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Database issue

TPDdb: the comprehensive database of *targeted protein degrader*

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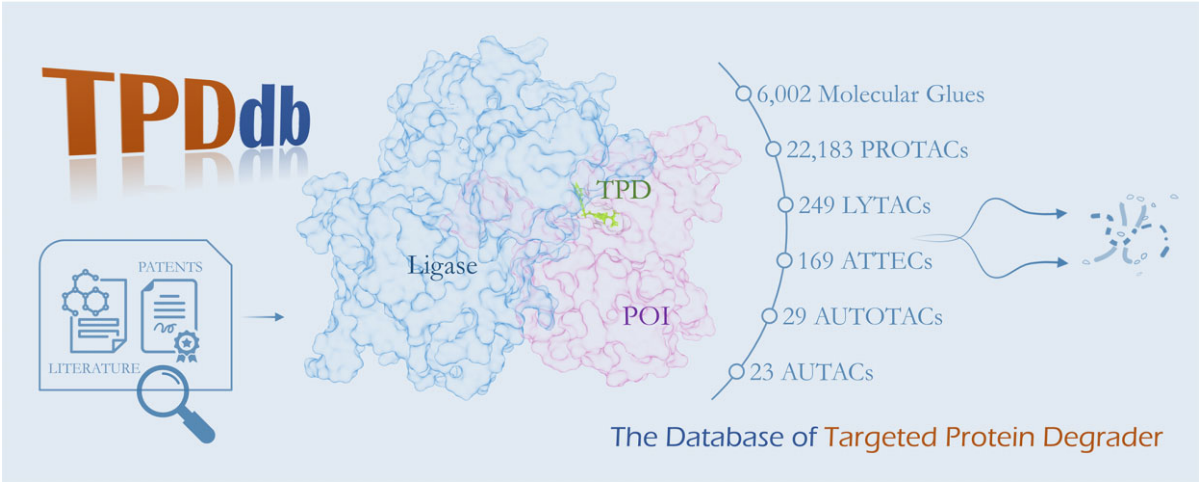
Abstract

Targeted protein degraders (TPDs) have emerged in the past decade as a new drug modality of transformative paradigm, offering a powerful strategy to catalytically remove disease-relevant proteins, especially those long considered as "undruggable." With the rapid advancement in this direction, there is increasing demand for a database describing TPDs. Herein, a comprehensive database of TPDs, titled TPDdb, was therefore developed. TPDdb is unique in (i) covering the largest amount of TPDs among existing databases (6002 Molecular Glues, 22 183 PROTACs, 249 LYTACs, 169 ATTECs, 29 AUTOTACs, and 23 AUTACs targeting 580 proteins of interest and associated with 274 diseases) with their structural and physicochemical properties offered; (ii) describing 27 796 activities (IC50, DC50, Dmax, etc.) for all collected TPDs related to 201 cell lines; and (iii) providing the structures of TPDs, proteins of interest, ligase, and experimentally determined ternary complexes. TPDdb is now accessible at https://idrblab.org/TPDdb/

Graphical abstract



Introduction

In the recent decade, *targeted protein degraders* (TPDs) have emerged as a major new drug modality of transformative paradigm, offering a powerful strategy to catalytically remove disease-relevant proteins, especially those long considered "undruggable" [1]. As depicted in Fig. 1, there are

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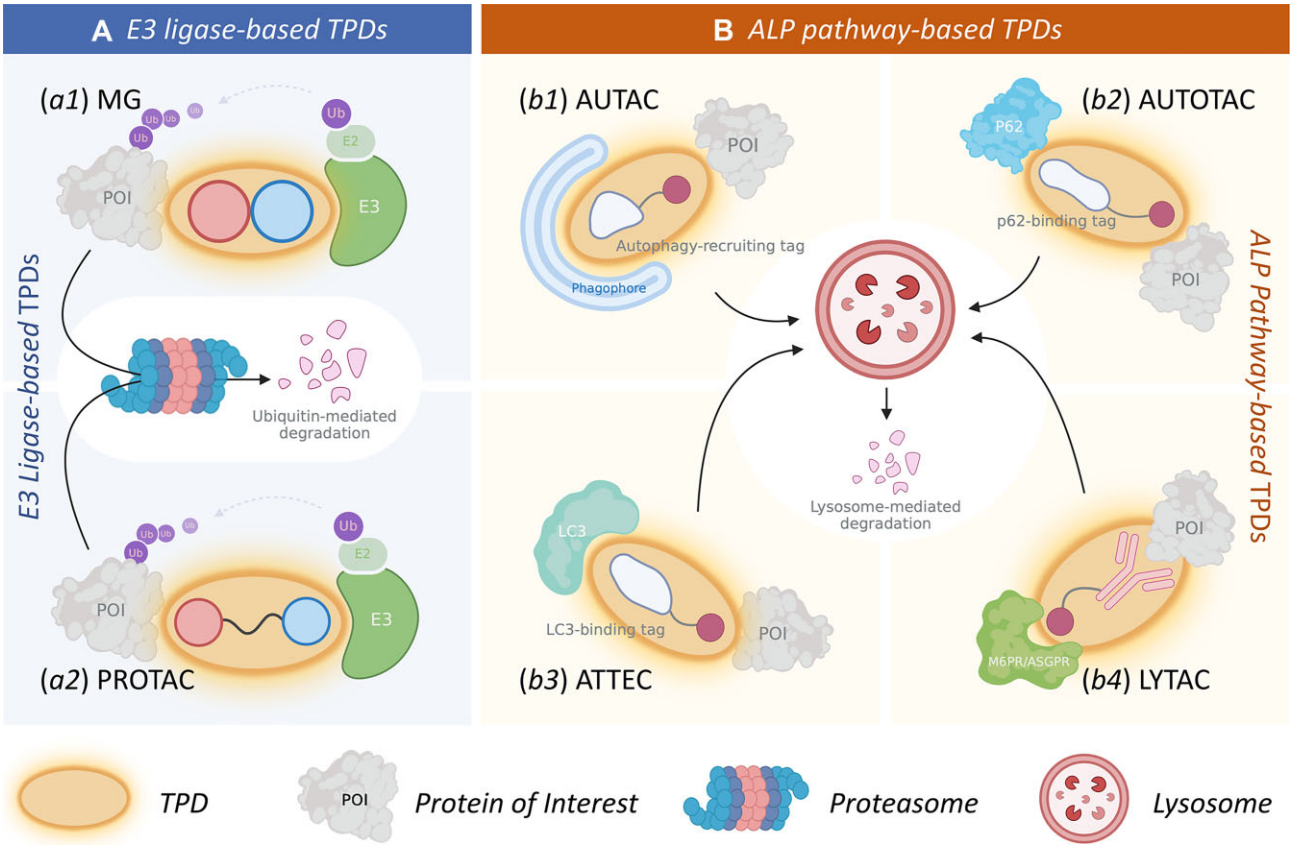

Figure 1. Two types of TPDs and underlying molecular mechanisms. (**A**) E3 ligase-based TPDs, including MG and PROTAC. MGs are small molecules that bind to an E3 ligase, inducing a conformational change that creates a new binding surface for a POI. This induced proximity facilitates the transfer of ubiquitin from an E2 conjugating enzyme to the POI. The resulting poly-ubiquitinated POI is then recognized and degraded by the proteasome. PROTACs are heterobifunctional molecules that simultaneously bind to a POI and an E3 ligase. By acting as a bridge, they bring the POI into close proximity with the ligase, leading to its ubiquitination by an E2 enzyme and subsequent degradation by the proteasome. (**B**) ALP-based TPDs, containing AUTAC, AUTOTAC, ATTEC, and LYTAC. This type involves various chimeric molecules designed to traffic POI to lysosome. Those modalities of this type utilized different tags to engage the lysosomal pathway. AUTACs attach an autophagy-recruiting tag to the POI, marking it for engulfment by a phagophore, the precursor to the autophagosome. AUTOTACs act as bifunctional tethers that directly link a POI to the autophagy receptor p62, thereby mediating its sequestration into the autophagosome. ATTECs tether a POI directly to the core autophagy protein LC3 on the autophagosome membrane, ensuring its incorporation. LYTACs target extracellular or membrane-bound POIs by linking them to a lysosome-shuttling receptor (e.g. M6PR/ASGPR). This complex is then internalized and trafficked to the lysosome for degradation.

two major types of TPD. (i) E3 ligase-based type: Molecular Glue (MG) and PROteolysis-TArgeting Chimera (PROTAC) and (ii) Autophagy–lysosomal pathway (ALP)-based one: AUtophagy-TArgeting Chimera (AUTAC), LYsosome TArgeting Chimera (LYTAC), Autophagosome-Tethering Compound (ATTEC), and AUTOphagy-TArgeting Chimera (AUTOTAC) [2]. Until now, 3 TPDs have been approved by the US FDA and over 30 are currently tested in clinical trial [3]. The mechanistic understanding of TPDs—including their protein of interest (POI), biological/pharmaceutical activity, molecular structure, and TPD physicochemical property—is critical for expanding degradable proteome using selective MG [4], designing RNA-related PROTAC for a studied POI [5], and introducing new TPD for the treatment of intractable diseases [6], among other applications [7–9]. In other words, it is highly demanded to accumulate those valuable data of TPDs, which holds immense promise for addressing the challenge in the treatment of refractory diseases [10].

To date, several databases are available to provide TPD-relevant data. As summarized in Table 1, these can be broadly categorized into general-purpose chemical repositories and specialized TPD resources. Large databases, including *PubChem* [11], *ChEMBL* [12], *TTD* [13], and *DrugBank* [14], contain entries for some TPD molecules, but this information is scattered among millions of other compounds and lacks the specific categorization required for dedicated TPD research. This makes it highly inconvenient for researchers to efficiently query and analyze data for modalities such as MGs or LYTACs. On the other hand, specialized resources such as PROTAC-DB [15] offer focused, valuable data but limited to a single TPD modality. While these databases have gained significant attentions from research communities, a comprehensive resource covering all TPD groups/types—including not only PROTAC but also MGs, AUTACs, LYTACs, ATTECs, and AUTOTAC—has been notably absent. Given the intrinsic connections among TPD groups/types and emerging demands for cross-disciplinary knowledge transfer [16–18], a dedicated TPD database is needed to serve as an indispensable complement to existing resources.

In this study, we developed TPDdb, a comprehensive knowledge base for TPDs, through systematic review of literature and patents. Key features include: First, TPDdb contains the largest collection of TPDs among existing databases, including 6002 MGs, 22 183 PROTACs, 249 LYTACs,

Table 1. Feature comparison of TPDdb against other relevant chemical and biological databases

	TPDdb	PROTAC-DB	PubChem	ChEMBL	TTD	DrugBank
Specialization	Comprehensive, specialized TPD database	Specialized PROTAC database	General chemical/ bioactivity database	General chemical/ bioactivity database	General drug/target database	General drug/target database
TPD types covered	All major TPD types	PROTAC only	Not categorized	Not categorized	Not categorized	Not categorized
Data source	Literature and patent	Literature	Literature and patent	Literature and patent	Literature and patent	Literature and patent
Curation method	Manual curation by experts	Manual curation	Automated and depositor-supplied	Automated and depositor-supplied	Automated and manual (general)	Automated and manual (general)
Search functionality	TPD-specific (by text, structure, TPD type, target)	PROTAC-specific (by text, structure, target)	General text/structure search	General text/structure search	General text/structure search	General text (by drug, target, pathway, indication)
Activity types	TPD-specific (degradation affinities, binding affinities, cytotoxic activities)	TPD-specific (degradation affinities, binding affinities, cytotoxic activities)	General bioactivities	General bioactivities	General pharmacological	General pharmacological
Ternary complex structures	Yes (experimental)	Yes (experimental and predicted)	No	No	No	No

169 ATTECs, 29 AUTOTACs, and 23 AUTACs targeting 580 POIs, with structural and physicochemical properties provided for each TPD. An analysis of this target landscape reveals a research focus on key proteins such as GSPT1, IKZFs, CK1alpha, CDKs, AR, and KRAS across various TPD modalities. Second, the biological/pharmaceutical activities of the collected TPDs (target degradation activity, cytotoxic activity, etc.) were systematically retrieved from published papers and granted patents, resulting in 27 796 activity measurements (IC50, DC50, Dmax, etc.) from both biochemical and cellular assays across 201 cell lines. Third, the database provides extensive biological context, documenting associations with 274 unique diseases. Our analysis of this therapeutic landscape shows a broad scope, with disease types distributed across both oncological (112 types) and nononcological (162 types) conditions. Fourth, TPDdb provides a uniquely comprehensive and specialized resource that overcomes the limitations of existing databases (Table 1). A key distinction is our focus on not only literature- but also much larger volumn of patent-derived compounds; for instance, TPDdb includes over 20 000 patent-protected PROTACs, which serves as a crucial complement to the 6111 literature-reported molecules in PROTAC-DB [15]. Fifth, experimentally determined 3D structures of ternary complexes (POI–TPD–E3 ligase) were also systematically collected in TPDdb. Given the significance of this accumulated data, TPDdb is expected to generate broad interest from research communities. TPDdb is now open to all users without login requirement at https://idrblab.org/TPDdb/.

Factual content and data retrieval

Systematic collection of the information of targeted protein degraders

Explicit data of TPDs and their biological activities were collected using the following procedure. First, data of MGs and ALP-based TPDs (ATTECs, AUTOTACs, AUTACs, and LYTACs) were exhaustively collected by searching the peer-reviewed literature in PubMed [19] and granted patents recorded in SureChEMBL [20]. This search targeted different TPD modalities using specific keywords. Queries for MGs used a keyword combination as "MOLECULAR GLUE," "CEREBLON MODULATOR," or "CELMoD;" lysosome-mediated degraders were identified using "LYTAC," "ATTEC," "AUTOTAC," or "AUTAC." Second, PROTAC data were collected via retrieving the patent data from SureChEMBL using the keyword "PROTAC" [20]. SureChEMBL is a publicly available database extracting data from 28 million patents granted by global intellectual property administrations, including USPTO, WIPO, EPO, JPO, CNIPA, and others [21]. Third, every collected entry underwent an in-depth manual curation process to ensure data accuracy, consistency, and richness. Initially, we included only those molecules that conform to the established definitions of the various types of TPDs and for which a complete chemical structure and its corresponding linker, binder, and targeting units could be unambiguously determined. Crucially, entries were excluded if the source literature or patent did not provide direct experimental evidence supporting their intended function (e.g. target degradation or stabilization). For the retained entries, a meticulous data standardization procedure was applied. Particularly, as molecular structures are often presented as images or in nonstandard formats, collected TPD structures were manually reconstructed and standardized into MOL files, with corresponding canonical SMILES strings collected. Fourth, based on the collected TPD structures, physicochemical properties of TPDs were either collected from PubChem [11] or calculated using the RDKit Toolkit (https://github.com/rdkit). Fifth, extensive functional and structural annotations were also provided. Specific POIs, E3 ligases, or interacting protein partners for each TPD were manually extracted from literature/patents and standardized to UniProtKB identifiers, and additional protein data (e.g. sequence and individual 3D structure) were retrieved from the UniProtKB [22] and the Protein Data Bank [23]. Where available, 3D structures of ternary complexes (POI–TPD–E3 ligase) were curated to provide structural insights into degradation mechanism. Finally, biological activities of TPDs (target degradation activity, binding affinity, cytotoxic activity, etc.) were further curated from peer-reviewed literature and patent records. To provide crucial context for data interpretation, essential experimental details such as cell lines, assay conditions, and measurement units were also extracted from literature/patents and displayed alongside each activity in TPDdb. In addition, to provide therapeutic context, disease association data were systematically curated

using a dual-source strategy. First, for TPDs with reported activity in specific cell lines, disease relevance was established by mapping cell lines to their originating diseases using the curated annotations from the Cellosaurus database [24], a comprehensive knowledge resource on cell lines used in biomedical research. This was supplemented by retrieving established gene–disease associations for each POI from the Orphanet database (https://www.orpha.net/). To ensure data consistency and enable systematic analysis, all collated disease terms were standardized using the World Health Organization (WHO) International Classification of Diseases 11th Revision (ICD-11). This systematic curation resulted in a total of 98 680 disease associations covering 274 unique diseases.

As a result, TPDdb provided comprehensive data on two major types of TPDs: the ones hijacking the ubiquitin-proteasome system (UPS) and the ones harnessing the ALP. As shown in Fig. 1, TPDdb encompassed six groups of TPDs from these types, including the well-established modalities of MGs and PROTACs, as well as emerging lysosomal TPDs, such as LYTACs, ATTECs, AUTACs, and AUTOTACs. Each entry provides curated data including molecular structures, physicochemical properties, specific protein targets (e.g. POIs, E3 ligases), detailed biological activities, available ternary structures, and more.

The TPDs hijacking the ubiquitin-proteasome system

The comprehensive information of molecular glues

MGs are small molecules that stabilize a ternary complex between two proteins that otherwise lack extensive affinity [25, 26]. They typically bind to a protein and create an induced binding interface that can be recognized by a second neo-substrate protein [27, 28]. The most well-characterized examples include thalidomide and its derivatives (lenalidomide, pomalidomide), which bind to an E3 ubiquitin ligase to alter its substrate specificity and subsequently induce the degradation of target proteins [29, 30]. Such induced proximity can also lead to targets' inhibition or stabilization [31, 32]. In other words, MGs represent a broad class of proximity-inducing agents with functional modulation effects ranging from degradation to inhibition or stabilization [33, 34]. Compared to PROTACs, a primary advantage of MGs lies in their low molecular weights, which may confer favorable cell permeability and enhanced pharmacokinetic profiles [35, 36].

In TPDdb, a total of 6002 MGs together with their corresponding biological activities were collected. Each MG is shown on a dedicated page that organizes comprehensive information into three main sections (as illustrated in Fig. 2 using *lenalidomide* as an example). As shown in Fig. 2A, the first section provides the basic information of MG, such as name, synonyms, chemical formula, canonical SMILES, physicochemical properties, and interactive 2D and 3D structures. Additionally, a mechanistic annotation is also provided for each MG, such as *degradation*, *inhibition*, and *stabilization* [37, 38]. In the second section (described in Fig. 2B), the mode of action (MOA) of each MG is illustrated, including detailed descriptions of POIs and E3 ligases. The crystal structures of each POI and E3 are also provided together with their corresponding ternary complex, offering critical insight into the induced-proximity mechanism. In the third section (demonstrated in Fig. 2C), an explicit table containing all curated biological activities of the MG (e.g. degradation capacities, binding and cytotoxic activities, etc.) is provided along with the corresponding experimental context.

The patented PROteolysis-TArgeting Chimera

PROTACs are heterobifunctional molecules consisting of a ligand that binds a protein of interests, a ligand that binds E3 ligases, and a chemical linker connecting them [39, 40]. Unlike MGs, which induce a new protein–protein interaction surface, PROTACs bring the studied POI into close proximity with the E3 ligase by binding two entities simultaneously, triggering ubiquitination and subsequent proteasomal degradation of the POI [41, 42]. Some key advantages of PROTACs include a rational design process, a catalytic MOA, and the ability to regulate the POI previously considered undruggable [43, 44]. PROTAC-DB has been developed to dedicate this modality [15], and its latest version features 6111 PROTACs curated from peer-reviewed literature, describing invaluable data on POIs, segmented structures, biological activities, pharmacokinetic parameters, and both experimentally resolved and predicted ternary structures [15]. However, a large volume of PROTACs with novel scaffolds and application-oriented compounds resides were reported in granted patents [20], which remained largely unindexed in the existing knowledge bases.

To address this issue, TPDdb systematically collected the PROTAC data from patent-relevant data sources, such as USPTO, WIPO, EPO, JPO, and CNIPA, which resulted in a total of 22 183 patent-protected PROTACs. Such data were further enriched by collecting biological activities and experimentally determined ternary complex structures for each PROTAC. Since this study focuses on the patent-protected data, TPDdb could be considered a crucial complement to the existing PROTAC data repository based on comprehensive literature.

The TPDs harnessing the autophagy–lysosomal pathway

In addition to the proteasome-mediated pathway, the second type of TPDs leverages the ALP to eliminate POIs [45, 46]. The advantage of ALP lies in its ability to degrade exceptionally large and complex substrates that are physically too large to enter the proteasome [47, 48]. ALP-based TPDs are particularly valuable for degrading these large substrates such as protein aggregates, entire organelles, and extracellular or membrane-bound proteins that are typically inaccessible to the UPS [49]. Such technologies include four main types: LYTACs, AUTACs, AUTOTACs, and ATTECs. LYTACs are chimeric molecules that link an extracellular protein to lysosome-shuttling receptor, directing it for uptake and degradations [50]; AUTACs are small molecules that induce a specific K63-polyubiquitination tag on a POI, marking it for recognition by autophagy receptors [51]; AUTOTACs act as bifunctional tethers that directly link a POI to the autophagy receptor p62 [52]; ATTECs function via tethering a target to core autophagy proteins such as LC3 [53]. Collectively, all these technologies expand the scope of TPD strategies to a broader range of intracellular and extracellular targets [54, 55].

In this study, a variety of TPDs that operate via the lysosomal pathway were collected, currently comprising 470 entries. This includes 249 LYTACs and 169 ATTECs alongside a

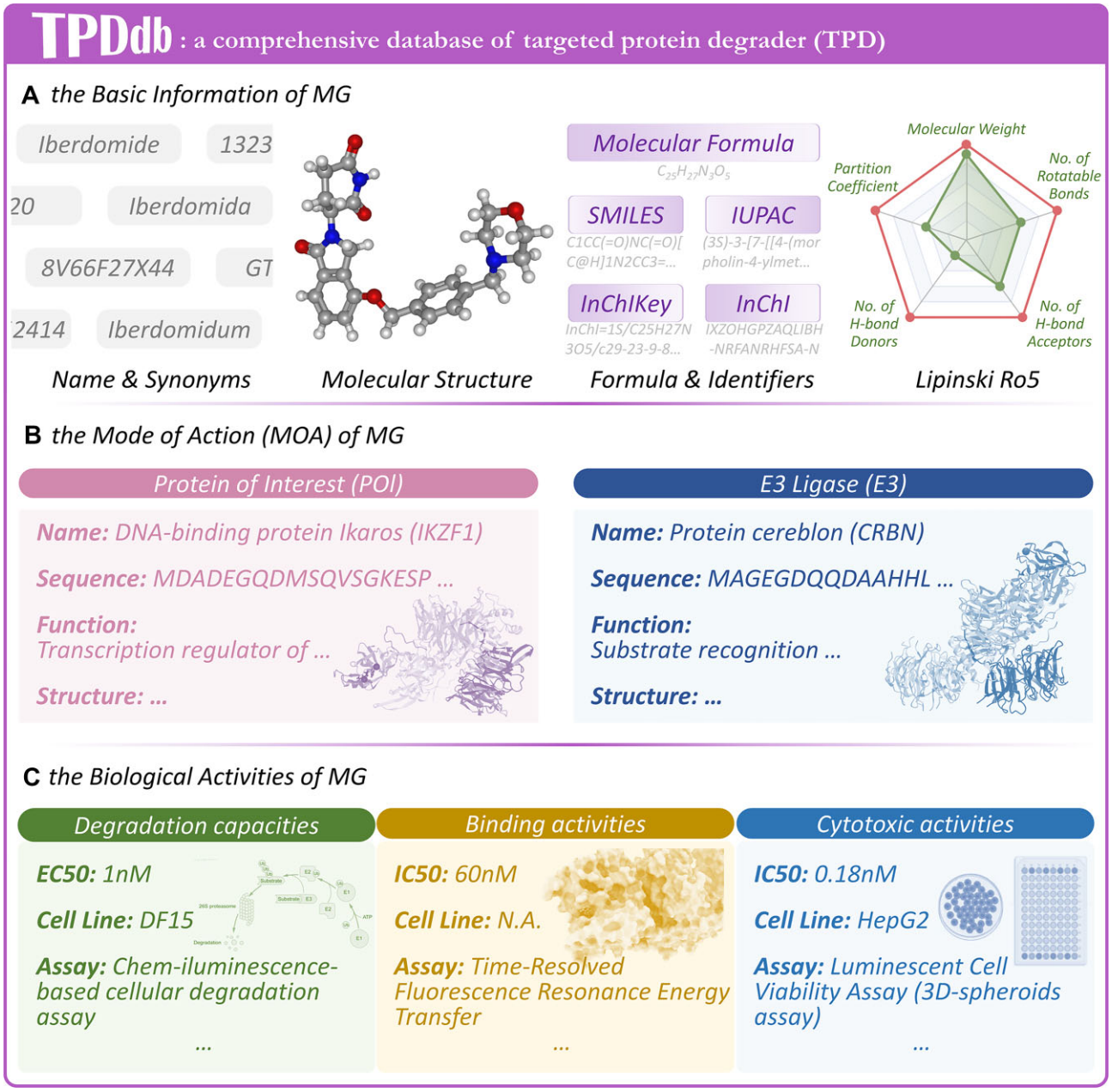

Figure 2. Schematic illustration of the information offered in a typical page of TPDdb (using the molecular glue lenalidomide as an example). (**A**) Basic information, containing name, synonyms, formula, canonical SMILES, physicochemical property, and interactive structures. (**B**) MOA, including the detailed description on POI and E3 ligase (E3) together with the structure of the corresponding ternary complex. (**C**) Biological activities, comprising degradation capacities, binding affinities, cytotoxic activities, along with the corresponding experimental context for measuring those activities.

smaller but growing number of AUTACs and AUTOTACs, accompanied by diverse biological activities. The number of curated lysosome-mediated degraders reflects the status of this rapidly evolving field. As the technologies are more nascent and often involve more complex chemical structures (e.g. antibody, glycopeptide conjugate, etc.) compared to traditional small molecular degraders, the volume of publicly available compounds is correspondingly smaller. Consistent with other categories in TPDdb, each lysosome-mediated TPD is depicted on a dedicated page describing comprehensive overview, including its structure, physicochemical properties, specific protein targets, and a detailed table of biological activities with associated experimental conditions. By systematically capturing these emerging modalities, TPDdb provides the researchers with a centralized resource to monitor and analyze the latest advancements in the field of TPD beyond the UPS.

Standardization, access, and download of TPDs and their activity data

To make the access and analysis of TPDdb data convenient for all readers, the collected raw data were carefully cleaned up and then systematically standardized. These standardizations included: (i) all the TPDs, POIs, E3 ligases, and cell lines were cross-linked to established databases; (ii) all diseases were standardized using the latest ICD-11 officially released by the WHO. Additionally, a user-friendly interface was created to enable the convenient browse and search of data. All TPD-

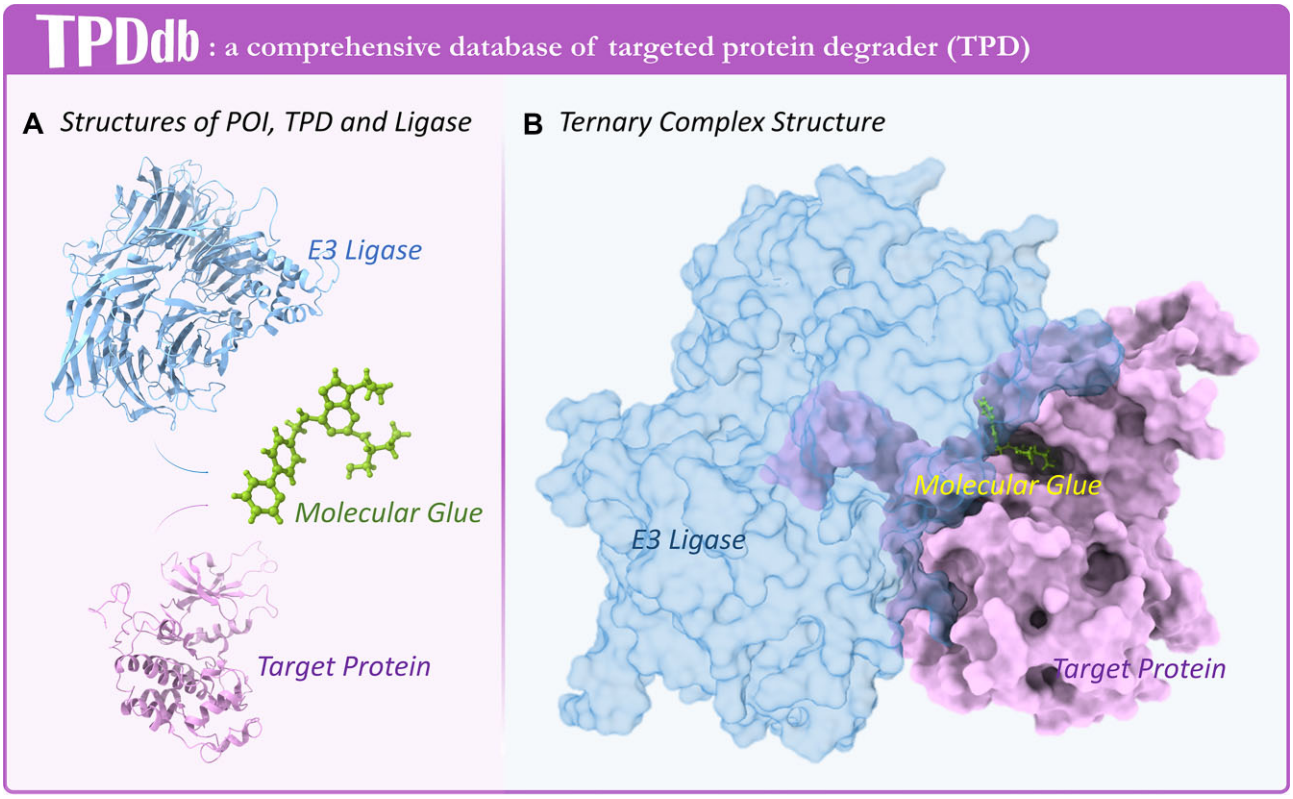

Figure 3. The availability of structure data in TPDdb. (**A**) The structure of POI, TPD, and ligase illustrated in online database. (**B**) The experimentally determined ternary complex structures among POI, TPD, and ligase depicted in online database.

related data can be viewed, accessed, and downloaded without any login requirement from https://idrblab.org/TPDdb/. TPDdb offers a multifaceted data retrieval mechanism, designed to facilitate efficient data exploration. Notably, this database offers several important features for accessing the TPD data, catering to a wide range of scientific inquiries. First, direct retrieval by molecule names and identifiers. For readers with a studied TPD/POI, TPDdb offers a straightforward text-based retrieval mechanism. Users can identify their TPD of interest by searching its name or synonyms or the name of the POI, gene symbol, or UniProtKB ID. Such function provides immediate access to a list of relevant entries, from which users can navigate to the detailed TPD pages. Second, guided navigation via biological categories. This feature enables users to explore the database from a biological context, which is implemented through a two-step selection interface streamlining the discovery of related entries. Users can first select a specific POI name from a comprehensive dropdown list, which then populates a second menu with all TPDs known to target that POI. Alternatively, users can begin with selecting a TPD type (e.g. Molecular Glue, PROTAC) and then filter the second menu to show all TPDs of that type. Such approach is particularly friendly for those investigating TPD related to a POI or exploring the landscape of a degradation technology. Third, structure-centric exploration. To support chemical biology and medicinal chemistry applications, TPDdb incorporates a structure-based retrieval engine. This functionality allows users to identify TPDs with structure similarity to a molecule of interest. Input can be supplied in multiple formats: by drawing a structure using the *integrated JSME editor*, by uploading a structure in SDF format, or by pasting a SMILES string. On the backend, the queried molecule will be then converted into a chemical fingerprint and its similarity to all molecules in this database is then calculated based on *Tanimoto coefficient* [56]. The corresponding results are then presented as a list of molecules ranked by their similarity scores, providing an intuitive tool for discovering structural analogues and exploring structure–activity relationships (SARs). Moreover, the structures of POI, TPD, and ligase are depicted in the online database (as illustrated in Fig. 3A), and experimentally determined ternary complex structures (if available) are also explicitly offered in TPDdb (as shown in Fig. 3B).

Conclusion and future directions

The research direction of TPDs is expanding at an unprecedented rate, making the chemical, biological, and structural data of TPDs largely scattered in scientific literature and patent records. TPDdb was therefore constructed to provide the comprehensive data for this emerging direction. It systematically collected and organized information on the main groups of TPDs, encompassing both the ubiquitin-mediated and emerging lysosome-mediated modalities. Our commitment to manual curation by domain experts ensured the high degree of data accuracy and richness, including standardized structures, detailed biological activity profiles with essential experimental context, and structural information on ternary complexes. The database is equipped with user-friendly interface, featuring both text-based and structure-based search. By integrating those diverse datasets into a single accessible platform, TPDdb aims at accelerating research in TPDs across the entire discovery pipeline. The database directly supports the rational design and optimization of novel degraders, as medicinal chemists can leverage the extensive collection of

patent-protected compounds and the structure-based search functionality to explore novel chemical scaffolds and systematically investigate SARs. Beyond the design of new chemical entities, the platform provides critical data for deeper mechanistic studies. Unlike repositories focused on a single modality (e.g. PROTAC-DB), TPDdb uniquely integrates a broad spectrum of TPD modalities with a rich annotation of their biological activities. This allows for direct cross-modality comparisons and provides the crucial context needed for in-depth functional studies. On a broader scale, the aggregation of such a large, well-annotated dataset creates significant opportunities for computational approaches, representing an ideal training ground for developing novel machine-learning models capable of predicting TPD activity, optimizing linker design, or even identifying new degradable targets, thereby enabling new data-driven discovery pipelines.

The comprehensive disease annotation in TPDdb also offers novel insights into the therapeutic landscape of targeted protein degradation. Given that experimental data for TPDs often originate from cancer cell lines, a common perception is that the primary application of this modality is concentrated in oncology. However, our dual-source curation strategy, which supplements cell line-derived data with established gene–disease relationships, reveals a much broader potential. Our analysis shows that while nearly half of all TPD–disease associations are linked to cancer, the majority of unique disease types (162 out of 274) are nononcological. This finding highlights that the underlying biology of TPD targets is relevant to a wide spectrum of human pathologies beyond cancer, including immunological, metabolic, and neurodegenerative disorders. It underscores the value of TPDdb as a discovery tool, enabling researchers to identify novel therapeutic hypotheses and expand the application of targeted protein degradation to a wider range of diseases.

We are committed to keeping TPDdb at the forefront of the field through regular, semiannual updates to incorporate new entries from the latest publications and patent filings. The cornerstone of our data integrity strategy will continue to be the meticulous manual curation process performed by our domain experts, which is applied to every new and existing entry. To further enhance data quality and community engagement, we will implement a user feedback mechanism and a submission portal on our website. These features will allow researchers to report potential inaccuracies, suggest missing data, or recommend relevant new publications. All community-submitted data will undergo the same rigorous internal validation and curation process before being integrated into the database, ensuring the high standards of TPDdb are consistently maintained.

Future development will focus on expanding the data coverage to include additional modalities and incorporate new computational tools. First, we plan to broaden data coverage to include additional emerging modalities beyond the current TPD groups, such as AbTAC [57], GlueTAC [58], and CMA-based degrader [59]. We will also introduce a more granular classification system for the collected molecules, allowing users to browse and filter them based on more detailed functional roles and compositional features. Second, to enhance the database's utility in supporting rational degrader design and building predictive computational models, we will begin to incorporate curated negative data (i.e. compounds tested but found to be inactive). In addition, we will create dedicated datasets for well-validated linkers and binders (ligands for POIs and E3 ligases), providing a valuable resource for modular drug design. Third, we will enhance the platform by integrating new computational and predictive modeling tools. Building upon the rich dataset, we envision developing and embedding online modules for predicting key TPD properties, such as degradation efficacy or identifying potential off-target effects, which will provide invaluable support for the rational design of next-generation therapeutics.

We believe TPDdb will serve as an invaluable resource for the scientific community, empowering researchers to navigate the complex landscape of targeted protein degradation and drive the development of next-generation therapeutics.

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Conflict of interest

None declared.

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Data availability

All TPD data can be viewed, accessed, and downloaded from TPDdb, which is freely accessible without any login requirement by all users at https://idrblab.org/TPDdb/

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