UMR 7255

New selective inhibitors for deciphering lipid metabolism and virulence in *Mycobacterium tuberculosis*

A PhD position (see https://bit.ly/2Cq1AYY) at the chemistry/biochemistry interface, starting October 2020 and financed by the ANR on the **LipInTB** project, is available at LISM UMR7255 CNRS in the *Lipolysis and Bacterial Pathogenicity* team.

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Keywords: drug susceptibility; intracellular activity; activity based-protein profiling; mycobacteria; Tuberculosis

Study background summary

Tuberculosis, caused by the mycobacteria *Mycobacterium tuberculosis* (*M. tb*), still affects one third of the world's population and is responsible for nearly 1.5 million deaths per year, thus remaining a major public health problem. One of the main characteristics of *M. tb* is its ability to use host lipids for its own: renewal of the lipids of the envelope, formation of lipid reserves for its entry into dormancy and their consumption upon reactivation. These different stages imply the existence of extra- and intracellular lipolytic enzymes. Therefore, finding ways to block the action of these lipolytic enzymes would pave the way for the discovery of new treatments against tuberculosis.

This thesis project is part of the ANR **LipInTB** project (2019-2023), involving 5 partners, which aims to use two newly reported families of inhibitors, Cyclipostins/Cyclophostins analogs [1-4] and Oxadiazolone derivatives [5-7], as probes to decipher the lipid metabolism of *M. tb* during its growth and virulence.

The main objectives of this ambitious project at the interface between chemistry, biochemistry, biology and antibiotic therapy are: **1)** to study the penetration and distribution of our inhibitors in the bacterium as well as in host cells; **2)** to use our inhibitors as probes to study the lipid metabolism in *M. tb* by identifying the enzymes impacted by our compounds during the active replication, latency and reactivation phases in infected macrophages; **3)** to biochemically and structurally characterize the identified target enzymes, and **4)** to validate them *in vitro* and *ex vivo* by building deletion/complementation/overexpression mutant strains and studying their susceptibility and viability in infected macrophages.

References: [1] Nguyen, P. C., *et al.*, *Scientific Reports* **2017**, *7*, 11751. [2] Nguyen, P. C., *et al.*, *Int J Antimicrob Agents* **2018**, *51*, 651-654. [3] Point, V., *et al.*, *J Med Chem.* **2012**, *55*, 10204-10219. [4] Spilling, C. D., *et al.*, "*Fluorescent Labeled Inhibitors*", **US10047112B2**. [5] Delorme, V., *et al.*, *PLoS ONE* **2012**, *7*, e46493. [6] Nguyen, P. C., *et al.*, *Bioorg Chem.* **2018**, *81*, 414-424. [7] Point, V., *et al.*, *Eur J Med Chem.* **2016**, *123*, 834-848.

Work Context and expected profile of the candidate

The research work will be carried out at the Laboratoire d'Ingénierie des Systèmes Macromoléculaires (LISM) in the "*Lipolysis and Bacterial Pathogenicity*" (LBP) team (https://tuberculosis-lbp.wixsite.com/tuberculosis-lbpteam).

We are seeking highly motivated candidates (master or equivalent with honors) and with a solid background in therapeutic chemistry, biochemistry, microbiology and/or biological chemistry (chemistry-biology interface). Experiences in biochemistry and/or molecular biology would be an asset.

The candidate must also be motivated to train in various area complementary to his or her initial training, be organized, dynamic and communicative, and open-minded.

All applications must be submitted **exclusively** *via* the **CNRS job portal** (https://bit.ly/2Cq1AYY) and must include a **detailed CV** with the contact details of at least **two referees** (teachers or internship supervisors), **a motivation letter**, and **transcripts of Master 1 and 2** as well as corresponding rankings.