# Understanding the structure and function of Fatty Acid Pathway proteins of *Leishmania major* to identify potent anti-leishmanials

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Leishmaniases imposes devastating impacts on world's population. The increasing prevalence of drug resistance, necessity for long-term treatment regime, unavailability of functional drugs, the related expenditure, and the growing number of immuno-compromised individuals, due to coinfection of HIV underscores the need for new drugs as well as drug targets. Proteins of the fatty acid biosynthetic pathway (FAS) are validated drug targets in pathogenic bacteria and certain viruses. Likewise, this pathway has been speculated as a suitable target against parasite infections. The FAS pathway is highly active in blood stream stage (virulent stage) of the parasite and also found to be altered in the drug resistant strains, directly associating it with virulence and pathogenesis of the disease. Moreover, being distinct from the counterpart mammalian host makes the fatty acid pathway proteins as viable and attractive drug targets for emerging therapeutics.

Genome sequencing has led to the discovery of Type II Fatty acid synthesis pathway in *Leishmania*. An indispensable enzyme of the pathway is 4' phosphopantetheinyl transferase (PPT) which catalyzes the transfer of 4'-phosphopantetheine arm from Coenzyme A to the conserved serine residue of the Acyl carrier protein. Phosphopantetheinyl transferase from other pathogens viz *M. tuberculosis, P. aeroginosa* have been shown to be important for the survival and pathogenecity of the microorganism. Since, *Leishmania* genome encodes a single PPT, it can act as a potential drug target and the understanding of the PPT as well ACP proteins may lead to the design of novel therapeutics against the deadly disease leishmaniasis.

Thus, the present study involves biophysical (Fluorescence, Circular Dichroism Spectroscopy) and biochemical characterization (Native PAGE, C18 reverse phase HPLC, Surface Plasmon Resonance) along with structure determination (X-ray crystallography and Nuclear Magnetic Resonance) of 4' phosphopantetheinyl transferase (PPT) and its substrate Acyl carrier protein

(ACP) of the type II fatty acid pathway of *Leishmania*. Followed by insights into the interaction interface of both the proteins. To speed up the search of a novel inhibitor the study also focuses on exploring the current state-of-the-art of drug repurposing strategies by screening small molecule chemical libraries as well as synthesized compounds against the *Leishmania donovani* promastigotes, axenic amastigotes and intramacrophagic stages of the parasite followed by calculation of the $IC_{50}$ values and determining the cytotoxic effects of the molecules.

In future the hits obtained from whole cell based screening can be evaluated against the characterized fatty acid pathway proteins using in vitro enzymatic assays to determine the specific target of these molecules. We also aim to take forward these inhibitors to animal models of Leishmaniasis.

**References:**


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