TACKLING ANTIBIOTIC RESISTANCE BY TARGETING THE DAP-PATHWAY FOR THE DEVELOPMENT OF NOVEL ANTI-BACTERIAL AGENTS

DIRECTEUR DE THESE : SEBASTIEN ALBRECHT
LABORATOIRE D'INNOVATION MOLECULAIRE & APPLICATIONS, MULHOUSE
TÉL : 03 89 33 67 14 / E-MAIL : SEBASTIEN.ALBRECHT@UHA.FR

Antimicrobial resistance (AMR) represents a serious and growing threat to human and animal health worldwide and poses a significant burden on healthcare systems and national budgets. It already kills 700 000 people globally every year. In Europe alone, AMR bacteria kill an estimated 33 000 people every year. Besides these devastating human losses, AMR also poses an economic burden to society of €1.5 billion per year. With the rise of AMR, we are now heading towards a "post-antibiotic era" where common infections may once again be fatal. By 2050, AMR infections are estimated to kill 10 million people if no action is taken.[1] There is an urgent need for new antimicrobial therapies, but few new drugs make it to the market.[2] Developing new antibiotics is crucial, yet highly challenging in a scientific, regulatory and business sense. Despite the recognized need for new antimicrobials for clinical use, only two new classes of antibiotics have been brought to market in the last 30 years and neither of these target Gram-negative bacteria, which are often deadly. To combat the growing threat of AMR, there is an urgent need for new chemical classes of antibiotics, especially with new targets or novel mechanisms of action.

The overall objective of this project is to identify novel molecular scaffolds as potential antibiotics clearly differentiated from existing ones, hence escaping the actual scope of drug resistance. To reach this objective, this project targets the diaminopimelic acid (DAP) pathway and the identification of efficient inhibitors of a very attractive and underexplored bacterial enzyme target, the N-succinyl-L,L-diaminopimelic acid desuccinylase enzyme (DapE, EC 3.5.1.18), that is present in all Gram-negative and most Gram-positive bacteria.

Expected results :
- Synthesis, purification & characterization of potential inhibitors of DapE
- Getting involved in a medicinal chemistry program
- Sharing ideas and chemical know-how with PhD students and other undergraduate students.
- Supervision of undergraduates

Key words :
Chemical synthesis, medicinal chemistry, structure-based drug design,

Candidate's skills :
We are looking for a student with a Master's degree (specialty in organic chemistry) motivated by a project in medicinal chemistry. The candidate must be actively involved in the life of a research team, be autonomous, curious and have good integration skills. Excellent notions and experimental know-how in organic synthesis are essential. Notions in analytical chemistry will be appreciated.

[1] Home | AMR Review Available online: https://amr-review.org/home.html (accessed on 2 October 2019)
[2] Antibiotics Currently in Global Clinical Development Available online: http://pew.org/1YkUFkT (accessed on 2 October 2019).