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Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics

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ABSTRACT

Knowledge of therapeutic targets and early drug candidates is useful for improved drug discovery. In particular, information about target regulators and the patented therapeutic agents facilitates research regarding druggability, systems pharmacology, new trends, molecular landscapes, and the development of drug discovery tools. To complement other databases, we constructed the *Therapeutic Target Database* (TTD) with expanded information about (i) target-regulating microRNAs and transcription factors, (ii) target-interacting proteins, and (iii) patented agents and their targets (structures and experimental activity values if available), which can be conveniently retrieved and is further enriched with regulatory mechanisms or biochemical classes. We also updated the TTD with the recently released International Classification of Diseases ICD-11 codes and additional sets of successful, clinical trial, and literature-reported targets that emerged since the last update. TTD is accessible at http://bidd.nus.edu.sg/group/ttd/ttd.asp. In case of possible web connectivity issues, two mirror sites of TTD are also constructed (http://db.idrblab.org/ttd/ and http://db.idrblab.net/ttd/).

INTRODUCTION

The efficiency of drug discovery depends critically on the selection of appropriate candidates of therapeutic target (1) and targeted agent (2,3). The investigation and acquired knowledge of these targets and agents are highly useful for accelerating drug discovery processes (4–6). Many open-access databases have provided comprehensive and complementary data of therapeutic targets. These include targets of different classes (7–11), drug-binding domains and targeted sites (12), target expression profiles in patients (13,14), activities of targeted agents (15–17), target-regulators (18–22), target-affiliated pathways (23,24), target–drug interaction networks (25–27), and target–disease associations (28,29). Integration of some of these data with knowledge of genetics, genomics, transcriptomics, animal models and literature enable the scoring and ranking of target–disease associations for target identification (28,29).

The targets of the TTD are validated with clinical evidence of the efficacy targets of the clinically tested drugs or with patent/literature report about the therapeutic targets of research agents. Specifically, the TTD targets are grouped into classes of successful (with at least one approved drug), clinical trial (with a clinical trial drug, but without an approved drug), patent-recorded (referenced in a patent and subsequent literature), and literature-reported targets. Differences in the target selection procedure may render TTD targets that partially differ from other databases. For in-

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stance, the TTD contains 2954 human and 465 infectious species targets, and all of the 2954 human targets, yet none of the 465 infectious species targets, are in the Open Targets Platform, which contains 27 024 targets associated with human diseases (28,29).

Some data content and access facilities, such as target regulators and patented agents, may be further improved. Knowledge of target regulators (e.g. microRNAs, transcription factors and interacting proteins) is useful for drug discovery tasks (Supplementary Table S1) such as the investigations of target druggability (6,30), systems pharmacology (31) and the discovery of multi-target and combination therapies (32,33). The structural and activity data of patented agents are useful for such tasks as the study of discovery landscapes and opportunities (34,35), as well as the development of artificial intelligence tools (36). While target regulators and patented agents can be accessed from several databases (10,11,18–22), the data access facilities are limited because no therapeutic targets or targeted-diseases are explicitly labeled, which makes it difficult for searching data with respect to therapeutic classes and disease areas.

To provide the expanded information and improved data access facilities, several major improvements were made to the Therapeutic Target Database (TTD). The *first* is the inclusion of two classes of target regulators, microRNAs (miRNAs) and transcription factors (TFs), for the successful (approved), clinical trial, patent-recorded and literature-reported targets in the TTD (Figure 1A). The *second* is the addition of the proteins directly interacting with the targets in the TTD (Figure 1A). The *third* is the inclusion of patented therapeutic agents and their targets searched from the patent contents and literature (Figure 1B). The *fourth* is the update of the recently released International Classification of Diseases codes ICD-11 for the targets in the TTD, which facilitates the access of target information using the ICD codes. The *fifth* is the update of the recently emerged targets and drugs since the last update (Table 1), including the previously nonincluded classes of targeted antigens of chimeric antigen receptor T-cell (CAR-T) therapy and small molecular and peptidomimetic inhibitors of immunotherapy targets. The newly added features, together with their statistics, are summarized in Supplementary Table S2.

TARGET REGULATORS

Target-regulating MicroRNAs

MicroRNAs (miRNAs) are reported to negatively regulate the expression of ∼30% of human genes. miRNA has demonstrated profound pharmacological/pharmacokinetic implications in the regulation of therapeutic targets, drug metabolism enzymes or transporters (37). For example, miR-125b inhibits the expression of vitamin D receptor (therapeutic target of the drug calcitriol), which results in the reduced efficacy of calcitriol by a lowered target level (38); another study has shown that the overexpression of miR-24 downregulates dihydrofolate reductase (target of chemotherapeutic drug methotrexate), which induces methotrexate resistance (39). Thus, the information regarding target-regulating miRNAs is helpful for studying the regulation of targeted therapeutics in individual patients (37,40) and exploring multi-target treatment strategies (41).

Since the target-regulating miRNA data were largely dispersed in the literature, the PubMed database was systematically searched using the combination of the keywords 'microRNA'/'micro-RNA'/'mi-RNA'/'miR'/'miRNA'/'hsa-miR'/'hsa-let' and the names/synonyms of TTD targets. The collected data include the following: (i) the names and sequences of mature miRNAs and (ii) the experiments confirming the regulation of a studied target by certain miRNAs. The collected experiments include reporter assay, quantitative polymerase chain reaction (qPCR), *in situ* hybridization, northern blot, and so on (42,43). Some of the above experiments (e.g. western blot and reporter assay) are typically applied methods for discovering protein-regulating miRNAs, and some methods (e.g. qPCR, *in situ* hybridization and northern blot) have been frequently used to identify miRNAs coexpressed with the genes of therapeutic targets (42–45). These literature-reported regulation mechanisms are provided in the TTD.

The latest version of the TTD collected 179 successful, 298 clinical trial, 62 patent-recorded and 330 literature-reported targets that are regulated by 587 miRNAs, involving 3707 miRNA and target regulation pairs. The confidence level of an experimentally observed regulation can be tentatively measured by the number of published experimental sources of evidence (46,47). Thus, an evidence score (*E-score*, the number of published research articles of experimental evidence) was defined for the tentative measurement of the confidence level of target-regulating miRNAs. The target-regulating miRNAs are listed with respect to their *E-scores*. A typical webpage providing the target-regulating miRNA is shown in Figure 2.

Target-regulating transcription factors

Transcription factors (TFs) regulate the expression of genes by controlling transcription of genetic information from DNA to messenger RNA. TFs that regulate the therapeutically relevant genes have been explored as the targets of approved drugs (48). For example, both premarin (for treating osteoporosis) and tamoxifen (for treating breast cancer) target the transcription factor estrogen receptor (ER), which regulates the expression of estrogen-responsive genes that control both osteoporosis and breast cancer, thereby manifesting their osteoporosis-preventive and anticancer effects (48). Although many TFs are important disease regulators, and thus potential therapeutic targets, many of them have been considered to be undruggable, partly owing to the large protein–protein interaction interfaces or lack of deep protein pockets for small molecule drug binding (49). Progress has been made for drug discovery against the targets previously considered to be undruggable (50). Thus, it is useful to provide the data with respect to target-regulating TFs for facilitating future efforts in targeting TFs.

Target-regulating TF data were collected by comprehensively searching the PubMed database using the combinations of the keywords 'transcription factor'/'TF'/'DNA-binding factor'/'DNA-binding'/'transcription regulation'/'promoter'/'enhancer'/'silencer' and

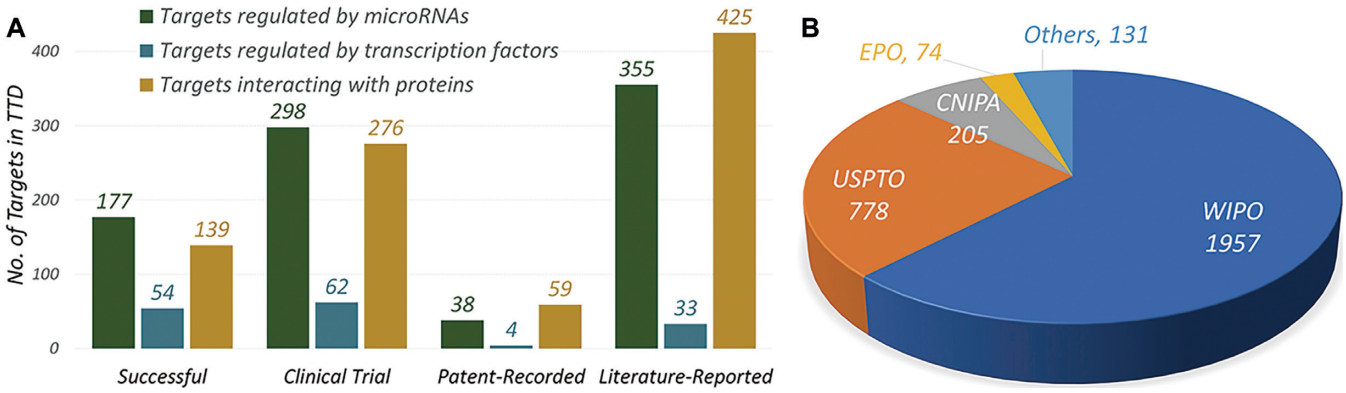


Figure 1. The statistics of the features newly added to the 2020 version of the TTD. (**A**) The inclusion of two classes of target regulators (microRNAs and transcription factors) and the addition of the proteins directly interacting with the targets; (**B**) the inclusion of patented therapeutic agents and their targets searched from the patent contents and literature.

Table 1. Accumulation of drugs and their corresponding targets in the latest version and previous versions of the TTD

	2020	2018	2016	2014	2012		2020	2018	2016	2014	2012
All Targets	**3419**	**3101**	**2589**	**2316**	**1981**	**All Drugs**	**37 316**	**29 570**	**27 165**	**20 006**	**17 816**
Successful	461	445	397	388	364	Approved	2649	2544	2071	2003	1540
Clinical Trial	1191	1121	723	461	286	Clinical Trial	9465	8103	7291	3147	1423
Patent-Recorded	207	0	0	0	0	Patented	5,059	0	0	0	0
Literature-Reported	1560	1535	1469	1467	1331	Experimental	20 143	18 923	17 803	14 856	14 853

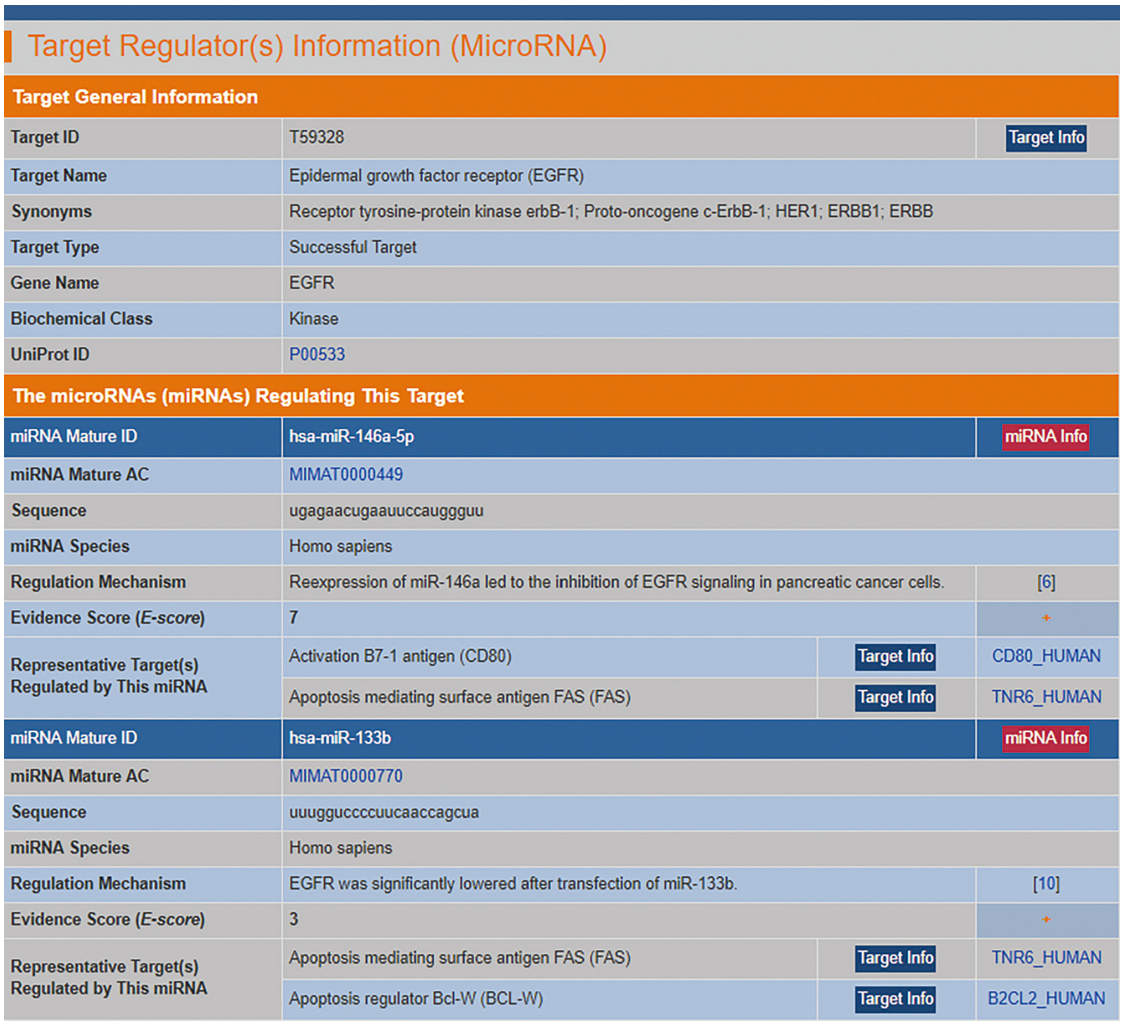
Patented drugs and their corresponding targets were, for the first time, collected and integrated into this version of the TTD.

names/synonyms of each therapeutic target in the TTD. In total, 55 successful, 61 clinical trial, 6 patent-recorded and 31 literature-reported targets regulated by 135 TFs were collected. These collected data include the following: (i) the names and sequences of TFs regulating each target, (ii) TF classifications (superclass, class, family and subfamily) defined by TRANSFAC (51,52) and (iii) the experiments used to confirm the regulation of a studied target by TFs. These experiments include electrophoretic mobility shift assays (53), chromatin immunoprecipitations (54), DNase footprinting assays (55), and so on. They have been used for probing the direct binding of a TF to the promoter, enhancer or silencer region of a target gene, thus leading to the initiation (56), increase (57) or repression of the transcription of the studied gene (58), respectively. These literature-reported regulation mechanisms are provided in the TTD. The target-regulating TFs are listed in the TTD with respect to their *E-scores*, which were derived using the numbers of papers describing the experimental evidence. Moreover, the genes coregulated by each target-regulating TF are provided in the TTD and grouped by biochemical class (Figure 3).

TARGET-INTERACTING PROTEINS

Knowledge of target-protein interactions is important for network pharmacology studies (59) and target druggability assessments (60,61). Particularly, the analysis of the human target-protein network topological properties (derived from the human target-protein interaction data) has revealed that successful targets are more highly connected to other proteins and have higher network betweenness (the number of times a studied protein appears in the shortest path between two other proteins in network divided by the total number of protein pairs) than other proteins (60); the human target-protein network topological features and human systems druggability characteristics of 89 innovative targets of the first-in-class drugs approved from 2004 to 2017 have led to a simple rule describing the clinical trial progression speed of innovative drug targets (50), which states that the human target entering clinical trials may progress more speedily through the trials if it has no violations of the following criteria: (i) two human target-protein network topological properties are within specified values (neighborhood connectivity <15 and degree <15) and (ii) three system druggability properties are within specified ranges (affiliated with <5 human signal pathways, distributed in <5 human tissues and similar to <15 human similarity proteins outside the target family) (50). The degree is the total number of interacting proteins of a given target, and neighborhood connectivity of a given target denotes the average number of human interacting proteins of its own neighbors/interacting proteins. These and other studies have shown that the target-interacting protein information is essential for facilitating the pharmacological, druggability and clinical investigations of therapeutic targets.

The target-interacting protein data were collected from *BioGrid*, which provides experimentally documented human protein physical interactions (62) based on evidence from such experimental methods as affinity capture-western blotting, colocalization studies, yeast two-hybrid screens, fluorescence resonance energy transfer, protein-fragment complementation assays, reconstituted complexes, far western blotting, proximity label-MS, and so on. Only the target-interacting proteins validated by no less than two experiments were collected, and the numbers of papers de-



Target Regulator(s) Information (MicroRNA)

Target General Information			
Target ID	T59328		Target Info
Target Name	Epidermal growth factor receptor (EGFR)		
Synonyms	Receptor tyrosine-protein kinase erbB-1; Proto-oncogene c-ErbB-1; HER1; ERBB1; ERBB		
Target Type	Successful Target		
Gene Name	EGFR		
Biochemical Class	Kinase		
UniProt ID	P00533		
The microRNAs (miRNAs) Regulating This Target			
miRNA Mature ID	hsa-miR-146a-5p		miRNA Info
miRNA Mature AC	MIMAT0000449		
Sequence	ugagaacugaauuccauggguu		
miRNA Species	Homo sapiens		
Regulation Mechanism	Reexpression of miR-146a led to the inhibition of EGFR signaling in pancreatic cancer cells.		[6]
Evidence Score (*E-score*)	7		+
Representative Target(s) Regulated by This miRNA	Activation B7-1 antigen (CD80)	Target Info	CD80_HUMAN
	Apoptosis mediating surface antigen FAS (FAS)	Target Info	TNR6_HUMAN
miRNA Mature ID	hsa-miR-133b		miRNA Info
miRNA Mature AC	MIMAT0000770		
Sequence	uuuggucccuucaaccagcua		
miRNA Species	Homo sapiens		
Regulation Mechanism	EGFR was significantly lowered after transfection of miR-133b.		[10]
Evidence Score (*E-score*)	3		+
Representative Target(s) Regulated by This miRNA	Apoptosis mediating surface antigen FAS (FAS)	Target Info	TNR6_HUMAN
	Apoptosis regulator Bcl-W (BCL-W)	Target Info	B2CL2_HUMAN

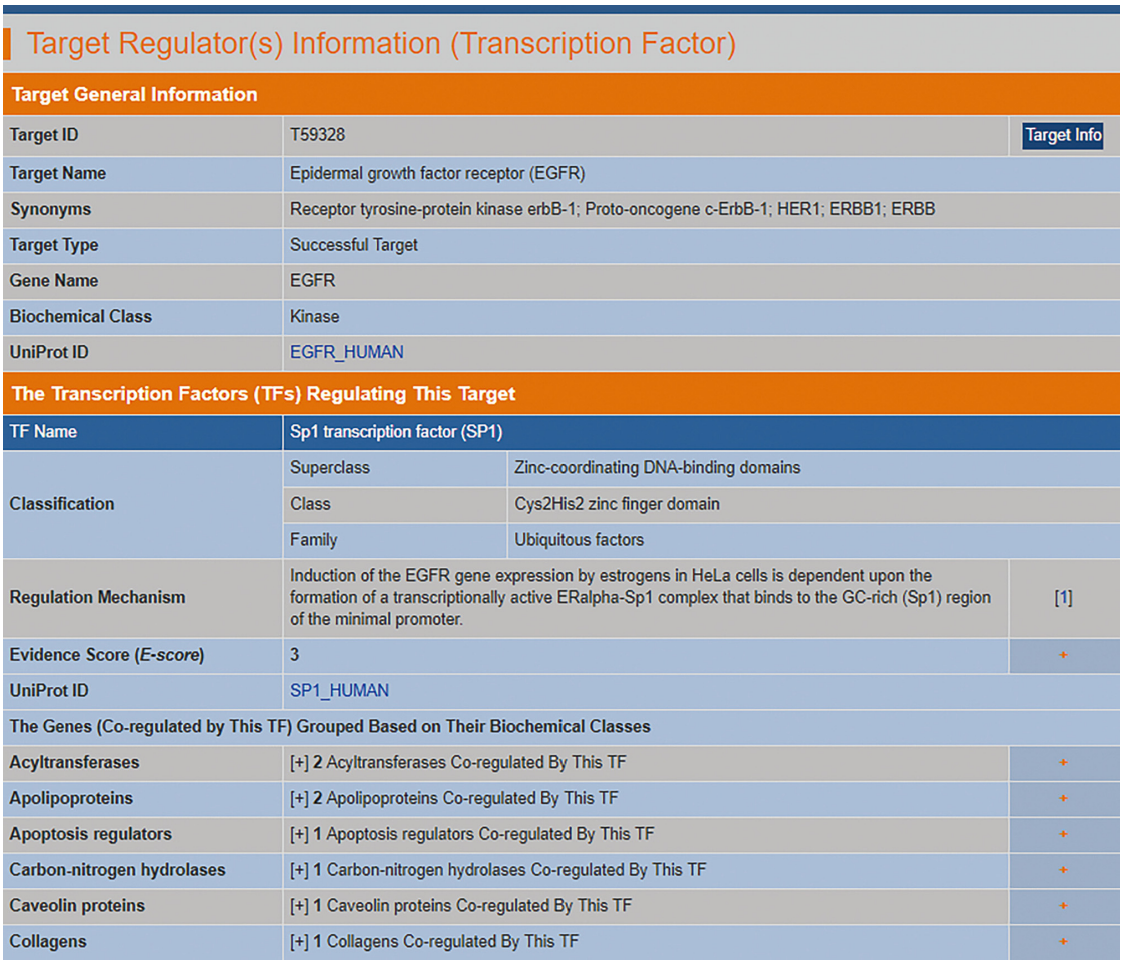
Figure 2. A typical page in the TTD providing target-regulating microRNA information. The detailed information on microRNA sequences, supporting experiments, and other targets regulated by the collected microRNA. The target-regulating microRNAs are listed on the TTD webpage with respect to the *E-scores*, which were derived using the number of papers describing the experimental evidence. The details of each microRNA can be found by clicking the 'miRNA Info' button.

scribing the experimental evidence were directly used as the evidence score (*E-score*). Overall, there are 139 successful, 276 clinical trial, 86 patent-recorded and 398 literature-reported targets with 2458 interacting proteins in the TTD, involving 6975 pairs of target-protein interactions. Moreover, due to the high number of target-interacting proteins (32.8% of the targets in the TTD interact with >10 proteins), it was difficult to produce a complete interaction profile of a target by simply crosslinking to other protein interaction databases. Thus, the target-interacting proteins are provided in groups of biochemical classes (GPCR, peptidase, virus penetration channel, etc.) on the webpage (Figure 4), and the target-interacting proteins within each class are listed with respect to their *E-scores*.

PATENTED THERAPEUTIC AGENTS AND THEIR TARGETS

Patented therapeutic agents represent special classes of bioactive molecules in the stage of early drug discovery. These agents differ from other bioactive molecules with respect to the perception of high development potential by drug developers, which makes them good indicators of drug development trends, emerging/evolving molecular landscapes and collaborative opportunities in the early developmental stage (34,35). Thus, there is a particular need for expanding the coverage of the target and drug data to cover the patented therapeutic agents and their targets. The targets of patented therapeutic agents are referred to here as the patent-recorded targets.

The patented therapeutic agents and their corresponding targets were searched and processed by the following procedure: *first*, all papers published during the period of 2004–2018 in *Expert Opinion on Therapeutic Patents* were manually reviewed; *second*, those key data describing the collected agents together with their targets were recorded, which included the following: (i) the title, abstract, applicants, issued ID and patent agency, (ii) potential therapeutic indications, 3D structures, and compound classes of patented agents and (iii) experimental binding activi-



Target Regulator(s) Information (Transcription Factor)

Target General Information		
Target ID	T59328	Target Info
Target Name	Epidermal growth factor receptor (EGFR)	
Synonyms	Receptor tyrosine-protein kinase erbB-1; Proto-oncogene c-ErbB-1; HER1; ERBB1; ERBB	
Target Type	Successful Target	
Gene Name	EGFR	
Biochemical Class	Kinase	
UniProt ID	EGFR_HUMAN	

The Transcription Factors (TFs) Regulating This Target			
TF Name	Sp1 transcription factor (SP1)		
Classification	Superclass	Zinc-coordinating DNA-binding domains	
	Class	Cys2His2 zinc finger domain	
	Family	Ubiquitous factors	
Regulation Mechanism	Induction of the EGFR gene expression by estrogens in HeLa cells is dependent upon the formation of a transcriptionally active ERalpha-Sp1 complex that binds to the GC-rich (Sp1) region of the minimal promoter.		[1]
Evidence Score (*E-score*)	3		+
UniProt ID	SP1_HUMAN		
The Genes (Co-regulated by This TF) Grouped Based on Their Biochemical Classes			
Acyltransferases	[+] 2 Acyltransferases Co-regulated By This TF		+
Apolipoproteins	[+] 2 Apolipoproteins Co-regulated By This TF		+
Apoptosis regulators	[+] 1 Apoptosis regulators Co-regulated By This TF		+
Carbon-nitrogen hydrolases	[+] 1 Carbon-nitrogen hydrolases Co-regulated By This TF		+
Caveolin proteins	[+] 1 Caveolin proteins Co-regulated By This TF		+
Collagens	[+] 1 Collagens Co-regulated By This TF		+

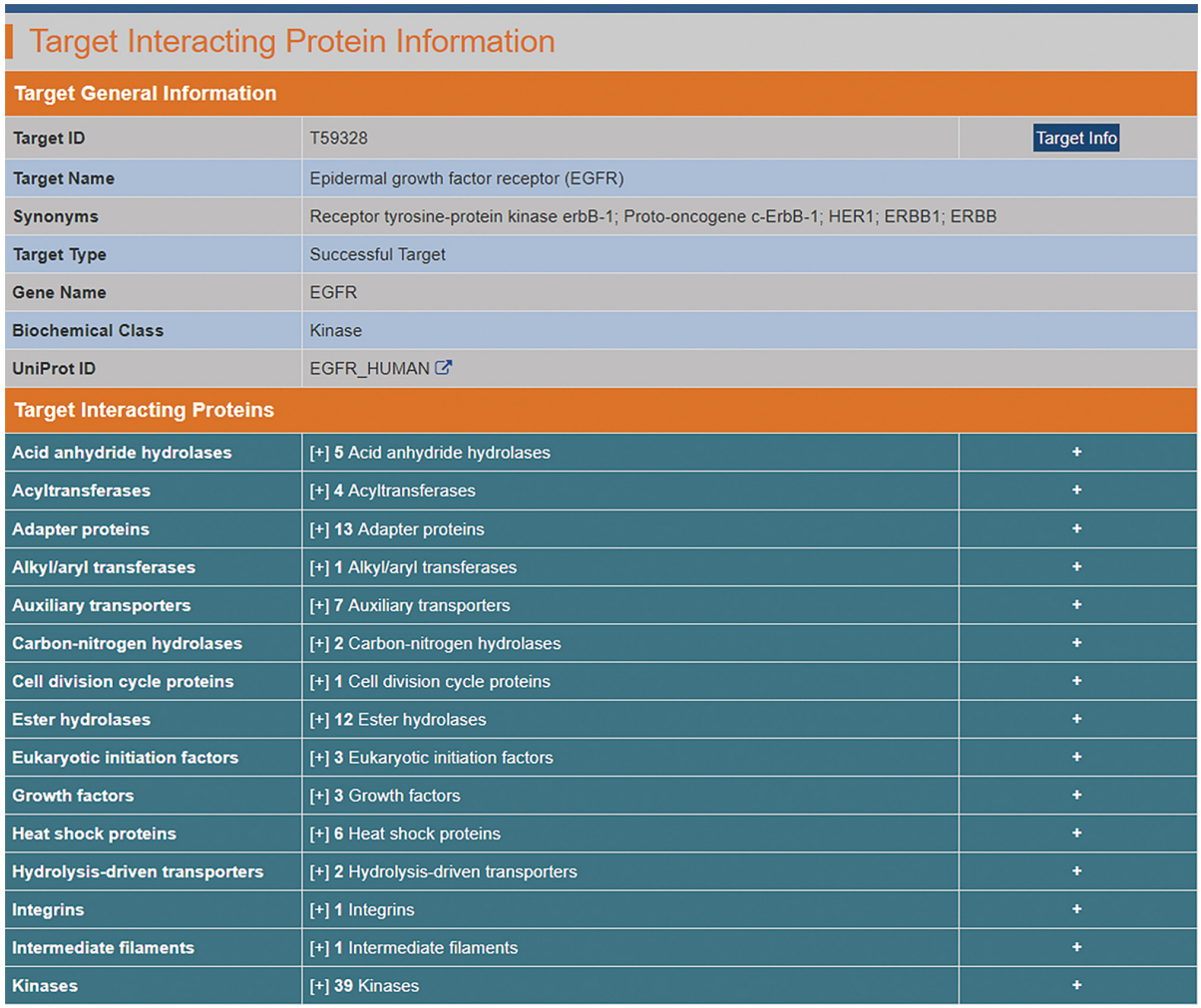
Figure 3. A typical page in the TTD providing information about target-regulating transcription factors (TFs). The target-regulating TFs are listed on the TTD webpage with respect to their *E-scores*, which were derived using the number of papers describing the experimental evidence. The genes coregulated by each target-regulating TF are provided in the TTD and grouped using biochemical classes (GPCR, peptidase, virus penetration channel, *etc.*).

ties (if available) between patented agents and their corresponding targets. In total, 5059 patented agents (belonging to 571 compound classes) included in 3145 patents issued by very diverse intellectual property authorities (World Intellectual Property Organization, United States Patent and Trademark Office, European Patent Office, National Intellectual Property Administration of China, etc.) were collected. Based on a fingerprint-based *Tanimoto* search, 86.7% of the patented agents collected in the TTD are different from, and 85.4% of the agents are of remote to intermediate similarity to, the patented agents in the databases with explicit target data (17). Therefore, the TTD complements the available database in collectively providing comprehensive information about the patented agents.

The TTD patented agents target 215 successful, 236 clinical trial and 207 patent-recorded targets. Among those patented agents, 4774 include 2D/3D structures provided in corresponding papers. These structures are manually drawn using *ChemDraw* (63) and can be viewed and downloaded from the TTD. Moreover, 3388 of the 5,059 agents include experimental target binding activity data and 2215 of the 5059 agents were mapped with PubChem IDs (11) according to a structural search (*Tanimoto coefficient* (64) between molecular fingerprints equals to one) and a subsequent visual inspection of all matches. The remaining nonmatched agents were not found in PubChem. A typical webpage of the patented agents in the TTD is shown in Figure 5.

THE INTERNATIONAL CLASSIFICATION OF DISEASE ICD-11 CODES

The International Classification of Diseases (ICD) is a health statistics and diagnostics coding tool for describing human disease conditions (65), and it has been applied to other applications such as the development of artificial intelligence diagnostic tools (66). The 11th revision of ICD (ICD-11) launched in 2018 (65), which accomplished substantial improvement upon its previous version (ICD-10), with 55 000 unique codes compared with 14 400 for ICD-10. In addition to the more detailed description of the disease conditions, there are significant changes in the coding system. These include new code chapters for sexual health and traditional medicines, stroke being listed as a neurological disorder instead of a circulatory disorder, allergies being



Target Interacting Protein Information

Target General Information		
Target ID	T59328	Target Info
Target Name	Epidermal growth factor receptor (EGFR)	
Synonyms	Receptor tyrosine-protein kinase erbB-1; Proto-oncogene c-ErbB-1; HER1; ERBB1; ERBB	
Target Type	Successful Target	
Gene Name	EGFR	
Biochemical Class	Kinase	
UniProt ID	EGFR_HUMAN	

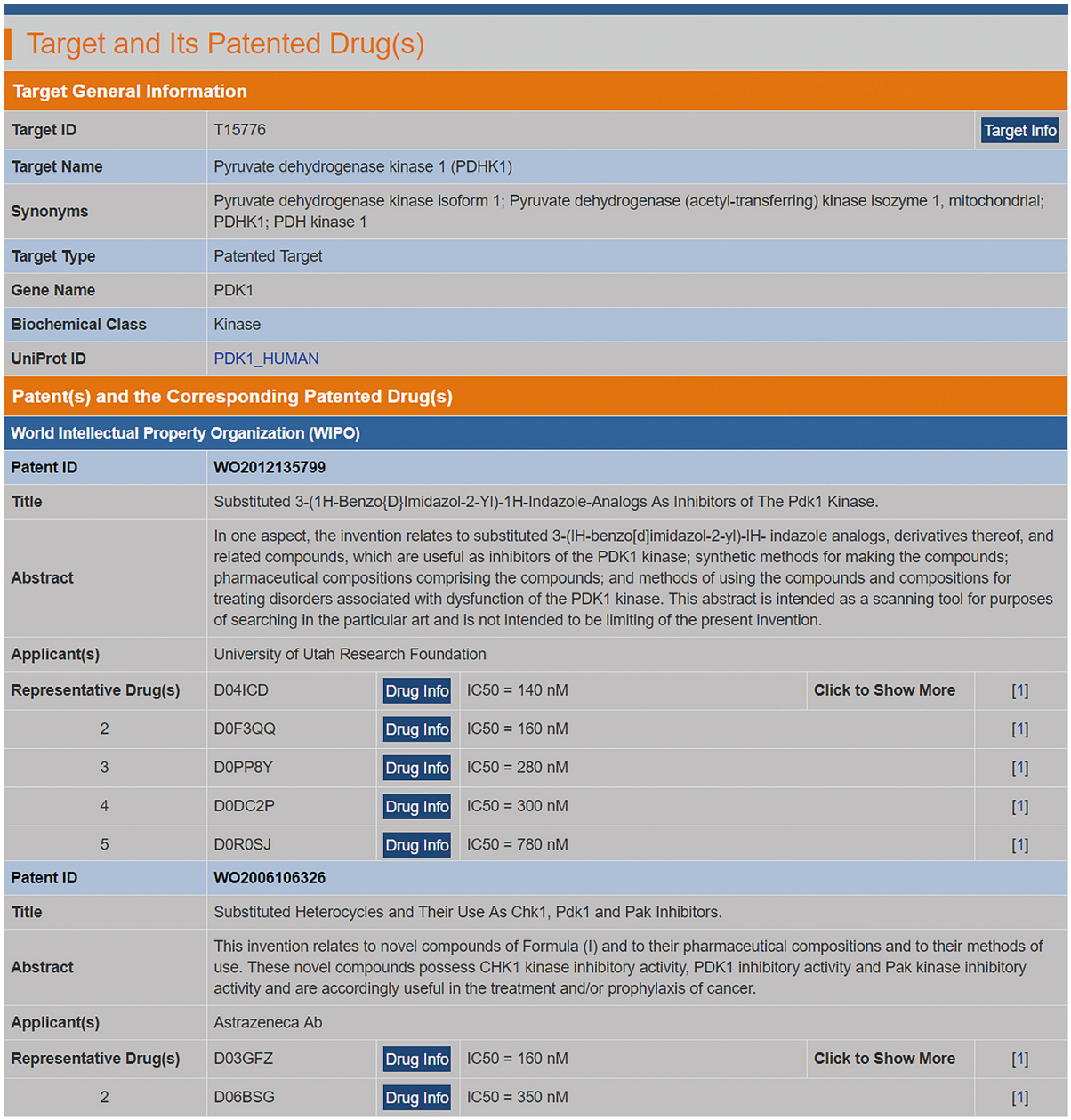
Target Interacting Proteins		
Acid anhydride hydrolases	[+] 5 Acid anhydride hydrolases	+
Acyltransferases	[+] 4 Acyltransferases	+
Adapter proteins	[+] 13 Adapter proteins	+
Alkyl/aryl transferases	[+] 1 Alkyl/aryl transferases	+
Auxiliary transporters	[+] 7 Auxiliary transporters	+
Carbon-nitrogen hydrolases	[+] 2 Carbon-nitrogen hydrolases	+
Cell division cycle proteins	[+] 1 Cell division cycle proteins	+
Ester hydrolases	[+] 12 Ester hydrolases	+
Eukaryotic initiation factors	[+] 3 Eukaryotic initiation factors	+
Growth factors	[+] 3 Growth factors	+
Heat shock proteins	[+] 6 Heat shock proteins	+
Hydrolysis-driven transporters	[+] 2 Hydrolysis-driven transporters	+
Integrins	[+] 1 Integrins	+
Intermediate filaments	[+] 1 Intermediate filaments	+
Kinases	[+] 39 Kinases	+

Figure 4. A typical page in the TTD providing information about target-interacting proteins. The target-interacting proteins are provided in groups of biochemical classes (GPCR, peptidase, virus penetration channel, etc.) on a webpage, and the target-interacting proteins within each class are listed with respect to their *E-scores*. Detailed information of each interacting protein or target can also be found by clicking the 'Interacting Protein Info' or 'Target Info' button.

coded under immune system disease, and HIV infection being described as a chronic condition. Due to the significant changes in ICD codes, the TTD was updated with ICD-11 codes while retaining the original ICD-9 and ICD-10 codes that were introduced in previous TTD versions (7,27,67). Users can use a pull-down manual to search TTD data by means of an ICD-11 code menu.

SPECIAL CLASSES OF TARGETS OF IMMUNOTHERAPY AGENTS

New classes of immunotherapy agents have emerged. One class is CAR T-cell therapy, which is a form of immunotherapy that uses specially altered T-cells to treat cancer (68). A sample of a patient's T cells, collected from the blood, are modified to produce chimeric antigen receptors (CARs) on their surfaces. When these CAR-T cells are reinfused into patients, the new receptors on these cells enable them to bind to specific antigens on the patients' cancer cells, thereby killing them. Knowledge regarding the target antigens of clinically used or tested CAR-T therapy is thus very useful for the study and discovery of this special class of agent. Therefore, the antigens of approved and clinical trial CAR-T therapies were systematically searched based on the following procedures: *first*, approved CAR-T therapies were collected from the February issue of *Nature Reviews Drug Discovery* (69), and the CAR-T therapies in clinical trials were obtained from the official websites or recent reports of 122 pharmaceutical companies/research institutes/hospitals; *second*, the clinical status of each CAR-T therapy was further validated by the *ClinicalTrials.gov* (70), and the corresponding disease indications and NCT numbers were confirmed; *third*, the target antigen of each CAR-T therapy was identified using *ClinicalTrials.gov* and PubMed. In total, 2 approved, 4 phase III, 166 phase II and 187 phase I CAR-T therapies for treating of 92 diseases were collected, which targeted 17 successful and 35 clinical trial targets in the TTD.



Target and Its Patented Drug(s)

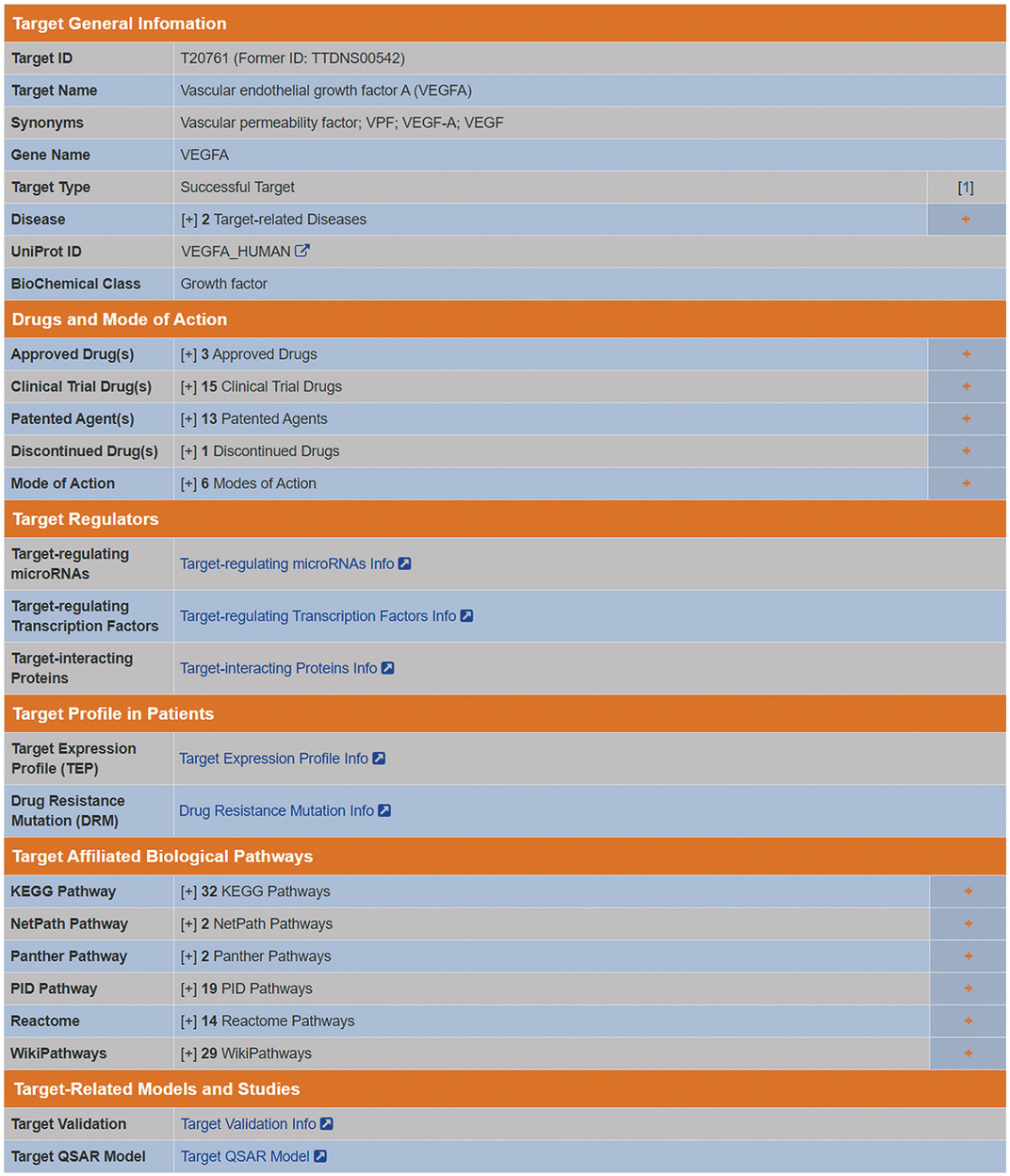
Target General Information					
Target ID	T15776				Target Info
Target Name	Pyruvate dehydrogenase kinase 1 (PDHK1)				
Synonyms	Pyruvate dehydrogenase kinase isoform 1; Pyruvate dehydrogenase (acetyl-transferring) kinase isozyme 1, mitochondrial; PDHK1; PDH kinase 1				
Target Type	Patented Target				
Gene Name	PDK1				
Biochemical Class	Kinase				
UniProt ID	PDK1_HUMAN				
Patent(s) and the Corresponding Patented Drug(s)					
World Intellectual Property Organization (WIPO)					
Patent ID	**WO2012135799**				
Title	Substituted 3-(1H-Benzo{D}Imidazol-2-Yl)-1H-Indazole-Analogs As Inhibitors of The Pdk1 Kinase.				
Abstract	In one aspect, the invention relates to substituted 3-(lH-benzo[d]imidazol-2-yl)-lH- indazole analogs, derivatives thereof, and related compounds, which are useful as inhibitors of the PDK1 kinase; synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of using the compounds and compositions for treating disorders associated with dysfunction of the PDK1 kinase. This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.				
Applicant(s)	University of Utah Research Foundation				
Representative Drug(s)	D04ICD	Drug Info	IC50 = 140 nM	**Click to Show More**	[1]
2	D0F3QQ	Drug Info	IC50 = 160 nM		[1]
3	D0PP8Y	Drug Info	IC50 = 280 nM		[1]
4	D0DC2P	Drug Info	IC50 = 300 nM		[1]
5	D0R0SJ	Drug Info	IC50 = 780 nM		[1]
Patent ID	**WO2006106326**				
Title	Substituted Heterocycles and Their Use As Chk1, Pdk1 and Pak Inhibitors.				
Abstract	This invention relates to novel compounds of Formula (I) and to their pharmaceutical compositions and to their methods of use. These novel compounds possess CHK1 kinase inhibitory activity, PDK1 inhibitory activity and Pak kinase inhibitory activity and are accordingly useful in the treatment and/or prophylaxis of cancer.				
Applicant(s)	Astrazeneca Ab				
Representative Drug(s)	D03GFZ	Drug Info	IC50 = 160 nM	**Click to Show More**	[1]
2	D06BSG	Drug Info	IC50 = 350 nM		[1]

Figure 5. A typical page in the TTD providing information about the targets of patented therapeutic agents. The information included the patent details (patent office, title, abstract, etc.), representative patented drugs, and their corresponding activities with respect to their targets. Detailed information of each drug or target can also be found by clicking the 'Drug Info' or 'Target Info' button.

The second class of immunotherapy agents include small molecular and peptidomimetic immune checkpoint inhibitors (71). Although the monoclonal antibody immune checkpoint inhibitors are highly successful in cancer treatment, they present such problems as difficulty in penetrating into tumors and the need for slow intravenous infusion treatment (72). These problems may be partially overcome by the introduction of small molecule drugs. Successful efforts have been directed at discovering small molecular and peptidomimetic immune checkpoint inhibitors (71). Thus, PubMed was systematically searched using such combinations as the keywords 'small molecular inhibitor'/'small molecular agent'/'peptidomimetic agent'/'peptidomimetics'/'peptidomimetic inhibitors' and 'immune checkpoint'. In total, 2 clinical trial, 121 patented, 2 preclinical, and 56 investigative immunotherapies for treating five classes of disease were collected.

ACCESS FACILITIES FOR THE NEWLY ADDED FEATURES

The addition of new information has made the TTD webpages too crowded, which hinders the ability of users to find the preferred information. To resolve this problem, the TTD



Target General Infomation		
Target ID	T20761 (Former ID: TTDNS00542)	
Target Name	Vascular endothelial growth factor A (VEGFA)	
Synonyms	Vascular permeability factor; VPF; VEGF-A; VEGF	
Gene Name	VEGFA	
Target Type	Successful Target	[1]
Disease	[+] **2** Target-related Diseases	+
UniProt ID	VEGFA_HUMAN	
BioChemical Class	Growth factor	
Drugs and Mode of Action		
Approved Drug(s)	[+] **3** Approved Drugs	+
Clinical Trial Drug(s)	[+] **15** Clinical Trial Drugs	+
Patented Agent(s)	[+] **13** Patented Agents	+
Discontinued Drug(s)	[+] **1** Discontinued Drugs	+
Mode of Action	[+] **6** Modes of Action	+
Target Regulators		
Target-regulating microRNAs	Target-regulating microRNAs Info	
Target-regulating Transcription Factors	Target-regulating Transcription Factors Info	
Target-interacting Proteins	Target-interacting Proteins Info	
Target Profile in Patients		
Target Expression Profile (TEP)	Target Expression Profile Info	
Drug Resistance Mutation (DRM)	Drug Resistance Mutation Info	
Target Affiliated Biological Pathways		
KEGG Pathway	[+] **32** KEGG Pathways	+
NetPath Pathway	[+] **2** NetPath Pathways	+
Panther Pathway	[+] **2** Panther Pathways	+
PID Pathway	[+] **19** PID Pathways	+
Reactome	[+] **14** Reactome Pathways	+
WikiPathways	[+] **29** WikiPathways	+
Target-Related Models and Studies		
Target Validation	Target Validation Info	
Target QSAR Model	Target QSAR Model	

Figure 6. A redesigned TTD target webpage categorizing the information into the groups of (i) target general information, (ii) drugs and modes of action, (iii) target regulators, (iv) target profiles in patients, (v) target affiliated pathways and (vi) target-related models and studies.

target webpage was redesigned by categorizing the information into multiple groups: (i) target general information, (ii) drugs and their modes of actions, (iii) target regulators, (iv) target profiles in patients, (v) target affiliated pathways and (vi) target-related models and studies (Figure 6). The information in each group is itemized within a small block on the webpage, and users can access detailed information by clicking each item. The newly added features of target regulators (miRNA and TF), target-interacting proteins and the targets of patented therapeutic agents can be accessed via the 'Target Group' manual bar, and the small molecular and peptidomimetic inhibitors of immunotherapy targets and the patented therapeutic agents are provided under the 'Drug Group' manual bar. Figure 1 provides a typical page in the TTD describing the information about target-regulating miRNAs. Figure 2 shows the page illustrating the data regarding target-interacting proteins. Figure 3 exhibits the page showing the data of patented therapeutic agents together with their corresponding targets. The database platform *Drupal* was employed in the TTD to enhance data storage and extraction. Extensively accelerated data access and transmission were achieved via the cloud platform of *Aliyun* located in Silicon Valley.

CONCLUDING REMARKS

Intensive drug research and development efforts have led to extensively expanded knowledge of biological systems

(73,74), disease processes (75,76) and the mechanisms of targeted therapeutics (77–79). The expanded knowledge has facilitated the successful development of new therapies (68), and it will further facilitate the discoveries of such therapeutic approaches as polypharmacology (80) and RNA therapeutics (81). For better serving the drug discovery communities, additional efforts have been directed at further enriching the TTD and other established databases with comprehensive information about drugs, targets, and their regulation.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

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