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DRUG TRANSLOCATION AND MEMBRANE BARRIER: A CHALLENGE TO COMBAT BACTERIAL RESISTANCE

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With the increasing prevalence of antibacterial resistance, a challenge in antibacterial research is to better understand membrane permeation of antibiotics in bacterial cell: 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 cell to determine the parameters modulating this internal accumulation. New concepts, RTC2T and SICAR (Masi *et al*, 2017) have been proposed to evaluate the relationship between membrane permeability and antibiotic accumulation. Recently by using microspectrofluorimetry and time-course analyses (Cinquin et al, 2016; Allam *et al*., 2017; Vergalli *et al*., 2017), the translocation of antibiotics across bacterial membranes is studied within bacterial population and at single bacteria level to determine the antibiotic concentration/location in multi-drug resistant strains. In parallel, antibacterial activities were determined on same bacterial strains in order to correlate the intracellular accumulation of antibiotic to the bacterial susceptibility. With new original methodologies the uptake and location of antibiotics can be followed and studied in bacterial population and individual bacterial cell. The respective involvement of influx and efflux in the internal concentration of various molecules are analyzed with special attention to the bacterial susceptibility. 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 paves the way for the development of a future rational antibacterial chemotherapy.

Recent Publications:

1. Cinquin B, Maigre L, Pinet E, Chevalier J, Stavenger RA, Mills S, Réfrégiers M and Pagès J.-M (2015) Microspectrometric insights on the uptake of antibiotics at the single bacterial cell level. Sci Rep. 11;5:17968.

2. Allam A, Maigre L, Vergalli J, Dumont E, Cinquin B, Alves de Sousa R, Pajovic J, Pinet E, Smith N, Herbeuval JP, Réfrégiers M, Artaud I and Pagès J.-M (2017) Microspectrofluorimetry to dissect the permeation of ceftazidime in Gram-negative bacteria.Sci Rep. 7(1):986.

3. Masi M, Refregiers M, Pos KM and Pages J.-M (2017) Mechanisms of envelope permeability and antibiotic influx and efflux in Gram-negative bacteria. Nat Microbiol. 2:17001.

4. Vergalli J, Dumont E, Cinquin B, Maigre L, Pajovic J, Bacqué E, Mourez M, Refregiers M and Pagès JM (2017) Fluoroquinolone structure and translocation flux across bacterial membrane. Sci Rep ; 7(1):9821

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