Job offer –Post-doctorate in Biology: Host-parasite metabolic interactions as drug target

Research Project Short Title as Submitted to CEFIPRA: "Targeting lipid metabolism of the malaria parasites to develop novel anti-malarial drugs**"**
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Reference Number of the Job Offer: IFI_CEF_24_05

Project description

- **Keywords:** Malaria, host-parasite metabolic interactions, membrane biogenesis, lipid synthesis, lipidomics, drug development

- **Context:**

Apicomplexa parasites are widespread unicellular pathogens responsible for major human diseases such as malaria and toxoplasmosis. Malaria affect ~300millions/year and kills ~1/2million people every year, mostly children. Toxoplasmosis affect ~1/3 of the world population and is a lethal threat for any immunocompromised patient. There is no current vaccine and the parasites are developing resistance to most marketed molecules. Therefore, there is a pressing need for the identification of new potential drug targets. Throughout their life cycle, Apicomplexa require large amount of nutrients, especially lipids for propagation and survival. Understanding lipid acquisition is key to decipher host-parasite metabolic interactions. Parasite membrane biogenesis, relies on a combination of (a) host lipid scavenging and (b) de novo lipid synthesis in the parasite, and (c) intense fluxes of lipids between the host, the parasite and within. We recently uncovered that parasite need to store the host scavenged lipids to avoid their toxic accumulation and to mobilise them specifically during division. How can the parasite orchestrate the many lipids fluxes essential to its survival and can we target these pathways for drug treatment? Based on our work, we have identified pertinent target essential for parasite survival that will be pursued as promising drug target throughout our proposed project.

- **Abstract of the Research Project:**

The overall aim of the project is to develop novel antimalarial that target key lipid biosynthetic pathways. Based on solid preliminary data we generated over the study of key lipases enzymes sustaining malaria parasite survival, we will identify specific inhibitors targeting such key parasite proteins as drug candidates, and further develop these candidate compounds into novel antimalarial. The study will be focused on novel components of lipid metabolism pathways associated with the trafficking, and recycling of phospholipids. (i) lysophospholipases allowing the recycling of FA; (ii) P4-Type ATPases or lipid flippases allowing the trafficking of lipid across biological membranes; (iii) Acyl-CoA synthetases allowing the metabolic activation of FA to allow the parasite to use them; and (iv) novel components of phospholipid synthesis machinery associated with ER-mitochondrion in the parasite. Detailed in vitro assay based screening will identify hit compounds targeting the selected proteins (we have already identified novel inhibitors for selected targets as hit compounds); extensive medicinal chemistry approaches will be carried out for derivatization of selected hits and development of improved hit/lead candidates, these approaches will be combined with assessing parasiticidal effects as well as lipidomics and fluxomics analyses to validate the efficacy and mode of action of each of these drug candidates. Animal malaria model-based study will further assess their efficacy; compounds having protective efficacy in animal model will be followed for PK/ADME and detailed toxicology studies in small animals to select compound as candidate drugs.

- **Scientific Objectives of the Project:**

1. Identify specific inhibitors for selected targets as hit/lead compounds to develop new antimalarial
2. Development of lead antimalarial compounds based upon selected hit compounds

3. Assess specificity of selected hit compounds on lipid homeostasis and determine the mode of action in the parasite
4. Detailed toxicity study and drug-combination studies to develop the anti-malarial drug candidates

- **Methodology and Timeline of the Project:**

Task 1. In vitro activity assay of recombinant proteins and screening of compound libraries to identify specific inhibitor of selected targets. (Indian and French Group). For the validated drug targets we will try to identify specific inhibitors as putative hit/lead to develop new anti-malarials.

Task 2. Development of lead antimalarial compounds based upon selected hit compound
(Indian and French group along with industrial partner): Extensive medicinal chemistry approaches will be carried out for derivatization of selected hits and development of improved hit/lead candidates.

Task 3. Assess specificity of selected hit compounds on lipid homeostasis (French group):
To ascertain specific targeting of the selected hit/lead compound on different components of lipid synthesis pathways, we will assess their effect on parasite lipid homeostasis. Total lipid composition, lipid class profiling and quantification will be determined in the French partner's own dedicated lipidomic platform (gas-chromatography/liquid chromatography coupled to mass spectrometry: GCMS, LCMSMS).

Overall, these studies will lead to development of patentable outcomes in the form of new and highly potent anti-malarial drug candidates.

Candidate profile

- Only Indian candidates or candidates with a research experience in India are eligible; French candidates are not eligible
- Applicants for post-doctorate must have a PhD degree (or be in the process of obtaining one)
- No competences in French language is required
- Candidate competences: Cell culture, molecular biology, biochemistry, strong expertise with Plasmodium falciparum is required
- Candidate know-how: Parasite cell culture/manipulation, generation of inducible KO, immunofluorescence, basic protein biochemistry
- Expected starting date: **Second semester 2024**

How to candidate ?

Documents to be provided :

i. A cover letter (reasons for the candidature, professional project …) max 2 pages
ii. A copy of the master's degree or a proof of the program followed (and expected date of end) OR A copy of the PhD degree or a proof of the PhD program followed (and expected date of defense) max 1 page
iii. A copy of results for previous scholarship (max 3 pages)
iv. International curriculum vitae (max 2 pages)
v. Two letters of recommendation: one from any Indian institution and one from the French institution planned to host the candidate –mandatory- (max 2 pages)
vi. All should be submitted within 1 pdf file of no more than 10 pages.

Applications should be submitted to the following email address: msi@ifindia.in mentioning the reference number of the Job offer clearly.

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Candidates are requested to contact the French scientific principal investigator of the project before submission. A recommendation letter from the scientific principal investigator is mandatory.

Benefits:

- Monthly allowance of 2400 euros for Post-Doc
- Travel allowance
- University fee
- Carte de séjour fee
- Campus France management fee
- Registration to the French social security scheme

Selection process:

Selection is made by a dedicated selection committee of at least 4 persons. Decisions will be transmitted by the Embassy of France to CEFIPRA. **No consideration will be given for candidates with no recommendation letter from the French institution.**

Criteria for applicants' selection:

Academic excellence

- Excellence of the Academic background, Academic records, Honors, Letters of support, Participation to international research projects, exchange programmes and conferences.

Motivation and qualities

- Academic maturity: appropriation of the thesis project (stakes and contexts) • Quality of the presentation (oral expression, skills for synthesis, English level) • Maturity of the professional project: capacity to project her/himself within five years in terms of career development.

About CEFIPRA:
Indo-French Center for the Promotion of Advanced Research (CEFIPRA/IFCPAR) is an Indian body which promotes scientific cooperation between France and India in advanced fields of Science and Technology. It is supported by the Department of Science and Technology, Government of India and the Ministry of Europe and Foreign Affairs of the French government.