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Therapeutic target database update 2018: enriched resource for facilitating bench-to-clinic research of targeted therapeutics

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ABSTRACT

Extensive efforts have been directed at the discovery, investigation and clinical monitoring of targeted therapeutics. These efforts may be facilitated by the convenient access of the genetic, proteomic, interactive and other aspects of the therapeutic targets. Here, we describe an update of the Therapeutic target database (TTD) previously featured in NAR. This update includes: (i) 2000 drug resistance mutations in 83 targets and 104 target/drug regulatory genes, which are resistant to 228 drugs targeting 63 diseases (49 targets of 61 drugs with patient prevalence data); (ii) differential expression profiles of 758 targets in the disease-relevant drug-targeted tissue of 12 615 patients of 70 diseases; (iii) expression profiles of 629 targets in the non-targeted tissues of 2565 healthy individuals; (iv) 1008 target combinations of 1764 drugs and the 1604 target combination of 664 multi-target drugs; (v) additional 48 successful, 398 clinical trial and 21 research targets, 473 approved, 812 clinical trial and 1120 experimental drugs, and (vi) ICD-10-CM and ICD-9-CM codes for additional 482 targets and 262 drugs against 98 disease conditions. This update makes TTD more useful for facilitating the patient focused research, discovery and clinical investigations of the targeted therapeutics. TTD is accessible at http://bidd.nus.edu.sg/group/ttd/ttd.asp.

INTRODUCTION

Collective efforts in the development and practice of modern medicines by the research communities, pharmaceutical companies and clinical communities have been primarily directed at the discovery, investigation and clinical monitoring of the targeted therapeutics (1–6). These efforts have been partly facilitated by the knowledge of the genomics, transcriptomics, structures, interactions, biological systems and functional profiles of the therapeutic targets (7–10). In particular, a number of freely accessible databases complementarily provide comprehensive information about the therapeutic targets with additional information about the clinical trial drugs (11–13), biomarkers (11), molecular activity data (11,13–15), drug-binding sites (16,17) and target-affiliated biological pathways (11,18) of the targets, as well as the therapeutics (12,14,15,19,20) and ADME-Tox properties (12) of the targeted drugs.

The clinical efficacies of the targeted therapeutics and the outcomes of target evaluation studies frequently depend on the states of drug-resistance mutations (21,22) and the gene expression profiles (23,24) of the targets and their regulators in the patients. Moreover, the multi-target drugs (25,26) and drug combinations (25,27,28) directed at specific target combinations have been extensively tested and used for enhanced therapeutics. The knowledge of the drug resistance mutations (21,29), patient gene expression profiles (30) and the target combinations of the multi-target drugs (26,31) and drug combinations (27) has facilitated our understanding of the mechanisms of drug therapeu-

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Table 1. Statistics of the target and drug data in TTD

		2018 update	2016 update
Statistic of targets	Number of all targets	3101	2589
	Number of successful targets	445	397
	Number of clinical trial targets	1121	723
	Number of research targets	1535	1469
Statistic of drugs	Number of all drugs	34 019	31 614
	Number of approved drugs	2544	2071
	Number of clinical trial drugs	8103	7291
	Number of investigative drugs	18 923	17 803
	Number of bi-specific antibody	21	0
	Number of stem cell drugs	10	0
	Number of multi-target agents	26 459	26 368
	Number of drugs withdrawn from the market	158	154
	Number of drugs discontinued in clinical trial	2349	2237
	Number of pre-clinical drugs	417	357
	Number of drugs terminated in unspecified investigative stage	1929	1701
	Number of small molecular drugs with available structure	21 936	17 356
	Number of approved drugs with available structure	2326	1896
	Number of clinical trial drugs with available structure	4258	2161
	Number of investigative with available structure	15 352	13 308

tics, the assessment of druggability of the targets (7,32,33) and the development and practices of stratified and precision medicines (34–36). However, the relevant information is insufficiently covered by the existing database. As of August 2017, the Cancer Genome Interpreter (https://www.cancergenomeinterpreter.org/), Catalogue of Somatic Mutations in Cancer (37), Comprehensive Antibiotic Resistance Database (38), HIV Drug Resistance Mutation Database (39) and Tuberculosis Drug Resistance Mutation Database (40) collectively provide 1688 drug resistance mutations in 85 targets of 90 drugs, which are significantly less than the reported drug resistance mutation studies for ∼200 targets and ∼200 drugs we found from the literature. While the GEO (41) and TCGA (42) databases provide comprehensive genome-scale gene expression data of the patients of different diseases and healthy individuals, the therapeutic targets and regulators are not explicitly marked for convenient access of the relevant data. The DCDB database (43) contains the 761 target combinations of 1363 drug combinations, which are significantly <1008 target combinations of 2042 drug combinations we searched from literature and the ClinicalTrials.gov service (https://clinicaltrials.gov/).

To provide more comprehensive information about the drug resistance mutations, gene expressions and target combinations data for the targets and drugs, we updated the Therapeutic target database (TTD, http://bidd.nus.edu.sg/group/ttd/ttd.asp) with several major improvements. The first improvement is the inclusion of the literature-reported drug resistance mutations in 83 targets (40 successful, 34 clinical trial and 9 research targets) and 104 target/drug regulatory genes, which reportedly are resistant to 228 drugs (128 approved, 56 clinical trial and 44 investigative) targeting 63 diseases. While available from the literature search, the prevalence of the drug resistance mutations in the targeted patient populations was also included. The second is the inclusion of the differential expression profiles of 309 successful and 449 clinical trial targets in the disease-relevant drug targeted tissue of 12 615 patients of 70 diseases. The differential expression profile contains the gene expression levels of the targeted individual patients and those of the healthy individuals. The third is the inclusion of the expression profiles of 372 successful and 257 clinical trial targets in the non-targeted tissues of 2565 healthy individuals. Typically, for each target, the average gene expression levels in 37–45 tissues are provided. The fourth is the inclusion of 1008 target combinations of 626 and 1138 combinations of approved and clinical trial drugs, and the 1604 target combination of 122 approved, 542 clinical trial and 25 333 research multi-target drugs. Moreover, we also added additional 48 successful, 398 clinical trial and 21 research targets, 473 approved, 812 clinical trial and 1120 experimental drugs, and the ICD-10-CM and ICD-9-CM codes for additional 482 targets and 262 drugs against 98 disease conditions. Table 1 provides the statistics of the latest TTD target and drug data with respect to that of previous release.

DRUG RESISTANCE MUTATIONS

Drug resistance is a global public health problem particularly for the treatment of infectious diseases and cancers (21). The clinical efficacy of the antibiotic drugs is rapidly decreasing partly due to the occurrence of drug resistance mutations in the targets or the target/drug regulatory genes in the bacteria (44). Cancers' acquisition of drug resistance is partly linked to specific somatic mutations of the anticancer targets and the target/drug regulatory genes (45). The knowledge of the drug resistance mutations in the targets and target/drug regulatory genes are important for the understanding of the mechanisms of drug therapeutic efficacies (21,45), the prediction of drug resistance mutations (29) and the development and practices of stratified and precision medicines (34).

The drug resistance mutations were searched from the PubMed database using the combinations of the keywords 'resistance', 'resistant', 'mutation', 'mutations' and the name and synonyms of each of the targets and drugs in the TTD database (11). The identified literatures were manually evaluated to extract the relevant drug resistance mutations in each target or the target/drug regulatory genes. The collected information includes the drug resistance mutations and mutation types (missense mutation, nonsense

mutation, deletion, frameshift and insertion), level of resistance (defined by the fold-change of the IC50 values with and without the respective mutation) and the prevalence of mutations in the patients of the drug targeted diseases. The wild-type sequence of each target or target/drug regulatory gene product from the UniProt database (46) was also included for reference. Overall, there are 2000 drug resistance mutations in 83 targets (40 successful, 34 clinical trial and 9 research) and 104 target/drug regulatory genes, which are resistant to 228 drugs (128 approved, 56 clinical trial and 44 investigative) targeting 63 diseases (49 targets of 61 drugs with patient prevalence data).

TARGET GENE EXPRESSION

Drug interaction with its target frequently induces a positive or negative feedback loop that adjusts the expression level of the target (30). Systematic gene expression analysis of the successful and phase III clinical trial targets across a diverse collection of normal human tissues have shown that most targets are expressed in a disease-affected tissue under healthy conditions (23). The human tissue distribution profile of a target, determined by the level of the target expression in different human tissues, is a key druggability indicator (7). This indicator together with other druggability indicators have been used to prospectively predict 16 promising targets among 31 phase III targets of small molecule drugs in 2009, 10 of which have become successful following the publication of the target assessments (32). Therefore, there is a need for the gene expression data of the targets in both the disease-relevant drug targeted tissue and other tissues of the patients and healthy individuals.

The relevant gene expression data for the targets were searched by the following procedures. First, 2538 series records of human gene expression raw data based on the *Affymetrix U133 Plus 2.0* platform were collected from the GEO database (41), and their corresponding disease and tissue information were recorded from the sample annotation. Then, 569 series records of 70 diseases and 45 tissues covered by TTD (11) were selected. Those samples from the same disease and the same tissue were selected for meta-analysis of the gene expression profiles. Second, data preprocessing and quality control were conducted based on the normalized unscaled standard error and the relative log expression (47,48), which retained 34 355 samples from all gene expression raw data. Thirdly, those gene expression data from the same disease and the same tissue were combined and normalized using the robust multiarray average, quantile normalization, perfect match correction and median polish, based on the *R package affy* (49). Fourth, fold-change and *Z*-score transformation allowed the comparison of data across a wide range of experiments, by choosing a baseline of array expression that had the median intensities (excluded the highest and lowest 2% of probe intensities), and then standardizing all arrays to this baseline (50). In this study, fold change, *Z*-scores and Student's *t*-test were applied to reveal the differential expression of targets among three sample groups. The first group covers target gene expression profiles of the patients in the disease section of the disease-relevant drug targeted tissue, the second group covers the profiles of the patients in the normal section of the tissue adjacent to the disease section and the third group covers the profiles in the tissue of healthy individuals (51). Finally, the *R package ggplot2* was further applied to generate the gene expression plots which were displayed on the TTD official website.

TARGET COMBINATIONS OF MULTI-TARGET DRUGS AND DRUG COMBINATIONS

Targeted therapeutics directed at individual target are frequently insufficient against heterogenetic diseases like cancers, or diseases that affect multiple tissues or cell types such as diabetes and immune-inflammatory disorders. Multi-target drugs (25,26,31) and drug combinations (27,28,52) have been increasingly tested and used for the improved treatment of these heterogenetic and multi-tissue/multi-cell-type diseases, and for overcoming drug resistances. Knowledge of the multiple targets of multi-target drugs are important for determining the clinical therapeutic efficacy particularly in the patients of active drug-bypass genes (26), and for network analysis of the therapeutic efficiency of the multi-targeting actions (31). Knowledge of the multiple targets of the drug combinations is important for optimization of drug combinations (52), selection of different mechanisms of action to minimize resistance (28) and understanding of the mechanisms of the synergistic drug combinations (27). Hence, a resource with convenient access of the target combinations of the multi-target drugs and drug combinations is useful for facilitating the relevant investigations.

The target combinations of the multi-target drugs and drug combinations were collected from the existing database and literature. Specifically, multi-target drugs were from the TTD (11) and ClinicalTrials.gov databases, followed by the literature search for finding their primary therapeutic efficacy targets, and the developmental status of these drugs were also collected. Drug combinations were obtained from the Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/), ClinicalTrials.gov service and additional literature search of PubMed (53) using the combinations of keywords 'drug', 'combination', 'combine', 'plus' and individual target or drug name or synonyms. The primary therapeutic target of each drug in a specific drug combination was identified based on TTD data. By combining the primary therapeutic targets of all drugs in a certain drug combination, a target combination was generated. The biochemical class, structural fold and pathway information of each target in a specific target combination were further searched from the UniProt database (46), CATH Gene3D (54) and KEGG database (55) respectively. By using these information, target combinations can be classified and searched according to their target family pairs, target structural fold pairs and pathway pairs, and such search options are provided in this update of TTD to facilitate the customized search of each target combination.

THE NEW TTD DATA STORAGE AND ACCESS FACILITIES

The TTD database architecture and interface were redesigned for facilitating more convenient access of the new

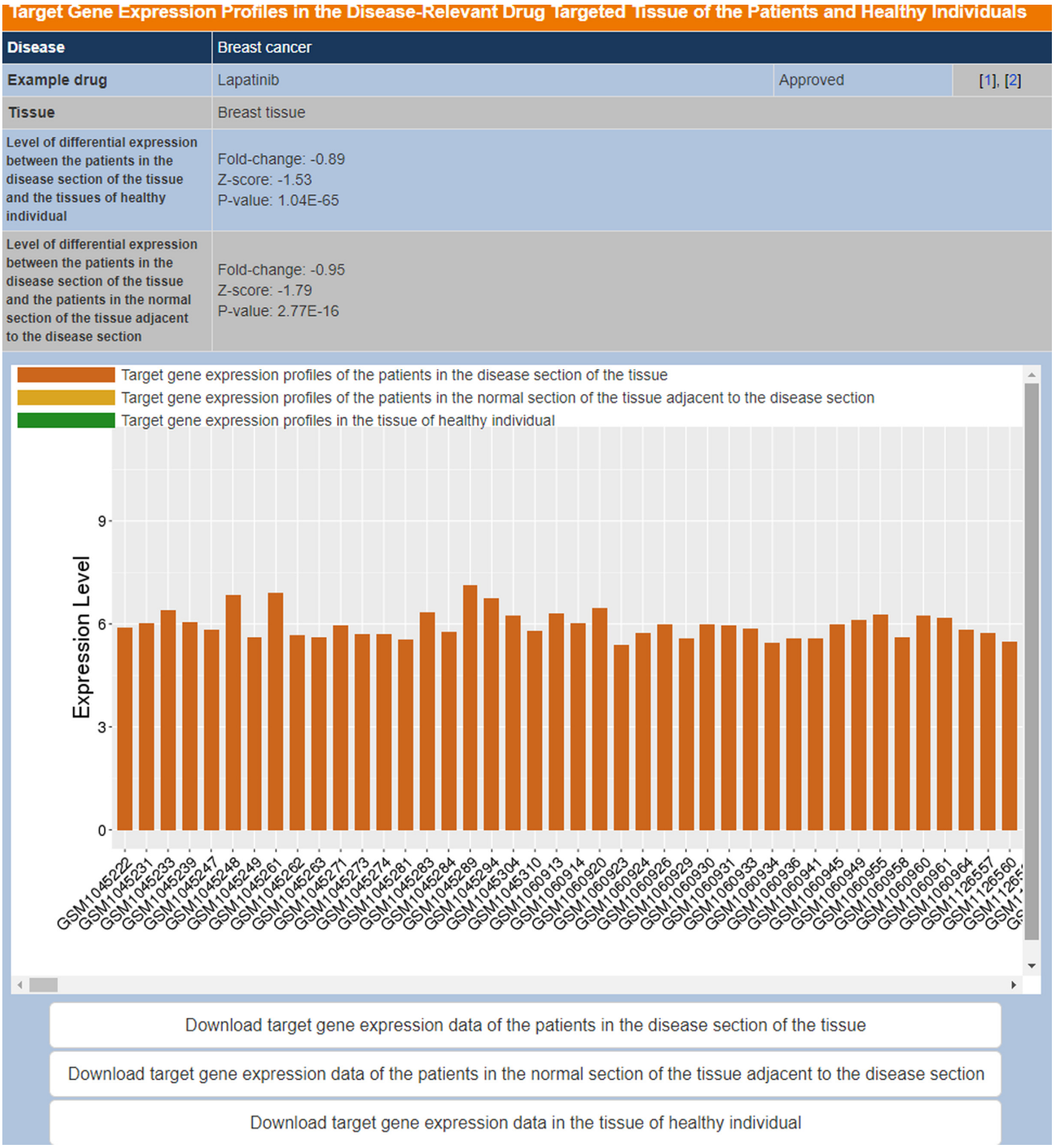

Figure 1. The section of the search result page that presents the gene expression profiles in the disease-relevant drug-targeted tissue of the patients and healthy individuals.

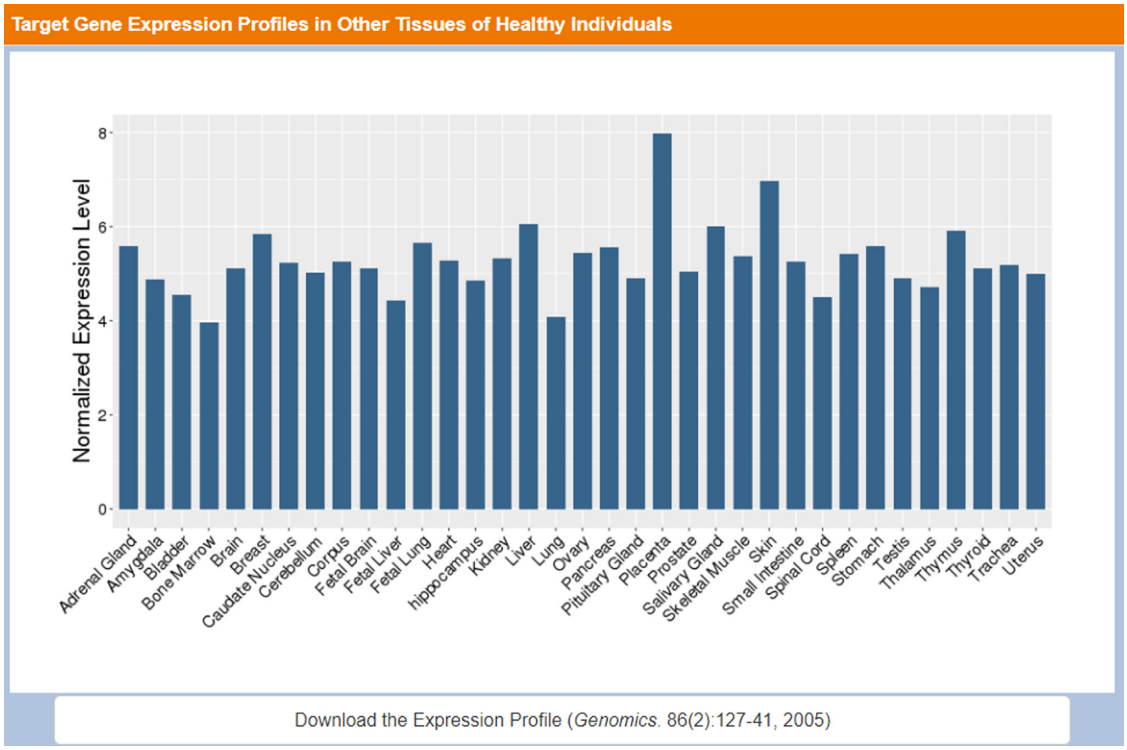

Figure 2. The section of the search result page that presents the gene expression profiles in the other tissues of healthy individuals.

Drug Resistance Mutation and Corresponding Drugs

Mutation Info	Missense: C125S		
Drugs	**Drug Name**	Trametinib	**Drug Info**
	Targeted Disease	Cutaneous Melanoma	[1]
	Mutation Prevalence	1 out of 4 patients	
	Drug Name	Vemurafenib	**Drug Info**
	Targeted Disease	Melanoma	[1]
	Mutation Prevalence	1 out of 76 patients	
	Drug Name	Dabrafenib	**Drug Info**
	Targeted Disease	Melanoma	[1], [2]
	Mutation Prevalence	2 out of 10 patients	
Mutation Info	Missense: E207K		
Drugs	**Drug Name**	Dabrafenib	**Drug Info**
	Targeted Disease	Melanoma	[2]
	Mutation Prevalence	1 out of 10 patients	

Figure 3. The search result page of drug resistance mutations.

as well as existing data. In particular, we employed *Drupal* as the database platform for enhanced data storage and extraction. The more accelerated data access and transmission was made possible by using the cloud platform of *Aliyun* located in the Silicon Valley of USA. In the new TTD interface, the newly added drug resistance mutation and target expression data can be accessed through the Patient Data manual bar, and the target combination information can be accessed through the Targets/Drugs Group manual bar. The Drugs Group manual bar also includes multi-target agents and nature-derived drugs search option. The Advanced Search manual bar includes customized search, target similarity search, drug similarity search and pathway search options. The drug similarity search facility is

further divided into small molecule drug structural similarity search, anti-sense drug nucleotide sequence similarity search and antibody drug amino acid sequence similarity search based on molecular fingerprint Tanimoto coefficient (11), blastn (56) and blastp (56) similarity search methods respectively. Moreover, the JSME Molecule Editor (57) were added for facilitating users to draw a molecule and subsequently search the TTD drug entries that are similar in structure to the input molecule. The Model & Study Data manual bar includes target validation data and QSAR models search options. Figure 1 shows the section of the search result page that presents the gene expression profiles in the disease-relevant drug-targeted tissue of the patients and healthy individuals. Figure 2 shows the section of the search result page that presents the gene expression profiles in the other tissues of healthy individuals. Figure 3 shows the search result page of drug resistance mutations.

PERSPECTIVES

The continuous development of the relevant databases (11,24,58–60) has provided richer and increasingly useful information resources for the therapeutic targets and drugs to better serve the drug discovery and clinical medicine communities. With increasing movement of the modern therapeutics toward stratified and personalized medicines (34), extensive efforts from the research, industry, clinical, regulatory and management communities and the chemistry, biology, pharmaceutics and medicine disciplines have been collectively directed at the discovery, investigation, application, monitoring and management of targeted therapeutics (1). and the novel treatment strategies such as multi-target drugs (25,26,31), drug combinations (27,28,52), monoclonal antibodies (61) and RNA therapeutics (62) for enhanced therapeutics and for overcoming drug resistances (21,22). The TTD and other databases may be further expanded to incorporate the newly derived data and novel knowledge to cater the new needs for the development of novel therapeutics.

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