Therapeutic target database update 2012: a resource for facilitating target-oriented drug discovery

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ABSTRACT

Knowledge and investigation of therapeutic targets (responsible for drug efficacy) and the targeted drugs facilitate target and drug discovery and validation. Therapeutic Target Database (TTD, http://bidd.nus.edu.sg/group/ttd/ttd.asp) has been developed to provide comprehensive information about efficacy targets and the corresponding approved, clinical trial and investigative drugs. Since its last update, major improvements and updates have been made to TTD. In addition to the significant increase of data content (from 1894 targets and 5028 drugs to 2025 targets and 17 816 drugs), we added target validation information (drug potency against target, effect against disease models and effect of target knockout, knockdown or genetic variations) for 932 targets, and 841 quantitative structure activity relationship models for active compounds of 228 chemical types against 121 targets. Moreover, we added the data from our previous drug studies including 3681 multi-target agents against 108 target pairs, 116 drug combinations with their synergistic, additive, antagonistic, potentiative or reductive mechanisms, 1427 natural product-derived approved, clinical trial and pre-clinical drugs and cross-links to the clinical trial information page in the ClinicalTrials.gov database for 770 clinical trial drugs. These updates are useful for facilitating target discovery and validation, drug lead discovery and optimization, and the development of multi-target drugs and drug combinations.

INTRODUCTION

Modern drug discovery is primarily focused on the search or design of drug-like molecules, which selectively interact and modulate the activity of one or a few selected therapeutic targets (1–3). One challenge in drug development is to choose and explore promising targets from a growing number of potential targets (4). Target selection and validation are important not only for achieving therapeutic efficacy but also for increasing drug development odds, given that few innovative targets have made it to the approved list each year [12 innovative targets in 1994–2005 (5) and 10 new human targets in 2006–2010 (6) for small molecule drugs]. Apart from target selection and validation, drug discovery efforts can be facilitated by enhanced knowledge of bioactive molecular scaffolds (7,8), structure–activity relationships (9), multi-target agents (10,11) and synergistic drug combinations (12) against selected target or multiple targets, and information about the sources of drug leads such as the species origins of natural product-derived drugs (13).

Internet resources such as Therapeutic Target Database (TTD) (14,15) and DrugBank (16) provide comprehensive information about the targets and drugs in different development and clinical stages, which are highly useful for facilitating focused drug discovery efforts and pharmaceutical investigations against the most relevant and proven targets (17–19). In addition to the update of these databases by expanded target and drug data

contents, the usefulness of these databases for facilitating drug discovery efforts can be further enhanced by adding additional information and knowledge derived from the target and drug discovery processes. Therefore, we updated TTD by both significantly expanding the target and drug data and adding new information about target validation, quantitative structure–activity relationship (QSAR) models of a variety of molecular scaffolds active against selected targets and specific types of drugs (multi-target drugs and natural product-derived drugs) and drug combinations (synergistic, additive, antagonistic, potentiative and reductive combinations).

The significantly expanded target and drug data cover 364 successful, 286 clinical trial, 44 discontinued clinical trial and 1331 research targets, and 1540 approved, 1423 clinical trial, 345 discontinued clinical trial, 165 pre-clinical and 14 853 experimental drugs linked to their primary targets (14 170 small molecule and 652 anti-sense drugs with available structure and sequence data) (Table 1). These are compared to 348 successful, 249 clinical trial, 43 discontinued clinical trial and 1254 research targets, and 1514 approved, 1212 clinical trial and 2302 experimental drugs in our last update (15). To facilitate the access of clinical trial information of the clinical trial drugs, cross-links to the relevant page in ClinicalTrials.gov database are provided for 770 clinical trial drugs. The newly added target validation data includes the experimentally measured potency of 11 810 drugs against 915 targets, the observed potency or effects of 497 drugs against disease models (cell lines, *ex vivo*, *in vivo* models) linked to 393 targets, and the observed effects of target knockout, knockdown or genetic variations for 307 targets (Table 2). The QSAR data consists of 841 QSAR models for active compounds of 228 chemical types against 121 targets (Table 2).

Moreover, we added the data partly derived from our previous studies of multi-target drugs (20,21), drug combinations (12) and natural product derived drugs (13)

(Table 2). The multi-target drug data is composed of 3681 multi-target agents active against 108 target pairs together with their potencies against the target pairs. The drug combination data includes 72, 14 and 4 pharmacodynamically synergistic, additive and antagonist combinations, and 19 and 7 pharmacokinetically potentiative and reductive combinations together with their mode of actions and combination mechanisms. The natural product-derived drug data includes the drug names and their species origins and species families for 939 approved, 369 clinical-trial and 119 pre-clinical drugs.

NEW TARGET AND DRUG DATA COLLECTION

Additional target and drug data, including the approved, clinical trial and experimental drugs and their primary targets, were collected by using the same methods described in our previous publications (14,15). In particular, all TTD targets are primary targets (i.e. efficacy targets) directly responsible for the claimed therapeutic efficacies (in

Table 2. Summary and statistics of newly added data in 2012 version of TTD

Data Category	Number of Information
Target validation data	
Experimentally measured potency of drugs against targets	
Number of drugs	11 810
Number of targets	915
Drug potency against disease model (cell-lines, *ex vivo*, *in vivo* models)	
Number of drugs	497
Number of targets	393
The observed effects of target knockout, knockdown or genetic variations	
Number of targets	307
QSAR models	
Number of QSAR models	841
Number of Chemical types	228
Number of targets	121
Structure and potency information of multi-target agents against target pairs	
Number of multi-target agents	3681
Number of target pairs	108
Drug combination data	
Pharmacodynamically synergistic drug combinations	
Number of drug combinations due to anti-counteractive actions	22
Number of drug combinations due to complementary actions	30
Number of drug combinations due to facilitating actions	20
Number of pharmacodynamically additive drug combinations	14
Number of pharmacodynamically antagonistic drug combinations	4
Number of pharmacokinetically potentiative drug combinations	19
Number of pharmacokinetically reductive drug combinations	7
Natural product-derived drugs and their species origins	
Number of natural product-derived approved drugs	939
Number of natural product-derived clinical trial drugs	369
Number of natural product-derived pre-clinical drugs	119

Table 1. Statistics of drug targets, drugs and structure and sequence data in TTD database

Data Category	2012 update	2010 update
Statistics of drug targets		
Number of all targets	2025	1894
Number of successful targets	364	348
Number of clinical trial targets	286	249
Number of discontinued targets	44	43
Number of research targets	1331	1254
Statistics of drugs		
Number of all drugs	17 816	5028
Number of approved drugs	1540	1514
Number of clinical trial drugs	1423	1212
Number of discontinued drugs	345	274
Number of pre-clinical drugs	165	142
Number of experimental drugs	14 853	2302
Statistics of drugs with available structure or sequence data		
Number of small molecular drugs with available structure	14 170	3382
Number of antisense drugs with available sequence data	652	649

drug approval, clinical trial or investigations) of the corresponding drugs as confirmed by biochemical assay and strong cell based and/or *in vivo* evidence linking the target to drug (15,17,22). The status of approved drugs and clinical trial drugs is up-to-date as of December 2010. The discontinued clinical trial drugs are based on the report from US National Institutes of Health (NIH, http://clinicaltrials.gov/). The discontinued clinical trial targets are those clinical trial targets that no longer have an active clinical trial drug at the end of 2010. Pre-clinical drugs are drug candidates that have passed discovery stages and started such pre-clinical studies as safety, PK/ADME, active pharmaceutical ingredient preparation and formulation (23). The newly added experimental drugs were selected based on a potency cut-off value of ≤20 µM against their targets.

TARGET VALIDATION DATA

Target validation has been routinely performed to demonstrate the functional role of the potential target in disease phenotype and the ability of drug-like molecules to modulate the activities of the target to achieve therapeutic efficacies (24,25). Target validation normally requires the determination that the target is expressed in the disease-relevant cells/tissues, it can be directly modulated by a drug or drug-like molecule with adequate potency in biochemical assay, and that target modulation in cell and/or animal models ameliorates the relevant disease phenotype (24,26). *In vivo* target validation has been conducted mostly in knockout mice, transgenetic *in vivo* models, and also in RNA interference, antibody and antisense treated *in vivo* models (26,27). We therefore searched the PubMed database (28) to collect from literature three types of

target validation data: experimentally determined potency of drugs against their primary target or targets, observed potency or effects of drugs against disease models (cell lines, *ex vivo*, *in vivo* models) linked to their primary target or targets, and the observed effects of target knockout, knockdown, transgenetic, RNA interference, antibody or antisense-treated *in vivo* models. Target validation data can be retrieved by clicking the 'Target Validation' field in the TTD home page, which lead to the TTD target validation information page wherein a user can select the relevant data for a particular target from the target name list (Figure 1).

QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIP MODELS AGAINST SPECIFIC TARGET

QSAR models for active compounds against many different targets have been developed and explored for drug lead discovery and optimization (9,29). These models elucidate the chemical characteristics favorable to the modulation of the activity of specific target at sufficient potency by establishing quantitative correlations between molecular properties and biological activities (e.g. 50% inhibition concentration or binding affinities) (30). In drug lead optimization projects, QSAR models against specific target can be recursively developed and used for guiding the design or search of more potent compounds or compounds with more desired drug-like properties as the new activity or drug-like property data from newly synthesized compounds become available (9,29). Therefore, knowledge of developed QSAR models for different molecular scaffolds active against different targets is highly useful for facilitating further drug

Figure 1. The target validation information page of TTD.

development and lead optimization efforts. In addition to the QSAR models, we have collected in our previous analysis of QSAR models of bioactive compounds (31), we searched PubMed database (28) to collect 309 papers that describe 841 ligand-based QSAR models for active compounds of 228 chemical types against 121 targets. While there are also a high number of papers describing receptor-based QSAR models, these models were not included in TTD because they are not easily displayed in explicit form in a database setting without obtaining copyrights from the relevant journals. The included QSAR models can be accessed by clicking the 'QSAR Models' field in the TTD home page, which lead to the TTD QSAR model page wherein a user can select the relevant model for a particular chemical class against a specific target either from the target name list or the chemical type list (Figure 2). The retrieved QSAR model page (Figure 3) contains the information about target and ID, target species, chemical type, compound mode of action, QSAR models, the molecular descriptors in the QSAR models, references and hyperlinks to the molecular descriptor computation web servers MoDeL (32) and e-dragon (33).

MULTI-TARGET AGENTS

Therapeutic agents directed at an individual target frequently show reduced efficacies, undesired safety profiles and drug resistances due to network robustness,

redundancy, cross-talk, compensatory and neutralizing actions, anti-target and counter-target activities (34–36). Multi-target agents directed at selected multiple targets have been increasingly explored for enhanced therapeutic efficacies, improved safety profiles and reduced resistance activities by simultaneously modulating the activity of a primary target and the counteractive elements (3,37,38). In addition to the multi-target agents we have collected in our previous studies of multi-target drugs (20,21), we further searched PubMed (28) using such keywords as 'multi-target', 'dual target' and 'dual inhibitor'. Multi-target agent against a target pair refers to a compound active against both targets at potency values of $\leq 20\,\mu M$ regardless of their possible activities against other targets. The 3D structures of these multi-target agents were generated by using CORINA (39) from the 2D structures manually drawn based on the literature provided structures or the structures found in such chemical databases as BindingDB (40), ChEMBL (41) and PubChem (28). These multi-target agents can be retrieved by clicking the 'Multi-Target Agents' field in the TTD home page, which lead to the TTD multi-target agents page wherein a user can download the multi-target agents against a specific target pair from the target pair list (Figure 4).

DRUG COMBINATIONS

Apart from multi-target agents, drug combinations have also been extensively explored for enhanced therapeutic

Figure 2. QSAR model page of TTD.

Target Name	HIV-1 protease
Target TTD ID	TTDS00319

Target Species	Human immunodeficiency virus 1
Chemical Type	N-Aryl Heteroarylisopropanolamines
Mode of Action	Inhibitor
QSAR Model 1	$pIC_{50} = -4.284 - (0.659)^*Sfit + (0.010)^*Dip\text{-}mom - (0.340)^*HOMO + (0.008)^*MW + (0.008)^*Volume - (0.053)^*G\_CDS\_aq$
Molecular Descriptor	Access the following web-servers to compute molecular descriptors: **MoDel** and **e-dragon** Parameter - description: Sfit - Steric fit between ligand and receptor; Dip-Mom - Dipole moment (AMSOL); HOMO - HOMO ligand energy (AMSOL); MW - Molecular weight (AMSOL); Volume - Molecular volume (AMSOL); G_CDS_aq - Cavity-dispersion-solvent free energy (AMSOL).
Reference	Design, Synthesis and QSAR Studies on N-Aryl Heteroarylisopropanolamines, a New Class of Non-Peptidic HIV-1 Protease Inhibitors. *Bioorganic & Medicinal Chemistry* 10 (2002) 2511–2526

Figure 3. The page of the QSAR models for a particular chemical class against a specific target in TTD.

efficacies, improved safety profiles and reduced resistance activities (12,38,42). When two drugs produce the same broad therapeutic effect, their combination collectively produces the same effects of various magnitudes in contrast to the summed response of the individual drugs. A drug combination is pharmacodynamically synergistic, additive or antagonistic if the effect is greater than, equal to or less than the summed response of the individual drugs (43). Drug combinations may also produce pharmacokinetically potentiative or reductive effects such that the therapeutic activity of one drug is enhanced or reduced by another drug via regulation of the first drug's ADME (43). In our earlier studies of drug combinations (12), we have searched PubMed (28) to select those literature-reported drug combinations evaluated by rigorous combination analysis methods and with known molecular mechanism of combination retrievable from PubMed by using combinations of the keywords 'drug combination', 'drug interaction', 'multi-drug', 'additive', 'antagonism', 'antagonistic', 'infra-additive', 'potentiated', 'potentiative', 'potentiation', 'reductive', 'supra-additive', 'synergism', 'synergistic' and 'synergy'.

All major classes of drug combinations can be further divided into groups of specific action types (12). Pharmacodynamically synergistic drug combinations can be divided into three groups: each one with anti-counteractive, complementary and facilitating actions, respectively. Anti-counteractive actions reduce network's counteractive activities against a drug's therapeutic effect. Complementary actions positively regulate a target or process by interactions with multiple target/pathway sites, different target subtypes and states, and competing mechanisms (3). Facilitating actions are secondary actions of one drug in enhancing the activity or level of another drug. Pharmacodynamically additive drug combinations can be divided into two groups, one with equivalent or overlapping actions, and the other with independent actions of the drugs involved. Pharmacodynamically antagonistic drug combinations can also be divided into two groups, one with mutually interfering actions at the same target, another with mutually counter-active actions at different targets of related pathways that regulate the same target. Pharmacokinetically potentiative drug combinations can be divided into three groups, each one with positive modulation of drug transport or permeation, drug distribution or localization and drug metabolism, respectively. Pharmacokinetically reductive drug combinations can be divided into three groups, each one with negative modulation of drug transport or permeation, drug distribution or localization and drug metabolism, respectively.

Figure 4. Multi-target agents page of TTD.

These drug combinations and their combination mechanisms can be accessed by clicking the 'Drug Combinations' field in the TTD home page, which lead to the TTD drug combinations page wherein a user can download the relevant drug combination data from the drug combination type list (Figure 5).

NATURAL PRODUCT-DERIVED DRUGS

Many of the approved and clinical trial drugs are derived from natural products (44,45). Although drug discovery focus has been shifted from natural products to synthetic chemicals, natural product-derived drugs still constitute a substantial percentage of recently approved drugs (26% of the 46 FDA approved new molecular entities in 2009–2010 are natural product derived) (13). There is a renewed interest in natural products as sources for drug discovery (46). Knowledge of the natural sources of drugs, the species origins of the natural product-derived approved, clinical trial and pre-clinical drugs, are highly useful for

facilitating the search and development of new drug leads. In our earlier analysis of the species origins of natural product-derived drugs, we have collected the species origins and species families of natural product-derived approved, clinical trial and pre-clinical drugs (13).

The species-origins of these drugs have been identified as follows. First the literature-reported approved drugs (44), clinical trial (45,47) and pre-clinical (13) drugs of natural origin were evaluated with respect to the drugs in our TTD database (15) to check their current approval or clinical trial status. Then the species-origin of every drug was searched from books, review and regular articles by using combinations of such keywords as drug name and alternative names, species, natural product and nature. The species-origin of a drug is confirmed if it is specifically mentioned that it 'originates from', 'derived from', 'isolated from' or 'comes from' a species or species-group (e.g. genus or family). For drugs of semi-synthetic derivatives, mimics and peptidomimetics, their parent natural product leads were first searched followed by the search of host

Figure 5. Drug combination page of TTD.

Figure 6. Natural product-derived drugs page of TTD.

species as described above. The corresponding species-families of the host-species of these drugs as well as all the known species-families in the nature are from the NCBI taxonomy database (28). These natural product-derived drugs and their species origins and families can be retrieved by clicking the 'Nature-Derived Drugs' field in the TTD home page, which lead to the TTD natural product-derived drugs page wherein a user can download the relevant data from the drug status list (Figure 6).

REMARKS

A goal in updating TTD is to make it into a more useful target and drug discovery resource in complement to other related databases. Continuous efforts will be made to provide the latest and comprehensive information about the primary (efficacy) targets of approved, clinical trial, pre-clinical and experimental drugs and other relevant data for these drugs. Intensive efforts in drug and target discovery have led to and will continue to enable the generation of new information, knowledge and models from existing targets (18), drugs (9,29,48,49), multi-target drugs (20) and drug combinations (12,38,42). Drug discovery efforts have benefited and are continuing to be benefited from the exploration of multiple lead sources including synthetic chemicals (1–3), biologics (50–53) and natural products (13,44,45). Inclusion of these information, knowledge and models into TTD and other databases will further enable these databases to better serve the drug discovery and research communities in their efforts for discovering new targets and new drugs from different sources.

FUNDING

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