

## PhD project 2021-2022 (one-page proposal)



### Title of the PhD project: Bis(monoacylglycerol)phosphate, a putative regulator of *Leishmania* virulence towards macrophages

Laboratory: Laboratoire d'Automatique, de Génie des Procédés et de Génie Pharmaceutique (LAGEPP)

Research team: Génie Pharmacotechnique

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#### EDISS fellowship 2021

#### Other funding

Leishmaniasis are a complex of tropical and sub-tropical human diseases caused by unicellular parasites of the genus *Leishmania* transmitted by a sand-fly vector and displaying various clinical expressions. Nearly 350 million people are exposed to leishmaniasis in more than 90 countries worldwide. To date, leishmaniasis remains a critical issue as current chemotherapy has limited efficiency due to toxicity/resistance. In last decades, the potential of lipids as functional players in parasite infection and therapeutic targets has attracted growing interest. Current projects of our research team are part of this challenge, aiming to identify specific lipids with relevant properties towards parasite infection, especially *Leishmania*<sup>1</sup>.

The *Leishmania* life cycle involves two different stages: the promastigote inside the vector and the amastigote in the host macrophages. The promastigotes inoculated by the vector and internalized by host macrophages via phagocytosis, a particular endocytosis, then differentiate into amastigotes. The intracellular survival of the parasite requires interactions/fusion mechanisms of the parasitophorous vacuole with the late endosome/lysosome compartment of macrophages, as well as the mobilization of host cell cholesterol. Parasite infectivity is favored by exosome-based secretion mechanism in promastigotes for the release of virulence and immunosuppressive factors.

Bis(monoacylglycerol)phosphate (BMP) is a peculiar phospholipid mainly found in the late endosome, that is well documented for its involvement in endocytosis pathway, fusion mechanisms, and sorting functions of late endosomes. Previous works from our team have demonstrated that BMP regulates cholesterol homeostasis in macrophages, by regulating its intracellular transport out of late endosome and its oxidative metabolism<sup>2</sup>. More recently, we highlighted the involvement of BMP in exosome formation and release by macrophages<sup>3</sup>. Our recent observations showed that BMP is also present in *Leishmania* promastigotes but its role has not been investigated.

The main objective of the thesis is to evaluate the role of BMP in host cell/parasite interactions and parasite development inside the macrophage through the following hypotheses: Host cell BMP might control parasite internalization and/or intracellular survival due to 1/ its presence in late endosomes and fusogenic properties; 2/ its regulation on sterol transfers that are mandatory for the intracellular survival of the parasite; 3/ BMP in *Leishmania* may be involved in exosome pathway and release of virulence factors. The work programs will include characterization of BMP in *Leishmania* parasites and macrophages using both analytical biochemistry (LC-MS/MS), and cell imaging (immunofluorescence and electron microscopy). The role BMP on host cell/parasite interactions will be evaluated using a number of tools to alter BMP structure/quantity in macrophages. Parasite virulence will be estimated by several indicators including internalization and survival of the parasite inside the macrophage, oxidative and inflammatory responses of the macrophage, relying on both biochemical, cellular and molecular approaches.

#### References

1. Changes in Lipid and Fatty Acid Composition During Intramacrophagic Transformation of *Leishmania donovani* Complex Promastigotes into Amastigotes. Bouazizi-Ben Messaoud H et al. *Lipids*. 2017 doi: 10.1007/s11745-017-4233-6
2. Bis(monoacylglycerol)phosphate regulates oxysterol binding protein-related protein 11 dependent sterol trafficking. Arnal-Levron M et al. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2019 doi: 10.1016/j.bbalip.2019.05.011
3. Bis(monoacylglycerol)phosphate, a new lipid signature of endosome-derived extracellular vesicles. Rabia M et al. *Biochimie*. 2020 doi: 10.1016/j.biochi.2020.07.005.

**Skills required:** Master in biochemistry, cellular and molecular biology, parasitology; technical skills in cell culture, biochemistry, molecular biology

**Application procedure:** send a detailed CV and the contact details of 2 academic referees to the PhD supervisor