ISCR – Institut des Sciences Chimiques de Rennes, UMR 6226
UFR des Sciences pharmaceutiques et biologiques

Offre de stage 6 mois à partir de Mars 2023 – Master II/ Ingénieur 3ème année
Chimie des peptides

Equipe d'accueil/ Responsable Adresse	Equipe **COrInt**, **ISCR** – UMR 6226 Laboratoire de Chimie thérapeutique Bâtiment 5 RDC, Campus Villejean Responsable : François-Hugues Porée 2 Avenue du Pr. Léon Bernard 35000 Rennes Cedex
Encadrant du stage/ adresse/ téléphone/ Mail	Merci d'adresser CV et lettre de motivation à : Dr. Charlène Gadais (MCU) Charlene.gadais@univ-rennes1.fr 02 23 23 47 36
Titre du stage	Development of new peptide-based antimicrobial compounds targeting *trans*-translation in multiresistant bacteria.
Mots-clés	*Organic synthesis, peptide and peptidomimetic synthesis, protein mimicry, antimicrobial resistance*

Despite the increasing number of studies proving the antibio-resistance spreading, especially among ESKAPE pathogens, Big Pharma interest for new antibiotic drugs is minimal since economic stakes are too high and a return on investment too low.[1] To overcome this therapeutic dead end, new drug strategies must be developed, in particular through the identification of new therapeutic targets.

Project context: Errors in ribosomal protein synthesis are inevitable events that could lead to cell death. To prevent such fatal consequences, bacteria activates a rescue system called ***trans*-translation** that permits resuming mRNA reading and translation. In this process, a small protein, called SmpB, recognizes stalled ribosomes via insertion of its C-terminal tail in the ribosome A-site allowing the correct positioning of the messenger-like domain of its transfer-messenger (tmRNA) partner (Figure 1). The nascent "error" peptide is tagged for degradation and the ribosome recycled for a new translation.[2] Exclusive to prokaryotic cells, these "rescue systems" are highly valuable targets for the development of new antibiotics with potentially broad-spectrum activity, and expected limited side-effects on host cells.[3,4]

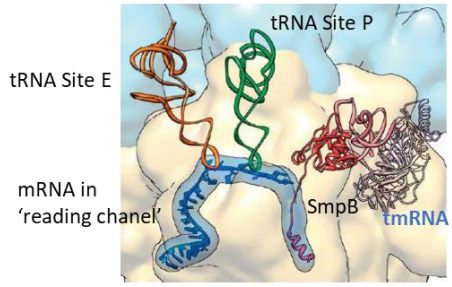

Figure 1 SmpB/tmRNA complexe in ribosome

Hypothesis, object and methodology: Based on high resolution Cryo-EM technology, elucidation of the interactions between tmRNA, SmpB and the stalled ribosome by Gillet's group, has unveiled the importance of the SmpB C-terminal tail,[5,6] and provides thus a powerful template for the design of new compounds with potent antibiotic activity. Therefore, **we plan to work on peptides mimicking the C-terminal tails of SmpB's from ESKAPE pathogens as decoys for *trans*-translation inhibition**. This proof-of-concept was already validated by isolating the peptide which corresponds to the 29-residues C-terminal extremity of *E. coli* SmpB, for which *trans*-translation inhibitory activity in *E. coli* was demonstrated.[7]

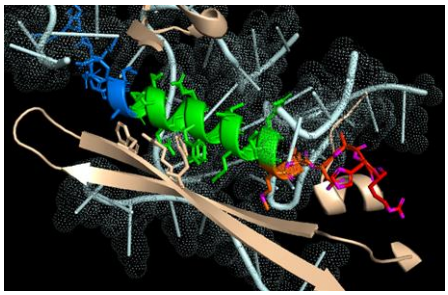

Figure 2 SmpB C-ter tail in E. Coli ribosome

ESKAPE SmpB C-ter tail mimetics will be designed based upon the structural studies of tmRNA-SmpB complexes in the ribosome (7ac7 for SmpB).[5] For that purpose, C-terminal SmpB tail will be cut into two regions of interest and peptides mimetics will be synthesized and evaluated. Further chemical modifications will be planned to improve efficacy and eventually overall pharmacokinetical properties.

This interdisciplinary project is directed in collaboration with Pr. Reynald Gillet from IGDR, Rennes.

Internship expectations :
The master II level student will be expected to synthesize on solid phase (SPPS), purify and characterize a series of peptides mimicking SmpB function.
High-standard quality knowledge and lab skills in organic synthesis are expected for this project. The recruited person will have to show autonomy in her/his work organization but also a good team spirit. She/he will have to be rigourous in the results presentation and scientific curiosity for this interdisciplinary project.
Knowledge and interest for peptide chemistry will be an appreciated bonus.
This project might further proceed with a PhD fellowship (grant under application, not guaranteed yet).
To apply, please send CV and cover letter to Dr. Charlène Gadais (charlene.gadais@univ-rennes1.fr).