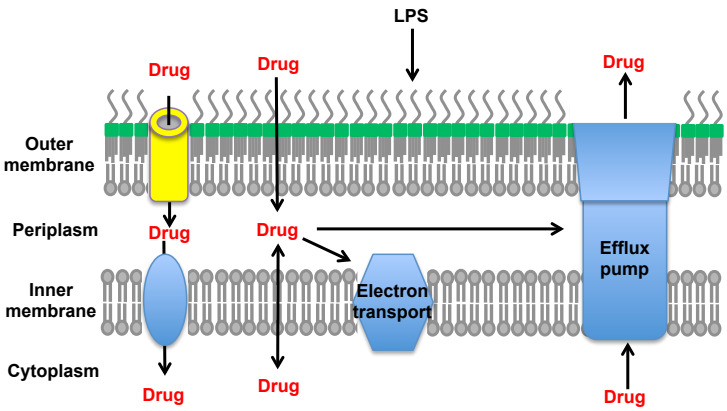
Strategic analysis of the physicochemical properties that enable small-molecule accumulation in Gram-negative bacteria

Michelle F. Richter and Paul J. Hergenrother

Modern medicine is in critical need of novel classes of antibiotics. Resistance has been observed to every class of antibiotics currently available in the clinic, making the discovery of new classes of antibiotics vital to the future of public health. Highly resistant Gram-negative pathogens are particularly alarming due to their intrinsic resistance to many traditional therapeutics, including drugs of last resort vancomycin, linezolid, and daptomycin. As a result, a number of Gram-negative species are resistant to all or almost all drug treatment options. For example, carbapenem-resistant Enterobacteriaceae (CREs) kill up to half of all patients who contract these deadly infections. Despite this growing health concern and decades of research, a first-in-class antibiotic effective against Gram-negative bacteria has not been introduced into the clinic since trimethoprim in 1968. Thus, new approaches to find Gram-negative antibiotics are desperately needed.

One of the major obstacles in discovering antibiotics for Gram-negative bacteria is that a large percentage of small-molecules are unable to accumulate inside these cells. Gram-negative bacteria posses two lipid bilayers and non-specific multidrug efflux pumps that function synergistically to prevent the net accumulation of many foreign substances. Presented herein, we seek to elucidate the physicochemical properties of small-molecules that are able to readily accumulate inside Gram-negative cells. This information should be invaluable in aiding in the discovery and development of antibiotics for difficult-to-treat Gram-negative pathogens.



The dual membranes and efflux pumps function synergistically to prevent the accumulation of most small molecules