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

Fighting against Leishmaniasis by developing new antiparasitic agents.

To be filled in October - November 2021

Laboratory:

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

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Financial support:

French National Research Agency (ANR) collaborative project "TEXLEISH" (**T**argeting host-parasite interactions through the inhibition of **EX**creted ***LEISH****mania* casein kinase 1) coordinated by Prof. Pascal Marchand.

Context of the project and objectives of the thesis:

Leishmaniasis is a severe public health issue and the current treatments are toxic, costly or lead to parasite resistance, thus there is an urgent need for new drugs. The TEXLEISH consortium proposes a new paradigm: inhibiting host-parasite interactions, through targeting *Leishmania* exoproteome, in order to limit the risk of parasite resistance. TEXLEISH synergizes important expertise in medicinal chemistry, kinase-based drug discovery, parasite biology and *in vivo* testing to optimize the imidazo[1,2-*a*]pyrazine derivative **CTN1122**, a potent antileishmanial lead compound, into an orally active, safe, effective drug candidate that could reach preclinical trial level. This process involves iterative rounds of chemical synthesis supported by *in silico* docking on L-CK1.2 using the dynamic model generated by one of the partners, assessment of its efficacy on the biological target and the parasite, toxicity, *in vitro* bioavailability, *in vivo* efficiency on animal models and the study of its mechanism of action. The TEXLEISH project will constitute a proof of concept to validate pathogen exoproteome as the future of target-based strategies.

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 heterocyclic 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 (EA 1155 – IICiMed, Institut Pasteur – Paris, UMR CNRS 8076 BioCIS Université Paris-Saclay).

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. Rachidi, N.; Taly, J.-F.; Durieu, E.; Leclercq, O.; Aulner, N.; Prina, E.; Pescher, P.; Notredame, C.; Meijer, L.; Späth, G. F. *Antimicrob. Agents Chemother.* **2014**, *58*, 1501-1515. DOI: 10.1128/AAC.02022-13.

2. Marchand, P.; Bazin, M.-A.; Pagniez, F.; Rivière, G.; Bodero, L.; Marhadour, S.; Nourrisson, M.-R.; Picot, C.; Ruchaud, S.; Bach, S.; Baratte, B.; Sauvain, M.; Castillo Pareja, D.; Vaisberg, A. J.; Le Pape, P. *Eur. J. Med. Chem*. **2015**, *103*, 381-395. DOI: 10.1016/j.ejmech.2015.09.002.

3. 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.

4. 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.

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