TTD: *Therapeutic Target Database* describing target druggability information

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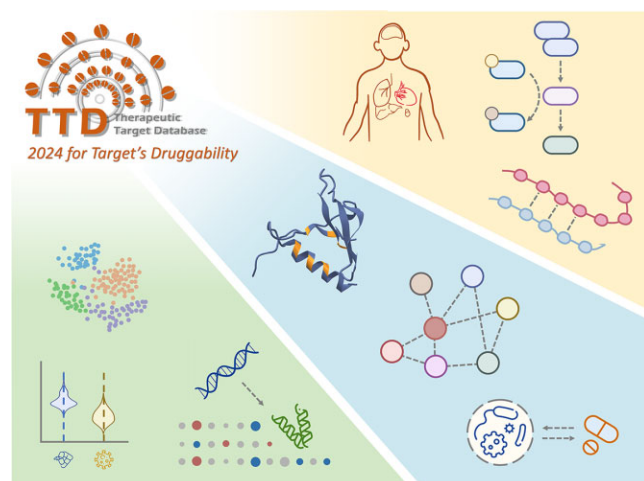Correspondence may also be addressed to Yunqing Qiu. Email: qiuyq@zju.edu.cn
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Abstract

Target discovery is one of the essential steps in modern drug development, and the identification of promising targets is fundamental for developing first-in-class drug. A variety of methods have emerged for target assessment based on druggability analysis, which refers to the likelihood of a target being effectively modulated by drug-like agents. In the *therapeutic target database* (TTD), nine categories of established druggability characteristics were thus collected for 426 successful, 1014 clinical trial, 212 preclinical/patented, and 1479 literature-reported targets via systematic review. These characteristic categories were classified into three distinct perspectives: *molecular interaction/regulation*, *human system profile* and *cell-based expression variation*. With the rapid progression of technology and concerted effort in drug discovery, TTD and other databases were highly expected to facilitate the explorations of druggability characteristics for the discovery and validation of innovative drug target. TTD is now freely accessible at: https://idrblab.org/ttd/.

Graphical abstract

Introduction

Target discovery is one of the essential steps in modern drug development, and the identification of promising targets lays the foundation for the successful development of first-in-class drug (1). To ensure the success and efficiency of drug development, the quality of the selected target needs to be assessed during the early stage of drug discovery, which has been frequently conducted by evaluating the druggability of target (2–4). The druggability of a target refers to the likelihood of target being effectively modulated by drug-like agents with various evaluation methods proposed (5–7). For example, *the presence of suitable binding pocket* is crucial for the target's druggability, which is known as one standard procedure in target selection (8); *the human system profiles* such as human similarity proteins and affiliated pathways have been explored for characterizing target druggability, with their ability to differentiate the targets of rapid (speedy) and slow (non-speedy) clinical development process (9). Moreover, *diverse cell-based differential expressions of targets* are found informative for identifying new targets that play a crucial role in disease (10).

Notably, the target assessment using single druggability characteristics is often insufficient, and comprehensive evaluation of multiple druggability characteristics is a more helpful approach (9). Therefore, related databases are needed to provide comprehensive druggability characteristics of targets from multiple perspectives. So far, a variety of established databases have been developed to collectively provide drug & target data. Some describe pharmacological information on drugs, such as DrugBank (11), DrugCentral (12), SuperDRUG2 (13), DrugMap (14) and DRESIS (15); some others focus on presenting therapeutic targets, such as TTD (16) and Open Target (17); the remaining offer general molecule and bioactivity information, such as PubChem (18), ChEMBL (19) and BindingDB (20). Although these databases have already accumulated great popularities and substantial impacts on chemical/biological/pharmaceutical communities, the information of target druggability characteristics have not yet be covered by any of the existing databases.

Herein, the *therapeutic target database* (TTD) was thus significantly updated to its 2024 version, which provided comprehensive information on the druggability characteristics of 426 successful, 1014 clinical trial, 212 preclinical/patented and 1479 literature-reported targets. Particularly, such characteristics were of three perspectives (Figure 1): *molecular interactions/regulations*, *human system profiles* and *cell-based expression variations*. Molecular interactions/regulations offered (1*a*) ligand-specific spatial structures of target in its drug binding pocket, (1*b*) network properties of target measured based on protein-protein interactions & (1*c*) bidirectional regulations between the microbiota and therapeutic agents. Human system profiles provided (2*a*) similarity profile of target to human proteins outside its families, (2*b*) involvements of target in well-established life-essential pathways & (2*c*) distributions of target among a variety of organs in human. Cell-based expression variations described (3*a*) varied expression of target across cells of different diseases, (3*b*) differential expressions of target induced by exogenous stimuli & (3*c*) modified expressions of target altered by human endogenous factors. The statistics of targets & drugs in TTD over the past decade were provided in Table 1, and the detailed data on the major contents integrated into TTD were explicitly described in following sec-

tions. With the rapid progression in the techniques of drug discovery, the wealth of druggability data incorporated into TTD are expected to establish a solid foundation for the identification of novel targets and discovery of new therapeutics. TTD is now freely accessible without any login requirement at: https://idrblab.org/ttd/.

Factual content and data retrieval

Due to the importance of target druggability data (as described above) in modern drug discovery, *therapeutic target database* (TTD) was mainly updated to its 2024 version by comprehensively providing three types of druggability information for each therapeutic target. As shown in Figure 1, compared with the previous versions, the TTD 2024 updated three major types of druggability: *molecular interactions/regulations*, *human system features* and *cell-based expression variations*. These druggability data were not covered by any of the previous versions of TTD. Each of these three types of druggability was further elaborated using three distinct sub-sections of data, which were explicitly discussed and described as follows.

Druggability illustrated by *molecular interactions or regulations*

Ligand-specific spatial structure of a target within drug binding pocket

The drug binding site of therapeutic target was usually considered to be indispensable for modern drug discovery (21–25). The binding pocket structure of established targets was essential for drug design and lead optimization (26), and the binding pocket of promising new targets could further expand the druggable genome and enable development of new strategies for targeted therapeutics (8). Among the >80 FDA-approved kinase inhibitors, many of them were inspired by the binding pocket structure of the catalytic domain of kinases (27). In other words, it is essential to have the valuable drug-specific spatial structures of studied target within its drug binding pocket.

Such structures of drug binding pocket were systematically collected to TTD using the following procedure. *First*, a comprehensive search of all TTD targets in PDB (28) was realized based on the name and synonyms of the targets. *Second*, all retrieved structures were carefully checked to remove false matches, which resulted in >25 000 target crystal structures. *Third*, the availability of drug binding to these structures was investigated, and the corresponding drugs were identified. *Forth*, the co-crystal structures containing both target and its interacting drug were obtained, and the distance between drug and each residue was calculated based on *biopython* (29). All residues that interacted with drug at a distance of <5 Å were defined as the 'drug binding pocket' (30). As shown in Figure 2A, the binding pocket information was provided in ligand-specific manner for any studied target. For certain complex, the pocket residues together with detailed distances were provided in TTD and highlighted based on their van der Waals surface calculated by iCn3D (31). Additional information (such as structure resolution, sequence, and mutation) was also provided in online TTD. As a result, the ligand-specific binding pockets of 319 successful (targeted by at least one FDA-approved drug), 427 clinical trial (not targeted by any approved drug, but targeted by at least
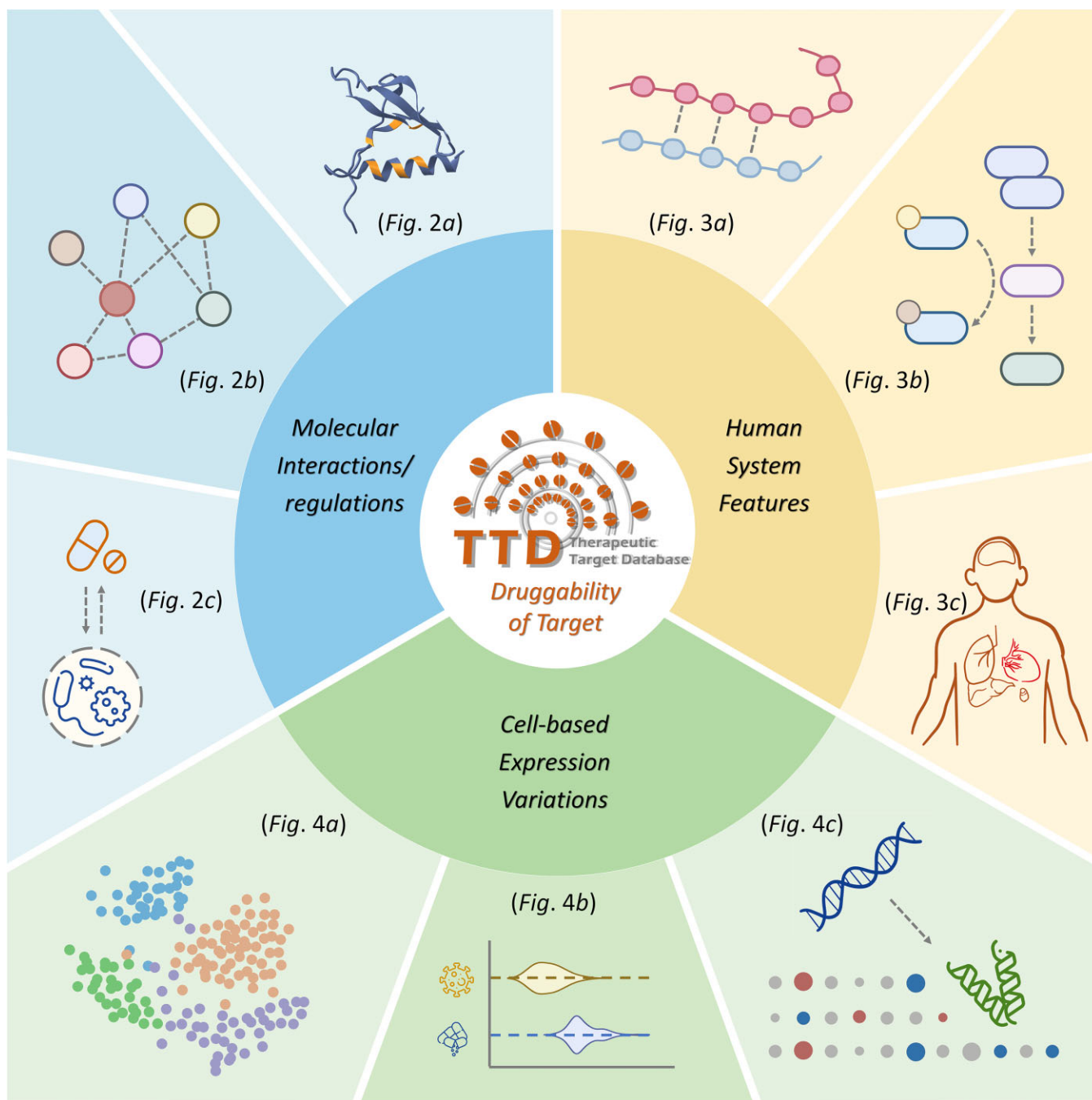
Figure 1. Three major contents integrated into the TTD 2024. A wealth of data was collected to describe target druggability from three distinct perspectives: *molecular interactions/regulations*, *human system features* and *cell-based expression variations*. Each perspective was elaborated in detail through three different sections of data, which were further explicitly described.

one clinical trial drug), 116 preclinical/patented (not targeted by any approved/clinical trial drug, but targeted by at least one preclinical/patented drug), 375 literature-reported (targeted by experimental drugs only) targets were identified from 22 431 complex structures.

Network properties of target measured by protein–protein interactions

Target's network properties derived from complex connections among numerous protein–protein interactions (PPI) have been extensively employed for evaluating the target druggability (32–36). Proteins demonstrating high node degrees are posited to exert considerable influence on network function due to the huge amount of interactions (37), while proteins exhibiting high betweenness centrality are considered pivotal in network communication and signaling information flow (38). A multitude of network descriptors have been reported as potential indicators to differentiate the targets of rapid (speedy) and slow (non-speedy) clinical development process (9).

The collection of target's network properties to TTD was accomplished in the following manner. *First*, PPIs with high confidence score ($\geq$0.95) were collected from STRING database (39), and a human PPI network consisting of 9309

Table 1. Number of drugs and their corresponding therapeutic targets in different versions of TTD over the past decade

Statistics of targets and drugs in different versions of TTD	Different versions of TTD published during the past decade					
	2024	2022	2020	2018	2016	2014
All targets	3730	3578	3419	3101	2589	2360
Successful targets	532	498	461	445	397	388
Clinical trial targets	1442	1342	1191	1121	723	461
Preclinical/patented targets	239	185	155	0	0	0
Literature-reported targets	1517	1553	1612	1535	1469	1467
All drugs	39 862	38 760	37 102	34 019	31 614	20 667
Approved drugs	2895	2797	2649	2544	2071	2003
Clinical trial drugs	11 796	10 831	9465	8103	7291	3147
Preclinical/patented drugs	5041	5009	4845	0	0	0
Experimental drugs	20 130	20 123	20 143	18 923	17 803	14 856

proteins and 52 713 PPIs was then constructed. *Second*, nine representative network properties (including: betweenness centrality, clustering coefficient, *etc.*) were calculated for each target ([40]). As shown in Figure [2]B, a two-layer PPI network for a target was illustrated, together with a downloadable file of the complete human PPI network. As an outcome of this process, a variety of network properties for 426 successful, 727 clinical trial, 143 preclinical/patented, and 867 literature-reported targets were provided in TTD 2024.

Bidirectional regulations between microbiota and targeted agents

The regulation between microbiota and targeted agents is complex and bidirectional ([41]). On the one hand, microbiota can modulate bioavailability, bioactivity and toxicity of drugs; on the other hand, drugs can impact growth, composition, and function of microbiota ([42]). Taking *irinotecan* (one medication for treating colon cancer) as an example, it is metabolized to *SN-38 glucuronide* by *beta-glucuronidase* of gut microbiota, which resulted in the great elevation of gastrointestinal toxicity ([43]), and the selective inhibition of bacterial betaglucuronidase showed the potential to alleviate drug-induced toxicities ([44]). In other words, unraveling such regulations is anticipated to shed light on the identification of novel therapeutic targets, the discovery of new therapies and the potential modification of existing drug prescription methodologies ([45,46]).

Bidirectional regulation data between microbiota and targeted drugs were collected to TTD using the following procedure. *First*, systematic literature review was conducted in PubMed ([47]) using such keyword combinations as 'drug + microbiota', 'drug + microbe', 'drug + microbiome', *etc.* All retrieved literatures were carefully reviewed, and the interactions between drugs and microbe were manually recorded. As illustrated in Figure [2]C, all the interactions were classified into two categories: *microbes affecting drug metabolism* & *drugs regulating microbe abundance*. For the former interaction type, the detailed information (such as involved microbial enzymes, metabolic reactions of studied microbiota, resulting metabolites, and metabolic effects) was also explicitly described. For the latter type of interaction, the detailed information (such as abundance variation of microbe, a variety of species origins and specific experimental samples) was further extracted. As a result, a total of 9812 interactions between 663 drugs and 686 microbes were collected to TTD, which came from 20 phyla, 36 classes, 59 orders, 101 families and 135 genera.

Druggability characterized by different human system profiles

Similarity profile of target to human proteins outside Its family

Drug candidates are typically designed to selectively interact with their intended target, and their interactions with other proteins outside target's biochemical family should therefore be carefully evaluated at the early stage of drug development ([48]). As reported, the target having fewer human similarity proteins outside its biochemical family is commonly regarded to have greater capacity to avoid undesired interaction and thus increase the possibility of discovering drug-like molecule ([9]). Therefore, it is highly demanded to have the valuable data on the number of human similarity proteins outside target's functional family to assess the off-target collateral interactions ([9]).

As shown in Figure [3]A, such similarity profiles were included into TTD. *First*, the sequences of TTD targets and all human proteins were extracted from UniProt ([49]). *Then*, the protein families to which each protein belonged were obtained from InterPro ([50]). For a TTD target, its similarity to human proteins was calculated using BLAST ([51–53]). The similarity proteins of a target were defined as those with *E*-value <0.005 and outside the protein families of the target. On the target page, the data of protein name, protein family, BLAST identities, and *E*-values were listed. As a result, the similarity profile information was made available for 389 successful, 933 clinical trial, 204 preclinical/patented and 1479 literature-reported targets in TTD 2024.

Involvements of Target in the Well-established Life-essential Pathways

Targets affiliating with fewer life-essential pathways were reported to have greater likelihood of success, while those associated with more signaling pathways were found to increase the chances of undesirable interferences with other human process ([48]). The target-directed toxicity had been identified as originating from the participation of the targets in potentially harmful pathways ([1]). Furthermore, in circumstances where the understanding of drug targets' functions is inadequate, the valuable information of target-affiliating pathways can be very informative ([54]).

As illustrated in Figure [3]B, the life-essential pathways that TTD targets involved were gathered. *First*, all available pathway information for each target was collected from KEGG ([55]). *Second*, the target-affiliated pathways were double-checked based on two criteria: (*Ca*) the pathways of the stud-
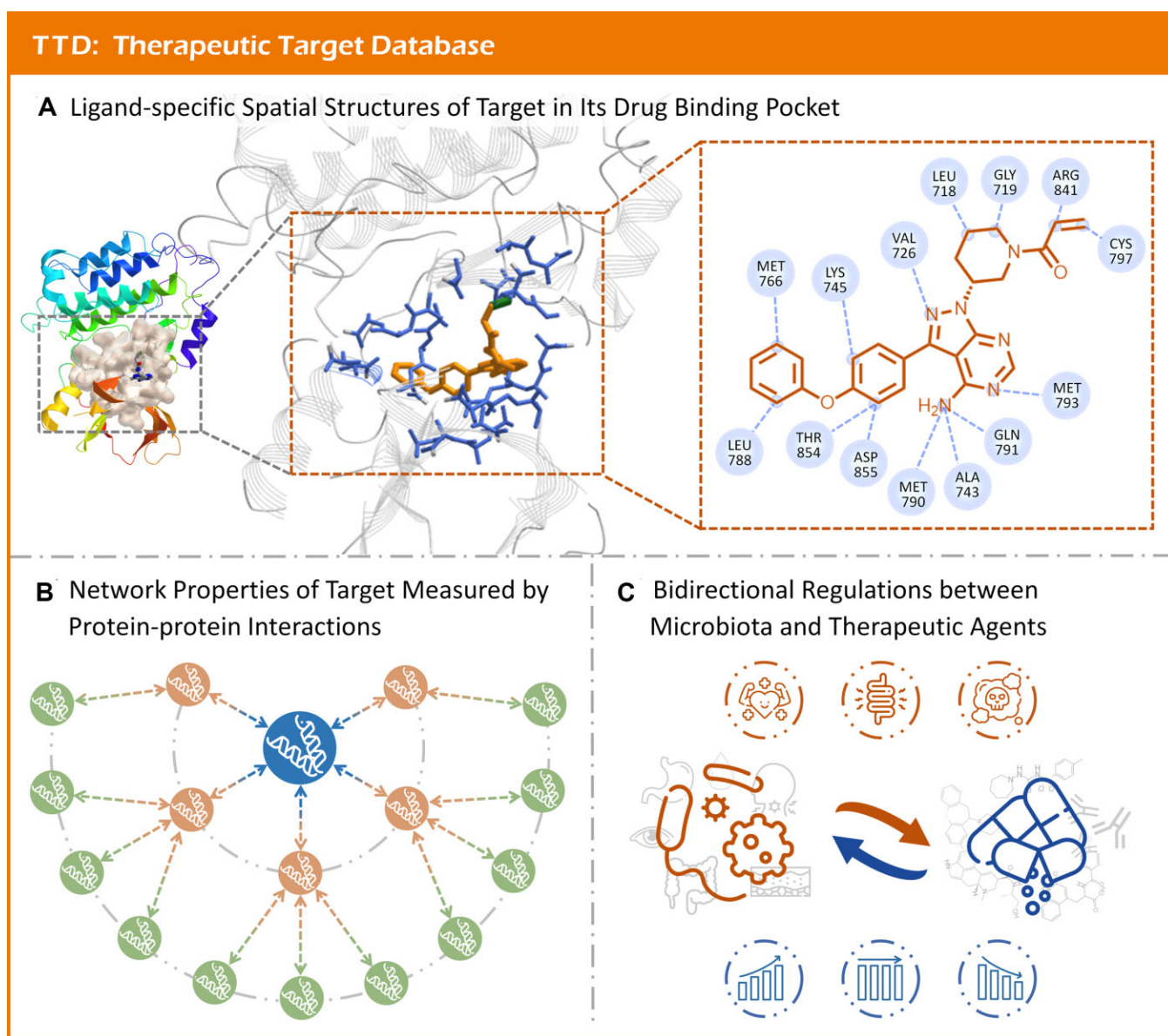
Figure 2. Druggability of therapeutic target illustrated by molecular interactions and regulations. (**A**) *ligand-specific spatial structure of targets in their drug binding pocket*. The crystal structures complexed with ligands were comprehensively collected for a target, and the residues interacting with drugs at a distance of <5 Å were defined as drug binding pockets and highlighted using their van der Waals surface for each complex. (**B**) *network properties of target measured using protein-protein interactions*. The human protein-protein interaction network consisting of 9309 proteins and 52 713 interactions was constructed based on the STRING data with confidence score ≥0.95, and diverse network descriptors (degree, connectivity, *etc.*) were calculated for each target based on PPI network. (**C**) *bidirectional regulations between microbiota and therapeutic agents*. On the one hand, microbiota in diverse human tissue or organs (eye, lung, oral cavity, *etc.*) can alter the bioavailability, bioactivity, and toxicity of therapeutic agent; on the other hand, therapeutic agent can also change the abundance and composition of microbiota.

ied target should be life-essential for both healthy individuals and patients, and (*Cb*) the studied targets should occupy an upstream position in pathway, and thus are capable of regulating biological function. *Finally*, 241 life-essential pathways were included. For a target, all affiliated pathways were integrated to online TTD with the detailed data of pathway hierarchy. Moreover, other targets that belonged to the same pathway were also fully described. All in all, a variety of target-affiliating life-essential pathway data were made available for 373 successful, 897 clinical trial, 196 preclinical/patented, and 1415 literature-reported targets in TTD 2024.

Distributions of target among a variety of tissues or organs in human

The distribution of targets among different tissues/organs needs to be carefully considered, when assessing the target druggability, as it is widely known that the wider the target distributions, the greater the concern over adverse drug reaction (1,56). A previous study on the distribution of 158 successful targets identified that over 50% of these targets were distributed in no more than three tissues, indicating the significance of tissue selectivity in target discovery (48).
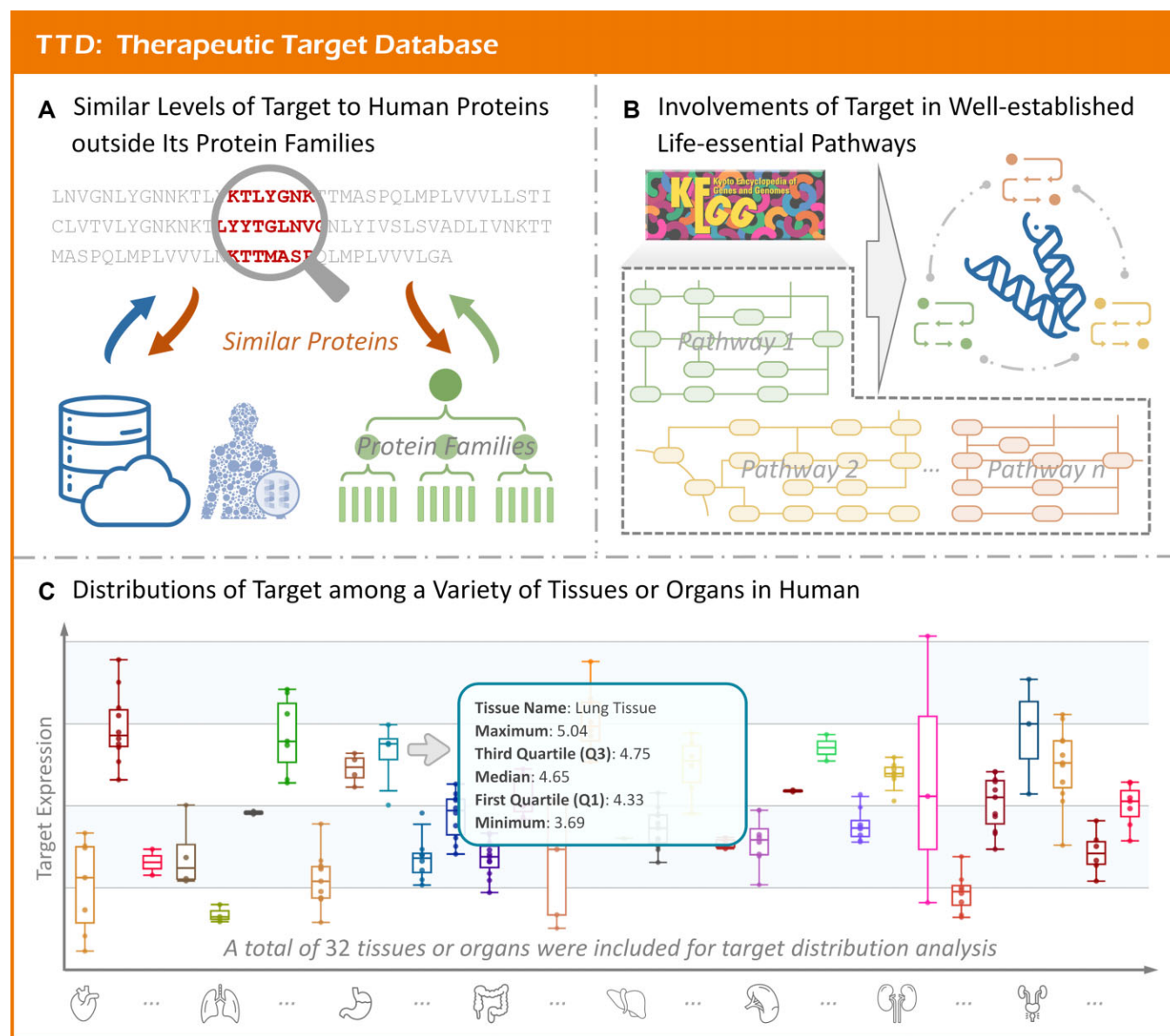
Figure 3. Druggability of therapeutic targets illustrated by human system features. (**A**) *Similarity profile of target to human proteins outside its family.* The degree of similarity between target and all human proteins was calculated using BLAST, and the cutoff of *E*-values was set to 0.005 (the similar proteins of targets were defined as those with *E*-value <0.005 and outside those functional families of the targets). (**B**) *Involvements of target in the well-established life-essential pathways.* All life-essential pathways involved by a target were described on the TTD website with detailed information provided, such as the name, hierarchy & map of, and other targets belonging to these pathways. (**C**) *Distributions of target among a variety of tissues/organs in human.* The expressions of studied target across different tissues/organs were provided in the boxplot format, and detailed data (such as tissue name and various statistic values describing the boxplot) were specified.

Considering the substantial discordance in target's expression at the levels of proteins and RNAs (57), the distributions of TTD targets among various tissues/organs were determined. A landmark study that quantified over 12 000 genes across 32 normal human tissues at both protein and RNA levels was adopted to fulfill our research needs (57). For a target, the relative expressions among tissues/organs were provided, which were displayed in boxplot format together with the detailed abundances (Figure 3C). As a result, the distributions across 32 human tissues of 338 successful, 600 clinical trial, 143 preclinical/patented and 920 literature-reported targets were provided.

Druggability reflected by *diverse cell-based expression variations*

Varied expressions of target across different cells of diverse diseases

Recent studies had indicated that the heterogeneity among cell types could result in distinct drug responses (58). For instance, FGFR2-amplified gastric cancer cell lines (KatoIII & SNU16) were sensitive to AZD4547 (an FGFR2 inhibitor), while those without FGFR2 amplification (AGS & SNU1) were reported insensitive to AZD4547 (59). In other words, understanding the pattern of target expression among cell types is essential for the selection of representative cell line models and the un-

derstanding of the mechanism underlying drug response or resistance (60–64).

Such expression pattern among different cell lines were collected using the following procedure. *First*, an exhaustive review was carried out in GEO (65) & Expression Atlas (66) employing the keyword combinations of 'cell line + expression', 'cell type + expression', 'cell line + differential expression', *etc.* This approach generated a total of 226 datasets containing the expression profile of thousands of proteins across cell lines. *Second*, detailed information for each dataset, including cell type, disease, *etc.*, was meticulously recorded, which resulted in a total of 1742 types of cell lines from 7289 samples, spanning 121 disease classes as defined by the WHO ICD-11 (such as tuberculosis, skin cancer, allergic rhinitis, and ulcerative colitis). *Third*, various OMIC data types were processed independently. For microarray data, the original *CEL* files were downloaded and processed using the RMA function in *oligo* package (67) to calculate the gene expression matrix; for RNA-seq data, the raw count data were normalized using *DESeq2* package (68). For a studied target, its varying expression levels across diverse cell types were visually represented (as shown in Figure 4A). In summary, varying expressions across various cell types for 347 successful, 939 clinical trial, 188 preclinical/patented, and 1371 literature-reported targets were provided.

Differential expressions of target induced by many exogenous causes

Different cell types manifest diverse perturbation signals in response to exogenous stimuli, such as drug administration (69). For the same stimulus (such as particular kinase inhibitor), a variety of cell lines were reported to be phenotypically responsive, but the transcriptomic profiles among these cell lines after the stimulation (such as the treatment by kinase inhibitor) were identified to be extremely different (70). Such perturbation signals were valuable for providing novel insights into understanding drug mechanisms of action and identifying potential drug targets (70–73).

The target's expression profiles induced by exogenous stimuli were collected and provided using the following procedure. *First*, the differential expression data induced by exogenous cause were retrieved from GEO (65) & Expression Atlas (66) using the keyword combination of 'cell line + drug', 'cell line + exogenous causes', 'cell line + therapy', 'cell line + environment', *etc. Second*, all retrieved datasets were carefully examined, and the detailed exogenous stimuli were recorded, which were classified into three groups: *treatment with drugs*, *infection by bacterium/virus* and *stimulation by environmental factors*. Moreover, the explicit description of each dataset was also provided, which included cell line, disease, perturbation factor, *etc. Third*, different OMIC-based data types were processed independently. For microarray data, the *CEL* files were processed with the RMA function of *oligo* package (67) to normalize expression matrix; for RNA-seq data, raw count data were normalized using *DESeq2* package (68). *Finally*, the cell line-specific expression profile was shown in TTD using violin plots for any studied target (shown in Figure 4B). All in all, a total of 625 exogenous stimuli (hypoxia, interferon treatment, influenza infection, *etc.*) that modified the expression profiles of 357 successful, 926 clinical trial, 197 preclinical/patented & 1382 literature-reported targets among 313 cell lines were made available in TTD 2024.

Modified expressions of target altered by human endogenous factors

Given that a gene can play distinct roles in different contexts, particularly where the cell-specific function is involved, human endogenous gene perturbation (mutation, expression variation, *etc.*) is considered as a powerful way to explore target functions under different cell contexts (74–77). In other words, cell line-specific gene perturbations are valuable for understanding the molecular mechanism underlying target differential expression among cell lines, which can help to identify new cell-specific functions, protein-protein interactions and regulatory cascades (78–81).

Such target's expressions regulated by endogenous factors were collected based on the following procedure. *First*, the GEO (65) & Expression Atlas (66) were manually reviewed to retrieve gene expression data altered by diverse human endogenous factors, which included protein mutations, expression variations, *etc. Second*, detailed information of each dataset (such as cell line, disease, and human endogenous factor) was meticulously extracted, which resulted in over 400 types of human endogenous factors (such as KRAS mutation, and MYC over-expression), and the factor-induced expression variation was also illustrated in Figure 4C. The process and normalization of OMIC-based raw data were conducted by following the same procedure as that was discussed in the above two sections. All in all, the expression profile of 352 successful, 934 clinical trial, 192 preclinical/patented, and 1363 literature-reported targets among 198 cell lines were provided.

Regular update on the drug & target data and diverse functions

The integration of newly emerged drugs and targets to TTD was also routinely conducted in this update. *First*, the drugs approved during the past two years were collected from two authoritative publications (82,83). *Second*, new drugs in clinical trials were collected from various established resources, such as ClinicalTrials.gov, PhRMA medicines in development reports, and numerous *Drug Pipeline Reports* of >200 companies (such as *Pfizer*, *Roche*, *Sanofi* and *GlaxoSmithKline*). *Third*, the trial status of drugs available in TTD were continuously updated using the timely data provided in ClinicalTrials.gov, company's official reports, *etc. Fourth*, the preclinical and patented drugs were collected from diverse data sources, such as company's pipeline reports, large number of patents authorized by the patent offices of many countries, and recent literature reports.

For each of the collected drugs, its corresponding therapeutic target(s) was *further* validated by following a routine process that showed the functional roles of the target(s) in disease phenotype and the ability of drug-like molecule to modulate the activities of the target to achieve therapeutic efficacies (84). *Finally*, the status of each therapeutic target was determined based on the highest status of its corresponding drugs, which were then classified to successful target (approved drug), clinical trial target (clinical trial drug), preclinical target (drug in preclinical trial), patented target (drug protected by the authorized patent), and literature-reported target (investigative agent). As a result (provided in Table 1), a total of 3730 targets and 39 862 drugs were finally provided in TTD 2024 and the total numbers of drugs and their corresponding therapeutic targets in different versions of TTD over the past decade was also described.
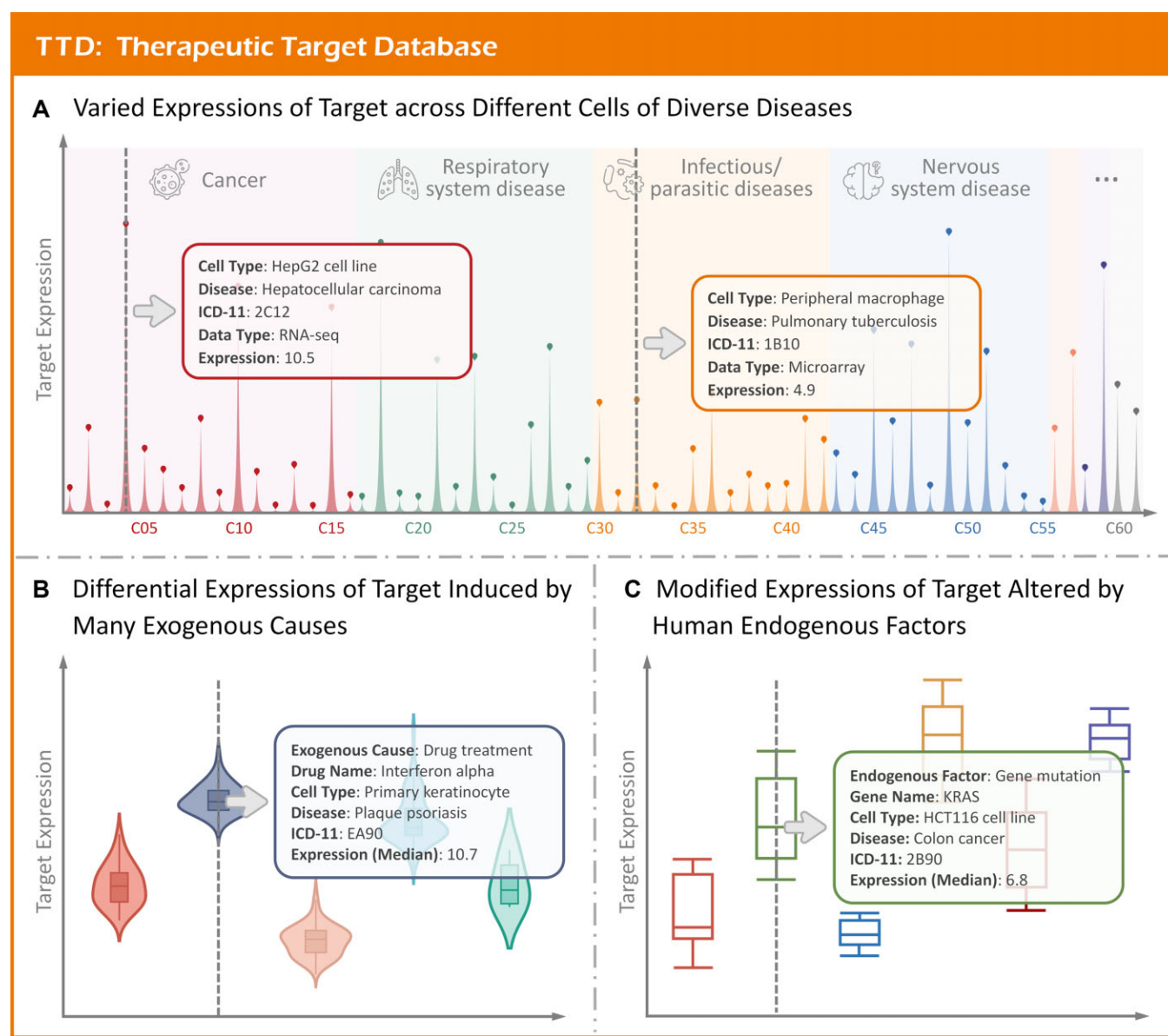
Figure 4. Targets' druggability showed by cell-based expression variation. (**A**) *Varied expressions of target across different cells of diverse diseases*. Targets' expression data for different cell types in normal and untreated conditions were collected and illustrated by pictorial bar chart, and 1742 cell types from 7289 experimental samples were reported, which covered several (a total of 121) disease classes (such as skin cancers, tuberculosis, allergic rhinitis, and ulcerative colitis) defined by ICD-11. (**B**) *Differential expressions of a target induced by exogenous stimuli*. Cell type-based differential expressions of targets induced by exogenous causes (a total of 625 exogenous causes, such as interferon treatment, influenza infection and hypoxia) among 313 cell types were shown. (**C**) *modified expressions of a target altered by human endogenous factor*. Cell type-based target's expression modifications mediated by exogenous causes (a total of 447 endogenous factors, such as KRAS mutation and MYC over-expression) among 198 cell types were explicitly described.

Moreover, a '*batch search*' function allowing the upload of a list of TTD drug IDs or Target IDs was implemented to the TTD 2024 (https://db.idrblab.net/ttd/ttd-search/batch-search), and a '*full download*' function of all search results was also realized by simply clicking the '*Download the Search Results*' button. Such functions could be very helpful to broad audiences, especially those pharmacologically inclined users. It should be noted that, although it was technically feasible to implement the search function based on multiple types of entries other that drug/target IDs (such as drug/target name/synonyms), that function could have substantial chance to return many false positive search results, which had therefore not been made available in TTD 2024 yet.

Conclusion and perspectives

Identification and validation of therapeutic targets is one of the critical steps in drug development (85). Insufficient analysis of target druggability in the early stage of drug discovery remains one of the key issues of high drug attrition rates, which should therefore be systematically considered and carefully assessed (86). Taking a recent study as an example (9), it identified several essential features of target druggability (such as '*distribution of target among various tissues or organs in human*', '*similarity profile of target to human proteins outside its family*', '*involvements of target in well-established life-essential pathways*' and two

Table 2. Three major contents and their corresponding statistics integrated to this version of TTD, which included: target druggability illustrated by molecular interactions or regulations, characterized by different human system features and reflected by diverse cell-based expression variations

Target druggability illustrated by molecular interactions or regulations					
☆ *Ligand-specific spatial structures of target in its drug binding pocket*					
No. of targets with drug binding sites information				No. of ligands	No. of structures
Successful	Clinical trial	Preclinical/patent	Literature-reported		
319	427	116	375	16373	22431
☆ *Network properties of target measured by protein–protein interactions*					
No. of targets with protein–protein interaction information				No. of Interacting Protein	No. of protein–protein interactions
Successful	Clinical trial	Preclinical/patent	Literature-reported		
426	727	143	867	9309	52713
☆ *Bidirectional regulations between microbiota and therapeutic agents*					
No. of microbe(s) affecting the metabolism of drugs				No. of drugs	No. of microbe and drug interactions
Order	Family	Genus	Species		
59	101	135	194	663	9812
Target druggability characterized by different human system features					
☆ *Similarity profile of target to human proteins outside its amily*					
No. of targets with human similarity proteins outside the target families				No. of similarity proteins	No. of protein families
Successful	Clinical trial	Preclinical/patent	Literature-reported		
389	933	204	1479	3128	1004
☆ *Involvements of target in the well-established life-essential pathways*					
No. of targets with affiliated life-essential pathways information				No. of life-essential pathways	No. of targets with only one pathway
Successful	Clinical trial	Preclinical/patent	Literature-reported		
373	897	196	1415	241	679
☆ *Distributions of target among a variety of tissues or organs in human*					
No. of targets with human tissues or organs distribution information				No. of tissues/organs	No. of experimental samples
Successful	Clinical trial	Preclinical/patent	Literature-reported		
338	600	143	920	32	201
Target druggability reflected by diverse cell-based expression variations					
☆ *Varied expressions of target across different cells of diverse diseases*					
No. of targets with varied expressions across different cell types				No. of cell types	No. of disease classes
Successful	Clinical trial	Preclinical/patent	Literature-reported		
347	939	188	1371	1742	121
☆ *Differential expressions of target induced by many exogenous causes*					
No. of targets with differential expressions induced by exogenous causes				No. of cell types	No. of exogenous causes
Successful	Clinical trial	Preclinical/patent	Literature-reported		
357	926	197	1382	313	625
☆ *Modified expressions of target altered by human endogenous factors*					
No. of targets with modified expressions altered by endogenous factors				No. of cell types	No. of endogenous factors
Successful	Clinical trial	Preclinical/patent	Literature-reported		
352	934	192	1363	198	447

'*network properties of target measured by PPIs*') from 89 successful targets. These features were reported to denote the difference between the targets of rapid and slow clinical progression processes. In the TTD 2024, all those 'essential features' of target druggability were collected and significantly extended to 426 successful, 1014 clinical trial, 212 preclinical/patented, and 1479 literature-reported therapeutic targets. All in all, the valuable data on target druggability provided in TTD 2024 (as described in Table 2) together with the future updates of established databases were essential in facilitating the explorations of the druggability characteristics of targets for guiding target and drug discovery.

TTD has been committing to provide comprehensive data on therapeutic targets to facilitate new drug and target discovery. Since the beginning of the 21st century, it has undergone many updates (16,87–89) and accumulated worldwide impacts during the past twenty years. Particularly, there were many online tools that adopted TTD data for server development. Some of them used TTD data to establish servers facilitating drug repurposing, such as *LigAdvisor* (90) & *DrugRep* (91); discovery of drug/target, such as *CoVex*

(92) & *DeepCancerMap* (93); prediction of adverse drug reaction/synergistic combination, such as *MEDICASCY* (94) & *H-RACS* (95); compound-based functional enrichments, such as *MBROLE3* (96) & *MMEASE* (97). Moreover, TTD information has also been adopted by recent studies to promote various scientific discoveries. Some identified the association between genetic variant and disease (98–103); some others revealed the molecular characteristics crucial in virus infection (104), target variability key in determining drug response (62), and target promising in discovering antifungal therapy (105). With the rapid progression of modern technology and concerted effort in current drug discovery, the wealth of data amassed in TTD and other databases (11–20) over the past decades collectively established solid foundations for the identification of novel targets and the discovery of new therapeutics (98–100).

Data availability

TTD is freely accessible to all users without any login requirement at: https://idrblab.org/ttd/.

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Conflict of interest statement

None declared.

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