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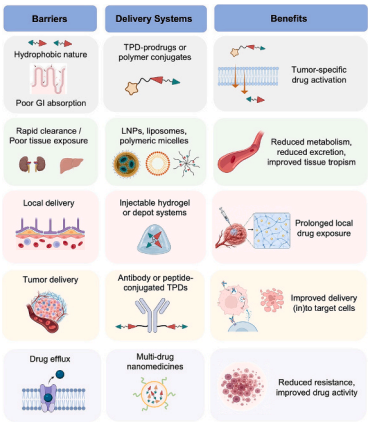
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Targeted delivery of proteolysis-targeting chimeras (PROTAC) and molecular glue degraders (MGD)☆

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GRAPHICAL ABSTRACT



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ABSTRACT

Targeted protein degraders (TPDs), including proteolysis-targeting chimeras (PROTAC) and molecular glue degraders (MGD), are among the most promising small-molecule-based drug treatments in oncology. The May 2026 U.S. Food and Drug Administration (FDA) approval of vepdegestrant provides a regulatory milestone for heterobifunctional protein degradation and for PROTAC therapeutics. First-generation TPDs were developed for oral delivery; however, the intrinsic physicochemical properties of TPDs impose constraints on their oral bioavailability, systemic exposure, target-site accumulation, and therapeutic efficacy. As the field transitions toward a second wave of TPD development, nanoparticle-based targeted protein degraders (nano-TPD) are gaining momentum for broadening the therapeutic landscape of protein degradation. In this context, drug delivery systems

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offer opportunities to overcome key translational barriers by improving pharmacokinetics, tissue distribution, target site localization, cellular uptake, and therapeutic index. Here, we provide an overview of TPD discovery, from early laboratory to (pre-) clinical progress, discuss translational challenges, and suggest advanced drug delivery solutions to help realize the full potential of TPD therapies.

1. Introduction

Pharmacological drug treatments have historically relied on inhibiting protein function, but many disease-driving proteins are considered "undruggable". Targeted protein degradation offers solutions to address the limitations of traditional inhibitors and engage previously inaccessible targets (Fig. 1A)). Preclinical and clinical targeted protein degraders (TPDs) are primarily developed for oral administration, which may result in suboptimal biodistribution, poor treatment responses and/or development of side effects. Recent reviews have thoroughly described the biological mechanisms, medicinal chemistry perspectives, and oral delivery-oriented clinical progress of molecular TPDs including proteolysis-targeting chimeras (PROTAC) and molecular glue degraders (MGD) [1–3]. In parallel, there is a growing body of studies and reviews highlighting the potential advantages of drug delivery systems (DDS) for targeted protein degraders [4–7]. Notably, however, most delivery-based approaches explored to date rely predominantly on intravenous administration given the sensitivity of DDS to the gastrointestinal system. Emerging studies suggest that nanoparticle-based TPD (nano-TPD) could mitigate intrinsic challenges of molecular degraders, including poor bioavailability, rapid clearance, and inadequate tissue selectivity [8,9]. Despite this surge of interest in the nano-TPD field, a systematic, top-down evaluation bridging patient outcomes of a small-molecule back to preclinical pharmacology remains lacking. We aimed to assess whether oral regimens are inherently optimal for TPD modalities or whether alternative routes of administration and the generation of novel DDS should be more deliberately considered.

This mini-review starts from a simple translational premise: the clinical reach of TPDs will not be determined by target degradation alone, but by whether degraders can be delivered to the right tissue, enter the right cells, avoid efflux and sustain intracellular exposure at pharmacologically useful levels. We therefore use the limitations of first-generation oral degraders to define a delivery-centered rationale for next-generation TPD development. The central question is which DDS architecture is best suited to each translational barrier, and which limitations remain after delivery intervention. This barrier-to-solution framework directly maps major translational challenges of TPDs, including poor intestinal absorption, inadequate pharmacokinetics, limited tissue access, and restricted intracellular release and retention to delivery strategies such as lipid nanoparticles, antibody and ligand-guided conjugates, hydrogels, prodrugs, and combination carrier systems.

Here we examine three linked translational questions: (1) why targeted protein degradation remains clinically compelling over

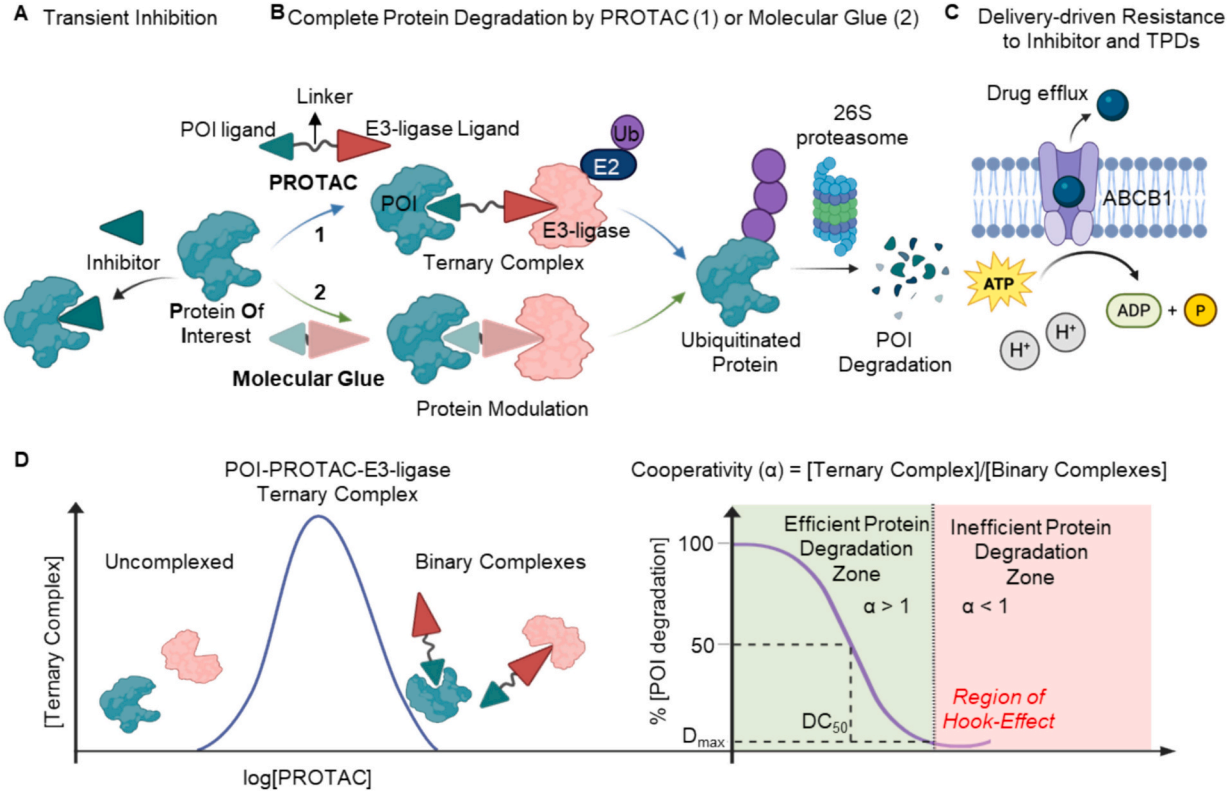


Fig. 1. Comparison of protein of interest (POI) inhibition by a conventional small-molecule inhibitor (A) *vs.* by a PROTAC or MGD (B), highlighting how catalytic protein degradation can mitigate drug resistance mechanisms (*e.g.*, target overexpression or activating mutations). Delivery-driven resistance, including ATP-binding cassette transporter 1 (ABCB1)–mediated drug efflux from cancer cells, remains a barrier for inhibitor-based therapies (C). Ternary complex formation and target protein degradation dose-response curve (D, left panel) showing that the efficacy of PROTAC with lower DC_{50} and high DC_{50} values (D, right panel) is dependent on the co-operativity factor (α), which is the ratio between ternary and binary complexes. Dmax = the maximum target degradation achieved; DC50 = concentration giving 50% POI degradation; Ub = ubiquitin; ADP = adenosine diphosphate, ATP = adenosine triphosphate, P = inorganic phosphate. Image D adapted from reference 10.

therapeutic protein inhibition, (2) what current data reveal about their translational limitations, and (3) whether rationally engineered delivery systems can expand the therapeutic scope of protein degradation. By integrating medicinal chemistry constraints with delivery-driven solutions and incorporating both academic and industrial perspectives, we position drug delivery not as a secondary formulation consideration, but as an enabling strategy for next-generation TPD development. Importantly, this review systematically situates nanoparticle-mediated degradation within the broader TPD landscape, outlining how advanced delivery technologies may expand degrader chem-bio space, administration routes, and ultimately clinical applicability.

2. Principles of targeted protein degradation

2.1. Mechanism and pharmacology of targeted protein degraders

TPDs can efficiently degrade disease-driving proteins by hijacking the ubiquitin-dependent proteolysis pathway that is routinely used to regulate post-translationally modified proteins [1,2,11]. Ubiquitination of any protein of interest (POI) occurs through the sequential activity of three enzymes: (1) ubiquitin-activating enzymes (E1), (2) ubiquitin-conjugating enzymes (E2), and (3) ubiquitin-protein ligases (E3). These enzymes work sequentially to catalyze the attachment of ubiquitin to lysine residues of POI and E3 ligases confer specificity to ubiquitination reactions by binding directly to POI. The two main TPD strategies rely on PROTAC and MGD [1,12,13]. They both exploit the ubiquitin-proteasome system for selective protein degradation (Fig. 1B, Path 1), but they are based on different structural designs and protein-protein interaction-driven mechanisms. PROTAC are large hetero-bifunctional molecules consisting of three components: a target protein-binding small molecule, a linker of optimized length and composition, and a ligand that engages an E3 ubiquitin ligase [2]. These molecules thus simultaneously bind to the POI and to an E3 ligase, promoting ubiquitination and subsequent proteasomal degradation of the protein.

The effective protein degradation pharmacology of a PROTAC is defined by the combination of its half-maximal degradation (DC_{50}) and the maximum degradation achieved (D_{max}). The ability of a PROTAC to form stable and productive ternary complexes directly influences both parameters. Cooperativity (α) governs how efficiently the target-PROTAC-E3 ligase assembly forms beyond binary binding affinities. Hence, when $\alpha > 1$, positive cooperativity stabilizes the ternary complex, typically lowering the DC_{50} and enabling higher D_{max} values to facilitate ubiquitin transfer to the POI, even when the two proteins would not naturally interact. Conversely, when $\alpha < 1$, negative cooperativity destabilizes the ternary complex, often resulting in higher DC_{50} values and reduced D_{max}, as higher concentrations are required and non-productive binary complexes (between E3 ligase or POI and PROTAC) become favored leading to the classical "hook effect" [14,15]. Thus, cooperativity serves as a central mechanistic determinant linking molecular design to the observable degradation potency and depth. Key linker properties, including length, rigidity, and stereochemistry, significantly impact eventual PROTAC efficacy by co-determining the ratio of possible ternary and binary complexes and their stabilities. In addition to influencing the ternary complex formation by PROTAC, the linker plays a critical role in their *in vivo* pharmacokinetic properties including oral bioavailability, which is a combined outcome of their hydrophilicity, metabolic stability, and cellular uptake [3]. Mechanistically, polyethylene glycol (PEG)-based flexible linkers provide conformational freedom [16] that can enhance ternary complex formation and improve solubility and pharmacokinetics, but they may introduce entropic constraints that reduce complex stability. In contrast, piperazine or semi-rigid linkers restrict geometry, lower entropic compensation, and often improve metabolic stability, making them attractive for orally bioavailable clinical PROTAC candidates [17–20]. Despite these advances, the first wave of clinical PROTAC has achieved only moderate oral bioavailability (~50%), highlighting the need for further optimization in this direction [21].

MGD, on the other hand, are small monovalent compounds that stabilize novel interactions between a target protein and an E3 ligase, by altering the E3-ligase surface to accommodate new substrates (*i.e.* neo-substrates) rather than by physically connecting them *via* a linker, eventually triggering effective protein degradation (Fig. 1B, Path 2). Conventionally, the discovery and protein degradation success of MGD are ideally not linked to linker optimization; however, a study showed that subtle structural modifications to a PROTAC scaffold can shift its mechanism of action toward that of a MGD, promoting mouse double minute 2 homolog (MDM2) degradation through allosteric stabilization rather than through induced proximity [22]. Notably, the recent discovery of a hybrid degrader capable of degrading androgen receptor/androgen receptor splice variant-7 (AR/AR-V7) and G1 to S phase transition 1 (GSPT1) by simultaneous PROTAC- and MGD-like mechanisms illustrates the continuum between bifunctional PROTAC and monovalent MGD [23]. Collectively, these advances demonstrate that the conceptual boundary between classical PROTACs and MGD is progressively narrowing, expanding the design space and broadening the druggable proteome.

2.2. Clinical relevance of protein degradation over protein inhibition

Less than 20% of disease-related proteins (approximately 750 proteins of more than 4500 protein coding genes) can be targeted using standard drugs, with the majority being small-molecule protein inhibitors. Emerging TPD strategies have already enabled potent and persistent knockdown of more than 400 target protein of the 'undruggable' proteome, which is an impressive achievement given the field's young age (starting in 2001) [3,24,25]. The first PROTAC was designed to degrade methionine aminopeptidase-2 (MetAP-2) protein by recruiting the SCF-β-TrCP E3 ubiquitin ligase complex (where SCF denotes Skp1-Cullin-F-box and β-TrCP stands for beta-transducin repeat-containing protein) by chemically linking phosphorylated peptide (an inhibitor of NF-κB) to the MetAP-2-binding ligand ovalicin, a known angiogenesis inhibitor [11]. Over the last two decades, the TPDs advanced from *in vitro* studies to *in-patient* POI-degradation, and on May 1, 2026, the United States Food and Drug Administration (FDA) approved vepdegestrant (ARV-471) for adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, and estrogen receptor 1 (ESR1)-mutated advanced or metastatic breast cancer after progression following at least one endocrine therapy [26–28]. The Phase 3 VERITAC-2 clinical trial (NCT05654623) of vepdegestrant showed clinical efficacy in advanced or metastatic breast cancer patients even in ESR1-mutated patients who had developed resistance to prior antiestrogenic therapy. Traditional inhibitors that block protein function, and clinically face challenges such as: (1) requiring high occupancy of binding at the functional sites of the protein of interest, (2) triggering compensatory protein overexpression through feedback mechanisms [29,30], (3) the inability to target non-catalytic protein functions [31,32], and (4) development of resistance through mutations in binding sites and overexpression of multidrug resistance transporter proteins such as ATP binding cassette (ABC) transporters (Fig. 1C) [33].

Both PROTAC and MGD can bypass drug resistance, as they induce complete degradation of target proteins rather than relying on the stoichiometric inhibition, as conventional inhibitor drugs do; such drugs often require high concentrations for efficacy. By removing the entire protein catalytically rather than transiently blocking its activity, these degraders achieve more durable effects and exert a broader impact on downstream signaling pathways [34–36]. The catalytic nature of this mechanism was first demonstrated by injecting estrogen-related receptor alpha (ERRα)-targeting PROTAC in mice carrying MDA-MB-231 breast cancer, where sub-stoichiometric dosing resulted in sustained target depletion [37]. However, a recent study on poseltinib-based covalent PROTAC (PSIRC3) showed that *in vitro* Bruton's tyrosine kinase

(BTK) degradation is primarily dictated by optimized ternary complex stability rather than catalytic turnover alone [38]. Computational modeling revealed that balanced affinities for the target and E3 ligase are essential, as excessive ligase binding can induce a hook effect (Fig. 1D) and compromise degradation efficiency. Importantly, productive ternary complex formation also depends on the relative cellular abundance of the E3 ligase and the POI, underscoring the context-dependent nature of PROTAC efficacy. Emerging clinical studies have demonstrated that PROTAC targeting oncoproteins such as BCR-ABL [39], epidermal growth factor receptor (EGFR) [40], and androgen receptor (AR) [41] can achieve more durable responses than small-molecule inhibitors [42]. As an example, in a Phase 1/2 trial in heavily pretreated metastatic castration-resistant prostate cancer patients not responding to enzalutamide and abiraterone, the PROTAC ARV-110 containing enzalutamide analogue as the warhead produced sustained AR degradation and antitumor activity [43]. Similarly, the ER degrader ARV-471 demonstrated robust ER reduction (>90%) and achieved a 38% clinical benefit rate in advanced breast cancer patients, including those with ESR1 mutations [44,45]. Previously, the asofoxifene-like benzopyran selective estrogen receptor modulator (SERM)-derived ER warhead incorporated into ARV-471 has been shown to overcome several limitations of conventional endocrine therapies [44]. Unlike fulvestrant, which induces only ~40–60% ER destabilization, ARV-471 actively recruits cereblon (CRBN)-mediated ubiquitination machinery to achieve >90% ER degradation. Importantly, ARV-471 retains potent anti-proliferative activity in endocrine-resistant ESR1-mutant T47D-Y537S cells at subnanomolar concentrations, highlighting the therapeutic potential of catalytic protein degradation to overcome resistance mechanisms associated with incomplete receptor suppression.

Most E3 ligases currently amenable to targeted protein degradation belong to the Cullin-RING ligase (CRL) family, with $CRL4^{CRBN}$ and $CRL2^{von\ Hippel\ Lindau(VHL)}$ representing the two ligase systems most successfully hijacked by clinically advanced degraders. At present, the clinical landscape of targeted protein degradation remains predominantly CRBN-driven, with most clinically advanced and orally administered degraders incorporating lenalidomide- or pomalidomide-derived cereblon recruiters, likely reflecting the favorable oral bioavailability. Nevertheless, clinical experience with lenalidomide and pomalidomide has revealed multiple CRBN-associated resistance mechanisms, including CRBN downregulation, copy-number loss, splice alterations, epigenetic silencing, and mutations affecting substrate recognition [46]. More recently, an important study has opened a new branch of investigation into E3 ligase-centric degrader resistance, moving beyond the traditional focus on target mutation or loss of target engagement. Using functional mutational scanning, the authors identified degrader-specific "functional hotspots" within CRBN, defined as mutation-sensitive residues whose alteration disproportionately impairs productive degradation despite preserved ligand binding or E3 ligase expression. Importantly, resistance depended not only on the recruited E3 ligase itself, but also on the specific ternary complex geometry imposed by individual degraders, suggesting that structurally distinct degraders may exhibit different resistance liabilities despite engaging the same ligase. Residues such as histidine-57 (H57), proline-352 (P352), phenylalanine-381 (F381), and histidine-397 (H397) emerged as clinically relevant CRBN functional hotspots, several of which overlap with mutations reported in relapsed multiple myeloma patients following lenalidomide treatment [47]. These findings suggest that E3 ligase topology, ternary cooperativity, and hotspot sensitivity may become important determinants of degrader efficacy and future degrader design.

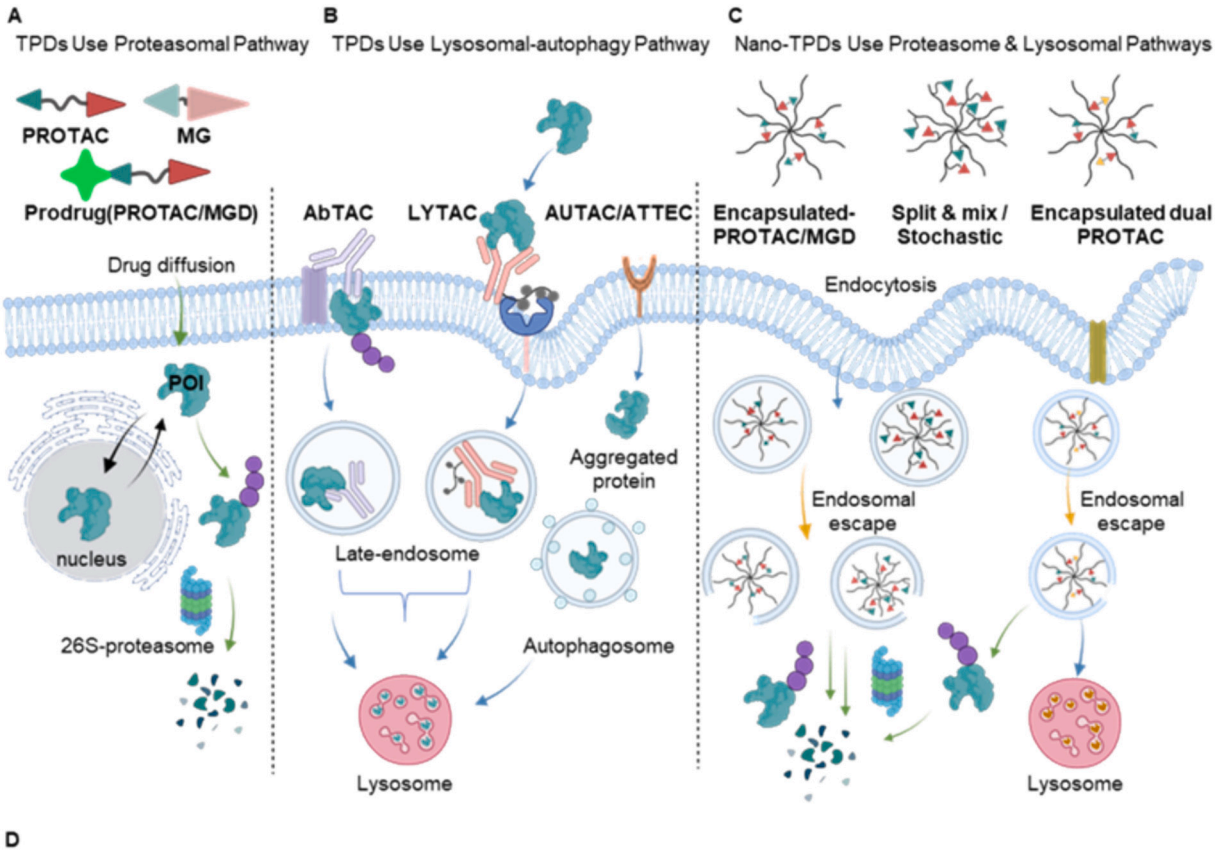
Importantly, the resistance-bypassing advantage of TPDs primarily concerns mechanisms that compromise conventional inhibitor binding, including target overexpression or mutations that reduce inhibitor affinity for the protein of interest (Fig. 1B). However, TPDs still remain vulnerable to intracellular delivery-related resistance mechanisms, including active efflux by transporters such as ATP-binding cassette subfamily B member 1 (ABCB1; also known as multidrug-resistance 1 (MDR1)), which can reduce intracellular degrader exposure and limit efficacy [48,49]. These delivery-associated resistance mechanisms and their implications for TPD design and therapeutic performance are further elaborated in Section 4.2. While TPDs have emerged as powerful tools to mitigate drug-resistance mechanisms by eliminating disease-relevant proteins, an important question remains: can any protein be degraded by such technology?

2.3. Discovery workflow for targeted protein degraders

2.3.1. Cellular target location drives the clinical relevance of conventional protein degraders

Selecting appropriate targets is critical for successful clinical development of TPD. Not all proteins make good candidates for degradation approaches, and certain features predict a higher likelihood of success [50,51]. The following factors are to be considered when selecting targets for degradation: (1) proteins with multiple functional domains where complete elimination offers advantages over single-site inhibition, (2) proteins with high affinity ligands already identified (particularly relevant for PROTAC development), (3) proteins with moderate-to-slow turnover rates to achieve sustained degradation effects, (4) scaffolding proteins whose functions extend beyond catalytic activity, (5) proteins involved in resistance mechanisms to existing therapies, and (6) selectivity in protein-protein interactions between a set of an E3 ubiquitin ligase and the POI [52]. Good candidates include transcription factors (like signal transducer and activator of transcription protein 3/6 (STAT3/6)) [53,54], a GTP-binding signal transducer proteins (like Kirsten rat sarcoma viral oncogene homolog (KRAS)) [55], multi-domain kinases (breakpoint cluster region-Abelson (BCR-ABL)), hormone receptors (AR, ER) [41,44], and epigenetic readers (bromodomain-containing protein 4 (BRD4)) [56,57]. Conversely, proteins with rapid turnover rates [58,59] or those localized in cellular compartments yet unstable for lysine-based ubiquitination (like Cyclophilin A) [60,61] or proteins that form aggregates (Tau, α-synuclein) [62,63] may be less suitable for degradation approaches. Beyond the ability of TPD to recruit the appropriate ligand and control POI turnover kinetics [64,65], subcellular localization has emerged as a critical determinant of degrader susceptibility and delivery requirements [66,67].

In the PROTACtable Genome framework, Schneider *et al.* proposed a "PROTACtability" workflow incorporating UniProt /Gene Ontology (GO) localization data to stratify human proteins into eight degradability buckets [68]. These buckets reflect increasing confidence in successful PROTAC-mediated degradation, based on integrated features such as ligandability, structural accessibility, E3 ligase compatibility, and experimental degradation evidence. These buckets are further refined by a location score, which captures subcellular localization as a dominant determinant of their clinical success rate (Fig. 2 A-B, D). Proteins localized to the cytosol and nucleus consistently populate the highest-confidence buckets, as their accessibility to both small molecules and the ubiquitin-proteasome machinery enable robust ternary complex formation and efficient degradation, thereby defining the primary pool of clinically precedented PROTAC targets. Intermediate buckets comprise proteins with mixed or conditional accessibility such as shuttling nuclear-cytosolic proteins or tightly regulated complexes, which are typically suited for preclinical or early translational exploration, often requiring optimized linker design, alternative E3 ligases, or delivery enhancement. In contrast, proteins assigned to the lowest-confidence buckets are enriched in membrane-associated, luminal, or organelle-confined compartments, where limited proteasomal access and unfavorable topology impose major translational barriers, relegating these targets largely to preclinical investigation unless enabled by novel ligase biology or advanced drug delivery strategies [5,36,69]. The localization of the non-cytosolic proteins or integral membrane proteins poses a barrier to their degradation via TPD technology; however, *in vitro* and *in vivo* degradation of EGFR [70] and programmed death-ligand 1 (PD-L1) [36,71] demonstrate that localization barriers can be



D

Location score	Localization	Confidence level	Clinical/preclinical precedence
1	Cytosolic, nucleoplasmic	high	Clinical (AR, ER)
2-3	Cytosolic-nucleoplasmic shuttling	medium-high	Clinical, translational (kinases)
4-5	unknown	medium	Preclinical (PD-L1)
5-6			
7	Unfavorable (membrane)	high	Preclinical (GPCR)

Fig. 2. Proteasome-mediated degradation of cytosolic and nuclear proteins by PROTAC, MGD, and their prodrugsfai (A). Lysosome and autophagy-mediated degradation of membrane-bound and cytosolic proteins by lysosome targeting chimeras (LYTAC) and autophagy targeting chimeras (AUTACs) (B). Mix of proteasomal, lysosomal, and autophagy-mediated degradation of proteins by nanoparticle-based protein degraders (C). Protein target selection according to cellular location and degradability score (D). Table adapted from reference 68. LYTAC and AUTAC modalities are included as contextual boundary examples rather than as the primary focus of this review.

overcome with rational drug design based on ligand binding and recycling phenomena [72]. In-depth studies on Aurora kinase (AURKA) PROTAC selectively degraded spindle-associated but not centrosomal pools of the kinase, illustrating that repulsive interactions or steric hindrance due to binding to certain large structures, such as spindles, may restrict degrader access [14,73,74]. Overall, the clinical success of TPD technologies in degrading cytosolic and nuclear proteins has been demonstrated in patients, and, new approaches are required to target proteins that are less accessible to the ubiquitin-proteasome system.

2.3.2. *Scope of lysosome-mediated protein degradation scheme*

Beyond proteasome-based protein degradation, lysosome-mediated protein destruction strategies such as lysosome-targeting chimeras (LYTAC) [75,76] and autophagy-targeting chimeras (AUTAC) [77] expand the degradable proteome by also enabling clearance of extracellular membrane proteins (Fig. 2B, D). LYTACs are chimeric molecules that couple a POI ligand with a lysosomal receptor binder to induce receptor-mediated endocytosis and subsequently lysosomal degradation, enabling durable knockdown of extracellular and membrane proteins beyond the reach of PROTAC [76,78]. Autophagy-targeting degraders such as AUTAC, autophagy-targeted chimera (AUTOTAC), and autophagosome-tethering compound (ATTEC) exploit the autophagosome-lysosome degradation pathway to selectively eliminate intracellular proteins and can even enable the breakdown of non-protein cargos [75]. Tissue-specific target selection further expands the arsenal of possibilities (and also complexity), necessitating strategies to specifically deliver degraders across physiological barriers, such as the blood-brain barrier, to address central nervous system (CNS) targets [79].

Details on this will be provided below, when specifying advantages of TPD conjugated to or entrapped within drug delivery systems over free TPD molecules [8,9]. Although LYTAC, AUTAC, AUTOTAC, and ATTEC expand the degradable proteome beyond classical proteasome-based TPDs, they also illustrate a broader delivery principle. Subcellular localization defines not only whether a target can be degraded, but also which trafficking route, intracellular compartment, and delivery strategy are required. In this review, these modalities are therefore used as contextual examples, while the subsequent analysis focuses on delivery strategies for PROTAC and MGD.

3. Current clinical landscape of targeted protein degrader technology

3.1. Advancements of PROTAC and MGD in cancer therapy

Today, almost 30 PROTAC are evaluated in the clinic, with several already advanced to Phase 2 and Phase 3 trials (**Table 1**) [43,45]. ARV-471, which is also referred to as vepdegestrant and which targets the estrogen receptor in ER^+ / $HER2^-$ breast cancer [13,26,44], is the most advanced PROTAC, with FDA clearance obtained. BMS-986365 [45,80,81] and ARV-766 [82] target androgen receptor in prostate cancer, and are currently in Phase 3 and Phase 2 trials, respectively. The frontrunner PROTAC thus aim at degrading disease-driving hormone receptors in hormone-dependent cancers, and they hold particular promise for these indications because the androgen and estrogen receptors often develop resistance to traditional small-molecule inhibitors through overexpression of multidrug resistance transporter proteins [33], mutations in ligand-binding domains or alternative splicing. This clinical milestone of ARV-471 validates targeted protein degradation as a clinical modality, while emphasizing that route, exposure, and tissue delivery remain central determinants of broader translation.

Targeting Ikaros family zinc finger proteins (Ikaros and Aiolos) and GSPT1 with MGD has emerged as a compelling therapeutic approach for cancers that rely on these proteins for survival and proliferation [83]. In Phase 1/2 clinical trials, MGD such as BTX-1188 and CC-90009, which target GSPT1, have demonstrated therapeutic efficacy in acute myeloid leukemia (AML), while CC-92480, which targets Ikaros and Aiolos, is currently in Phase 1/2 clinical trials for multiple myeloma [84–87]. Interestingly, the standard-of-care regimen for multiple myeloma is subcutaneous administration of bortezomib (a proteasome inhibitor) in combination with lenalidomide and dexamethasone [86,88,89]. Partial proteasome inhibition with bortezomib does not abolish cereblon-dependent degradation of IKZF1/3 induced by lenalidomide; instead,

Table 1
Overview of clinical and preclinical grade PROTACs and MGD.

Clinical Compounds	Developer	Target	E3 Ligase	Type	Indication	Development Stage	Administration route for clinical grade TPDs	Key Results
ARV-471 (vepdegestrant)	Arvinas / Pfizer	ER	CRBN	PROTAC	ER+/HER2- breast cancer	FDA approved	200 mg orally QD with food ($T_{1/2\ human} = \sim 24$ h)	Clinical benefit in 38% of pretreated patients, ER degradation >90%
ARV-110 (bavdegalutamide)	Arvinas	AR	CRBN	PROTAC	mCRPC	Phase 2	35–700 mg orally, QD, ($T_{1/2\ Rat} = \sim 17$ h)	PSA reduction in 46% of patients with specific AR mutations
BMS-986365 (gridegalutamide)	BMS / C4-Therapeutics	AR	CRBN	PROTAC	mCRPC	Phase 3	20–500 mg twice daily ($T_{1/2} =$ NF)	overcomes androgen receptor pathway inhibitors (ARPI) resistance with promising efficacy and tolerability
ARV-766 (luxdegalutamide)	Arvinas	AR	CRBN	PROTAC	mCRPC	Phase 2	400–900 mg twice daily ($T_{1/2\ human} = \sim 20$-28 h)	Enhanced activity against AR splice variants
KT-474	Kymera / Sanofi	IRAK4	VHL	PROTAC	Inflammatory diseases	Phase 1	25–200 mg once daily ($T_{1/2\ human} = \sim 35$-60 h)	>95% IRAK4 degradation in skin and PBMC
ARV-102	Arvinas	LRRK2	CRBN	PROTAC	Parkinson's disease	Phase 1	200 mg orally QD ($T_{1/2\ human} = \sim 6$)	First CNS PROTAC, central and peripheral LRRK2 degradation
MRT-2359	Monte Rosa	GSPT1	CRBN	MGD	MYC-driven cancers	Phase 1/2	2 mg orally ($T_{1/2mouse} = 2.3$ h)	Preliminary activity in MYC-driven solid tumors
CC-92480 (mezigdomide)	Bristol Myers Squibb	IKZF1/3	CRBN	MGD	Multiple myeloma	Phase 1/2	1 mg orally QD ($T_{1/2} =$ NF)	Responses in IMiD-resistant myeloma
DT2216	Dialectic Therapeutics	BCL-XL	VHL	PROTAC	Hematologic malignancies	Phase 1	0.4 mg/kg intravenous ($T_{1/2} = 7.1$–12.8 h)	Reduced thrombocytopenia *vs* BCL-XL inhibitors
KT-333	Kymera	STAT3	VHL	PROTAC	Lymphomas	Phase 1	1.5 mg/kg intravenous ($T_{1/2} = 4.01$–6.60 h)	First clinical STAT3 degrader
CFT8634	C4 Therapeutics	BRD9	CRBN	PROTAC	Synovial sarcoma	Phase 1	2–50 mg oral ($T_{1/2} = 10$-14 h)	Targeting BAF complex dependency
NX-5948	Nurix	BTK	CRBN	PROTAC	B-cell malignancies	Phase 1	300 mg oral ($T_{1/2} = 24$ h)	CNS penetration, activity in ibrutinib-resistant models
Preclinical grade TPDs	Developer	Target	E3 Ligase	Type	Indication	Key Results		
FRM-024	Frontier Medicines	KRAS G12C	CRBN	PROTAC	KRAS-mutant cancers	Superior to G12C inhibitors in resistant models		
JNJ-TEW-7197	Janssen	TGF-βR1	VHL	PROTAC	Fibrosis	Reduced fibrosis in multiple tissue models		
ABBV-CLS-484	AbbVie	TAU	CRBN	PROTAC	Alzheimer's disease	Brain-penetrant tau degrader		
XL01126	Xylogen Bio	α-synuclein	CRBN	PROTAC	Parkinson's disease	Reduced α-synuclein aggregates in models		
SIAIS125	SIAIS	MCL-1	CRBN	PROTAC	AML, multiple myeloma	Overcomes MCL-1 inhibitor resistance		
PZ-677	Promonta	PCSK9	VHL	PROTAC	Hypercholesterolemia	Sustained LDL reduction in animal models		
GNE-987	Genentech	BRD4	VHL	PROTAC	Solid tumors	Sustained BRD4 degradation in animal models		

residual proteasomal activity is sufficient and permits selective degradation of short-lived transcription factors while simultaneously enhancing proteotoxic stress, resulting in synergistic anti-myeloma activity. Bortezomib kills myeloma cells by blocking the proteasome, causing toxic protein buildup and NF-κB inhibition, while thalidomide and lenalidomide act as molecular glues that reprogram cereblon to degrade IKZF1/3, leading to anti-myeloma, anti-angiogenic, and immune-modulating effects (Fig. 3). Taken all together, the clinical success of lenalidomide-derived MGD, which exploit the proteasomal degradation machinery rather than merely blocking enzymatic activity, highlights the therapeutic potential and future promise of MGD.

The MGD compound MRT-2359, which targets the translational termination factor GSPT1, is undergoing Phase 1 evaluation for the treatment of Myc-driven lung cancer [90]. DKY709, which binds to the E3 ligase CRBN, induces the formation of a CRBN−DKY709 − IKZF2 complex and is currently undergoing clinical trials in patients with advanced solid tumors, including melanoma [91]. The first wave of clinical-grade MGD has been mostly successful in hematologic cancers; emerging preclinical and early clinical evidence shows expansion toward solid tumors such as lung cancer and melanoma. The preclinical efficacy of sulfonamide molecular glues (like E7820 and E7070) on patient-derived xenograft (PDX) solid cancers, including bile duct, pancreatic, gastric, and uterine cancers, demonstrates the therapeutic potential of molecular glues beyond hematologic malignancies [92,93]. Indeed solid tumors tend to present with additional barriers compared with blood cancers, including dense extracellular matrix deposition and heterogeneous cancer cell populations, which can all limit TPD delivery, distribution and efficacy [6,94,95].

3.2. Clinical proof of concept for protein degradation in other diseases beyond oncology

While the majority of clinical-grade PROTAC and MGD are focused on cancer, the therapeutic benefits of TPD technology in other disease areas are expanding. Degraders such as ARV-102 successfully target leucine-rich repeat kinase 2 (LRRK2), both peripherally and in the central nervous system [96], supporting its development for Parkinson's disease and related neurodegenerative disorders. In addition, Kymera Therapeutics has managed to advance KT-413 [97] and KT-474 [98] into clinical trials for non-oncological conditions. KT-413 is a dual interleukin-1 receptor-associated kinase 4 (IRAK4)/BTK degrader for autoimmune diseases, and KT-474 degrades IRAK4 [99] for conditions such as hidradenitis suppurativa and atopic dermatitis. In 2024–2025, TPD remained among the top ten licensing deals for pharma companies, with Novartis and AbbVie being the frontline licensors [100,101]; it is likely that the pharmaceutical industry focus and market for targeted protein degraders will continue to grow in the years to come [102]. The recent FDA approval for vepdegestrant [26], marking a major milestone for the TPD field, is likely to further accelerate industrial investment [28].

Overall, clinical data indicate that linker optimization, particularly the introduction of shorter, semi-rigid, and polarity-balanced motifs such as piperazine-containing linkers, has been successful in reinforcing productive ternary complex formation and oral bioavailability [10]. Notably, more than ten clinical-stage PROTAC incorporate such linker architectures, underscoring the translational value of controlled rigidity and physicochemical tuning in degrader design. However, clinical dosing data reveal that AR-targeted PROTAC such as ARV-110 [103] and BMS-986365 [81] require doses comparable to or higher than conventional AR inhibitors, and the ER degrader ARV-471 (vepdegestrant) is administered at doses more than five-fold greater than tamoxifen [43,45,104,105]. These observations raise questions about the *in vivo* catalytic pharmacology, and highlight the compromised bioavailability of PROTAC and MGD due to their fast clearance (**Table 1**). Accordingly, a second phase of TPD development must place greater emphasis on improving systemic exposure, reducing intrinsic clearance, and optimizing localized delivery to fully realize the catalytic potential of targeted protein degradation [106].

4. Pitfalls in targeted protein degradation

4.1. Drug discovery and drug delivery associated challenges

While PROTAC and MGD hold transformative potential, they face distinct and shared challenges impeding their clinical translation (summarized in **Table 2**) [34,107,108]. These challenges can be categorized into: (1) drug discovery-related barriers and (2) small-molecule delivery-associated limitations, and they are further described below:

(1) From a drug discovery perspective, a key advantage of PROTAC is their rational design framework (choice of E3-ligase ligands and linkers), which can leverage greater *in vitro* level success [109,110], while MGD are typically discovered serendipitously, making the study of structure-activity relationships (SAR) and the identification of potential hits difficult. Lack of predictability in glue-based degrader design requires better computational and screening technologies [111]. Overall, the first phase of clinical-grade PROTAC and MGD has focused on CRBN (**Table 1**) due to the favorable pharmacological properties of CRBN ligands, driven by their low molecular weight and single hydrogen bond donor site [112] in addition to the limited availability of E3-ligase small-molecule binders [113]. Most clinically advanced and orally administered degraders rely on lenalidomide- or pomalidomide-derived cereblon recruiters. This trend likely reflects the comparatively favorable pharmacological properties of CRBN ligands, including oral bioavailability, intracellular accessibility, and broad systemic tissue exposure, which facilitate medicinal chemistry optimization despite the additional physicochemical burden introduced by PROTAC assembly. In contrast, VHL ligands (*e.g.*, VH032/VH298-derived binders) are intrinsically larger, more polar, hydroxyproline-containing, and partially peptidic, with properties associated with reduced gastrointestinal permeability, lower cellular uptake, and more challenging oral pharmacokinetic behavior. Consequently, while CRBN-based degraders have thus far demonstrated comparatively superior oral tractability and systemic exposure, whereas VHL-based degraders may more frequently benefit from alternative formulation approaches or non-traditional delivery strategies, particularly when medicinal chemistry optimization alone proves insufficient to overcome permeability and tissue-exposure constraints [114]. Furthermore, broadening the set of usable E3-ligases through ligand discovery and chemical biology is essential for expanding the degradable proteome and enhancing tissue specificity and *in vivo* stability [115]. Mechanistically, this requires a deep understanding of degron motifs, ternary complex stability, and ubiquitination kinetics. Tools such as proteomics, degron mutagenesis, and structure-guided modeling are valuable for improving selectivity and reducing off-target degradation [52,116]. Besides expanding the E3-ligase ligand scope, linker design and optimization are essential for *in vitro* PROTAC functionality, but not for molecular glues as they do not rely on linkers, reflecting a key structural and mechanistic difference between PROTAC and MGD [86,111]. Linker features such as linker length, rigidity, polarity, and flexibility can drastically affect the ternary complex cooperativity and intracellular trafficking [10,106,117]. Overall, the identification and *in vitro* POI degradability of hit PROTAC and MGD remain a moderately uncertain and lengthy process. As such, and the principles governing efficient *in vitro* to *in vivo* translation are complex and in the discovery phase.

(2) In addition to the discovery-level limitations described above, several translational barriers curb the *in vitro* to *in vivo* transition of TPDs, largely arising from the physicochemical properties of PROTAC and MGD, which govern their oral absorption [118,119], and intracellular or intra-tumoral delivery [5,8].

4.1.1. Pursuit of oral delivery-centric PROTAC and MGD design

Oral administration remains the preferred drug dosing route for

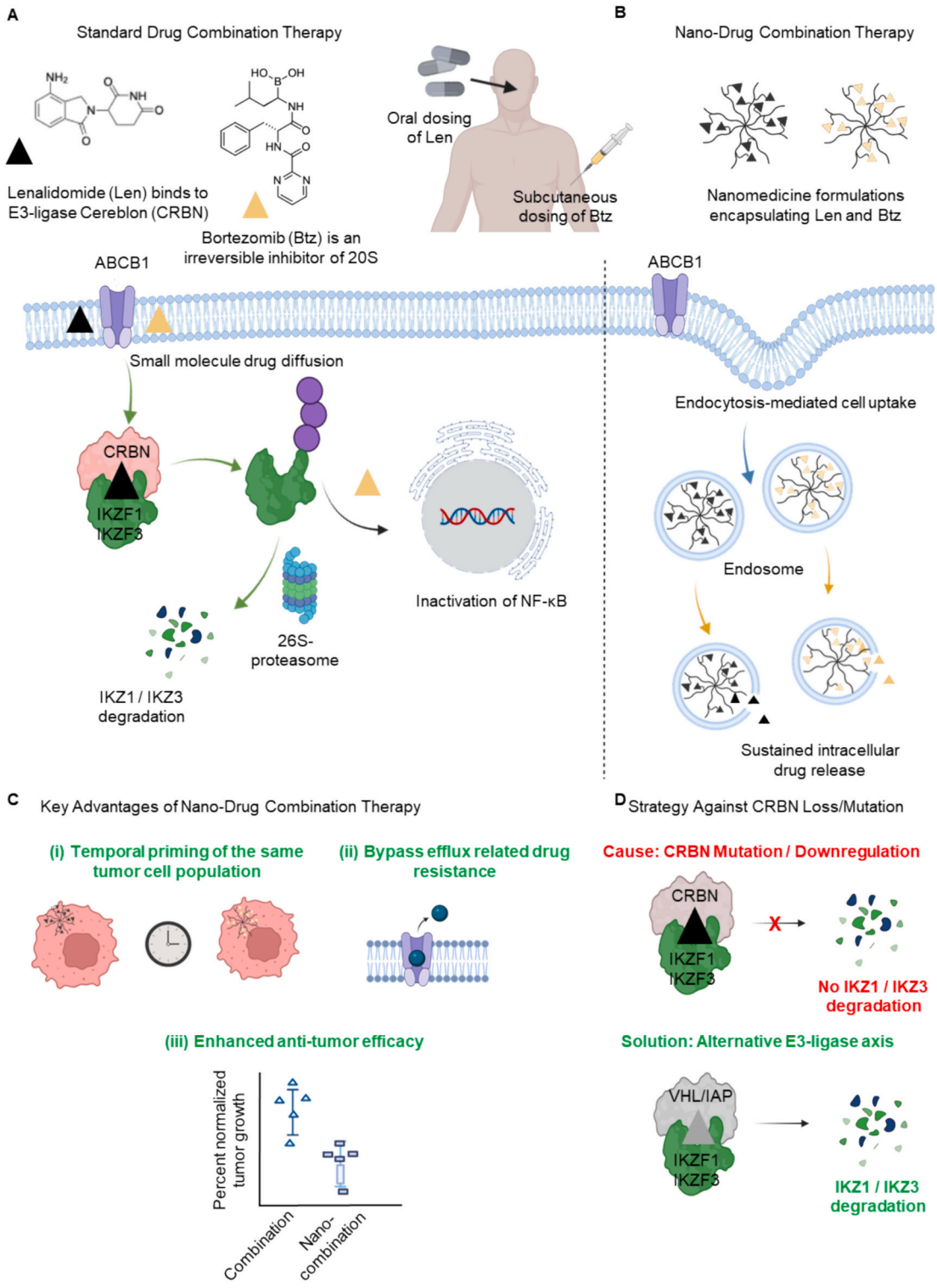


Fig. 3. Schematic distinguishing the standard lenalidomide and bortezomib combination in multiple myeloma (A, conventional therapy) from a nano-enabled combination strategy (B, nano-drug combination therapy). The conventional approach relies on lenalidomide-mediated cereblon (CRBN) recruitment and IKZF1/3 degradation together with bortezomib-mediated proteotoxic stress. The nano-enabled strategy illustrates a delivery approach in which carrier-based systems enhance tumor accumulation and promote cellular uptake through endocytic internalization mechanisms. The key advantages of nano-combination therapy over combination therapies (C), are (i) temporal priming of the same cancer cell population by sequential drug-delivery administration of two drugs, (ii) bypassing efflux-mediated drug resistance improved tumor localization, and (iii) exhibiting enhanced anti-tumor efficacy. The schematic also clarifies that CRBN mutation or loss is not solved by encapsulation alone and would require incorporation or substitution of a CRBN-independent degrader axis, such as a von Hippel Lindau (VHL)- or inhibitor of apoptosis proteins (IAP)-recruiting degrader (D).

Table 2
Overview of translational hurdles in the application of PROTAC and MGD development.

Category	Challenges	Potential Solutions
Discovery scheme	PROTACs rationally designed MGD are discovered serendipitously, and linker optimization is completely uncertain	*in silico* modeling, machine learning and artificial intelligence guide results predictability for PROTACs but not for glues
E3-ligase scope	broader and more exploited for PROTACs (cereblon (CRBN) and von Hippel Lindau (VHL), than MGD which are mostly centered around CRBN, leading to restricted POI targeting	expanding the E3 ligand-toolbox *via* chemi-proteomics
Mechanistic Understanding of Degradation	TPD efficacy depends on understanding degron recognition, E3-substrate pairing, and off-target degradation; challenges shared by both PROTACs and MGD	proteomics, degron mutagenesis, and structure-guided design tandem with activity-based protein profiling, cellular thermal shift assay promises higher selectivity, efficacy, and reduced toxicity
Role of linker	linker length and flexibility of PROTACs highly related with their activity and relatively controllable for PROTACs. MGD lack defined linker-related modulation	computational and structural analyses are key
Cell permeability and uptake	PROTACs are large molecule (typically >700 Da) and violate Lipinski's Rule of 5, limiting membrane diffusion; MGD are smaller, more soluble, and ionizable	cell-penetrating peptides, antibody–PROTAC conjugates (abTACs), and stimuli-responsive nanocarrier-based DDS can improve intracellular delivery
Suboptimal pharmacokinetics and biodistribution	TPDs in general susceptible to enzymatic degradation such as human cytochrome P450 3A4, human aldehyde oxidase (*h*AOX), and liver CYP enzymes leading to shortened systemic half-life and extensive metabolism	injectable hydrogels, implantable depots, encapsulated drug molecules within a polymeric matrix can result in an extended half-life compared with the free drug, reduce dosing frequency
Mode of administration	PROTACs and MGD are administered *via* oral route, which is patient-friendly, however narrows transport across various physiological barriers	lipid-based delivery systems and prodrug approaches can improve bioavailability by enhancing intestinal absorption and lymphatic transport
Delivery-driven resistance and barrier mapping	efflux transporters, heterogeneous tumor penetration, low intracellular exposure, endosomal trapping and route-dependent PK can all limit TPD efficacy	match the DDS to the dominant barrier. Nanocarriers or conjugates for efflux and cellular uptake, hydrogels or depots for local drug-exposure, LNPs or ligand-targeted systems for organ tropism

small-molecule therapeutics due to patient compliance and chronic dosing feasibility; however, achieving adequate oral exposure represents a major challenge for PROTAC as they exhibit large molecular sizes (>700 Da), high polarity, and frequent Lipinski's rule violations [119,120]. By design, PROTACs occupy chemical space far beyond the classical Rule of Five (Ro5), exhibiting high molecular weight, elevated polarity, and substantial conformational flexibility, all of which are detrimental to intestinal permeability and absorption [1,120]. In this regard, Hornberger and Araujo performed a comprehensive *in vivo* analysis in correlating oral absorption of PROTACs with their key physicochemical parameters and normalized clearance parameters [119]. Their results demonstrate that oral bioavailability is nevertheless achievable within defined regions of extended and beyond-Ro5 chemical space, while most PROTACs display limited oral absorption and consequently restricted plasma exposure [120–122]. Importantly, the study shows that oral absorption is not governed by a single parameter but instead emerges from a balance of molecular size, lipophilicity, polarity, and flexibility. Clinical degraders such as ARV-110 and ARV-471 achieve oral exposure not merely by occupying "extended Rule-of-Five" space, but through intramolecular hydrogen bonding (IMHB) that enables conformational adaptability to adopt conformationally compact, less polar states to facilitate membrane permeation and unfolding intracellularly to engage targets [123–125]. This chameleonic behavior of PROTAC molecules provides a structural explanation for why certain large PROTACs are orally bioavailable while others are not [125]. Importantly, this framework also rationalizes why non-chameleonic degraders may require alternative routes of administration and delivery strategies. Poor bioavailability poses a greater challenge for PROTAC than for MGD, as MGD, being smaller and more water-soluble, exhibit relatively higher bioavailability [126]. Chemical enhancers such as sodium caprate [127] and sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC) have enabled clinical approval of peptide drugs (*e.g.*, semaglutide and octreotide) [128]; however, these approaches typically achieve very low oral bioavailability (<2%). These limitations prompt a reassessment of alternative routes of administration and delivery strategies to improve the bioavailability and translational performance of potent TPDs.

4.1.2. *Improvement of cellular uptake of hydrophobic protein degraders*

Multiple experimental and computational studies indicate that limited passive cellular uptake is a central bottleneck in PROTAC development. Permeability measurements using parallel artificial membrane permeability assay (PAMPA) and lipophilic permeability efficiency (LPE) metrics, together with cellular uptake assays, consistently show that many PROTACs enter cells inefficiently [117,119], even when they display strong target binding and robust degradation in biochemical systems. These studies highlight a gap between *in vitro* potency and intracellular exposure, demonstrating that degradation efficacy is frequently constrained by insufficient compound accumulation within target cells. Importantly, small structural modifications can lead to large, non-linear changes in cellular uptake. Collectively, these findings establish that impaired passive permeability contributes to variable cellular activity, suboptimal oral exposure, and translational attrition.

4.2. *Appearance of preclinical resistance phenomena*

Beyond overcoming the delivery and pharmacokinetic challenges, resistance mechanisms represent a new tier of obstacles that must be addressed as TPD technologies advance further in clinical development. As discussed in Section 2.2, TPDs offer a key advantage over conventional inhibitors because they eliminate the target protein rather than merely blocking its activity, thereby potentially overcoming resistance mechanisms such as target overexpression or mutations that reduce inhibitor binding affinity (Fig. 1B). Efflux pumps like ATP-binding cassette subfamily C member 1 (ABCC1) or MDR1 limit PROTAC efficacy by exporting them from cancer cells, and this resistance could limit long-term efficacy of degrader therapies (Fig. 1C) [48,49]. In particular, the up-regulation of MDR1-dependent drug efflux pumps across several ovarian cancer cells under chronic exposure to BRD4-targeting PROTAC, led to reduced intracellular degrader concentration. Moreover, co-treatment with kinase inhibitor lapatinib, capable of suppressing MDR1 activity, restored intracellular PROTAC accumulation and enhanced BRD4-degradation efficacy. These findings suggest that future PROTAC optimization should not only focus on ternary complex formation and E3 ligase recruitment, but also on minimizing transporter-

mediated efflux through rational molecular design or delivery systems capable of bypassing efflux pathways. In parallel, transporter expression itself may serve as a predictive biomarker for treatment response and emerging resistance. Overcoming such resistance requires co-targeting ABCC1, designing non-substrate PROTACs, or using delivery strategies such as nanoparticles or antibody conjugates to bypass efflux and improve intracellular retention, enhancing therapeutic effectiveness in resistant cancers [129]. This highlights that, while TPDs can address target-driven resistance, their therapeutic performance remains strongly dependent on intracellular delivery [130]. However, before addressing these advanced resistance mechanisms, several more immediate optimization priorities must be addressed to improve the *in vivo* fate and intracellular access of TPDs [131,132].

5. Delivery strategies to overcome translational barriers of PROTAC and MGD

The translational limitations of targeted protein degraders stem from well-recognized physicochemical and biological barriers that occur sequentially from systemic administration to intracellular target engagement. These include limited solubility and intestinal permeability (absorption), suboptimal pharmacokinetics and biodistribution, inadequate tumor accumulation, and efflux pump-mediated resistance (Fig. 4, A1–5). Delivery cannot be treated as a downstream rescue of poorly behaving degraders. It is a design variable that determines whether a beyond-Rule-of-Five molecule can reach the correct tissue, enter the correct cell, escape efflux and maintain an intracellular concentration compatible with catalytic degradation. The delivery strategies described below are organized by the dominant bottleneck addressed by each platform rather than by route or technology alone. Chemical and receptor-triggered prodrug strategies aim to improve intestinal epithelial permeability and tissue entry. Systemic nanocarriers aim to improve pharmacokinetics, biodistribution, cellular uptake, and endosomal escape; local depot systems aim to sustain exposure at the target site and ligand/antibody-guided conjugates aim to restrict activity to antigen-positive tissues. Ccombination delivery systems aim to control drug ratios and manage adaptive resistance.

5.1. Prodrugs enabled by on-target activation

Prodrug approaches for TPDs lead to temporary masking of polar functional groups and enhance their plasma stability [133], cell permeability [134], and reduced off-target toxicity [134–136] with subsequent intracellular activation (Fig. 4 A1). Common approaches include esterase-cleavable linkers, reductase-sensitive moieties, and pH- or glutathione-responsive triggers, which ensure selective release of the active degrader within the target cell [137,138]. Prodrug-based pharmacokinetic/pharmacodynamic (PK/PD) parameter improvement strategies for PROTACs and MGDs have emerged as an effective means of improving plasma stability, cell permeability, and reducing off-target toxicity, with subsequent intracellular activation [133,135,136]. For instance, substitutions of amide linkers with esters in PROTAC can increase membrane permeability by up to tenfold, while maintaining full plasma stability for at least 90 min without detectable degradation. These modifications also enhanced therapeutic potency, with up to 4-fold reductions in DC_{50} values compared to the free molecules. An asialoglycoprotein receptor (ASGPR)-based selective protein degradation platform was developed for liver-specific protein degradation in hepatocytes by conjugating a triantennary *N*-acetylgalactosamine (triGalNAc) ligand to a BRD4-targeting PROTAC *via* a cathepsin B-cleavable Val-Cit-PABC linker. This design enables ASGPR-mediated endocytosis and lysosomal trafficking, where linker cleavage releases the active degrader to induce VHL- and proteasome-dependent BRD4 degradation in a liver cancer xenograft model. The platform demonstrated selective uptake in ASGPR-positive hepatocellular carcinoma models and robust liver accumulation *in vivo*, validating its tissue-targeted degradation strategy [139]. Interestingly, the advantage of BRD4 degradation beyond oncology and its local delivery was established by a reactive oxygen species (ROS) responsive DDS system that enabled targeted degradation of BRD4 for the treatment of liver fibrosis [140]. Mechanistically, these approaches address the gastrointestinal permeability and premature-exposure barrier rather than the biodistribution problem alone, because activation is designed to occur after receptor-mediated uptake or within the intracellular reductive, acidic or enzymatic environment. However, variability in the trigger environment across cancer types and premature cleavage in plasma remain important limitations, and these approaches offer limited control over tissue specificity [141,142].

5.2. Systemic nanocarriers for improved pharmacokinetics, biodistribution and cellular uptake

Nanoparticle-based formulations can enhance oral bioavailability and tissue-specific delivery of PROTACs by protecting them from premature metabolism and improving membrane permeability [4,9]. Considering liposomes and polymeric micelles have shown their utility as carriers for hydrophobic drugs in general, their PROTAC formulations can overcome the poor bioavailability and stability of PROTACs. Liposomes with a favorable size around 100 nm can achieve nearly 80% encapsulation efficiency with a maximum 10% loading capacity, and confer a two- to fourfold of increase in area under the curve (AUC) compared with the free PROTACs, while enhancing antitumor efficacy [143]. Polymeric-based micelles offer 60–75% encapsulation efficiency with a relatively higher loading (~7–12%) and smaller particle sizes (50–100 nm), improving solubility, uptake, and intracellular degradation [144]. While liposomes benefit from established clinical translation, micelles provide more tunable release and higher drug loading [145]. The success of lipid nanoparticles (LNP)-based messenger RNA (mRNA) vaccines during the COVID-19 pandemic has validated lipid nanoparticles as clinically scalable and translatable delivery platforms. Importantly, LNPs exhibit inherent liver tropism through apolipoprotein E (ApoE)-mediated uptake, making them particularly attractive for liver-targeted PROTAC applications. Moreover, ionizable lipids promote efficient endosomal escape, directly addressing one of the major intracellular delivery bottlenecks limiting effective PROTAC activity [146]. Pre-fused PROTAC, where the degrader is conjugated to an E3 ligase–related protein, were encapsulated in lipid nanoparticles (LNPs) to simplify the conventional ternary mechanism into a more efficient binary-like system. Delivery of ARV-771 *via* LNPs significantly enhanced intracellular BRD4 degradation (up to ~2.3-fold in efficiency and ~ 1.8-fold in rate), highlighting how post-COVID advances in LNP technology can expand the delivery landscape for PROTAC therapeutics. Emerging non-oncology TPDs such as ARV-102 [147] for Parkinson's disease and KT-474 [98] for inflammatory disorders highlight the expanding therapeutic scope of targeted protein degradation beyond cancer. However, the delivery challenges specific to these indications remain underexplored. For CNS degraders, efficient blood-brain barrier penetration represents a major translational hurdle that warrants dedicated consideration [63,79]. Together, these systems highlight nanocarrier encapsulation as a powerful strategy (Fig. 4 A2) to expand the therapeutic window of PROTAC and MGD. For TPD, the value of these carriers is not generic solubilization alone; it is the possibility to decouple degrader potency from systemic exposure by controlling circulation time, organ tropism, tumor penetration, endosomal escape, and intracellular release.

5.3. Local depot systems for sustained targeted protein degradation

Subcutaneous slow-release formulations such as hydrogels (Fig. 4 A3) can maintain localized delivery of PROTAC, thereby avoiding systemic exposure while enabling durable degradation of the POI. Such DDS offer a novel and clinically viable strategy for the topical

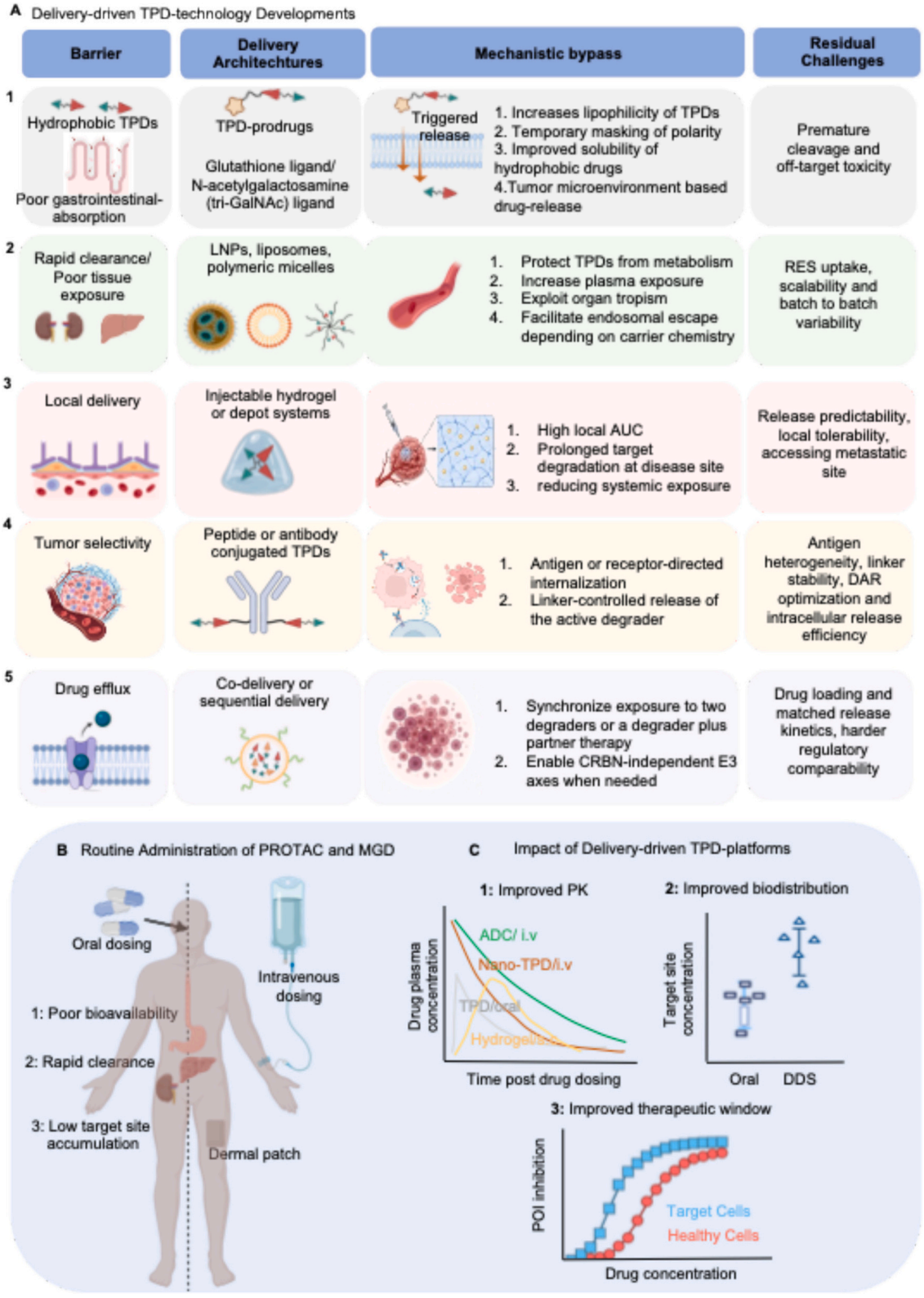


Fig. 4. Mechanism-led delivery map for PROTAC and MGD therapies (A). The schematic links the main biological and pharmacological barriers to delivery architectures, the mechanistic solutions provided by each platform, and the remaining translational challenges that should guide platform selection. Administration routes and limitations of oral delivery for hydrophobic targeted protein degraders (TPD) (B). Drug delivery systems for TPD are typically administered intravenously, whereas TPD-loaded hydrogels are generally applied subcutaneously. Drug delivery systems help overcome key limitations associated targeted protein degrader administration (C), improving *e.g.* plasma circulation times (1), tumor targeting, (2) and the therapeutic window (3). RES = reticuloendothelial system, DAR = drug-antibody ratio, AUC = area under the curve, CRBN = cereblon.

deployment of protein degraders [4,148]. In particular, a physiologically responsive hydrogel demonstrated sustained intratumoral release, precise tumor accumulation, and potent B lymphome Mo-MLV insertion region 1 homolog (BMI1)-directed PROTAC activity, combined with paclitaxel chemotherapy and immune reprogramming. A sono-responsive hydrogel enabled fractionated intra-tumoral release of BRD4-targeting PROTAC, timed with radiotherapy, thereby overcoming DNA repair-mediated resistance and suppressing immunosuppressive cytokines. Hydrogel-based intra-tumoral TPD delivery strategy significantly enhanced tumor control, reduced recurrence in head and neck squamous cell carcinoma and breast cancer, and achieved strong immune reprogramming without systemic toxicity. Although the AUC values were not reported, the formulations achieved strong local retention with minimal systemic leakage, effectively mimicking a "high local AUC" within the tumor microenvironment [149]. This resulted in marked tumor suppression and prevention of metastasis, underscoring the translational potential of hydrogel-based PROTAC delivery platforms. The clinical outcome of resistance in myeloma patients receiving bortezomib underscores that dose and schedule are fundamentally PK/PD-driven [150], as the subcutaneous formulation (Velcade SC) was specifically developed to optimize pharmacokinetics and reduce peripheral neuropathy [151] compared to intravenous administration. While the formulation of Velcade SC is not directly translatable to TPD, this example suggests that optimizing administration routes and delivery strategies may similarly improve the pharmacological performance of targeted protein degraders. This class of TPD delivery is most relevant when the therapeutic objective is sustained local degradation rather than broad systemic exposure, for example in accessible tumors, post-surgical beds, or inflammatory sites where repeated high local AUC may be pharmacologically useful but is not suitable for metastatic indications [152]. In addition, leakage of injected therapeutic cargo into surrounding tissues or along the needle track due to backflow can compromise local drug retention, reduce therapeutic efficacy, and increase off-target toxicity following intratumoral hydrogel administration [152,153].

5.4. Tumor-specific targeted protein degradation

As discussed in the previous section, E3 ligases display distinct tissue-specific expression patterns, in which CRBN is broadly expressed across healthy and tumor tissues, potentially increasing systemic toxicity risk; VHL shows tissue enrichment such as in kidney, and inhibitor of apoptosis proteins (IAP) are often overexpressed in tumors, creating a biologically exploitable spatial map. While tissue-selective TPDs can be rationally designed at the molecular level by leveraging such differential E3 expression or target biology [113,115], molecular selectivity alone does not guarantee tissue-restricted activity *in vivo* due to systemic drug distribution. Aligning the biodistribution of a delivery vehicle with the expression profile of the recruited E3 ligase could therefore substantially enhance therapeutic index. Integrating E3 biology with delivery strategy should thus represent a central conceptual advance in next-generation TPD development. Targeted delivery systems such as peptide and antibody-PROTAC conjugates or tissue-specific ligand-PROTAC conjugates (Fig. 4 A4) can improve delivery to the tumor and reduce off-target effects [154–156]. Antibody-PROTAC and antibody-molecular glue conjugates (MACs) harness antibody specificity to deliver degraders directly to antigen-positive cells. By targeting tumor-associated antigens such as HER2 or receptor tyrosine kinase-like orphan receptor 1 (ROR1), they restrict degrader activity to diseased tissue and minimize systemic toxicity [155]. Cleavable linkers ensure the active degrader is released only after internalization, reducing off-target exposure. These conjugates markedly extend pharmacokinetic half-life (up to ~5 days) and increase AUC compared to free degraders. Preclinical models demonstrate potent on-target degradation, tumor suppression, and improved immune responses with favorable safety. Orum therapeutics has advanced GSPT1 targeting MACs, including ORM-5029, which links a potent GSPT1 degrader to a HER2 antibody *via* a valine-citrulline PABAC linker at a drug-antibody ratio (DAR) of approx. 4 and demonstrates superior *in vitro* and *in vivo* efficacy compared to approved HER2 antibody-drug conjugates (ADC), with ongoing Phase I evaluation [157]. ORM-6151 employs the same degrader conjugated to a CD33 antibody through a β-glucuronide lysosome-cleavable linker and incorporates Fc engineering to reduce immune activation, achieving picomolar potency and strong xenograft efficacy at low doses [158,159]. Together, these candidates highlight the clinical maturation of antibody-guided PROTAC and MGD delivery glue strategies and the pharmaceutical validation of targeted degradation-ADC convergence. This makes targeted conjugates conceptually different from passive nanocarriers. They can align antigen expression, E3-ligase biology, and intracellular release within the same target cell, if antigen heterogeneity and linker stability are controlled [160,161].

5.5. Dual TPD delivery to enhance therapeutic efficacy and overcome resistance

While the first round of preclinical DDS of PROTAC and MGD are addressing (Fig. 4A) the challenges associated with them at the molecular level, more sophisticated therapeutic strategies to overcome resistance can be envisioned. In this context, DDS offer exciting opportunities to enhance the translational impact of TPD through alternative routes of cellular uptake that have proven beneficial to mitigate resistance [129,162]. Resistance to CRBN-dependent degraders in myeloma frequently arises from downregulation or mutation of CRBN itself, representing vulnerability of both immunomodulatory drug (IMiD)-like MGD and CRBN-based PROTAC [163,164]. This highlights an intrinsic limitation of relying on a single E3 ligase axis for sustained therapeutic efficacy. From a delivery perspective, co-delivering CRBN and VHL-recruiting degraders targeting the same protein could mitigate ligase-specific resistance (Fig. 4 A5). Such nano-enabled combination strategies provide a mechanistically grounded and translationally stronger rationale for next-generation TPD therapies. Toward this, the construction of a stimuli-responsive liposomal nanocarrier enabling precise co-delivery of two PROTACs targeting BRD4 and poly(ADP-ribose) polymerase 1 (PARP1), enhancing solubility, stability, and controlled stoichiometry is promising. Dual degradation amplified DNA damage and cytoplasmic DNA accumulation, activating stimulator of interferon genes (STING) signaling and thereby potentiating immune checkpoint blockade in 4T1 breast tumor-bearing mice [165]. Given that multidrug nanotherapy has been observed to be highly effective across different cancer types [162,166], the codelivery of two or more degraders within a single DDS should be explored further. Encapsulation of multiple degraders within a single carrier may be advantageous when simultaneous intracellular exposure within the same target cell is required to achieve synergistic degradation, coordinated pathway inhibition, or suppression of adaptive resistance mechanisms. In contrast, delivery of distinct degraders using separate nanocarriers may offer greater flexibility when the therapeutic effect relies on differential tissue distribution, asynchronous exposure, or targeting of distinct cellular populations within the tumor microenvironment [162]. However, encapsulation-based co-delivery faces substantial formulation hurdles, particularly related to differential release kinetics leading to suboptimal synergy, and manufacturing complexity is significantly higher. Moreover, ensuring consistent drug-to-carrier ratios and achieving reproducible large-scale production remain critical bottlenecks [167].

5.6. Translational challenges of TPD delivery platforms

Delivery systems do not remove the need for potent degrader chemistry and can introduce new translational hurdles. Key challenges include maintaining high drug loading for hydrophobic and beyond-rule-of-five molecules, preventing premature leakage, achieving sufficient endosomal escape, matching release kinetics to protein resynthesis

rates, controlling carrier heterogeneity during manufacturing, and defining pharmacokinetic/pharmacodynamic comparability for regulatory review. These limitations argue for mechanism-led platform selection rather than default encapsulation of every degrader candidate. At the same time, nano-enabled TPD-delivery strategies should be evaluated within a realistic pharmacological and translational framework. While nanoparticle-based systems may improve tissue retention, reduce pharmacokinetic variability, protect degraders from premature metabolism, and potentially enhance intracellular accumulation, they may not universally outperform freely diffusible soluble degraders. Because many nanocarriers rely on endocytosis-dependent uptake, intracellular delivery may remain restricted to subsets of cells capable of particle internalization, whereas soluble small molecules can diffuse more broadly through tissues and directly cross plasma membranes *via* passive or transporter-mediated uptake. Moreover, preferential perivascular accumulation, heterogeneous tissue penetration and distribution, *endo*-lysosomal sequestration, and inefficient endosomal escape may limit intracellular degrader exposure and activity [168]. Conversely, nano-delivery may become particularly advantageous in settings where intracellular drug exposure is already compromised by poor permeability or active efflux mechanisms, as endocytosis-mediated uptake may partially bypass transporter-mediated TPD export and prolong intracellular retention of degraders.

An important unresolved question is whether the optimal formulation behavior of nano-TPDs is primarily dictated by the intrinsic physicochemical properties of the degrader payload, particularly the highly hydrophobic nature of many PROTACs or by the characteristics of the carrier system itself. A deeper mechanistic understanding of how PROTAC structure, carrier composition, intracellular trafficking and endosomal escape collectively influence formulation stability and biological performance will be essential for the rational design of next-generation nano-TPDs [169,170].

6. Conclusion

With vepdegestrant now FDA-approved, targeted protein degradation has progressed beyond clinical proof of concept, establishing PROTAC and MGD as a promising therapeutic modalities. The key challenge now is not whether these molecules can function in patients, but how broadly they can be deployed across targets, tissues, and dosing regimens. Despite their promise, TPDs continue to face translational barriers that resemble those of conventional small molecules, including efflux-mediated resistance, suboptimal biodistribution, insufficient intracellular exposure, and off-target toxicities. Drug delivery systems can mitigate these hurdles by altering pharmacokinetics, tissue distribution, cellular uptake, and intracellular release of the TPDs. Importantly, delivery should be considered a core design parameter, rather than a downstream optimization, as it ultimately determines whether a degrader can achieve therapeutically relevant exposure *in vivo*. Future development of nano-TPDs should therefore follow a barrier-driven framework, where platforms are selected based on their ability to address specific bottlenecks such as limited AUC, poor tissue selectivity, endosomal entrapment, or dependence on a single E3 ligase axis. In this context, lipid and polymeric nanocarriers improve intracellular access and retention, antibody and ligand-guided conjugates enable cell-specific targeting, and depot systems support sustained local exposure. Co-delivery TPD strategies may further enhance efficacy by synchronizing pharmacokinetics and mitigating adaptive resistance. In parallel, expansion of the E3 ligase repertoire remains essential to improve selectivity and broaden the degradable proteome. Ultimately, integrating advances in chemical biology with nanotechnology will be critical to unlocking the full clinical potential of targeted protein degradation.

Declaration of competing interest

M.B.: Given his role as Theme Issue Editor, M.B. has had no involvement in the peer review of this article and had no access to information regarding its assessment.

T.L.: T.L. is a co-founder of SonoMAc GmbH. He has served on the supervisory board and/or received consulting fees from Cristal Therapeutics, CureVac, Biorion Therapeutics, Nektar Therapeutics, and Nanoworx.

A.D.: A.D. is a co-founder and shareholder of Recobia Therapeutics, Theraguix, and TherO2.

Data availability

No data was used for the research described in the article.

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