

# Regulatory crosstalk between siderophore-drug transport systems in *Pseudomonas aeruginosa*

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One possibility to increase the non-specific uptake of antibiotic molecules across the outer membrane of Gram-negative bacteria is to modify these drugs to promote their uptake through specific and more efficient transport systems. A promising example is the coupling of antibiotics with siderophore molecules to direct the transport of the conjugates through dedicated siderophore receptors. We and others previously identified the PiuA and the PirA siderophore receptors of *Pseudomonas aeruginosa* as the major transporters of the siderophore-drug conjugates BAL30072 [1] and MC-1 [2]. These drugs consist of a monobactam and a dihydroxyipyridone Fe-chelator moiety. Within the frame of the ND4BB Translocation project, we show here that a two component system (TCS), termed PirR-PirS and located next to the PirA receptor gene, positively regulates the constitutively expressed PiuA receptor gene, as determined by gene fusion experiments and proteomic analysis. We further identified the plant derived flavonoid quercetin as an inducer of the PirR-PirS TCS. Quercetin induces in a dose dependent manner the expression of the *pirA* receptor gene and increases susceptibility to siderophore-drug conjugates by increasing expression of their transporters PirA and PiuA.

## References

- [1] Van Delden et al., *Antimicrob. Agents Chemother.*, **57**: 2095 (2013)
- [2] McPherson et al., *Antimicrob. Agents Chemother.*, **56**: 6334 (2012)