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TTD: Therapeutic Target Database

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ABSTRACT

A number of proteins and nucleic acids have been explored as therapeutic targets. These targets are subjects of interest in different areas of biomedical and pharmaceutical research and in the development and evaluation of bioinformatics, molecular modeling, computer-aided drug design and analytical tools. A publicly accessible database that provides comprehensive information about these targets is therefore helpful to the relevant communities. The Therapeutic Target Database (TTD) is designed to provide information about the known therapeutic protein and nucleic acid targets described in the literature, the targeted disease conditions, the pathway information and the corresponding drugs/ligands directed at each of these targets. Cross-links to other databases are also introduced to facilitate the access of information about the sequence, 3D structure, function, nomenclature, drug/ligand binding properties, drug usage and effects, and related literature for each target. This database can be accessed at http://xin.cz3.nus.edu.sg/group/ttd/ttd.asp and it currently contains entries for 433 targets covering 125 disease conditions along with 809 drugs/ligands directed at each of these targets. Each entry can be retrieved through multiple methods including target name, disease name, drug/ligand name, drug/ligand function and drug therapeutic classification.

INTRODUCTION

Pharmaceutical agents generally exert their therapeutic effect by binding to a particular protein or nucleic acid target (1,2). So far, hundreds of proteins and nucleic acids have been explored as therapeutic targets (1). Rapid advances in genetic (3), structural (4) and functional (5) information of disease related genes and proteins not only raise strong interest in the search of new therapeutic targets, but also promote the study of various aspects of known targets including molecular mechanism of their binding agents and related adverse effects (6), and pharmacogenetic implications of sequence or proteomic variations (7), etc. The knowledge gained from such a study is important in facilitating the design of more potent, less toxic and personalized drugs. Development of advanced computational methods for bioinformatics (4), molecular modeling (8), drug design and pharmacokinetics analysis (9–11) increasingly uses known therapeutic targets to refine and test algorithms and parameters.

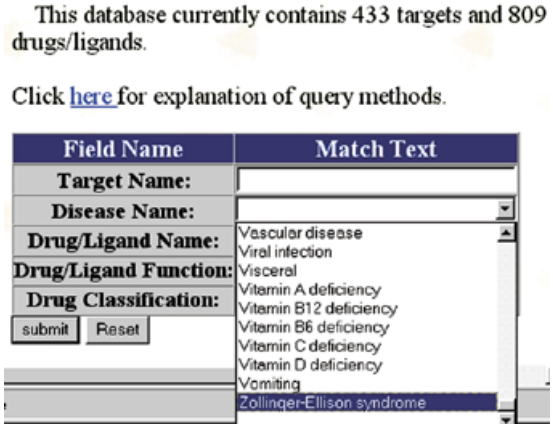

Figure 1. The web interface of TTD. Five types of search mode are supported. This database is searchable by target name, disease name, drug/ligand name, drug/ligand function, drug classification or any combination of these.

A publicly accessible database that provides comprehensive information about these targets is therefore helpful in catering for the need and interest of the relevant communities in general and those unfamiliar with a specific therapeutic target in particular. To the best of the authors' knowledge, such a publicly accessible database is not yet available. In this work, we introduce a Therapeutic Target Database (TTD), which contains information about the known therapeutic protein and nucleic acid targets together with the targeted disease conditions, the pathway information and the corresponding drugs/ligands directed at each of these targets. Cross-links to other databases are introduced to facilitate the access of information regarding the function, sequence, 3D structure, nomenclature, drug/ligand binding properties and related literatures of each target.

The therapeutic targets collected in TTD are from a search of the available literature. It has been reported that, at present, approximately 500 therapeutic targets have been exploited in the currently available medical treatment (1). An effort has been made to collect as many of these known targets as possible. However, description of some of these targets in the literature was not specific enough to point to a particular protein or nucleic acid as the target. Hence these targets are not included in our database.

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Table 1. Disease names listed in TTD (synonyms of disease names are also included to facilitate searching)

Acute lymphoblastic leukemia	Erectile dysfunction	Neuropathic
Addiction	Fever	Obesity
Advanced pancreatic tumor	Fungal infection	Obstructive pulmonary disease
Affective disorder	Gastric tumor	Ocular hypertension/glaucoma
AIDS	Glaucoma	Oral
Allergic rhinitis	Gout	Osteoporosis
Allergy	Heart disease	Ovarian
Alzheimer's	Heart failure	Pain
Analgesic	Helminth infection	Parkinson's
Anesthesia	Hepatitis C	Peptic ulcer
ANF degradation	Herpes	Phaeochromocytoma
Angiogenesis	High blood glucose level	Platelet adhesion
Anxiety	High blood sugar level	Platelet disease
Arthritis	High cholesterol	Posterior pituitary disorder
Asthma	Hirsutism	Postsurgical
Autoimmune disease	Hormone-dependent tumors	Prostate adenocarcinoma
B cell	Human African trypanosomiasis	Prostate tumor
Bacterial infection	Hypertension	Prostatic hyperplasia
Baldness	Hyperthyroidism	Psychiatric illness
Blood coagulation	Hypocalcaemia	Psychomotor
Bone Loss	Immune response	Reproduction
Brain ischaemia	Immunodeficiency	Respiration
Breast	In transplantation, etc.	Rheumatoid
Calcium deficiency	Inflammation	Riboflavin deficiency
Cancer	Influenza A and B	Schizophrenia
Carcinoid syndrome	Insomnia	Seizure
Cardiac failure	Irritable bowel syndrome	Smoking
Cardiovascular disease	Kidney failure	Smooth muscle
Chronic myelogenous leukemia	Leukemia	Solid tumor
Cognitive dysfunction	Liposarcoma	Thiamine deficiency
Colon	Liver	Tuberculosis
Common cold	Local anesthetic	Urinary tract infection
Common roundworm	Lung	Urticaria
Congestive heart failure	Lupus	Uterus contraction
Cystic fibrosis	Malaria	Vascular disease
Dementia	Malignant pain	Viral infection
Depression	Melanoma	Visceral
Diabetes	Metastasis	Vitamin A deficiency
Diabetic retinopathy	Migraine	Vitamin B12 deficiency
Diarrhea	Morning sickness	Vitamin B6 deficiency
Drug dependence	Motion sickness	Vitamin C deficiency
Drug induced	Motor disorder	Vitamin D deficiency
Dry eye	Movement disorder	Vomiting
Dysrhythmic	Nasal congestion	Zollinger-Ellison syndrome
Emphysema	Neurodegeneration	
Epilepsy	Neurological symptom	

Table 2. Drug functions listed in TTD (synonyms of drug functions are also included to facilitate searching)

Activator	Cofactor
Agonist	Immunotoxin
Alkylator	Inactivator
Antagonist	Inhibitor
Antibody	Intercalator
Antisense	Opener
Blocker	Stimulator
Chain breaker	Substrate
Coenzyme	Vaccine

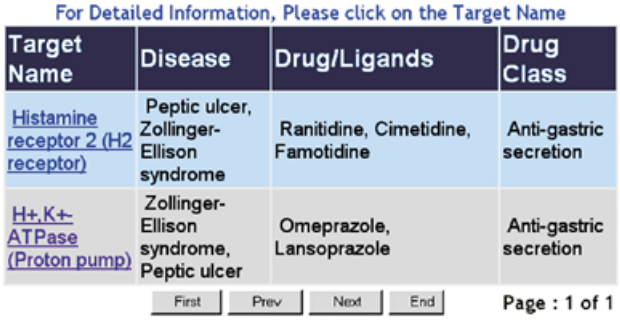


Figure 2. The interface of a search result on TTD. All the targets that satisfy the specified search criteria are listed along with disease, drug/ligand name and drug classification.

Table 3. Drug classifications listed in TTD (synonyms of drug classifications are also included to facilitate searching)

Anesthetic	Antimalarial	Lipid-lowering
Anti-allergic	Antimotility	Local anesthetic
Anti-allergy	Anti-neurodegenerative	Lupus
Anti-androgen	Anti-obesity	Nasal decongestion
Anti-angiogenic	Antiplatelet	Neurological
Anti-asthmatic	Antipsychotic	Opioid overdose
Antibacterial	Antipyretic	Osteoporosis
Anticancer	Antirheumatoid	Ovulation induction
Anti-cholesterol	Antiseptics	Pain-killer
Anticoagulant	Antiviral	Parkinson's
Anticonvulsant	Anxiolytic	Platelet
Antidepressant	Anxiotic	Procoagulant
Antidiabetic	Arthritis	Psychomotor stimulant
Antidiarrheal	Bronchodilator	Psychostimulant
Antidiuretic	Cardiotonic	Psychotomimetic
Antidysrhythmic	Contraceptive	Respiratory stimulant
Anti-emetic	Convulsant	Sedative
Anti-emetics	Depressant	Supplement
Antiepileptic	Diuretics	Uterine contractant
Antifungal	Drug dependence	Uterine relaxant
Anti-gastric secretion	Erectile dysfunction	Vasodilator
Antihelminthic	Glaucoma treatment	Vitamin

DATABASE STRUCTURE AND ACCESS

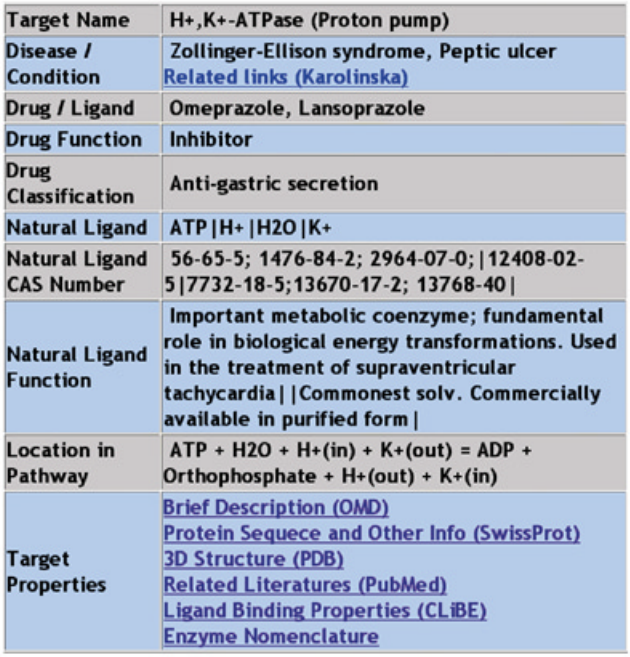
TTD has a web interface at http://xin.cz3.nus.edu.sg/Group/ttd/ttd.asp. The entries of this database are generated from a search of pharmacology textbooks (12,13), review articles (14–21) and a number of recent publications. Our database currently contains 433 entries of protein and nucleic acid targets found from the literature. These targets cover 125 different disease conditions, which are described in the database. Drugs and ligands directed at each of these targets are searched and included in the database. A total of 809 different drugs and ligands are listed in the database.

The TTD database web interface is shown in Figure 1. This database is searchable by target name or drug/ligand name. It can also be accessed by selection of disease name, drug/ligand function or drug therapeutic classification from the list provided in the corresponding selection field. Searches involving any combination of these five search or selection fields are also supported. The lists of disease names, drug/ligand functions and drug classifications are given in Tables 1, 2 and 3, respectively.

The search is case insensitive. In a query, a user can specify full name or any part of the name in a text field, or choose one item from a selection field. Wild characters of '%' and '_' are supported in text field. Here, '_' represents any one character and '%' represents a string of characters of any length. For example, input of 'phosphatase' in the target name field finds entries containing 'phosphatase' in their name, such as Cdc25A phosphatase or tyrosine phosphatase. On the other hand, input of 'Cdc25_ phosphatase' finds entries with names like Cdc25A phosphatase, Cdc25B phosphatase and Cdc25C phosphatase. Likewise, input of Cdc% phosphatase finds the same entries as above. In this case, '%' represents '25A', '25B', '25C', respectively.

The result of a typical search is illustrated in Figure 2. In this interface, all the therapeutic targets that satisfy the search criteria are listed along with the disease conditions to be treated, drugs or ligands directed at the target, and the drug class. More detailed information of a target can be obtained by clicking the corresponding target name. The result is displayed in an interface shown in Figure 3. From this interface, one finds target name, corresponding disease condition and cross-link to Karolinska disease database (http://www.kib.ki.se/), target function in pathway and corresponding natural ligand, known drugs or ligands directed at the target, drug function (such as inhibitor, antagonist and blocker, etc.), drug therapeutic classification, and additional cross-links to other databases that provide useful information about the target.

The functional properties of an identified target can be obtained through cross-linking to the On-line Medical Dictionary (OMD) database (http://www.graylab.ac.uk/omd/) and the SWISS-PROT database (22). The target sequence can be retrieved from cross-link to the SWISS-PROT database. The available 3D structure of this target can be accessed through cross-linking to the Protein Data Bank (PDB) database (23). For an enzymatic target, its nomenclature can be obtained from cross-link to the Enzyme Data Bank (24). Ligand-binding properties may be obtained from cross-link to the Computed



Target Name	H+,K+-ATPase (Proton pump)
Disease / Condition	Zollinger-Ellison syndrome, Peptic ulcer Related links (Karolinska)
Drug / Ligand	Omeprazole, Lansoprazole
Drug Function	Inhibitor
Drug Classification	Anti-gastric secretion
Natural Ligand	ATP|H+|H2O|K+
Natural Ligand CAS Number	56-65-5; 1476-84-2; 2964-07-0;|12408-02-5|7732-18-5;13670-17-2; 13768-40|
Natural Ligand Function	Important metabolic coenzyme; fundamental role in biological energy transformations. Used in the treatment of supraventricular tachycardia||Commonest solv. Commercially available in purified form|
Location in Pathway	ATP + H2O + H+(in) + K+(out) = ADP + Orthophosphate + H+(out) + K+(in)
Target Properties	Brief Description (OMD) Protein Sequece and Other Info (SwissProt) 3D Structure (PDB) Related Literatures (PubMed) Ligand Binding Properties (CLiBE) Enzyme Nomenclature

Figure 3. Interface of the detailed information of target in TTD. Information related to disease, drug/ligand, pathway and some of the cross-database shortcuts are provided. In the case of one target having multi ligands, the ligands are separated with '|', as well as their functions and CAS numbers.

Ligand Binding Energy database (CliBE) (http://xin.cz3.nus.edu.sg/group/CLiBE.asp). The related literature can be accessed from cross-link to the relevant entries in the PubMed database (25).

As the research in proteomics (26) and pathways (27) progresses, the relevant information can be incorporated or the corresponding databases can be cross-linked to TTD to provide more comprehensive information about the drug targets and their relationship to other biomolecules and cellular processes.

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