



VECTORIZATION OF ANTIBIOTICS USING SIDEROPHORES

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Iron is essential for various biological functions in eukaryotes and prokaryotes. This metal is involved in crucial biological processes (cellular respiration, DNA synthesis, etc.). However, in aerobic conditions iron (III) is poorly soluble and in the human body, iron is mainly sequestered by storage proteins, making it difficult for pathogenic bacteria to access to this nutrient. To overcome this limitation, bacteria secrete siderophores, small iron-chelating molecules, able to complex iron(III) in the extracellular environment.¹ Ferric siderophores are further recognized and translocated into the bacterial cell through specific membrane transporters.

Pseudomonas aeruginosa, an opportunistic pathogen responsible for severe infections, is naturally resistant to many antibiotics due to the low permeability of the bacterial outer membrane. Siderophore-dependent iron absorption systems, which cross this physical barrier, can be used to circumvent permeability problems and improve antibiotic delivery in *P. aeruginosa*. Following approaches were more specifically investigated. 1) conjugates between siderophores and antibiotics can hijack iron uptake systems to deliver an antibacterial agent directly inside the bacterial cell using a so-called Trojan Horse strategy.² 2) taking advantage of the nM affinity of siderophores for their specific transporter, the delivery of antibiotics included into fusogenic liposomes decorated with siderophores was also investigated.

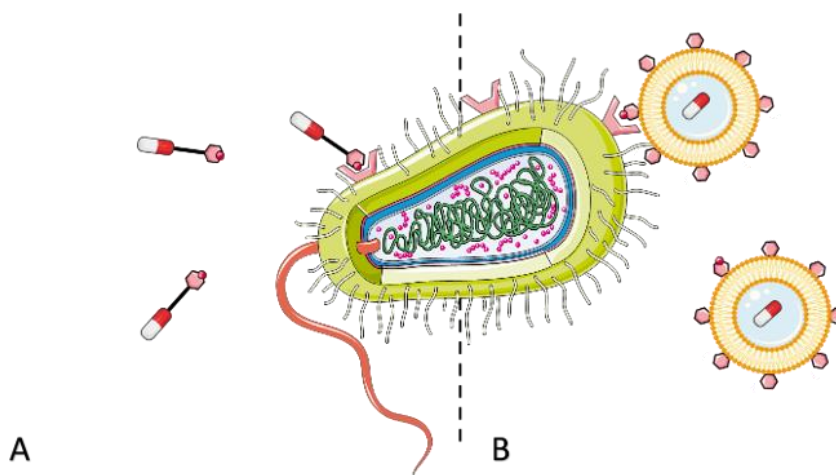


Figure 1 : A. Siderophores-antibiotic conjugate for a Trojan horse strategy B. Liposomes encapsulating an antibiotic and functionalized with siderophores

Reference(s)

¹ Hider, R. C.; Kong, X. Chemistry and Biology of Siderophores. *Nat Prod Rep* **2010**, 27 (5), 637–657. <https://doi.org/10.1039/b906679a>.

² Mislin, G. L. A.; Schalk, I. J. Siderophore-Dependent Iron Uptake Systems as Gates for Antibiotic Trojan Horse Strategies against *Pseudomonas Aeruginosa*. *Metallomics* **2014**, 6 (3), 408–420. <https://doi.org/10.1039/c3mt00359k>.