

ENERGY-COUPPLING FACTOR TRANSPORTER, A NOVEL TARGET FOR ANTIBIOTIC DEVELOPMENT

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In an attempt to find new antibiotics, novel ways of interfering with important biological functions should be explored, especially those which are necessary or even irreplaceable for bacterial survival, growth and virulence. To address this issue, we are focusing on Energy-Coupling Factor (ECF) transporters. [1]

ECF transporters are a class of ATP-binding cassette (ABC) transporters that regulate the uptake of vitamins in prokaryotes, such as *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Clostridium difficile*, a function crucial for their growth and survival. They consist of an energizing module and a substrate-binding protein (S-component). Different S-components can interact with the same energizing module. [2] In other words, the same energizing module can facilitate the uptake of several micronutrients such as folic acid, pantothenate, thiamine and riboflavin.

Through a structure-based virtual screening campaign, we discovered the first inhibitors of the ECF transporters. A synthetic medicinal-chemistry campaign enabled us to develop inhibitors that exhibit antimicrobial activity in the low micromolar range against several Gram-positive species, namely *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium*. [3]

In order to evaluate and investigate the behavior of the compounds in a cell-based environment, we developed a novel cell-based assay by using *Lactobacillus casei* and measured the uptake of several vitamins, including folic acid and riboflavin, in the presence and the absence of the compounds. [4]

[1] S. Bousis et al., *Advance Therapeutics*, **2018**, DOI: 10.1002/adtp.201800066.

[2] D. J. Slotboom. *Nature Rev. Microbiol.* **2014**, *12*, 79–87.

[3] E. Diamanti et al., *J. Am. Chem. Soc.* **2018**, under review.

[4] S. Bousis et al., under review.