Rational design of new DltB inhibitorsTitle

Côme Ghadi[1], Charline Kieffer[1], Johanna Giovannini[1], Aurelie Verneuil[2], Nicolas Verneuil[2], Axel Hartke[2], Jana Sopkova-De oliveira Santos[1]

[1]*CERMN (UR 4258), Université de Caen Normandie, UNICAEN, F-14032 Caen, France*
[2]*CBSA (UR 4312), Université de Caen Normandie, UNICAEN, 14032 CAEN Cedex 5, France*

Antibiotic resistance represents a major public health challenge globally, resulting in a significant increase in the number of deaths and socioeconomic costs associated with infections. In response to this threat, the WHO published a list of twelve priority families of multidrug-resistant microorganisms in 2017[1]. Among these, Gram-positive cocci bacteria, such as Staphylococcus aureus and Enterococcus faecium, were highlighted. While some antibiotics remain effective against these pathogens, therapeutic options are limited. Recent studies have shown that targeting the D-alanylation of teichoic acids (TAs) could potentially restore the sensitivity of antibiotics[2]. TAs are crucial components of Gram-positive bacterial cell walls, contributing to cellular stability by maintaining peptidoglycans at the plasma membrane. The phosphate groups within TAs carry a negative charge, which is partially neutralized by the addition of D-alanine groups, creating an electrochemical barrier against positively charged molecules like antibiotics. [3]

The process of D-alanylation of TAs is mediated by the products of the genes of the dlt operon (d-alanyl-lipoteichoic acid operon), including DltA, DltB, DltC, DltD, DltX proteins.[4] Our objective is to inhibit DltB, a transmembrane transporter containing a catalytic histidine. Working in conjunction with other proteins of the Dlt operon, DltB mediates the transport of D-alanine from the intracellular to the extracellular milieu. Currently, only two inhibitors of DltB are documented in the literature: Amsacrine and DBI-1[5,6]. Amsacrine has a high toxicity to humans, thus excluding its use and DBI-1 in vitro activity was not found in vivo. Consequently, these inhibitors are not viable medications. Therefore, the goal of this project is to rationally design new inhibitors of the DltB protein in the studied Gram-positive cocci.

Bibliography :

[1] Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf
[2] Revollo, B. et al. J. Antimicrob. Chemother. 2022; 77(6): 1738-1740.
[3] Neuhaus, F.C. & Baddiley, J. A Microbiol. Mol. Biol. Rev. 2003; 67: 686–723.
[4] Perego, M. et al. J. Biol. Chem. 1995; 270: 15598–15606.
[5] Pasquina, L. et al. Nat. Chem. Biol. 2016; 12: 40–45.
[6] Matano, L. M. et al. Bioorg Med Chem. 2016; 24: 6307-6314.