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Molecular Basis of Antibiotics permeation through bacterial porins: *Can we understand and improve gram-negative antibacterials?*

This lecture will review the data accumulated from the RTN project 19335- FP6 “Translocation”, an interdisciplinary project that aimed at combining theoretical and experimental methods to unravel the determinants and molecular basis of antibiotic selectivity and transport through bacterial porins.

Gram-negative bacteria are protected by an outer membrane and to function, antibiotics have to permeate through outer membrane channels, or porins, such as OmpF and OmpC in *E. coli*. Bacterial strains can modulate their susceptibility to antibiotics by under-expressing or mutating the structures of porins. We performed accelerated atomistic molecular dynamic simulations of wild type and mutated porins to reveal the complete permeation pathways of β-lactams antibiotics, such as ampicillin, enrofloxacine, ertapenem. From in-depth analysis of the simulations we extracted the effective energy barriers for translocation and the key determinants, such as the required flexibility, solvation and balance of interactions at the constriction region of the porin channel, which compensate the loss of entropy of the antibiotic and facilitate its diffusion. Remarkably, we found a good agreement between the predictions from computer simulations and a wide range of experiments using electrophysiology, spectroscopy and swelling assays techniques.

Furthermore, we discuss how our multi-scale approach can benefit rational antibiotics design and screening as we extend it to (i) novel antibiotics of pharmaceutical and therapeutical interest or (ii) novel porins from novel pathogenic strains which shows interesting antibiotic resistance profiles. Indeed, while we might have reached a consensus for transport of molecules through the general diffusion porins of *E.Coli,* very little is known on the porins and the antibiotics permeation mechanism in severely pathogenic and clinical strains of bacteria. Species such as *Enterobacter aerogenes, Klebsiella pneumoniae, Providencia stuartii* are of serious concern in infectious diseases due to their particular resistance to antibiotics. Here again, we find that a multi-disciplinary and molecular basis approach is needed to better identify and characterize the responsible outer membrane porins of these pathogenic strains.