



The TDR Targets Database

An introduction



What is TDR Targets?

TDR Targets is an online [resource, database, tool] that integrates genomic information relevant for drug discovery on pathogens that cause human diseases.

TDR Targets facilitates the prioritization of targets in complete genomes by allowing users to search for targets using defined criteria AND to weight these searches.

Which organisms and diseases are covered?

- **Malaria**
 - *Plasmodium falciparum*
 - *Plasmodium vivax*
- **Tuberculosis**
 - *Mycobacterium tuberculosis*
- **Leprosy**
 - *Mycobacterium leprae*
- **Toxoplasmosis**
 - *Toxoplasma gondii*
- **Filariasis**
 - *Brugia malayi*
- **African trypanosomiasis**
(Sleeping sickness)
 - *Trypanosoma brucei*
- **Leishmaniasis**
 - *Leishmania major*
- **American trypanosomiasis**
(Chagas Disease)
 - *Trypanosoma cruzi*
- **Schistosomiasis**
 - *Schistosoma mansoni*

An overview of the website

Search for targets using relevant criteria

View your searches, and prioritize targets by weighting and combining your queries

Look for lists of targets posted by others

Read or Participate in our survey on drug targets to know about targets that are being pursued by different groups

The screenshot shows the TDR Targets Database website. At the top, there is a blue header with the title 'TDR Targets Database' and the subtitle 'Identification and ranking of targets against neglected tropical diseases'. A search bar is located on the right side of the header. Below the header is a yellow navigation bar with links for 'home', 'new search', 'history', 'posted lists of targets', 'drug targets survey', and 'user manual'. The main content area is white and contains a 'Welcome' message, a 'Getting started' section with a bulleted list of instructions, and a 'Summary of available data:' section. On the right side, there is a blue sidebar with two news items: 'TDR Targets site updated' and 'Pilot survey on drug targets for Human African Trypanosomiasis'. Arrows from the surrounding text point to specific elements: 'Search' points to the search bar, 'View your searches...' points to the 'history' link, 'Look for lists...' points to the 'posted lists of targets' link, and 'Read or Participate...' points to the 'drug targets survey' link.

TDR Targets Database
Identification and ranking of targets against neglected tropical diseases

Search

Login | Register | Documentation | Contact | FAQ

home | new search | history | posted lists of targets | drug targets survey | user manual

Welcome
This site is part of a WHO/TDR project seeking to exploit the availability of diverse datasets, from multiple species, to facilitate target identification and prioritization in pathogens causing neglected diseases.

Drug target discovery has provided the primary motivation for this project, but these tools may also be useful for other applications (e.g. diagnostic or vaccine target identification). See [Enhancing Drug Discovery for Neglected Tropical Diseases](#) and [Innovative lead discovery strategies for tropical diseases](#) for insight into how this project fits into the larger landscape of parasite drug discovery efforts.

Getting started

- ◆ To search for gene/protein targets, click on **search** above.
- ◆ To examine queries that you have previously run, click on **history**.
- ◆ Below you will find a table summarizing the available data for each TDR target organism.

Summary of available data:

TDR Targets site updated
Posted: 7.June.2007

The TDR Targets site has been updated. This update brings new functionality that allow users to publish individual queries and/or query sets; and an update of the data from the ongoing curation effort that now includes *Leishmania* and *Plasmodium*.

Pilot survey on drug targets for Human African Trypanosomiasis.
Posted: 11.April.2007

A pilot survey on drug targets for Human African Trypanosomiasis is being run now. The idea to survey the scientific community came from a workshop on Drug Discovery for Trypanosomatid Diseases (Dundee, February 2007). This exercise will be used to design similar surveys for other neglected infectious diseases. The output of this community-driven survey will be posted on this site. For more information about the survey see [The Scientific Community Human African Trypanosomiasis Drug Target Survey](#).

<http://tdrtargets.org>

Searching for targets

- In the next slides, we will give you a tour of **TDR Targets**, showing you how you can search for targets.
- In this first example we will be interested in searching for targets in *Plasmodium falciparum*, the causative agent of Malaria.

Start a new search

TDR Targets Database

Identification and ranking of targets against neglected tropical diseases

Search

[Login](#) | [Register](#) | [Documentation](#) | [Contact](#) | [FAQ](#)

1. →

[home](#) | [new search](#) | [history](#) | [posted lists of targets](#) | [drug targets survey](#) | [user manual](#)

2. →

1. Select pathogen species of interest

- | | |
|---|--|
| <input type="checkbox"/> <i>Mycobacterium leprae</i> | <input type="checkbox"/> <i>Mycobacterium tuberculosis</i> |
| <input type="checkbox"/> <i>Wolbachia endosymbiont of Brugia malayi</i> | <input type="checkbox"/> <i>Brugia malayi</i> |
| <input type="checkbox"/> <i>Schistosoma mansoni</i> | <input type="checkbox"/> <i>Plasmodium falciparum</i> |
| <input type="checkbox"/> <i>Plasmodium vivax</i> | <input type="checkbox"/> <i>Toxoplasma gondii</i> |
| <input type="checkbox"/> <i>Leishmania major</i> | <input type="checkbox"/> <i>Trypanosoma brucei</i> |
| <input type="checkbox"/> <i>Trypanosoma cruzi</i> | |

search

reset

Specify your search criteria (1)

Our first search will look for *enzymes* as these are usually good drug targets. For this, we expand the corresponding section, and check the corresponding box for **Functional category**.

3. →

Name / Annotation

[+](#) Search for targets using keywords (names, functions, identifiers).

Name:	<input type="text"/>	[e.g. farnesyl, kinase, pyrophosphatase]
Identifier /Accession	<input type="text"/>	[e.g. LmjF22.1360, PF11_0295, tbr3370]
EC number:	<input type="text"/>	[e.g. 2.5.1.10, or use ** or type 'any']
Gene Ontology:	<input type="text"/>	[GO id/term (GO:0020011, apicoplast)]
Pfam / Interpro domains:	<input type="text"/>	[accession number or description]
Functional category:	<input checked="" type="checkbox"/> Enzyme <input type="checkbox"/> Receptor <input type="checkbox"/> Transporter	[This is a curated classification]
GO Slim category:	<input type="text" value="--"/>	[based on GO slim subsets]
KEGG high-level pathway:	<input type="text" value="--"/>	[pathway mappings according to KEGG]
KEGG detailed pathway:	<input type="text" value="--"/>	[pathway mappings according to KEGG]

Specify your search criteria (2)

Our next search will look for genes that don't have orthologs in humans or mice. To do this, we expand the *Phylogenetic distribution* section of the search page and select the appropriate options in the pull down menus.

4. →

Phylogenetic distribution

[+](#) Search for targets based on their phylogenetic distribution.

Restrict to targets with orthologs (present/absent) in:

<input type="text" value="—"/>	<i>Drosophila melanogaster</i>	<input type="text" value="—"/>	<i>Escherichia coli</i>
<input type="text" value="—"/>	<i>Mycobacterium leprae</i>	<input type="text" value="—"/>	<i>Mycobacterium tuberculosis</i>
<input type="text" value="—"/>	<i>Wolbachia endosymbiont of Brugia malayi</i>	<input type="text" value="—"/>	<i>Saccharomyces cerevisiae</i>
<input type="text" value="—"/>	<i>Brugia malayi</i>	<input type="text" value="—"/>	<i>Caenorhabditis elegans</i>
<input type="text" value="—"/>	<i>Schistosoma mansoni</i>	<input type="text" value="Not in"/>	<i>Homo sapiens</i>
<input type="text" value="Not in"/>	<i>Mus musculus</i>	<input type="text" value="—"/>	<i>Plasmodium falciparum</i>
<input type="text" value="—"/>	<i>Plasmodium vivax</i>	<input type="text" value="—"/>	<i>Toxoplasma gondii</i>
<input type="text" value="—"/>	<i>Leishmania major</i>	<input type="text" value="—"/>	<i>Trypanosoma brucei</i>
<input type="text" value="—"/>	<i>Trypanosoma cruzi</i>		

Specify your search criteria (3)

Next, we look for genes that showed essential phenotypes upon knockout. Because there is no genome-wide data for *P. falciparum*, **TDR Targets** does an **indirect search**, looking for essential genes in model organisms first and then mapping these genes to the corresponding *P. falciparum* orthologs.

5. →

Essentiality

[+ Search for targets that are essential/inviable.](#)

Retrieve targets for which genome-wide information about their essentiality is available.
If genome-wide information for an organism is not available, you can evaluate the essentiality of t different species from the options below. Also note that essential genes for your organism of inter the **Validation data** search option further down).

Any evidence of essentiality in *any* species

Or

Select the species and the type of 'essential' phenotype from the options below: note that if you s genes will be the UNION (boolean OR) of the selection.

<input type="text" value="C. elegans"/>	<input type="text" value="--"/>
<input type="text" value="E. coli"/>	<input type="text" value="--"/>
<input type="text" value="M. tuberculosis"/>	<input type="text" value="--"/>
<input type="text" value="S. cerevisiae"/>	<input type="text" value="--"/>

Combine the three queries

TDR Targets Database

Identification and ranking of targets against neglected tropical diseases

Search

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6. →

[home](#) | [new search](#) | **[history](#)** | [posted lists of targets](#) | [drug targets survey](#) | [user manual](#)

7. →

Select: All, None.

1: pfalciparum enzymes, 862 records. [Export](#) | [Show parameters](#) | [Delete](#)

Weight: | Rename:

2: pfalciparum not in the host, 3468 records. [Export](#) | [Show parameters](#) | [Delete](#)

Weight: | Rename:

3: pfalciparum essential in any, 1162 records. [Export](#) | [Show parameters](#) | [Delete](#)

Weight: | Rename:

Select: All, None.

Combine or act on selected queries

Union: genes that appear in **any** of the selected queries.

Intersection: genes that appear in **all** of the selected lists.

In this example, we ask for the INTERSECTION of the three queries.

As a result we will obtain genes that meet all the criteria specified in these three queries.

Browse results

Click the links to go to the corresponding gene page.

8. →

Organism	Name	Ortholog group	Product
P. falciparum 3D7	MAL13P1.214	OG1.2_6498	phosphoethanolamine N-methyltransferase, putative
P. falciparum 3D7	PFB0505c	OG1.2_4172	beta-ketoacyl-acyl carrier protein synthase III precursor, putative
P. falciparum 3D7	PFB0890c	OG1.2_2634	pseudouridine synthetase, putative
P. falciparum 3D7	PFD0980w	OG1.2_4601	holo-(acyl-carrier protein) synthase, putative
P. falciparum 3D7	PFE0150c	OG1.2_4390	4-diphosphocytidyl-2c-methyl-D-erythritol kinase (CMK), putative
P. falciparum 3D7	PFE0705c	OG1.2_1171	helicase, belonging to UvrD family, putative
P. falciparum 3D7	PFE1030c	OG1.2_2632	phosphomethylpyrimidine kinase, putative
P. falciparum 3D7	PFF0730c	OG1.2_4181	enoyl-acyl carrier reductase
P. falciparum 3D7	PFF1105c	OG1.2_2862	chorismate synthase
P. falciparum 3D7	PFI1100w	OG1.2_3806	para-aminobenzoic acid synthetase
P. falciparum 3D7	PFL1120c	OG1.2_2861	DNA GyrAse a-subunit, putative
P. falciparum 3D7	PFL1270w	OG1.2_664	cof-like hydrolase, had-superfamily, subfamily iib
P. falciparum 3D7	PFB0420w	OG1.2_4173	2C-methyl-D-erythritol 2,4-cyclodiphosphate synthase
P. falciparum 3D7	PFA0225w	OG1.2_3660	LytB protein

Viewing information for a gene

- In the next few slides we will show you how the information for each gene is layed out in **TDR Targets**.
- Apart from the usual collection of information derived from the genome annotation (EC numbers, Pfam domains, GO terms), **TDR Targets** also includes information on druggability, orthologs, essentiality, validation and assayability, expression, and other pieces of information relevant for drug target validation.
- Furthermore, there is an ongoing process of curation. Although not complete, some targets have curated information on phenotypes caused by gene knockouts/knockdowns, or by inhibition with drugs.

Detailed view for *P. falciparum* PFB0505c

- **TDR Targets** includes the same information that can be found in other genome databases

Detailed view for PFB0505c

Basic information

TDR Targets ID: 3378

P. falciparum 3D7, beta-ketoacyl-acyl carrier protein synthase III precursor, putative

Source Database / ID: [PlasmoDB 5.0](#) / PFB0505c

pi: 8.69 | **Length (AA):** 371 | **MW (kDa):** 42325 | **Number of Paralogs:** 1 | **EC number:** | **EC number:** 2.3.1.41 2.3.1.85

Signal peptide: Y | **GPI Anchor:** N ([Show evidence](#)) | **Predicted trans-membrane segments:** 0

Detailed view for *P. falciparum* PFB0505c

- But **TDR Targets** also integrates information from other databases.
- In this example it integrates information from **KEGG** (metabolic pathways), **Modbase** (structural models), **PlasmoDB** (expression), **OrthoMCL** (orthologs), and **Antigenicity** (predicted in-house).

Pfam domains

No Pfam domain information for this protein.

Gene Ontology

Biological Process:

⇒ [GO:0006633](#) fatty acid biosynthesis

Cellular component:

⇒ [GO:0020011](#) apicoplast

Molecular Function:

⇒ [GO:0004315](#) 3-oxoacyl-[acyl-carrier-protein] synthase activity

Metabolic Pathways

⇒ [Fatty acid biosynthesis](#) (KEGG)

Functional classes

[GO:0009987](#) cellular process

[GO:0016740](#) transferase activity

Structural information

Modbase 3D models: ⇒ [PFB0505c](#)

PDB structures: no structure available for this protein in the PDB.

Expression

Upregulation ranking: this gene ranks in the upper 60-80% group of genes.
Shows this level of upregulation in: merozoite.

Upregulation ranking: this gene ranks in the mid 40-60% group of genes.
Shows this level of upregulation in: late trophozoite.

Upregulation ranking: this gene ranks in the lower 20-40% group of genes.
Shows this level of upregulation in: early schizont, early trophozoite.

References

PlasmoDB: Data on upregulation of *P. falciparum* genes in different life cycle stages. PlasmoDB.

Antigenicity

Number of putative antigenic epitopes: 17

Cumulative epitope score: 18.9

Normalized epitope score: 5.1

Percentile: 90.5 (this protein belongs to the top 9.5% proteins in the genome)

[+/-] [More information on this prediction ...](#)

Orthologs

OrthoMCL cluster: [OG1.2_4172](#)

Number of Paralogs: 1

Escherichia coli K12 [gi|16129054|ref|NP_415609.1|](#) | ⇒ [OrthoMCL](#)

Mycobacterium tuberculosis [Rv0533c](#) | ⇒ [OrthoMCL](#)

P. falciparum 3D7 PFB0505c (**this record**). | ⇒ [OrthoMCL](#)

Plasmodium vivax [Pv002960](#) | ⇒ [OrthoMCL](#)

Toxoplasma gondii [44.m00012](#) | ⇒ [OrthoMCL](#)

Wolbachia endosymbiont of *Brugia malayi* [Wbm0614](#) | ⇒ [OrthoMCL](#)

Detailed view for *P. falciparum* PFB0505c

- **TDR Targets** also includes information relevant to drug target validation.
- **Essentiality** data is collected from many experimental studies done mostly on model organisms.
 - In this example, the *M. tuberculosis* ortholog of PFB0505c has been shown to be non-essential. Furthermore, out of 4 genome-wide studies in *E. coli* 3 have found the gene also to be non-essential in this organism.
- **Phenotypes** have been manually curated from the literature.
 - In this case, there are two curated phenotypes: a lethal phenotype affecting growth of bloodstream forms, observed *in vivo*; and a decreased catalytic activity observed *in vitro* by specific inhibition.

Essentiality

PFB0505c has essentiality data

Gene/Ortholog: mtu541 (OG1.2_4172); **Phenotype:** non-essential; **Source study:** nmpdr

Gene/Ortholog: eco1055 (OG1.2_4172); **Phenotype:** undefined; **Source study:** blattner

Gene/Ortholog: eco1055 (OG1.2_4172); **Phenotype:** essential; **Source study:** gerdes

Gene/Ortholog: eco1055 (OG1.2_4172); **Phenotype:** non-essential; **Source study:** keio

Gene/Ortholog: eco1055 (OG1.2_4172); **Phenotype:** non-essential; **Source study:** shigen

[\[+/-\] Show essentiality data references.](#)

Phenotypes (curated)

Annotated phenotypes:

Affected entity: growth (GO:0040007) [\[+/-\] show term definition](#)

Phenotypic quality: lethal (sensu genetics) (PATO:0000718) [\[+/-\] show term definition](#)

Occurs in (anatomic term): single cell organism (CARO:0000064) [\[+/-\] show term definition](#)

Occurs at (time term): bloodstream stage (PLO:0040)

Evidence: in vivo inhibition (TDR:00016)

Observed in: Plasmodium falciparum (⇒ NEWT:5833)

Annotated by: saralph@unimelb.edu.au.

References: ⇒ 11856024 ⇒ 15047563 ⇒ 8917558

Affected entity: catalytic activity (GO:0003824) [\[+/-\] show term definition](#)

Phenotypic quality: decreased (PATO:0000468) [\[+/-\] show term definition](#)

Occurs in (anatomic term): in vitro (MI:0492) [\[+/-\] show term definition](#)

Occurs at (time term): NULL (NULL:0000000)

Evidence: inferred from specific protein inhibition (ECO:0000020) [\[+/-\] show term definition](#)

Observed in: Plasmodium falciparum (⇒ NEWT:5833)

Annotated by: saralph@unimelb.edu.au.

References: ⇒ 7909690 ⇒ 9425362 ⇒ 9598156

No validation aspects annotated for this target.

Detailed view for *P. falciparum* PFB0505c

- **TDR Targets** also includes information relevant to drug target validation.
- **Druggability** data has been contributed from pharma partners (Pfizer, Inpharmatica).
 - In this example, PFB0505c has a druggability index of **0.6** (max is 1), and the known drug target orthologs have a mean number of 10 compounds with a chemical desirability index of **0.47** (max is 1).
- **Associated compounds** have been manually curated, collected from homologues in DrugBank or extracted from the literature for this gene.
- Information on **assays** has been obtained from Sigma-Aldrich; and availability of **recombinant soluble proteins** has been obtained from structural genomics consortia.

Druggability

Druggability index (max is 1): 0.6

Mean compound desirability (max is 1): 0.47

Mean number of compounds: 10.75

Associated compounds

Note: at this moment the information about chemical compounds linked to a gene coming from a semi-automated scanning of a relevant subset of the literature.

Do send us a note: if you have information about compounds for this gene.

5 chemical compounds are associated with this gene.

Contact us: if you have information about compounds for this gene.

Assayability

Assay information

No assay information for this target.

Reagent availability (recombinant soluble protein)

No reagent availability information for this target.

Bibliographic references

8 literature references were collected for this gene.

Contact us: if you have references for this gene.

That's all for now

- In this quick tour of the **TDR Targets** database, we showed you which organisms are the focus of our database, how you can search for potential targets, and what types of information we have collected for each gene.
- There are other aspects of **TDR Targets** that we didn't cover in this tutorial. For more quick guides, please head to
 - <http://tdrtargets.org/tutorials> or
 - <http://slideshare.net/tdrtargets>
- Some of the slideshows available are:
 - Prioritizing targets in whole genomes using TDR Targets
 - Target Surveys in TDR Targets
 - Sharing information with others in TDR Targets