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Quantification of antibiotic influx and efflux in Gram-negative bacteria, impact of outer membrane porins and drug efflux pumps on intracellular antibiotic accumulation

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Antibiotics are a mainstay of modern clinical medicine. However, many bacterial pathogens have acquired multidrug resistance, cause untreatable infections and represent an urgent threat to public health. This situation is especially troubling with respect to Gram-negative pathogens such as *Pseudomonas aeruginosa, Acinetobacter baumannii* and members of the *Enterobacteriaceae* family. Meanwhile, the discovery of novel classes of active antibiotics against these pathogens has been impeded by a fundamental lack of understanding of the molecular determinants underlying the intracellular accumulation of small molecules. Gram-negative bacteria are surrounded by two membranes, with the liposaccharide-coated outer membrane that represent a real challenge for small molecules to cross. Small molecules typically translocate through this outer membrane through β-barrel proteins called porins, which form narrow hydrophilic channels lined with charged amino acids. Once inside the cell, these small molecules are susceptible to efflux pumps. Thus, to accumulate in Gram-negative bacteria and reach an active concentration at the vicinity of their intracellular target, small molecules such as antibiotics must cross porins faster than they are pumped out. However, central to the problem of discovering antibiotics that are effective against Gram-negative bacteria is the limited understanding of the physico-chemical properties that enables small-molecule accumulation in Gram-negative bacteria. As a first step to answer this question, we assembled a set of diverse fluoroquinolones and quantified their capacity to accumulate in *Escherichia coli*. Because porins and efflux pumps represent the main variables that affect small-molecule accumulation, compounds were assessed in accumulation assays using intact cells of isogenic strains and complementary approaches of (micro) spectrofluorimetry and liquid chromatography in tandem with mass spectrometry (LC-MS/MS). From these experiments and subsequent structure-to-intracellular accumulation-and-activity relationship (SICAR) studies, we are developing rules that can predict compounds with high accumulation rates in Gram-negative bacteria.

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