PhD position 2023-2026

Medicinal Chemistry – Peptide Chemistry

In the frame of an emerging project in the antimicrobial agents development field, we are looking for an highly motivated candidate for a 36 months PhD contract in Rennes, France.

This interdisciplinary PhD project is directed by a complementary consortium: with chemistry supervised by Dr C. Gadais & Pr. F.-H. Porée (ISCR UMR 6226 team COrInt, partner 1) and biology supervised by Pr. R. Gillet (IGDR UMR 6290, QCPS team, partner 2). Both teams are located in Université de Rennes.

Subject

Development of new peptide-based antimicrobial agents targeting the *trans*-translation pathway in multi-resistant bacteria

Key words : *antimicrobial resistance, ribosome, medicinal chemistry, peptide and peptidomimetic synthesis, trans-translation, Cryo-EM*

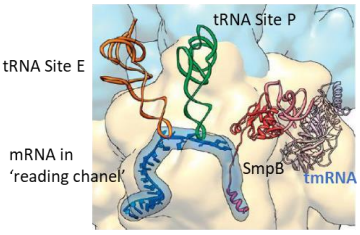

Figure 1 SmpB/tmRNA complexe in ribosome

Despite the increasing number of studies proving the worldwide antibio-resistance spreading, Big Pharma interests for new antibiotic drugs are minimal since economic stakes are high and return on investment low. In particular, the ESKAPE group of bacteria (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp*.) represents a serious concern for which the WHO urges the scientific community to find new therapeutic solutions. In this context, we would take advantage of the identification of a unique bacterial process to develop a new class of antibiotics. Errors in ribosomal protein synthesis are inevitable events that can lead to cell death. To prevent such fatal consequences, bacteria activate a rescue system called ***trans*-translation** that permits resuming translation and destroying faulty proteins. In this process, a small protein called SmpB recognizes stalled ribosomes by inserting its C-terminal tail in the vacant mRNA path of stalled ribosomes. In that way, SmpB insertion allows the correct positioning of its partner, transfer-messenger (tmRNA), into the ribosomal A-site (Figure 1). The nascent faulty peptide is tagged for degradation, the problematic mRNA is destroyed and the ribosome is recycled for a new round of translation.[1] Exclusive to prokaryotic cells, this "rescue system" constitutes a highly valuable target for the development of new classes of antibiotics with potentially broad-spectrum of activity, and limited side-effects on host cells.[2,3]

Hypothesis, object and methodology: Based on high resolution Cryo-EM technology, elucidation of the interactions between tmRNA, SmpB and the stalled ribosome by partner 2 has unveiled the importance of the SmpB C-terminal tail in the *trans*-translation process.[4,5] Proof-of-concept of this hypothesis was validated in *E. coli* for which *trans*-translation inhibition was demonstrated using its SmpB-29-residues C-terminal domain.[6] Since inhibition of this pathway could ultimately lead to bacterial death, SmpB C-terminal tail constitutes a promising starting point for the design of new series of potent antibiotics displaying a unique mechanism of action. In this project, **we plan to work on peptides mimicking the SmpB C-terminal tails of ESKAPE pathogens as decoys for *trans*-translation inhibition and their antibiotic applications.**

PhD project plan:

The PhD student will be responsible for the identification of the optimal peptide sequence lengths together with the critical residues of SmpB's tail necessary to inhibit *trans*-translation in the ESKAPE pathogens and eventually the design of an optimized hit. To achieve this goal, the PhD student will synthesize customized peptides (SPPS – Solid-Phase Peptide Synthesis, manual and/or automated) and carry out their chemical characterization (HPLC/MS, NMR, CD). Routine *in vitro* screening assays will be carried out to evaluate peptides series and select best candidates (training provided). Conception of further optimized targets will be assisted by modelisation studies (training provided), based on the recent structural studies of tmRNA-SmpB complexes in the ribosome (pdb data 7ac7 for SmpB in *E. Coli,* Guyomar *et al., 2022*), and by Cryo-EM experiments.

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Candidate profile

The candidate should hold a **Master II degree or equivalent** (or should be holding it by September 1, 2023) with a profile in **molecular chemistry** (organic synthesis, purification, and characterization of organic compounds – HPLC and Mass spectrometry). She/he should also be highly interested in strengthening her/his skills in **peptide chemistry** and in working on a **project at the interface** of chemistry and biology. A previous experience in peptide synthesis (SPPS) would be appreciated. Basic skills in HPLC and mass spectrometry would be also considered.
No technical skills in biology and modelling are requested but general culture and interest for both would be considered (training provided).

If interested, please submit your full application to charlene.gadais@univ-rennes.fr that should include your **curriculum vitae**, a **cover letter describing your interest for this project**, your transcripts of Master degree, and the **name and email address of two persons** that could be contacted for recommendation.

For further information:

- Scientific project manager: charlene.gadais@univ-rennes.fr
- Head group (chemistry): francois-hugues.poree@univ-rennes.fr
- Head group (biology): reynald.gillet@univ-rennes.fr

Application deadline : 30/04/2023

References:

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