Comparison of proteomic responses as global approach to antibiotic mechanism of action elucidation.

Senges CHR, Stepanek JJ, Wenzel M, Raatschen N, Ay Ü, Märtens Y, Prochnow P, Vázquez Hernández M, Yayci A, Schubert B, Janzing NBM, Warmuth HL, Kozik M, Bongard J, Alumasa JN, Albada B, Penkova M, Lukežič T, Sorto NA, Lorenz N, Miller R, Zhu B, Benda M, Stülke J, Schäkermann S, Leichert LI, Scheinpflug K, Brötz-Oesterhelt H, Hertweck C, Shaw JT, Petković H, Brunel JM, Keiler KC, Metzler-Nolte N, Bandow JE (2021) Comparison of proteomic responses as global approach to antibiotic mechanism of action elucidation. *Antimicrob Agents Chemother* 65(1), e01373-20.

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Abstract

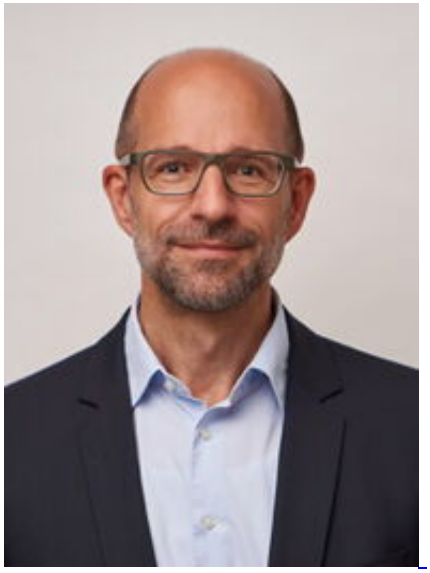
New antibiotics are urgently needed to address the mounting resistance challenge. In early drug discovery one of the bottlenecks is the elucidation of targets and mechanisms. To accelerate antibiotic research, we provide a proteomic approach for the rapid classification of compounds into those with precedented and unprecedented modes of action. We established a proteomic response library of Bacillus subtilis covering 91 antibiotics and comparator compounds, and a mathematical approach was developed to aid data analysis. The Comparison of Proteomic

Responses (CoPR) allows the rapid identification of antibiotics with dual mechanisms of action as shown for atypical tetracyclines. It also aids in generating hypotheses on mechanisms of action as presented for salvarsan (arsphenamine) and the antirheumatic agent auranofin, which is under consideration for repurposing. Proteomic profiling also provides insights into the impact of antibiotics on bacterial physiology through analysis of marker proteins indicative of the impairment of cellular processes and structures. As demonstrated for trans-translation, a promising target not yet exploited clinically, proteomic profiling supports chemical biology approaches to investigating bacterial physiology.

Involved units

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Identifier

doi: 10.1128/AAC.01373-20

PMID: 33046497