

Sup Table 1. Potential drug targets expressed by *Leishmania*

Category	Pathways / enzymes	Reference
Detoxification	trypanothione pathway, glyoxalase system, peroxidase and superoxide dismutase	(1-4)
Nucleotide & Lipid metabolism	polyamine, folate and sterol metabolisms	(5-9)
Energy metabolism	glycosomal and mitochondrial enzymes	(10-12)
Post-translational modification & signaling	enzymes involved in ubiquitination, myristoylation, phosphorylation processes, calcium homeostasis	(13-17)
Proteolysis and turnover	metallo-proteases, serine and cysteine proteases, metacaspases, proteasomal proteins	(18, 19)
Transporter molecules	for nucleotides, fatty acids, metals, amino acids and polyamines	(20-24)
Topoisomerases	type II	(25)
Cell cycle regulation/parasite stage differentiation	heat-shock proteins, kinases	(26-31)
Unknown parasite-specific functions	hypothetical proteins, proteins of prokaryotic origin	(32-37)

Reference list

- Benitez D, Medeiros A, Fiestas L, Panozzo-Zenere EA, Maiwald F, Prousis KC, et al. Identification of Novel Chemical Scaffolds Inhibiting Trypanothione Synthetase from Pathogenic Trypanosomatids. *PLoS Negl Trop Dis*. 2016 Apr;10(4):e0004617. doi: 10.1371/journal.pntd.0004617. <http://www.ncbi.nlm.nih.gov/pubmed/27070550>. PMID:27070550
- Leroux AE, Krauth-Siegel RL. Thiol redox biology of trypanosomatids and potential targets for chemotherapy. *Mol Biochem Parasitol*. 2016 Mar-Apr;206(1-2):67-74. doi: 10.1016/j.molbiopara.2015.11.003. <http://www.ncbi.nlm.nih.gov/pubmed/26592324>. PMID:26592324
- Sousa Silva M, Ferreira AE, Tomas AM, Cordeiro C, Ponces Freire A. Quantitative assessment of the glyoxalase pathway in *Leishmania infantum* as a therapeutic target by modelling and computer simulation. *Febs J*. 2005 May;272(10):2388-98. doi: 10.1111/j.1742-4658.2005.04632.x. <http://www.ncbi.nlm.nih.gov/pubmed/15885089>. PMID:15885089
- Padmanabhan PK, Mukherjee A, Singh S, Chattopadhyaya S, Gowri VS, Myler PJ, et al. Glyoxalase I from *Leishmania donovani*: a potential target for anti-parasite drug. *Biochem Biophys Res Commun*. 2005 Dec 2;337(4):1237-48. doi: 10.1016/j.bbrc.2005.09.179. <http://www.ncbi.nlm.nih.gov/pubmed/16236261>. PMID:16236261
- Ilari A, Fiorillo A, Baiocco P, Poser E, Angiulli G, Colotti G. Targeting polyamine metabolism for finding new drugs against leishmaniasis: a review. *Mini Rev Med Chem*. 2015;15(3):243-52. <http://www.ncbi.nlm.nih.gov/pubmed/25769972>. PMID:25769972
- de Macedo-Silva ST, Visbal G, Urbina JA, de Souza W, Rodrigues JC. Potent In Vitro Antiproliferative Synergism of Combinations of Ergosterol Biosynthesis Inhibitors against *Leishmania amazonensis*. *Antimicrob Agents Chemother*. 2015 Oct;59(10):6402-18. doi: 10.1128/AAC.01150-15. <http://www.ncbi.nlm.nih.gov/pubmed/26239973>. PMID:26239973
- Pomel S, Cojean S, Loiseau PM. Targeting sterol metabolism for the development of antileishmanials. *Trends Parasitol*. 2015 Jan;31(1):5-7. doi: 10.1016/j.pt.2014.11.007. <http://www.ncbi.nlm.nih.gov/pubmed/25498194>. PMID:25498194
- Roberts CW, McLeod R, Rice DW, Ginger M, Chance ML, Goad LJ. Fatty acid and sterol metabolism: potential antimicrobial targets in apicomplexan and trypanosomatid parasitic protozoa. *Mol Biochem Parasitol*. 2003 Feb;126(2):129-42. <http://www.ncbi.nlm.nih.gov/pubmed/12615312>. PMID:12615312
- Nare B, Luba J, Hardy LW, Beverley S. New approaches to *Leishmania* chemotherapy: pteridine reductase 1 (PTR1) as a target and modulator of antifolate sensitivity. *Parasitology*. 1997;114 Suppl:S101-10. <http://www.ncbi.nlm.nih.gov/pubmed/9309772>. PMID:9309772

10. Moyersoen J, Choe J, Fan E, Hol WG, Michels PA. Biogenesis of peroxisomes and glycosomes: trypanosomatid glycosome assembly is a promising new drug target. *FEMS Microbiol Rev.* 2004 Nov;28(5):603-43. doi: 10.1016/j.femsre.2004.06.004. <http://www.ncbi.nlm.nih.gov/pubmed/15539076>. PMID:15539076
11. Silva LA, Vinaud MC, Castro AM, Cravo PV, Bezerra JC. In silico search of energy metabolism inhibitors for alternative leishmaniasis treatments. *Biomed Res Int.* 2015;2015:965725. doi: 10.1155/2015/965725. <http://www.ncbi.nlm.nih.gov/pubmed/25918726>. PMID:25918726
12. Ortiz D, Forquer I, Boitz J, Soysa R, Elya C, Fulwiler A, et al. Targeting the Cytochrome bc1 Complex of *Leishmania* Parasites for Discovery of Novel Drugs. *Antimicrob Agents Chemother.* 2016 Aug;60(8):4972-82. doi: 10.1128/AAC.00850-16. <http://www.ncbi.nlm.nih.gov/pubmed/27297476>. PMID:27297476
13. Gannavaram S, Bhattacharya P, Ismail N, Kaul A, Singh R, Nakhasi HL. Modulation of Innate Immune Mechanisms to Enhance *Leishmania* Vaccine-Induced Immunity: Role of Coinhibitory Molecules. *Front Immunol.* 2016;7:187. doi: 10.3389/fimmu.2016.00187. <http://www.ncbi.nlm.nih.gov/pubmed/27242794>. PMID:27242794
14. Wright MH, Paape D, Storck EM, Serwa RA, Smith DF, Tate EW. Global analysis of protein N-myristoylation and exploration of N-myristoyltransferase as a drug target in the neglected human pathogen *Leishmania donovani*. *Chem Biol.* 2015 Mar 19;22(3):342-54. doi: 10.1016/j.chembiol.2015.01.003. <http://www.ncbi.nlm.nih.gov/pubmed/25728269>. PMID:25728269
15. Brannigan JA, Roberts SM, Bell AS, Hutton JA, Hodgkinson MR, Tate EW, et al. Diverse modes of binding in structures of *Leishmania major* N-myristoyltransferase with selective inhibitors. *IUCrJ.* 2014 Jul 1;1(Pt 4):250-60. doi: 10.1107/S2052252514013001. <http://www.ncbi.nlm.nih.gov/pubmed/25075346>. PMID:25075346
16. Nascimento M, Zhang WW, Ghosh A, Houston DR, Berghuis AM, Olivier M, et al. Identification and characterization of a protein-tyrosine phosphatase in *Leishmania*: Involvement in virulence. *J Biol Chem.* 2006 Nov 24;281(47):36257-68. doi: 10.1074/jbc.M606256200. <http://www.ncbi.nlm.nih.gov/pubmed/17005559>. PMID:17005559
17. Benaim B, Garcia CR. Targeting calcium homeostasis as the therapy of Chagas' disease and leishmaniasis - a review. *Trop Biomed.* 2011 Dec;28(3):471-81. <http://www.ncbi.nlm.nih.gov/pubmed/22433874>. PMID:22433874
18. Singh J, Srivastava A, Jha P, Sinha KK, Kundu B. L-Asparaginase as a new molecular target against leishmaniasis: insights into the mechanism of action and structure-based inhibitor design. *Mol Biosyst.* 2015 Jul;11(7):1887-96. doi: 10.1039/c5mb00251f. <http://www.ncbi.nlm.nih.gov/pubmed/25893895>. PMID:25893895
19. Das P, Alam MN, Paik D, Karmakar K, De T, Chakraborti T. Protease inhibitors in potential drug development for Leishmaniasis. *Indian J Biochem Biophys.* 2013 Oct;50(5):363-76. <http://www.ncbi.nlm.nih.gov/pubmed/24772958>. PMID:24772958
20. de Koning HP, Bridges DJ, Burchmore RJ. Purine and pyrimidine transport in pathogenic protozoa: from biology to therapy. *FEMS Microbiol Rev.* 2005 Nov;29(5):987-1020. doi: 10.1016/j.femsre.2005.03.004. <http://www.ncbi.nlm.nih.gov/pubmed/16040150>. PMID:16040150
21. Landfear SM, Ullman B, Carter NS, Sanchez MA. Nucleoside and nucleobase transporters in parasitic protozoa. *Eukaryot Cell.* 2004 Apr;3(2):245-54. <http://www.ncbi.nlm.nih.gov/pubmed/15075255>. PMID:15075255
22. Huynh C, Sacks DL, Andrews NW. A *Leishmania amazonensis* ZIP family iron transporter is essential for parasite replication within macrophage phagolysosomes. *J Exp Med.* 2006 Oct 2;203(10):2363-75. doi: 10.1084/jem.20060559. <http://www.ncbi.nlm.nih.gov/pubmed/17000865>. PMID:17000865
23. Alberca LN, Sbaraglini ML, Balcazar D, Fraccaroli L, Carrillo C, Medeiros A, et al. Discovery of novel polyamine analogs with anti-protozoal activity by computer guided drug repositioning. *J Comput Aided Mol Des.* 2016 Apr;30(4):305-21. doi: 10.1007/s10822-016-9903-6. <http://www.ncbi.nlm.nih.gov/pubmed/26891837>. PMID:26891837
24. Mittra B, Laranjeira-Silva MF, Perrone Bezerra de Menezes J, Jensen J, Michailowsky V, Andrews NW. A Trypanosomatid Iron Transporter that Regulates Mitochondrial Function Is Required for *Leishmania amazonensis* Virulence. *PLoS Pathog.* 2016 Jan;12(1):e1005340. doi: 10.1371/journal.ppat.1005340. <http://www.ncbi.nlm.nih.gov/pubmed/26741360>. PMID:26741360
25. Singh G, Dey CS. Induction of apoptosis-like cell death by pentamidine and doxorubicin through differential inhibition of topoisomerase II in arsenite-resistant *L. donovani*. *Acta Trop.* 2007 Sep;103(3):172-85. doi: 10.1016/j.actatropica.2007.06.004. <http://www.ncbi.nlm.nih.gov/pubmed/17655815>. PMID:17655815
26. Requena JM, Montalvo AM, Fraga J. Molecular Chaperones of *Leishmania*: Central Players in Many Stress-Related and -Unrelated Physiological Processes. *Biomed Res Int.* 2015;2015:301326. doi: 10.1155/2015/301326. <http://www.ncbi.nlm.nih.gov/pubmed/26167482>. PMID:26167482

27. Doerig C, Späth G, Wiese M. Protein phosphorylation in parasites. Selzer PM, editor: WILEY Blackwell; 2014.
28. Merritt C, Silva LE, Tanner AL, Stuart K, Pollastri MP. Kinases as druggable targets in trypanosomatid protozoan parasites. *Chem Rev.* 2014 Nov 26;114(22):11280-304. doi: 10.1021/cr500197d. <http://www.ncbi.nlm.nih.gov/pubmed/26443079>. PMID:26443079
29. Dacher M, Morales MA, Pescher P, Leclercq O, Rachidi N, Prina E, et al. Probing druggability and biological function of essential proteins in *Leishmania* combining facilitated null mutant and plasmid shuffle analyses. *Mol Microbiol.* 2014 Jul;93(1):146-66. doi: 10.1111/mmi.12648. <http://www.ncbi.nlm.nih.gov/pubmed/24823804>. PMID:24823804
30. Naula C, Parsons M, Mottram JC. Protein kinases as drug targets in trypanosomes and *Leishmania*. *Biochim Biophys Acta.* 2005 Dec 30;1754(1-2):151-9. doi: 10.1016/j.bbapap.2005.08.018. <http://www.ncbi.nlm.nih.gov/pubmed/16198642>. PMID:16198642
31. Brumlik MJ, Pandeswara S, Ludwig SM, Murthy K, Curiel TJ. Parasite mitogen-activated protein kinases as drug discovery targets to treat human protozoan pathogens. *J Signal Transduct.* 2011;2011:971968. doi: 10.1155/2011/971968. <http://www.ncbi.nlm.nih.gov/pubmed/21637385>. PMID:21637385
32. Kumar SS, Gokulasuriyan RK, Ghosh M. Comparative *in silico* genome analysis of *Leishmania* (*Leishmania*) *donovani*: A step towards its species specificity. *Meta Gene.* 2014 Dec;2:782-98. doi: 10.1016/j.mgene.2014.10.003. <http://www.ncbi.nlm.nih.gov/pubmed/25606461>. PMID:25606461
33. Nirujogi RS, Pawar H, Renuse S, Kumar P, Chavan S, Sathe G, et al. Moving from unsequenced to sequenced genome: reanalysis of the proteome of *Leishmania donovani*. *J Proteomics.* 2014 Jan 31;97:48-61. doi: 10.1016/j.jprot.2013.04.021. <http://www.ncbi.nlm.nih.gov/pubmed/23665000>. PMID:23665000
34. Leprohon P, Fernandez-Prada C, Gazanion E, Monte-Neto R, Ouellette M. Drug resistance analysis by next generation sequencing in *Leishmania*. *Int J Parasitol Drugs Drug Resist.* 2015 Apr;5(1):26-35. doi: 10.1016/j.ijpddr.2014.09.005. <http://www.ncbi.nlm.nih.gov/pubmed/25941624>. PMID:25941624
35. Berg M, Mannaert A, Vanaerschot M, Van Der Auwera G, Dujardin JC. (Post-) Genomic approaches to tackle drug resistance in *Leishmania*. *Parasitology.* 2013 Oct;140(12):1492-505. doi: 10.1017/S0031182013000140. <http://www.ncbi.nlm.nih.gov/pubmed/23480865>. PMID:23480865
36. Moreira Dde S, Pescher P, Laurent C, Lenormand P, Spath GF, Murta SM. Phosphoproteomic analysis of wild-type and antimony-resistant *Leishmania braziliensis* lines by 2D-DIGE technology. *Proteomics.* 2015 Sep;15(17):2999-3019. doi: 10.1002/pmic.201400611. <http://www.ncbi.nlm.nih.gov/pubmed/25959087>. PMID:25959087
37. Vikeved E, Backlund A, Alsmark C. The Dynamics of Lateral Gene Transfer in Genus *Leishmania* - A Route for Adaptation and Species Diversification. *PLoS Negl Trop Dis.* 2016 Jan;10(1):e0004326. doi: 10.1371/journal.pntd.0004326. <http://www.ncbi.nlm.nih.gov/pubmed/26730948>. PMID:26730948