

Bioinformatics of Thymidine metabolism in camels and *Trypanosoma evansi*: nucleoside deoxyribosyltransferase (NDRT) as a drug target

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Abstract

Background *Trypanosoma evansi* (*T. evansi*), the causative agent for surra or camel trypanosomiasis, is characterized by the widest geographic distribution and infects the widest range of hosts among the known trypanosomes. The recent zoonotic importance and increasing reports of drug resistance necessitate the discovery of new drug targets. Drug discovery process entails finding an interesting difference between the host and the parasite.

Results In this study, the thymidine metabolic pathways were compared in camel and *T. evansi*. Metabolic maps, protein sequence comparisons, domain and motifs contents analysis, phylogenetic relations and 3D structure models were used in comparisons. A unique difference in thymidine metabolism was at the level of recycling of thymidine which was performed by thymidine phosphorylase in camel, while this role in *T. evansi* was associated with nucleoside deoxyribosyltransferase (NDRT), which is a unique enzyme for the trypanosome and was absent in camel. Thymidine in *T. evansi* seems to be governed by thymine through NDRT. In contrast to camel, in which thymidine can be produced from thymidylate by the action of 5'-nucleotidase.

Conclusions NDRT can be regarded as a drug target against *T. evansi* for its strict presence in the parasite but not in the host.

Background

By the decoding of camel genome sequences [1], drug discovery studies against camel pathogens are to be accelerated. In investigating the pyrimidine metabolic pathways, finding unique differences in structure, function, sequence or phylogenetic could contribute to the identification of new drug targets.

Thymidine metabolism was traced by the KEGG maps [2–4] to compare the enzymes involved in pathways in thymidine metabolism in camel and *T. evansi*. In this work, comprehensive bioinformatics tools were used to investigate enzyme sequences and its comparisons, domain and motif content, searching similar proteins and its phylogenetic relations.

In this work, the pathway of thymidine metabolism was plotted in both camel and *T. evansi*. Here, we provide bioinformatics evidence of the presence of unique differences in thymidine metabolism in both camel and *T. evansi*. This could be used for the future drug discovery process.

Results

The pyrimidine metabolic maps at KEGG were used to trace the pathways of thymidine [5]. The de novo pathway, thymidine kinase converts thymidine to thymidine monophosphate (TMP). In the catabolic direction, TMP is converted to thymidine by the action of 5'-nucleotidase (Fig. 1). Further, conversion of

thymidine to thymine by thymidine/pyrimidine phosphorylase. Whereas, nucleoside deoxyribosyltransferase catalyses' the interconversion of thymidine and thymine.

In the camel thymidine pathway, camels were expected to be devoid of nucleoside deoxyribosyltransferase (Fig. 2). Therefore, there is no interconversion between thymine and thymidine in camel pyrimidine metabolism. Thus, the sole source of thymidine in camels is from TMP by the action of 5'-nucleotidase or potentially by the transport of ready formed thymidine from outside the cells.

In *T. evansi*, the enzymes 5'-nucleotidase and thymidine/pyrimidine phosphorylase were not confirmed, suggesting interesting differences in thymidine metabolism, compared with camels. TMP cannot be converted to thymidine in *T. evansi* due to the absence of 5'-nucleotidase. The sole metabolic source of thymidine could be from thymine by the action of nucleoside deoxyribosyltransferase, which is absent in camel (Fig. 3). The list of enzymes of thymidine pathway as well as the predicted content in camel and *T. evansi* are provided in Tables 1-3.

Camel thymidine/pyrimidine phosphorylase (TP)

Thymidine phosphorylase (EC 2.4.2.4;TP): pyrimidine phosphorylase); thymidine orthophosphate deoxyribosyltransferase; animal growth regulators, blood platelet-derived endothelial cell growth factors; blood platelet-derived endothelial cell growth factor; deoxythymidine phosphorylase; gliostatins; pyrimidine deoxynucleoside phosphorylase; thymidine:phosphate deoxy-D-ribosyltransferase. It is a glycosyltransferase stimulate reversible dephosphorylation of thymidine phosphate supplying thymine and 2-deoxy -D-ribose 1-phosphate. In addition, it catalyzes deoxyribosyltransferase reactions that catalyzed by nucleoside deoxyribosyltransferase in various tissues. The enzyme can also convert thymidine to thymine, which is not used by the trypanosomes [6]. The properties of the phosphorylases differ significantly from prokaryotes to those of the mammalian animals. *Giardia lamblia* is mainly dependent on salvage synthesis for its pyrimidine requirements. In which, one enzyme of uridine, deoxyuridine and thymidine phosphorylases are responsible for the activities of three enzymes. The enzyme could utilize both uracil and thymine as substrates [7]. Complicated infection with Mycoplasmas reduced the efficiency of anticancer and antiviral nucleoside analogue-based therapies due to the presence of Mycoplasma TP. Impaired activity of TP provoked the elevated uptake and inclusion of deoxyuridine and uracil but thymidine uptake was not affected. Thus, enzymes of Mycoplasma nucleotide synthesis pathway are prospective targets for imminent creation of antibiotics [8]. In *Trypanosoma cruzi*, a phosphorylase activity was detected but was more specific to uridine phosphorylase without specificity to thymidine or purine phosphorylase [9, 10].

The obtained sequence of camel TP was low quality protein and very short amino acids length compared with human TP. The recorded sequence of camel TP was 202 amino acids, bearing 18.44% similarity rate, compared with 482 amino acids length in human TP (Fig. 4). The same finding applies for the TP sequence in the three camel species, dromedary, Bactrian and ferus camels, in which *Camelus ferus* showed the shortest length of 162 amino acids (Fig 5). Comparison of TPs from different prokaryotic and eukaryotic sources (Fig. 6) showed a general low similarity rate from 9.5-41.8% among the tested species.

Owing to this difference, the camel TPs were forming a monophyletic group that shared common origin with the prokaryotic TPs and not the vertebrate TPs (Fig. 7). The motif search retrieved zero hits by using the motif finder, pfam and prosite prediction tools, while a phosphorylase domain was predicted by using the NCBI conserved domain search tool.

***evansi* nucleoside deoxyribosyltransferase (NDRT)**

This enzyme was found to be a unique enzyme for *T. evansi* and not present in camel, suggesting its use as a safe drug target. After searching the gene databases, NDRT could be predicted in some protozoa and bacteria e.g. *Lactobacillus*, *Leishmania* spp., and *Trypanosomes*. A previous study investigated the crystal structure of *T. brucei* NDRT and found that its structure is highly similar to NDRT from *Lactobacillus helveticus* [11]. In the previous study, several crystal bound compounds were tested against the blood forms of *T. brucei* and found weak inhibition of parasite growth with IC50 values above 100 μ M.

Sequence comparisons between *T. evansi*, *Lactobacillus fecum* and *Enterococcus fecum* NDRTs revealed 17.68-21.21% sequence similarity (Fig. 8). Comparison of *T. evansi* and *T. brucei* NDRTs revealed 100% similarity. This may account for sharing the common features in the published structure, function and inhibition.

The models for *T. evansi* NDRT were built at Swiss-Model server [12]. The model of *T. evansi* was predicted based on the deposited PDB ID 2a0k, which is the NDRT from *T. brucei* (Fig. 9). The modeling statistics comprised 99% coverage, 0.6 sequence similarity and 98% sequence identity.

Discussion

The blood-protozoa *T. evansi* is the causative agent for Surra or camel trypanosomiasis, which is a devastating disease in camels and other animals. *T. evansi* is characterized by the widest geographic distribution and large number of hosts including camels, large and small ruminant farm animals, bats, equines, pigs, carnivores, deer, gazelles and elephants [13]. The recent affections of humans with *T. evansi* raised its public health importance [14, 15].

The discovery of new drug targets against *T. evansi* is essential to combat this infection, which is ubiquitous in animals and has zoonotic importance. The ideal target is that is present in the parasite and absent in host. Recently, we have introduced several new antimicrobial targets, which were investigated by bioinformatics tools to elucidate the differences between the host and microbial proteins [16–24]. In this context, pyrimidine enzymes are indispensable for life owing to its role in the synthesis nucleic acids.

NDRT was found to an important drug target in *T. brucei* [11]. Additionally, owing to its efficient broad-spectrum activity, NDRT had been used as a catalyst in the industrial synthesis of nucleotides [25, 26] and antiviral drugs [27].

In this study, NDRT was confirmed in *T. evansi*. While, by bioinformatics tools, the enzyme was not detected in camels. This renders NDRT as an attractive drug target against *T. evansi*. Future drug

discovery studies targeting *T. evansi* NDRT is expected to yield safe and specific inhibitory compounds.

Conclusions

In analyzing the thymidine pathways in both camel and *T. evansi*, we could predict the differences in nucleosides recycling. The recycling of thymidine nucleosides in camels is governed by thymidine phosphorylase, which is absent in *T. evansi*. On the other hand, the thymidine recycling in *T. evansi* is performed by nucleoside deoxyribosyltransferase, which a unique enzyme for the protozoan. This signifies the importance of nucleoside deoxyribosyltransferase as a drug target in *T. evansi*.

Methods

Construction of metabolic map

The website of Kyoto Encyclopedia of genes and genomes (KEGG) was used to retrieve the thymidine pathways maps. The structure of nucleotides were written by ChemDraw software.

Retrieval of protein sequences

The database of proteins at NCBI was used to obtain the sequences of camel enzymes (<http://www.ncbi.nlm.nih.gov/protein>). The sequences of *T. evansi* proteins were retrieved from the Kinetoplastom genome project (<http://tritrypdb.org/tritrypdb/>). The sequence files in FASTA format were stored and processed by several software including CLC main workbench, Geneious and Genedoc.

Basic Local Alignment Search Tool (BLAST): BLAST search was performed at the NCBI search engine [28]. The BLAST tool was used to find orthologues with high similarity with the retrieved sequences by searching a database of non-redundant (nr) protein sequences.

Proteins multiple and pairwise sequence alignment Clustal omega was used to align the protein sequences [29]. The obtained alignment file was processed by CLC main workbench.

Construction of phylogenetic tree

The phylogenetic tree was implemented from the obtained alignment files and visualized by Dendroscope phylogenetic tree viewer [30] or CLC main workbench [31].

Putative domains and motifs search the NCBI domain prediction program available at (<http://www.ncbi.nlm.nih.gov/Structure/cdd/cdd.shtml>) [32] was used to map the domains and motifs of the retrieved proteins. Domains and motifs were also explored at KEGG motif finder tool.

Proteomic and genomic tools the tools available at ExPASy Proteomics tools (<http://us.expasy.org/tools/>) [33] and (<http://www.ebi.ac.uk/Tools/>) [34] were used to analyze the protein sequences.

Building structure model. A model of structure, based on *T. evansi* sequence, was built by using the SwissModel server.

Declarations

Acknowledgements

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Author's contribution

MK and AA designed the study, performed research, analyzed data, contributed new methods or models and wrote the paper.

Availability of data and materials

All data are within the manuscript.

Compliance with Ethical Standards

- **Disclosure of potential competing interest**

The authors declare no conflict of interest.

- **Research involving Human Participants and/or Animals**

No animals / humans were used for the studies of this research.

- **Informed consent**

Not applicable in this research.

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Tables

Table 1. Enzymes involved in metabolic pathways of thymidine

no	ID (E.C. number)	Definition (Enzyme name)	comment
19	2.7.1.21	Thymidine kinase	in camel and Trypanosoma
54	3.1.3.89	5'-deoxynucleotidase; 2'-deoxyribonucleoside 5'-monophosphate phosphohydrolase	<i>E. coli</i> only
30	3.1.3.5	5'-nucleotidase; uridine 5'-nucleotidase	Present in camel but not in Trypanosoma
17	2.4.2.6	nucleoside deoxyribosyltransferase	This is unique enzyme for Trypanosoma not present in camel
16	2.4.2.4	thymidine phosphorylase; pyrimidine phosphorylase	Present in camel but not in Trypanosoma

Table 2. The expected enzymes involved in metabolic pathways of thymidine in camels

no	ID (E.C. number)	Definition (Enzyme name)	comment
19	2.7.1.21	Thymidine kinase	in camel and Trypanosoma
30	3.1.3.5	5'-nucleotidase; uridine 5'-nucleotidase	Present in camel but not in Trypanosoma
16	2.4.2.4	thymidine phosphorylase; pyrimidine phosphorylase	Present in camel but not in Trypanosoma

Table 3. The expected enzymes involved in metabolic pathways of thymidine in *Trypanosoma evansi*

no	ID (E.C. number)	Definition (Enzyme name)	comment
19	2.7.1.21	Thymidine kinase	in camel and Trypanosoma
17	2.4.2.6	nucleoside deoxyribosyltransferase	This is unique enzyme for Trypanosoma not present in camel

Figures

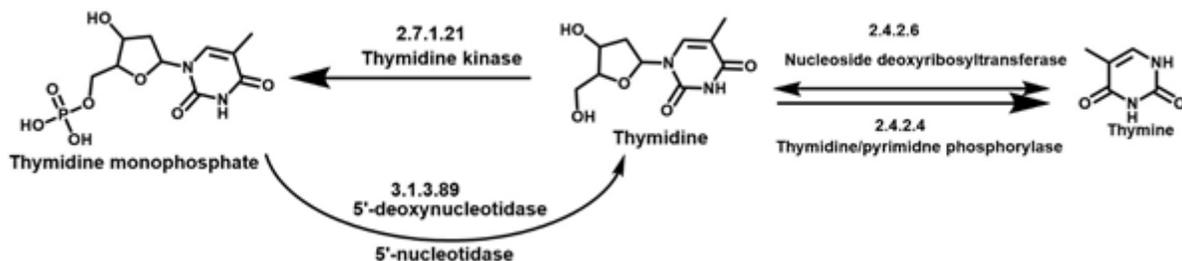


Figure 1

The proposed metabolic pathways of thymidine.

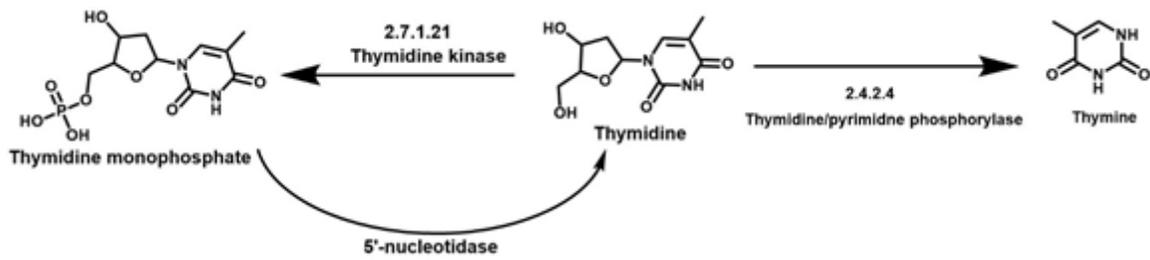


Figure 2

The proposed metabolic pathways of thymidine in camels.

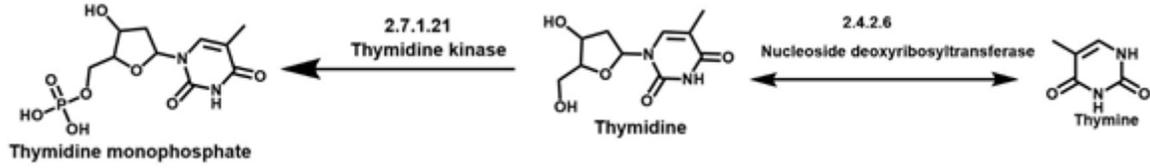


Figure 3

The proposed metabolic pathways of thymidine in *Trypanosoma evansi*.

	1	2
CamelusdromedariusthymidinephosphorylaseXP_010998301		398
HomosapiensthymidinephosphorylaseADP91533	18.44	

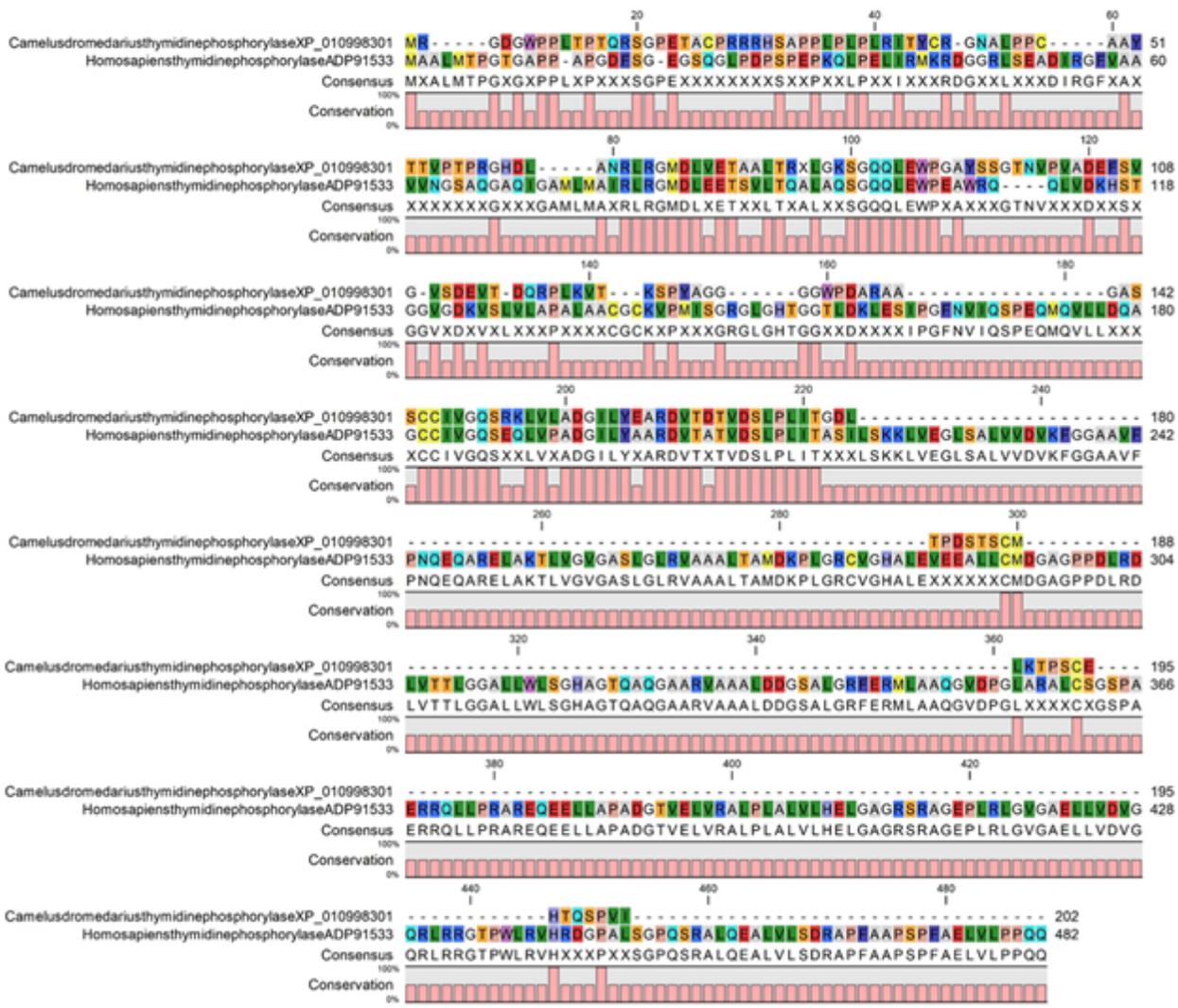


Figure 4

Multiple sequence alignment of dromedary camel and human thymidine/pyrimidine phosphorylase. The upper panel represents sequence comparison statistics. The upper right diagonal region explains the number of differences between two sequences, while the lower left diagonal region explains the % of identity between two sequences.

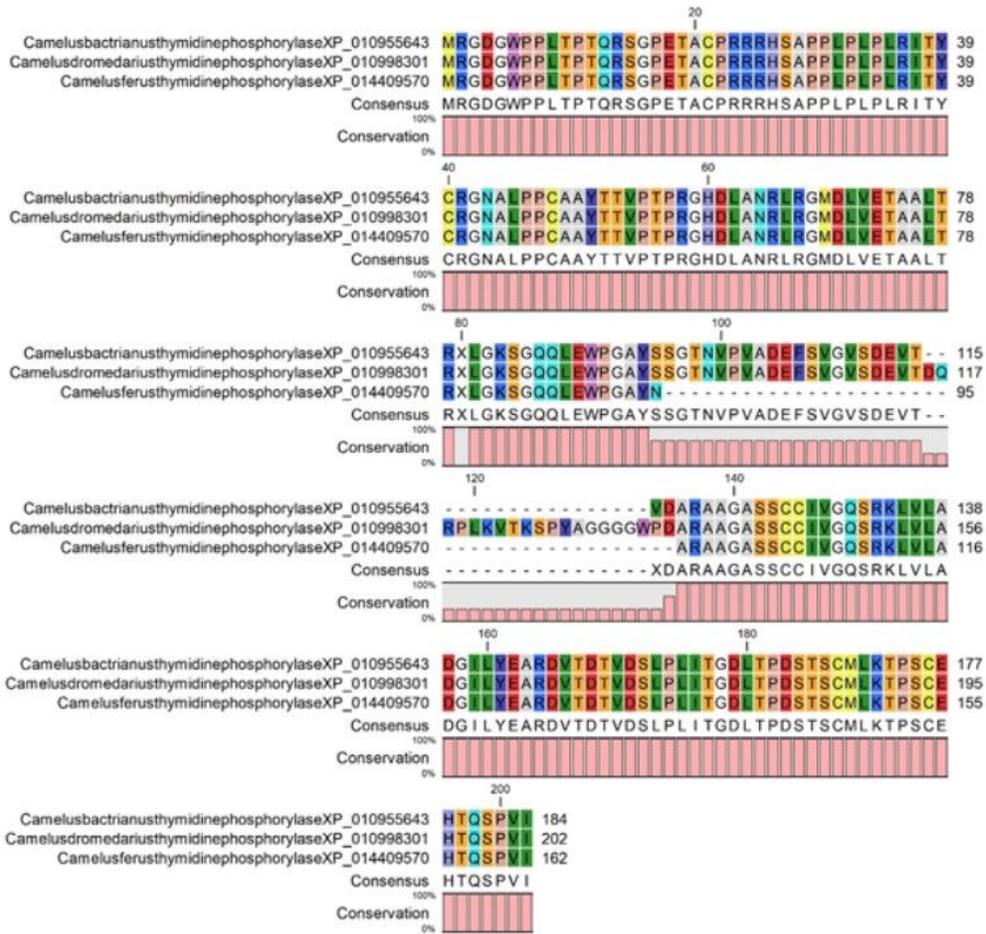


Figure 5

Multiple sequence alignment of dromedary and Bactrian camels thymidine/pyrimidine phosphorylase.

	1	2	3	4	5	6	7	8	9	10	11	12	13
<i>Escherichia coli</i> thymidine phosphorylase VAX51408			22	283	261	263	320	326	417	318	327	415	419
<i>Salmonella enterica</i> thymidine phosphorylase RXM16575	95.00			281	263	266	332	327	416	320	329	415	419
<i>Corynebacterium pseudotuberculosis</i> thymidine phosphorylase ANH23382	39.40	39.83		278	279	326	326	414	326	332	419	418	424
<i>Staphylococcus aureus</i> thymidine phosphorylase RIZ63567	41.48	41.03	40.47		172	334	326	432	320	320	410	411	414
<i>Clostridium tetani</i> thymidine phosphorylase SJZ79245	41.03	40.36	40.26	60.73		332	322	425	320	321	412	413	418
<i>Homo sapiens</i> thymidine phosphorylase ADP91533	34.26	33.66	34.80	32.39	33.20		85	190	101	96	424	425	427
<i>Oryctolagus cuniculus</i> thymidine phosphorylase XP_002723933	34.41	34.21	34.67	32.92	34.69	82.44		202	100	99	420	421	423
<i>Equus caballus</i> thymidine phosphorylase XP_023487342	29.09	29.91	29.35	26.15	27.35	67.15	65.47		226	226	324	325	327
<i>Mus musculus</i> thymidine phosphorylase NP_612175	34.84	34.43	34.27	33.33	33.88	79.19	79.25	81.37		98	414	415	417
<i>Rattus norvegicus</i> thymidine phosphorylase NP_01012122	33.34	33.04	34.00	32.65	34.40	80.25	79.79	81.37	82.06		420	421	423
<i>Camelus bactrianus</i> thymidine phosphorylase XP_010955643	10.17	10.17	9.00	10.48	10.24	14.17	14.45	12.98	14.84	14.29		19	25
<i>Camelus dromedarius</i> thymidine phosphorylase XP_010998301	10.86	10.96	10.11	10.65	10.41	14.31	14.60	12.21	14.79	14.42	80.01		45
<i>Camelus ferus</i> thymidine phosphorylase XP_014409570	8.71	8.71	7.83	9.01	8.77	13.03	13.32	11.13	13.40	13.14	87.50	79.70	

Figure 6

The sequence comparison statistics of thymidine/pyrimidine phosphorylase. The upper right diagonal region explains the number of differences between two sequences, while the lower left diagonal region explains the % of identity between two sequences.

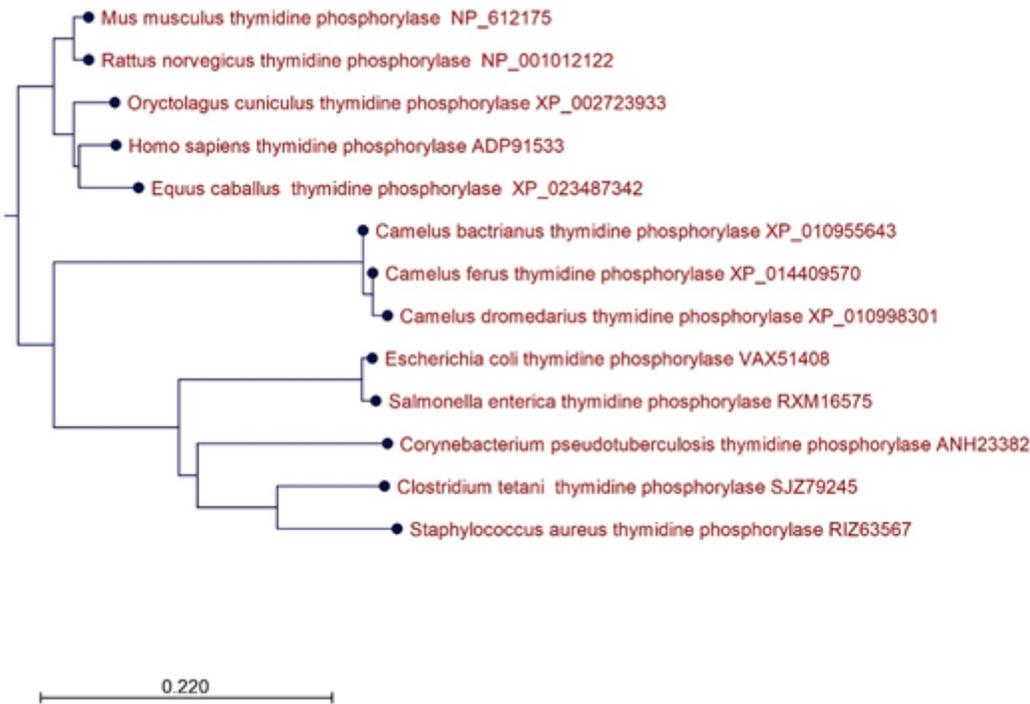


Figure 7

Phylogram of camel thymidine/pyrimidine phosphorylase in relation to a set of prokaryotic and eukaryotic organisms.

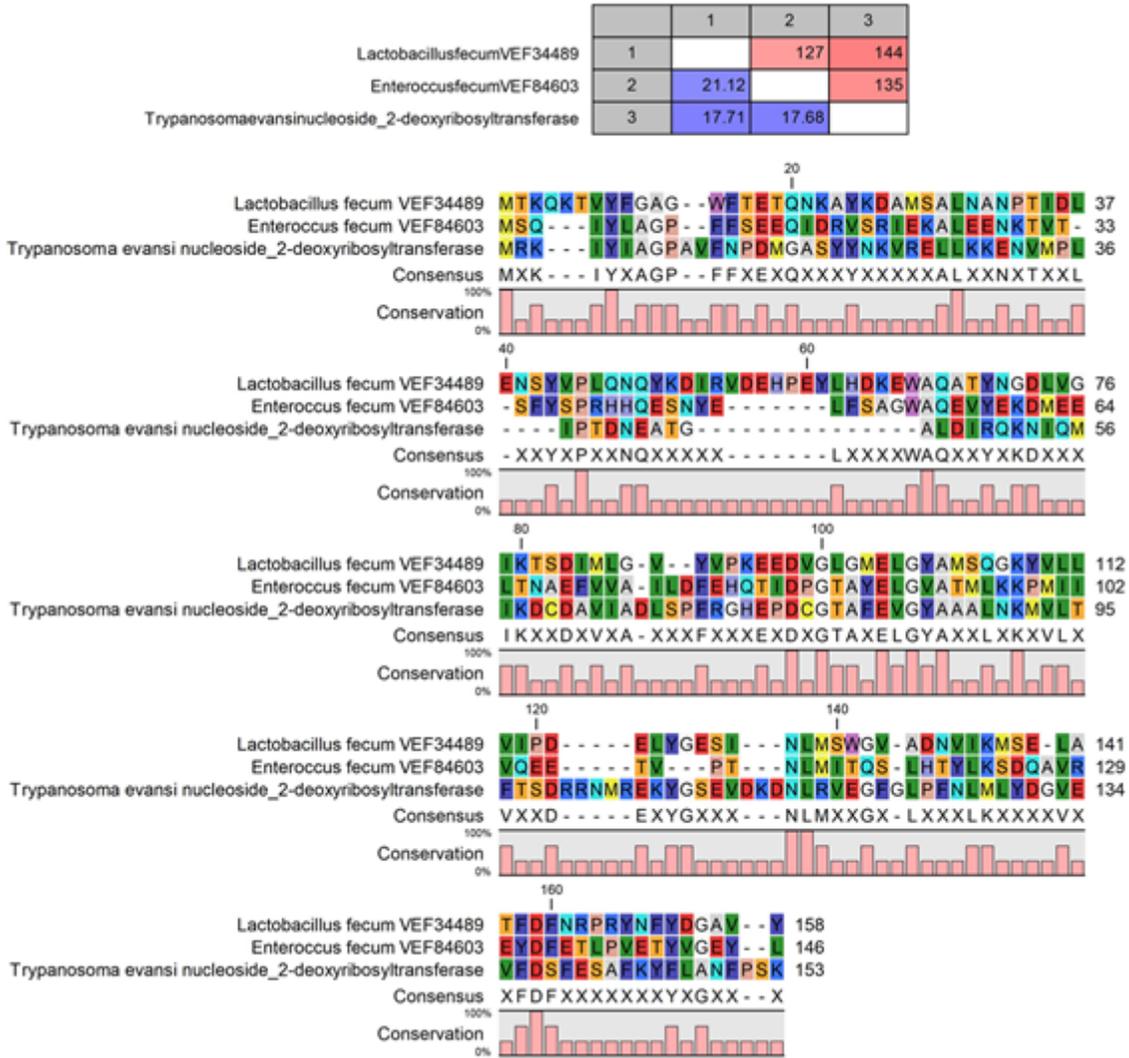


Figure 8

Multiple sequence alignment of Trypanosoma evansi, Lactobacillus fecum and Enterococcus fecum nucleoside deoxyribosyltransferase. The upper panel represents sequence comparison statistics. The upper right diagonal region explains the number of differences between two sequences, while the lower left diagonal region explains the % of identity between two sequences.

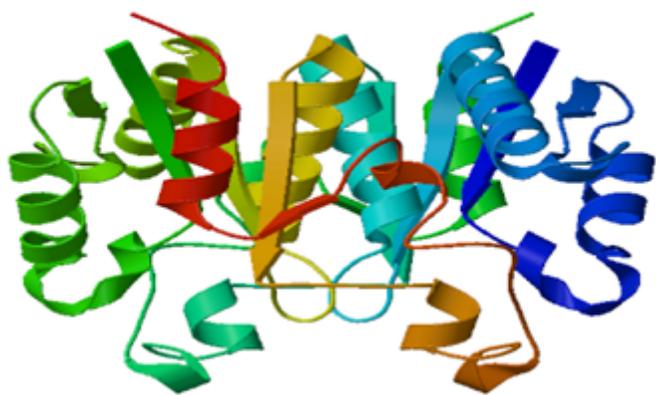


Figure 9

Molecular model of *T. evansi* NDRT. The model was built by using SwissModel.