3-Year PhD student position in Medicinal Chemistry – Antiparasitic chemotherapy

Fighting against Leishmaniasis by developing new antiparasitic agents.

To be filled in November 2026

Laboratory:

UR 1155 – IICiMed (https://iicimed.univ-nantes.fr/en), Nantes Université, Institut de Recherche en Santé 2, 22 Boulevard Bénoni Goullin, 44200 Nantes - France

Contact:

Prof. Pascal Marchand – pascal.marchand@univ-nantes.fr

Financial support:

French National Research Agency (ANR) collaborative project "OMAP-CK1" (**O**ptimized **M**acrocyclic compounds **A**gainst **P**arasites and targeting **CK1**) coordinated by Prof. Pascal Marchand.

Context of the project and objectives of the thesis:

Leishmaniasis, a neglected tropical disease affecting over 12 million people, remains a major global health threat with limited and toxic treatments and increasing drug resistance. The current ANR TEXLEISH project identified *Leishmania* casein kinase 1 paralog 2 (L-CK1.2) as a crucial excreted enzyme involved in parasite survival and host immune modulation, establishing it as a novel therapeutic target. Through iterative medicinal chemistry, modelling, and biological screening, several orally active inhibitors were developed, showing high selectivity for L-CK1.2, low mammalian toxicity, and strong *in vivo* efficacy against *L. major* and *L. donovani*.

Building on these results, the OMAP-CK1 project aims to finalize preclinical development by optimizing these compounds and advancing them toward translational readiness. The project's main objectives are: (1) conduct detailed DMPK analyses; (2) enhance oral bioavailability using a **macrocyclic drug design approach**; (3) use hepatic organoids to study metabolism, host–parasite interactions, and potential resistance; (4) determine compound biodistribution; and (5) elucidate parasite clearance mechanisms and macrophage recovery through biomarker studies.

OMAP-CK1 unites three complementary partners: IICiMed - Nantes Université (medicinal chemistry, *in vitro*/*in vivo* evaluation), UMR BIPAR - ANSES/INRAe (pharmacokinetics and resistance studies), and Institut Pasteur (kinase biology and mechanistic analyses). By targeting the parasite exoproteome, proteins vital for host–parasite interactions and less prone to resistance, the consortium tackles two critical barriers in drug development: the emergence of resistance and the translational gap between academia and industry.

OMAP-CK1 thus represents a decisive step toward effective, safe, and affordable therapies against neglected parasitic diseases.

During the thesis project devoted to antiparasitic Drug Discovery, the candidate will be in charge of the design and the synthesis of imidazo[1,2-*a*]pyrazine-based macrocyclic compounds. The step-by-step pharmacomodulation will see the generation a novel chemical library to guide structure-activity relationship study and will be supported by all the biological and *in silico* tools depicted above, and available through the partnership.

As part of this project, the candidate will have to promote his (her) research work in consortium meetings, but also by participating to conferences. The completion of this PhD will give to the candidate a good expertise in drug development within a project at the interface of chemistry and biology.

Required profile:

The applicant, from university or engineer school, will possess a solid knowledge in organic and medicinal chemistry. He will be motivated to work closely with biological partners and collaborators involved in molecular modelling.

Application procedure:

All required documents are listed below:

• All degree certificates,

• Detailed CV,

• Cover Letter,

• Two recommendation letters (or contact information of at least 2 references).

References:

1. Durieu, E.; Prina, E.; Leclercq, O.; Oumata, N.; Gaboriaud-Kolar, N.; Vougogiannopoulou, K.; Aulner, N.; Defontaine, A.; No, J. H.; Ruchaud, S.; Skaltsounis, A. L.; Galons, H.; Späth, G. F.; Meijer, L.; Rachidi, N. *Antimicrob. Agents Chemother.* **2016**, *60*, 2822-2833. DOI: 10.1128/AAC.00021-16.

2. Bazin, M.-A.; Cojean, S.; Pagniez, F.; Bernadat, G.; Cavé, C.; Ourliac-Garnier, I.; Nourrisson, M.-R.; Morgado, C.; Picot, C.; Leclercq, O.; Baratte, B.; Robert, T.; Späth, G.F.; Rachidi, N.; Bach, S.; Loiseau, P. M.; Le Pape, P.; Marchand, P. *Eur. J. Med. Chem.* **2021**, *210*, 112956. DOI: 10.1016/j.ejmech.2020.112956.

3. Rachidi, N.; Knippschild, U.; Späth, G. F. *Front. Cell. Infect. Microbiol.* **2021**. DOI: 10.3389/fcimb.2021.655700.

4. Silvestre, A.; Shintre, S. S.; **Rachidi, N.** *Front Cell Infect. Microbiol*. **2022**, *12*, 825458. [Open Access] DOI: 10.3389/fcimb.2022.825458.

5. Tisseur, L.; Cojean, S.; Gassama, K.; Logé, C.; Pagniez, F.; Cavé, C.; Bernadat, G.; Loiseau, P. M.; Bach, S.; Thiéfaine, J.; Picot, C.; Tomasoni, C.; Leclercq, O.; Baratte, B.; Robert, T.; Le Pape, P.; Rachidi, N.; Bazin, M.-A.; Marchand, P. *ChemMedChem* **2025**, *20*, e202400862. DOI: 10.1002/cmdc.202400862.

6. Tisseur, L.; Logé, C.; Cojean, S.; Gassama, K.; Karcher, L.; Pagniez, F.; Cavé, C.; Bernadat, G.; Loiseau, P. M.; Bach, S.; Thiéfaine, J.; Bonnet, J.; Picot, C.; Tomasoni, C.; Leclercq, O.; Baratte, B.; Robert, T.; Le Pape, P.; Rachidi, N.; Bazin, M.-A.; Marchand, P. *RSC Med. Chem.* **2025**, *16*, 3746–3763. DOI: 10.1039/d5md00257e.