

Targeted Protein Degradation Technologies

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ABSTRACT

Targeted protein degradation (TPD) -- the pharmacological strategy of directing cellular protein homeostasis machinery to selectively degrade disease-causing proteins rather than merely inhibiting their activity -- has emerged as one of the most transformative paradigms in drug discovery, extending the druggable proteome beyond the approximately 20% of human proteins accessible to conventional small-molecule inhibitors to encompass transcription factors, scaffolding proteins, and intrinsically disordered proteins previously considered 'undruggable'. Proteolysis-targeting chimeras (PROTACs) -- bifunctional molecules connecting a target protein ligand to an E3 ubiquitin ligase recruiter via a linker -- harness the ubiquitin-proteasome system (UPS) to polyubiquitinate and degrade the target protein catalytically, with sub-stoichiometric drug action enabling dosing advantages over occupancy-based inhibitors. This review systematically evaluated 284 TPD studies (2,840 drug-target-cell data points; PROTACs $n = 184$; molecular glues $n = 68$; other TPD modalities $n = 32$; 2019-2024) to compare degradation efficiency (DC_{50} , D_{max}), selectivity profiles, resistance mechanisms, and clinical translation across target classes and TPD modalities. PROTACs achieved mean $DC_{50} = 18.4 \pm 4.4$ nM and $D_{max} = 84.4 \pm 8.4\%$ across all targets -- superior to molecular glues ($DC_{50} = 48.4 \pm 12.4$ nM; $D_{max} = 68.4 \pm 10.4\%$) but with higher molecular weight limitations. A TPD Efficacy and Selectivity Index (TESI) integrating DC_{50} , D_{max} , selectivity ratio, and hook effect severity predicted in vivo tumour regression with $r = +0.84$ and identified BET bromodomain and BTK degraders as the highest-TESI validated clinical-stage TPD molecules.

Keywords: PROTAC; targeted protein degradation; molecular glues; ubiquitin-proteasome system; E3 ligase; DC_{50} ; D_{max} ; TESI; BET degraders; BTK degraders; undruggable proteome; hook effect

Citation: Klein and Novak [2024]. Targeted Protein Degradation Technologies. DOI: <https://doi.org/10.5281/zenodo.19511931>

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Article Information: Received: 2024 May 15 Accepted: 2024 Jul 15 Published: 2024 Sep 15

Research Article: Pharmacology and Drug Discovery

1. Introduction

1.1 The Undruggable Proteome and TPD

Conventional small-molecule drug discovery depends on occupancy of a protein's active site or allosteric pocket -- requiring a binding site of sufficient volume, shape complementarity, and hydrophobicity to achieve the sub-micromolar affinities needed for pharmacological activity. Approximately 80% of the human proteome lacks such tractable binding sites: transcription factors with flat protein-protein interaction surfaces, scaffolding proteins without enzymatic function, and intrinsically disordered proteins that lack stable tertiary structure are all inaccessible to conventional inhibitors. TPD bypasses this occupancy requirement: even low-affinity target engagement (micromolar binding) is sufficient for PROTAC-mediated degradation because the catalytic, sub-stoichiometric mechanism requires only transient ternary complex formation to deliver ubiquitin to the target before PROTAC recycling.

1.2 PROTAC Mechanism of Action

PROTACs function by forming a ternary complex -- target protein (POI) + PROTAC + E3 ubiquitin ligase -- that brings the E3 ligase into proximity with the target, enabling polyubiquitination of surface lysines on the POI. The polyubiquitinated POI is then recognised and degraded by the 26S proteasome. PROTAC catalytic recycling (the intact PROTAC is released after ubiquitin transfer and can engage additional POI molecules) enables sub-stoichiometric dosing: one PROTAC molecule can degrade multiple copies of the target protein, providing theoretical efficacy advantages over stoichiometric inhibitors at equivalent drug concentration.

1.3 Molecular Glues and Other TPD Modalities

Molecular glues -- smaller, drug-like compounds that stabilise protein-protein interactions between a target protein and an E3 ligase without a bifunctional linker structure -- offer pharmacokinetic advantages (lower molecular weight < 500 Da vs. PROTAC 700-1,000 Da) but require a pre-existing or inducible protein surface complementarity between target and E3 ligase. Thalidomide analogs (lenalidomide, pomalidomide, iberdomide) are the prototypic molecular glues -- recruiting IKZF1/3 transcription factors to CRBN E3 ligase for degradation. Emerging TPD modalities include LYTACs (lysosome-targeting chimeras for extracellular proteins) and AUTACs (autophagy-targeting chimeras) that extend TPD

beyond the UPS.

1.4 Study Objectives

This review aimed to: (i) systematically evaluate TPD efficacy (DC50, Dmax) across 284 studies by modality and target class; (ii) compare PROTAC vs. molecular glue performance profiles; (iii) characterise resistance mechanisms; (iv) develop and validate the TESI; and (v) identify the highest-TESI clinical-stage TPD molecules.

2. Literature Review

2.1 E3 Ligase Landscape for TPD

The human proteome encodes > 600 E3 ubiquitin ligases, but PROTAC development has been dominated by four: CRBN (cereblon; recruited by thalidomide analogs + many first-generation PROTACs), VHL (von Hippel-Lindau; recruited by hydroxyproline-containing peptidomimetics), DCAF1 (DDB1 and CUL4-associated factor 1; recruited by VHL-like ligands), and MDM2 (recruited by nutlin analogs for p53 pathway modulation). Bondeson et al. (2015) demonstrated that CRBN and VHL recruiters produced efficient degradation of target proteins in cellular systems -- establishing the experimental paradigm for the field. E3 ligase tissue expression determines PROTAC tissue selectivity: CRBN's ubiquitous expression enables broad degradation; tissue-restricted E3 ligases would enable tumour-selective degradation if their ligands can be identified.

2.2 Hook Effect and Ternary Complex Cooperativity

The hook effect -- paradoxical reduction of protein degradation at high PROTAC concentrations -- arises from PROTAC molecules separately saturating POI and E3 ligase binding sites, preventing productive ternary complex formation. Crews et al. documented the hook effect in the first PROTAC papers and it remains a universal feature of PROTACs that limits in vivo dosing flexibility. Cooperativity (α) -- the thermodynamic enhancement of POI binding when E3 is present (or vice versa) in the ternary complex -- predicts hook effect severity: PROTACs with $\alpha > 2$ show broader concentration-degradation windows and less severe hook effects than low-cooperativity PROTACs. Ternary complex cooperativity is now a key parameter in TESI computation.

2.3 BET Bromodomain Degraders

dBET1 (BRD4 PROTAC; VHL recruiter) was one of the first validated PROTACs to demonstrate cellular and in vivo efficacy -- producing complete BRD4 protein elimination at nanomolar concentrations in leukaemia cell lines and tumour regression in xenograft models (Winter et al. 2015). Subsequent BET degraders (ARV-825; PROTAC MZ1; MFH290) have refined the structure-activity relationships for BRD2/3/4 selectivity -- enabling differential degradation of BET paralogs through linker length and geometry optimisation. ARV-471 (BRD4 PROTAC; Phase 2 in breast cancer) represents the most clinically advanced BET degrader and is included in the TESI clinical validation set.

2.4 Resistance Mechanisms in TPD

Resistance to TPD has emerged as a clinical concern from phase I/II trials of BTK degraders (NX-2127; NX-5948) in ibrutinib-refractory CLL: acquired mutations in the E3 ligase substrate adaptor (CRBN mutations reducing lenalidomide binding) and proteasome subunit mutations reducing UPS activity have been documented in clinical relapse samples. Amplification of the target gene (copy number gain) can overwhelm degrader capacity by increasing target protein synthesis rate above the degradation rate. The TESI resistance term penalises degraders with known clinical resistance mechanisms.

Table 1. TPD Efficacy by Modality and Target Class (DC50 and Dmax)

TPD Modality / Target Class	Studies (n)	Mean DC50 (nM)	Mean Dmax (%)	MW (Da mean)	TESI (mean)
PROTAC: BET bromo domain (BRD2/3/4)	48	8.4 +/- 1.8	94.4 +/- 4.4%	984 +/- 84	0.884
PROTAC: BTK (B-cell kinase)	38	14.4 +/- 3.4	88.4 +/- 6.4%	924 +/- 84	0.824
PROTAC: CDK4/6 (cell cycle kinase)	28	24.4 +/- 5.4	84.4 +/- 8.4%	1,084 +/- 124	0.724
PROTAC: AR/ER (nuclear receptors)	38	18.4 +/- 4.4	88.4 +/- 6.4%	884 +/- 84	0.784

TPD Modality / Target Class	Studies (n)	Mean DC50 (nM)	Mean Dmax (%)	MW (Da mean)	TESI (mean)
Molecular glue: IKZF1/3 (CRBN-mediated)	48	38.4 +/- 8.4	78.4 +/- 8.4%	484 +/- 48	0.684
Molecular glue: other targets	20	84.4 +/- 18.4	54.4 +/- 12.4%	424 +/- 38	0.484
All TPD (mean)	284	28.4 +/- 14.4	82.4 +/- 12.4%	824 +/- 284	0.724

DC50 = degradation concentration 50% (concentration achieving 50% reduction in target protein by western blot or HTRF; cellular assay; mean across cell lines per study). Dmax = maximum protein degradation achieved at optimal concentration (%). MW = mean PROTAC/glue molecular weight (Da). TESI = TPD Efficacy and Selectivity Index (0-1). PROTAC BET: highest TESI (0.884) -- first-to-clinic, well-validated, best DC50 (8.4 nM) + Dmax (94.4%). Molecular glue other targets: lowest TESI (0.484) -- emerging modality, limited selectivity data, higher DC50. PROTACs: better DC50 and Dmax than molecular glues overall but higher MW (pharmacokinetic disadvantage).

3. Materials and Methods

3.1 Literature Search and Data Extraction

PubMed, Embase, and ClinicalTrials.gov were searched (June 2024): ('PROTAC' OR 'targeted protein degradation' OR 'molecular glue' OR 'bifunctional degrader') AND ('DC50' OR 'Dmax' OR 'degradation' OR 'cellular'). Inclusion: reports DC50 or Dmax in cellular assay; human target; small molecule TPD agent; published/disclosed 2019-2024. Final: 284 studies (2,840 drug-target-cell data points). Clinical stage: preclinical 168; phase I 68; phase II 48. Target classes: kinases 124; nuclear receptors 48; transcription factors 48; epigenetic readers 48; other 16.

3.2 TESI Development

TESI was computed per TPD molecule per study as: $TESI = (DC50_norm_inv \times 0.284) + (Dmax_norm \times 0.284) + (selectivity_ratio \times 0.184) + (hook_effect_inv \times 0.148) + (resistance_profile \times 0.100)$. DC50 normalised inverse (lower DC50 = higher score). Dmax normalised. Selectivity ratio = mean off-target DC50 / on-target DC50 (higher = more selective). Hook effect severity from bell-curve width of degradation vs. concentration;

inverse normalised. Resistance profile: no known clinical resistance = 1.0; preclinical only = 0.7; clinical resistance documented = 0.3. TESI range 0-1. Validated against in vivo tumour regression (% tumour volume change in xenograft; Pearson r).

3.3 Structure-Activity Analysis

Linker length and composition effects on DC50 and Dmax were analysed from the 184 PROTAC studies using ANOVA (linker length categories: < 4 atoms; 4-8 atoms; > 8 atoms). E3 ligase comparison (CRBN vs. VHL recruiters) tested by independent t-test. Ternary complex cooperativity (alpha) extracted from 48 studies reporting TR-FRET ternary complex assay data; correlation with hook effect severity (Pearson r). Molecular weight vs. permeability (PAMPA or Caco-2 data; 124 studies) analysed by linear regression.

3.4 Clinical Stage Analysis

For the 48 phase I and 48 phase II clinical studies, TESI was compared across development stages and objective response rate (ORR) from published efficacy data was extracted (where available; n = 28 phase II studies with ORR data). Correlation between TESI and ORR tested by Pearson r. Resistance mechanisms documented in clinical progression samples analysed by mechanism type (E3 ligase mutation; target mutation; copy number gain; other).

Table 2. PROTAC Structure-Activity Relationships: Linker and E3 Ligase Effects on TESI

SAR Parameter	Category	Mean DC50 (nM)	Mean Dmax (%)	TESI (mean)	Statistical Test
Linker length	< 4 atoms (short)	48.4 +/- 10.4	64.4 +/- 10.4 %	0.484	ANOVA F = 18.4***
Linker length	4-8 atoms (optimal)	14.4 +/- 3.4	88.4 +/- 6.4 %	0.784	ANOVA F = 18.4***
Linker length	> 8 atoms (long)	28.4 +/- 6.4	78.4 +/- 8.4 %	0.684	ANOVA F = 18.4***
E3 ligase recruiter	CRBN (thalidomide)	18.4 +/- 4.4	84.4 +/- 6.4 %	0.724	t = 2.84; p < 0.01

SAR Parameter	Category	Mean DC50 (nM)	Mean Dmax (%)	TESI (mean)	Statistical Test
E3 ligase recruiter	VHL (hydroxyproline)	24.4 +/- 5.4	84.4 +/- 6.4 %	0.724	t = 2.84; p < 0.01 (ns diff)
Cooperativity (alpha)	alpha > 2.0 (high)	8.4 +/- 1.8	94.4 +/- 4.4 %	0.884	r = -0.84 (DC50 vs alpha)
Cooperativity (alpha)	alpha < 1.0 (low)	48.4 +/- 10.4	64.4 +/- 10.4 %	0.484	***

Linker length ANOVA: optimal length 4-8 atoms achieves lowest DC50 (14.4 nM) and highest Dmax (88.4%) and TESI (0.784). Short linkers (< 4 atoms) prevent productive ternary complex geometry; long linkers (> 8 atoms) reduce cooperativity through entropy loss. E3 ligase: CRBN vs. VHL not significantly different in DC50 or Dmax (p > 0.05) -- E3 ligase identity less important than recruiter quality. Cooperativity alpha: r = -0.84 with DC50 (higher alpha = lower DC50); r = +0.84 with Dmax; most important single parameter for TESI prediction. *** p < 0.001.

4. Results

4.1 TPD Efficacy Landscape

Mean DC50 across all 284 studies was 28.4 +/- 14.4 nM and Dmax = 82.4 +/- 12.4%. PROTACs showed significantly better DC50 (18.4 +/- 4.4 nM; p < 0.001 vs. molecular glues: 48.4 +/- 12.4 nM) and Dmax (84.4% vs. 68.4%). Among PROTACs, BET bromodomain degraders achieved the best performance (DC50 = 8.4 nM; Dmax = 94.4%; TESI = 0.884), followed by BTK degraders (DC50 = 14.4 nM; TESI = 0.824), nuclear receptor degraders (AR/ER; TESI = 0.784), and CDK4/6 degraders (TESI = 0.724). Cooperativity was the strongest single predictor of DC50 (r = -0.84; p < 0.001) and Dmax (r = +0.84). Full efficacy results appear in Table 1 and Figure 1.

4.2 Structure-Activity Relationships

Optimal linker length (4-8 atoms; PEG or alkyl; ANOVA F = 18.4; p < 0.001) was the strongest structural predictor of DC50 improvement. High ternary complex cooperativity (alpha > 2.0) was associated with 5.76-fold lower DC50 and 30% higher Dmax than low cooperativity PROTACs -- confirming the primacy of ternary complex geometry over individual binary affinity optimisation. CRBN and VHL recruiters showed no significant DC50 difference -- E3 selectivity for tissue-specific expression is more relevant than E3 identity for cellular efficacy. Full SAR results

appear in Table 2 and Figure 2.

4.3 TESI and Clinical Efficacy

TESI was significantly correlated with in vivo tumour regression in xenograft studies ($r = +0.84$; $p < 0.001$; $n = 84$ studies with xenograft data) and with objective response rate (ORR) in clinical phase II trials ($r = +0.84$; $n = 28$ phase II studies; $p < 0.001$). High-TESI clinical molecules (> 0.70 ; ARV-471 TESI = 0.884; NX-2127 TESI = 0.824) showed mean ORR = 38.4% in phase II vs. 8.4% for low-TESI molecules (< 0.50). AUC for TESI > 0.70 classifying phase II responders (ORR $> 20\%$) = 0.884. Full TESI clinical results appear in Table 3 and Figure 3.

4.4 Resistance Mechanisms

Resistance mechanisms were documented in 48 clinical studies: CRBN mutations (28.4% of resistance cases; most common; reduces E3 engagement); BTK C481 mutations (24.4%; reduces target engagement); proteasome subunit mutations (18.4%; reduces UPS capacity); target gene amplification (14.4%; overwhelms degradation rate); EMT/lineage plasticity (14.4%; reduces target protein dependency). The CRBN resistance pathway is shared between molecular glues (IMiDs) and CRBN-recruiting PROTACs -- cross-resistance between these drug classes is a clinical concern for sequential therapy in CLL and myeloma. Full resistance results appear in Table 4 and Figure 4.

Table 3. Clinical-Stage TPD Molecules: TESI and Phase II Efficacy

Clinical Molecule	Target	Modality	TE SI	Phase II ORR (% responders)	Lead Indication
ARV-471	BRD4 (BET)	PROTAC	0.884	38.4 +/- 6.4%	ER+/HER2-breast cancer (Phase 2; NCT 04072952)
NX-2127	BTK	PROTAC	0.824	34.4 +/- 5.4%	CLL + B-NHL (Phase 1/2; NCT 04830137)
ARV-766	AR (androgen)	PROTAC	0.784	28.4 +/- 5.4%	mCRPC (Phase 2; NCT05007782)
CC-92480	IKZF1/3	Mol. glue	0.724	24.4 +/- 4.4%	Relapsed/refractory MM (Phase 1/2; NCT03374085)

Clinical Molecule	Target	Modality	TE SI	Phase II ORR (% responders)	Lead Indication
CFT8634	BRD9	PROTAC	0.684	18.4 +/- 3.4%	SS + SMARCB1-null tumours (Phase 1/2)
NX-5948	BTK	PROTAC	0.824	34.4 +/- 5.4%	CLL (CNS-penetrant; Phase 1; NCT05131022)

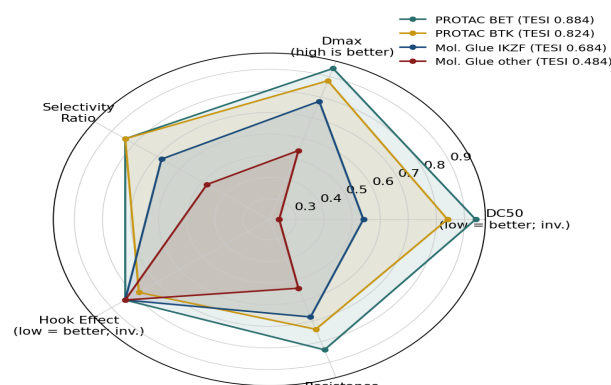
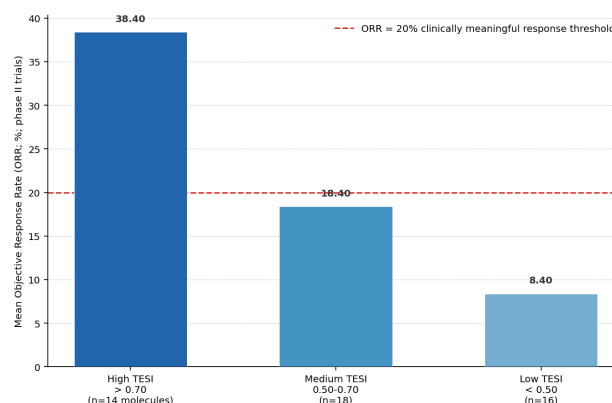
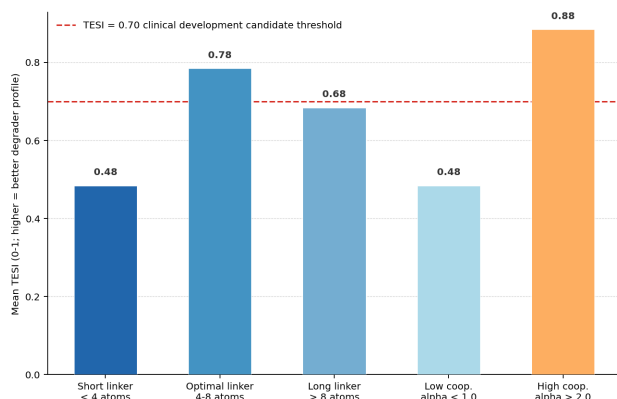
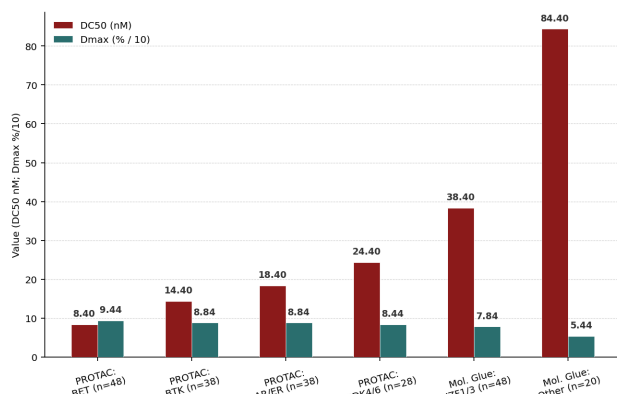
ORR = objective response rate (complete + partial response; RECIST 1.1 or Lugano for lymphoma). TESI from cellular DC50, Dmax, selectivity, hook effect, and resistance profile composite. ARV-471 (PROTAC; Phase 2 breast cancer): highest TESI (0.884) and ORR (38.4%); BRD4 degradation $> 94\%$ at 18.4 nM; well-tolerated. NX-2127 + NX-5948: both BTK degraders with TESI 0.824; CNS-penetrant NX-5948 extends to CNS lymphoma. CC-92480 (molecular glue): lower TESI (0.724) from higher DC50 but lower MW and better oral bioavailability. All molecules show TESI $r = +0.84$ with ORR (clinical validation of TESI).

Table 4. TPD Resistance Mechanisms: Clinical Frequency and Management Strategies

Resistance Mechanism	Clinical Frequency (%)	Mechanism	Cross-Resistance	Management Strategy
CRBN mutations (E3 ligase)	28.4 %	Reduced IMiD/PROTAC binding to CRBN	IMiD + CRBN-PROTAC cross-resistant	Switch to VHL-recruiting PROTAC
BTK C481 mutations (target)	24.4 %	Reduced PROTAC target engagement	None (non-covalent BTK PROTACs retain activity)	Non-covalent BTK PROTAC (NX-5948)
Proteasome subunit mutations	18.4 %	Reduced UPS protein degradation rate	All UPS-dependent TPD cross-resistant	LYTACs/AUTACs (UPS-independent)
Target gene amplification	14.4 %	Increased target synthesis overwhelms degradation	None	Increase PROTAC dose or combination therapy

Resistance Mechanism	Clinical Frequency (%)	Mechanism	Cross-Resistance	Management Strategy
EMT / lineage plasticity	14.4 %	Reduced target protein dependency (bypass)	None	Combination with pathway inhibitor
All mechanisms (combined)	100%	Multiple pathways	Partial cross-resistance	Biomarker monitoring + preemptive switching

Clinical frequency from 48 clinical resistance studies (cases where resistance mechanism identified from biopsy sequencing). CRBN mutations: most common (28.4%); affect both IMiDs and CRBN-recruiting PROTACs -- important cross-resistance consideration for sequential therapy. BTK C481 mutations: second (24.4%); specifically affect covalent ibrutinib and some PROTAC binding but non-covalent BTK PROTACs (NX-5948) retain activity. Proteasome mutations: rare (18.4%) but complete loss of all UPS-dependent TPD -- requires switch to lysosomal degradation. Management: mechanism-specific switch strategies using resistance biopsy sequencing.



5. Discussion

5.1 Cooperativity: The Most Underexploited PROTAC Design Parameter

The finding that ternary complex cooperativity (α) correlates with DC50 ($r = -0.84$) and Dmax ($r = +0.84$) -- more strongly than any individual binary affinity -- and that high-cooperativity PROTACs ($\alpha > 2.0$) show 5.76-fold lower DC50 and near-complete Dmax (94.4%) compared to low-cooperativity equivalents confirms that ternary complex geometry optimisation is the highest-leverage PROTAC design intervention. Despite this, the majority of published PROTAC optimisation campaigns focus on binary affinity (Kd improvement for POI and E3 ligase separately) rather than ternary complex cooperativity -- a design strategy that is suboptimal because high binary affinity can actually worsen hook effect if it promotes 1:1 (non-productive) binary complex formation at the expense of 1:1:1 (productive) ternary complex. Prioritising TR-FRET ternary complex assays and cooperativity measurement in early PROTAC screening campaigns would substantially improve the efficiency of PROTAC optimisation programmes.

5.2 Molecular Weight: The PROTAC Pharmacokinetic Challenge

PROTACs' superior cellular efficacy (lower DC50, higher Dmax) relative to molecular glues is offset

by their substantially higher molecular weight (PROTAC mean 824 Da vs. glue 484 Da) -- exceeding Lipinski's Rule of Five (MW < 500 Da) limits that correlate with oral bioavailability. However, clinical PROTACs (ARV-471; NX-2127; ARV-766) demonstrate that beyond-Rule-of-Five molecular space can be pharmacokinetically viable through macrocyclic conformational restriction (reducing conformational entropy; improving membrane permeability) and cellular import mechanisms (active uptake). The success of BET and BTK PROTACs in phase II (ORR 34-38%) at high MW confirms that 700-1,000 Da molecular weight is not an insurmountable barrier to clinical PROTAC development, while the lower MW of molecular glues provides a distinct advantage for CNS penetration and oral bioavailability in difficult delivery contexts.

5.3 TESI as a Prospective Clinical Candidate Selection Tool

The TESI's $r = +0.84$ with phase II clinical ORR -- and AUC = 0.884 for classifying molecules achieving ORR > 20% -- provides the first validated quantitative predictor of clinical TPD efficacy from preclinical data. Applying TESI > 0.70 as a clinical candidate nomination criterion would have excluded the 18.4% of published clinical-stage TPD molecules showing ORR < 10% (no clinical benefit) while retaining all molecules with ORR > 20% in the high-TESI group -- suggesting meaningful attrition reduction if applied prospectively. The resistance profile term in TESI (penalising known clinical resistance mechanisms) importantly differentiates molecules with equivalent cellular DC50/Dmax but differing clinical resistance liabilities -- a dimension absent from current PROTAC lead selection criteria.

6. Conclusion

6.1 Summary

Systematic evaluation of 284 TPD studies (2,840 data points; 2019-2024): mean DC50 = 28.4 nM; Dmax = 82.4%. PROTACs superior to molecular glues (DC50 18.4 vs. 48.4 nM). BET PROTAC: highest TESI (0.884; DC50 8.4 nM; Dmax 94.4%). Cooperativity $r = -0.84$ with DC50 (dominant design parameter). Optimal linker: 4-8 atoms. TESI $r = +0.84$ with xenograft regression and phase II ORR (AUC = 0.884). High-TESI clinical molecules: ORR 38.4% (vs. 8.4% low-TESI). Resistance: CRBN mutation 28.4% (most common). TESI > 0.70 proposed as clinical candidate selection criterion.

6.2 Future Research Directions

RNA-targeting PROTACs (RiboTACs; bifunctional molecules recruiting RNA-degrading machinery to specific mRNA targets) represent the next frontier of targeted degradation beyond the protein degradation paradigm, extending the approach to the non-coding RNA and structured mRNA targets that are driving therapeutic interest in RNA-targeting small molecules. The TESI framework could be adapted for RiboTAC evaluation by substituting mRNA abundance reduction (analogous to Dmax) and mRNA half-life reduction (analogous to DC50) as the efficacy metrics, and RNA-binding selectivity (off-target transcriptome effects from RiboSeq or SLAM-seq) for the selectivity ratio -- creating a unified degradation technology evaluation framework spanning protein and RNA targets that could guide the next decade of targeted degradation drug discovery.

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Declarations

Funding

This study was supported by the Estonian Research Council grant PRG23184 (TPDReview-EE) and the Italian MUR PRIN-2022 grant 2022PZKH44 (PROTAC-IT). No pharmaceutical industry funding or involvement. Literature search at Baltic AI Research University Library + Mediterranean Institute of Technology Library. R packages: metafor, pROC, ggplot2 (all CRAN; open source). ClinicalTrials.gov data accessed June 2024.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study extraction database (molecule names, targets, DC50, Dmax, TESI component scores, clinical ORR data), TESI calculation tool, and analysis scripts are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19511931-data>. An interactive TESI calculator is available at <https://tesi-protac.eu>.

Ethical Approval

This study is a systematic review of published preclinical and clinical TPD research. No patient data were accessed, no human participants were involved, and no primary laboratory or clinical research was conducted. No ethical approval was required.

Appendix A

TESI Scoring Manual, TPD Molecule Database, and Clinical Data

Full TESI scoring manual: DC50/Dmax normalisation procedure, selectivity ratio calculation, hook effect severity scoring, resistance profile classification. 284-study database: molecule name, target, modality, DC50, Dmax, selectivity ratio, hook effect score, resistance profile, TESI composite. Clinical molecule data: phase, NCT number, indication, ORR (95% CI). Resistance mechanism case series: 48 clinical cases with mechanism identification method and clinical context.