A Multidisciplinary Approach toward Identification of Antibiotic Scaffolds for Acinetobacter baumannii

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Research efforts to discover potential new antibiotics for Gram-negative bacteria suffer from high attrition rates due to the synergistic action of efflux systems and the limited permeability of the outer membrane (OM). One strategy to overcome the OM permeability barrier is to identify small molecules that are natural substrates for abundant OM channels and use such compounds as scaffolds for the design of efficiently permeating antibacterials. Here we present a multidisciplinary approach to identify such potential small-molecule scaffolds. Focusing on the pathogenic bacterium Acinetobacter baumannii, we use OM proteomics to identify DcaP as the most abundant channel during infection in rodents. The X-ray crystal structure of DcaP reveals a trimeric, porin-like structure and suggests that dicarboxylic acids are potential transport substrates. Electrophysiological experiments and all-atom molecular dynamics simulations confirm this notion and provide atomistic information on likely permeation pathways and energy barriers for several small molecules, including a clinically relevant β-lactamase inhibitor.
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