Discovery & Exploratory Research at GARDP
Objectives and Progress

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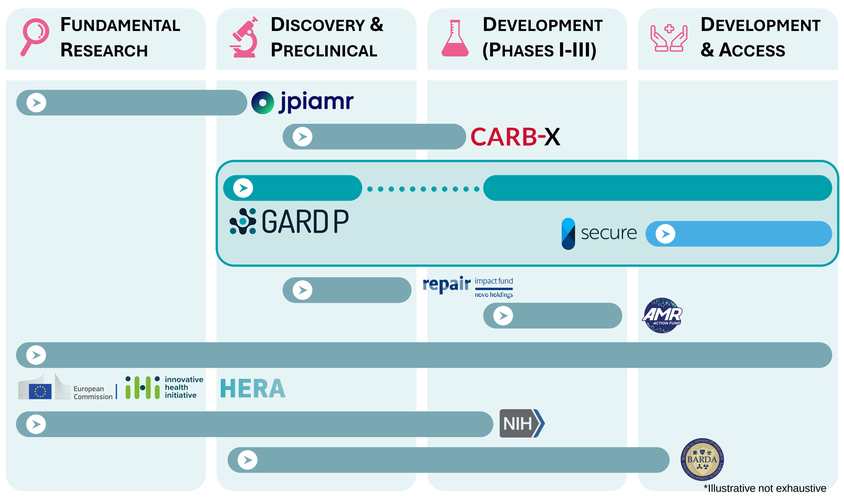
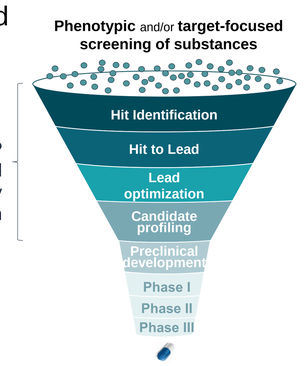
GARDP's Discovery and Exploratory Research (DER) programme

The Global Antibiotic Research & Development Partnership (GARDP) accelerates the development and access of treatments for drug-resistant bacterial infections that pose the greatest threat to human health. Together with public, private and non-profit partners, GARDP works to put public health needs at the centre of the antibiotic research and development to ensure that they are made accessible to people that need them.



GARDP's Discovery & Exploratory Research (**DER**) programme seeks to address critical gaps in the global pre-clinical antibiotic pipeline and focuses on **Gram-negative bacterial pathogens deemed by the WHO as a critical priority for new treatments**. The DER programme's mission is to work with partners to **discover and develop** treatments for drug-resistant infections.



The DER project portfolio spans five research areas, two of which are further described below:

SMALL MOLECULES
Identification of new active hit compounds from diverse, previously unscreened libraries

NATURAL PRODUCTS
Identification of new active compounds from untapped microbial sources

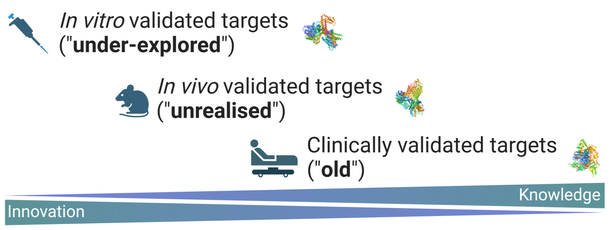
POTENTIATORS
Aminoglycoside potentiators and efflux inhibitors

UNREALISED TARGETS
Target selection, validation and discovery of new target-specific inhibitors

UNDEVELOPED AGENTS
Reevaluation of compounds whose development was stopped for non-scientific reasons

Target-Centric Discovery: Focus on Unrealised Targets

Although antibacterial discovery has included target-oriented approaches over the last decades, the **choice and prioritization** of the most promising targets for discovery programmes remains challenging.

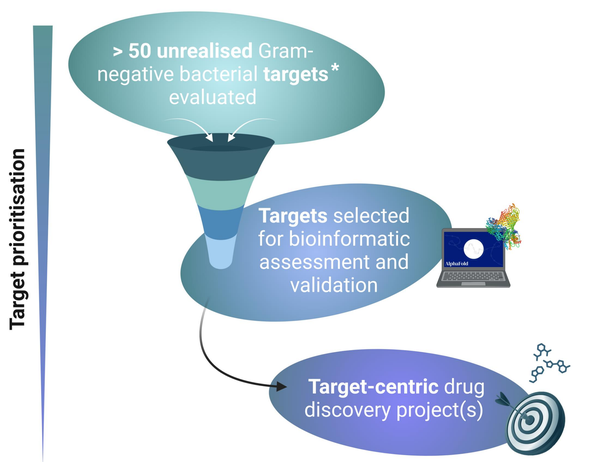


'Good' drug targets are widely accepted as those with demonstrated clinical proof-of-concept, but new targets, by definition, do not come with a data package providing this level of confidence. A **balance between risk and innovation** must therefore be found in the target prioritisation process.

Antibacterial target prioritization is a **multicriteria optimization** activity, based on intrinsic properties of the target (e.g., subcellular location, essentiality, conservation, human homology, resistance potential and druggability) and technical feasibility aspects.

We recently reviewed **>50 unrealized Gram-negative bacterial targets** using publicly available drug discovery-relevant knowledge (including reported inhibitors) and considered the current challenges and prospects for target-centric discovery programmes.[1]

Current **GARDP-led** work assesses a subset of selected unrealised targets in order to identify novel inhibitors active against Gram-negative bacteria.

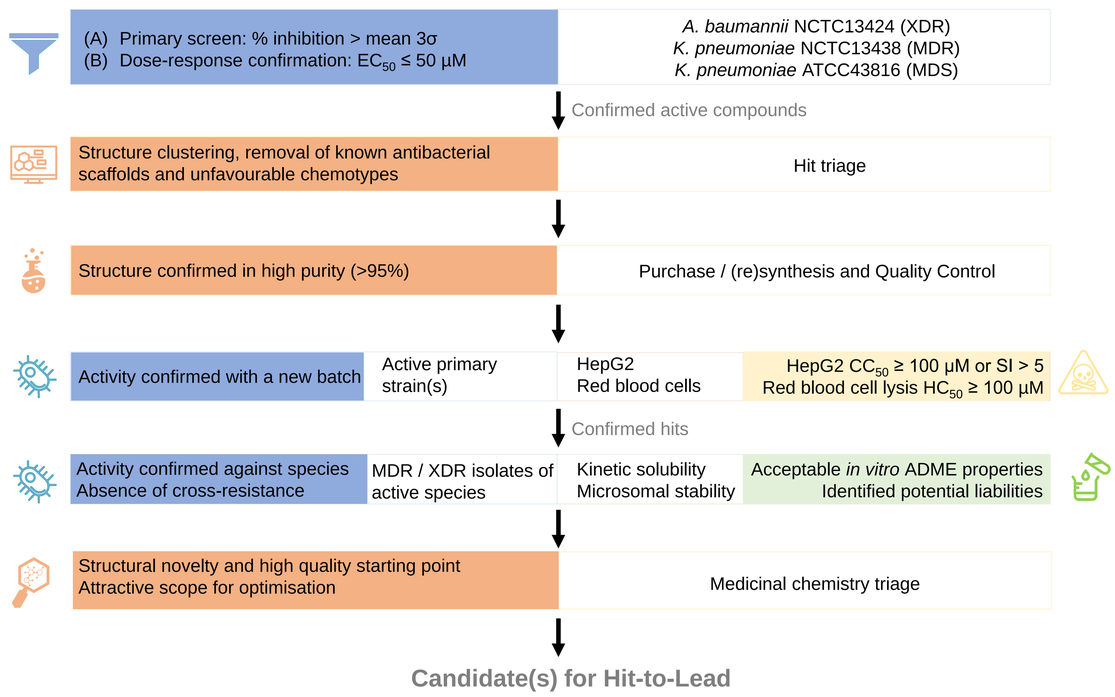


*Targets from major pathways such as outer membrane assembly machines, peptidoglycan cell wall biosynthesis, key metabolic pathways and protein synthesis

[1]Theuretzbacher, U., Blasco, B., Duffey, M. & Piddock, L. *Nat Rev Drug Discov* 22, 957–975 (2023).

Identification of new hits by High Throughput Screening (HTS)

To address the current shortcomings of the antibiotic pipeline we aim to identify new chemical entities (NCEs) with activity against **multidrug-resistant (MDR) *Klebsiella pneumoniae* and *Acinetobacter baumannii*** that could be developed into a new treatment for drug-resistant infections. We recently shared our HTS phenotypic and selection cascade.[2] Since 2019, we have analysed >3.5 million NCEs from diverse libraries and sources and screened >196,000 compounds or microbial metabolites for direct antibacterial activity. We are currently further investigating six novel chemical series.



EC_{50}, concentration to inhibit the growth of 50% of the bacterial population; MDS, multidrug sensitive; MDR, multidrug resistant; XDR, extensively drug resistant; CC_{50}, concentration to kill 50% of the cell population; HC_{50}, concentration to lyse 50% of the red blood cells; SI, selectivity index; ADME, absorption, distribution, metabolism, excretion.

[2]Blasco, B. *et al*, *eBioMedicine*, 2024, in press

Funding and disclaimers:
GARDP has been or is currently funded by the governments of Australia, Germany, Japan, Monaco, the Netherlands, the Public Health Agency of Canada, South Africa, Switzerland, the United Kingdom, the Canton of Geneva, the European Union (via the Health Emergency Preparedness and Response Authority), as well as the RIGHT Foundation, Wellcome and other private foundations.
The funders of GARDP had no role in study design, data collection, data analysis, data interpretation, or writing of this article. The views expressed in this publication are those of the authors and not necessarily those of the funding bodies.