# رقم البحث: ( ٥ )

**عنوان البحث باللغة الانجليزية:**

Combating multidrug□resistant bacteria by integrating a novel target site penetration and receptor binding assay platform into translational modeling

**إسم المجلة – سنة النشر:**

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## ABSTRACT

Multidrug-resistant bacteria are causing a serious global health crisis. A dramatic decline in antibiotic discovery and development investment by pharmaceutical industry over the last decades has slowed the adoption of new technologies. It is imperative that we create new mechanistic insights based on latest technologies, and use translational strategies to optimize patient therapy. Although drug development has relied on minimal inhibitory concentration testing and established in vitro and mouse infection models, the limited understanding of outer membrane permeability in Gram-negative bacteria presents major challenges. Our team has developed a platform using the latest technologies to characterize target site penetration and receptor binding in intact bacteria that inform translational modeling and guide new discovery. Enhanced assays can quantify the outer membrane permeability of β-lactam antibiotics and β-lactamase inhibitors using multiplex liquid chromatography tandem mass spectrometry. While β-lactam antibiotics are known to bind to multiple different penicillin-binding proteins (PBPs), their binding profiles are almost always studied in lysed bacteria. Novel assays for PBP binding in the periplasm of intact bacteria were developed and proteins identified via proteomics. To characterize bacterial morphology changes in response to PBP binding, high-throughput flow cytometry and time-lapse confocal microscopy with fluorescent probes provide unprecedented mechanistic insights. Moreover, novel assays to quantify cytosolic receptor binding and intracellular drug concentrations inform target site occupancy. These mechanistic data are integrated by quantitative and systems pharmacology modeling to maximize bacterial killing and minimize resistance in in vitro and mouse infection models. This translational approach holds promise to identify antibiotic combination dosing strategies for patients with serious infections.