The project must contains the following parts (maximum 4 pages):

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- **Title of the project :Structural investigation and target based anti-filarial drug design against filarial nematode, *Brugia malayi***

- **Keywords : Filarial nematode, *Brugia malayi, wolbachia*, PPDK**

- **Introduction**

  Lymphatic filariasis caused by the nematodes is transmitted by infected mosquitos and is one of the major public health issues in tropical countries. *Wucherria bancrofti* and *Brugia malayi* are two important parasitic nematodes are majorly responsible for disease transmission and the disease makes long term disability in the form of elephantiasis in limbs, genital organs, hydrocele and repeated fever followed by inflammation. Recently many studies proved that this infection may be acquired in their childhood and the disease manifestations are seen only after several years later in the adulthood. This filarial disease is

prevalent only among the socioeconomically challenged population in the tropical countries. Several studies have highlighted the social, psychological, and economic implications of the disease and hence this should be completely eradicated. The World Health Organization (WHO) has taken many initiatives to eliminate lymphatic filariasis through Mass Drug administration and other measures.

It is estimated that nearly 150 million people are infected with the filarial nematodes and more than billion people are at risk. *Wuchereria bancrofti* and *Brugia malayi* are important nematode causing lymphatic filariasis. *Wolbachia* is an intracellular α-proteobacteria found in nematode's hosts. Various studies have proved that the *wolbachia is* required for nematode embryogenesis, larval development and adult worm survival. This has indicated the use of antibiotics as an alternative approach to treat and control filariasis. However, the long treatment regimens that are required using doxycycline in human's present logistical problems for mass drug administration and compliance, necessitating the need to develop improved methods to target *wolbachia*.

Control of filariasis currently relies on the drugs of ivermectin, albendazole and diethylcarbamazine. Despite their relative efficacy, these drugs are considered inadequate on adult worms due to limited potency. In the case of ivermectin, increased use worldwide has resulted the development of drug resistance. Hence, development of new anti-filarial agents is becoming inevitable. Target-based drug discovery is a versatile approach to identify new therapeutics. The recently completed genome sequence of *wolbachia* endosymbiont of *Brugia malayi* has enabled a genome wide search for new nematode drug targets. One interesting drug target identified using bioinformatics approach is the enzyme pyruvate phosphate dikinase (*wBm*-PPDK). *wBm* PPDK is a 96 kDa protein which may function as a dimer or tetramer and catalyses the reversible conversion of AMP, PPi and phosphoenol pyruvate into ATP, Pi and pyruvate. The PPDK enzyme consists three active domains and the conversion occurs in three steps where the outcome depends on the organisms.

PPDK is an energy conserving, reversible alternative of pyruvate kinase (PK) producing four ATPs per molecule compared to two produced by PK in standard glycolysis. Most organisms including mammals exclusively possess PK. The filarial parasite, *Brugia malayi* lacks PK and instead utilizes the enzyme *wBm*- PPDK. Therefore the absence of PPDK in mammals as well as the dependence of *Brugia malayi* on *Wolbachia* makes the enzyme as an attractive *Wolbachia* drug target. Since there is no amino acid sequence homology between PPDK and PK, it is feasible that highly specific inhibitors may be identified. Based on these studies, our team has proposed this project to develop more efficient antibiotics which kills effectively filarial worms in low dosage of drugs with minimal side effects. So our group has done model of these wBm-PPDK enzyme and want to create the structure based drugs screening with huge chemical data bases.

- Objectives

    1. To investigate structure of wBm-PPDK enzyme through bioinformatics and X-ray structural study
    2. Virtual library drug screening (VLS) against wBm-PPDK structure to find drug leads.
    3. To find drug efficacy activity analysis against the enzymatic function

- Methodology

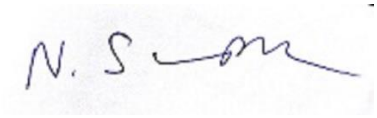
    1. Cloning and expression of target enzyme.
    2. Purification of expressed enzyme
    3. Crystallization of wBm-PPDK enzyme
    4. X-ray structure determination and structure solution and refinement.
    5. Structural analysis by Bioinformatics tools.
    6. Virtual library screen against finally refined model to bring drug lead.
    7. Enzymatic assay against the drugs using drug leads.

- **Perspectives**

The proposed work involves the structural elucidation of potential drug targeted *Wolbachia* proteins from *B. malayi* that have significant medical applications. The successful execution of this proposed work is expected to give results as given below.

1. Structure of potential *Wolbachia* proteins from *B. malayi may* be elucidated.
2. Structure elucidation of the *Wolbachia* proteins may lead to the identification of existing/ novel antifilarial drug leads.
3. The binding efficiency of the wolbachia based structure with identified drug leads may be understood.
4. The efficacy of the *Wolbachia* based drugs in anti-filarial nematode treatment may be determined.
5. Structural elucidation of *Wolbachia* proteins may lead to the understanding of molecular interaction between nematode and endosymbiont.

Signature



(N. Sampath)