Thesis: Antimicrobial peptides to fight *Mycobacterium abscessus* infections in cystic fibrosis (RIGATONI)

Laboratory: LISM UMR7255 CNRS, Marseille / Universidade Catolica de Brasilia (UCB), Brazil

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Scientific context. *Mycobacterium abscessus* (*Mabs*), a rapidly growing opportunistic non-tuberculous mycobacterium, is responsible for severe pulmonary infections in immunocompromised individuals, such as patients with cystic fibrosis (CF). Its strong propensity to develop resistance to a wide range of antibiotics, its capacity to form biofilms, and the presence of intracellular forms of *Mabs* make this mycobacterium a public health concern associated with poorly effective treatments.[1]

We have recently identified natural antimicrobial peptides (AMPs) that inhibit *Mabs* growth *in vitro* in culture medium with moderate (Lynronne peptides)[2] to potent (Arenicin peptides)[3] antibacterial activities. Non-toxic to human cells, these AMPs act by insertion into the mycobacterial membrane resulting in the rapid lysis of the bacteria.[3] Based on these data, 10 new Lynronne-based AMPs have been designed and synthesized. They are currently being tested for their ability to inhibit *Mabs* growth *in vitro*.

Research project. The RIGATONI project; which combines a wide range of interdisciplinary scientific techniques, including peptide synthesis, chemobiology, microbiology, host-pathogens interaction, and drug susceptibility testing; aims to address the following objectives:

▶ (1) Evaluate the therapeutic potential of the AMPs against *Mabs* growth *in vitro* and under biofilm forms by using a physiological artificial cystic fibrosis sputum (ACFS) medium,[4] and study their synergy with current drugs.

▶ (2) Elucidate their cellular uptake & intracellular delivery through in-cell labeling combined with fluorescence microscopy imaging.[5]

The approach will include the development of azide-tagged analogs (**AMP$_{N_3}$**), and cell-penetrating peptide (CPP) conjugates—with and without an azide tag (**CPP-AMP** and **CPP-AMP$_{N_3}$**)—of the best selected three AMP candidates. These constructs will be optimized through the use of artificial intelligence (AI) in close collaboration with **Prof. Octávio Luiz Franco**, who is expert in AI and machine learning to optimize AMP sequences in terms of safety, antibacterial activity and in-cell delivery.[6] Following synthesis and secondary structure elucidation, each AMP probe will be involved in a Strain-Promoted Alkyne-Azide Cycloaddition reaction to quantify its accumulation/penetration, and assess its localization *in cellulo*.

▶ (3) Assess their intracellular activity and mode of action against *Mabs* in infected human macrophages.

The results generated will provide valuable data for future chemotherapeutic developments against one of the most drug-resistant mycobacterial species.

Profile. Strongly motivated student with a solid background at the chemistry-biology interface in therapeutic chemistry and chemobiology. Experiences in cellular biology and microbiology would be an asset. The candidate should be curious, well-organized, dynamic, communicative, open-minded, able to interact with multiple people, and have a teamwork spirit.

Importantly, the PhD candidate will be trained to AI-design/optimization of the AMP probes by **Prof. Octávio Luiz Franco**.

Requirements. Candidates should send a CV, a motivation letter, transcripts of academic records and the contact information of two referees. Deadline: **20/04/2026**.

Bibliographic References

[1] Nessar *et al.*, "*Mycobacterium abscessus*: a new antibiotic nightmare", *J Antimicrob Chemother* **2012**, *67*, 810. [2] Boidin-Wichlacz *et al.*, "Potency of all-D amino acid antimicrobial peptides derived from the bovine rumen microbiome on tuberculous and non-tuberculous mycobacteria", *Curr Res Microb Sci* **2025**, *8*, 100395. [3] Casanova *et al.*, "Promising antibacterial efficacy of arenicin peptides against the emerging opportunistic pathogen *Mycobacterium abscessus*", *J Biomed Sci* **2024**, *31*, 18. [4] Baker *et al.*, "Cystic fibrosis sputum media induces an overall loss of antibiotic susceptibility in *Mycobacterium abscessus*", *NPJ Antimicrob Resist* **2024**, *2*, 34. [5] Dash *et al.*, "Systematic Determination of the Impact of Structural Edits on Peptide Accumulation into Mycobacteria", *ACS Chem Biol* **2025**, *20*, 1962-1979. [6] Porto *et al.*, "Joker: An algorithm to insert patterns into sequences for designing antimicrobial peptides", *Biochim Biophys Acta Gen Subj* **2018**, *1862*, 2043.