AMR Accelerator Programme – Pillar C: Portfolio Building Networks to advance the R&D pipeline of new and innovative agents to address AMR Topics

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topics:

Topic 1: Progress new assets (one pre-new molecular entity (preNME) and one first-time-in-human (FTIH) start) for tuberculosis (TB) that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline and cytochrome bc drugs

Topic 3: Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

Topic 5: Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections

Topic 6: Functional Ethionamide boosters: a novel combination for tuberculosis therapy

Topic 7: Intravenous treatments of serious infections (urinary tract infections (UTI), intra-abdominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- *Pseudomonas* and/or *Acinetobacter*)

Topic details

Topic code	IMI2-2018-16-01 IMI2-2018-16-02 IMI2-2018-16-03 IMI2-2018-16-04 IMI2-2018-16-05 IMI2-2018-16-06 IMI2-2018-16-07
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	single-stage

Specific challenges to be addressed

The Portfolio Building Network (PBN), Pillar C of the IMI2 JU AMR Accelerator programme, will address the limited pipeline of treatments and preventions for AMR infections by enabling vibrant and

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nimble collaborations between EFPIA companies and small and medium-sized enterprises (SMEs) and/or academics that will advance the R&D pipeline of new and innovative agents to address AMR.

Scope

The PBN will provide a mechanism for partnerships between EFPIA constituent and affiliated entities and SMEs and/or academic teams for the discovery and development of new antibacterial assets to address the broad topic of AMR including Gram-positive and Gram-negative bacteria, including tuberculosis (TB) and non-tubercular mycobacteria (NTM) and prevention (vaccines/mAbs, immunoprophylaxis and others) and treatment (new antibiotics, non-antibiotic alternatives, and combinations) approaches. Assets and projects can originate from SMEs, academia, or EFPIA companies, and will be jointly progressed, including potentially pre-clinical and clinical development work. The potential generation of new clinical pathways, or the potential contribution to regulatory pathways for pathogens such as NTM is included in the scope, as is the conduct of phase 2 TB trial(s). Consortia arising from the IMI2 JU Call 16 topics may have a limited number of partners, and will require the participation of an EFPIA partner (e.g. 1 EFPIA partner + 1 SME/academic partner) (see details under the section '*Applicant consortium*').

There are seven topics under the current single-stage Call topic described below. Additional single-stage Calls may be published in the future.

Topics 1-3: Advancing a portfolio of novel compounds with the potential to treat TB and NTM

The goal of these actions is to develop and advance a portfolio of anti-TB drugs that may be used in combination with bedaquiline and cytochrome bc inhibitors to shorten treatment regimens and improve safety and efficacy.

Bedaquiline, currently in Phase 3 clinical development, is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adults with pulmonary multi drug resistant tuberculosis (MDR TB). It specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*. The cytochrome bc inhibitor 901 is in the late lead optimisation phase.

IMI2 JU Call 16, topics 1-3 target different innovative novel assets, mechanisms and combinations for TB.

Topic 1: Progress new assets (one preNME and one FTIH start) for TB that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

These compounds can target any stage of energy metabolism, including ATP synthase, cytochrome bc and bd, NDH-2, menaquinone synthesis, but also glycolysis and the citric acid cycle, or any other metabolic pathway. Other assets, targeting the host cell instead of the bacilli itself, are also potentially interesting to combine with energy metabolism inhibitors.

The scope of this topic will be to identify and progress novel lead compounds towards design and implementation of phase 1.

As part of the project objectives, several models and tools are needed to further profile the targets of the respiratory chain and evaluate the effect of the combinations, that include but are not limited to:

Evaluation in several *in vitro* and *in vivo* models including but not limited to dormancy models, models to characterise the response to the antibiotic in real time, models to study the interaction between *M. tuberculosis* and human bronchial epithelial cells, evaluation of infected macrophage models and animal zebrafish larvae pharmacokinetics / pharmacodynamics (PK/PD), animal mouse infection models as follows:

- perform structural characterisation of cytochrome bd and bc targets;
- generation/access to a library of MTB mutants to profile cytochrome bc and bd inhibitors;
- progress assets to FTIH by evaluation of the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to evaluation of mitochondrial toxicity);
- design and implementation of phase 1 studies towards the development of TB candidates.

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Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline, and cytochrome bc drugs

The project goal is to develop and advance a portfolio of anti-NTM drugs that may be used in combination with bedaquiline and cytochrome bc inhibitors to shorten treatment regimens and improve safety and efficacy.

The EFPIA partner's internal assets as well as external compounds will be profiled alone and in combination. The scope of this topic will be to progress novel lead compounds by performing medicinal chemistry optimisation, *in vitro* and *in vivo* characterisation, as well as PK, toxicology studies, formulation and CMC (chemistry, manufacturing and controls) studies. The scope also includes implementation of phase 1 studies towards the development of novel NTM candidates. For this topic, expertise in the field of NTM is necessary. The activities of this topic include but are not limited to:

- generation/access to a library of NTM mutants and access to an extensive panel of NTM isolates to profile cytochrome bc and bd inhibitors;
- *in vitro* and *in vivo* efficacy testing (including but not limited to determination of minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and time-kill kinetics), animal mouse infection models, animal zebrafish larvae PK/PD, and profiling of new agents/combinations in a panel of NTM clinical isolates and in Gram negative and Gram positive bacteria;
- progress assets to FTIH by determining the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to the evaluation of mitochondrial toxicity);
- design and implementation of phase 1 studies towards the development of NTM candidates;
- expertise (key opinion leaders (KOL)) in clinical treatment of NTM and treatment outcomes is crucial.

Topic 3: Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

Novel assets with new mechanisms of action will be identified through high throughput screening campaigns for TB and NTM, with a special focus on *M. avium* complex. Novel screening platforms and tools are needed for this evaluation. The resulting hits will be profiled and further optimised *in vitro* and *in vivo*. In addition, a better understanding of the host-mycobacteria interaction and the impact of coexisting viral infections can provide insights about biomarkers and new targets for mycobacteria**.**

The objectives include, but are not limited to the following.

- The development of high throughput assays to test TB and NTM in *in vivo* relevant conditions. Target identification and characterisation including exploration of mechanism of action by transcriptomics and the generation of resistant mutants.
- *In vitro* and *in vivo* efficacy testing (including but not limited to determination of minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and time-kill kinetics), animal mouse infection models, animal zebrafish larvae PK/PD, and profiling of new agents and combinations in a panel of clinical isolates and in Gram negative and Gram positive bacteria as appropriate.
- Progress assets to FTIH by determining the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to the evaluation of mitochondrial toxicity).

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

Gepotidacin (GSK2140944) is a novel antibiotic that selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism, which is not utilised by any currently approved human

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therapeutic agent. Structural data with a type II topoisomerase, DNA gyrase, reveals the novel binding mode of the triazaacenaphthylene class and distinguishes it from the binding mode of the quinolone antibacterials. As a consequence of its novel mode of action, gepotidacin is active *in vitro* against most target pathogens carrying resistance determinants to established antibacterials, including fluoroquinolones. Gepotidacin has broad Gram positive activity and selective Gram negative activity.

With increasing antimicrobial resistance, there are fewer options to treat gonorrhoea (Centers for Disease Control and Prevention (CDC) and World Health Organisation (WHO) urgent need), in particular at the pharyngeal site where tissue penetration is essential to activity and extended spectrum beta-lactamases (ESBL)/MDR (CDC and WHO serious need) urological infections due to *Escherichia coli*. In addition, few orally available agents have favourable penetration characteristics which are essential to activity.

The topic goal would be to assess penetration of gepotidacin in the following groups.

- Tonsils following elective tonsillectomy in adults aged >18 years or adolescents aged 12-17 years. 20 evaluable subjects willing to participate would receive a single oral or intravenous dose of gepotidacin at defined timepoints prior to tonsillectomy. Gepotidacin levels will be measured in homogenates or extracellular fluid using validated methods that may include *ex vivo* microdialysis.
- Prostatic tissue following elective prostate biopsy or TURP in adult males. 20 evaluable subjects willing to participate would receive a single oral dose of gepotidacin at defined timepoints prior to TURP or prostate biopsy. Gepotidacin levels will be measured in homogenates or extracellular fluid using validated methods that may include *ex vivo* microdialysis.

Topic 5: Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections

The topic goal would be threefold:

to identify a bacterium or infection site targeting ligand (small molecule preferred);
to incorporate this ligand into a nanoparticle system which can be retained selectively in infected tissues for long periods;
to encapsulate an appropriate antibiotic into the targeted nanoparticle and confirm improved efficacy over the free antibiotic and non-targeted encapsulated antibiotic, driven by higher local concentration at the infection site, in addition to other criteria such as reduced toxicity or side effects, longer half-life, etc.

Topic 6: Functional Ethionamide Boosters: a novel combination for tuberculosis therapy

The topic goal is to generate a small molecule clinical candidate that can boost the activity of Ethionamide and revert the existing resistance to this drug, by acting on bacterial transcriptional regulators. The associated, dose dependant side effects for Ethionamide observed at the currently required human doses together with the high pre-existing levels of resistance in patients has limited the use of Ethionamide as a TB front-line agent. However, Ethionamide is considered an essential drug for MDR-TB treatment even today and could well be positioned back into first line, replacing Isoniazid as the ‘fast killing’ agent acting on mycolic acid synthesis, once the bio-activation of Ethionamide is optimal. This project aims at identifying novel small molecules that are capable of:

a) increasing the level of bioactivation of Ethionamide, therefore reducing the levels of ETH required to achieve maximal efficacy both *in vitro* (>10-fold) and *in vivo* (>3-fold);
b) revert pre-existing ETH clinical resistance using a very low oral dose.

This will make it possible to open up the scope of the ETH field of use to both drug sensitive and multi-drug-resistant (MDR) patients. This project intends to progress these new compounds from the candidate selection stage to a proof of concept as Ethionamide booster in TB patients.

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Topic 7: Intravenous treatments of serious infections (urinary tract infections (UTI), intra-abdominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- *Pseudomonas* and/or *Acinetobacter*

In the various threats encompassed in the global AMR crisis, Gram(-) bacteria and especially ESBL-producing and carbapenemases-producing *Enterobacteriaceae* consistently rank among the most problematic organisms for which novel ways of managing the infections they cause are lacking. The scope of this topic will be to progress novel lead compounds against these organisms by performing medicinal chemistry optimisation, *in vitro* and *in vivo* activity characterisation, as well as PK, ADMET, formulation and CMC studies. A particular focus will be on compounds identified from phenotypic screens of natural product extracts / libraries, and on compounds identified through non-traditional phenotypic screens (i.e. screens in non-traditional rich media and/or screens where a proxy for bacterial cell death is employed). These require specific areas of expertise in natural products (fermentation, dereplication and microbial genetics), as well as medicinal chemistry applied to natural products (including hemi-synthesis), for instance. In addition, expertise in novel approaches to de-orphan lead compounds and strong translational capabilities will be particularly useful to progress these compounds and evaluate potency as well as toxicity and resistance liabilities

Expected key deliverables

Topic 1: Progress new assets (one preNME and one FTIH start) for TB that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

- one preNME candidate for TB;
- profiling and phase 1 studies of a novel TB preclinical candidate to deliver a phase 2 ready TB asset.

Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline, and cytochrome bc drugs

- profiling and phase 1 studies of a novel NTM preclinical candidate to deliver a phase 2a ready NTM asset.

Topic 3*:* Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

- two preNME candidates, one for TB and one for NTM.

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

- plasma samples, tissues homogenates and possibly extracellular unbound levels of novel antibacterial in the tonsils following oral or intravenous dosing;
- pharmacokinetic analysis to evaluate penetration and exposure in the tonsils;
- plasma samples, tissue homogenates and possibly extracellular unbound levels of novel antibacterial in the prostate following oral dosing;
- pharmacokinetic analysis to evaluate penetration and exposure in the prostate.

Topic 5: Infection site targeting, antibiotic encapsulated nanoparticles for treating extracellular bacterial infections

- one candidate-selection of an infection site targeting, antibiotic encapsulated nanoparticle system for treatment of extracellular bacterial infections.

Topic 6: Functional Ethionamide boosters: a novel combination for TB therapy

- clinical candidate ready to enter into phase 2 for the treatment of tuberculosis;
- preclinical candidate backup on a different chemical series.

Topic 7: Intravenous treatments of serious infections (UTI, IAI & HAP/VAP) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter

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- up to two NMEs having completed preclinical profiling, including GLP toxicity studies so as to be ready to enter into phase 1 studies;
- up to four NMEs having completed lead optimisation process (showing acceptable *in vitro* and *in vivo* activities and toxicity/resistance profiles) so as to be ready to enter phase 1 enabling studies such as GLP toxicity studies.

Expected impact

The expected impact of actions selected under this Call will be to:

- contribute to the development of a vibrant AMR research environment in the EU and strengthen the competitiveness and industrial leadership of Europe;
- contribute to the EU's ambition of being a 'best practice region' for addressing AMR;
- enhance the overall pipeline of medicines for patients with AMR infections and advance new and innovative agents.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Example of relevant IMI/IMI2 JU and non-IMI projects include:

- aspects of the research of ND4BB TRANSLOCATION (http://www.nd4bb.eu/) (e.g. the ND4BB Information Centre as a possible framework for data sharing);
- ND4BB ENABLE project (http://nd4bb-enable.eu/);
- ND4BB COMBACTE projects and iABC Programme, (https://www.combacte.com; http://www.iabcproject.com) in particular in relation to networks (CLIN-NET, LAB-NET, STAT-NET and EPI-NET);
- projects funded by other organisations/programmes supporting AMR R&D e.g. the EU Framework Programmes for Research and Innovation FP7 and Horizon 2020, the Joint Programming Initiative AMR, Wellcome Trust, Biomedical Advanced Research and Development Authority (BARDA), Medical Research Council (MRC), CARB-X, Global Antibiotic Research and Development Partnership (GARDP), National Institute of Allergy and Infectious Diseases (NIAID), TB Alliance and TB Drug Accelerator etc. to ensure synergy and avoid duplication of research.

Indicative duration of the actions

The indicative duration of the actions under the different topics is shown below. Due to the uncertain nature of drug discovery and development, a shorter duration could be envisioned depending on the scientific progress of the project.

Topic 1: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 2: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and

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progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 3: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 4: 18 months

Topic 5: 36 months

Topic 6: 48 months

Topic 7: 72 months

Indicative budget

The IMI2 JU financial contribution is a maximum of EUR 46 900 000 for this Call. The IMI2 JU maximum financial contribution for each topic is:

Topic 1: EUR 6 840 000

Topic 2: EUR 5 690 000

Topic 3: EUR 1 770 000

Topic 4: EUR 7 300 000

Topic 5: EUR 6 000 000

Topic 6: EUR 7 000 000

Topic 7: EUR 12 300 000

Proposals will be ranked under each topic separately. Under each topic, only the top ranked proposal will be selected for funding within the budget available under each topic.

Applicant consortia

The applicant consortia will be selected based on submitted proposals. Each applicant consortium must include at least one EFPIA constituent or affiliated entity, i.e. EFPIA company. This requirement is justified by the particular nature of the scientific challenge to be addressed under these topics. One of the goals of the European One Health Action Plan against AMR is ‘to increase the development and availability of new effective antimicrobials inside and outside the EU’. EFPIA companies are uniquely placed to have the capability to ensure that during the rapid progression of new compounds and candidate drugs and vaccines in the projects to be selected, all the relevant regulatory and other requirements from jurisdictions around the world are appropriately considered, so that the data generated can be used when regulatory filings will be made.

The applicant consortia (e.g. EFPIA company + SME) may be limited in size but they must involve at least two independent legal entities established in different EU Member States, or countries

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associated to Horizon 2020[1], while addressing all of the objectives and having the necessary expertise to produce the deliverables and ensure the expected impact of the topic they are applying to. The condition for having a minimum of two legal entities is justified by the specificity of the AMR return on investment (RoI) where small consortia are sufficient to rapidly progress towards the development of new compounds while maintaining the agility of operations.

Applicants are expected to take advantage of and exploit support from different stakeholders with the necessary expertise, including the mobilisation of funds through the inclusion of contributing partners under the IMI2 JU framework of public-private consortia. Such contributing partners may include, in addition to EFPIA companies (i.e. its constituent or affiliated entities), Associated Partners to IMI2 JU.

Topics 1-3: Advancing a portfolio of novel compounds with potential to treat TB and NTM

To achieve the scientific objectives of topics 1-3, each applicant consortium is expected to mobilise as appropriate, and taking into account the .cope of the different topics as described above, the following capabilities:

- Discovery capabilities including but not limited to:
  - development of animal infection models, to improve reproducibility and predictability for both single drugs and combinations;
  - development of dormancy models, such as RPF-dependent mycobacteria, low-oxygen recovery assay, nutrient starvation;
  - development of *in vitro* models to characterise the response to antibiotics in real time, such us reported-based growth inhibition and time-kill kinetics, and real-time single-cell analysis in a microfluidic device;
  - development of infected macrophage models to study the effect of single drugs and combinations, including direct antibacterials and host-directed compounds, as well asexploration of the secretome of lung epithelial cells upon interaction with mycobacteria to identify new targets and biomarkers;
  - exploration of mechanism of action, transcriptomics, generation of resistant mutants and characterisation of targets: purification, crystallisation and modelling;
  - profiling new inhibitors/ combinations in a panel of clinical isolates, and in Gram negative and Gram positive bacteria;
  - Expertise in high throughput screening campaigns.
- Basic preclinical research capabilities to be able to develop and conduct specific PK/PD studies/models and tolerability studies including toxicology profiling, non-GLP and GLP toxicology profiling.
- PDMS (GMP manufacturing and formulation development) including capacity for long acting formulations of agents and combinations, and also including scale-up synthesis of non GMP and GMP selected candidates.
- In addition, applicants should have access to a network of patients of different socio-economic backgrounds on mycobacterial therapy and/or paediatric patients with underlying lung disease and carrying a mycobacterial infection.
- In depth infectious disease (TB, NTM) expertise, operational and quality capabilities required to design, implement, conduct, collect and analyse full data (bio, microbiology and clinical), and draft/finalise clinical study reports. Significant documented track record on the conduct of registrational phase 1 clinical studies in healthy volunteers, TB and/or NTM patients is mandatory.
- To achieve the objectives of topics 1-3, bedaquiline and cytochrome bc/bd inhibitors could be brought to the combination, as well as expertise in discovery and development activities.
- Access to compounds in the field of TB/NTM.

[1] http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/3cpart/h2020-hi-list-ac_en.pdf

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Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- access to patients undergoing tonsillectomy;
- access to patients undergoing TURP or prostate biopsy;
- experience with clinical trials;
- training in International Council of Harmonisation (ICH) guidelines and good clinical practice (GCP);
- expertise and capacity to perform PK analysis.

Topic 5: Infection site targeting, antibiotic encapsulated nanoparticles for treating extracellular bacterial infections

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- experience with bacterial or infection site targeting;
- experience with nanoparticles with clear regulatory path, e.g. nanoparticles that have reached suitable levels of drug development (e.g. phase 3 or marketed, for any indication, not necessarily for infectious disease) as a demonstration that there are no insurmountable technical or regulatory challenges;
- experience with the incorporation of surface modifications of nanoparticles;
- experience in production, characterisation, and scale-up of nanoparticles, including preferably GMP-production;
- experience and capacity to run *in vivo* animal models of infection;
- experience in running rodent toxicology studies, including immunotoxicology, with nanoparticle agents;
- experience with preclinical PET imaging;
- experience working with regulators.

Topic 6: Functional Ethionamide boosters: a novel combination for TB therapy

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- experience with the use of bacterial transcriptional regulators;
- experience with bacterial or infection site targeting;
- experience setting up, validating, and running In vitro biochemistry assays;
- experience in using HPLC/mass spectrometry for the identification of metabolites;
- experience and capacity to run *Mycobacterium tuberculosis* animal models of infection including PK/PD;
- experience in running toxicology, pharmacokinetics and pharmaceutical development studies, including human dose projection;
- experience with preclinical PET imaging;
- experience in active pharmaceutical ingredient (API) production;
- experience working with regulators;
- GMP manufacturing / CMC / clinical experience;
- medicinal chemistry experience.

Topic 7: Intravenous treatments of serious infections (UTI, IAI & HAP/VAP) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- compounds and expertise in novel phenotypic screening assays, including the expertise in new natural products (fermentation, extract purification, dereplication);
- expertise in technologies necessary to quickly de-orphan hits from phenotypic screens;

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- expertise in approaches and techniques to translationally validate novel mode of action to the clinical situation; expertise and capacity in medicinal chemistry, microbiology, pharmacology and early ADMET optimisation programmes as well as pharmaceutical development techniques to maximise the evaluation of the therapeutic index of novel compound;
- expertise in innovative PK/PD approaches, including hollow-fibre models;
- expertise in development of companion diagnostics and biomarkers, enabling special stratification and/or monitoring of treatment response such as, for instance, antibody-focused and/or broader immune profiling of patients.
- ability to perform preclinical development studies (e. g. GLP toxicity studies, formulation, synthesis of material of clinical degree);
- ability to undertake first into human studies (FTIH) on heathy volunteers to determine key pharmacokinetic parameters in humans.

Note that, as stated above, the scope of this topic will be to progress novel ead compounds. These lead compounds should be proposed by the applicant consortium and might come either from the EFPIA company or from any other partner of the consortium. Thus, in addition to or in place of novel compound(s), novelty brought in by the applicant consortium might be new tools, new competence and/or specific knowledge in a novel targeted pathway that are applicable to the progression of an EFPIA compound.

Note regarding all topics

Note that for all topics, most day-to-day management such as rigorous project, programme, and alliance management (including but not limited to supporting the coordinator in the management of scientific and financial reporting, prosecution of legal agreements such as confidentiality agreements (CDA), material transfer agreements (MTA), meeting facilitation and secretariat) of projects across the Accelerator will be supported by the coordination and support group within the CBN (established through the IMI2 JU Call 15, topic 7 action). Therefore only minimal project and financial management capabilities will be required from the applicant consortium in the PBN.

In addition, representatives from all selected projects will contribute to an advisory and communications board (containing independent experts and representatives from all the projects running in the AMR Accelerator) created as part of the coordination and support group within the CBN. This group will meet regularly to share summary level, non-confidential progress reports on projects and where appropriate make recommendations to the AMR Accelerator overall.

Suggested architecture of the full proposal

The applicant consortia should suggest complete architectures in the submitted proposals.

Decision making: Each applicant consortium must agree on a fair and robust go/no-go decision-making process to ensure that only the most promising compounds or approaches are pursued. Note that go / no go milestones will need to be proposed in each proposal and later formalised in the relevant Annex 1 of the Grant Agreement, and consortium agreement. These milestones will then assist in the decision-making process to help ensure that projects funded under the PBN remain dynamic.

Each consortium's decision making would be governed by a committee whose makeup will take into account the nature and scope of the work planned, and be detailed in the respective consortium agreement and agreed to by all partners. The committee must include at least one independent expert to be selected by a process established by the full consortium and to be detailed in the consortium agreement. This committee will track the progress of the project against its own internal milestones and will be empowered (as outlined in each project's consortium agreement) to make recommendations for progression/stopping tasks based on each consortium's pre-agreed go / no go milestones in an e.g. quarterly, streamlined, single-meeting process. It is anticipated that the consortium agreements will be structured such that independent experts can recommend termination or continuation of a project, but they cannot force a project to continue if all partners suggest termination. The decision-making process by the committee may result, in case of 'no-go' decision, in the recommendation from the committee/consortium to IMI2 JU for terminating the grant based on Art. 50.3.1 (h) of IMI2 JU MGA. The final decision about the project continuation or termination will be

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taken by the IMI2 JU in line with the provisions of the Grant Agreement. However, the JU may also make such a decision without prejudice to any decision-making process at the level of the consortium, i.e., even without the aforementioned recommendation.

Applicants to Calls launched as part of the Accelerator should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement, as well as a short questions and answers document available at https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf.

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