

Degradomics turns TPD into systems pharmacology

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TPD NEEDS A SYSTEMS-LEVEL READOUT

Targeted protein degradation (TPD) has changed how small molecules can be used in drug discovery. Proteolysis-targeting chimeras (PROTACs) and molecular glues do not merely occupy a functional site; they recruit an E3 ubiquitin ligase to a protein of interest and trigger ubiquitination and proteasomal degradation.¹ This event-driven mechanism is powerful, but it also makes drug response harder to interpret. A compound may bind the intended target and still fail to degrade it, or it may degrade a different protein that explains both efficacy and toxicity.

The central message of this Commentary is therefore simple: degradomics should not be treated as a late quality-control assay. It is the systems pharmacology layer that turns a degradation phenotype into evidence about mechanism, selectivity, safety, and resistance. In this sense, degradomics has moved beyond its original use in protease biology and now describes the proteome-wide measurement of induced protein loss, ubiquitination, and ligase-dependent cellular response in TPD programs.² The proposed workflow is summarized in Figure 1.

WHAT DEGRADOMICS SHOULD PROVE

A useful degradomics experiment should answer more than the question "did the target go down?" It should establish whether degradation is dose-dependent, time-dependent, and mechanistically plausible; whether neosubstrates appear; and whether the same pattern holds across disease-relevant cellular contexts. Tandem mass tag (TMT) proteomics is well suited to dose-response and time-course matrices, while data-independent acquisition (DIA) provides reproducible label-free proteome coverage. Ubiquitin-remnant profiling can then test whether early ubiquitination precedes later protein loss, rather than merely following downstream stress or pathway collapse.³

These measurements are most convincing when they are designed as a chain of evidence. Early time points help separate direct degradation from secondary biology. Proteasome or cullin-RING ligase controls test whether the observed loss depends on the expected degradation machinery. Orthogonal validation by immunoblotting, targeted mass spectrometry, or rescue experiments is still needed for key targets and neosubstrates. The value of global proteomics is not that it replaces careful biology, but that it makes

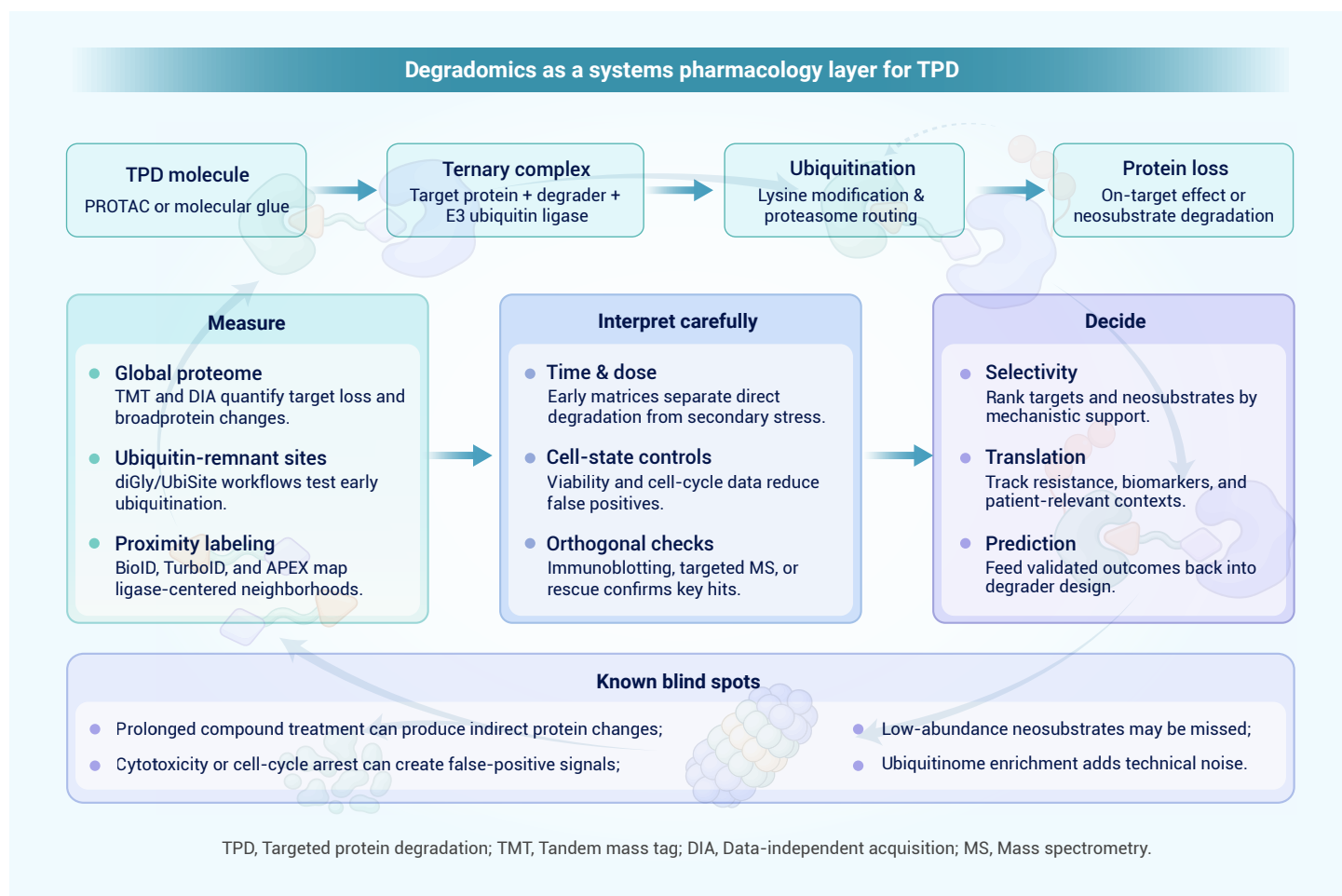


Figure 1. Degradomics as a systems pharmacology layer for targeted protein degradation TPD molecules such as PROTACs and molecular glues recruit an E3 ubiquitin ligase to a target protein, leading to ubiquitination and protein loss. Quantitative degradomics combines global proteome profiling, ubiquitin-remnant analysis, and proximity-labeling methods to connect these molecular events with selectivity, neosubstrate discovery, resistance mechanisms, pharmacodynamic biomarkers, and predictive degrader design. Interpretation requires safeguards against indirect protein changes caused by prolonged treatment, detection bias against low-abundance proteins, cytotoxicity or cell-cycle effects, and technical noise from ubiquitinome enrichment.

careful biology less blind.

TECHNICAL LIMITS THAT CAN MISLEAD

Degradomics is powerful, but it is not neutral. Prolonged compound treatment can create off-target protein changes through cell-cycle arrest, apoptosis, transcriptional rewiring, or general cytotoxicity. Low-abundance neosubstrates may be missed because they fall below detection limits, whereas abundant pathway proteins may look important simply because they are easier to quantify. Ubiquitinome enrichment adds another layer of technical noise: antibody enrichment efficiency, peptide stoichiometry, site localization, and sample input can all distort the apparent signal.³

These limitations should shape experimental design. Degradation screens need matched viability and cell-cycle measurements, multiple time points, biological replicates, and clear statistical thresholds. A late protein change should not be called a direct substrate without kinetic or ubiquitination support. Conversely, a missing signal should not be treated as proof of absence when the protein is poorly covered by the proteomic workflow. The best use of degradomics is not to generate a long list of hits, but to rank hypotheses by how well abundance, ubiquitination, cellular state, and structure agree.

SELECTIVITY, RESISTANCE, AND CLINICAL TRANSLATION

The thalidomide experience remains a useful warning. Cereblon-binding immunomodulatory drugs can induce degradation of zinc-finger proteins, including SALL4, linking an unexpected neosubstrate to developmental toxicity.⁴ For modern degraders, selectivity must therefore be defined as a proteome-wide property, not only as affinity for the intended target. Medicinal chemistry should use degradomics to learn which changes in the warhead, linker, or ligase binder preserve the desired ternary complex while removing liabilities.

Clinical translation adds further pressure. Tumors may downregulate an E3 ubiquitin ligase, alter cullin-RING ligase components, change target expression, or select for pathway states that make degradation less consequential.^{1,2} Degradomics can help identify these escape routes in resistant models and patient-derived systems. It may also support pharmacodynamic biomarkers: a sentinel protein that is reliably degraded could show whether the drug reached the relevant tissue and engaged the cellular machinery. Such biomarkers will be especially important when TPD moves beyond oncology into tissues where repeated biopsies are difficult.

BUILDING A PREDICTIVE DEGRADER DISCIPLINE

The future of TPD will depend on whether empirical degradomics can be connected to prediction. Ternary-complex structural biology has shown that cooperativity, protein-protein contacts, linker geometry, and surface complementarity can determine whether a degrader is selective and productive.⁵ Yet structure alone is not enough. Cellular abundance, subcellular localization, protein turnover, and ligase availability all change the outcome. A degrader that looks elegant in a model may fail in the cell, and a modest-looking

compound may work because the cellular context is favorable.

This is where degradomics can make the field more mature. Standardized dose-time proteomics, DIA-compatible workflows, well-annotated negative results, and public reporting of hit criteria would make datasets more useful for computational models. The goal is not to replace experiments with prediction, but to create a tighter loop: models nominate degrader designs and contexts; degradomics measures what actually happens in cells; and the next design cycle learns from both success and failure.

CONCLUSION

TPD drug discovery needs degradomics because degradation is a systems event. The relevant question is no longer whether a molecule binds a target, but whether it rewires the proteome in a way that is selective, durable, and therapeutically useful. Used carefully, degradomics can expose neosubstrates, separate direct degradation from downstream stress, reveal resistance mechanisms, and guide more rational degrader design. Its limitations are real, but they are manageable when proteomic readouts are interpreted as part of a broader mechanistic argument rather than as a final answer.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

AI-assisted tools were used only for language polishing, document formatting, and reference-format checking during revision. The authors reviewed and edited the manuscript, selected the literature, interpreted the content, and take full responsibility for the final text.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The author declares no competing interests.