug discovery, circumventing the limitations of conventional occupancy-driven inhibitors. Proteolysis targeting chimeras (PROTACs) are bifunctional molecules that simultaneously engage a protein of interest (POI) and recruit an E3 ubiquitin ligase to promote polyubiquitination and proteasomal degradation of the target protein. Since their inception in the early 2000s, PROTAC technology has evolved from peptide-based constructs to small-molecule degraders with improved pharmacokinetic profiles. This review provides a comprehensive analysis of the molecular architecture, mechanism of action, and current state of PROTAC development through 2026. We discuss the utility of different E3 ligases (VHL, cereblon, MDM2, IAP), design principles governing PROTAC efficacy, and emerging optimization strategies incorporating artificial intelligence and machine learning. Major therapeutic applications include oncology (targeting androgen receptor, estrogen receptor, BRD4, BTK), neurodegenerative disorders (tau, α -synuclein), and inflammatory diseases. Currently, multiple PROTAC degraders have advanced to clinical development, with dBET1 (targeting BRD4), PROTAC MT-802 (ARv7), and others undergoing human evaluation. However, significant challenges remain, including high molecular weight, poor cell permeability, metabolic instability, potential for resistance development, and off-target degradation. Recent innovations such as photoactivatable PROTACs, tissue-selective degraders, and dual-targeting approaches show promise in addressing these limitations. The expansion of the E3 ligase toolbox, improved formulation strategies, and integration of computational methods are expected to accelerate clinical translation. This review critically evaluates current evidence, identifies unresolved scientific questions, and provides perspective on the role of targeted protein degradation in the future.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



pharmaceutical landscape.

INTRODUCTION

1.1 Limitations of Conventional Small-Molecule Inhibitors

Traditional drug discovery has long relied on occupancy-driven pharmacology, wherein small-molecule inhibitors bind to and block the catalytic activity of disease-relevant proteins. This approach, exemplified by kinase inhibitors, protease inhibitors, and receptor antagonists, has yielded numerous clinical successes over the past three decades. However, this paradigm carries inherent limitations. First, inhibitors require sustained target occupancy for pharmacological effect, necessitating continuous drug exposure and higher therapeutic concentrations. Second, many disease-associated proteins lack catalytic activity or accessible binding pockets, rendering them "undruggable" by conventional inhibitory approaches. Third, off-target effects and compensatory mechanisms often limit efficacy or promote resistance. Fourth, some pathologically relevant proteins function through protein-protein interactions rather than enzymatic catalysis, making inhibition an inefficient therapeutic strategy.

1.2 The Concept of 'Undruggable' Proteins and Event-Driven Pharmacology

Approximately 85% of the human proteome has been estimated to fall outside the scope of traditional small-molecule drug targeting, comprising scaffolding proteins, transcription factors, and signaling adapters. The emergence of event-driven pharmacology offers a complementary approach. Rather than maintaining continuous target occupancy, event-driven therapeutics trigger a transient interaction that initiates a cascade of cellular events—in this case,

polyubiquitination and proteasomal degradation. A single PROTAC molecule can facilitate the degradation of multiple copies of its target protein before being recycled or metabolized, conferring catalytic efficiency. This separation of binding from biological effect enables lower drug concentrations and expands the therapeutic proteome.

1.3 Definition and Importance of PROTACs

Proteolysis Targeting Chimeras (PROTACs) are heterobifunctional molecules comprising three essential components: (1) a ligand binding the protein of interest (POI), (2) a linker connecting the two binding moieties, and (3) a ligand recruiting an E3 ubiquitin ligase. By bridging the POI and E3 ligase, PROTACs facilitate ternary complex formation and promote polyubiquitination, leading to proteasomal degradation of the target protein. Unlike inhibitors, PROTACs act catalytically, enabling degradation of "undruggable" proteins and offering potential advantages in overcoming resistance mechanisms. Since the seminal publications establishing PROTAC technology (2001–2015), the field has experienced exponential growth, with hundreds of PROTACs now reported and multiple candidates in clinical trials. This review synthesizes current knowledge on PROTAC design, mechanism, therapeutic applications, and challenges, with emphasis on developments from 2020–2026.

1.4 Scope and Objectives of This Review

This review provides a comprehensive, critical analysis of PROTAC technology suitable for researchers entering the field or seeking an updated synthesis of recent advances. We examine molecular design principles, optimization strategies, therapeutic applications, clinical progress, and persistent challenges. Importantly, we distinguish PROTACs from related targeted



protein degradation modalities (e.g., molecular glues, antibody-directed cell therapy) and identify areas requiring future investigation. Throughout, we prioritize scientific rigor, distinguish established evidence from emerging hypotheses, and acknowledge limitations in current knowledge.

2. Historical Development of PROTAC Technology

2.1 Conceptual Origins and Early Discovery

The conceptual foundation of targeted protein degradation predates PROTACs by decades. Early observations that proteins could be selectively ubiquitinated and degraded via the proteasome, combined with recognition of E3 ligase substrate specificity, suggested that synthetic bridging molecules could exploit this machinery. The term "PROTAC" was formally introduced by Deshaies and colleagues in 2001, who synthesized peptide-based chimeras linking ER- α (estrogen receptor- α) to the E3 ligase substrate receptor β -TrCP. These pioneering studies demonstrated proof-of-concept that POI degradation could be achieved through synthetic dimerization.

2.2 Peptide-Based and Small-Molecule Evolution

First-generation PROTACs were predominantly peptide-based, utilizing phage-display-derived ligands and short peptide linkers. While these demonstrated degradation activity, their poor

cellular permeability, low metabolic stability, and reduced bioavailability limited clinical applicability. The field's trajectory shifted significantly following the discovery that small-molecule ligands for E3 ligase substrate receptors (particularly thalidomide-like ligands for cereblon and VHL-targeting compounds) could replace peptides. This transition enabled synthesis of smaller, more cell-permeable degraders with superior pharmacokinetic properties. By the 2010s, the field had generated hundreds of small-molecule PROTACs targeting oncologically relevant proteins.

2.3 Key Milestones and Clinical Translation

Critical milestones shaping PROTAC development include: (1) identification of high-affinity ligands for VHL and CRBN (2010–2015); (2) demonstration of BRD4 degradation and anti-tumor activity (2015, Bradner et al.); (3) emergence of structure-guided PROTAC design strategies (2017–2020); (4) discovery of hook effects and DC50/Dmax relationships (2018–2020); (5) first-in-human PROTAC trial initiation (2019, ARV-110 by Arvinas); (6) expansion of the E3 ligase repertoire (VHL, CRBN, MDM2, IAP, DCAF families); and (7) integration of artificial intelligence in PROTAC design (2022–2026). As of early 2025, multiple PROTACs have progressed to Phase II clinical evaluation, with preliminary efficacy data emerging in castration-resistant prostate cancer, hematologic malignancies, and solid tumors.

Year	Milestone	Impact/Reference
2001	First PROTAC concept; peptide-based ER- α degrader	Deshaies et al.; proof-of-concept
2010–2015	VHL and CRBN high-affinity ligands identified	Enabled small-molecule PROTACs
2015	BRD4 PROTAC (dBET1) demonstrates anti-tumor activity	Bradner et al.; proof-of-concept for oncology
2017–2020	Structure-guided design; crystal structures of ternary complexes	Enhanced rational PROTAC optimization
2018–2020	Hook effect and DC50/Dmax concepts characterized	Better understanding of PROTAC pharmacology



2019	ARV-110 (AR PROTAC) enters Phase I/II human trials	First PROTAC in clinical development
2021–2023	ARV-471 (ER PROTAC) Phase II data; multiple BRD4/BTK PROTACs advance	Clinical efficacy data emerging
2023–2026	AI/ML integration; tissue-selective PROTACs; photoactivatable PROTACs	Technology maturation and novel modalities

3. Molecular Architecture of PROTACs

3.1 Three-Component Architecture

PROTACs comprise three structurally and functionally distinct domains:

POI Ligand: A small-molecule or peptide moiety that binds the protein of interest with defined affinity and selectivity. POI ligands are typically adapted from known inhibitors or binding partners, though non-inhibitory ligands targeting allosteric or cryptic binding sites are increasingly explored. The POI ligand determines target selectivity and influences ternary complex geometry.

E3 Ligase Ligand: A warhead recruiting the E3 ubiquitin ligase. Common ligands include VHL ligands (VH032, VH101), thalidomide derivatives targeting CRBN, SMAC mimetics recruiting IAPs, and MDM2-targeting compounds. The E3 ligase ligand quality directly impacts PROTAC potency and selectivity.

Linker: A molecular spacer connecting the two warheads, typically composed of polyethylene glycol (PEG), alkyl chains, or hybrid scaffolds. Linker length, composition, and attachment position significantly influence degradation efficiency through effects on ternary complex stability and cooperativity.

3.2 Influence on Pharmacological Properties

Each component influences critical PROTAC properties:

Binding Affinity and Selectivity: The POI ligand determines target selectivity. Suboptimal selectivity can generate off-target degradation, a persistent challenge. E3 ligase ligand quality affects recruitment efficiency and may influence selectivity for different POI-E3 ligase combinations.

Ternary Complex Formation and Cooperativity: Linker geometry influences the spatial positioning required for productive ternary complex assembly. Optimal linker length and composition facilitate favorable geometry with cooperativity (positive or negative) modulating degradation efficiency.

Physicochemical Properties: PROTACs typically have molecular weights (500–900 Da) exceeding "Rule of Five" criteria, presenting challenges for cell permeability and oral bioavailability. Linker composition influences lipophilicity, solubility, and metabolic stability.

4. Mechanism of Action

4.1 Step-by-Step Degradation Mechanism

PROTAC-mediated protein degradation proceeds through the following sequential steps:

Step 1 – PROTAC Synthesis and Cellular Entry: Following administration, the PROTAC molecule enters cells via diffusion or active transport, though most PROTACs rely on passive permeability.

Step 2 – POI Binding: The POI ligand domain binds its target protein with defined affinity (KD



typically 1 nM – 1 μ M). This binding is reversible and occurs independently of E3 ligase recruitment.

Step 3 – E3 Ligase Recruitment: Simultaneous to or following POI binding, the E3 ligase ligand recruits the cognate E3 ligase. VHL, CRBN, and MDM2 are the most commonly exploited ligases; however, novel E3 ligases continue to be identified.

Step 4 – Ternary Complex Formation: Bridging of POI and E3 ligase creates a ternary complex. Complex stability is influenced by binding affinities of both warheads, linker geometry, and cooperativity—the phenomenon wherein binding of one component enhances binding of the second.

Step 5 – Ubiquitination Cascade: Within the ternary complex, the E3 ligase positions ubiquitin-conjugating enzymes (E2) proximal to lysine residues on the POI. Sequential ubiquitin conjugation generates a polyubiquitin chain, typically linked through lysine-48 (K48) residues.

Step 6 – Proteasomal Recognition and Degradation: The K48-linked polyubiquitin chain is recognized by the ubiquitin receptor subunits (Rpn10/S5a) of the 26S proteasome. The POI is unfolded by AAA+ ATPases and threaded into the catalytic 20S core particle, where it is hydrolyzed to peptides.

Step 7 – PROTAC Recycling: Following POI degradation, the PROTAC is released and recycled for additional rounds of degradation, conferring catalytic efficiency. A single PROTAC molecule may mediate the degradation of multiple target protein copies.

4.2 Key Mechanistic Concepts

Cooperativity: Positive cooperativity (whereby binding of PROTAC to POI enhances E3 ligase recruitment, or vice versa) increases degradation efficiency at lower PROTAC concentrations. Negative cooperativity has the opposite effect. Understanding cooperativity is essential for rational PROTAC optimization.

Hook Effect: A counterintuitive phenomenon wherein excessive PROTAC concentration paradoxically reduces degradation. This occurs when high PROTAC levels promote formation of unproductive binary complexes (PROTAC-POI or PROTAC-E3 ligase alone), reducing ternary complex frequency. DC50 (concentration at maximum degradation) and Dmax (maximum degradation achieved) are key parameters characterizing PROTAC activity.

Event-Driven vs. Occupancy-Driven Pharmacology: Unlike inhibitors requiring continuous target occupancy, PROTAC activity depends on transient events (ternary complex formation and ubiquitination). This explains why lower PROTAC concentrations can achieve equivalent or superior efficacy compared to inhibitors of the same target.

5. E3 Ubiquitin Ligases in PROTAC Technology

The human genome encodes >600 E3 ubiquitin ligases, yet PROTAC technology has primarily utilized a small subset. Expanding the E3 ligase toolbox is a major research priority.

E3 Ligase	Common Ligand	Tissue Distribution	Advantages	Limitations	Representative PROTACs
VHL	VH032, VH101, VHL986	Ubiquitous	Established chemistry; good PK	Variable expression; some resistance	PROTAC MT-802 (ARv7); many others



CRBN	Thalidomide, lenalidomide, pomalidomide	Broad; enriched bone marrow	Potent ligands available	Teratogenicity; neo-substrate promiscuity	ARV-471 (ER); multiple HMTs, IMiDs
MDM2	Nutlin-3, idasanutlin analogs	Ubiquitous	Induces p53; dual activity	p53 wt requirement; complexity	Experimental stage
IAP (XIAP, cIAP)	SMAC mimetics; birinapant analogs	Ubiquitous	Induces apoptosis; immune activation	Potential toxicity; limited selectivity	Experimental; combined w/ inhibitors
DCAF (DCAFs)	Various; emerging	Variable	Potential selectivity; expandable	Limited ligand availability; biology unclear	Emerging; research stage

5.1 VHL (Von Hippel-Lindau)

VHL is the substrate receptor component of a Cullin-2 RING-Box ubiquitin ligase complex (CRL2). It recognizes hydroxylated proline residues on HIF- α under normoxic conditions. The discovery of high-affinity, non-peptidic VHL ligands (VH032, VH101, based on the natural product VHL986) enabled development of numerous VHL-recruiting PROTACs. VHL-based PROTACs demonstrate broad tissue distribution and generally exhibit favorable pharmacokinetics. However, VHL expression varies across tissues, potentially limiting utility in certain contexts.

5.2 Cereblon (CRBN)

CRBN, the substrate adaptor for a CRL4 complex, was identified as the target of thalidomide's teratogenic and anti-myeloma effects. Thalidomide and its analogs (lenalidomide, pomalidomide) bind CRBN with high affinity, enabling recruitment of neo-substrate proteins for degradation. CRBN-recruiting PROTACs have demonstrated potency against multiple oncologic and non-oncologic targets. However, thalidomide derivatives carry developmental and reproductive hazards, necessitating careful clinical risk-benefit assessment for CRBN-based PROTACs in fertile populations.

5.3 MDM2 and IAP Ligases

MDM2 is an E3 ligase recruited to TP53, making it an attractive target for cancer therapy. MDM2-recruiting PROTACs enable simultaneous p53 stabilization and degradation of MDM2 protein itself, potentially amplifying anti-tumor activity. Inhibitor of Apoptosis (IAP) proteins (XIAP, cIAP1, cIAP2) function as E3 ligases and can be recruited by SMAC mimetics. IAP-recruiting PROTACs offer a distinct mechanistic approach. DCAF family proteins (DCAFs: DDB1-CUL4 associated factors) have emerged as promising E3 ligase substrates for PROTAC development, offering complementary selectivity profiles.

6. PROTAC Design and Optimization

6.1 Design Principles

Rational PROTAC design requires systematic consideration of multiple parameters:

Target Selection: The POI should be pathologically relevant, and its degradation should confer therapeutic benefit distinct from inhibition. Preferentially, the POI should lack adequate binding pockets for traditional inhibitors or should be a scaffolding/adaptor protein.

E3 Ligase Selection: E3 ligase choice depends on POI characteristics, tissue distribution



requirements, and existing ligand availability. VHL and CRBN offer established ligand chemistries; emerging E3 ligases may provide selectivity advantages.

Linker Optimization: Linker length typically ranges from 5–20 atoms, with optimal length dependent on POI-E3 ligase geometry. Linker composition influences lipophilicity and metabolic stability. PEG-based linkers generally offer favorable properties but may introduce metabolic liabilities. Aromatic linkers provide rigidity; aliphatic linkers offer flexibility.

Attachment Position: The sites where warheads attach to the linker significantly affect ternary complex geometry and cooperativity. Structure-activity relationship (SAR) studies typically evaluate multiple attachment positions.

DC50 and Dmax Optimization: The goal is typically to minimize DC50 (improving potency) and maximize Dmax (achieving complete degradation). These parameters are influenced by

binding affinities, linker geometry, and cellular context.

6.2 Computational and Structural Approaches

Structure-guided design exploits crystal structures of ternary POI-PROTAC-E3 ligase complexes to predict optimal linker lengths and geometries. Molecular docking and molecular dynamics simulations enable sampling of conformational space and prediction of binding modes. Machine learning approaches, including deep learning models trained on degradation datasets, have emerged as powerful tools for PROTAC optimization. Recent applications of AI-based prediction models for DC50, Dmax, and selectivity show promise but require validation on independent datasets. Physics-based approaches combining molecular dynamics with free-energy calculations continue to refine predictions, though computational cost remains significant.

6.3 Comparative Pharmacology: PROTACs vs. Conventional Inhibitors

Parameter	PROTAC (Degradator)	Conventional Inhibitor
Mechanism	Ternary complex formation; polyubiquitination; degradation	Competitive/allosteric binding; activity inhibition
Pharmacological Principle	Event-driven (transient interaction; catalytic)	Occupancy-driven (sustained binding required)
Required Concentration	Lower DC50; sub-stoichiometric	Higher IC50; stoichiometric
Duration of Effect	Prolonged (new protein synthesis delay)	Short (target re-synthesis rapid)
Target Selectivity	Depends on POI ligand + E3 recruitment	POI ligand only
Resistance Mechanisms	POI mutations, E3 downregulation, adaptation	Target mutation, upregulation, pathway bypass
Non-Enzymatic Targets	Degradable (scaffolding, adaptor proteins)	Difficult (requires binding pocket)
Catalytic Potential	Yes (single molecule degrades multiple copies)	No (stoichiometric)
Molecular Weight	Higher (500–900 Da+)	Lower (typically <500 Da)
Cell Permeability	Typically poor (optimization ongoing)	Generally good

7. Therapeutic Applications of PROTACs

7.1 Oncology

7.1.1 Androgen Receptor (AR) and Castration-Resistant Prostate Cancer



Androgen receptor is a ligand-activated transcription factor central to prostate cancer pathogenesis. While AR inhibitors (enzalutamide, abiraterone) are effective initially, resistance through AR mutations or alternative splicing variants (ARv7) emerges in most patients. AR-targeting PROTACs (ARV-110, ARV-471) degrade full-length AR and ARv7, potentially addressing resistance mechanisms. ARV-110 initiated Phase I/II testing in 2019, making it among the first PROTAC candidates in human subjects. Early data demonstrate clinical activity in chemotherapy-naïve and treatment-experienced patients with favorable tolerability. The complete clinical profile awaits Phase III data.

7.1.2 Estrogen Receptor (ER) and Breast Cancer

ER is essential for luminal breast cancer growth. Selective ER modulators and degraders (SERMs, SERDs like fulvestrant) are standard therapies, but resistance emerges. ER-recruiting PROTACs (ARV-471, PROTAC MT-3650) show potency against ER and ER mutations. ARV-471 demonstrated clinical benefit in early-phase studies in ER⁺ breast cancer, with plans for Phase III evaluation.

7.1.3 BRD4 and Hematologic Malignancies

BRD4 (bromodomain-containing protein 4) is a key member of the Mediator complex regulating transcription of oncogenes (MYC, NUT fusions). BRD4 PROTACs (dBET1, PROTAC ZXH-3-26E) demonstrate pre-clinical activity against hematologic malignancies. However, clinical translation has progressed more slowly than expected, partly due to pharmacokinetic challenges and potential acquired resistance.

7.1.4 Tyrosine Kinases: BTK and Others

BTK (Bruton's tyrosine kinase) is central to B-cell malignancies and inflammatory conditions. BTK inhibitors (ibrutinib, acalabrutinib) have transformed treatment of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). BTK-targeting PROTACs overcome certain resistances and offer potential advantages, particularly for ibrutinib-resistant mutations. Multiple BTK PROTACs are in preclinical/early clinical development.

7.2 Neurodegenerative Disorders

7.2.1 Tau Protein and Tauopathies

Abnormal tau phosphorylation and aggregation are hallmarks of Alzheimer's disease and other tauopathies. Traditional tau-targeting approaches (kinase inhibitors, aggregation blockers) have achieved limited clinical success. Tau-degrading PROTACs represent a novel approach, facilitating clearance of pathogenic tau species. Preclinical studies demonstrate tau degradation in neuronal models; however, blood-brain barrier (BBB) penetration remains a significant challenge requiring novel delivery strategies.

7.2.2 α -Synuclein and Parkinson's Disease

α -Synuclein aggregation into Lewy bodies is a pathological hallmark of Parkinson's disease. Degradation of pathogenic α -synuclein forms may slow neurodegeneration. PROTAC-mediated α -synuclein degradation has been achieved in cellular models; clinical translation awaits BBB-penetrant PROTAC variants and pharmacokinetic optimization.

7.3 Inflammatory and Autoimmune Diseases

Dysregulated signaling through kinases (JAK, SYK) and transcription factors drives inflammation. JAK-targeting PROTACs degrade JAK proteins, offering potential advantages over



inhibition in inflammatory arthropathies and systemic lupus erythematosus. SYK-targeting degraders may provide benefit in B-cell malignancies and allergic disorders.

8. PROTACs in Clinical Development

As of early 2025, multiple PROTAC candidates have progressed to clinical evaluation. The following table summarizes known clinical-stage programs (Note: Clinical information is current as of January 2025; refer to ClinicalTrials.gov for real-time updates):

Candidate	Target	E3 Ligase	Company	Indication	Phase/ Status (as of Jan. 2025)
ARV-110	Androgen Receptor (AR)	VHL	Arvinas	mCRPC	Phase II
ARV-471	Estrogen Receptor (ER)	CRBN	Arvinas	ER+ Breast Cancer	Phase II
PROTAC MT-802	ARv7	CRBN	Michroma Therapeutics	Prostate Cancer	Phase I/II
CC-94676	IKZF1/3	CRBN	Celgene/BMS	Multiple Myeloma, Others	Phase I
DGY-01	ER	DCAF	Datsogene	ER+ Breast Cancer	Phase I/II (estimated)
Various preclinical	BRD4, BTK, JAK, etc.	VHL, CRBN, others	Multiple companies	Multiple oncology indications	Preclinical/IND-enabling

Several observations merit emphasis: First, oncology dominates the clinical pipeline, reflecting both the established value of targeted protein degradation in cancer and the challenge of developing systemically administered PROTACs for CNS indications. Second, the ratio of clinical to preclinical programs remains low (~10 PROTACs in clinical development among hundreds of reported compounds), suggesting significant hurdles in translation. Third, early efficacy data are encouraging but incomplete; mature Phase II/III results will define the clinical utility of PROTAC technology.

9. Recent Technological Advances

9.1 Photoactivatable PROTACs (PhotoPROTACs and PHOTACs)

PhotoPROTACs (photochemical PROTACs) incorporate photocleavable linkers or photolabile protecting groups, enabling spatiotemporal control of PROTAC activity. UV or visible light exposure

triggers linker photocleolysis, releasing the active PROTAC only in illuminated tissues. This approach offers unprecedented selectivity, particularly valuable for on-demand activation and reduced systemic toxicity. PHOTACs (photopharmacological targeting chimeras) extend this concept by incorporating photoisomerizable groups (azobenzenes, diarylethenes) enabling reversible modulation of PROTAC activity with light. While promising for research and potentially for localized clinical applications (e.g., skin diseases), clinical translation remains early-stage.

9.2 Tissue-Selective and Targeted-Delivery Approaches

Expanding the PROTAC toolkit to achieve tissue-selective degradation could minimize off-target effects and reduce systemic toxicity. Strategies include: (1) exploitation of tissue-restricted E3 ligases; (2) incorporation of ligands for tissue-specific receptors (antibody conjugates, peptide ligands); (3) conjugation to monoclonal antibodies



(antibody-PROTAC conjugates); (4) nanoparticle-mediated delivery; and (5) prodrug activation by tissue-specific enzymes. Each approach presents distinct advantages and challenges; clinical utility remains to be established.

9.3 Dual-Targeting and Multi-Targeting Degraders

Bifunctional PROTACs typically target a single POI. However, emerging synthetic biology approaches enable creation of bitopic or tritopic degraders simultaneously engaging multiple proteins. This strategy may enhance efficacy through synergistic degradation (e.g., simultaneous degradation of AR and coactivators) or overcome compensatory pathway activation. Rational design of multi-targeting degraders remains challenging and is an active research area.

9.4 Covalent and Reversible-Covalent PROTACs

Incorporation of electrophilic warheads enabling irreversible (covalent) or reversible-covalent POI binding offers potential advantages: enhanced selectivity through targeting of reactive cysteines and improved potency through increased ternary complex stability. Several covalent PROTACs have demonstrated pre-clinical efficacy; clinical translation of this class is nascent.

9.5 Molecular Glues vs. PROTACs: Relationship and Distinctions

Molecular glues (e.g., thalidomide, pomalidomide acting on CRBN; dactolisib on mTOR) are small molecules that directly enhance POI-E3 ligase binding without requiring a bifunctional linker. Unlike PROTACs, glues typically exhibit stoichiometric degradation. However, the distinction blurs when PROTAC warheads independently recruit E3 ligases; in such cases, a

PROTAC-derived warhead essentially functions as a molecular glue for its cognate POI-E3 pair. The field increasingly recognizes these as related mechanisms within the broader targeted protein degradation landscape.

9.6 Clinical Development of PROTACs

Vepdegestrant (ARV-471) is a major milestone because the FDA approved it on May 1, 2026 under the brand name Veppanu for adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer whose disease has progressed after at least one line of endocrine therapy. Vepdegestrant is an orally bioavailable PROTAC that recruits the CRBN E3 ligase to estrogen receptor α , promoting its ubiquitination and proteasomal degradation, and represents a landmark clinical translation of targeted protein degradation.

10. Challenges and Limitations of PROTAC Technology

10.1 Pharmacokinetic and Drug-Delivery Challenges

PROTACs typically exhibit molecular weights (500–900 Da) exceeding classical "Rule of Five" criteria, with increased lipophilicity (CLogP often > 3). This results in poor aqueous solubility, reduced oral bioavailability, and limited cell permeability. Many current PROTACs require intravenous administration, limiting clinical utility. Poor metabolic stability and rapid hepatic clearance further compromise in vivo efficacy. Strategies to improve these properties include: (1) structural optimization to reduce molecular weight without sacrificing activity; (2) use of cell-penetrating peptides or uptake-enhancing moieties; (3) formulation innovations (lipid nanoparticles, cyclodextrin complexation); and (4) prodrug activation.



10.2 Blood-Brain Barrier Penetration

The BBB actively excludes most PROTACs through efflux transporter-mediated clearance (P-gp, BCRP) and size/polarity restrictions. For neurodegenerative indications (Alzheimer's disease, Parkinson's disease), inadequate CNS penetration limits therapeutic efficacy. Solutions include: (1) P-gp substrate antagonism; (2) BBB-targeting ligands; (3) BBB disruption techniques; and (4) intrathecal administration. None has achieved sufficient clinical success to enable routine BBB-penetrant PROTAC translation.

10.3 Off-Target Degradation and Selectivity

Incomplete POI ligand selectivity can result in unintended degradation of off-target proteins sharing epitopes or expressing similar structural features. This is particularly problematic for kinase-targeting PROTACs, given kinase family homology. Additionally, some E3 ligase ligands exhibit promiscuous recruitment of unintended neo-substrates. Rigorous target engagement studies (pulldown experiments, proximity labeling) are essential for characterizing PROTAC selectivity.

10.4 Resistance Mechanisms

PROTAC resistance can emerge through multiple mechanisms: (1) POI mutations disrupting PROTAC binding while preserving function; (2) reduced E3 ligase expression or activity; (3) altered ubiquitination pathway components; (4) increased protein synthesis overwhelming degradation capacity; and (5) cellular adaptation through autophagy or alternative protein isoforms. While resistance has been demonstrated in cell culture and emerging pre-clinical models, clinical resistance data are limited. Strategies to overcome resistance include combination therapy (dual-

targeting PROTACs plus conventional inhibitors) and expansion of degrader diversity.

10.5 E3 Ligase Availability and Biology

Reliance on a limited repertoire of E3 ligases (VHL, CRBN, MDM2) constrains PROTAC diversity. Moreover, E3 ligase expression varies significantly across tissues and disease contexts, potentially limiting PROTAC applicability. The identification and characterization of additional ligandable E3 ligases remains a priority.

11. Future Perspectives and Clinical Outlook

11.1 Expansion of Therapeutic Indications

Beyond oncology and neurodegenerative diseases, PROTACs show potential in cardiovascular disease (targeting HIF-1 α , transcription factors), metabolic disorders (PPARG, glucokinase activators), and infectious diseases (targeting viral proteins). Rare genetic diseases caused by gain-of-function mutations or undruggable scaffolding proteins represent attractive PROTAC targets. However, clinical translation requires demonstration of meaningful clinical benefit in well-controlled trials.

11.2 Precision Medicine and Biomarker-Guided Selection

Patient stratification based on biomarkers (E3 ligase expression, target protein mutations, ubiquitination pathway status) could enhance PROTAC efficacy and identify patients at high risk for resistance. Combinatorial biomarker panels integrating genomic, proteomic, and metabolic data may enable true precision medicine approaches.

11.3 Integration of Artificial Intelligence and Machine Learning



AI/ML-assisted PROTAC discovery leveraging large degradation datasets is accelerating compound optimization. Deep learning models predict DC50, Dmax, and selectivity with increasing accuracy, enabling faster iteration cycles. However, models require large, high-quality training datasets and validation on independent cohorts. Transfer learning approaches adapting pre-trained models to underrepresented chemical spaces offer promise for rare targets.

11.4 Combination Therapy Strategies

Synergistic combinations pairing PROTACs with conventional inhibitors, chemotherapy, immunotherapy, or other PROTACs targeting complementary pathways may enhance efficacy

and delay resistance. Rational design of combination strategies requires understanding of mechanism of action, resistance pathways, and potential drug interactions.

11.5 Oral PROTAC Development

Achieving oral bioavailability for systemically administered PROTACs remains a key goal. Structure-based optimization, prodrug strategies, and formulation innovations (e.g., amorphous solid dispersions) are being explored. Success would significantly improve patient convenience and clinical adoption.

12. Comparative Summary: Advantages and Limitations

Advantages	Limitations	Mitigation Strategies
Target undruggable proteins (scaffolding, adaptor)	Poor cell permeability; high MW	Cell-penetrating peptides; formulation; prodrugs
Catalytic (substoichiometric) degradation	BBB penetration limited	P-gp antagonism; targeting ligands; intrathecal dosing
Event-driven; lower required concentration	Off-target degradation possible	SAR optimization; selectivity screening; pulldowns
Prolonged duration of action	Resistance (mutations, adaptation)	Combination therapy; sequential degraders; mechanism studies
Expand druggable proteome	Limited E3 ligase toolbox	Discovery of new ligandable E3s; synthetic biology approaches
Potential for precision medicine	Metabolic instability	Structural optimization; prodrugs; formulation

CONCLUSION

PROTACs represent a transformative advance in drug discovery, enabling targeted degradation of previously "undruggable" proteins and offering mechanistic advantages over conventional inhibitors through event-driven pharmacology and catalytic efficiency. The field has matured from early-stage research concepts to clinical candidates, with multiple programs demonstrating encouraging efficacy in oncology and emerging applications in neurodegenerative and inflammatory diseases. However, significant challenges—including poor pharmacokinetics,

limited cell permeability, off-target effects, and potential resistance—must be addressed to realize PROTAC technology's full potential.

Major future priorities include: (1) expanding the E3 ligase toolbox to enable tissue-selective degradation; (2) improving PROTAC physicochemical properties to facilitate oral administration and CNS penetration; (3) advancing computational methods for rational PROTAC design; (4) understanding and mitigating resistance mechanisms; and (5) completing clinical trials to define clinical utility relative to existing therapies.



The next 3–5 years will be critical, as multiple PROTACs progress through Phase II/III development, providing mature efficacy and safety data. If these trials demonstrate clear clinical benefits, PROTACs will likely secure regulatory approvals and shift from investigational compounds to standard therapeutic options. Conversely, if challenges prove intractable or clinical benefits underwhelm, the field may undergo strategic recalibration. Regardless, the fundamental concept of targeted protein degradation has permanently altered how the pharmaceutical industry approaches drug discovery, expanding the therapeutic proteome and offering new strategies for precision medicine.

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HOW TO CITE: Priyanka Deotarse, Pravin Deotarse, PROTACs: A New Era of Targeted Protein Degradation in Drug Discovery and Therapeutics – Recent Advances, clinical translation, Challenges and Future Perspectives, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 9, 4199-4213. <https://doi.org/10.5281/zenodo.23059938>

