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École doctorale **ED659 Recherches Biomédicales**
Spécialité **Maladies infectieuses et microbiote**
Domaine Scientifique **Biologie, médecine et santé**
Unité de recherche **LAI – Laboratoire Adhésion et Inflammation (INSERM U1067 CNRS UMR 7333)**
Encadrement de la thèse **Magali CASANOVA : magali.casanova@univ-amu.fr**

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Better understanding Leishmania apoptosis

Leishmaniases, which encompass three major clinical forms (cutaneous, mucosal and visceral), are considered as **neglected diseases** by the World Health Organization. They are caused by **flagellated protozoan parasites** belonging to the ***Leishmania*** genus, transmitted by the bite of an insect, the **phlebotomine sandfly**. Inside the insect's gut, parasites proliferate as a flagellated mobile form called the **promastigote form**. Inside the mammalian host, promastigotes are phagocytised into macrophages where they differenciate in an intracellular form with a reduced flagellum, the **amastigote form**. Leishmaniases cover 88 countries all over the five continents, with annual mortality between 20,000 and 30,000, constituting a real scourge for **developing countries** where it **impedes socioeconomic development**. But they also impact **more-developed** countries, notably due to **overlapping cases of HIV infection and visceral leishmaniasis** (Annals of Tropical Medicine and Parasitology, 2003). More recently, some cases appeared after organ transplants, whereas organ transplants increase in Europe (Berenguer *et al.*, 1998).

However, no really satisfying treatment against leishmaniases exist, due to **toxic effects**, their **mode of administration** and their **cost**. Furthermore, **drug resistance** is becoming common in some areas. As a consequence, due to the medical importance of leishmaniases and to the limitations of current treatments, it is highly desirable **to identify new drugs** to fight against these diseases. For this, we are interested in a key metabolic process: **apoptosis**. Indeed, in *Leishmania*, different stimuli like reactive oxygen species, heat shock or leishmanicidal drugs, induce morphological and biochemical apoptosis-like features: cell rounding up, chromatin condensation, DNA fragmentation, mitochondrial depolarization, release of cytochrome c... Physiologically, cell death has been described in this parasite as a selfish altruism, regulating parasite densities within the vector and the mammalian host, and avoiding hyperparasitism (Duszenko *et al.*, 2006; Lüder *et al.*, 2010). *Leishmania* cell death may also permit successful infection by modulating host immunity (Lüder *et al.*, 2010). However, despite this evidence of *Leishmania* apoptosis, **very little is known about the cell death pathways and about the executioner proteins involved** (Basmaciyan and Casanova, 2019a). Indeed, essential proteins involved in mammalian apoptosis, like death receptors or caspases, are not encoded in the genome of *Leishmania* (Smirlis *et al.*, 2010). And even if the presence of small pro- and anti-apoptotic molecules has been suggested, it has not been really demonstrated for the moment (Genes *et al.*, 2016). Only few proteins have been unequivocally demonstrated, by our group or by other researchers, as involved in the *Leishmania* cell death like the metacaspase, the hydrolase LmjF.36.06540 (Casanova *et al.*, 2015; Basmaciyan L. *et al.*) or the potential acetyltransferase LmjF.22.0600 (Basmaciyan and Casanova, 2019b). The aim of this project is to identify new proteins involved in *Leishmania* apoptosis.

In this project, several proteins potentially involved in *Leishmania* apoptosis will be studied: metacaspase substrates, protein families such as calpains, proteins involved in *Leishmania* autophagy, proteins overexpressed in drug-resistant *Leishmania*,… (Basmaciyan and Casanova, 2019a). We will perform gene deletion using CRISPR/Cas9, as well as gene overexpression. Subsequently, we will investigate the consequences of these modifications on *Leishmania*: growth, motility, morphology, metabolism,… We will also try to better understand the relationships between proteins involved in *Leishmania* apoptosis, that is to say the apoptotic metabolic pathways. We will work on the promastigote and intracellular amastigote forms of *L. mexicana*, the species responsible for American mucosal leishmaniasis, which represents a major public health concern in the Americas due to the disfiguring effects of the disease and the significant risk of secondary infections.

This work will enable the identification of new proteins involved in the apoptosis of the ancestral eukaryotes *Leishmania*, as well as the completion of the apoptotic metabolic pathways in these parasites. The goal is to gain a deeper understanding of *Leishmania* apoptosis, with the aim of subsequently targeting this process to develop a novel therapeutic tool (for example, based on the encapsulation of proteins involved in *Leishmania* apoptosis). This new tool, based on highly specific metabolic pathways of *Leishmania*, should, in principle, induce few side effects.

Profile and required skills:

A basic understanding of molecular and cellular biology is expected. In general, curiosity, independence and tenacity are some of the “must have” for such a project. Excellent command of French or English is also required.