Title

Discovery & Exploratory Research at the Global Antibiotic Research & Development Partnership (GARDP): Objectives and Progress

Abstract

Discovery & Exploratory Research at the Global Antibiotic Research & Development Partnership (GARDP) seeks to address critical gaps in the global pre-clinical antibiotic pipeline. This is in areas of key medical need where existing efforts are insufficient. The journey to novel antibiotics begins with the earliest stage of drug development: discovery and exploratory research. GARDP leverages cutting-edge technologies and engages in strategic partnerships to accelerate the discovery of compounds that have the potential to become innovative antibiotics. Our main research areas are small molecule phenotypic screening, novel natural product discovery, potentiator screening, and evaluation of unrealised targets and undeveloped agents. We will discuss these different research streams and highlight our progress, including high-throughput screening efforts against multidrug-resistant (MDR) *K. pneumoniae* and extensively drug-resistant (XDR) *A. baumannii*.

In a recent article, we detailed our high-throughput phenotypic screening process and selection cascade for generating hit compounds with activity against drug-resistant strains of *K. pneumoniae* and *A. baumannii*. We screened compound libraries selected from the proprietary collections of three pharmaceutical companies that had exited antibacterial drug discovery but continued to add new compounds to their collection. Compounds from two out of three libraries were selected using “eNTRy rules” criteria associated with an increased likelihood of intracellular accumulation in *Escherichia coli*.

We identified 72 compounds with confirmed activity against *K. pneumoniae* and/or drug-resistant *A. baumannii*. Two new chemical series with activity against XDR *A. baumannii* were identified meeting our criteria of potency and absence of cytotoxicity. The activity of close analogues of the two chemical series was also determined against *A. baumannii* clinical isolates.

This work provides proof of principle for the screening strategy developed to identify new chemical entities with antibacterial activity against multidrug-resistant critical priority pathogens such as *K. pneumoniae* and *A. baumannii*. The screening and hit selection cascade established here provide an excellent foundation for further screening of new compound libraries to identify high-quality starting points for new antibacterial lead generation projects.