

*Abstract*

# Antibiotic Translocation and Membrane Barrier: New Insights to Combat Bacterial Resistance

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## 1. Introduction

The increasing prevalence of antibacterial resistance is a worrying health concern. A challenge in antibacterial research is to better understand membrane permeation of antibiotics in infective bacteria: passing the membrane barrier to reach the threshold of active concentration inside the bacterium is a pivotal step for all antibiotics. This is particularly acute for Gram-negative bacteria that have two membranes, the outer and the inner membranes that strongly limit the transport and the intracellular accumulation of antibiotics. A key point is to determine the real concentrations of antibiotics inside bacterial cells to determine the parameters modulating this internal accumulation.

## 2. Methods

Recently, new concepts, RTC2T and SICAR (Masi et al., *Nat. Microbiol.* 2, 17001 (2017) have been proposed to evaluate the relationship between membrane permeability and antibiotic accumulation. A spectrofluorimetric methodology has been developed to detect fluoroquinolones in bacterial population and inside individual Gram-negative bacterial cells. The antibiotic accumulation was studied in cells expressing various levels of efflux pumps.

## 3. Results and Discussion

The assays allow the determination of the intracellular concentration of the fluoroquinolones to study the relationships between the level of efflux activity and the antibiotic accumulation, and finally to evaluate the impact of fluoroquinolone structures in this process. This clearly validates the recently proposed “Structure Intracellular Concentration Activity Relationship” (SICAR) concept.

## 4. Conclusions

The combination of these studies that include drug imaging studies, evaluation of antibacterial activity and determination of membrane permeability, represents a promising research strategy. This strongly stimulates the molecular understanding of resistance mechanisms and the development of a future rational antibacterial chemotherapy.

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