HORIZON SCANNING FOR **ANTIBACTERIAL DRUG DISCOVERY PROJECTS** FOCUSED ON WHO CRITICAL PRIORITY **GRAM-NEGATIVE BACTERIAL PATHOGENS**

Benjamin Blasco, Renata Da Costa, Ruth Kelly and Laura J.V. Piddock

Global Antibiotic Research & Development Partnership

GARDP

TABLE OF CONTENTS

5. DISCUSSION AND CONCLUSIONS

6. REFERENCES

7. APPENDICES

1. EXECUTIVE SUMMARY

INTRODUCTION

There is an urgent need for innovation and new classes of antibacterial agents to provide alternative treatment options for drug-resistant serious bacterial infections that are increasingly difficult to treat with drugs from existing antibiotic classes (and their many derivatives). Of particular importance are the multidrug-resistant Gram-negative bacteria listed by the WHO as critical priorities for antibacterial drug research and development (Tacconelli *et al.* 2018).

OBJECTIVES OF THE STUDY

The objective of this horizon scan was to identify promising early phase discovery projects working on novel Gram-negative antibacterials.

METHODS

We searched publicly available databases detailing projects funded by the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) Member States (n=21 in the 2014 database, n=22 in the 2017 database), the Wellcome Trust, and the European Commission from 2007 until 2019. We then filtered and prioritised projects based of new chemical classes and/or bacterial targets that have the potential to deliver new antibiotic classes targeting Enterobacterales and/or *Acinetobacter baumannii*, that are on the WHO critical priority list (Appendix 5). The same inclusion/exclusion criteria were also applied to the 2019 WHO open access database listing antibacterial agents in preclinical development. We have also compared data in the Global AMR R&D Hub's Dynamic Dashboard (accessed in February 2021) with that obtained in this project.

RESULTS

An initial triage identified 123 projects in the JPIAMR databases potentially matching the selection criteria. These were further assessed by review of additional project information (including project abstracts, principal investigator names and institutions) from the JPIAMR office and national funding agencies. Further information regarding the project scope, pathogen focus, stage and status was collected directly from project principal investigators (PIs) via a survey. When a project PI could not be identified or the project PI did not respond to the survey, wherever possible, survey questions were answered using information collected from publications and PI web sites. Assessment of this information prioritized 39 of these projects that potentially focused on either novel chemical matter or new or under-exploited targets for antibacterials with a focus on Enterobacterales (in particular, *Klebsiella* spp.) and/or *Acinetobacter* spp.

To complement this analysis, the same selection criteria were applied to projects listed in WHO's 2019 review of antibacterial agents in preclinical development. This resulted in the shortlisting of 21 additional lead optimisation projects.

We have also compared our findings with data in the Global AMR R&D Hub's Dynamic Dashboard released in February 2021. Four projects had been previously identified in our analysis of the JPIAMR databases and five projects identified in our analysis of the WHO's 2019 preclinical pipeline review database. There were twenty-two projects that had not been included in either database.

This report summarizes the categorization, antibacterial spectrum, and main features of the 60 shortlisted projects, 39 from JPIAMR and 21 from WHO databases.

This report provides a view of the early antibacterial discovery pipeline projects funded by JPIAMR member states, the Wellcome Trust, and the European Commission from 2007 until 2019. It is noted that there are other funding agencies (e.g., US National Institutes of Health (NIH), CARB-X, BEAM Alliance) and hence projects in countries other than those of these funders and so this report is not an exhaustive global review.

CONCLUSIONS

The early discovery antibacterial pipeline is scientifically diverse and at least 39 projects listed in the JPIAMR databases, and 21 projects listed in the 2019 WHO database focused on early antibacterial discovery focusing on carbapenem-resistant *A. baumannii* and/or Enterobacterales. For many projects there was no information on the chemical class or the mode of action/target (either not known or not disclosed). There were also projects that focused on new chemical classes targeting 'old' targets that are already targeted by existing antibiotic classes (e.g., ribosome, DNA gyrase/topoisomerase, RNA polymerase, etc.) and thus may be at risk of exhibiting cross-resistance to these existing antibiotic classes or rapid emergence of resistance. The 'new' targets (as defined in the Methods section of this report) arising from our evaluations were:

- ClpP (cell metabolism, proteostasis)
- IspG (also known as GcpE) (cell metabolism, non-mevalonate pathway of isoprenoid biosynthesis)
- DnaA (DNA replication)
- DNA polymerase III (DNA replication)
- KAS III (cell wall synthesis)
- TolC (drug efflux)
- LpxC (cell wall synthesis, lipid A biosynthesis)

Given the anticipated high attrition rates that have been seen with other antibiotics, and the remaining challenges to understanding the properties of compounds to accumulate within Gram-negative bacteria, the discovery pipeline of new Gram-negative antibacterial targets and classes remains insufficient to deliver the much-needed new antibacterial treatments to replace current frontline agents and those under clinical development when they fail due to drug resistance or other reasons.

2. INTRODUCTION

The success of health care is contingent on the sustained clinical efficacy of antibiotics, for which the emergence of resistance has been a constant threat since the introduction of penicillin in the 1940s.

Many large pharmaceutical companies abandoned antibacterial drug discovery activities due to the lack of profit and enormous scientific challenges, especially about compound accumulation in Gram-negative bacteria. One consequence is that few new-class antibiotics have entered clinical development since the start of the 21st century.

In this report, we searched information on early Gram-negative antibacterial drug discovery projects funded by the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) member states, the Wellcome Trust (Wellcome Trust), and the European Commission (EC) from 2007 until 2019 and applied GARDP's Discovery and Exploratory Research (DER) selection criteria to both JPIAMR member states/Wellcome Trust/EC-funded antibacterial projects and antibacterial projects at the lead optimisation phase listed by the WHO in their 2019 preclinical pipeline analysis.

The aim of this horizon scanning exercise was to identify new chemical entities and/or new or under-exploited Gram-negative bacterial targets.

3. METHODS

DATA SOURCE AND COLLECTION

This horizon scanning exercise used the publicly available databases of the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) published in 2014 and 2017 (https://www.jpiamr.eu/resources/documents-library/). These databases listed 3,364 publicly funded research projects and large programmes (1,425 for 2014 and 1,939 for 2017) on antimicrobial resistance across JPIAMR member countries, the Wellcome Trust and at the European Union (EU) level.

The JPIAMR database published in 2014 included antibacterial resistance research projects funded within a seven-year period (2007–13) across the 21 JPIAMR member countries (at that time), the Wellcome Trust, and EU agencies (Kelly *et al.* 2016) and (https://www.jpiamr.eu/app/uploads/2021/08/JPI-AMR-mapping-report-Final.pdf). The JPIAMR database published in 2017 included any active project or projects for which funding was committed as of January 1, 2017 across 22 JPIAMR member countries, the Wellcome Trust and the EC (https://www.jpiamr.eu/app/uploads/2021/08/Mapping-of-AMR-research-funding-2017-report.pdf). The project summary or principal investigator (PI) or institution details were not provided in this 2017 database. Therefore, as the title did not allow for an accurate review to be made further, investigation and follow up was required to obtain information on certain projects.

In addition, projects funded via the sixth and eighth JPIAMR joint calls were also considered in the analysis.

The full list of JPIAMR member countries and associated national funding agencies at the time of publication of these databases are listed in the Appendices 1 and 2.

Other sources of information used for this report are:

- National Research Programme on AMR in Switzerland, programme meeting report 2019 (cross-checked with Switzerland mapping and JPIAMR funded projects)
- Antibacterial agents in preclinical development: an open access database. Geneva: World Health Organization; 2019 (WHO/EMP/IAU/2019.12). (https://apps.who.int/iris/handle/10665/330290)

Of note, antibacterial projects funded through/by the EU Innovative Medicines Initiative (IMI), Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) or Biotech companies in Europe combating AntiMicrobial Resistance (BEAM) Alliance were not included in this analysis. The Pew Trust pipeline review was also not considered in this report. This is because this activity focused on identifying early Discovery activities and not those in the later stages of preclinical or clinical development. It is noted that since 2016 CARB-X has funded projects earlier in the pre-clinical development pipeline (from the hit-to-lead phase). These were included in the 2019 WHO preclinical pipeline review. Further potential additional data sources are listed in Appendix 3.

As most of the projects listed in the JPIAMR databases did not have sufficient information to assess the projects versus the inclusion/exclusion criteria (e.g., bacterial species of interest, novelty, discovery phase), additional information including project PI and abstract were obtained from the JPIAMR office or national funding agencies. When possible, this data was supplemented with information collected from publications, conference abstracts or posters, institutional websites, and other information in the public domain. Project duplicates (identical project title, PI, and institution) were eliminated.

An online survey was conducted from April to July 2020 to systematically collect information of the project scope (species focus, antibacterial agent category, bacterial target, mechanism of action) and status (as of July 2020, discovery stage, related publications and patents) directly from project PIs. The survey questionnaire and, when applicable, the multiple-choice survey responses are reproduced herein in Appendix 4. Data were sourced, categorised, and analysed during the period of 1 July 2019 to 8 January 2021. Data analyses and generation of figures and graphs were done with Microsoft Excel.

SCOPE AND INCLUSION/EXCLUSION CRITERIA

The scope of this study was limited to horizon scanning for antibacterial research projects with a therapeutic application in humans as a potential outcome. Projects not classified within the therapeutics category (the five other JPIAMR priority topic categories are diagnostics, surveillance, transmission, environment, and interventions) were excluded. In the case of the 2017 JPIAMR database, projects were assigned to antibacterial, anti-fungal or anti-parasitic, or a combination of them, and only projects featuring the antibacterial category were included. Project titles and abstracts, where available, were used to identify projects meeting the inclusion/exclusion criteria (Table 1).

Table 1. Inclusion and exclusion criteria per category.

CATEGORY	INCLUDED OR EXCLUDED	DESCRIPTION
Pathogens (spectrum)	Included	**Filtering phase I:** • Gram-negative bacteria in the 2017 WHO priority pathogens list **Filtering phase II:** • Enterobacterales and/or *A. baumannii*
	Excluded	• Gram-positive bacteria
Indications	Included	• Human health and therapeutics
	Excluded	• Animal health and therapeutics • Anti-virals • Anti-fungals • Anti-parasitics
Antibacterial approach	Included	• Direct-acting small molecules • Potentiators, including efflux inhibitors
	Excluded	• Non-traditional products such as phage/phage-derived peptides, microbiome-modifying agents, anti-virulence agents, immunomodulators, antimicrobial peptides • Diagnostics • Preventive interventions, such as vaccines, topical decolonizing agents, probiotics
Discovery phase	Included	• Hit identification • Hit-to-lead • Lead optimisation
	Excluded	• Assay development • Target validation • Training network
Novelty	Included	• Absence of cross-resistance to existing antibiotics • New chemical class • New target or new mechanism of action • New tools and platforms
	Excluded	• Basic bacteriology research and fundamental understanding of mechanisms of resistance and/or pathogenesis • Structural analogues of existing antibiotic classes (including new ß-lactamase inhibitors) • New formulations of existing antibiotics

This horizon scanning exercise focused on antibacterial agents that target Gram-negative bacteria in the WHO priority pathogen list (Appendix 5), more specifically, *K. pneumoniae* and *A. baumannii*. Inclusion criteria required the projects to be in one of the discovery phases (i.e., hit identification, hit-to-lead, or lead optimisation) and focus on direct-acting antibacterials and/or potentiators (e.g., efflux inhibitors). Because the potential benefit of most "non-traditional" approaches such as phage and phage-derived peptides and anti-virulence agents largely remains to be demonstrated in clinical settings (Theuretzbacher and Piddock 2019; Rex *et al.* 2019), projects focusing on approaches falling in one of these categories (listed in Table 1) were excluded. Vaccines and diagnostics were excluded.

The following definitions were used for this report:

- A 'new' target is any biological target that is not targeted by any antibiotic in clinical use. It is noted that the terms 'under-researched', 'under-explored' and 'under-exploited' target have been used variably and interchangeably in the literature as a synonym of 'new' target. As a result of this horizon scanning project, we considered the terminology used to define different 'new' targets for discovery of new treatments for bacterial infections. This is indicated in the conclusion section of this report.
- An 'old' target is any biological target that is targeted by existing antibiotic classes (e.g., ribosome, DNA gyrase/topoisomerase, RNA polymerase, etc.). It is noted that in 'old' targets, there are binding sites that are not targeted by any drug from the antibiotic classes in clinical use and thus molecules acting through these 'new' binding sites in 'old' targets could overcome existing cross-resistance.

4. RESULTS

4.1 | JPIAMR

This horizon scanning exercise identified 2,679 funded antibacterial research projects with a potential therapeutic application outcome (973/1,425 from the 2014 JPIAMR database and 1,706/1,939 from the 2017 JPIAMR database). In addition, 5/18 projects from the 6th and 8th JPIAMR joint calls were also identified as potentially falling within the scope of this horizon scanning exercise.

In the first filtering phase, 123 projects were identified. These were classified as either meeting the inclusion criteria ("Yes"; 29/123 projects) or as "Maybe" or "Cannot tell" as it was difficult to determine from the information supplied whether they met the inclusion criteria (94/123 projects). When the title and/or abstract suggested that the project potentially met the inclusion criteria, further information was required for confirmation (Table 2).

Table 2. Number of projects meeting the inclusion criteria.

	NUMBER OF PROJECTS MEETING INCLUSION CRITERIA			
	YES	MAYBE[1]	CANNOT TELL[2]	TOTAL
2014 JPIAMR database	11	11	4	**26**
2017 JPIAMR database	14	42	36	**92**
2018 JPIAMR joint calls 6 & 8	4	1	0	**5**
TOTAL	**29**	**54**	**40**	

1 Too early stage but potentially some are of interest or promising but not enough information to completely rule in or out or they received significant funding so could have made significant progress since receiving the funding; Potentially involving a new tool or platform.

2 Mostly large grants in Germany and Canada with no information on details of work but title indicates potential area of interest.

Collection of missing information on the 123 shortlisted projects from the JPIAMR office and national funding agencies enabled further filtering of projects according to the inclusion/exclusion criteria.

Thirty-five projects were excluded as they were at too early a stage to meet the inclusion criteria (i.e. at the target validation or assay development stage) or were focusing on other anti-microbial areas (for example, anti-virals). Projects also excluded were those aiming at identifying improved derivatives of marketed antibiotic classes (n=6) or new ß-lactamase inhibitors (n=13). Of the remaining 69 shortlisted projects, 19 were also excluded as they were focusing on WHO priority Gram-negative bacteria other than Enterobacterales and *A. baumannii* (for example, *Pseudomonas aeruginosa*). One project was not evaluated further due to insufficient information (name of principal PI or institution unknown). Three project titles were duplicated[3] in the source databases and thus were counted only once.

To collect further information on the remaining 39 projects (Appendix 6) in a systematic manner, an online survey specifically designed by GARDP was sent to project PIs (the survey questionnaire is reproduced in the Appendix 4). The following sections present the analysis of the data obtained for these 39 shortlisted projects.

INSTITUTIONS

Thirty-nine research institutions across 13 countries (among which ten are European countries) are working on at least one early antibacterial discovery project that met the inclusion/exclusion criteria. Unsurprisingly, most of these institutions are universities (n=34) conducting academic research and most were funded by public funding agencies within their respective country. There were also three consortia (namely "Train2Target", "NABARSI" and "AntiPathoGN") regrouping several academic groups, small and medium enterprises (SMEs) and/or industry partners that were funded at the European level and were co-ordinated by an academic PI located in an European country.

Three projects were conducted by SMEs. One of them, Galapagos (Belgium), is no longer active in antibacterial discovery research and one other, DnaAcos (Norway), no longer exists. The third company is not publicly disclosed.

One project was conducted by the Defence Science and Technology Laboratory (DSTL) in the UK and one project was performed at the Institute Pasteur Korea, a non-profit private research organisation.

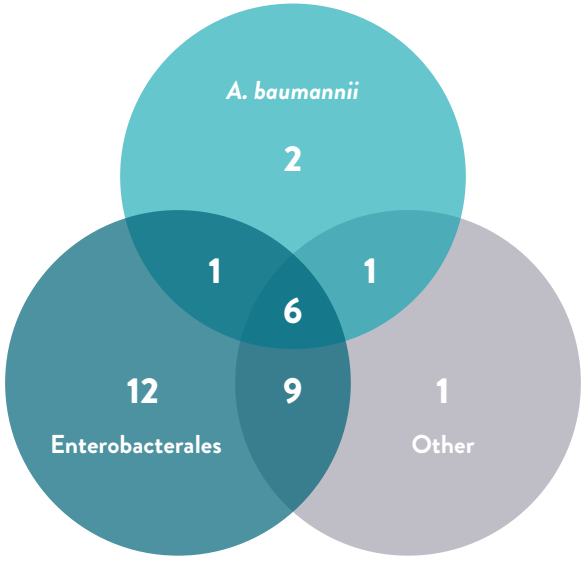
ANTIBACTERIAL SPECTRUM

Of the 2017 WHO priority pathogens, the GARDP DER programme currently focuses on *K. pneumoniae* and *A. baumannii*. This is because these pathogens are a major cause of serious drug-resistant paediatric and adult infections globally and these are the strategic priorities set by the GARDP Scientific Advisory Committee in November 2017. Examination of the antibacterial spectrum focus of the 39 projects indicated that the majority (n=25) were focused on Gram-negative bacteria, either broadly (Enterobacterales and non-fermenters including *Pseudomonas* and/or *Acinetobacter*, n=7) or more specifically on *A. baumannii* (n=2) or Enterobacterales (*E. coli* only (n=8); *E. coli* and *K. pneumoniae* (n=3); *E. coli* and *Klebsiella* spp. and *Enterobacter* spp. (n=1)). One project was focused on *Francisella tularensis* (n=1). For three projects indicated as focusing on Gram-negative bacteria, the bacterial species of interest were not indicated.

Twelve projects had an even broader spectrum and covered both Gram-negative and Gram-positive bacteria (mostly *S. aureus*) from all three WHO priority pathogen criteria tiers.

3 "Microbial Chemical Biology", Eric Brown *et al.*; "Health and Genomics", Robert Hancock *et al.*, and "Lead optimisation and development of novel bacterial DNA synthesis inhibitors for the treatment of nosocomial infections caused by multi-drug resistant Gram-negative bacteria" Art Branstrom *et al.* at PTC Therapeutics.

Figure 1. Antibacterial focus of shortlisted projects (total n=32/39). For seven projects, the bacterial species of interest were not indicated by project PIs and could not be deduced.



ANTIBACTERIAL TARGETS

For 11 projects, the mechanism of action (including "function inhibited", "target" and "target location") could not be categorized due to insufficient information (either not known or not defined or not disclosed). This may be expected for projects at such an early stage (Table 3).

Most projects for which the antibacterial agent category was informed or deduced (n=30/39) focused primarily on direct-acting small molecules (n=24).

Six projects were primarily exploring potentiators that enhance, augment, or increase the efficacy of another compound, usually an existing antibiotic. Two projects were targeting different drug efflux pump components, including TolC. One project was exploring compounds targeting cell membrane components, presumably to increase partner drug penetration into the bacterial cell. Another approach followed in one project was potentiators that impact bacterial redox and iron homeostasis.

Table 3. Distribution of 39 shortlisted projects by bacterial target category, target/s and target location.

TARGET/S (by category)	TOTAL	TARGET LOCATION		
		CYTO PLASMIC	EXTRA-CYTOPLASMIC	NOT KNOWN
Cell membrane integrity	**3**		**3**	
Cell membrane components	1		1	
LPS transport proteins and Bam complex	2		2	
Cell metabolism	**9**	**7**	**2**	
[Fe–S] cluster proteins	1	1		
ClpP protease	1	1		
DegP (HtrA)	1		1	
GcpE	1	1		
Phosphopantetheinyl transferases (PPTases)	1	1		
Riboswitches	1	1		
Thiamine pyrophosphate (TPP) biosynthesis	1	1		
Thiamine pyrophosphate (TPP) riboswitch	1	1		
Type I signal peptidases (SP-I)	1		1	
Cell wall synthesis	**5**	**1**	**4**	
Cell membrane components	1		1	
Cell wall components	2		2	
PBP3	1		1	
ß-ketoacyl-acyl carrier protein synthase III (KAS III)	1	1		
DNA metabolism	**3**	**3**		
DNA polymerase III	1	1		
DnaA	1	1		
Not known	1	1		
Drug accumulation	**1**		**1**	
Cell wall components	1		1	
Drug efflux	**2**		**2**	
Efflux pumps	1		1	
TolC efflux pump	1		1	
Not known	**11**			**11**
Multiple	3			3
Not known	8			8
Protein synthesis	**5**	**5**		
Aminoacyl-tRNA synthetases	2	2		
Ribosome	3	3		
TOTAL	**39**	**16**	**12**	**11**

Interestingly, there was no bias towards extracytoplasmic targets even though these are thought to be more accessible to drugs compared with cytoplasmic ones.

Of the 14 projects from PIs who indicated the molecular target of their project in the GARDP survey (answering the question "Please can you tell us the molecular target of this chemical entity", Appendix 4), seven indicated a family of proteins (e.g., [Fe–S] cluster proteins, aminoacyl-tRNA synthetases), the cellular location of their target(s) of interest (e.g., cell membrane components) or the biological pathway their target of interest belonged to (e.g., thiamine pyrophosphate (TPP) biosynthesis). Thus, for those, the specific target name was not informed (either not known or not disclosed). The seven other target names disclosed through the GARDP survey are indicated in Table 4.

Table 4. Target molecules indicated through the GARDP survey.

PI NAME | INSTITUTION	TARGET LOCATION	FUNCTION OR BIOLOGICAL PROCESS INHIBITED	TARGET MOLECULE (full name)	TARGET NEW OR OLD?[4]	PRIMARY ANTIBACTER. AGENT CATEGORY	TOTAL PRO-JECTS
University of Toronto	Cyto-plasmic	Cell metabolism/ proteostasis	ClpP (caseinolytic protease proteolytic subunit)	New	**Direct-acting small molecule**	1
University of Hamburg; Université de Rennes	Cyto-plasmic	Protein synthesis	Ribosome	Old	**Direct-acting small molecule**	2
University of Bergen	Cyto-plasmic	Cell metabolism/ gene regulation of essential metabolites	TTP (thiamine pyrophosphate) riboswitch	New	**Direct-acting small molecule**	1
University of Warwick	Cyto-plasmic	Cell wall synthesis	PBP3 (penicillin binding protein 3)	Old	**Direct-acting small molecule**	1
Institut de Chimie de Strasbourg	Cyto-plasmic	Cell metabolism/ non-mevalonate pathway of isoprenoid biosynthesis	IspG, also known as GcpE	New	**Direct-acting small molecule**	1
Fraunhofer Institute for Molecular Biology and Applied Ecology	Extracyto-plasmic	Drug efflux	TolC	New	**Potentiator**	1

4 As defined in the Methods section.

Other specific target molecule names deduced from project titles or abstracts, or from the literature and web-based searches performed during this horizon scanning exercise were:

- DegP (HtrA) (n=1)
- DNA polymerase III (n=1)
- DnaA (n=1)
- KAS III (ß-ketoacyl-acyl carrier protein synthase III) (n=1)

The groups or families of target molecules being the focus of at least one direct-acting small molecule project were:

- Aminoacyl-tRNA synthetases (n=2)
- LPS transport proteins and Bam complex (n=2)
- PPTases (Phosphopantetheinyl transferases) (n=1)
- Riboswitches (n=1)
- Type I signal peptidases (SP-I) (n=1)

The groups or families of target molecules being the focus of at least one potentiator project were:

- [Fe–S] cluster proteins (n=1)
- Efflux pumps (n=1)

4.2 | WHO ANTIBACTERIAL PRECLINICAL PIPELINE REVIEW

To expand our analysis to other data sources, the inclusion/exclusion criteria were applied (Table 1) to the 252 projects in the 2019 preclinical pipeline report (and the respective database) by the WHO (World Health Organization (WHO) 2020).

Out of the 252 antibacterial agents identified by the WHO to target pathogens on the WHO priority pathogens list (Appendix 5), *Mycobacterium tuberculosis* and *Clostridioides difficile*, there were 51 "direct-acting small molecules" and six "potentiators or enablers" at the lead optimisation stage[5] – the earliest discovery phase included in the scope of this WHO preclinical review report/database.

Among these 57 projects, four were focusing on Gram-positive WHO priority bacteria in general, or specifically on *Staphylococcus aureus* (n=1) or *M. tuberculosis* (n=18), and thus were excluded. Seven projects were also excluded as they focused on new ß-lactams or ß-lactam/ß-lactamase inhibitor combinations.

Of the remaining 27 shortlisted projects, three were also excluded based on one of the following "indication" comments:

- "cystic fibrosis-associated lung infection", indicating that the target pathogen is *P. aeruginosa*
- "antibiotic-resistant gonorrhoea, VRE, MRSA and VRSA", indicating that the target pathogens are Gram-positive bacteria and *Neisseria gonorrhoeae*
- "prosthetic orthopaedic infection, endocarditis, burn wounds", indicating that the target pathogens include *S. aureus*, *Enterococcus faecium* and/or *P. aeruginosa* (Regules *et al.* 2008)

Thus leaving **24 projects** meeting the inclusion/exclusion criteria for this GARDP horizon scan.

5 The definition of **lead optimisation** in the WHO preclinical review report was: "iterative *in vitro* and *in vivo* screens of lead compounds to generate suitable pharmacological, safety and pharmacokinetic profiles of one or more candidates to progress into preclinical development".

INSTITUTIONS

Twenty institutions across 11 countries (9 located in the USA, 7 in Europe, 2 in South-East Asia and 2 in Western Pacific) had at least one antibacterial agent at the lead optimisation stage meeting the inclusion/exclusion criteria. Two institutions had more than one agent or project meeting these criteria:

- AGILeBiotics, Netherlands (n=2)
- The United States Army - Walter Reed Army Institute of Research, USA (n=4)

As of 01 December 2020, two projects were funded and supported by CARB-X (Trans-translation inhibitors, Microbiotix, USA and DaaRSi, Aminoacyl-tRNA synthase inhibitor, Oxford Drug Design, UK) and indicated as being at the hit-to-lead phase in the CARB-X pipeline (version 2020.12.12). Two projects were formerly funded but are no longer supported by CARB-X (Novel macrolide antibiotic, Zikani Therapeutics, USA and CZ-02, Curza, USA). The project CZ-02 (Curza, USA) is now in the REPAIR Impact Fund portfolio (https://www.repair-impact-fund.com/investment/curza/).

To collect information from the 24 shortlisted projects, carried out by 23 institutions, we assessed their institutional websites. Two additional projects were excluded from this horizon scan activity as they were focusing on new aminoglycoside(s). **Thus, from hereon, 22 projects were considered.**

ANTIBACTERIAL SPECTRUM

The main focus of the remaining 22 shortlisted projects (Table 5) was Gram-negative bacteria in the WHO critical priority list (listed in the Appendix 5) (n=7) or more broadly Gram-negative bacteria of WHO critical and high/medium priority (n=3). One project (DDS-04 Program, Summit Therapeutics, UK) was targeting Enterobacterales infections and two projects (ABAC-40105, ABAC therapeutics, Spain and VT-03, Vitas Pharma, India) were targeting *A. baumannii* specifically. All three "potentiators or enablers" projects in the list had a broad spectrum, covering both Gram-positive and Gram-negative bacteria. This was also the case for six projects focusing on direct-acting small molecules.

ANTIBACTERIAL TARGETS

Eight antibacterial compounds shared their target and/or mode of action with at least one antibiotic class and thus are at risk of exhibiting some level of cross-resistance to these existing antibiotic classes and fast adaptation of bacterial populations (see Table 5):

RNA synthesis (e.g., rifampicin):

- Arylmyxopyronins (APYs), Ebright Laboratory, Waksman Institute, Rutgers University, USA

DNA replication (e.g., fluoroquinolones):

- VT-03, Vitas Pharma, India
- TopESKAPE, Idorsia Pharmaceuticals Ltd, Switzerland

Protein synthesis (e.g., aminoglycosides and tetracyclines):

- DaaRSi, Oxford Drug Design, UK
- Protein synthesis inhibition by small molecules, United States Army - Walter Reed Army Institute of Research, USA
- Trans-translation inhibitors, Microbiotix, USA
- Synthetic macrolides, Zikani Therapeutics, USA
- CZ-02, Curza, USA

Three projects focused on new chemical classes targeting cell wall synthesis processes not connected to pathways inhibited by ß-lactam / ß-lactamase inhibitor combinations. Only one of these "novel" targets was disclosed:

- **LpxC (n=1)** - first committed step in lipid A biosynthesis pathway

Note that LpxC was extensively investigated by industry (e.g., Merck, Pfizer, AstraZeneca, Novartis, Achaogen, Forge) and academia, and thus cannot be considered as an "under-exploited" target despite that no antibacterial compound inhibiting LpxC function has reached market approval yet (Kalinin and Holl 2017).

One other new target was involved in nutrient suppression. For seven projects, the mode of action was not disclosed.

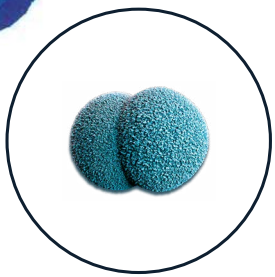
Table 5. Shortlisted projects from the 2019 WHO preclinical pipeline report/database.

COMPANY | INSTITUTION	PRODUCT NAME OR DESCRIPTOR	MODE OF ACTION	INDICATION
SINGLE AGENTS			
Ebright Laboratory, Waksman Institute, Rutgers University	Arylmyxopyronins (APYs)	RNA synthesis	MRSA/VRSA, Pseudomonas/Acinetobacter/ Enterobacteriaceae
Oxford Drug Design	DaaRSi	Protein synthesis (Aminoacyl-tRNA Synthase inhibitor)	cUTI
Bioxiness Pharmaceuticals, Inc.	BXN-1001	Not disclosed	cUTI, and possibly other serious Gram-negative infections
Nosopharm	NOSO-A4	Not disclosed	HAP/VAP
Vitas Pharma	VT-03	DNA replication	*Acinetobacter* lung infections
United States Army - Walter Reed Army Institute of Research	LpxC Inhibition	Lipid A (LpxC)	Healthcare-associated infections
	Acinetobacter-specific antibiotic	Not disclosed	Healthcare-associated infections
	Nutrient suppression	Not disclosed	Healthcare-associated infections
	Protein synthesis inhibition by small molecules	Protein synthesis inhibition	Healthcare-associated infections
Idorsia Pharmaceuticals Ltd	TopESKAPE	Not disclosed	Not disclosed
Summit Therapeutics	DDS-04 Program	Cell wall synthesis	Enterobacteriaceae infections
SinSa Labs AB	CL000ZX	Not disclosed	Not disclosed
ABAC therapeutics	ABAC-40105	Not disclosed	*A. baumannii* infections
Prokaryotics	Cell wall inhibitors	Cell wall synthesis	Not disclosed
Microbiotix	Trans-translation inhibitors	Protein Synthesis	Not disclosed
DA-7310	Dong-A Research Institute	Not disclosed	Not disclosed

Table 5. Shortlisted projects from the 2019 WHO preclinical pipeline report/database.

COMPANY | INSTITUTION	PRODUCT NAME OR DESCRIPTOR	MODE OF ACTION	INDICATION
SINGLE AGENTS			
Synthetic macrolides	Zikani Therapeutics	Protein synthesis – ribosome inhibitor	**cUTI**
Curza	CZ-02	Protein synthesis inhibition	**Not disclosed**
POTENTIATORS OR ENABLERS			
Aequor, Inc.	Aequor2001	Direct membrane effect	**Not disclosed**
Binghamton University	Pyruvate depletion	Anti-virulence	**Not disclosed**
Singapore Centre for Environmental Life Sciences Engineering	COE compound library	Not disclosed	**Not disclosed**

In April 2021, the WHO updated their 2019 preclinical pipeline review and released their 2020 analyse of the preclinical antibacterial product pipeline. The updated 2020 preclinical pipeline review listed 292 preclinical projects targeting WHO priority pathogens, *M. tuberculosis*, and *C. difficile* (vs 252 in 2019). Of the 21 projects we shortlisted from the 2019 WHO preclinical pipeline review (Table 5), ten projects remained in the 2021 preclinical pipeline update, while eleven were not.



4.3 | THE GLOBAL AMR R&D HUB

To identify the priorities in AMR research and development, the Global AMR R&D Hub (launched in May 2018) has recently collected information on AMR R&D investments and market interventions from countries, foundations, organizations and initiatives (https://globalamrhub.org/dynamic-dashboard/). Consolidated information available in the Global AMR R&D Hub's Dynamic Dashboard indicated that the public sector was funding most AMR projects (83%, n=776), whilst only 9% of AMR projects were funded by public/private entities and private non-for-profit entities (n= 56 and 30, respectively).

In February 2021, the Global AMR R&D Hub released more detailed analysis of the funding and allowed projects to be identified. The filters that we applied when accessing data for comparison with that in this report were:

- Research area = Therapeutics
- Infectious Agent = Bacteria
- R&D Stage = Discovery
- Status = Active or Closed

Categorization by discovery phase (i.e., hit-to-lead, lead optimisation, preclinical) was not available in the Dynamic Dashboard and thus it is noted that some projects included in the Dynamic Dashboard selection would have been excluded from the JPIAMR and WHO database analysis for being at a too 'early' or too 'late' discovery stage (see Table 1).

Examination of the antibacterial spectrum focus (referred to as "Infectious Agent") of the 958 projects obtained after applying the above-indicated filters indicated that 133 projects were focused on Gram-negative bacteria broadly (Enterobacterales and non-fermenters including *Pseudomonas* and/or *Acinetobacter*) or more specifically on bacterial species in the Enterobacterales family (n=27), *Klebsiella* spp. only (n=12), *Escherichia* spp. only (n=18) or *Acinetobacter* spp. only (n=17). Out of the projects that target Enterobacterales, *Klebsiella* spp. and/or *Acinetobacter* spp., we selected those investigating 'direct-acting small molecules' and/or 'potentiators or enablers', totalling 31 projects. Of those, four projects had been previously identified in our analysis of the JPIAMR databases and five projects identified in our analysis of the WHO preclinical pipeline database. Twenty-two projects were not included in either database.

5. DISCUSSION AND CONCLUSIONS

This report describes GARDP's analysis of the early antibacterial discovery pipeline based on available data in the following publicly available sources:

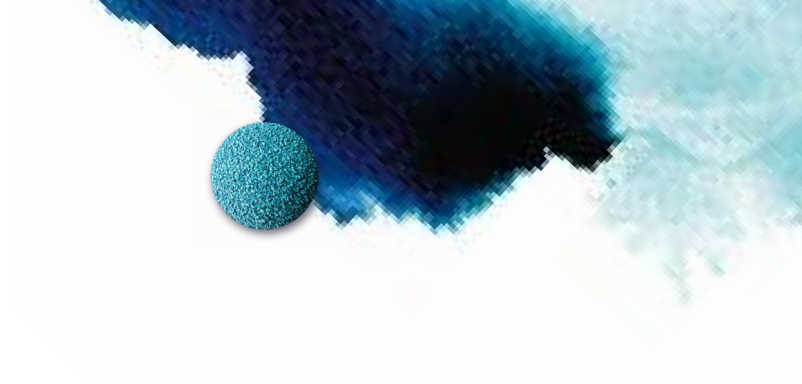
- The JPIAMR databases 2014 and 2017 (plus information from JPIAMR joint calls 6 & 8 2018) containing information on antibacterial resistance research projects funded by JPIAMR member states, the Wellcome Trust, and EU agencies
- The WHO database 2019 capturing the WHO global analysis of the preclinical antibacterial pipeline

This data was supplemented with information from relevant publications, abstracts, institutional websites and other information in the public domain, and information communicated to GARDP via a specifically designed survey, email conversations and oral discussions.

Thirty nine of 2,679 (<2%) antibacterial research projects funded by JPIAMR member states, the Wellcome Trust or the European Union and 21 / 252 (8.3%) projects in the 2019 WHO preclinical pipeline database fulfilled the inclusion/exclusion criteria in terms of novelty (chemical class, target and mechanism of action), spectrum (species and mechanisms of resistance) and discovery stage (hit identification to lead optimisation). There was no overlap between the two shortlists of projects.

Although there is some innovation in terms of chemical classes and targets being investigated, at least 13 of the shortlisted projects focus on new chemical classes targeting new binding sites in 'old' targets (i.e., targeted by antibiotic classes in clinical use) such as ribosomes, PBPs, RNA polymerase or DNA gyrases/ topoisomerases.

Despite several limitations in project information, notably in JPIAMR databases (discussed in Appendix 7, 'Limitations'), the data generated observations and indicated several trends for the institutions carrying out the research, the antibacterial spectrum of activity, and antibacterial targets. These have been summarised below.



INSTITUTIONS

Most large pharmaceutical companies have now exited antibacterial discovery research. Those still active in this area (e.g., Genentech/Roche) may not need to apply for public funding and thus their projects would not be captured in this report.

Academic institutions carry out the majority of early antibacterial discovery research. Due to constraints related to funding and 'translational' expertise required to optimise and progress promising molecules to preclinical and then clinical development phases, investigation of promising molecules and targets may stop once the discovery has been reported in a peer-reviewed publication.

ANTIBACTERIAL SPECTRUM

While the WHO reported a "shift towards pathogen-specific agents" (Theuretzbacher *et al.* 2019; World Health Organization (WHO) 2020), and likewise the AMR R&D Hub, the analysis in this GARDP horizon scan project does not concur with this observation. This may be because pathogen-specificity is a strategic decision taken at a later stage in the antibacterial development process when the achieved spectrum of activity of the investigated antibacterial compound and its mechanism of action (and by inference, the level of target binding site conservation between bacterial species) is known. In early antibacterial discovery, the spectrum of activity is usually not precisely defined and thus may change throughout the discovery phases. Most antibacterial research typically starts with a panel of ESKAPE bacteria (Smith *et al.* 2018) as opposed to being based upon a target candidate profile (TCP) where the target spectrum of activity is defined. Specificity of an approach for a bacterial species may also be more frequent for non-traditional approaches such as anti-virulence molecules and biologics; these were not included in this GARDP horizon scan.

ANTIBACTERIAL TARGETS

Most of the 'new' targets or mechanisms of action were described in the literature before 2014 (i.e., before the JPIAMR funding period evaluated in this report), this has the advantage that they are already known to be druggable, some with *in vivo* validation. However, validation with clinical data remains absent for most of these targets (e.g., LpxC, DNA polymerase III, etc.).

CONCLUSIONS

This GARDP analysis indicates that the early Gram-negative antibacterial discovery pipeline is not adequately populated or sufficiently innovative to deliver the much-needed new classes of antibacterial drugs for clinical development and that have the potential to replace current antibiotics failing in the clinic because of drug resistance. This conclusion concurs with those of others (Theuretzbacher *et al.* 2020); https://amr.solutions/2019/11/24/looking-forward-the-global-pre-clinical-antibacterial-pipeline-how-will-we-care-for-these-precious-jewels/). Indeed, many of the antibacterial discovery projects currently in the preclinical pipeline may be expected to fail to deliver a clinical candidate owing to the numerous discovery and development challenges (McDowell *et al.* 2019). Thus, continuous collaborative efforts are needed to keep feeding the pipeline with new antibacterial chemical entities that have the potential to address the challenges associated with the silent pandemic of drug-resistant bacterial infections (https://gardp.org/news-resources/drug-resistant-infections-the-silent-pandemic-we-must-tackle-now/).

6. REFERENCES

Kalinin, Dmitrii V., and Ralph Holl. 2017. "LpxC Inhibitors: A Patent Review (2010-2016)." *Expert Opinion on Therapeutic Patents* 27 (11): 1227–50. https://doi.org/10.1080/13543776.2017.1360282.

Kelly, Ruth, Ghada Zoubiane, Desmond Walsh, Rebecca Ward, and Herman Goossens. 2016. "Public Funding for Research on Antibacterial Resistance in the JPIAMR Countries, the European Commission, and Related European Union Agencies: A Systematic Observational Analysis." *The Lancet Infectious Diseases* 16 (4): 431–40. https://doi.org/10.1016/S1473-3099(15)00350-3.

McDowell, Laura L., Cheryl L. Quinn, Jennifer A. Leeds, Jared A. Silverman, and Lynn L. Silver. 2019. "Perspective on Antibacterial Lead Identification Challenges and the Role of Hypothesis-Driven Strategies." *SLAS Discovery* 24 (4): 440–56. https://doi.org/10.1177/2472555218818786.

Regules, Jason A., Jessie S. Glasser, Steven E. Wolf, Duane R. Hospenthal, and Clinton K. Murray. 2008. "Endocarditis in Burn Patients: Clinical and Diagnostic Considerations." *Burns* 34 (5): 610–16. https://doi.org/10.1016/j.burns.2007.08.002.

Rex, John H., Holly Fernandez Lynch, I. Glenn Cohen, Jonathan J. Darrow, and Kevin Outterson. 2019. "Designing Development Programs for Non-Traditional Antibacterial Agents." *Nature Communications* 10 (1): 3416. https://doi.org/10.1038/s41467-019-11303-9.

Smith, Peter A., Michael F.T. Koehler, Hany S. Girgis, Donghong Yan, Yongsheng Chen, Yuan Chen, James J. Crawford, et al. 2018. "Optimized Arylomycins Are a New Class of Gram-Negative Antibiotics." *Nature* 561 (7722): 189–94. https://doi.org/10.1038/s41586-018-0483-6.

Tacconelli, Evelina, Elena Carrara, Alessia Savoldi, Stephan Harbarth, Marc Mendelson, Dominique L. Monnet, Céline Pulcini, et al. 2018. "Discovery, Research, and Development of New Antibiotics: The WHO Priority List of Antibiotic-Resistant Bacteria and Tuberculosis." *The Lancet Infectious Diseases* 18 (3): 318–27. https://doi.org/10.1016/S1473-3099(17)30753-3.

Theuretzbacher, Ursula, Karen Bush, Stephan Harbarth, Mical Paul, John H. Rex, Evelina Tacconelli, and Guy E. Thwaites. 2020. "Critical Analysis of Antibacterial Agents in Clinical Development." *Nature Reviews Microbiology*. https://doi.org/10.1038/s41579-020-0340-0.

Theuretzbacher, Ursula, Kevin Outterson, Aleks Engel, and Anders Karlen. 2019. "The Global Preclinical Antibacterial Pipeline." *Nat Rev Micro*. https://doi.org/10.1038/s41579-019-0288-0.

Theuretzbacher, Ursula, and Laura J.V. Piddock. 2019. "Non-Traditional Antibacterial Therapeutic Options and Challenges." *Cell Host & Microbe* 26 (1): 61–72. https://doi.org/10.1016/j.chom.2019.06.004.

World Health Organization (WHO). 2020. "Antibacterial Agents in Preclinical Development." *WHO*. https://apps.who.int/iris/handle/10665/330290

7. APPENDICES

APPENDIX 1

JPIAMR Database 2014 Participating Member States, the Wellcome Trust, and EU Public Funding Agencies

Belgium	Agency for Innovation by Science and Technology (IWellcome Trust), Research Foundation Flanders (FWO), and Fonds de la Recherche Scientifique (FNRS)
Canada	Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council (NSERC). Other funding agencies were contacted but had no data meeting the inclusion criteria.
Czech Republic	Internal Grant Agency of Ministry of Health (IGA) and Czech Science Foundation (GAČR)
Denmark	The Danish Council for Strategic Research and the Danish Council for Independent Research
DG SANCO	Directorate General for Health and Consumer Affairs
DG Research	Directorate General for Research and Innovation
ECDC	European Centre for Disease Prevention and Control
ERC	European Research Council
Estonia	Archimedes Foundation, Enterprise Estonia, Estonian Research Council, Ministry of Agriculture, Ministry of Education & Research
Finland	Academy of Finland
France	National Agency for Research (ANR), National Institute for Agricultural Research (INRA), Agency for Food, Environment and Occupational Health and Safety (ANSES), National Institute of Health and Medical Research (INSERM), the Medical Research Foundation (FRM), Hospital Clinical Research Program (PHRC), the Public Hospitals of Paris (APHP), the Ministry of Higher Education and Research, Ministry of Health, Single Inter-ministerial Fund, National Institution of Agriculture and Sea Products, the French Alternative Energies and Atomic Energy Commission, Carnot Institute for Animal Health (ICSA), Principality of Monaco, Association Raoul Follereau, and the Infectiopole-sud Foundation.
Germany	Projektträger Jülich (PtJ), Projektträger DLR (PT-DLR), and Deutsche Forschungsgemeinschaft (DFG)
IMI	
Ireland	Science Foundation Ireland (SFI), Health Research Board (HRB), Department of Agriculture, Food and the Marine
Israel	Ministry of Health

Italy	Chief Scientists Office, Ministry of Health (CSO-MOH)
The Netherlands	The Netherlands Organisation for Health Research and Development (ZonMw), plus additional desk study to identify publically available funded projects by other organisations
Norway	The Research Council of Norway (RCN)
Poland	National Science Centre (NCN) and National Centre for Research and Development (NCBR)
Portugal	Health and Life Sciences Scientific Council (FCT)
Romania	Ministry of National Education, the National Authority for Research, Technological Development and Innovation
Spain	Instituto de Salud Carlos III, Ministry of Economy and Competitiveness (MINECO), and Spanish Network for Research in Infectious Diseases (REIPI)
Sweden	Swedish Research Council (SRC), Vinnova, Forte, Formas, and the Swedish Foundation for Strategic Research (SSF)
Switzerland	Swiss National Science Foundation
Turkey	The Scientific and Technological Research Council of Turke (TUBITAK)

APPENDIX 2

JPIAMR Mapping 2017 Participating Member States, the Wellcome Trust, and EU Public Funding Agencies

Argentina*	ANPCYT, Agencia Nacional de Promoción Científica y Tecnológica
Belgium	Agency for Innovation by Science and Technology (IWT), Research Foundation Flanders (FWO), and Fonds de la Recherche Scientifique (FNRS) *WIV-ISP, Belgian Scientific Institute of Public Health
Canada	Canadian Institutes of Health Research (CIHR)
Czech Republic	Ministry of Health, Czech Science Foundation (GAČR) Technology Agency*; Ministry of Agriculture*
Egypt	ASRT, Academy of Scientific Research and Technology
Estonia	Estonian Research Council; Enterprise Estonia; Ministry of Rural Affairs
European Commission	European Commission Framework Programs and European Research Council (excluding DG Research contribution to IMI)
Finland	Academy of Finland
France	ANR, National French Research Agency
Germany	BMBF, Federal Ministry of Education and Research; BMG, Federal Ministry of Health; BMEL, BMEL, Federal Ministry of Food and Agriculture; DZIF, German Center for Infection Research
Ireland	Science Foundation Ireland (SFI), Health Research Board (HRB), Department of Agriculture, Food and the Marine, Environmental Protection Agency (EPA)*
Israel	CSO-MOH, Chief Scientist Office - Ministry of Health, The Israel Science Foundation*

Italy	Ministry of Health (MOH)
Japan*	AMED, Japan Agency for Medical Research and Development
Korea*	Animal And Plant Quarantine Agency; Advanced Institute of Science and Technology; Centers for Disease Control & Prevention; Drug Development Fund; Environmental Industry & Technology Institute; Evaluation Institute of Industrial Technology; Health Industry Development Institute; Institute of Marine Science & Technology Promotion; Institute of Planning and Evaluation for Technology in Food, Agriculture and Forestry; Research Institute of Bioscience and Biotechnology; Technology and Information Promotion Agency for SMEs; Ministry of Health and Welfare; Nano-Convergence Foundation; National Research Foundation; Rural Development Administration
Norway	The Research Council of Norway (RCN) Helse Vest RHF (samarbeidsorganet)*, Matfondavtalen*, BIONÆR*, Northern Norway Regional Health Authority*
South Africa*	SAMRC, South African Medical Research Council
Spain	Instituto de Salud Carlos III, Ministry of Economy and Competitiveness (MINECO), and La Agencia Estatal de Investigación*
Sweden	Swedish Research Council (SRC), Vinnova, the Swedish Research Council Formas, the Swedish Foundation for Strategic Research (SSF), Statens energimyndighet*
Switzerland	Swiss National Science Foundation (SNSF), Agroscope (AGS)*, Federal Office for Agriculture (FOAG)*, Federal Food Safety and Veterinary Office (FSVO)*, Innosuisse*, Swiss Federal Office of Public Health (SFOPH)*
The Netherlands	The Netherlands Organisation for Health Research and Development (ZonMw), Ministry of Health*
The United Kingdom	Arts and Humanites Research Council, Biotechnology and Biological Sciences Research Council (BBSRC), Chief Scientist Office-Scotland, Department for International Development (DFID), Ministry of Defence*, Veterinary Medicines Directorate (VMD), Natural Environment Research Council (NERC), Economic and Social Research Council (ESRC), National Institute for Health Research (NIHR), Engineering and Physical Sciences Research Council (EPSRC), Medical Research Council (MRC), Food Standards Agency, Health and Care Research-Wales*, Healthcare Infection Society*, Health Education England*; HSC R&D Division Northern Ireland*, Public Health England*, Scottish Government*, Sustainable Intensification Research Network (SIRN)*
Turkey	The Scientific and Technological Research Council of Turkey (TUBITAK)

* New additions (Member State and/or Agency) compared to 2014.

APPENDIX 3

Possible additional sources of information

- UK capital funding (£32M from the Department of Health and Social Care (DHSC), call ran by NIHR in 2018 and announced in 2019): information on the successfully funded project were not easily identifiable on-line so no further action was taken (results can be obtained from Tracy.Parker@dhsc.gov.uk)
- UK-China co-funded projects, funding from the UK DHSC Global AMR Innovation Fund (call was led for the UK by Innovate UK in 2018/19): The list of funded projects were not easily identified, therefore no further investigation was conducted.

[Further information is available here: https://www.gov.uk/government/news/uk-china-partnerships-against-antimicrobial-resistance-get-funding and all information on GAMRIF investments (1. UK-China; 2. UK-Arg (not GARDP remit); 3. CARB-X; 4. FIND; 5. GARDP; 6. BACTIVAC (not GARDP remit); UK- Canada/IDRC (not GARDP remit)) can be obtained from Erice.Westwood@dhsc.gov.uk].

APPENDIX 4

Survey questionnaire and responses

1. On which bacteria did your project focus:
   - ☐ *E. coli*
   - ☐ *K. pneumoniae*
   - ☐ *Enterobacter* spp
   - ☐ *P. aeruginosa*
   - ☐ *A. baumannii*
   - ☐ Gram-positive bacteria

2. How would you categorize the chemical entity from your study (If more than one, please fill as many questionnaires as necessary)?
   - ☐ Direct-acting traditional agents (i.e. antibiotics that directly inhibit growth or kill bacteria)
   - ☐ Potentiators that enhance, augment or increase efficacy of another compound
   - ☐ Anti-virulence agents
   - ☐ Repurposed licensed drugs

3. Please can you tell us the molecular target of this chemical entity?

4. Please can you briefly describe the mechanism of action of this chemical entity?

5. Did this chemical entity display cross-resistance with any current class of antibiotics?
   - ☐ Yes
   - ☐ No

6. If yes, please specify

7. What is the current status of the project?
   - ☐ In progress
   - ☐ Compound in development
   - ☐ Finished and no further research

8. If the project is finished without further research, please can you tell us why no further work has been done?

9. What is the current stage of development of the chemical entity from this study?
   - ☐ Hit to Lead
   - ☐ Lead optimisation
   - ☐ Studies enabling CTA or IND application

10. Were the results from your study
    - ☐ Published
    - ☐ A patent application submitted

11. Please can you list the publications and/or patent submissions?

12. What is/are the type of the institution(s) involved in the project?
    - ☐ Academic institution
    - ☐ Non-profit institution
    - ☐ Small and medium-sized enterprises
    - ☐ Public-private partnership

APPENDIX 5

WHO priority pathogen list

Priority 1: **CRITICAL**

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, 3rd gen. cephalosporin-resistant

Priority 2: **HIGH**

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and -resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp, fluoroquinolone-resistant
- *Salmonella species*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, 3rd gen. cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: **MEDIUM**

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella species*, fluoroquinolone-resistant

Source: Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug resistant bacterial infections, including tuberculosis.

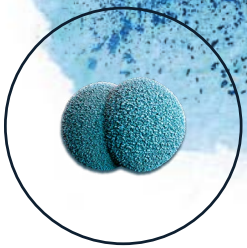
Geneva: World Health Organization; 2017.
https://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf?ua=1

APPENDIX 6

Details from the JPIAMR databases for shortlisted projects

JPIAMR database 2014

PROJECT 1		
Project Technical Details (if available)	Title	Novel antibacterial drugs active against DNA pol III in *E.coli*
	Summary	Non provided
	Phase	Discovery
	Target	DNA pol III
	Activity WHO PP	*E. coli*
	WHO category	1
Project Status Details	Status	Completed
	Years	Jan 2013 (error in end date)
	Amount	€2,925,266
	Country	Belgium
	Funder (s)	IWT
PI Details	Name	John Lowther
	Institution	Galapagos (https:/www.glpg.com/)



PROJECT 2		
Project Technical Details	Title	NABARSI: New antibacterials with inhibitory activity on aminoacyl- tRNA synthetases
	Summary	http://cordis.europa.eu/projects/rcn/108677_en.html
	Phase	Discovery
	Target	Aminoacyl t-RNA synthetases (aaRS)
	WHO PP	No information provided
	WHO category	Cannot tell
Project Status Details	Status	Completed
	Years	June 13- May 16
	Amount	€4,102,158
	Funder	EC FP 7
PI Details	Name	John Hays
	Institution	NL = co-ordinator

PROJECT 3		
Project Technical Details	Title	AntiPathoGN: Identification and validation of novel drug targets in Gram-negative bacteria by global search: a trans-system approach
	Summary	https://cordis.europa.eu/project/rcn/91036/factsheet/es
	Phase	Discovery
	Target	Cannot tell
	WHO PP	Gram negative bacteria
	WHO category	Cannot tell
Project Status Details	Status	Completed
	Years	2009- Dec 2012
	Amount	€5,943,961
	Funder	EC FP 7
PI Details	Name	Xavier Daura
	Institution	Spain = co-ordinator

PROJECT 4

Project Technical Details	Title	Antibacterial agents with novel mode of action; challenging the global threat of antimicrobial resistance
	Summary	The emergence of new human pathogens and increasing antimicrobial resistance in well-established pathogens are critical public health concerns. New classes of antimicrobials with novel mechanisms of action are urgently needed. We have developed a propriety screening assay, SF53, to identify antibiotic candidates that target the essential bacterial replication protein, DnaA. This a novel target for development of anti-microbial drugs. In collaboration with the Italian company, Ktedogen and DDL in Oslo, we wish to initiate a R&D project with the long-term goal of finding new candidate drugs. This will represent new class(es) of antibiotics, inhibiting DNA replication in microorganisms and may constitute a novel group of antibacterial drugs that can potentially target all types of bacteria. This is a revised application. Since submission of the application in October, we have realized that it will take longer time than anticipated to characterize suitable hits from the screening. The project has therefore been revised and we will need 2009 for characterization as well as further screening of the Actinomycetes library in Italy. We plan for a go no-go milestone at the end of 2009. This will be the phase with the highest risk.
	Phase	Hit Characterisation
	Target	DNAa
	Activity WHO PP	No information provided
	WHO category	No information provided
Project Status Details	Status	Completed
	Years	2009 – end date incorrect in database
	Amount	€258,000
	Country	Norway
	Funder	The Research Council of Norway
PI Details	Name	Harald Dugstad
	Institution	DnaAcos AS and involves the Italian company, Ktedogen and DDL in Oslo

PROJECT 5		
Project Technical Details	Title	CIHR Team in Novel Antibiotics Development Title: Towards the Development of a Novel Class of Antibiotics: Activators of Self-Compartmentalizing Proteases
	Summary	With the emergence of new forms of drug-resistant bacteria, it becomes essential that new classes of antibiotics be discovered and developed. A self-compartmentalizing serine protease termed ClpP is highly conserved in bacteria. The ClpP active sites are located inside a chamber formed by its cylindrical-shaped structure. Access to the active sites is through small axial pores through which only small peptides can diffuse. Hence, on its own, ClpP can only degrade small peptides and not larger proteins. Recently, it was reported that small molecules based on acyldepsipeptides can act as efficient antibiotics that activate ClpP to unspecifically degrade folded proteins resulting in bacterial cell death [Brötz-Oesterhelt et al. Nature Medicine (2005), 11(10), 1082-1087]. The efficacy of these small molecules was demonstrated in treating lethal systemic bacterial infections in mice. Hence, the use of activators of cylindrical proteases (ACP) is a novel strategy for the development of new antibiotics, however, this has not yet been investigated or applied. In the proposed research, we will carry out a systematic analysis to identify new ACPs by extensively screening a large library of small molecules. The ultimate goal of our efforts will be to develop new ACPs that can eventually be used in humans against bacterial infections that are resistant to currently available antibiotics. Our team includes four well-established groups at the University of Toronto of complementary expertise suitable for this project. The groups will collaborate very closely to establish and verify ACPs as a novel class of antibiotics.
	Phase	Discovery
	Target	
	Activity WHO PP	
	WHO category	P1
Project Status Details	Status	In development
	Years	
	Amount	€ 1073688.9
	Country	Canada
	Funder (s)	CIHR
PI Details	Name	HOURY, Walid A
	Institution	University of Toronto

PROJECT 6		
Project Technical Details	Title	Development of new antibacterial and antiparasitic agents that target the metalloenzyme GcpE
	Summary	In most pathogenic bacteria (including Mycobacterium tuberculosis, the pathogen that causes TB) and opportunistic bacteria (Pseudomonas spp, Citrobacter spp, Escherichia coli, etc.) as well as the parasite Plasmodium falciparum that causes malaria and in plant plastids, precursors for the synthesis of key terpenoids are synthesized according to the route of méthylérythritol phosphate (MEP). This channel is absent in humans and therefore a target for new antibacterial and antiparasitic agents. Fosmidomycin, a natural antibiotic, is a good inhibitor of 1-deoxy-D-xylulose-5-phosphate reductoisomerase, the second enzyme of the MEP pathway. Indeed, patients with P. falciparum (uncomplicated form) were successfully treated with fosmidomycin but in some cases the parasite has reappered after treatment. This first result demonstrates the promising potential of the use of enzymes in the MEP pathway as drug targets and also shows the need for more effective inhibitors. One way of improving efficiency is to use a combination of drugs. This could be achieved by blocking several enzymes of the MEP pathway. The penultimate stage of the MEP pathway is catalyzed by GcpE a metalloenzyme containing a center [4Fe -4S] very sensitive to oxygen. The ultimate goal of this project is to elucidate the mechanism of action of GcpE, and use this knowledge to design new drugs. The catalyzed GcpE mechanism requires the transfer of 2 electrons and involves radical intermediates. According to the proposed mechanism, there would be an interaction between the iron atom of the cluster [4Fe - 4S] clusters and the substrate. Substrate analogs are synthesized and used as molecular tools in the elucidation of the mechanism. After evaluating these inhibitory substrate analogs on GcpE power experiments and Mössbauer spectroscopy EPR will be made in an attempt to identify radical intermediates and to investigate the binding mode of the substrate analogs with cluster [4Fe -4S] active site. Differential FTIR spectroscopy, Raman spectroscopy and electrochemistry will also be used to obtain additional information on the mechanism GcpE. In order to get a better idea of the active site, we will try to solve the three-dimensional structure GcpE. The importance of amino acids identified in the structure will be confirmed by site-directed mutagenesis. Several proteins with point mutations will be generated to characterize the effect of the mutation kinetic parameters will be determined for each mutant. The three-dimensional structure of each enzyme is used as target in a virtual screening of combinatorial library in order to access the first drug in silico. These molecules are then synthesized and tested in vitro (structure/activity relationship). Finally, we propose to realize a high-throughput screening using the Prestwick chemical library (1200 medications that are no longer under patent) and an altered E. coli strain in order to identify antibacterial agents and/or pesticides.
	Phase	Discovery
	Target	
	Activity WHO PP	
	WHO category	P1
Project Status Details	Status	In development
	Years	2014
	Amount	€ 459999
	Country	France
	Funder (s)	ANR
PI Details	Name	Myriam SEEMANN, Jean-Bernard BEHR, Jean-Luc FERRER, Petra HELLWIG
	Institution	Institut de Chimie de Strasbourg, Institut de Chimie Moléculaire de Reims, Institut de Biologie Structurale, Institut de Chimie, LSVEB

PROJECT 7		
Project Technical Details	Title	Phenotypic biosensor-based HTS and mode of action analysis by metabolomics and transcriptomics for enhancing antimicrobial drug discovery against Gram-negative bacteria
	Summary	Infectious diseases are still one of the leading causes of morbidity and mortality worldwide, and the need for new antimicrobials is evident. Novel compounds with potential antimicrobial properties are continuously discovered, for example from natural products, but in many cases found activities are not being characterised beyond the initial discovery phase. This is most of all due to the lack of methods for elucidating the mode of action (MoA). We aim to develop predictive tools for pathway and MoA elucidation and for follow-up studies, and to validate the overall process by studying compounds with unknown MoA. The active agents potentially identified may provide experimental tools or antimicrobial lead compounds for applications for human and/or animal use. Importantly, the project will provide fast and efficient tools to carry initial findings forward towards becoming truly significant new antimicrobial compounds for the fight against microbial diseases.
	Phase	Discovery (too early but big grant for Finland scale of projects)
	Target	No info
	Activity WHO PP	Gram negatives
	WHO category	No info
Project Status Details	Status	Nearly completed
	Exact years	01/09/2014 - 01/09/2019
	Funding amount	€764,485.00
	Country	Finland
	Research funder	Academy of Finland
PI Details	Name	Dr Päivi Tammela
	Institution	Academy of Finland

PROJECT 8		
Project Technical Details	Title	Phosphopantetheinyl transferases as drug targets for the treatment of infectious diseases and colonization of the gut by multidrug-resistant bacteria.
	Summary (found online)	PPTases (phosphopantetheinyl transferases) catalyze the transfer of the 4'-phosphopantetheinyl (P-pant) moiety of coenzyme A to carrier protein domains found in fatty acid synthases, polyketide synthases and non-ribosomal peptide synthases. PPTases thus activate functionally important classes of megasynthases involved in the biosynthesis of a broad range of complex organic compounds that are often highly active biologically. Owing to their central role in both primary and secondary bacterial metabolism, PPTases represent new and attractive drug targets in bacteria. The aim of this project is to fully characterize these enzymes and to identify molecules that display inhibitory activity for the development of novel antibacterial agents. A set of five PPTases from human bacterial pathogens will be investigated: PptT from Mycobacterium tuberculosis, PptAb from M. abscessus, PcpS from Pseudomonas aeruginosa, and EntD and ClbA from Escherichia coli. Inhibition of the selected enzymes would prevent the formation of components essential for bacterial viability and/or involved in virulence and pathogenicity. Thus, the project will provide compounds active against different pathogenic bacterial species, with a well-characterized mode of action. These compounds could then in turn be subjected to lead optimization for subsequent development of new antibiotics or antivirulence drugs. Structural information will also be instrumental in understanding structure-function relationships of enzymes that are essential for cell viability. https://anr.fr/Project-ANR-16-CE18-0011
	Phase	Discovery (potential compounds for lead opt, antibiotics and anti-virulence)
	Target	PPTases
	Activity WHO PP	*Pseudomonas aeruginosa & Escherichia coli*
	WHO category	Priority 1
Project Status Details	Status	On-going
	Exact years	01/11/2016 - 30/04/2020
	Funding amount	€593,023.68
	Country	France
	Research funder	ANR, French research agency
PI Details	Name	Dr Lionel Mourey
	Institution	ANR, French research agency

PROJECT 9		
Project Technical Details	Title	From Structural and functional studies of essential and novel lipopolysaccharide transport and assembly membrane proteins to novel drug discoveries combating emerging multi-drug resistant pathogenic bacteria
	Summary	Not available
	Phase	Discovery (large grant)
	Target	lipopolysaccharide transport and assembly membrane proteins
	Activity against WHO PP	MDR resistant pathogenic bacteria
	WHO category	No info
Project Status Details	Status	On-going
	Exact years	01/05/2015 - 01/04/2020
	Funding	€2,331,784.75
	Country	Cannot tell
	Funder	Wellcome Trust
PI Details	Name	Dr Changjiang Dong
	Institution	Wellcome Trust

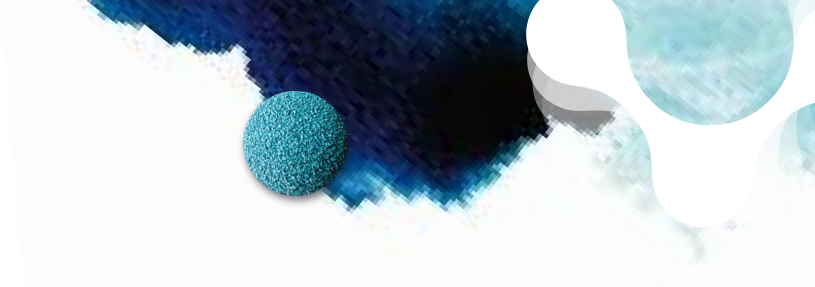
PROJECT 10		
Project Technical Details	Title	Novel class of Gram-negative antibiotics to treat hospital-acquired infections from drug-resistant ESKAPE pathogens
	Summary	The current compounds display a promising antibacterial activity towards Gram-negative pathogens. The further synthesis and experimentation will be intended to further improve the potency and spectrum of this activity. The screening of libraries will include a standard panel of 7 Gram-negative organisms, 2 in the presence of 50 % serum, S. aureus for selectivity and a haemolysis assay. Selected compounds will be further evaluated with an expanded panel of organisms which will include predominantly MDR strains (including polymyxin/colistin-resistant isolates) as well as testing cytoxicity towards 2 cell lines (HepG2 and HeLa). Promising candidates will be tested for in vivo efficacy and pharmacokinetic properties. From the onset, a clear goal will be to find compounds which have a low plasma protein binding (<80% protein bound), have favorable pharmacokinetic properties which will allow for sufficient exposure in mice to treat pathogens with an MIC greater than or equal to the MIC90. The preliminary PK/PD properties of the compounds will be evaluated to suggest an exposure achievable in animals with a sufficient safety margin.
	Phase	Discovery (large grant).
	Target	No info
	Activity against WHO PP	MDR gram negative ESKAPE pathogens
	WHO category	No info
Project Status Details	Status	Completed
	Years	01/07/2016 - 01/01/2018
	Amount	€1,409,675.58
	Country	Cannot tell
	Funder	Wellcome Trust
PI Details	Name	Glenn Dale
	Institution	Welcome Trust

PROJECT 11		
Project Technical Details	Title	Identification of riboswitch regulators as lead compounds of antibacterial drugs through computational virtual screening
	Phase	Discovery - lead compounds
	Target	Riboswitch regulators
	Activity WHO PP	No info
	WHO category	No info
	Status	Nearly completed
Project Status Details	Years	01/11/2016 - 31/10/2019
	Amount	€117,000
	Follow up funding	Cannot tell, no previous data
	Country	Korea
	Funder	National Research Foundation of Korea
PI Details	Name	Hyunjoo Park
	Institution	National Research Foundation of Korea
PROJECT 12		
Project Technical Details	Title	NMR studies of acyl carrier protein of Acinetobacter baumannii and its interaction with FAS proteins and discovery of antibiotics targetting FAS protein
	Phase	Discovery (too early)
	Target	FAS protein
	Activity WHO PP	*Acinetobacter baumannii*
	WHO category	Priority 1
Project Status Details	Status	Completed
	Exact years	01/06/2016- 31/05/2019
	Funding amount	288,461.54 €
	Follow up funding	Cannot tell, no previous data
	Country	Korea
	Funder	National Research Foundation of Korea
PI Details	Name	Prof. Yangme Kim
	Institution	National Research Foundation of Korea

PROJECT 13		
Project Technical Details	Title	Identification of novel inhibitors and activity-based probes for signal peptidase I
	Summary	Bacterial infections continue to be a threat to the well-being of mankind. As a result, there is a pressing need to find new protein targets for next-generation antibiotics. Bacterial signal peptidase I is an essential serine protease with an unusual catalytic machinery. It is involved in the secretory pathway and is considered a potential future drug target. In this project, we will set up an assay for this protease and screen an in-house collection of small molecules that have reactivity against serine residues. The assay itself will be based on a synthetic peptide that becomes fluorescent after cleavage. This assay will be compatible with future high throughput screening. The small molecules have shown reactivity against some unusual serine proteases before. It is therefore likely that some show activity towards signal peptidase I as well. The active small molecules will be derivatized in order to be used as "activity-based probes". These are molecules that modify the active target protease and allow detection by a variety of methods, including mass spectrometry and microscopy. Overall, successful execution of this project will form an important step forward towards novel compounds targeting bacteria. Moreover, it will enable a variety of future research in the development of antibiotics and methods to visualize infection.
Project Status Details	Status	On-going
	Years	Starts 01.01.2017- 31.12.2019
	Funding	€ 41340
	Follow up funding	FWO research grant KAN
	Country	Belgium
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Steven Verhelst
	Institution	

PROJECT 14

Project Technical Details	Title	Rational design of tRNA synthetase inhibitors as new antibacterials
	Summary	Since their development in the 20th century, antibiotics and the introduction of general hygiene have played a major part in improving human health by combating different kinds of infections. However, the widespread (mis)use of antibiotics has lead to increasing development of antibiotic resistant bacteria which has become a major problem worldwide. This has obviated the need for continuous development of new drugs able to ward off these resistant bacteria. The present project is a multidisciplinary effort in which we will develop new antibiotics by improving upon existing compounds. To this end, compounds with known strong inhibitory potential and targeted to bacterial protein synthesis, but as such unsuitable to be used as a drug, will be taken as a starting point. Different analogues will be synthesized with either increased uptake potential, higher stability or modified at specific positions to further improve the inhibitory properties. In parallel X-ray structure determination of the inhibitor-target protein complexes will guide us herein for further optimization of the lead compounds. These structures will also help us in fine tuning the selectivity, as human protein synthesis should not be hampered or at least to a much lower extent. With this joint project, we feel confident to be able to develop a new class of antibiotics which should enlarge the present armamentarium of antibiotics.
Project Status Details	Status	
	Years	Starts 01.01.2014 - 31.12.2017
	Funding	€ 293363.73
	Follow up funding	FWO research project
	Country	Belgium
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Arthur Van Aerschot
	Institution	FWO, Research Foundation Flanders, Belgium



PROJECT 15

Project Technical Details	Title	A new class of antibiotics inhibiting bacterial trans-translation
	Summary	Antibiotics are molecules that attack bacteria by blocking their growth (bacteriostatic affect) or by destroying them (bactericidal effect). Their introduction in civil and military therapies began during the Second World War, with the discovery and production of penicillin, which saved thousands of wounded soldiers. Then industrial methods of production of penicillin and other antibiotics allowed the treatment of many life-threatening bacterial diseases such as tuberculosis, pneumonia, syphilis, tetanus. Yet the intensive use of antibiotics quickly introduced a selection pressure leading today to an increased population of antibiotic-resistant microorganisms and an overall decrease in therapeutic efficacy. The emergence of resistant strains is characterized by north vs south and industrial vs developing countries gradients. So this problem is particularly important during military operations, when soldiers come into contact with these germs in developing countries and countries in the southern hemisphere. In a same way, the french military hospitals are also affected by the resurgence of many nosocomial infections, close to those found in public hospitals. The four most common bacteria isolated in the french military hospitals are Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli and Enterococcus. Finally, the development of a new class of broad-spectrum antibiotics should be considered as a therapeutic against major pathogens used as biological weapons, now classified as weapons of mass destruction. Our research project focuses on the development of new broad-spectrum antibiotics targeting the primary mechanism for quality control in bacterial protein synthesis, namely trans-translation. Indeed, the translation of the genetic code into proteins by the ribosome is the corner stone of life for all cells. Considering the amount of biological data to be processed, it happens regularly that the ribosome stalls and therefore jeopardizes the survival of the cell. In bacteria, the main rescue mechanism is driven by an hybrid ribonucleic acid (RNA): the transfer-messenger RNA (tmRNA), during the process of trans-translation. Surprisingly, this system is essential to the survival of many pathogenic bacteria (Staphylococcus aureus, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Helicobacter pylori, and Shigella flexneri) and is required for virulence of other species (Salmonella, Yersinia, Francisella). Today, structural and biological data on trans-translation allow us to address this pathway as an antibiotic target particularly attractive since it is absent in eukaryotic cells. During this translational project, we will synthesize new molecules anti trans-translation; validate their activity in vitro and in vivo and finally validate their use on multiresistant bacterial strains from hospitals and representing major civil and military threats.
Project Status Details	Status	
	Years	Starts 01.10.2014- 31.01.2018
	Funding	€ 299000
	Follow up funding	ANR, French research agency
	Country	France
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Reynald Gillet
	Institution	ANR, French research agency

PROJECT 16

Project Technical Details	Title	Novel drugs and drug combinations against bacterial growth, survival and persistence from high-throughput screening to mechanism of action
	Summary	Control of bacterial infections is threatened by the rapid emergence of drug resistance, drugtolerance that mitigates antimicrobial efficacy, and the lack of new antibiotics in recent years.Combination treatments and/or re-purposing of known drugs can provide a cost- and time-efficientsolution. We propose a comprehensive and powerful strategy to repurpose or improve FDAapproveddrugs including neglected/disused (ND) antibiotics, and identify combinations to resensitizeresistant/tolerant bacteria. Using high-throughput screening (HTS), we will test thousands ofpairwise drug combinations on bacterial growth, viability and bacterial persistence in three clinicallyrelevant pathogens: uropathogenic Escherichia coli (UPEC), Staphylococcus aureus (Sa), andStreptococcus pneumoniae (Sp). Our scope thus spans the Gram-negative/-positive divide, and targetsseveral bacterial states implicated in both acute and chronic infections, including pneumonia,pyelonephritis, bacteremia and endocarditis. To optimize antimicrobial treatment, we will use stateof-the-art and further advance translational pharmacokinetic (PK)/pharmacodynamic (PD) modeling.This will prioritize and validate lead combinations, which will be tested in resistant clinical isolates,for toxicity in cell-based assays and for efficacy in several animal models. In vivo PK/PD modeling willalso be performed for our top leading combinations. In vivo PK/PD modeling will be also performedfor our top leading combinations. Together, these approaches will provide vital preclinical data thatwill inform future drug development. In parallel, we will systematically probe for modes of action ofour top 40 synergistic drug combinations using HT reverse genetic screens to provide theframework for subsequent in-depth, focused mechanistic studies targeting processes such as the roleof redox and iron homeostasis, membrane permeability/stability, drug efflux/influx, and bacterialmetabolism and stress responses in antimicrobial activity. To be able to follow-up such diverse facetsof biology, we have assembled a strong team with extensive expertise in different cellular processesdirectly related to antimicrobial activity. Overall our cumulative expertise enables us to combinechemical and genetic screening, large-scale data analysis, mechanistic biology, PK/PD modeling andinfection models for enabling antimicrobial combination therapy. The breadth and scope of ourambitious strategy will undoubtedly significantly advance the quest for novel treatment strategiesagainst bacterial infections.
Project Status Details	Status	
	Years	Starts 01.04.2016- 31.03.2019
	Funding	€ 206496
	Follow up funding	ANR, French research agency
	Country	France
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Frédéric Barras
	Institution	

PROJECT 17		
Project Technical Details	Title	Discovery and development of novel antimicrobials against extensively drug-resistant gram-negative bacteria
	Summary	Masato Suzuki (National Institute of Infectious Diseases) and colleagues sequenced genomes of antimicrobial resistant (AMR) bacterial isolates collected from Asian countries including Japan, and analyzed the detailed genetic structures around important AMR genes. The clinically relevant AMR genes, such as genes for aminoglycoside N-acetyltransferases [aac(3)-Ia, aac(6')-Ia, aac(6')-Ib-cr and aac(2')-Ia], aminoglycoside O-adenyltransferases (ant(2")-Ia, ant(3")-Ia, ant(4')-Ia and ant(6)-Ia), aminoglycoside O-phosphotransferases [aph(2")-Ia, aph(3')-Ia, aph(3")-Ib and aph(6)-Id], 16S ribosomal RNA methylases (armA, rmtA and rmtA), lipid A phosphoethanolamine transferases (mcr-1 and mcr-2), and ß-lactamases (blaGES-1, blaGES-5 and blaGES-24), were cloned from AMR isolates or synthesized DNAs into pUC57 vectors and expressed under the class I integron Pc-P2 hybrid promoter in the insertion sequence-less and homologous recombination-defective strain (MDS42 ΔrecA strain) of Escherichia coli. Masayuki Igarashi (Institute of Microbial Chemistry) and colleagues screened for novel antibacterial agents effective against extensively drug-resistant Gram-negative bacteria from natural compound libraries on the basis of antibacterial activities against bacterial cells, including E. coli and Klebsiella pneumoniae, and low toxicities against mammalian cells, and discovered 7 potential compounds. 5 compounds among them belonged to aminoglycosides and other 2 compounds seemed to have antibacterial mechanisms distinct from those of the exiting drugs. Yoshiaki Takahashi (Institute of Microbial Chemistry) and colleagues made chemical modification, such as hydroxylation, fluorination and deoxygenation, or change of the amino acid side chain on the aminoglycosides discovered from natural compound libraries. The developed derivatives as potential lead compounds exhibited greater potency against AMR isolates and strains, including aminoglycoside modifying enzymes and 16S ribosomal RNA methylase-producing Enterobacteriaceae, MCR-1-producing colistin-resistant E. coli, Pseudomonas aeruginosa and Acinetobacter spp. Hidenori Naruse (JSR Corporation) and colleagues sythesized antibacterial polymers effective against the ESKAPE pathogens on the basis of antibacterial activities against both Gram-negative and Gram-positive bacteria, including E. coli and Staphylococcus aureus, improved chemical composition and molecular weight, and developed the optimized antibacterial polymers. The developed polymers were durable and mass producible, and showed substantial antibacterial activities against AMR clinical isolates, including biofilm-forming P. aeruginosa, MCR-1-producing colistin-resistant E. coli and daptomycin-nonsusceptible MRSA.
Project Status Details	Status	
	Years	Starts 01.04.2016- 31.03.2019
	Funding	
	Follow up funding	AMED, Japan Agency for Medical Research and Development
	Country	Japan
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Masato Suzuki
	Institution	National Institute of Infectious Diseases, Tokyo

PROJECT 18		
Project Technical Details	Title	Research on the Development of Inhibitors of Bacterial Multidrug Efflux Pumps
	Summary	Multidrug efflux pumps contribute to bacterial multidrug resistance by exporting multiple antimicrobial agents from inside to outside of the cells. As a result of post genomic analysis, it was revealed that bacteria possess a number of multidrug efflux pumps. Multidrug efflux systems are an attractive target of new drugs that enable to overcome the problem of bacterial multidrug resistance. In this project, random screening using compound libraries was performed to select candidates of inhibitors of efflux pumps in Salmonella enterica, Escherichia coli and Pseudomonas aeruginosa. Furthermore, we clarify the effect of inhibitors on drug susceptibilities of clinical isolates by using the combination of antibacterial drugs and inhibitors. The purpose of the study is the treatment of infectious diseases with multidrug resistant bacteria. In this fiscal year, among ten identified pumps (AcrAB, AcrD, AcrEF, MdtABC, MdsABC, MdfA, EmrAB, SmvA, MdtK, MacAB) in Salmonella, we constructed the MacAB-expressing strain because it was previously found that MacAB is related with Salmonella virulence. The minimum inhibitory concentration of various antimicrobial agents against this strain was measured and the strain exhibited the highest resistance to erythromycin. Thus, we selected erythromycin to verify the synergistic effect at the screening of inhibitors of MacAB. Two candidates were selected among Osaka University chemical library. Of these, one compound showed the antibacterial activity by itself, in addition to the MacAB inhibitory effect. Another compound did not show antibacterial activity, and when it was used in combination with erythromycin, the synergetic effect against the MacAB-expressing strain was confirmed. As a result of verifying the synergistic effect with clarithromycin, oleandomycin, and azithromycin, the candidate compound showed synergistic effect with a 14- and 15-membered ring macrolide. For the screening of E. coli drug efflux pump inhibitors, strains expressing AcrAB, MdtABC, AcrD, AcrEF and MdtEF were constructed and the minimum inhibitory concentrations of various drugs against the strains were measured. The strains shows resistance to oxacillin by expressing these pumps (> 256 fold, 8 fold, 32 fold, 128 fold, 32 fold-increase, respectively), it is considered that oxacillin is a first choice drug to verify the synergistic action with the inhibitor candidates. In addition, we constructed expression strains of drug excretion pumps MexAB and MexXY, which are highly expressed in multidrug-resistant Pseudomonas aeruginosa. And we investigatd the synergistic effect with antibiotics recognized by both efflux pumps by using Osaka University compound library for the screening. We select compounds that retain inhibitory effects on MexAB and MexXY, respectively, and also searched candidate compounds that inhibit both pumps simultaneously. In addition, among the candidate compounds, we selected the compounds having antibacterial activity by themselves, and the compounds having no antibacterial activity. We also tested the influence of each compound on the membrane damage and the effect on the bacterial drug efflux activity.
Project Status Details	Status	
	Years	Starts 01.04.2016- 31.03.2019
	Funding	
	Follow up funding	AMED, Japan Agency for Medical Research and Development
	Country	Japan
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Kunihiko Nishino
	Institution	Osaka University

PROJECT 19		
Project Technical Details	Title	Development of novel antibiotics with additional host-protective anti-inflammatory properties against life threatening infections caused by MDR Gram-negative ESKAPE pathogens
	Summary	In earlier work, POL7080 was discovered; an antibiotic targeting Pseudomonas aeruginosa with a novel mode-of-action, which is currently in Phase II clinical trials. In this project, a new series of peptidomimetics with a broader spectrum of antibacterial activity against multi-drug resistant (MDR) and colistin-resistant Gram-negative ESKAPE pathogens will be studied, possessing also potential host-protective anti-inflammatory activity.
Project Status Details	Status	
	Years	Starts 01.01.2016- 01.01.2019
	Funding	1'254'652.90 €
	Follow up funding	Innosuisse, Switzerland
	Country	Switzerland
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	John A. Robinson
	Institution	

PROJECT 20		
Project Technical Details	Title	Determination of the mode of action of candidate peptidoglycan synthesis antagonists
	Summary	Since the introduction of the first antibiotics in the 1940s (penicillin and streptomycin), the development of resistance to almost all clinically used antibiotics has become a serious concern and led to the constant requirement of new compounds. However the discovery of new antimicrobial drug is difficult and the genomics-based approaches conducted over the last 15 years have largely failed. Alternative approaches are therefore necessary to discover new molecules or new bacterial vulnerabilities. In this proposal, we describe an innovative high throughput chemical screen designed to identify small molecules that interfere with the activity of the conserved peptidoglycan synthesis machinery, the Escherichia coli Rod system. This screen has allowed us to pinpoint some interesting and promising molecules. The aim of this project is to pursue target identification of these chemical compounds (genetic screens) and to unravel their mode of action (various biochemical assays). This approach will likely help us to identify new control points and targets in peptidoglycan assembly pathway for the development of novel therapeutics.
Project Status Details	Status	
	Years	Starts 01.09.2015- 01.03.2017
	Funding	62'256.25 €
	Follow up funding	Innosuisse, Switzerland
	Country	Switzerland
	Funder (s)	SNSF, Swiss National Science Foundation
	Info Source	SNSF, Swiss National Science Foundation
PI Details	Name	Coralie Fumeaux
	Institution	

PROJECT 21		
Project Technical Details	Title	Accelerate CHNUK AMR discovery: Establishing joint China/UK training and research platforms enabling high throughput fragment based inhibitor discovery
	Summary	The synchrotrons at Harwell (UK) and Shanghai (China) and the Drug Discovery unit at Dundee are powerful technology hubs. In particular Diamond Light Source is developing the first synchrotron beamline with an integrated high-throughput fragment based lead discovery (FBLD) platform and Dundee has established expertise in medicinal chemistry and drug discovery. We plan to integrate these hubs with AMR centres of excellence in China and the UK, deliver state of the art training to these researchers (and the wider AMR community) and exploit FBLD capabilities to identify novel chemical probes. These new chemical probes, alongside high throughput structural biology and mechanistic insight, will all importantly, help validate a range of novel AMR targets and provide the structural insight to build new effective inhibitors for these and the panel of well validated targets in cell wall and protein biosynthesis. Specialist workshops in China and the UK will deliver training and outreach to the wider community. To optimise and develop workflows at the interfaces between target production, fragment screening and medicinal chemistry and aid high-throughput characterization of novel targets two posts covering computational chemistry and structural biology are proposed. We will hold workshop(s) in UK, and China to attract new China academic and industry partnership and be guided by medicinal chemistry at Dundee and antibiotic discovery industry experts during the collaboration to prioritise chemical approaches. Two PDRAs are required, based at Harwell, one to support protein production and crystallography the other in silico modelling and in support of the X-ray crystallography-based FBLD platform. They will be involved in construct designing, cloning, protein production and purification, crystallization, Xchem fragment screening and data processing and analysis chemical docking and design. Moreover, the PDRAs will be involved in Harwell-based workshops and ongoing support.
Project Status Details	Status	
	Years	Starts 01.07.2016-01.07.2019
	Funding	843 793.98 €
	Follow up funding	MRC, Medical Research Council, UK
	Country	United Kingdom
	Funder (s)	MRC, Medical Research Council, UK
	Info Source	
PI Details	Name	CG Dowson
	Institution	

PROJECT 22		
Project Technical Details	Title	New Antibiotic Targets in Bacterial DNA Double-strand Break Repair
	Summary	DNA replication and repair is are essential processes in all organisms but are surprisingly different between eukaryotes and eubacteria. This proposal seeks to examine targets within the DNA double-strand break (DSB) repair for antibiotic development. A key component in bacterial DSB repair is the RecBCD/AddAB system that processes broken ends to prepare them for repair by homologous recombination. Using structural information gathered over the last 10 years we have identified a weakness in the AddAB mechanism that might be exploited. Extending our understanding of the mechanism and regulation of these complex systems will likely reveal additional opportunities for antibiotic development. In particular, understanding of specific aspects of regulation of RecBCD may provide opportunities for drug development. Quinolone antibiotics act upon DNA gyrase by stabilising a normally transient DSB during the enzyme mechanism. Mutations of a number of proteins other than DNA gyrase that are involved in DSB repair show sensitivity to quinolones and combinations will be sought that enhance sensitivity to quinolones in strains that carry mutant forms of RecBCD or AddAB that have lost regulation by Chi sequences. Finally, two new players in DSB repair in bacteria have recently been identified I propose to determine the molecular mechanism of these proteins to seek opportunities for exploitation in drug development.
Project Status Details	Status	
	Years	Starts 01.07.2016-01.07.2021
	Funding	1 917 332.94 €
	Follow up funding	MRC, Medical Research Council, UK
	Country	United Kingdom
	Funder (s)	MRC, Medical Research Council, UK
	Info Source	
PI Details	Name	D Wigley
	Institution	

PROJECT 23		
Project Technical Details	Title	An integrated mulTidisciplinary appRoach towards a new generAtIon of aNtibiotics: Targeting function and cross-talk of bacterial Envelope proTein machineries
	Summary	Train2Target is a multidisciplinary European Training Network built to address the challenge of the discovery of alternative antimicrobials. Innovative strategies to deliver a next generation of drugs are urgently needed. The alarming threats and spread of multi-drug resistant bacteria is currently leaving clinicians with very limited options to combat infections especially those from Gram-negative pathogens. The Train 2Target research programme focuses on the assembly of the well-known bacterial cell envelope from a new perspective. Indeed it aims to inhibit novel targets in envelope biogenesis by altering the function and misbalancing the coordination of envelope assembly machines, which build and assemble the Gram-negative bacterial envelope. A wide variety of chemical classes and compounds sources will be screened using innovative biochemical, biophysical and genetic assays to identify valuable hit scaffolds to be optimized into druggable leads. The high quality and credibility of our consortium is ensured by a strong interdisciplinary academia-industry partnership to encompass different complementary expertise ranging from microbiology, bacterial genetics, biochemistry, cell imaging, structural biology, biophysics and chemical synthesis. Our 9 academic groups are all renowned leaders in the cell envelope biogenesis field, whereas the complementary 5 SMEs and 3 Industry partners are specialised in drug discovery and development of novel anti-infective drugs. This unique combination of scientific excellence and industrial know-how in drug discovery covers the entire process from the design to the implementation of innovative antibacterial strategies and lead identification. Train2Target also represents a unique research platform to train 15 Early Stage Researchers and equip them with the necessary scientific and transferable skills that will make them highly competitive for both top European research institutions and the pharma/biotech job market.
Project Status Details	Status	
	Years	Starts 01.01.2017-01.01.2021
	Funding	3870919.8 €
	Follow up funding	EC, European Commission
	Country	
	Funder (s)	
	Info Source	
PI Details	Name	Alessandra Polissi
	Institution	

PROJECT 24		
Project Technical Details	Title	Novel drugs and drug combinations against bacterial growth, survival and persistence; from high-throughput screening to mechanism of action
	Summary	
Project Status Details	Status	
	Years	Starts 01.03.2016-01.03.2019
	Funding	253465 €
	Follow up funding	JPIAMR
	Country	
	Funder (s)	ZonMw, The Netherlands Organisation for Health Research and Development
	Info Source	
PI Details	Name	Athanasios Typas
	Institution	

PROJECT 25		
Project Technical Details	Title	Target identification and exploitation for novel broad-spectrum antibiotic
	Summary	In year funding runs till 31st March 2017 Aim is to generate information to determine whether previously identified targets are valid drug targets and to lay the foundations for future drug discovery programmes
Project Status Details	Status	
	Years	Starts 01.04.2015-01.04.2017
	Funding	3464466.54 €
	Follow up funding	
	Country	
	Funder (s)	MoD, Ministry of Defence, UK
	Info Source	
PI Details	Name	Andy Scott
	Institution	

PROJECT 26		
Project Technical Details	Title	Development of the assay system and discovery of novel antibacterial molecules against superbugs
	Summary	
Project Status Details	Status	
	Years	Starts 22.09.2014-31.03.2017
	Funding	2 469 230.77 €
	Follow up funding	National Research Foundation of Korea
	Country	
	Funder (s)	National Research Foundation of Korea
	Info Source	
PI Details	Name	Soojin Jang
	Institution	Institut Pasteur Korea

PROJECT 27		
Project Technical Details	Title	Mechanism and development strategy of new activity-modulating molecules with antibiotic effects for DegP protease
	Summary	
Project Status Details	Status	
	Years	Starts 01.11.2014-30.04.2017
	Funding	116 010 €
	Follow up funding	National Research Foundation of Korea
	Country	
	Funder (s)	National Research Foundation of Korea
	Info Source	
PI Details	Name	Seokhee Kim
	Institution	

PROJECT 28		
Project Technical Details	Title	Microbial Chemical Biology
	Summary	Multidrug resistant bacteria continue to be a health-care burden in both hospital and community settings. Remarkably, in the past fifty years, only a few new chemical classes of antibiotics have reached the clinic. Existing antibiotics are directed at a small number of targets, principally cell wall, DNA and protein biosynthesis. Indeed, multidrug resistance among bacterial pathogens is thought to be due in large part to a limited repertoire of antibacterial chemical matter. Recognizing the need for new therapies, the Brown research group is searching for novel chinks in the armor of bacteria for the design of truly novel antibacterial drugs.
Project Status Details	Status	
	Years	Starts 01.10.2013-30.09.2020
	Funding	933800 €
	Follow up funding	Canada Research Chairs - CIHR Funded
	Country	
	Funder (s)	CIHR, Canadian Institutes of Health Research
	Info Source	
PI Details	Name	Brown, Eric D
	Institution	

PROJECT 29		
Project Technical Details	Title	Health and Genomics
	Summary	Antibiotics are the underpinning of all modern medicine, but are being undermined by an explosion of (multidrug) resistance, and a dearth of new antibiotics. Hancock is on the one hand engaged in understanding the basis for antibiotic resistance, especially complex resistance mechanisms termed adaptive resistance, and on the other is developing novel approaches to anti-infective therapy based on cationic antimicrobial, immunomodulatory and anti-biofilm peptides. His engagement in studying the systems biology of innate immunity is shedding new light on the mechanisms of inflammatory diseases.
Project Status Details	Status	
	Years	Starts 01.01.2015-31.12.2021
	Funding	933800 €
	Follow up funding	Canada Research Chairs - CIHR Funded
	Country	
	Funder (s)	CIHR, Canadian Institutes of Health Research
	Info Source	
PI Details	Name	Hancock, Robert Ernest W
	Institution	

PROJECT 30		
Project Technical Details	Title	Antibiotic resistance, discovery and biosynthesis
	Summary	Antibiotic resistance is arguably the health care challenge of our time, threatening to roll back over a century of advances in medicine. My research program strives to address the resistance crisis by exploring the mechanisms and origins of drug resistance and discovering new molecules and strategies that can be applied in drug discovery or management of our existing drugs. I have been working in this field for over 25 years and have established a laboratory that has international recognition as a leader and innovator in drug resistance and discovery. The vision of the lab is to build on this success and tackle some of the most challenging issues in antibiotics, including how to source new drug candidates, how to protect the ones we have, and how to predict and manage the emergence of new resistance elements.
Project Status Details	Status	
	Years	Starts 01.07.2016-30.06.2023
	Funding	2832192.722 €
	Follow up funding	Canada Research Chairs - CIHR Funded
	Country	
	Funder (s)	CIHR, Canadian Institutes of Health Research
	Info Source	
PI Details	Name	Wright, Gerard D
	Institution	

PROJECT 31		
Project Technical Details	Title	Innovative microbial resources for new anti-infectives
	Summary	In spite of major technological advances in chemical synthesis, natural products from microorganisms continue to be the major source for novel chemical anti-infective scaffolds exhibiting new modes of action. Recent reports by DZIF members and others have demonstrated that innovative cultivation techniques provide immense opportunities for finding novel antibiotic classes produced by microbes previously considered "nonculturable". Therefore this collaborative project aims at improving the earliest stage of antibiotic discovery and filling the development pipeline with novel antibiotic hits. In a concerted action, four DZIF partner sites renowned for natural compound research will develop and apply new cultivation, production and screening technology for the identification of novel producer microbes and the isolation of new antibiotic compounds. Each partner site pursues, in a complementary setup, different techniques and focuses on different groups of microorganisms.
Project Status Details	Status	
	Years	
	Funding	
	Follow up funding	
	Country	Germany
	Funder (s)	
	Info Source	
PI Details	Name	Müller, Rolf
	Institution	Helmholtz-Zentrum für Infektionsforschung
PROJECT 32		
Project Technical Details	Title	Innovative microbial resources for new anti-infectives
	Summary	In spite of major technological advances in chemical synthesis, natural products from microorganisms continue to be the major source for novel chemical anti-infective scaffolds exhibiting new modes of action. Recent reports by DZIF members and others have demonstrated that innovative cultivation techniques provide immense opportunities for finding novel antibiotic classes produced by microbes previously considered "nonculturable". Therefore this collaborative project aims at improving the earliest stage of antibiotic discovery and filling the development pipeline with novel antibiotic hits. In a concerted action, four DZIF partner sites renowned for natural compound research will develop and apply new cultivation, production and screening technology for the identification of novel producer microbes and the isolation of new antibiotic compounds. Each partner site pursues, in a complementary setup, different techniques and focuses on different groups of microorganisms.
Project Status Details	Status	
	Years	
	Funding	
	Follow up funding	
	Country	Germany
	Funder (s)	
	Info Source	
PI Details	Name	König, Gabriele; Schäberle, Till
	Institution	Rheinische Friedrich-Wilhelms-Universität Bonn

PROJECT 33		
Project Technical Details	Title	Exploiting underexplored translation inhibitors and combinations thereof
	Summary	The bacterial ribosome is a hot spot for the action of many successful antibiotics. The aim of the project is to identify and characterize novel and/or underexplored protein synthesis inhibitors. For this purpose the Tübingen strain collection is screened by a B. subtilis promoter-based reporter gene system for the identification of new translation inhibitor producers. These strains will be analyzed with the aim to assign new metabolites to the observed antimicrobial and translation inhibitory activity. In addition, negamycin will be analyzed in more detail as a protein synthesis inhibiting substance with a novel binding site at the 30S ribosomal subunit. Selected derivatives of negamycin will be produced total synthesis and by mutasynthesis and subjected to biological evaluation. The identification of the negamycin gene cluster in the producer strain is mandatory for this approach. In addition, a process for the production of negamycin will be established. Combinations of the newly identified protein synthesis inhibitors and negamycin (and derivatives) will be analysed for synergistic activity.
Project Status Details	Status	
	Years	
	Funding	
	Follow up funding	
	Country	Germany
	Funder (s)	
	Info Source	
PI Details	Name	Mast, Yvonne; Stegmann, Evi
	Institution	Eberhard Karls Universität Tübingen

PROJECT 34		
Project Technical Details	Title	Innovative microbial resources for new anti-infectives
	Summary	In spite of major technological advances in chemical synthesis, natural products from microorganisms continue to be the major source for novel chemical anti-infective scaffolds exhibiting new modes of action. Recent reports by DZIF members and others have demonstrated that innovative cultivation techniques provide immense opportunities for finding novel antibiotic classes produced by microbes previously considered “nonculturable”. Therefore this collaborative project aims at improving the earliest stage of antibiotic discovery and filling the development pipeline with novel antibiotic hits. In a concerted action, four DZIF partner sites renowned for natural compound research will develop and apply new cultivation, production and screening technology for the identification of novel producer microbes and the isolation of new antibiotic compounds. Each partner site pursues, in a complementary setup, different techniques and focuses on different groups of microorganisms.
Project Status Details	Status	
	Years	
	Funding	
	Follow up funding	
	Country	Germany
	Funder (s)	
	Info Source	
PI Details	Name	Gerbach, Sina; Brakhage, Axel
	Institution	Hans-Knöll-Institut, Jena

PROJECT 35		
Project Technical Details	Title	Development of enzyme inhibitors against Acinetobacter baumanii strain as pharmaceutical compounds
	Phase	Discovery
	Target	No info
	Activity WHO PP	*Acinetobacter baumanii*
	WHO category	Priority 1
Project Status Details	Status	Completed
	Exact years	15/01/2015 - 31/12/2017
	Funding amount	€115,384.62
	Follow up funding	Cannot tell, no previous data
	Country	Korea
	Funder	Rural Development Administration, Korea
PI Details	Name	Prof. Linwoo Kang
	Institution	Rural Development Administration, KoreaTranslocation

JPIAMR joint calls 6 and 8

PROJECT 36		
Project Technical Details	Title	Restoring E. coli Sensitivity for Antibiotics by blocking TolC-Mediated Efflux
	Summary	Overexpression of efflux pumps is a major factor for drug resistance in Gram-negative bacteria. In E. coli, the AcrAB-TolC efflux pump complex transports antibiotics from the periplasm or cytoplasm into the external medium. As TolC deletion has been shown to result in increased susceptibilities of E. coli to several antibiotics, it may represent an attractive drug target. Recently, we have identified the first organic small molecule that effectively blocks TolC function using virtual screening in combination with experimental validation of the in silico hits by surface plasmon resonance (SPR) and electrophysiology studies. Building on these results, we propose to further develop this compound and in parallel to identify and develop novel TolC blockers within an interdisciplinary consortium. The already known blocker will be progressed in three rounds of optimisation. Each round comprises compound modifications by medicinal chemistry, assessment of TolC binding and blockage using SPR and electrophysiology, various antimicrobial studies and ADMETox profiling. Novel small molecules blocking TolC will be identified and optimised using the same experimental platform, starting with virtual screening for identification of novel compounds targeting TolC. Experimentally validated TolC blockers will be progressed in two rounds of optimisation. Ultimately, this approach will allow to assess TolC target validity for adjuvants in antimicrobial therapies and result in potent TolC blockers that may be further developed into drugs restoring E. coli susceptibility to antibiotics.
	Phase	Discovery - optimisation
	Target	TolC
	Expected activity WHO PP	*E. coli*
	WHO category	Priority 1
Project Status Details	Status	On-going
	Years	Starts Dec 2018/ early 2019 - Unknown end date
	Amount €	Cannot tell
	Follow up funding	New JPIAMR collaboration
	Country	JPIAMR Call 6, Project led by Germany
	Funder	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Björn Windshügel
	Institution	Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Germany

PROJECT 37		
Project Technical Details	Title	Exploration of the TPP riboswitch as a new target for antibiotics
	Summary	We will explore the TPP riboswitch as a new drug target for antibiotics for key ESKAPE pathogens (E. coli, K. pneumoniae, A. baumannii, P. aeruginosa, S. aureus) and Streptococcus pneumoniae. The TPP riboswitch has already been validated as a drug target, however, potent and drug-like ligands with antibiotic activity are needed as starting points to develop novel strategies for anti-infective treatments. The goal of this proposal is to deliver such compounds. Using an innovative assay technology, we will develop a high-throughput assay that monitors simultaneously transcription efficiency and the regulatory activity of the riboswitch, which is crucial for its action, and use this assay to screen the CZ- and EU-OPENSCREEN libraries of lead-like compounds. The hits obtained will be thoroughly validated and the most promising hits will be optimised to improve their affinity. The advanced compounds will be evaluated for antibiotic activity against the key ESKAPE pathogens and Streptococcus pneumoniae. We will also assess the broad-spectrum potential of the compounds and carry out mode of action studies to ensure that the compounds act on target. If the TPP riboswitch holds up to its high promises, this project will pave the way for urgently needed new antibiotics.
	Phase	Discovery – hit optimisation, assay technology
	Target	TPP riboswitch
	Expected activity WHO PP	*E. coli, K. pneumoniae, A. baumannii, P. aeruginosa*
	WHO category	Priority 1
Project Status Details	Status	On-going
	Years	Starts Dec 2018/ early 2019- Unknown end date
	Funding	No info
	Follow up funding	New JPIAMR collaboration (but previous funding received by PI/CO-Is e.g. Canada projects captured in 2014 db)
	Country	JPIAMR Call 6, Project led by Norway
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Ruth Brenk
	Institution	University of Bergen, Norway

PROJECT 38		
Project Technical Details	Title	TRANSLOCATION-transfer (follow up from IMI project)
	Summary	In response to the pharmaceutical industry stepping back from antibiotic discovery, multiple public efforts, including the JPIAMR and IMI ND4BB, as well as the efforts of Biomedical Science (BMS) European Research Infrastructures community have stepped in to fill the gap. In this project, the TT network will set up a knowledge sharing network, Translocation-Transfer bringing together experts from with two major publicly funded programs, with the goal to improve the process of academically driven antibiotic drug discovery by capitalising on recently gained insights into a key bottleneck in anti-bacterial research, namely how compound penetration properties determine efficacy and resistance properties. Three existing communities forming the TT network are: 1) the partners associated with the multinational program Translocation (www.translocation.eu), part of IMI ND4BB; 2) partner sites from EU-OPENSCREEN, the European Research Infrastructure for chemical biology and screening (www.eu-openscreen.eu); 3) partners from the wider global community working on AMR issues and research.
Project Status Details	Status	On-going
	Years	Starts Dec 2018/ early 2019 - Unknown end date
	Funding	€50,000
	Follow up funding	New JPIAMR collaboration
	Country	JPIAMR Call 8, Network led by Germany
	Funder (s)	JPIAMR Member States
	Info Source	JPIAMR website
PI Details	Name	Mathias Winterhalter
	Institution	Jacobs University Bremen, Germany
PROJECT 39		
Project Technical Details	Title	Development of novel ribosome-targeting antibiotics
	Summary	The ribosome is one of the major targets for antibiotics. Multi-drug resistant pathogens are making our current arsenal of ribosome-targeting antibiotics obsolete, highlighting the need for development of new antimicrobial compounds. Here we focus on discovering novel ribosome targeting antibiotics with improved activity and selectivity, with chemical scaffolds that target novel sites on the ribosome and different steps of the translation cycle.
Project Status Details	Status	Cannot tell
	Years	Starts Dec 2018/ early 2019 - Unknown end date
	Funding	Cannot tell
	Follow up funding	
	Country	Germany
	Funder (s)	New JPIAMR
	Info Source	
PI Details	Name	Daniel Wilson
	Institution	University of Hamburg

APPENDIX 7

Limitations

JPIAMR DATABASES – general comments:

This analysis was undertaken with certain limitations, including reliance on data available in the source databases, in the public domain and input from the GARDP team, which may raise the potential for selection bias.

The data analysis highlighted several gaps in information, it is therefore likely that some projects of potential interest to GARDP were missed simply due to lack of information available.

Most of the projects in the JPIAMR mapping database do not have enough information to identify specific details (e.g., stage of development, target of small molecule, activity against specific pathogens, etc.).

Discovery phase information was not specified in JPIAMR databases and is rarely specified in project titles or abstracts, and when informed, the scope and stage gates of the different discovery phases are likely to have different meanings/criteria across project types and organisations.

For most projects, the status (as of Jan. 2021) was not informed. However, given the high attrition rate inherent to the discovery process, many these projects may be expected to fail to deliver molecules to progress after the end of the funding period.

The geographical distribution of projects in JPIAMR databases was limited to JPIAMR member states at the time the databases were published and thus mostly Europe-centric with the notable exceptions of Canada, Japan, and South Korea.

JPIAMR data does not include comprehensive data from all countries, i.e., not all funding agencies data within a country are included, although this improved from the 2014 to 2017 dataset. By 2020, JPIAMR has 28 member states. The additional countries that were not represented in the 2014 and 2017 calls are: Denmark, Greece, India and Moldova. In 2017, 4 countries were not represented in the 2014 call: Argentina, Japan, South Korea and South Africa. Denmark, Poland, Portugal, and Romania were represented in 2014 call, but not in 2017 call.

Only competitive grants are captured, and core/institutional funding is not, although JPIAMR have future plans to map this information.

IN THE 2014 JPIAMR DATABASE:

Since it was published in 2014, there were issues with end dates in the spreadsheet available on-line. For example, some end dates are before the start date of a project. This did not affect the GARDP horizon mapping. JPIAMR were given a copy of the preliminary report in December 2019.

IN THE 2017 JPIAMR DATABASE:

Not all information was provided in English; this meant Google translate had to be used for the titles, which took extra time.

Principle investigator and organisation/university details were not provided. This made it difficult to find more information on the project and it limited the ability to follow up on potential projects of interest and took extra time to identify the researchers details from the information provided. In general, it reduced the use of the database for researchers, organisations, and initiatives to identify collaborators/ partners etc.

Title of the projects were only included, i.e., no summaries of the projects were provided. Therefore, internet searches to find out more information for some projects and information were required. These were searched for based on title of project only (as no PI name or institution provided) and therefore for some projects were not identified.

Inconsistencies in the classification (based on JPIAMR six priority areas[6]) of projects was identified. The most likely reason was that the information provided publicly was not sufficient, i.e., the title did not give an accurate reflection of the work conducted, and the JPIAMR analyst had further information to make a judgement; or the classification was not fully accurate because they too did not have enough information to make an informed decision. However, the JPIAMR mapping report states that national representatives within each country validated the data and so did the analysis. An individual analyst was responsible for classifying the projects with support from one other person, and classification was done using the title, and summary or abstract provided. Therefore, the former reason is more likely.

- For this horizon scanning project, this meant all 1,939 projects were considered instead of just the 1,138 classified as therapeutics.
- However, when the results in the "yes, maybe and cannot tell" categories were checked all were included in the therapeutics category.
- It is therefore likely that if there were inaccuracies in the classification, or uncertainties in what category a project should be in, it was placed in the extremely broad "therapeutics" category. A consequence is that this inflates the amount of funding for this area.

As insufficient information was provided it was not possible to determine if a project captured in the 2014 database received follow up funding and was therefore captured in the 2017 database.

Basic research without reference to AMR was included in this 2017 database. It is likely most of those projects were not captured in this horizon scanning. However, this cannot be quantified as no summaries were provided and scanning was based on project titles.

- If this did occur, projects are more likely listed in the "Cannot tell" category.

6 Therapeutics, Diagnostics, Surveillance, Transmission, Environment, Interventions.

GARDP

Global Antibiotic Research & Development Partnership (GARDP)

15 Chemin Camille-Vidart, 1202 Geneva
Switzerland