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Gram-negative bacteria contain a conserved antibiotic target site accessible from outside

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The discovery void for antibiotics against multi-drug resistant Gram-negative bacteria is an ever-concerning challenge [1]. Gram-negative bacteria have two membranes, which together protect effectively against drug penetration. Thereby, the outer-membrane (OM) represents a promising, albeit underexploited target for new antibiotics. The protein insertase of the outer membrane, BAM, is an essential component of this defensive shield and therefore an attractive target for novel antibiotics [2]. Here, we resolve how BamA-OMPTA [3], a synthetic bicyclic peptide with potent antibacterial activity, inhibits BAM. Cryo-electron microscopy reveals that the protein epitope mimetic (PEM) part of BamA-OMPTA binds into a deep pocket at the extracellular face of BAM, which is freely accessible from the outside. Finding a conserved antibiotic target site accessible from outside solves the obstacles imposed by enzymatic degradation and efflux pumps which are the main bacterial resistance mechanism against antibiotics. The surface-accessible PEM-binding pocket is a second functional center of BAM besides the periplasmic lateral gate which is protected by the outer membrane [4]. Our study reveals a promising mode-of-action for inhibitors of a prime antibacterial target and opens new avenues for the systematic development of urgently needed novel antibiotics.

References:

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