COLLEGE DOCTORAL PAYS DE LA LOIRE | ED BIOLOGIE SANTE

Année 2024/2025

FICHE SUJET DE THESE

Sujet N° (à remplir par l'ED) :	**FINANCEMENT :** ☐ **Demandé** ☒ **Acquis**	**Origine du financement : CAPES - COFECUB**
Titre de la thèse : **Study of sterols biosynthesis in *Leishmania* spp.**		3 mots-clés : Sterols biosynthesis, drug resistance, antileishmanial drugs
Unité/équipe encadrante : **ER1155 - IICiMed Cibles et Médicaments des Infections et de l'Immunité**		
Directeurs de thèse : Dr Isabelle Ourliac-Garnier Pr Teresinha Goncalves da Silva (UFPE – Recife – Brésil)		N° de tél : 0253009160 Mail : isabelle.ourliac@univ-nantes.fr Mail : teresinha.goncalves@ufpe.br

Contexte socioéconomique et scientifique (env. 10 lignes) :

Leishmania spp are protozoan parasites that cause leishmaniasis, a neglected tropical disease transmitted to mammals in the form of promastigotes by the bite of sandflies. Once phagocytosed into human cells, the promastigotes transform into amastigotes, multiply, and infect other cells.

As is the case in fungi, the major membrane sterol in *Leishmania* amastigotes and promastigotes is ergosterol. Ergosta-5,7,24(28)-triene-3*b*-ol and ergosta-7,22-diene-3b-ol may also be present in significant amount. It has been shown that the sterol composition varies during the infection phase and that these variations play a role in the virulence of the parasite. Investigating the role of sterols in parasite pathogenesis is therefore of huge interest

There is a need to identify new therapeutic targets and/or new treatments against leishmaniasis, as the number of treatments is limited and resistance to conventional therapies is increasing. For example, resistance to amphotericin B in *Leishmania mexicana* has been shown to be associated with alterations in sterol metabolism. Furthermore, as in fungi, the emergence of resistance may trigger alternative sterol synthesis mechanisms that have to be investigated.

The objective of this project is to develop research work at the interface of analytical chemistry and biology in the fields of the understanding of new mechanisms of resistance established by parasites.

The proposed subject is based on the expertise of the two teams and their complementarity in sterol analysis by GC-MS, cell biology and parasite biochemistry.

Hypothèses et questions posées (env. 8 lignes) :

First the analysis of the sterols profile in *leishmania spp* should provide a better understanding of the mechanisms of resistance and of the failure of certain treatments.

Then the effects of antileishmanial compounds synthesized in the CAPES-COFECUB project on the ergosterol biosynthesis pathway will be investigated in order to characterize their mechanism of actions**.**

Grandes étapes de la thèse (env. 12 lignes) :

The first step of this project is to develop a protocol for the analysis of sterols in promastigote and amastigote forms of the parasite. The first steps of cell culture to obtain sufficient quantities of the different forms of the parasite, followed by the steps of sterol extraction, There will be great part of method development and fine-tuning, first in cell culture to obtain sufficient quantities of the different forms of the parasite, then in extraction steps that are preliminary to GC-MS analysis. Then, the protocol for sterol analysis by GC-MS developed by the IICiMed team for fungi will be applied once the parasite membrane extract is obtained.

In order to describe the sterol biosynthesis in the different species, the sterol analysis will be performed on different strains of *Leishmania* spp. from the IICiMed collection and from the collection of UFPE: *L major, L. mexicana, L donovani, L infantum, L brazilensis*. If possible more than one strain will be tested for each species.

A second step of this project is to test the effects of antileishmanial compounds synthesized in the CAPES-COFECUB project on the ergosterol biosynthesis pathway, in order to characterize their mechanism of actions.

The results will be communicated through international publications and conferences in Medicinal Chemistry and Parasitology, when possible.

Compétences scientifiques et techniques requises par le candidat (2 lignes) :

Profile biologist with cell culture skills and parasitology knowledge to understand the biological implications. An interest in analytical chemistry and method development should be great

3 publications de l'équipe d'accueil relatives au domaine (5 dernières années) :

Lavergne RA, Albassier M, Hardouin JB, et al. Impact of TR34/L98H, TR46/Y121F/T289A and TR53 Alterations in Azole-Resistant Aspergillus fumigatus on Sterol Composition and Modifications after In Vitro Exposure to Itraconazole and Voriconazole. Microorganisms. 2022;10(1):104. doi:10.3390/microorganisms10010104

Mossion A, Ourliac-Garnier I, Wielgosz-Collin G. Fungal Sterol Analyses by Gas Chromatography–Mass Spectrometry Using Different Derivatives. In: Barreiro C, Barredo JL, eds. Microbial Steroids: Methods and Protocols. Methods in Molecular Biology. Springer US; 2023:143-156. doi:10.1007/978-1-0716-3385-4_8

Collaborations nationales et internationales :

Institut Pasteur, Paris