Discovery & Exploratory Research at GARDP
Objectives and Progress

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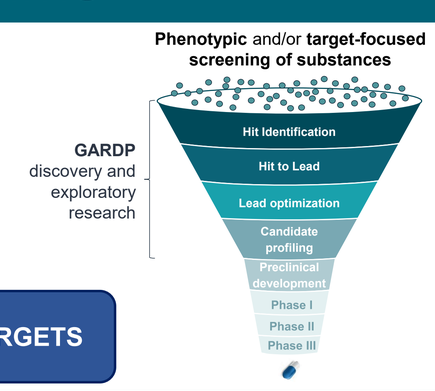
GARDP's Discovery and Exploratory Research (DER) programme

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 bacterial infections and make them accessible globally.

Our Discovery & Exploratory Research (**DER**) programme addresses critical gaps in the pre-clinical antibiotic pipeline, with a focus on discovering and advancing new treatments targeting **WHO priority Gram-negative pathogens**.

The DER project portfolio spans five research areas; this poster focuses on a part of the Small Molecules area:

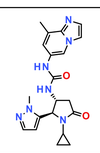
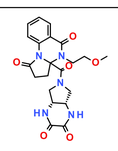
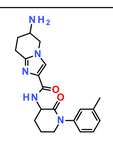
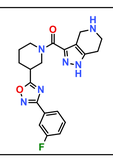
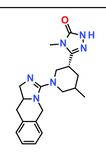
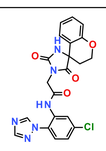
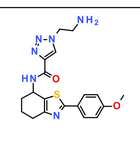
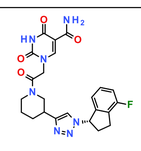
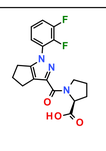
SMALL MOLECULES | **NATURAL PRODUCTS** | **POTENTIATORS** | **UNDEVELOPED AGENTS** | **UNREALISED TARGETS**



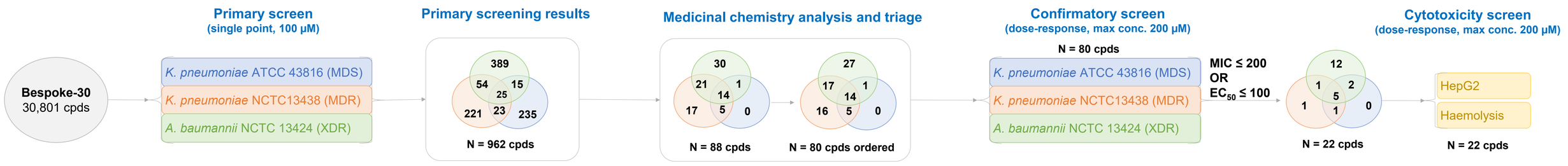
Introduction and Methods

Commercial diversity libraries are often poorly suited for antibacterial discovery, as many compounds lack the physicochemical properties needed for bacterial uptake, efflux avoidance, and activity. To address this, we assembled a bespoke library enriched with favourable physicochemical features to increase the likelihood of identifying tractable starting points for development.

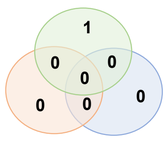
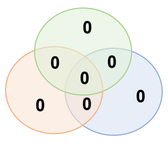
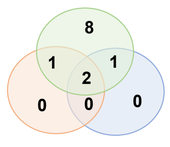
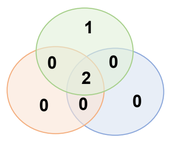
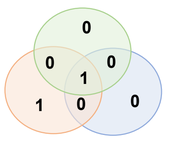
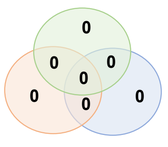
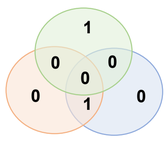
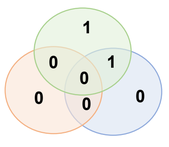
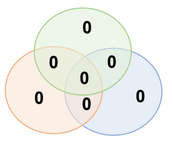
Designing a bespoke small-molecule library: tailored sets for defined hypotheses

Hypothesis	Target within cytoplasm (CP)	Target within periplasm (PP)	Primary amines	Secondary amines	Non-amine ionizable N-containing compounds	Compounds with a PEMPO* score >4.5	compounds with all six 'relaxed' PEMPO* filters	Random diverse set (control)	Neutral examples from Sets 3–5 (control)
Examples									
Sets	**Set-1**	**Set-2**	**Set-3**	**Set-4**	**Set-5**	**Set-6**	**Set-7**	**Set-8**	**Set-9**
Reference	Reck, Jansen, Moser, *Arkivoc*, **2019**		Richter, Hergenrother et al., *Nature*, **2017** Perlmutter, Hergenrother et al., *ACS Infect. Dis.*, **2021**			Smith et al., *SLAS Discov.*, **2019**		**NA**	Richter, Hergenrother et al., *Nature*, **2017**
Molecular weight (Da)	250–475	340–560	250–475	250–475	250–475	NA	NA	NA	250–475
Calculated logD pH 7.4	-1.4 to 1.1	-5.0 to -1.0	-3.0 to 1.1	-3.0 to 1.1	-3.0 to 1.1	≤ 0.2	≤ 0.4	NA	-3.0 to 1.1
Calculated logP	NA	NA	NA	NA	NA	≤ 3	≤ 3.2	NA	NA
TPSA	75–180	110–215	NA	NA	NA	100–200	100–200	NA	NA
Hydrogen bond donors	1–7	2–6	1–7	1–7	1–7	2–6	2–6	NA	1–7
Hydrogen bond acceptors	1–7	1–7	1–7	1–7	1–7	6–11	5–10	NA	1–7
# aromatic rings	0–3	0–3	0–3	0–3	0–3	NA	NA	NA	0–3
# rotatable bonds	1–5	NA	1–5	1–5	1–5	NA	NA	NA	1–5
Ionizable amine	NA	NA	Primary (max 1)	Secondary	Non-amine	NA	NA	NA	NA
Isoelectric point	NA	NA	NA	NA	NA	6.1–8.7	6.0-8.9	NA	NA
No. compounds selected	**4371**	**1863**	**4667**	**5113**	**409**	**2955**	**4029**	**3541**	**3823**

Results



Confirmed 'actives' per set (n = 80 tested in dose-response)

Hypothesis	Target within cytoplasm (CP)	Target within periplasm (PP)	Primary amines	Secondary amines	Non-amine ionizable N-containing compounds	Compounds with a PEMPO* score >4.5	Compounds with all six 'relaxed' PEMPO* filters	Random diverse set (control)	Neutral examples from Sets 3–5 (control)
Sets	**Set-1** (2 cpds)	**Set-2** (2 cpds)	**Set-3** (30 cpds)	**Set-4** (13 cpds)	**Set-5** (9 cpds)	**Set-6** (3 cpds)	**Set-7** (4 cpds)	**Set-8** (17 cpds)	**Set-9** (0 cpds)
Activity against three bacterial strains									
No. confirmed actives	**1**	**0**	**12**	**3**	**2**	**0**	**2**	**2**	**0**

Outlook

The 22 confirmed hits are currently undergoing cytotoxicity testing, and a subset of the library will be evaluated in influx and efflux assays to determine permeability and transport profiles. Insights from these studies will shape future hypotheses and guide the design of next-generation bespoke libraries, with potential integration of AI/ML-driven enrichment strategies.

GARDP

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