Discovery & Exploratory Research at GARDP: Progress on Undeveloped Agents

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GARDP's Discovery and Exploratory Research (DER) programme

As a not-for-profit research and development (R&D) and access organisation, the mission of the Global Antibiotic Research & Development Partnership (**GARDP**) is to collaborate to develop treatments for drug-resistant infections and make them accessible globally. Our Discovery & Exploratory Research (**DER**) programme focuses on **Gram-negative WHO bacterial priority pathogens**. The DER project portfolio spans five research areas, including an **undeveloped agents** research area.

SMALL MOLECULES | NATURAL PRODUCTS | POTENTIATORS | UNREALISED TARGETS | UNDEVELOPED AGENTS

Introduction

We aim to identify and develop innovative, cost effective, small molecule chemotypes with activity against multidrug-resistant (MDR) *Klebsiella* spp. and/or *Acinetobacter* spp. We believe that research on multiple such chemotypes may have been **abandoned for commercial rather than scientific reasons** and with modern approaches may be successfully advanced. Our evaluation of undeveloped agents as project starting points is complementary to screening for novel chemotypes via phenotypic or target-based approaches.

Searching Sources

We initiated three new small molecule undeveloped agent search projects:

Target-based searches: target-based chemotype searches, focusing on 67 Gram-negative bacterial targets shortlisted from an initial selection of 161.[1-2]

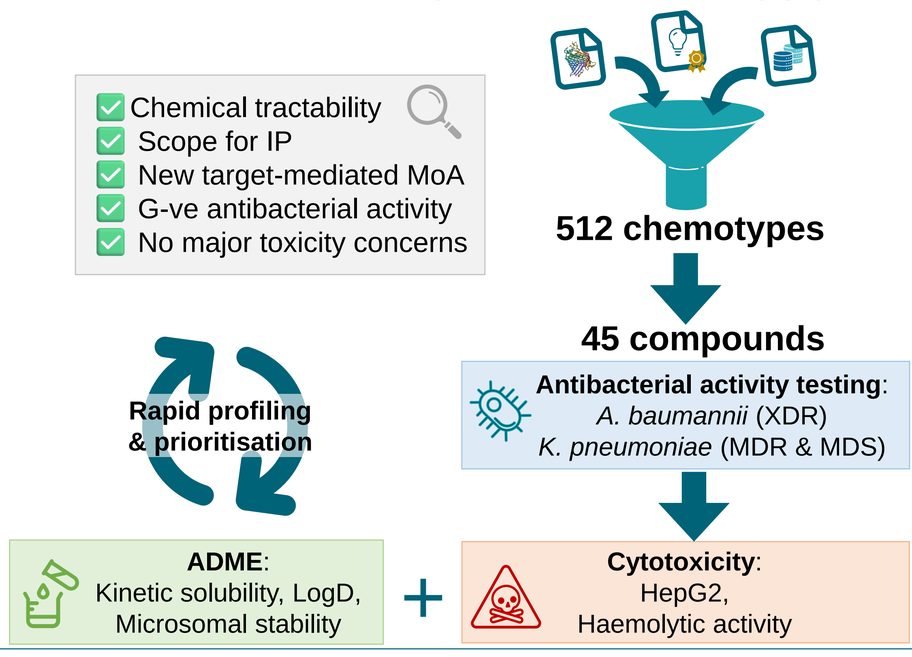
Database searches: compounds identification from

AntibioticDB (hosted by GARDP)[3] | PubChem | Spark | CO-ADD | ChEMBL

Patent searches: Analysis of antibacterial patents from >400 organisations, using IBM's PatCID technology for compound extraction on scale.[4]

Selection & Testing

45 prioritized compounds from our collated list of 512 unique chemotypes were synthetized or procured and then benchmarked through GARDP's testing pipeline.[5]

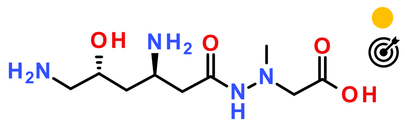


Results & Outlook

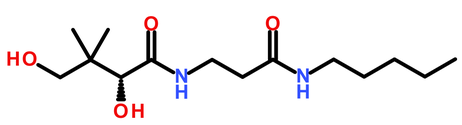
The most attractive chemotypes from our search projects, which matched our desired criteria, were experimentally benchmarked.

We identified some initially encouraging chemotypes, but did not pursue them further due to toxicity liability and/or insufficient antibacterial activity.

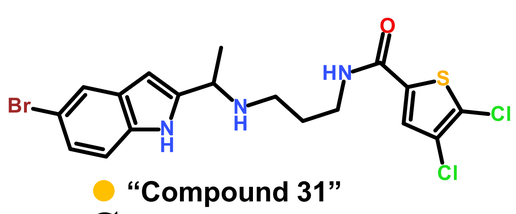
Holomycin and derivatives
Metal homeostasis
(Ciba and others)



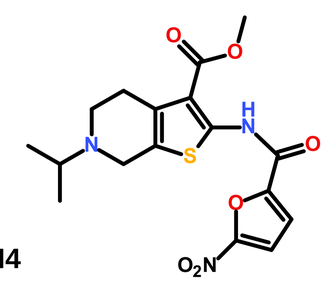
Negamycin + derivatives
Protein biosynthesis
(Institute of Microbial Chemistry, Tokyo and Astra-Zeneca)



Pantothenamide and derivatives
PanK
(Cornell University and others)

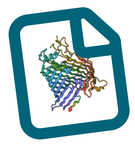


"Compound 31"
MreB
(Taxis and Rutgers)

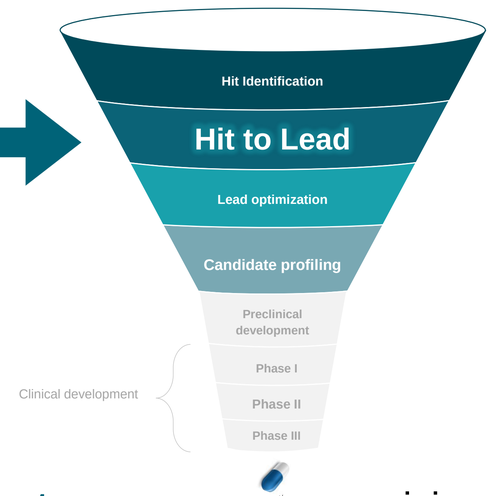


IMB-H4
BamA-D
(Chinese Academy of Medical Sciences and others)

Antibacterial activity: Inactive | Weak | Active | Toxicity | Target or MoA



3 chemotypes from the target-based searches



However, **3 chemotypes** proved promising enough to develop into new discovery projects. Analogues were also evaluated and confirmed a consistent antibacterial signal. They are currently part of active projects under optimization in our **discovery portfolio**.

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[1]Privalsky *et al.*, *J. Am. Chem. Soc., 2021*
[2]Theuretzbacher, Blasco, Duffey *et al.*, *Nat Rev Drug Discov, 2024*
[3]Galarion, Hennessy *et al.*, *in review*
[4]Morin *et al.*, *Nat Commun*, 2024
[5]Blasco *et al., EBiomedicine*, 2024