

PROTAC Technology: A Critical Appraisal of Targeted Protein Degradation-From Mechanistic Principles to First-in-Class Clinical Approval

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ABSTRACT

Proteolysis-Targeting Chimeras (PROTACs) have revolutionized small-molecule pharmacology by harnessing the ubiquitin-proteasome system to achieve catalytic, event-driven degradation of disease-associated proteins rather than transient inhibition. This approach has emerged as a promising therapeutic strategy for targeting conventionally druggable and previously undruggable proteins across multiple disease areas. This review critically appraises the evolution of PROTAC technology from its mechanistic foundations to its first clinical approval. It aims to integrate current knowledge on structural design, ternary complex formation, E3 ligase selection, computational advances, therapeutic applications, clinical progress, and the key challenges influencing future degrader development. A comprehensive critical review of the published literature was conducted by analyzing recent advances in PROTAC design, ubiquitin-proteasome biology, E3 ligase pharmacology, computational and artificial intelligence-assisted discovery methods, preclinical studies, clinical trials, and emerging targeted protein degradation technologies. Evidence from more than thirty clinical-stage PROTACs and recent regulatory milestones was synthesized to evaluate the current status and future prospects of the field. PROTACs comprise three essential components: a protein-of-interest ligand, an E3 ubiquitin ligase recruiter, and a chemical linker that collectively determine ternary complex formation and degradation efficiency. Cereblon and von Hippel-Lindau remain the predominant E3 ligases in clinical development, while emerging ligases such as MDM2, cIAP, RNF114, DCAF15, DCAF16, KEAP1, and FEM1B are expanding the therapeutic landscape. Clinical translation has advanced substantially, highlighted by the Approval of Vepdegestrant (ARV-471), the first marketed PROTAC, whereas agents such as bavdegalutamide (ARV-110) demonstrated biomarker-dependent clinical efficacy. Despite these advances, challenges including limited oral bioavailability, the hook effect, E3 ligase-mediated resistance, and off-target toxicities remain significant. Emerging innovations, including artificial intelligence-guided PROTAC design, tissue-selective E3 ligases, and next-generation degradation platforms such as photo-PROTACs, LYTACs, AUTACs, antibody-PROTAC conjugates, and nano-PROTACs, offer promising strategies to overcome these limitations. PROTAC technology has progressed from proof-of-concept chemical biology to a clinically validated therapeutic modality. Continued advances in medicinal chemistry, computational modeling, biomarker-guided patient selection, and targeted degradation technologies are expected to further expand its clinical applications. Addressing pharmacokinetic limitations, resistance mechanisms, and target selectivity will be critical for realizing the full therapeutic potential of PROTACs in precision medicine.

Keywords: E3 ubiquitin ligase, Molecular glue, Precision oncology, PROTAC, Targeted protein degradation, Ubiquitin-proteasome system.

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INTRODUCTION

Targeted protein degradation has emerged as one of the most consequential conceptual advances in drug discovery of the past two decades, challenging the long-standing assumption that pharmacological benefit requires sustained occupancy of a defined ligand-binding pocket. Conventional inhibitors act by



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competitive or allosteric occupancy of active sites, a strategy that is intrinsically poorly suited to scaffolding proteins, transcription factors, and other targets that lack deep, druggable clefts. Proteolysis-Targeting Chimeras (PROTACs) circumvent this constraint by repurposing the cell's own Ubiquitin-Proteasome System (UPS) to physically eliminate the target protein rather than merely blocking one of its functions (Fan *et al.*, 2025). Mechanistically, PROTACs are heterobifunctional small molecules built from three modular elements: a ligand for the Protein of Interest (POI), a ligand that recruits an E3 ubiquitin ligase, and a chemical linker joining them. This architecture allows a PROTAC to act as a molecular bridge that forces an unnatural, induced proximity between the target protein and the ubiquitination machinery, converting a binding event into a catalytic degradation event (Toure & Crews, 2016).

The field has progressed from early proof-of-concept peptidic degraders in the early 2000s to cell-permeable, orally bioavailable small-molecule PROTACs with genuine drug-like character, a trajectory made possible chiefly by the discovery and optimization of ligands for cereblon (CRBN) and von Hippel-Lindau (VHL) (Toure & Crews, 2016). Contemporary PROTAC research has expanded well beyond its original oncology focus into neurodegeneration, autoimmune and inflammatory disease, and infectious disease, reflecting a shared rationale across these areas: degradation, unlike inhibition, removes all functions of a target protein simultaneously, including enzymatically independent scaffolding roles, and does so catalytically, such that sub-stoichiometric drug exposure can, in principle, sustain pharmacological effect after clearance (Troup *et al.*, 2020).

Clinical translation of this concept is no longer hypothetical. Bavdegalutamide (ARV-110) and Vepdegestrant (ARV-471), targeting the androgen and estrogen receptors respectively, were the first PROTACs to enter human trials and have since diverged sharply in outcome: ARV-110 remains confined to Phase I/II development with efficacy concentrated in a genetically defined subgroup of patients bearing androgen receptor ligand-binding-domain mutations, whereas vepdegestrant received FDA approval in May 2026 for ESR1-mutated, ER-positive/HER2-negative advanced breast cancer, becoming the first approved PROTAC and a genuine inflection point for the field (Qi *et al.*, 2021; U.S. Food and Drug Administration [FDA], 2026). This divergence is itself instructive: it demonstrates that the theoretical advantages of degrader pharmacology do not translate uniformly across targets, and that clinical success depends on target biology, patient selection, and degrader chemistry in ways that a purely mechanistic account of PROTAC pharmacology cannot capture. A central aim of this review is to interrogate that gap explicitly, rather than to catalogue PROTAC biology and clinical programs as separate, loosely connected narratives, which has been the dominant format of prior reviews in this area.

This review therefore departs from earlier surveys of PROTAC technology in four respects. First, it is organized around a mechanism-to-outcome logic, in which every design parameter is subsequently reconnected to the clinical or preclinical evidence that validates or challenges it, rather than being presented as an isolated structural principle. Second, it incorporates the regulatory approval of vepdegestrant as a structuring event for the entire review, using it to critically re-examine claims about PROTAC advantages that were, until 2026, supported only by early-phase or preclinical data. Third, it integrates the most recent (2024-2026) computational and artificial intelligence-based approaches to ternary complex prediction (Yoon *et al.*, 2024), an area that has matured substantially since earlier reviews were written and that is beginning to change how degraders are prioritized before synthesis. Fourth, it treats resistance mechanisms, particularly class-effect loss of function in CRBN or VHL, as a first-order determinant of long-term clinical viability rather than a minor caveat, and links this directly to the rationale for diversifying the E3 ligase toolbox. Throughout, each mechanistic and technological advance is evaluated critically against its limitations, knowledge gaps, and unresolved controversies, consistent with the aim of producing a genuinely critical rather than descriptive review.

METHODOLOGY

A structured literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar to identify studies on PROTACs, targeted protein degradation, ubiquitin-proteasome system biology, E3 ubiquitin ligases, and the clinical development of degrader therapeutics. The search covered the period from January 2015 to June 2026, with deliberate emphasis on 2023-2026 publications to capture recent computational, resistance-mechanism, and regulatory developments that substantially post-date most existing PROTAC reviews.

Search terms combined "PROTAC", "proteolysis-targeting chimera", "targeted protein degradation", "ubiquitin-proteasome system", "cereblon", "VHL", "molecular glue", "LYTAC", "AUTAC", "ternary complex", "AlphaFold", "hook effect", "resistance", and "clinical trial" using Boolean operators, supplemented by manual screening of reference lists from key reviews and by direct retrieval of regulatory communications (FDA approval notices, sponsor press releases) for time-sensitive clinical milestones that are not yet indexed in bibliographic databases.

Original research articles, mechanistic studies, clinical trial reports, and peer-reviewed reviews addressing PROTAC design, degradation mechanisms, E3 ligase biology, and therapeutic translation were included. Conference abstracts without sufficient methodological detail, non-English articles, and duplicate publications were excluded. Retrieved literature was organized into thematic categories, including UPS biology, structural and computational design, E3 ligase pharmacology, mechanism of action, clinical development, resistance and toxicity, and

emerging degradation modalities, with priority given to landmark discoveries, clinical-stage degraders, and the most recent (2023-2026) primary literature to ensure the currency required for a critical, translation-focused synthesis.

The Ubiquitin-Proteasome System: Biological Basis for Targeted Degradation

The Ubiquitin-Proteasome System (UPS) is the principal route of regulated intracellular proteolysis in eukaryotic cells and constitutes the enzymatic machinery that PROTAC pharmacology hijacks for therapeutic purposes. Beyond simple protein turnover, the UPS governs cell cycle progression, signal transduction, and the cellular stress response, and an accurate understanding of its architecture is a prerequisite for interpreting why some PROTACs achieve efficient, sustained degradation while chemically similar analogues fail (Kim *et al.*, 2024).

Enzymatic Cascade: E1, E2, and E3 Components

Ubiquitin conjugation proceeds through a three-tier enzymatic cascade. E1 ubiquitin-activating enzymes, of which the human genome encodes only two, form a high-energy thioester bond with ubiquitin in an ATP-dependent step (Chaugule & Walden, 2016). Activated ubiquitin is then transferred to one of approximately 40 E2 ubiquitin-conjugating enzymes, which determine the topology of the polyubiquitin chain that will ultimately be assembled (Chaugule & Walden, 2016). The final and most consequential tier comprises the E3 ubiquitin ligases, of which more than 600 exist in the human proteome, organized into RING, HECT, and RBR structural families (Liu *et al.*, 2023b). E3 ligases confer substrate specificity to the entire cascade and represent the component that PROTACs directly co-opt; critically, fewer than a dozen of these 600-plus ligases currently have usable small-molecule recruiters, a bottleneck that is discussed at length.

Ubiquitin Chain Topology and Proteasomal Recognition Signals

Polyubiquitin chains, rather than monoubiquitin marks, constitute the canonical degradation signal. Ubiquitin possesses seven internal lysine residues capable of chain extension, but K48-linked chains of four or more ubiquitin moieties remain the best-characterized and most efficiently recognized signal for proteasomal delivery, engaging shuttle factors such as Rad23, Dsk2, and Ddi1 (Grice & Nathan, 2016; Morimoto *et al.*, 2015). The specific E2/E3 pairing recruited by a given PROTAC dictates chain topology: CRBN-based PROTACs, for instance, typically favor K48-linked chains through UbcH5-family E2 enzymes, whereas other E3 ligases may produce mixed or branched topologies whose degradation efficiency is comparatively less well characterized (Bricelj *et al.*, 2021). This mechanistic detail matters clinically, because a PROTAC that forms a stable ternary complex but fails to template a canonical K48 chain will show

binding without commensurate degradation, an outcome that binary-affinity assays alone cannot detect.

The 26S Proteasome as Terminal Effector

The 26S proteasome, a roughly 2.5 MDa complex composed of a 20S catalytic core flanked by two 19S regulatory particles, executes the terminal proteolytic step. The 19S particles recognize polyubiquitinated substrates, remove the ubiquitin chain, and unfold the substrate in an ATP-dependent manner before translocating it into the 20S chamber, where chymotrypsin-like, trypsin-like, and caspase-like active sites reduce the protein to short peptides of three to twenty-five amino acids (Bard *et al.*, 2018; Liu & Jacobson, 2013; Sahu *et al.*, 2021). Because this process achieves essentially complete proteolysis rather than partial cleavage, PROTAC-induced degradation is functionally irreversible for the protein molecules degraded, in contrast to the reversible occupancy achieved by conventional inhibitors, a distinction that underlies much of the pharmacological rationale developed later.

Cellular Determinants of PROTAC-Compatible UPS Activity

PROTAC efficiency is not a fixed property of the molecule alone but is co-determined by the cellular UPS context in which it operates. Expression levels of the recruited E3 ligase, availability of compatible E2 enzymes, and proteasomal capacity all vary across tissues and disease states and can produce substantial cell-type-dependent differences in degradation efficiency for an otherwise identical PROTAC (Cardno *et al.*, 2025; Dixon *et al.*, 2022). This variability has two direct clinical consequences that are frequently underappreciated in purely structural treatments of PROTAC design: first, degrader potency measured in one cell line cannot be assumed to generalize to a patient's tumor or tissue of interest without confirmatory biomarker data; second, disease-associated remodeling of UPS components, most notably acquired loss or downregulation of CRBN in hematologic malignancies, constitutes a resistance mechanism that is intrinsic to the degrader's mechanism of action rather than an off-target liability.

Structural Architecture of PROTAC Molecules

PROTACs are organized around a modular tripartite architecture: a POI-binding ligand, an E3 ligase-recruiting ligand, and a connecting chemical linker. This modularity is both the technology's principal strength, enabling systematic Structure-Activity Relationship (SAR) exploration by independently varying each element, and a central source of its optimization difficulty, because activity depends on emergent, whole-molecule properties, ternary complex geometry and cooperativity, that cannot be predicted from the properties of the individual components in isolation (Li & Song, 2020). A schematic representation of this architecture is provided in Figure 1.

Protein of Interest (POI) Ligands

The POI ligand defines the primary target-engagement profile of a PROTAC and is typically derived from a pre-existing inhibitor, natural product, or fragment-screening hit. Critically, the relationship between binary binding affinity and degradation potency is non-linear and, at high concentrations, can become inverse: excessively tight POI or E3 binding can suppress catalytic turnover by preventing PROTAC release after ubiquitination, contributing to the hook effect (Bond & Crews, 2021). Because of this, the traditional medicinal chemistry heuristic of maximizing binary affinity does not transfer cleanly to degrader design; ligands with only modest binary potency but solvent-exposed attachment points compatible with productive ternary geometry frequently outperform higher-affinity ligands lacking such vectors (Zhong *et al.*, 2024). Natural product-derived ligands, such as geldanamycin-class binders exploited in HSP90-targeting degraders, have proven particularly valuable for targets historically considered poorly druggable by synthetic small molecules (Wurnig *et al.*, 2023).

Chemical Linkers

The linker is frequently mischaracterized as a passive spacer; in practice it is an active determinant of ternary complex conformation, cooperativity, solubility, and cell permeability, and small changes in linker length or rigidity routinely produce order-of-magnitude shifts in degradation potency (Bond & Crews, 2021; Kelm *et al.*, 2023). Most clinically advanced PROTACs employ linkers of 10-30 atoms, though the optimal length is target- and E3-ligase-pair-specific and cannot be reliably generalized. Polyethylene Glycol (PEG)-based linkers remain the most widely used class owing to their synthetic accessibility and aqueous solubility, but their conformational flexibility can impose an entropic penalty on ternary complex formation; more rigid linkers incorporating alkyl, aromatic, or cyclic elements can pre-organize the molecule for productive geometry at the cost of a substantially larger and more resource-intensive synthetic optimization campaign (Gharbi & Mercado, 2024; "Unraveling the Role of," 2021). This is a genuine trade-off rather than a solved problem: rigidified linkers improve potency for some target/E3 pairs and abolish activity in others, and no generalizable rule yet predicts which regime will apply a priori, underscoring the continued empirical, iterative nature of linker optimization even as computational tools begin to narrow the design space.

Structure-Activity Relationships and Cooperativity

Unlike classical inhibitor SAR, in which potency typically tracks binding affinity, PROTAC SAR is governed by ternary complex cooperativity, the extent to which the measured ternary binding affinity exceeds the value predicted from the product of the two binary affinities alone. Positive cooperativity (α greater than 1) indicates favorable, degradation-competent protein-protein

contacts between the target and the recruited E3 ligase and is associated empirically with higher potency and reduced susceptibility to the hook effect, whereas negative cooperativity signals an unfavorable interface that may still permit binding without productive degradation (Wurz *et al.*, 2023). Cooperativity is measurable by isothermal titration calorimetry, surface plasmon resonance, or proximity-based biophysical assays, but these techniques are resource-intensive and are not yet routine in early-stage degrader screening, which remains a practical limitation on the field's ability to rationally design for cooperativity rather than discover it empirically after synthesis (Tan *et al.*, 2025).

Mechanism of Action

PROTAC pharmacology represents a categorical departure from occupancy-driven pharmacology: rather than requiring sustained target engagement to maintain a pharmacological effect, PROTACs initiate a self-limiting, catalytic degradation event whose consequences (loss of the target protein) persist independently of continued drug exposure (Němec *et al.*, 2022). This event-driven mechanism is summarized comparatively against conventional inhibition in Table 1 and is illustrated mechanistically in Figure 2.

Ternary Complex Formation

Formation of a productive ternary complex, target protein-PROTAC-E3 ligase, is the rate-limiting and most mechanistically decisive step in degrader pharmacology. The complex must adopt a geometry that positions accessible target-protein lysines within reach of the E3 ligase's catalytic machinery; this is a considerably more demanding requirement than simple co-localization; and both the thermodynamics (cooperativity, α) and kinetics (residence time, on/off rates) of complex formation and dissociation influence whether productive ubiquitin transfer occurs before the complex dissociates (Imaide *et al.*, 2020). Hydrogen-deuterium exchange mass spectrometry and chemical cross-linking studies indicate that successful PROTACs often induce conformational rearrangements in the target protein that expose lysines otherwise buried or poorly positioned in the unliganded state, a feature not captured by static co-crystal structures alone (Shaik *et al.*, 2024).

Ubiquitin Transfer and Chain Elongation

Following ternary complex assembly, the E3 ligase catalyzes iterative transfer of ubiquitin from charged E2 enzymes to accessible target-protein lysines, building the K48-linked polyubiquitin chain required for efficient proteasomal recognition; a single monoubiquitination event is generally insufficient (Sato, 2026; Wang *et al.*, 2025). Chain-building processivity varies substantially between E3 ligases, and this variation, rather than binary affinity, is an underappreciated determinant of why chemically similar PROTACs recruiting different E3 ligases

against the same target can show markedly different degradation kinetics (Lee *et al.*, 2022).

Proteasomal Recognition and Terminal Degradation

Polyubiquitinated substrates are delivered to the 26S proteasome by shuttle factors, deubiquitinated, unfolded in an ATP-dependent step, and translocated into the 20S catalytic chamber for complete proteolysis to short peptides (Zou *et al.*, 2025). Because this degradation is essentially exhaustive rather than partial, it produces a functionally complete loss-of-protein phenotype, which distinguishes PROTAC pharmacology from lysosomal or autophagic degradation pathways that can leave partially processed, potentially still-active fragments; this distinction is directly relevant to the design logic of the LYTAC and AUTAC modalities.

Catalytic Recycling and Sub-Stoichiometric Activity

A defining pharmacological feature of PROTACs is catalytic turnover: after a target molecule is committed to degradation, the PROTAC is released and can engage additional target molecules, in principle enabling one degrader molecule to eliminate many copies of the target protein. Turnover numbers exceeding 10:1 have been reported for optimized PROTACs, and this catalytic amplification is the mechanistic basis for claims of sub-stoichiometric dosing (Kim *et al.*, 2023; Li & Crews, 2022). However, this property depends critically on balanced dissociation kinetics: PROTACs binding too tightly to either the POI or the E3 ligase show reduced recycling efficiency, while excessively rapid dissociation curtails the residence time needed for productive ubiquitin transfer, so catalytic efficiency is an optimizable but fragile property rather than an automatic consequence of the PROTAC mechanism (Kosloski-Oh *et al.*, 2021).

Cellular and Tissue-Specific Determinants of Degradation Efficiency

The degradation efficiency for a given PROTAC is not an intrinsic molecular constant but is co-determined by the expression of the recruited E3 ligase, E2 enzyme availability, and proteasomal capacity in the target cell or tissue (Wang *et al.*, 2020). Most clinically advanced PROTACs rely on the broadly expressed CRBN or VHL complexes, which maximizes activity across tissues but forfeits the tissue-selectivity that could, in principle, be achieved with a more restrictively expressed E3 ligase; this tension between broad applicability and selective toxicity avoidance is a recurring theme (Guenette *et al.*, 2022). The complete degradation sequence, ternary complex formation, ubiquitination, proteasomal recognition, and catalytic recycling, is illustrated in Figure 2.

E3 Ubiquitin Ligases Recruited in PROTAC Design

Although more than 600 E3 ligases are encoded in the human genome, fewer than a dozen currently possess small-molecule

ligands suitable for PROTAC design, and clinical development remains overwhelmingly concentrated on just two, CRBN and VHL. This narrow toolbox is arguably the single greatest structural constraint on the field, limiting both the diversity of achievable selectivity profiles and the field's capacity to design tissue-restricted degraders; the discussion below evaluates each major E3 ligase class critically against this constraint rather than as an independent catalogue of options (Thomas *et al.*, 2023).

Cereblon (CRBN)

CRBN, a substrate receptor within the CRL4-CRBN complex, is the most widely used E3 ligase in PROTAC design, a position it owes to the discovery that thalidomide-class Immunomodulatory Drugs (IMiDs) bind CRBN and induce neo-substrate degradation, providing both a validated ligand scaffold and an extensive existing clinical safety record (Yamamoto *et al.*, 2022). CRBN is broadly expressed, and IMiD-derived ligands are compact and cell-permeable, properties that have made CRBN the default choice for most clinical-stage PROTACs, including bavdegalutamide and vepdegestrant (Thapa *et al.*, 2024). This broad utility, however, carries two liabilities that are frequently underweighted in favorable accounts of CRBN-based degraders: first, IMiD-derived recruiters can themselves induce degradation of endogenous CRBN neo-substrates (such as IKZF1/3), creating mechanism-based, on-target/off-tumor toxicity risk that is intrinsic to the chemotype rather than to the specific PROTAC; second, acquired CRBN loss or downregulation constitutes a class-effect resistance mechanism capable of abrogating activity across every CRBN-recruiting PROTAC simultaneously, regardless of POI, a vulnerability documented in the IMiD literature and increasingly recognized as a PROTAC-relevant liability as clinical experience accumulates (Steinebach *et al.*, 2023; Vicente *et al.*, 2025).

Von Hippel-Lindau (VHL)

VHL, the substrate-recognition subunit of the CRL2-VHL complex, is the second most widely recruited E3 ligase and offers a mechanistically orthogonal alternative to CRBN. VHL ligands, typically hydroxyproline-based mimetics of the natural HIF substrate, generally afford improved degradation selectivity and lower neo-substrate liability than CRBN recruiters, but this comes at the cost of larger, more polar molecules with correspondingly reduced passive membrane permeability (Smith *et al.*, 2019; Soares *et al.*, 2018). The choice between CRBN and VHL is therefore not simply a matter of relative potency but a genuine risk-benefit trade-off between permeability/oral bioavailability (favoring CRBN) and selectivity/reduced neo-substrate risk (favoring VHL), and this trade-off should be made explicitly and early in a discovery campaign rather than defaulted to CRBN by convention.

MDM2 and Dual-Mechanism Degraders

MDM2-recruiting PROTACs exploit Nutlin-class ligands to simultaneously degrade the intended POI while displacing MDM2 from p53, thereby stabilizing p53 and potentially conferring a synergistic anti-tumor effect distinct from POI degradation alone (Hines *et al.*, 2019). This dual pharmacology is a double-edged design feature: it can be therapeutically advantageous in p53-wild-type tumors but introduces an additional, target-independent toxicity vector in normal tissue, meaning that MDM2-based PROTACs plausibly require p53-mutational-status-based patient stratification, a biomarker requirement that is not shared by CRBN- or VHL-based degraders and that adds a layer of clinical development complexity not always acknowledged in preclinical proof-of-concept studies (Wang *et al.*, 2024).

cIAP and the Expanding E3 Ligase Toolbox

Cellular inhibitor of Apoptosis Proteins (cIAP1/2), recruited via SMAC-mimetic ligands, were historically among the first E3 ligases used in PROTAC proof-of-concept studies, but their tendency toward auto-ubiquitination and self-degradation has limited durable use of this chemotype. More recent efforts have identified small-molecule ligands for RNF114 (via the natural product nimbolide), DCAF15 (via indisulam-class sulfonamides), DCAF16, and KEAP1, and covalent recruitment strategies for FEM1B, each expanding the recruitable E3 ligase space and, in principle, offering tissue-restricted expression profiles that could enable more selective degradation than CRBN or VHL allow (Chen *et al.*, 2025; Yin *et al.*, 2025). Critically, however, these newer recruiters remain early-stage: ligand affinity, selectivity, and drug-likeness for RNF114, DCAF16, KEAP1, and FEM1B are substantially less mature than for CRBN or VHL, and none has yet produced a clinical-stage degrader, so their promise for tissue selectivity remains largely theoretical pending validation in more advanced preclinical or clinical settings. A comparative summary of the major E3 ligases currently exploited in PROTAC design, including expression pattern, principal advantages, limitations, and current clinical utilization, is presented in Table 1, and a structural comparison of the two dominant E3 ligases is shown in Figure 3.

Rational Design and Optimization of PROTAC Molecules

Rational PROTAC optimization requires simultaneous management of ternary complex formation, cooperativity, and downstream degradation efficiency, none of which is reliably predictable from the properties of individual components. Successful campaigns therefore integrate medicinal chemistry with biophysical characterization and, increasingly, computational modeling, a combination that is discussed critically below rather than presented as a settled methodology (Park & Jeon, 2025).

Target Assessment and Validation

Suitable PROTAC targets require an available high-quality ligand, cellular localization accessible to the UPS, and surface-exposed lysines positioned for ubiquitination; targets with longer half-lives generally provide a wider therapeutic window between degradation and resynthesis (Bondeson *et al.*, 2022). Genetic validation methods, siRNA, CRISPR-Cas9 knockout, or degron-tag systems, remain the standard for confirming that complete protein elimination, rather than partial functional inhibition, is required for the desired phenotype, a distinction that is especially important for scaffolding proteins whose non-catalytic functions may not be captured by inhibitor-based validation studies (Bondeson *et al.*, 2022).

E3 Ligase Selection Strategy

The selection of a recruited E3 ligase is not a minor implementation detail but a first-order decision governing permeability, tissue selectivity, and resistance liability. CRBN remains the default choice for its favorable physicochemical properties and extensive clinical precedent, but this default should be revisited whenever neo-substrate toxicity risk or class-effect resistance is a significant concern for the target indication, in which case VHL or one of the emerging tissue-restricted ligases may represent a more defensible starting point despite their comparatively less mature ligand chemistry (Bailey *et al.*, 2024; Girardini *et al.*, 2019).

Linker Design and Optimization

Linker optimization remains the most empirically driven element of PROTAC design, typically requiring synthesis of a length- and composition-matched series evaluated for degradation activity in cellular assays, since first-principles prediction of the optimal linker for a novel target/E3 pair remains largely unreliable (Maple *et al.*, 2019; Zagidullin *et al.*, 2020). PEG-based linkers offer synthetic tractability and solubility at the cost of potential entropic penalties; rigid, aromatic, or cyclic linkers can improve pre-organization but demand considerably more synthetic effort per analogue, and the trade-off cannot currently be resolved computationally with confidence sufficient to bypass empirical screening (Tedeschini *et al.*, 2021).

Physicochemical Property Optimization

Most PROTACs substantially exceed traditional Lipinski-rule thresholds, with molecular weights routinely above 800 Da and correspondingly high polar surface area, properties that constrain passive membrane permeability, oral bioavailability, and metabolic stability (Klein *et al.*, 2020). Strategies to mitigate these liabilities, more polar or fragment-based linker redesign, prodrug approaches, and formulation-based solubility enhancement, have achieved workable pharmacokinetics for a handful of clinical candidates (notably bavdegalutamide and vepdegestrant), but the majority of preclinical PROTACs still exhibit poor oral exposure, and no generalizable physicochemical

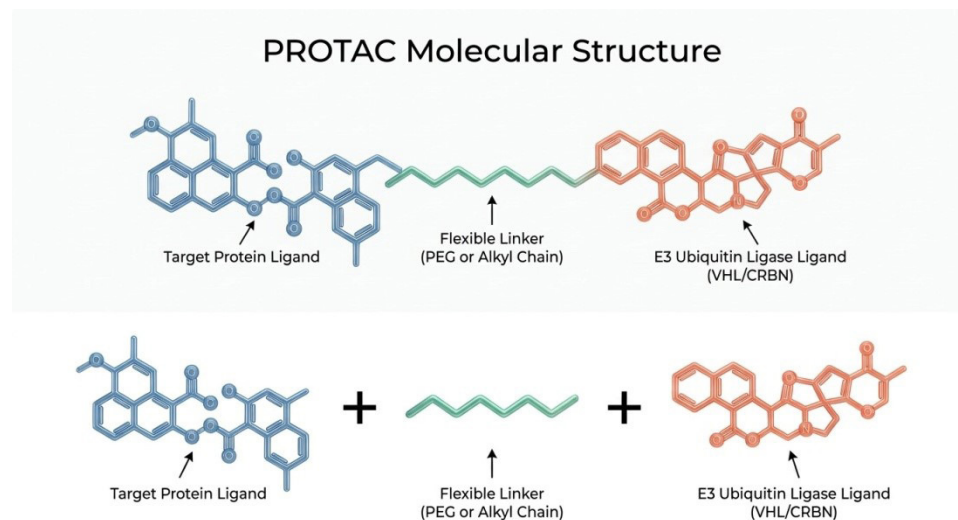


Figure 1: Molecular Architecture of a PROTAC. Schematic representation of the heterobifunctional design of a PROTAC molecule, comprising a protein-of-interest (POI) ligand, an E3 ubiquitin ligase-recruiting ligand (most commonly CRBN or VHL), and a chemical linker. Linker length and composition determine the spatial orientation of the two binding moieties and thereby influence ternary complex formation and degradation efficiency.

rule set yet exists that reliably predicts oral bioavailability for a novel degrader chemotype in advance of extensive medicinal chemistry investment (Liu *et al.*, 2024).

Computational and Artificial Intelligence-Driven Design

Computational prediction of PROTAC ternary complexes has advanced markedly since 2024 and now constitutes a genuinely active area of methodological development rather than an aspirational future direction. Systematic benchmarking of AlphaFold3 (AF3) and Boltz-1 against curated sets of crystallographically resolved PROTAC ternary complexes has shown that AF3, when supplied with explicit ligand atomic coordinates rather than SMILES strings alone, achieves markedly improved ligand-positioning accuracy, correctly modeling roughly half of benchmarked ternary complexes to sub-angstrom root-mean-square deviation (Dunlop *et al.*, 2025). Independent benchmarking against PROsettaC, an earlier constraint-based docking method purpose-built for PROTACs, indicates that AF3's apparent performance is partly inflated by accessory scaffold proteins (such as Elongin B/C or DDB1) that stabilize the overall assembly without being specific to degrader-mediated interfaces, and that PROsettaC can outperform AF3 once these confounds are controlled for, an important critical caveat that tempers unqualified enthusiasm for large structure-prediction models in this application (Schulz *et al.*, 2025). Complementary biophysical and computational work has identified interfacial "frustration", regions of unfavorable local energetics at the induced protein-protein interface, as a central determinant of ternary complex cooperativity, offering a mechanistic rationale that could in principle guide linker and attachment-point selection rather than relying on trial-and-error synthesis alone

(Ma *et al.*, 2025). Machine learning models trained on curated PROTAC activity datasets are similarly being developed to predict degradation potency directly from molecular structure, though these approaches remain constrained by the field's still-limited quantity of high-quality, standardized public degradation data relative to the chemical diversity of the design space, a data bottleneck that is likely to persist as a rate-limiting factor for purely data-driven degrader design in the near term (Lin *et al.*, 2026; Ribes *et al.*, 2024). Collectively, these computational advances are best characterized as promising decision-support tools that can narrow and prioritize synthetic effort, rather than as validated replacements for empirical cooperativity and cell-based degradation assays (Monteleone *et al.*, 2025).

Biomarker Development and Assay Design

Because PROTAC activity depends on ternary complex formation rather than simple target engagement, conventional binding assays are insufficient to characterize degrader pharmacology, and cell-based degradation assays (Western blotting, flow cytometry, high-content imaging) remain the essential functional readout (Spitz *et al.*, 2025). Biomarker strategies for clinical development should, at minimum, combine direct measurement of target protein levels (in tumor biopsies or circulating tumor cells) with functional biomarkers reflecting the downstream consequence of target loss, since target-level measurement alone does not guarantee that degradation has produced the intended pharmacodynamic effect; the current absence of validated companion diagnostics reflecting recruited E3 ligase expression status is a notable and likely consequential gap in most clinical PROTAC development programs to date (Rutherford & McManus, 2024).

Applications of PROTAC Technology in Human Disease

PROTAC technology has been applied most extensively in oncology, but its rationale, elimination rather than inhibition of disease-driving proteins, extends naturally to neurodegeneration, autoimmune and inflammatory disease, and infection. The strength of evidence supporting clinical translation, however, differs markedly across these areas, and this section evaluates each critically rather than presenting them as uniformly promising.

Oncology

Oncology remains the area of greatest clinical maturity, encompassing degraders directed against hormone receptors, epigenetic readers, and kinases. Hormone-dependent cancers have proven the most tractable indication to date: Androgen Receptor (AR) degraders for prostate cancer and Estrogen Receptor (ER) degraders for breast cancer benefit from well-validated target biology and mature ligand chemistry, and this class has produced the field's only approved agent, vepdegestrant (Luo *et al.*, 2022). Bromodomain-containing epigenetic targets, particularly BRD4, have shown potent anti-proliferative activity in preclinical models, and the ability to generate paralog-selective degraders among closely related BET family members illustrates a genuine degradation-specific selectivity mechanism (ternary complex cooperativity) not available to occupancy-based inhibitors of the same family (Maniaci *et al.*, 2017). Kinase degraders, including BTK degraders for B-cell malignancies, are being pursued as a strategy to overcome both gatekeeper resistance mutations and kinase-independent scaffolding functions that inhibitors cannot address; clinical data for this class remain earlier-stage than for hormone receptor degraders (Farnaby *et al.*, 2021).

Neurodegenerative Disease

Neurodegeneration presents a fundamentally different translational challenge than oncology, because pathogenic proteins such as tau, alpha-synuclein, and huntingtin frequently lack the well-defined binding pockets exploited in cancer-focused degrader chemistry, and any CNS-directed PROTAC must additionally achieve sufficient blood-brain barrier penetration, a bar that most current PROTACs, given their high molecular weight and polar surface area, do not clear (Kuemper *et al.*, 2024; Zhou *et al.*, 2025). Consequently, despite considerable preclinical interest in tau- and alpha-synuclein-targeting degraders for Alzheimer's disease and related tauopathies, no CNS-directed PROTAC has yet reached late-stage clinical development, and the chronic dosing required for neurodegenerative disease raises additional, still largely unaddressed long-term safety questions specific to sustained E3 ligase engagement in post-mitotic neurons.

Autoimmune and Inflammatory Disease

Degraders targeting signaling adaptors and transcription factors offer a plausible advantage over kinase inhibition in immunological disease, since complete removal of a scaffolding signaling node may achieve more thorough pathway blockade than catalytic-site inhibition alone. IRAK4 degraders exemplify this rationale: IRAK4 functions as an adaptor in Toll-like receptor and IL-1 receptor signaling, and its degradation, rather than catalytic inhibition, may more completely disrupt downstream inflammatory signaling, a hypothesis being tested clinically with KT-474 in atopic dermatitis and hidradenitis suppurativa (Liu *et al.*, 2023a). STAT3 degraders have shown anti-inflammatory activity preclinically, though achieving adequate tissue

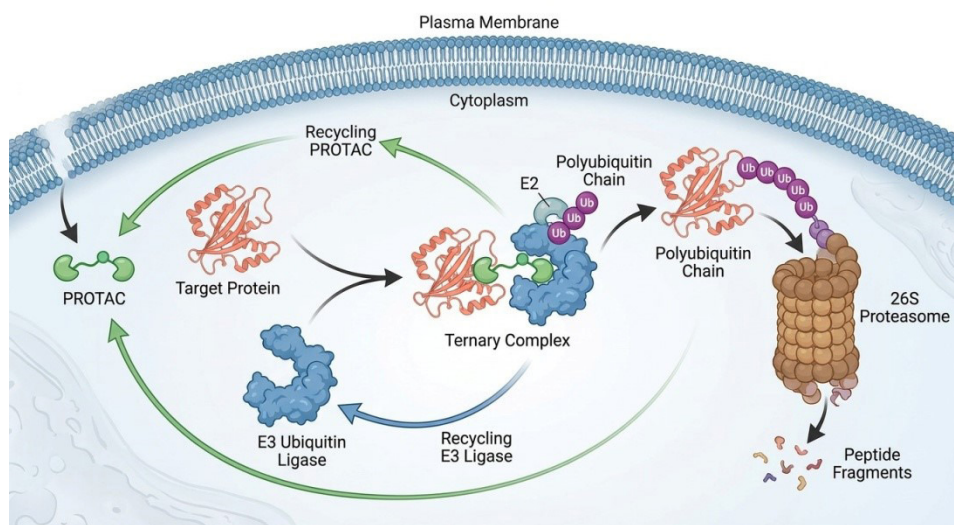


Figure 2: Mechanism of PROTAC-Mediated Protein Degradation. Ternary complex formation between the target protein, PROTAC, and E3 ubiquitin ligase facilitates ubiquitin transfer from E2 enzymes to the target protein, resulting in polyubiquitination and subsequent 26S proteasomal degradation. Catalytic recycling of the PROTAC molecule following target degradation is also depicted.

Table 1: Comparative Summary of Major E3 Ubiquitin Ligases Exploited in PROTAC Design.

E3 Ligase	Representative Ligand	Expression Pattern	Advantages	Limitations	Clinical Utilization
CRBN	Thalidomide, lenalidomide, pomalidomide	Widely expressed	Potent degradation; extensive clinical validation; orally active PROTACs	Neo-substrate degradation; class-effect resistance via CRBN loss	Highest
VHL	Hydroxyproline derivatives	Broad but variable	High selectivity; low neo-substrate liability	Larger ligand size; reduced membrane permeability	Very high
MDM2	Nutlin derivatives	p53-expressing tissues	Simultaneous p53 pathway activation	p53-status-dependent toxicity; requires stratification	Moderate
cIAP1	SMAC mimetics	Broad	Efficient ubiquitination	Auto-ubiquitination/self-degradation	Limited
RNF114	Nimbolide	Skin, immune tissues	Natural-product recruiter; tissue-restricted potential	Early-stage ligand validation	Emerging (preclinical)
DCAF15	Indisulam derivatives	Variable	Novel degradation mechanism	Limited ligand availability	Emerging (preclinical)
KEAP1	Bardoxolone derivatives	Oxidative-stress responsive	Tissue-selective potential	Limited validation	Emerging (preclinical)
FEM1B	EN106 derivatives	Broad	Covalent recruitment strategy	Early discovery stage	Experimental
DCAF16	Electrophilic ligands	Nuclear-localized	Nuclear protein degradation	Few known ligands	Experimental

Note: CRBN, cereblon; VHL, von Hippel-Lindau; MDM2, mouse double minute 2 homolog; cIAP1, cellular inhibitor of apoptosis protein 1; SMAC, second mitochondria-derived activator of caspases. Clinical utilization reflects the number and phase of PROTACs currently recruiting each E3 ligase in human trials as of mid-2026.

distribution without excessive systemic immunosuppression remains an open problem common to this entire target class.

Infectious Disease

Application of PROTAC technology to infectious disease is comparatively nascent and pursues two distinct strategies: degradation of host factors co-opted by pathogens for replication, which may be less prone to resistance than direct antiviral inhibition since the target is host- rather than pathogen-encoded, and, more speculatively, direct degradation of pathogen-encoded proteins (Grohmann *et al.*, 2022). The latter approach faces substantial and, to date, largely unresolved obstacles related to the divergence between prokaryotic and eukaryotic proteolysis systems, and antimicrobial PROTAC development remains at an early exploratory stage relative to the antiviral host-factor strategy (Delft *et al.*, 2023).

PROTACs in Clinical Development

As of mid-2026, more than thirty PROTAC compounds have entered clinical development, providing a substantially larger

and more mature evidence base than existed when most prior PROTAC reviews were written. This section evaluates the leading clinical programs critically, with explicit attention to where clinical outcomes have, or have not, borne out the theoretical advantages.

Bavdegalutamide (ARV-110): Proof-of-Concept with a Narrower-Than-Hoped Efficacy Signal

Bavdegalutamide, the first PROTAC to enter human trials (2019, NCT03888612), is a CRBN-recruiting AR degrader developed for metastatic castration-resistant prostate cancer (mCRPC) previously treated with enzalutamide or abiraterone. Phase I/II data established the essential proof-of-concept for oral PROTAC delivery, with dose-proportional exposure, acceptable tolerability (fatigue, nausea, and hematologic effects being the most common adverse events), and demonstrable AR degradation confirmed by biomarker studies in circulating tumor cells (Neklesa *et al.*, 2019). Critically, however, clinical benefit has proven substantially narrower than the initial mechanistic rationale for degradation-based AR targeting implied: PSA50 responses

have been concentrated almost exclusively in the genetically defined subgroup of patients harboring AR ligand-binding-domain mutations (T878X or H875Y), with limited activity in wild-type-AR mCRPC, and bavdegalutamide has not yet progressed to Phase III (Neklesa *et al.*, 2019). This outcome is an important corrective to the broader claim that PROTACs inherently overcome resistance mutations: bavdegalutamide does overcome specific resistance-conferring point mutations that block inhibitor binding, but its overall efficacy remains target- and genotype-restricted rather than uniformly superior to inhibition, underscoring the continued importance of biomarker-guided patient selection even for degrader therapeutics. Second-generation AR degraders, including luxdegalutamide (ARV-766) and gridegalutamide (BMS-986365), have since entered clinical evaluation with chemistry optimized for broader genotype coverage, reflecting the field's direct response to this limitation (Petrylak *et al.*, 2024).

Vepdegestrant (ARV-471): The First FDA-Approved PROTAC

Vepdegestrant, a CRBN-recruiting ER degrader developed by Arvinas and Pfizer, achieved a landmark regulatory milestone on 1 May 2026, when the FDA approved it (as VEPPANU) for adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer following progression on prior endocrine therapy, together with the Guardant360 CDx companion diagnostic, making it the first approved PROTAC degrader of any kind (Arvinas, Inc., & Pfizer Inc., 2026; FDA, 2026). Approval was supported by the Phase III VERITAC-2 trial (NCT05654623), a global, randomized, open-label study of 624 patients (270 with ESR1-mutated disease) comparing oral vepdegestrant monotherapy against fulvestrant; in the ESR1-mutated population, vepdegestrant achieved a median

progression-free survival of 5.0 months versus 2.1 months for fulvestrant, a 43% reduction in the hazard of progression or death, with a manageable safety profile dominated by Grade 1-2 hematologic and hepatic laboratory abnormalities, alongside a QTc-prolongation signal that will require label-directed monitoring in practice (Arvinas & Pfizer, 2026; FDA, 2026). This result is genuinely significant for the field beyond the individual indication: it is the first randomized, Phase III demonstration that a PROTAC's theoretical pharmacological advantages, complete receptor elimination rather than partial antagonism, translate into a clinically meaningful, regulator-accepted efficacy benefit, and it substantially strengthens the empirical case for the entire technology platform in a way that Phase I/II biomarker data, however encouraging, could not (Song *et al.*, 2024). The commercial and access implications of this approval, including third-party payer positioning, remain unresolved as of this writing.

Other Clinical Candidates

A broader clinical pipeline has emerged across CRBN- and VHL-recruiting chemotypes. NX-2127, a CRBN-based BTK/IKZF1/3 degrader, has shown preclinical and early clinical activity against kinase-impaired BTK resistance mutations that abrogate covalent inhibitor binding, directly illustrating the resistance-mutation advantage of degradation over inhibition for this target class (Montoya *et al.*, 2024). DT2216, a VHL-recruiting BCL-XL-selective degrader, was designed to spare BCL-2 and thereby reduce the thrombocytopenia associated with dual BCL-2/BCL-XL inhibition (Khan *et al.*, 2024); emerging preclinical data indicate that acquired resistance, while comparatively uncommon, does occur and correlates with reduced ternary complex formation rather than target mutation, reinforcing that PROTAC resistance mechanisms are mechanistically distinct from classical

E3 Ubiquitin Ligase Systems in PROTAC Design

Structural Comparison of CRBN and VHL

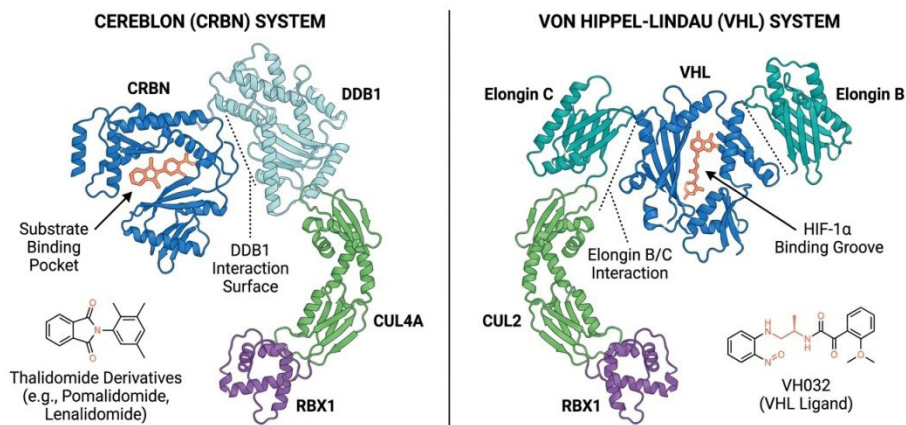


Figure 3: Structural Comparison of CRBN and VHL. Comparative Structural Representation of Cereblon (CRBN) and Von Hippel-Lindau (VHL), the two most extensively validated E3 ligases in PROTAC design, highlighting differences in ligand-binding architecture and recruitment mechanism that influence PROTAC selectivity, permeability, and degradation efficiency.

Table 2: Representative Clinical-Stage PROTACs and Their Therapeutic Applications.

PROTAC	Target	E3 Ligase	Indication	Clinical Status (mid-2026)	Developer
Bavdegalutamide (ARV-110)	Androgen receptor	CRBN	Metastatic castration-resistant prostate cancer	Phase I/II (biomarker-restricted activity)	Arvinas
Vepdegestrant (ARV-471)	Estrogen receptor α	CRBN	ESR1-mutated, ER+/HER2– advanced breast cancer	FDA-approved (VEPPANU®, May 2026)	Arvinas & Pfizer
Luxdegalutamide (ARV-766)	Androgen receptor	CRBN	Metastatic castration-resistant prostate cancer	Phase I/II	Arvinas
Gridegalutamide (BMS-986365)	Androgen receptor	CRBN	Metastatic castration-resistant prostate cancer	Phase I/II	Bristol Myers Squibb
NX-2127	BTK / IKZF1/3	CRBN	B-cell malignancies (incl. inhibitor-resistant)	Phase I	Nurix
NX-5948	BTK	CRBN	B-cell malignancies	Phase I	Nurix
KT-474	IRAK4	CRBN	Atopic dermatitis, hidradenitis suppurativa	Phase I/II	Kymera
DT2216	BCL-XL	VHL	Solid tumors, hematologic malignancies	Phase I	Dialectic Therapeutics
Cemsidomide (CFT7455)	IKZF1/3	CRBN	Multiple myeloma, non-Hodgkin lymphoma	Phase I	C4 Therapeutics
KT-333	STAT3	VHL	Advanced solid tumors, lymphoma	Phase I	Kymera

Note: BTK, Bruton tyrosine kinase; IKZF1/3, Ikaros family zinc finger 1/3; IRAK4, interleukin-1 receptor-associated kinase 4; BCL-XL, B-cell lymphoma-extra large; STAT3, signal transducer and activator of transcription 3. Clinical status reflects publicly disclosed trial phase and regulatory status as of June 2026; vepdegestrant is, to date, the only PROTAC to have received marketing approval.

inhibitor resistance and require dedicated monitoring strategies (Vetma *et al.*, 2025). Cemsidomide (CFT7455), a CRBN-based IKZF1/3 degrader, and KT-474, a CRBN-based IRAK4 degrader for inflammatory indications, remain in earlier-phase evaluation, with KT-474 notable as one of the first PROTACs to enter clinical development for a non-oncology indication (Zheng *et al.*, 2024).

Clinical Pharmacology and Biomarkers

Across these programs, clinical pharmacokinetic/pharmacodynamic relationships have consistently shown that target protein suppression can persist after plasma drug clearance, consistent with the catalytic mechanism, and this has informed dosing schedule design, including exploration of intermittent regimens (Hornberger & Araujo, 2023). Biomarker strategies combining tumor or circulating-tumor-cell target-protein measurement with functional pathway readouts have been essential for demonstrating mechanism of action in early trials, standardized companion diagnostics for E3 ligase expression

status remain largely absent from current development programs, a gap that the ARV-110 experiences suggests may be clinically consequential for patient selection in future programs. A summary of representative clinical-stage PROTACs, their targets, recruited E3 ligases, indications, current clinical phase, and sponsoring organizations is provided in Table 2.

Advantages of PROTAC Technology: Theoretical Rationale versus Clinical Evidence

PROTAC technology is frequently credited with a set of fundamental pharmacological advantages over occupancy-driven inhibition. This section states each advantage and then critically weighs it against the clinical evidence, since, as the divergent outcomes of ARV-110 and ARV-471 illustrate, these theoretical advantages do not translate uniformly across targets. A structural comparison of PROTACs against traditional inhibitors is summarized in Table 3.

Table 3: Structural and Pharmacological Comparison of PROTACs with Conventional Small-Molecule Inhibitors.

Feature	Traditional Inhibitors	PROTACs
Mechanism	Occupancy-driven inhibition	Event-driven, catalytic protein degradation
Target requirement	Requires a deep, active binding pocket	Requires only a ligandable (not necessarily functional) binding site
Protein fate	Protein remains intact; function blocked	Complete proteolysis via the ubiquitin-proteasome system
Catalytic activity	No (1:1 stoichiometry)	Yes; a single PROTAC molecule can degrade multiple target copies
Drug concentration required	Continuous target occupancy required	Transient exposure may be sufficient; risk of hook effect at high concentrations
Resistance	Common via active-site mutation	Can overcome selected binding-site mutations, but susceptible to class-effect E3 ligase loss
Undruggable proteins	Difficult or impossible to target	Can degrade transcription factors and scaffolding proteins lacking active sites
Duration of action	Limited to period of drug exposure	Can be sustained after drug clearance, dependent on protein resynthesis rate
Selectivity determinant	Binary binding affinity	Ternary complex cooperativity (target-E3 interface)
Representative clinical examples	Imatinib, gefitinib	Bavdegalutamide (ARV-110), vepdegestrant (ARV-471)

Note: This comparison reflects general mechanistic tendencies; individual exceptions exist for both drug classes, and the relative advantages of PROTACs are, as discussed in, target- and context-dependent rather than universal.

Event-Driven, Catalytic Pharmacology

The catalytic, sub-stoichiometric mechanism is well supported at the biochemical level, with turnover numbers exceeding 10:1 demonstrated for optimized degraders, and vepdegestrant's Phase III efficacy provides the first clinical-scale confirmation that sustained target suppression after dosing can translate into meaningful progression-free survival benefit (DeNardo & Ruffell, 2019; Kim *et al.*, 2023). This advantage is nonetheless conditional on achieving favorable dissociation kinetics; it is a design target to be optimized, not a guaranteed property of every PROTAC (Cecchini *et al.*, 2021).

Access to "Undruggable" Targets

The capacity to degrade scaffolding proteins and transcription factors lacking conventional binding pockets remains one of the most defensible unique advantages of PROTAC technology, since degradation requires only modest, ligandable binding rather than functional inhibition (Paiva & Crews, 2019). This advantage is best validated for hormone receptors and bromodomain proteins to date; its extension to classically undruggable transcription factors such as MYC or mutant p53 remains substantially preclinical, and no such degrader has yet reached the clinical maturity of the hormone-receptor programs, so this advantage should currently be regarded as proven-in-principle for a limited target set rather than generally realized (Kim *et al.*, 2023).

Overcoming Specific Resistance Mutations

Degradation can, in specific and mechanistically well-defined circumstances, retain activity against inhibitor-resistant point mutations that block drug binding without abolishing PROTAC binary affinity, as demonstrated for AR ligand-binding-domain mutants (bavdegalutamide) and kinase-impaired BTK mutants (NX-2127) (Sun & Rao, 2019). However, this advantage is mutation-specific, not categorical: mutations that disrupt the target-E3 protein-protein interface required for productive ternary complex formation, rather than the POI ligand-binding site itself, can confer PROTAC resistance while leaving conventional inhibitor sensitivity intact, loss of the recruited E3 ligase itself produces a class-effect resistance mechanism with no analogue in conventional inhibitor pharmacology. The claim that PROTACs "overcome drug resistance" is therefore only correct for a defined subset of resistance mechanisms and should not be generalized.

Enhanced Selectivity via Cooperativity

Because degradation requires productive ternary complex formation rather than binary affinity alone, PROTACs can, in principle, achieve selectivity among closely related protein family members that would be difficult to distinguish with conventional inhibitors, a phenomenon demonstrated for VHL-based BET-family degraders (Farnaby *et al.*, 2021). This cooperativity-derived selectivity is a genuine and mechanistically distinct advantage, though it is currently achievable only through iterative empirical optimization rather than rational a priori

design, limiting how readily it can be deployed as a general strategy across new target classes (Wurz *et al.*, 2023).

Challenges and Limitations of PROTACs

The preceding sections have already flagged specific limitations attached to individual advantages; this section consolidates the field's principal cross-cutting challenges, physicochemical, pharmacological, resistance-related, safety-related, and manufacturing, that any critical assessment of PROTAC technology must weigh against its genuine strengths.

Physicochemical and Pharmacokinetic Constraints

Most PROTACs violate multiple traditional drug-likeness guidelines, with molecular weights routinely exceeding 800 Da, and this directly constrains passive membrane permeability, oral bioavailability, and tissue distribution (Wang *et al.*, 2024). That bavdegalutamide and vepdegestrant both achieve oral dosing demonstrates that acceptable pharmacokinetics is achievable for this chemotype, but both required extensive, resource-intensive medicinal chemistry optimization campaigns to reach that point, and the majority of preclinical PROTACs across the field still show poor oral exposure, meaning oral bioavailability should be treated as a major, unsolved optimization burden for new programs rather than an established feature of the modality (Goracci *et al.*, 2020).

The Hook Effect

The hook effect, a bell-shaped concentration-response relationship in which degradation efficiency paradoxically declines at high PROTAC concentrations, arises when excess degrader saturates binary POI and E3 binding sites, favoring non-productive binary complexes over the ternary complex required for ubiquitination (Klein *et al.*, 2021). PROTACs with strong positive cooperativity

are less susceptible to this effect, and computational modeling can estimate the concentration range over which it is likely to occur, but the hook effect nonetheless imposes a genuine clinical constraint, requiring careful dose-escalation design and potentially limiting the maximum tolerated or pharmacologically effective dose, considerations that are specific to degrader pharmacology and have no direct analogue in conventional inhibitor dosing (Füzéry *et al.*, 2013). The phenomenon is illustrated in Figure 4.

Resistance Mechanisms

Resistance to PROTAC therapy arises through mechanisms that are partly shared with, and partly distinct from, conventional inhibitor resistance, and this distinction has direct implications for clinical monitoring. The most consequential and clinically alarming mechanism identified to date is loss of function of the recruited E3 ligase itself, through gene deletion, promoter methylation, or expression of a non-drug-binding splice variant, which produces a class-effect failure: a tumor that loses functional CRBN becomes simultaneously resistant to every CRBN-recruiting PROTAC, irrespective of the POI targeted, a vulnerability with no equivalent in conventional inhibitor pharmacology and one increasingly documented in the IMiD literature that likely extends mechanistically to CRBN-based degraders more broadly (Burke *et al.*, 2022; Vicente *et al.*, 2025). A second, mechanistically distinct route involves mutations at the induced target-E3 protein-protein interface that disrupt productive ternary complex formation without altering the POI ligand-binding pocket, a route of resistance that would be entirely invisible to inhibitor-resistance surveillance panels focused on active-site mutations (Patel *et al.*, 2018). Upregulation of deubiquitinating enzymes and proteasomal dysfunction or saturation represent additional, less well-characterized potential resistance routes (Vetma *et al.*, 2025). Collectively, these

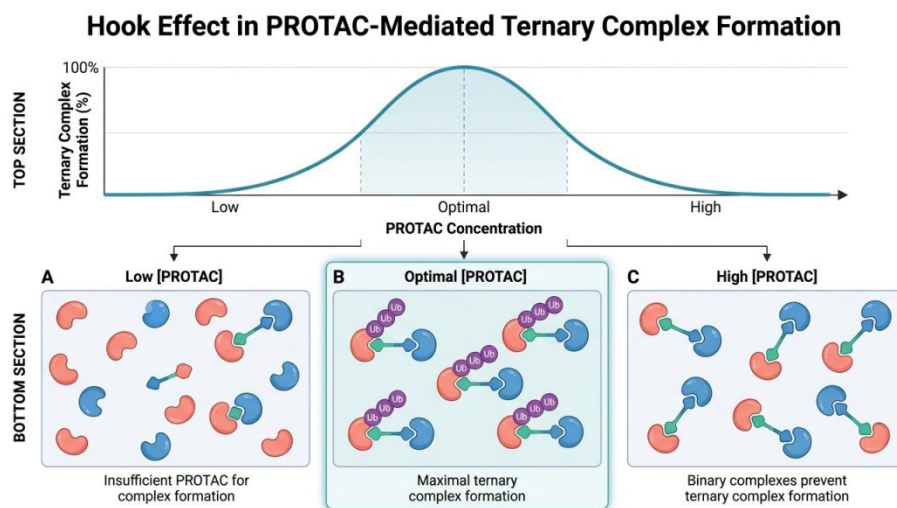


Figure 4: The Hook Effect in PROTAC Pharmacology. Bell-shaped dose-response curve characteristic of PROTAC activity. At optimal concentrations, efficient ternary complex formation produces maximal target degradation; at supraoptimal concentrations, excess formation of non-productive binary PROTAC-POI and PROTAC-E3 complexes reduces ternary complex assembly and consequently diminishes degradation efficiency.

Table 4: Emerging Targeted Protein Degradation Technologies Beyond Conventional PROTACs.

Technology	Mechanism	Target Compartment	Key Advantage	Representative Example	Development Stage (2026)
PROTAC	Proteasomal degradation via E3 ligase recruitment	Intracellular proteins	Clinically validated; catalytic, event-driven	Vepdegestrant (ARV-471)	FDA-approved
Photo-PROTAC	Light-controlled (photocaged/ azobenzene) degradation	Intracellular proteins	Spatiotemporal control	Opto-PROTACs	Preclinical / research tool
LYTAC	Lysosomal degradation via M6PR-mediated uptake	Extracellular & membrane proteins	Extends degradation beyond the proteasome	Anti-EGFR LYTAC	Preclinical
AUTAC	Autophagy-mediated degradation	Organelles & aggregation-prone proteins	Access to non-proteasomal substrates	Mitochondria-targeting AUTAC	Preclinical
Molecular Glue	Induced protein-protein interaction (single molecule)	Intracellular proteins	Smaller molecular size than PROTACs	Lenalidomide, indisulam	Clinically validated (as IMiDs)
AbTAC	Antibody-guided bispecific degradation	Cell-surface proteins	High cell-type selectivity	Anti-PD-L1 AbTAC	Preclinical
Nano-PROTAC	Nanoparticle-encapsulated delivery	Intracellular proteins	Improved solubility & tumor accumulation	Liposomal BRD4-targeting PROTAC	Preclinical

Note: M6PR, mannose-6-phosphate receptor; IMiD, immunomodulatory drug. Development stage reflects the most clinically advanced disclosed example of each modality as of mid-2026.

mechanisms argue for resistance-monitoring strategies specific to degrader pharmacology, tracking E3 ligase expression and interface-relevant mutations rather than simply repurposing inhibitor-resistance mutation panels, a clinical infrastructure need that has not yet been widely implemented.

Off-Target Effects and Safety

Beyond the neo-substrate risk discussed for CRBN, off-target protein degradation more broadly reflects the fact that E3 ligase engagement can promiscuously recruit unintended proteins into the ternary complex interface, producing toxicities mechanistically distinct from POI inhibition (Liu *et al.*, 2021). Long-term safety data for chronic PROTAC dosing remain limited relative to the extensive safety databases available for small-molecule inhibitors, and comprehensive proteomics-based selectivity profiling, while increasingly used in preclinical characterization, is not yet a uniformly applied regulatory expectation across programs, representing a genuine and only partially addressed safety-characterization gap for the field (Pei *et al.*, 2019; Spitz *et al.*, 2025).

Manufacturing, Formulation, and Intellectual Property

The synthetic complexity of PROTACs, multi-step routes with challenging couplings and purifications, presents genuine large-scale manufacturing challenges, and limited aqueous solubility necessitates specialized formulation strategies (Chen *et al.*, 2022). A dense and rapidly expanding patent landscape covering E3 ligands, linker chemotypes, and specific degrader

structures also creates freedom-to-operate complexity that is a practical, if non-scientific, barrier to entry for new programs entering this space (Deshmukh *et al.*, 2025).

Emerging Approaches in Targeted Protein Degradation

The limitations is, restriction to intracellular, cereblon/VHL-addressable targets; poor tissue selectivity; and susceptibility to hook-effect and resistance liabilities, have motivated a diverse set of next-generation degradation modalities. These are evaluated below by the specific limitation each is designed to address, rather than as an undifferentiated list of novel acronyms (Chen *et al.*, 2023).

Conditional and Spatiotemporally Controlled PROTACs

Photo-activatable PROTACs (photo-PROTACs) incorporate photocaging or bistable azobenzene-based photoswitchable linkers that mask degrader activity until light exposure, enabling reversible, spatiotemporally restricted degradation with a temporal resolution (seconds to minutes) unattainable with conventional small-molecule dosing (Chen *et al.*, 2023). This precision is valuable for basic research applications in neuroscience and cell biology but is not, at present, a clinically deployable strategy given the tissue-penetration limits of light delivery in vivo, so photo-PROTACs should be regarded as an important research tool rather than a near-term therapeutic modality.

Targeted Delivery Systems

Antibody-PROTAC conjugates (AbTACs and related antibody-degrader formats) address the tissue-selectivity limitation directly by physically restricting degrader delivery to antigen-defined cell populations; recombinant bispecific antibody-based degradation of the cell-surface protein PD-L1 and trastuzumab-conjugated degraders achieving HER2-dependent, cell-type-selective BRD4 degradation illustrate this strategy (Cotton *et al.*, 2021). Nano-PROTACs, encapsulating or conjugating degraders to liposomal, polymeric, or lipid nanoparticle carriers, aim to improve solubility, circulation time, and tumor accumulation via enhanced permeability and retention, though clinical validation of this delivery strategy for PROTACs specifically remains limited relative to the extensive experience with nanoparticle drug delivery in other therapeutic classes (Oberoi *et al.*, 2013).

Alternative Degradation Pathways

Lysosome-Targeting Chimeras (LYTACs), which couple antibodies to glycopeptide ligands for the cation-independent mannose-6-phosphate receptor, and Autophagy-Targeting Chimeras (AUTACs) extend targeted degradation to extracellular, membrane-bound, and organelle-associated substrates that are structurally inaccessible to proteasome-dependent PROTACs, directly addressing the intracellular-target restriction noted above (Daurat *et al.*, 2024; Wu *et al.*, 2023). Molecular glues represent a related but mechanistically distinct single-molecule strategy that induces target-E3 protein-protein interaction without a bipartite linker architecture; IMiDs and indisulam are clinically validated examples, and their smaller molecular size relative to PROTACs may offer physicochemical advantages, though molecular glue discovery currently lacks the modular, rational design logic available for PROTACs and remains comparatively more serendipitous (Wu *et al.*, 2023).

Next-Generation PROTAC Architectures

Homo-PROTACs, linking two copies of an E3 ligand to induce E3 self-degradation, provide proof-of-concept that the modular architecture can be repurposed for E3-directed rather than POI-directed degradation (Maniaci *et al.*, 2017). Trivalent PROTACs, incorporating an additional binding element to enhance ternary complex avidity and cooperativity, have achieved low-picomolar BRD2 degradation with favorable pharmacokinetics in reported VHL-based designs, illustrating that structural innovation beyond the canonical bipartite architecture remains a productive area of the field (Imaide *et al.*, 2021). A comparative summary of PROTACs and these emerging degradation modalities, including their mechanism, addressable target compartment, and principal advantage, is provided in Table 4.

FUTURE PERSPECTIVES

The trajectory of PROTAC technology from 2026 onward will likely be determined less by further validation of its core mechanistic premise, now substantiated by vepdegestrant's approval, than by the field's success in addressing the specific, well-defined limitations catalogued throughout this review. Four priorities stand out as most consequential.

First, expanding the recruitable E3 ligase repertoire beyond CRBN and VHL is essential both for reducing class-effect resistance risk and for enabling tissue-selective degradation; ligands for RNF114, DCAF15, DCAF16, KEAP1, and FEM1B represent a promising but still immature starting point that requires substantially more medicinal chemistry investment before reaching clinical readiness. Second, computational and artificial intelligence-based ternary complex prediction is maturing rapidly but should be adopted as a hypothesis-prioritization tool integrated with, rather than a substitute for, empirical cooperativity and cell-based degradation assays, given the demonstrated limitations of even the strongest current models (AlphaFold3, PROsettaC) on held-out, post-training-cutoff structures (Dunlop *et al.*, 2025; Schulz *et al.*, 2025). Third, biomarker-driven patient selection, an approach whose necessity is underscored by the narrow, genotype-restricted efficacy of bavdegalutamide relative to the broader efficacy of vepdegestrant, should be built into clinical development programs from Phase I onward rather than retrofitted after unexpectedly modest Phase II results, and this will require the companion-diagnostic infrastructure (E3 ligase expression assays, target-protein biomarkers) that is currently underdeveloped across the field. Fourth, systematic resistance surveillance specific to degrader pharmacology, tracking E3 ligase status and ternary-interface mutations rather than relying solely on inhibitor-resistance mutation panels, should be incorporated prospectively into ongoing and future trials, particularly for CRBN-recruiting programs given the class-effect risk (Vetma *et al.*, 2025).

Beyond these four priorities, continued expansion into transcription factors, intrinsically disordered proteins, and non-oncology indications, combined with next-generation delivery and alternative degradation modalities, will likely broaden the addressable target space substantially over the coming decade. The central lesson of the vepdegestrant approval, however, is that clinical success depends on the same rigorous, target-specific, biomarker-informed development discipline required of any other modality; PROTAC technology's catalytic, event-driven mechanism is a genuine and now clinically validated pharmacological advantage, but it is not, and should not be portrayed as, a shortcut around the fundamentals of target validation and patient selection.

CONCLUSION

PROTAC technology has completed a genuine transition from chemical-biology proof-of-concept to a clinically validated therapeutic modality, a transition anchored decisively by the May 2026 FDA approval of vepdegestrant, the first PROTAC to reach regulatory approval and market. This review has sought to demonstrate that the technology's core mechanistic advantages, catalytic, event-driven degradation; access to scaffolding proteins and transcription factors inaccessible to conventional inhibitors; and cooperativity-derived selectivity, are real and, in the case of vepdegestrant, now supported by Phase III clinical evidence rather than preclinical rationale alone. At the same time, the more circumscribed clinical trajectory of bavdegalutamide illustrates that these advantages do not translate uniformly across targets and that degrader development requires the same rigorous target validation and biomarker-guided patient selection demanded of any other therapeutic modality.

The field's most consequential unresolved challenges, persistent oral bioavailability constraints for the majority of preclinical candidates, the hook effect, class-effect resistance arising from E3 ligase loss, and a still-narrow toolbox of clinically usable E3 ligases, are well defined rather than mysterious, and each has an identifiable, actively pursued line of investigation: tissue-restricted E3 ligand discovery, artificial intelligence-assisted ternary complex prediction, degrader-specific resistance surveillance, and next-generation modalities (LYTACs, AUTACs, antibody-PROTAC conjugates, nano-PROTACs) that extend targeted degradation beyond the proteasome-dependent, intracellular target space. Continued progress will depend on the disciplined integration of medicinal chemistry, structural and computational biology, and clinical pharmacology described throughout this review, rather than on the mechanistic novelty of the platform alone. With a first approved agent now in clinical use and a substantially larger and more mature clinical evidence base than existed even two years ago, PROTAC technology is positioned to expand meaningfully across oncology and, contingent on solving the blood-brain-barrier and tissue-selectivity challenges, into neurodegenerative and inflammatory disease over the coming decade.

ABBREVIATIONS

PROTAC: Proteolysis-Targeting Chimera; **POI:** Protein of Interest; **UPS:** Ubiquitin-Proteasome System; **CRBN:** Cereblon; **VHL:** von Hippel-Lindau; **E3:** E3 Ubiquitin Ligase; **MDM2:** Mouse Double Minute 2 Homolog; **FDA:** U.S. Food and Drug Administration; **AR:** Androgen Receptor; **ER:** Estrogen Receptor; **HER2:** Human Epidermal Growth Factor Receptor 2; **ESR1:** Estrogen Receptor 1 (gene); **BTK:** Bruton's Tyrosine Kinase; **IRAK4:** Interleukin-1 Receptor-Associated Kinase 4; **BRD4:** Bromodomain-Containing Protein 4; **CNS:** Central Nervous System; **mCRPC:** Metastatic Castration-Resistant Prostate

Cancer; **LYTAC:** Lysosome-Targeting Chimera; **AUTAC:** Autophagy-Targeting Chimera; **IKZF1/3:** Ikaros Family Zinc Finger 1/3.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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