

Call: 6th transnational call for the JPIAMR within the ERA-NET JPI-EC-AMR:
Innovations against antibiotic-resistant bacteria: New targets, compounds and tools

Title: Restoring *E. coli* Sensitivity for Antibiotics by blocking TolC-Mediated Efflux

Acronym: RESET-ME

Consortium composition

Type	Name	Institute	Country
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Abstract

Overexpression of efflux pumps is a major factor for drug resistance in Gram-negative bacteria. In *E. coli*, the AcrAB-TolC efflux pump complex transports antibiotics from the periplasm or cytoplasm into the external medium. As TolC deletion has been shown to result in increased susceptibilities of *E. coli* to several antibiotics, it may represent an attractive drug target. Recently, we have identified the first organic small molecule that effectively blocks TolC function using virtual screening in combination with experimental validation of the *in silico* hits by surface plasmon resonance (SPR) and electrophysiology studies.

Building on these results, we propose to further develop this compound and in parallel to identify and develop novel TolC blockers within an interdisciplinary consortium. The already known blocker will be progressed in three rounds of optimisation. Each round comprises compound modifications by medicinal chemistry, assessment of TolC binding and blockage using SPR and electrophysiology, various antimicrobial studies and ADMETox profiling.

Novel small molecules blocking TolC will be identified and optimised using the same experimental platform, starting with virtual screening for identification of novel compounds targeting TolC.

Experimentally validated TolC blockers will be progressed in two rounds of optimisation.

Ultimately, this approach will allow to assess TolC target validity for adjuvants in antimicrobial therapies and result in potent TolC blockers that may be further developed into drugs restoring *E. coli* susceptibility to antibiotics.