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.

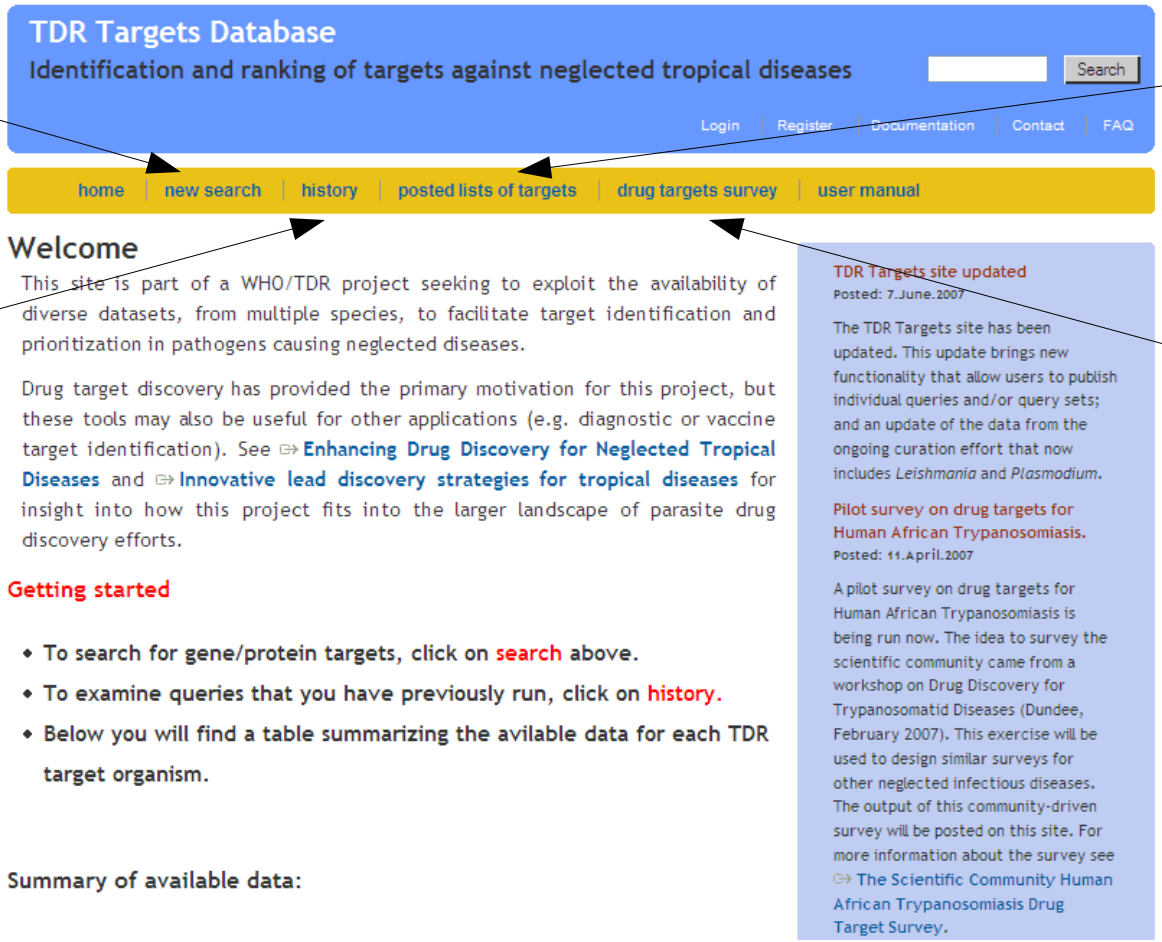
Which organisms and diseases are covered?

- **Malaria**
  - *Plasmodium falciparum*
  - *Plasmodium vivax*
- **Tuberculosis**
  - *Mycobacterium tuberculosis*
- **Leprosy**
  - *Mycobscterium 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

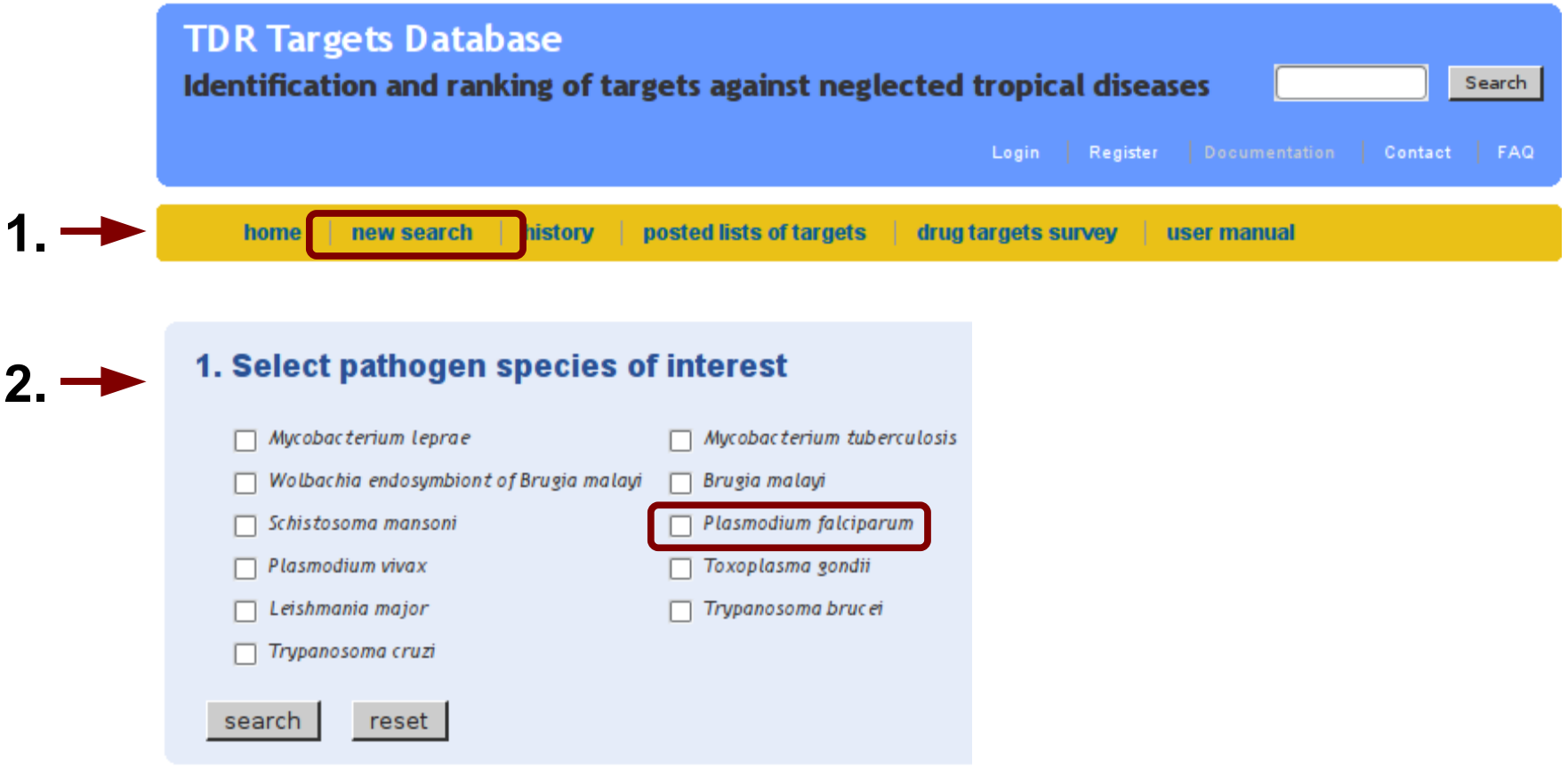
Read or **Participate** in our survey on drug targets to know about targets that are being pursued by different groups

http://tdrtargets.org

Searching for targets

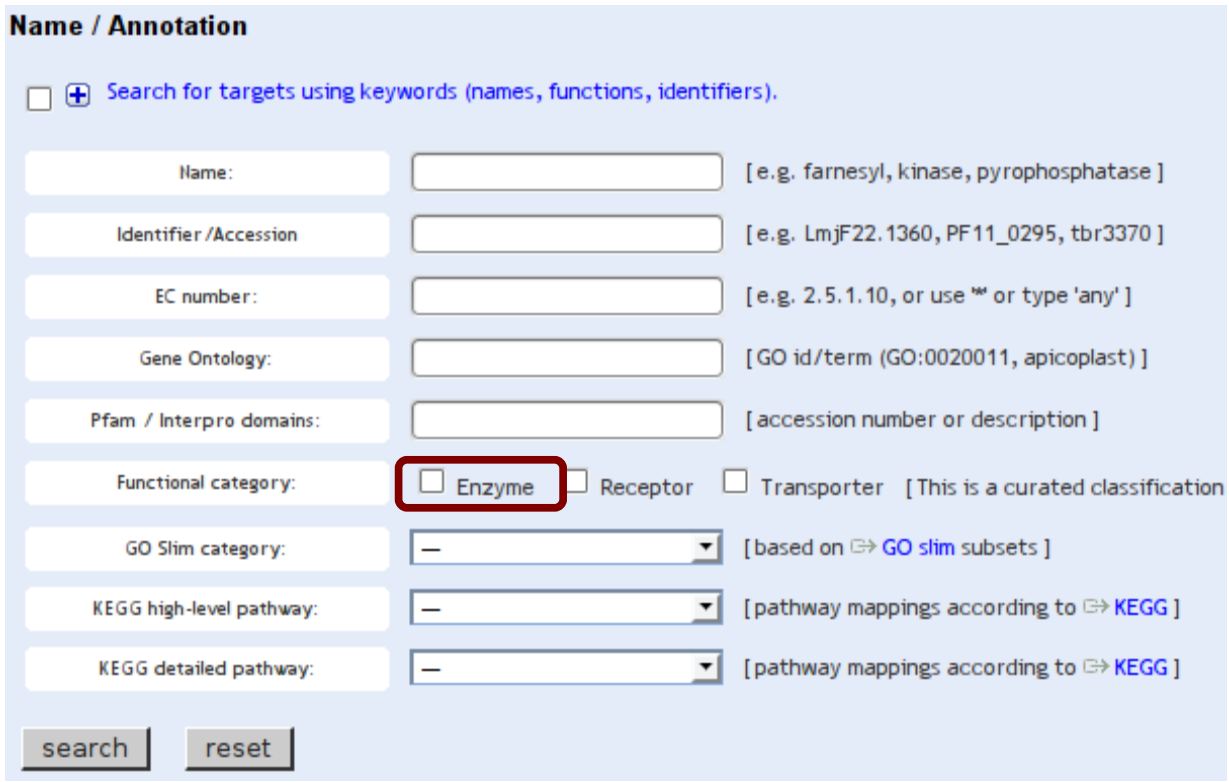
- In the next slides, we will give you a tour of **TDR Targets**, showing you how you can search for targets.
- In this first example we will be interested in searching for targets in *Plasmodium falciparum*, the causative agent of Malaria.

Start a new search



Specify your search criteria (1)

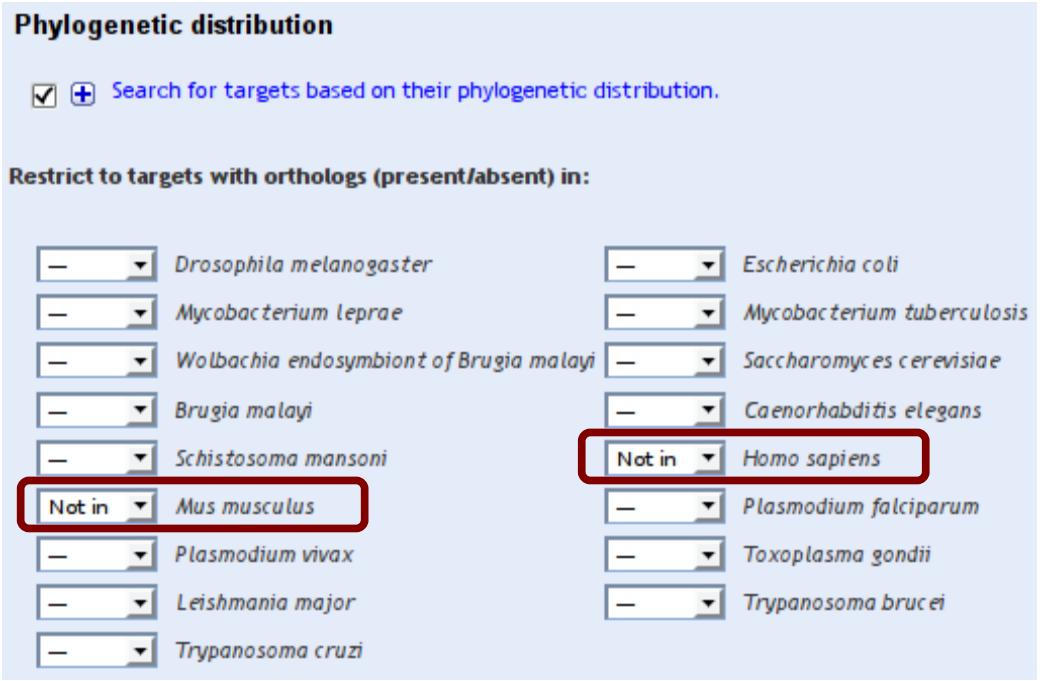
Our first search will look for *enzymes* as these are usually good drug targets. For this, we expand the corresponding section, and check the corresponding box for **Functional category.**

3. 

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.

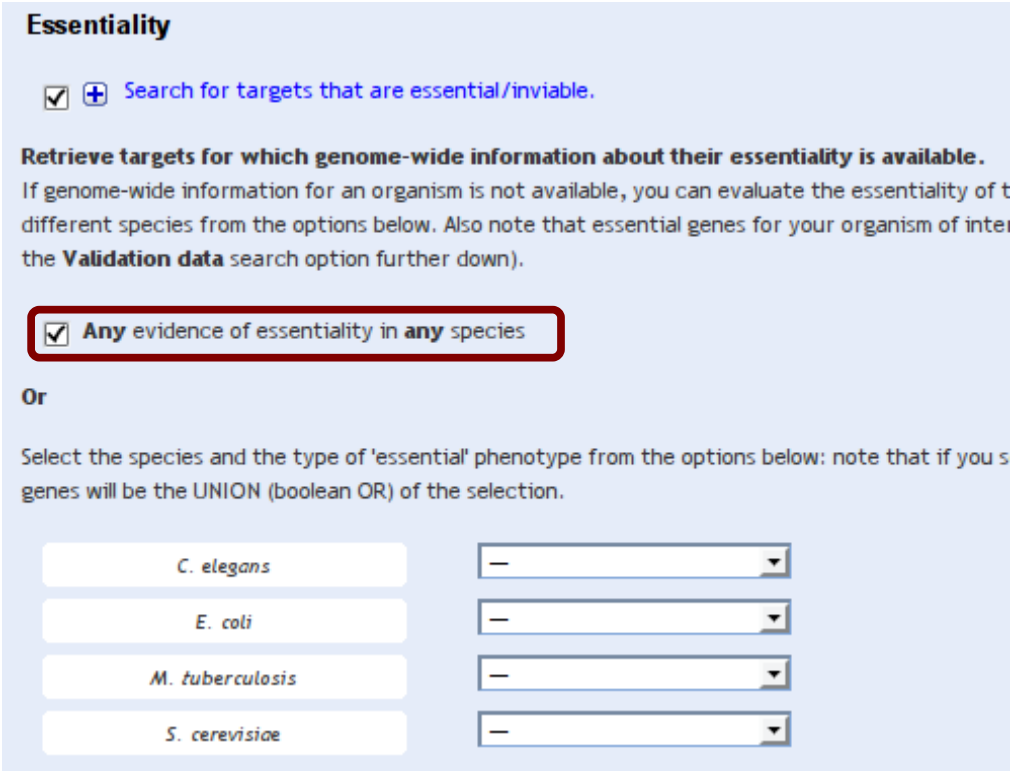
4. →



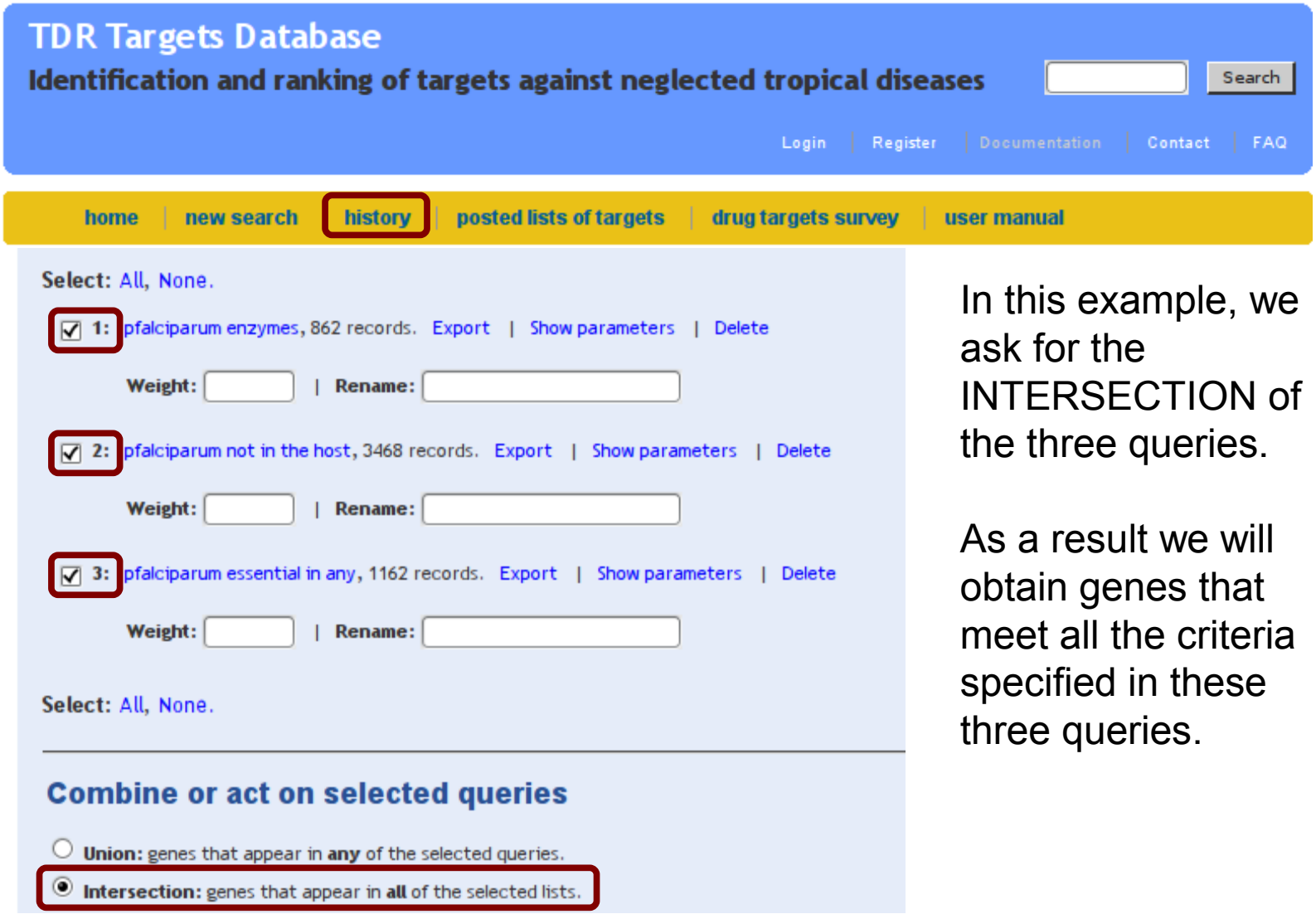
Specify your search criteria (3)

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. →



Combine the three queries



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.

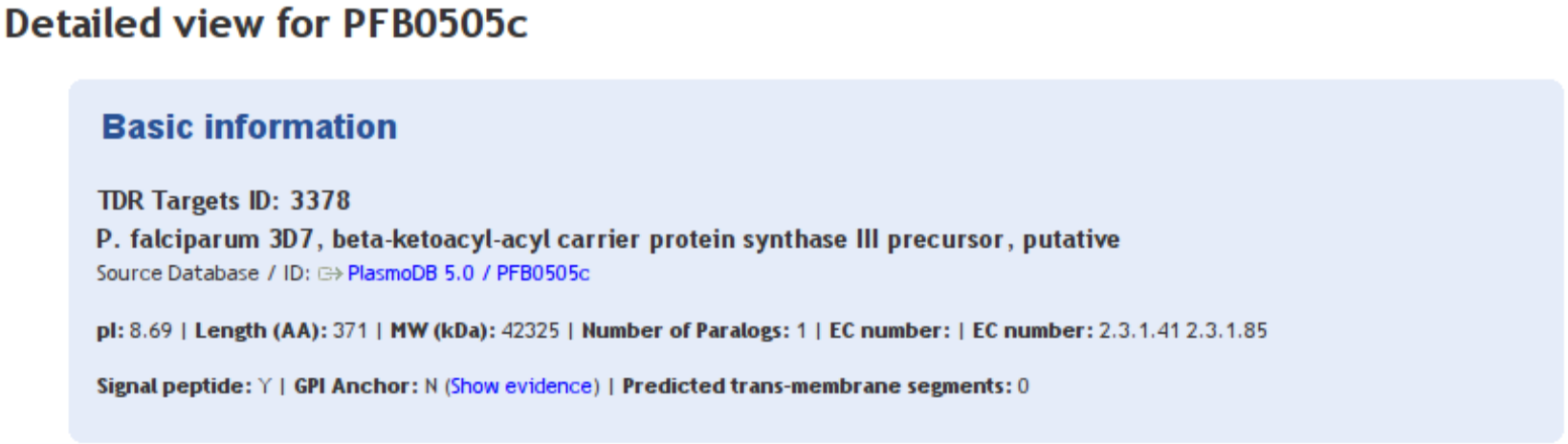
Organism	Name	Ortholog group	Product
P. falciparum 3D7	MAL13P1.214	OG1.2_6498	phosphoethanolamine N-methyltransferase, putative
P. falciparum 3D7	PFB0505c	OG1.2_4172	beta-ketoacyl-acyl carrier protein synthase III precursor, putative
P. falciparum 3D7	PFB0890c	OG1.2_2634	pseudouridine synthetase, putative
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.

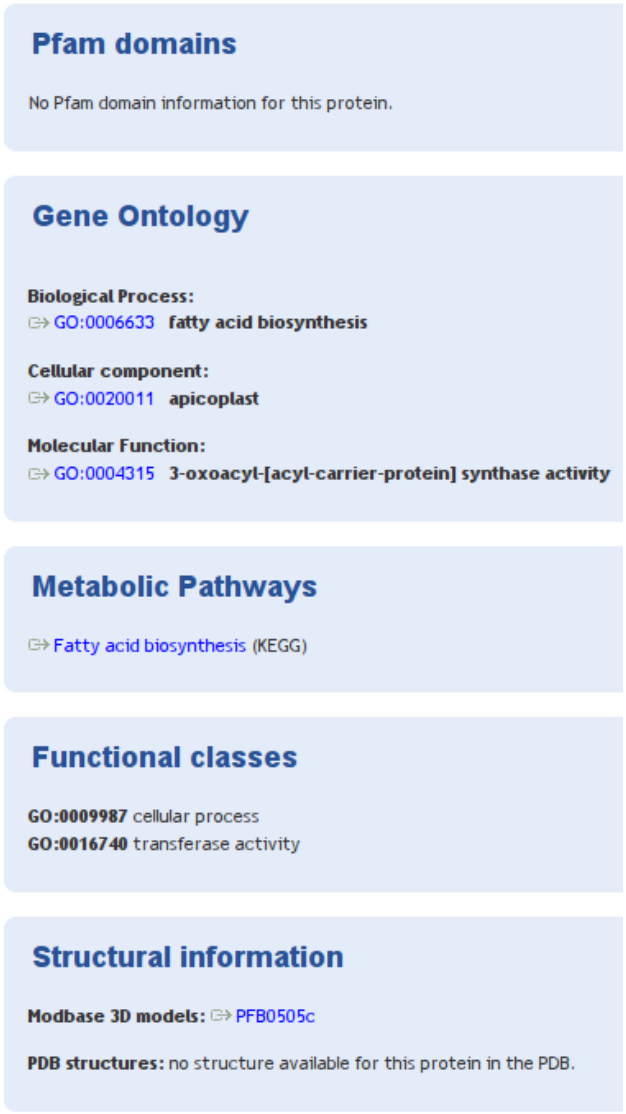
Detailed view for *P. falciparum* PFB0505c

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



Detailed view for *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)

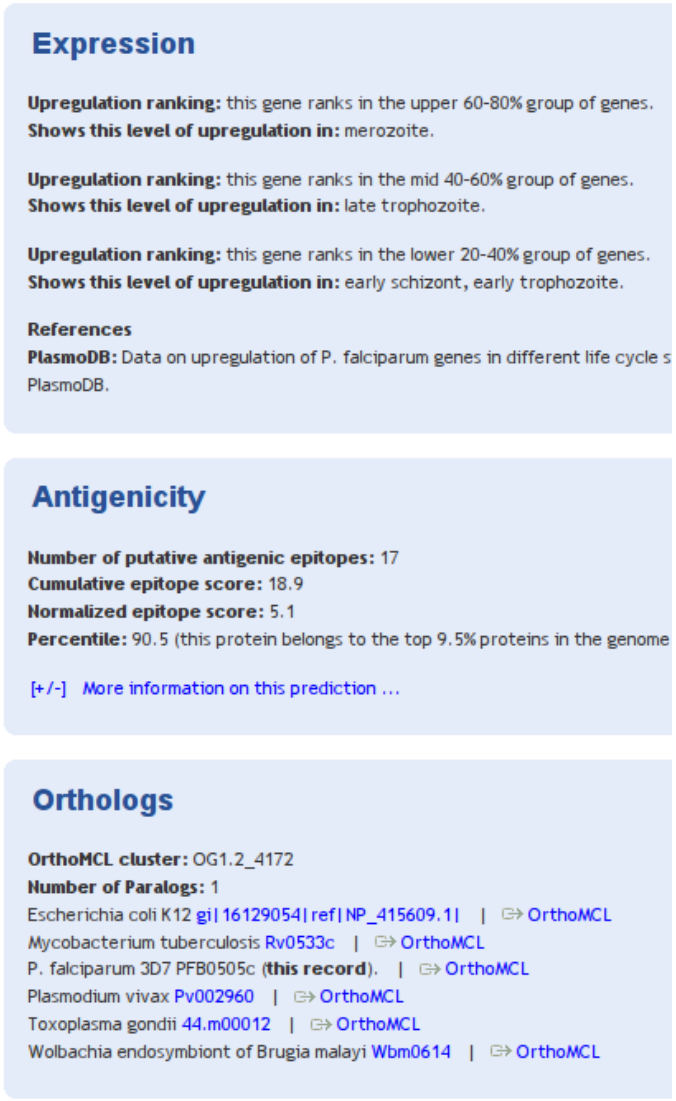
Functional classes

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 s
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

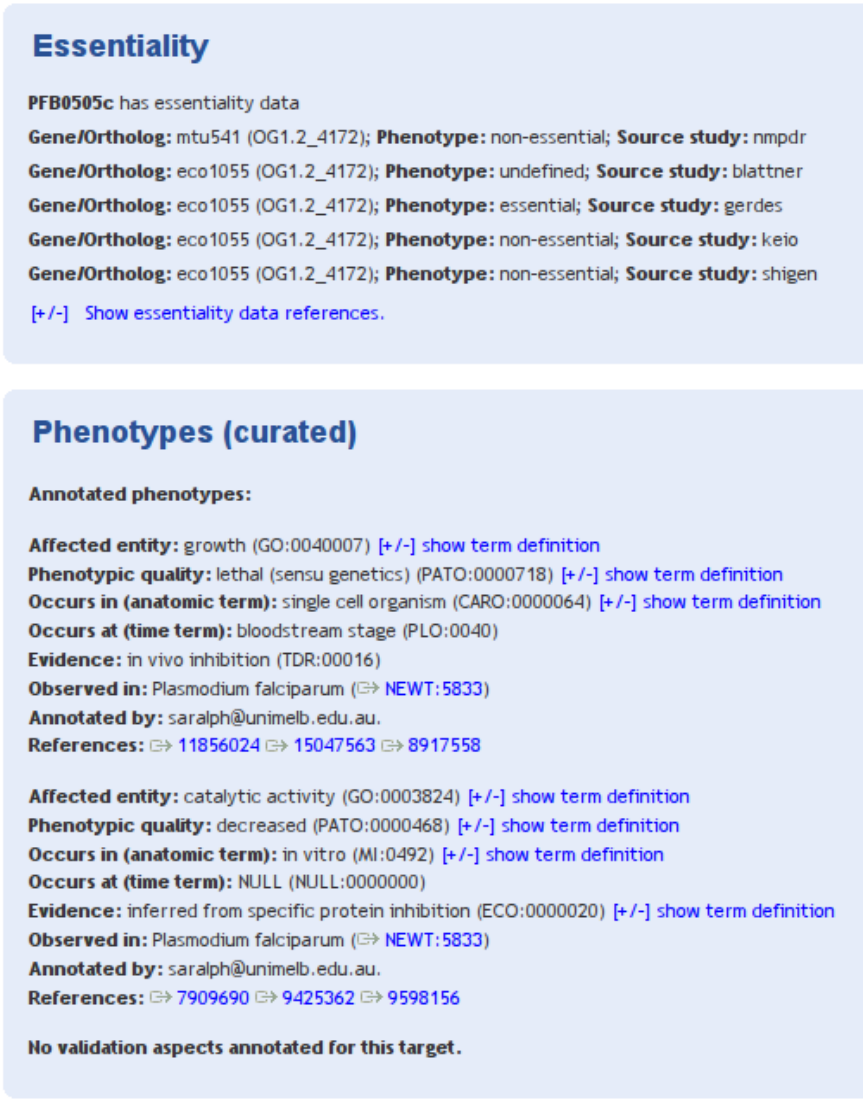
OrthoMCL cluster: OG1.2_4172
Number of Paralogs: 1
Escherichia coli K12 gi|16129054|ref|NP_415609.1| | OrthoMCL
Mycobacterium tuberculosis Rv0533c | OrthoMCL
P. falciparum 3D7 PFB0505c (**this record**). | OrthoMCL
Plasmodium vivax Pv002960 | OrthoMCL
Toxoplasma gondii 44.m00012 | OrthoMCL
Wolbachia 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.

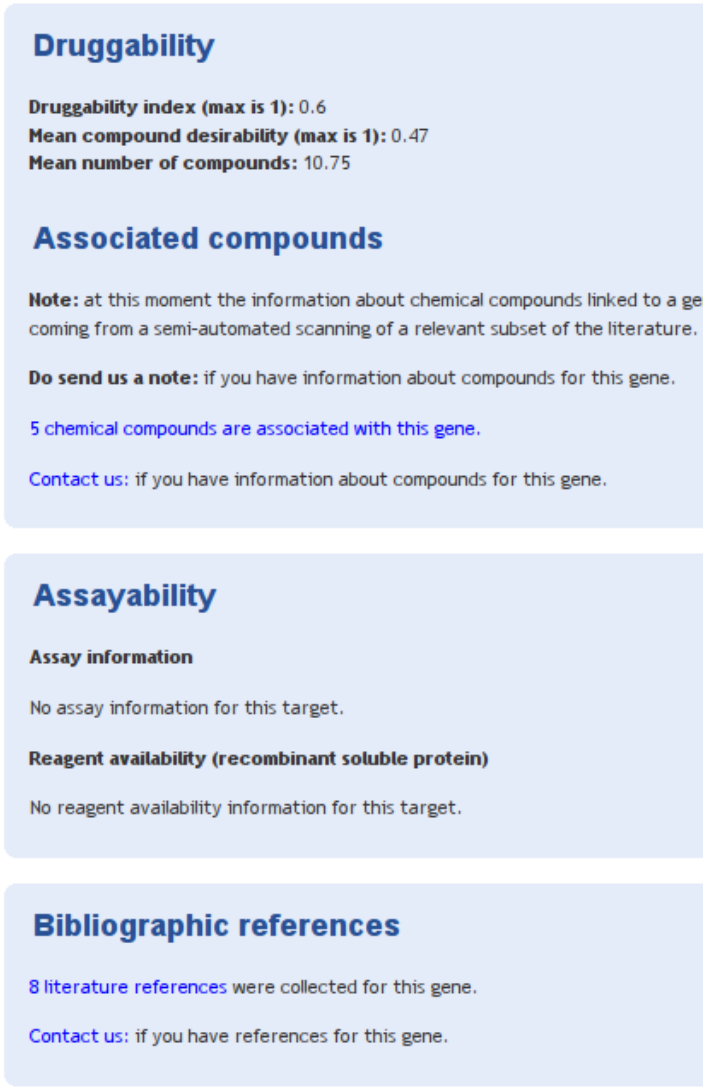
Detailed view for *P. falciparum* PFB0505c

- **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.



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