Antimicrobial resistance (AMR) Accelerator Programme

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.

Introduction to the AMR Accelerator programme

Background and problem statement

The discovery and development of new antimicrobials to address antimicrobial resistance (AMR) is an undisputed European and global challenge that is compounded by a low return on investment (RoI) for the pharmaceutical sector. This has subsequently led to a reduction in resources applied across the pharmaceutical industry and a decline in scientific discoveries. Overall this situation has compromised the delivery of new options to treat and prevent resistant infections. This was highlighted in the European One Health Action Plan against Antimicrobial Resistance (for more info please visit the following link: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf). Beyond Europe, it is of note that AMR is one of four public health concerns that has been raised to the level of discussion at the UN General Assembly (September 2016), putting it on par with subjects such as HIV and Ebola. Additionally, drug resistant tuberculosis (TB), the largest single contributor to AMR health, mortality, and economic impact, is scheduled to be discussed by Heads of State at the UN General Assembly (September 2018).

There are significant scientific challenges to the discovery and development of new agents to treat and prevent AMR infections, including those caused by Gram-positive and Gram-negative bacteria, Mycobacterium tuberculosis, and non-tubercular mycobacteria (NTM). As an example, despite there being an extensive number of essential bacterial targets, no novel mechanism antibiotics for Gram-negative infections have been approved in 40 years.

Furthermore, despite some recent progress, we have a poor understanding of how to rationally design potent small molecules that are optimised to treat life threatening Multi-Drug Resistant (MDR) Gram-negative pathogens. Models, approaches, and tools developed by large pharma or public entities to support antibiotic drug development need to be validated and shared more widely to serve the AMR community at large. At the same time, alternative approaches to treating infections require robust validation. The same is true for platforms that enhance the success of vaccines and monoclonal antibodies, or new imaging platforms to measure pharmacodynamic responses at the site of action.

In TB, the world's leading infectious disease killer with 1.7 million deaths in 2016, (from WHO TB report 2017 Executive Summary at the following link, http://www.who.int/tb/publications/global_report/Exec_Summary_13Nov2017.pdf) there is an acute need for the development of a novel combination regimen with an indication for the treatment of any form of TB ('pan-TB regimen') that will be more effective, shorter, and safer than current existing options, this applies to all types of TB (Drug-Sensitive (DS), Multi-Drug Resistant (MDR) and eXtensively-Drug Resistant (XDR-TB)). This pan-TB regimen would encompass at least three new chemical entities, with properties better suited to protect against emerging resistance both individually as well as in combination. Many scientific hurdles must be overcome to understand how multiple chemical entities

can be combined most successfully, keeping synergistic drug activity, drug-drug interactions, and translational aspects in mind. Regimen development in TB, has provided and will continue to lead to learning that will help to develop new treatments, including combination regimens, for other infections that have relied on mono-therapy thus far.

Overall objectives of the AMR Accelerator

The aim of the AMR Accelerator is to progress a pipeline of potential medicines to treat patients with resistant bacterial infections in Europe and across the globe. Specifically, if successful, projects in the Accelerator are expected to deliver up to >10 new preclinical candidates and >5 'Phase 2-ready' assets.

The AMR Accelerator will provide, under one operational structure, a wide-ranging series of projects that will address many of the scientific challenges in AMR. The scientific scope will be broad, including prevention (vaccines/mAbs, immunoprophylaxis) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). For clarity, the term 'AMR' should be interpreted to include Gram-positive and Gram-negative bacteria, tuberculosis (TB) and non-tubercular mycobacteria (NTM). Within this broad scope, projects in the Accelerator will develop new pre-clinical tools and methods, validate alternative or 'non-traditional' approaches, progress potential new treatments through Phase 1-3 clinical trials, and analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The Accelerator will also potentially generate new clinical/regulatory Phase 2-3 pathways. The AMR Accelerator will complement and augment the capabilities of the IMI ND4BB programme.

Progression of successful assets beyond the scope of the Accelerator (Pillar-dependent, see below) may occur, as appropriate, by other mechanisms such as EU funding programmes within Horizon 2020 (including SME instruments) or future Framework Programmes, InnovFin instruments, Structural Funds, Venture Capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance– January 2016 or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance – September 2016 (https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf[1]) should be taken into account.

The Accelerator will contribute to one of the 3 Pillars of the European One Health Action Plan against Antimicrobial Resistance *'Boosting research and development and innovation in AMR'* (June 2017: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf). The Accelerator will also directly address the IMI2 JU objective of *'develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance'* (Article 2(b)(iii) of the Council Regulation establishing IMI2 JU: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0557)

AMR Accelerator programme structure

The AMR Accelerator programme consist of three pillars under which multiple projects are expected:

- **Pillar A:** Capability Building Network (CBN)
- **Pillar B:** Tuberculosis Drug Development Network (TBDDN)
- **Pillar C:** Company-specific Portfolio Building Networks (PBNs)

In 2018 two calls are launched to cover the three pillars, one two-stage call (call 15) with two topics for pillars A and B, and one single stage call (call 16) with 7 topics for pillar C.

[1] For example, points 3 and 4 from the 'Roadmap for Progress'.

Applicants may submit a proposal to any of the topics under the different pillars and are not obliged to apply for all. If applicants wish to submit for more than one topic under the same or different pillars, separate proposals should be submitted.

Future call for proposals could be launched at a later stage to select under each pillar additional research projects or networks depending on developing scientific needs and objectives in AMR research.

Pillar A: Capability Building Network (CBN) to accelerate and validate scientific discoveries.

The CBN will: 1) create a coordination and support group to assist in the effective management of projects across the Accelerator and; 2) deliver pre-competitive science to accelerate scientific discoveries in AMR, the results of which will be disseminated widely. The CBN will include projects to further basic science and discoveries to enable future drug discovery and development in the prevention (vaccines, mAbs, immunoprophylaxis) and treatment of MDR bacterial infections including tuberculosis (TB), and non-tubercular mycobacteria (NTM). Although most research in the Accelerator related to TB will be conducted in the TBDDN (below), TB projects could occur in the CBN if the scientific concepts are of broader applicability (e.g. immunoprophylaxis).

The initial project in the CBN will implement an operational group that will support all projects in the AMR Accelerator with effective management, communication, and data capture capabilities. The initial CBN project also will focus on the collection, sharing, and analysis of vaccine and/or antibacterial clinical trial data and the optimization of animal infection models for bacterial infections.

Pillar B: TB Drug Development Network (TBDDN) to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global TB epidemic.

The TBDDN will work to address the innovation gap in the discovery and development of a pan-TB regimen by combining access to novel drug candidates with innovative tools and incorporation of clinical trial data to accelerate the discovery of new combination regimens for the treatment of TB.

The platform will be self-sustained and independent from other similar activities (Integrated Research Platform (IRP), TB Drug Accelerator (TBDA)). it is anticipated that there will be linkages with the TBDA (For more info on TB Drug Accelerator Programme (TBDA) please visit: http://partnerships.ifpma.org/partnership/tb-drug-accelerator-program). It will provide ready-to-use services for rapid progression of available (1st line) new and innovative candidates. The platform will be supported by the operational group from Pillar A but will include management resources to self-sustain its scientific and financial reporting as well as innovation management procedures.

This two-stage call will create a group to profile and progress anti-TB compounds from advanced lead through Phase 1 and the collection, sharing, and analysis of TB clinical trial data. Additionally, it will address the development of new alternative anti-tubercular drugs (for example, host-defence or virulence approaches).

Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR.

As in the CBN, the overall scientific scope in the PBN will be broad, including prevention (vaccines/mAbs, immunoprophylaxis) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). Within this broad scope, the PBN will provide a mechanism for dedicated partnerships between EFPIA companies and SMEs and/or academic teams for the discovery and development of new antibacterial assets, including in select cases TB and NTM. Assets and projects can originate from SMEs, academia, or EFPIA companies, and will be jointly progressed or studied, including both pre-clinical work and potentially Phase 1-3 clinical development. The PBN will also potentially be useful to generate new clinical / regulatory Phase 3 pathways for pathogens such as NTM and to conduct Phase 2 trials in TB.

Consortia selected under this pillar 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)[2]. The first call under Pillar C is divided in several topics, each dedicated to specific individual asset or research area. Additional single-stage calls, one or two per year, may be launched in the future pending available budget. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the first CBN Grant Agreement (selected under Pillar A from Call 15 topic 7, and containing the operational group) will be complementary to all the grant agreements selected under the call topics to be published for Pillars B and C (via call 15 topic 8 and call 16 topics, as well as potential future additional call topics), as well as possible future grant agreements selected under Pillar A. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[3] will be applied. The consortia selected under pillars A, B, and C will conclude collaboration agreements with the first CBN consortium selected from Call 15 topic 7 (which will include an operations group[4]). These collaboration agreements will provide the framework for the CBN to provide day-to-day support of projects in the Accelerator, including, exchange of relevant information, allowing consortia partners to focus on progressing the science.

Need and opportunity for public-private collaborative research

The discovery and development of new antibiotics and alternative treatment and prevention options for multi-drug resistant infections is a high medical and societal need. The AMR Accelerator will address multiple challenges in a coordinated programme, which offers excellent opportunities for collaborative work between different sectors and disciplines. Moreover, operating with the support of the operations group in the CBN will allow for greater efficiency, by reducing the need for duplicative management structures or processes.

Due to the current low return on investment that developers can expect for agents to address AMR, this scientific area has not received the investment that was seen in the 'call to action' to address HIV / AIDS and on par with the public health threat. Consequently, Public-Private Partnerships ("PPPs") such as the framework provided by the IMI2 JU continue to be critical to that effort.

Excellent examples have been the previous and current investments by the European Union (EU) (IMI2 JU, FP7 and Horizon 2020 (MM4TB, ORCHID, anTBiotic), NIH (TBRU) and Bill & Melinda Gates Foundation (TB Drug Development Accelerator and TB Alliance discovery portfolio)), wherein multiple new drug candidates are in the pipeline for the treatment of TB for the first time in decades, and are reaching or about to reach the clinic. Existing drugs are being repurposed or optimised for TB with the potential of shortened treatment duration for drug-sensitive TB and safer, shorter treatments for MDR-TB. In addition, the IMI2 JU-funded New Drugs for Bad Bugs programme (ND4BB) of projects wherein several points of progress have already been made from basic science through to running interventional clinical trials.

However, more work is critical to continue to address the constantly emerging global challenge of AMR. For example, there is a challenge of maturing the TB pipeline from the selection of candidates to progression through Phase 1 studies, in addition to parallel studies to determine the optimal combinations to create new pan-TB regimens. Also, the ever-evolving resistance landscape requires additional investment to validate new tools and approaches, in addition to progressing potential new therapies to prevent and treat bacterial infections.

Acting to address these challenges in a single, coordinated Accelerator offers excellent opportunities for collaborative work between different sectors and disciplines on an area of critical scientific need.

[2] See 'Applicant Consortium' section of topics text AMR Accelerator Programme Pillar C IMI2 Call 16 "Portfolio Building Network".
[3] See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf
[4] For additional details see the topic 7 "Capability Building Network" of IMI2 Call 15.

The development of the Accelerator will contribute to a vibrant AMR community in Europe and will offer potential opportunities for individual partners, such as:

- Capability Building Network
  - Play key role in a EU AMR programme with connectivity into the broader global agenda on AMR;
  - Enable SME, and/or academic groups to progress pre-competitive basic science project in the AMR field;
  - Opportunity to work within a broad network of researchers focused on AMR science and gain additional experience in AMR science and drug discovery.
- Tuberculosis Drug Development Network
  - Enable SME and/or academic groups to progress pre-competitive basic science project in the TB field;
  - Enable SME and/or academic groups to progress potential drugs from pre-candidate status through to 'ready for phase 2' status, including, but not limited to GLP and GMP scale up, formulation, toxicology studies, and Phase 1 clinical studies, including preclinical combinations of drugs;
  - Opportunity to work within a broad network on researchers focused on TB drug discovery.
- Portfolio Building Network
  - Opportunity for SMEs and/or academic groups to partner with EFPIA companies to enable progression of promising assets or technologies to key milestones, creating value, and sharing risk. There will be both potential to further extend such partnerships with EFPIA companies beyond the scope of the Accelerator following completion of project;
  - Will allow a vibrant partnering ecosystem that will benefit SMEs or academics with early stage assets based on pre-agreed conditions and milestone decision points.

Applicants to Calls launched as part of the Accelerator should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement.