Topic: AMR Accelerator programme Pillar B: Tuberculosis drug development network to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global tuberculosis epidemic

Part of the IMI2 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.

Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

On world TB Day, the EU Commissioners for Health, Research, Social Affairs and Development Cooperation issued a joint statement[1] highlighting the EU commitment to eradicate TB and the crucial role Research and Product Development plays in this. TB is the leading cause of death from a single infectious agent worldwide. An estimated 10.4 million people contracted TB in 2016. The lack of efficiency of current TB drugs is emphasized by the nearly 1.8 million annual deaths reported by WHO, of which 200,000 were confirmed cases of drug resistant TB real estimates could be much higher.

The majority of the 1.8 million annual TB deaths are caused by DS-TB. The current standard of care (SOC) HRZE (H=Isoniazid, R=Rifampin, Z=Pyrazinamide, E=Ethambutol has an efficacy (favourable outcome) in clinical trials of 90-95%, yet effectiveness in the field in high incident countries is merely ~75%. The spread of these resistant forms of TB is a continuum, with MDR-TB cases having already been detected in every country where there is an existing TB surveillance programme. Treatment options for MDR-TB are very poor; only 20% of patients receive an effective treatment which is excessively long and complex (combination treatment of 7-10 drugs given for 18-24 months for a total of 20000 pills and 240 painful injections). The lack of adequate compliance and the limited efficacy further reduces the success rate of MDR treatments to only 50%.

Although significant efforts have been made during the last decade, only 2 novel drugs have been approved by FDA and EMA since 1975 (Sirturo ® from Janssen and Delamanid® from Otsuka). Additionally, the lack of new drug candidates to combine with makes it challenging to impossible to develop a fully new combination.

[1] http://europa.eu/rapid/press-release_STATEMENT-18-2461_en.htm

As expressed by the UN, a massive scale-up[2] and a dynamic, global, multi-sectoral approach[3] is needed if the global target of eradicating tuberculosis by 2030[4] is to be met. At present, there is a strong consensus both in private and public research sectors working on TB that having a large number of new drug candidates, which are ready to enter into clinical combination studies, is the most critical step to achieve this aspirational goal that will have a tremendous impact into global health. These new candidates should be: 1) highly efficacious against all forms of TB, 2) safe for long term administration to all TB patients and 3) orally bioavailable.

The sum of initiatives financed by the European Union (IMI2 JU, FP7 and Horizon 2020), NIH (TBRU) and BMGF (TB Drug accelerator TBDA) together with the Global Alliance for TB have worked to create the framework and infrastructure required to support and accelerate the development of new drug candidates in TB. Bringing forward a new generation of candidates through Good Laboratory Practice (GLP) toxicity studies and First Time in Human (FTIH) and performing early combination studies to explore drug-drug interactions, efficacy and safety will accelerate the discovery of novel combination regimens with a higher probability of success. The TB drug development Network (TBDDN) within the AMR Accelerator brings together the collective will of all pharmaceutical companies involved in TB in a European initiative carefully conceived to be synergistic with other initiatives such as the TBDA platform.

The TB drug development Network (TBDDN), pillar B of the IMI2 JU AMR Accelerator programme, will function as a platform based on the principles of open innovation to advance discovery, preclinical and early clinical projects in the field of tuberculosis (TB) and multi-drug resistant Tuberculosis (MDR-TB). This component of the Accelerator will work to address the innovation gap in the discovery and early development of a pan-TB regimen by enabling the access to both novel drug candidates and innovative tools to accelerate the discovery of new combination regimens for the treatment of TB. One of the objectives of the TBDDN is to become a worldwide reference for the development of novel candidates and regimens by sharing results generated by partners and peers from SMEs, public institutions and Pharma companies following the IP rules set for the IMI2 JU grants[5]

Scope

The main objectives of the TBDDN is to provide a unique platform where discovery, development, and clinical trials readouts will occur allowing maximal engagement across groups in the TB field. Specifically:

- profile and progress the portfolio of anti-TB compounds existing within the industry consortium (EFPIA companies and Associated partners) from the advanced lead stage through Phase 1 (candidates ready to enter into Ph-2 clinical studies);
- identify preferred drug partners for preclinical combination studies that will facilitate the design of combination regimens consisting of new TB drugs with an indication for the treatment of any form, including MDR, of TB (pan-TB regimen);
- create additional tools and technologies to progress anti-TB compounds, and to provide learnings derived from analysis of shared anti-TB clinical trial data;
- development of new alternative anti-tubercular drugs (host-defence or virulence approaches).

[2] https://news.un.org/en/story/2016/10/542712-massive-scale-needed-if-global-targets-tuberculosis-are-be-met-top-un-health
[3] https://news.un.org/en/story/2017/10/569592-tuberculosis-worlds-top-infectious-killer-un-health-agency-calls-political
[4] http://www.who.int/tb/strategy/en/
[5] See https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf and https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/Annotated_Model_Grant_Agreement%E2%80%93AGA.pdf

Expected key deliverables

Deliverable 1: Development and implementation of new assays and tools to study anti-TB compounds:

- assays that can rapidly measure the efflux, outer membrane penetration, of both mycobacteria, infected macrophages, and caseum to enable rational design of novel pan-active anti-TB drug candidates;
- in vitro assays taking into account disease complexity, including host cells (foamy macrophages, granulomas, caseum medium, etc.) and relying on recent knowledge of TB pathogenesis and persistence;
- optimised animal infection models for both single drugs and combinations to i) improve / optimize translation to clinical efficacy, ii) improve reproducibility (study-to-study and lab-to-lab), iii) determine predictability of PK/PD parameters and iv) identify optimal study conditions and practices for minimizing variability;
- identify optimal study conditions and practices for minimizing variability;
- imaging platforms (in vitro/in vivo) to measure pharmacodynamic responses at the sites of action, including single cell microscopy, MALDI, PET/CT, hollow-fiber;
- standardized specific PK/PD studies/models required to support approval for limited use/accelerated pathways for novel TB investigational new drug (INDs) and combinations of INDs & acceptance with EMA & FDA with focus on human dose prediction to maximize efficacy and minimize risk of resistance;
- translational PBPK-PD models fed with preclinical and clinical data in the TB space (PBPK, PD and disease progression integrative models) to accelerate development of combination studies, associated with the development of novel biomarkers to assess treatment efficacy, disease evolution and cure at preclinical (MBL assay, CFU counting, microCT scan) and clinical (PET/CT scanning, biomarkers from urine vs blood, immunological markers) stages;
- new host-defence or virulence approaches: identify possible new targets and provide access to in vitro and in vivo translational assays to better select next generation of anti-TB drugs.

Deliverable 2: An advanced portfolio of anti-TB compounds

- new clinical candidates which have completed Phase 1 and are ready to enter into Phase-2 proof of concept studies in TB patients (note that Phase 2 studies are outside the scope of the TBDDN);
- new potential repurposed medicines ready to enter Phase 2;
- novel combination regimens that will be formed by combining the clinical candidates.

Deliverable 3: Learnings derived from shared TB clinical trial data (e.g. Phase 1-3 clinical trials related to TB) and associated enabling studies

- generation and collation of clinical trial data allow for analysis and the translation of preclinical to clinical data with respect to, for example, safety, tolerability, dose prediction, animal models of infection and efficacy, and greater disease understanding.

Expected impact

The impact of the TBDDN will help attain the UN 2030 objective by providing:

- new tools and understandings to progress TB science for the discovery of new preclinical candidates and novel combination regimens across the TB R&D landscape;
- contribution to the development of a vibrant TB research environment in the EU and strengthening the competitiveness and industrial leadership of Europe;
- contributing to EU's ambition of being a 'best practice region' for addressing AMR;
- enable the progression of potential new treatment solutions for TB patients worldwide to improve their live expectation and quality of life resulting from the expected improvement of current TB pipeline;

- strengthen interaction of TB R&D stakeholders from across EU and globally.

Applicants should indicate how their proposals will impact and strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short 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.

The project funded under TBDDN (facilitated by the operations group within the CBN) will work to maximise synergies with the following AMR projects and other PPPs:

- 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, (https://www.combacte.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 (projects such as AnTBiotic), the EDCTP (projects such as PanACEA), Joint Programming Initiative AMR, Wellcome Trust, BARDA, MRC, CARB-X, GARDP, NIAID, TB Drug Accelerator etc. to ensure synergy and avoid duplication of research.

Of note the TBDDN will ensure that:

- the current project will, where appropriate, build on the output of the PreDiCT-TB, MM4TB and Orchid projects;
- complementarities with TBDA, and other global platforms in TB by involving these organisations directly as associated partners in the project;
- experts from the Regulatory Agencies (EMA) and the Public and Medical Sector are consulted in the project so that the generated data can be used when regulatory filings will be made.

Industry consortium

To achieve the scientific objectives of the TBDDN, the industry consortium will:

- conduct standard medicinal chemistry, microbiology, pharmacology and early ADMET optimisation programmes for novel anti-TB compounds;
- conduct and share results and information of enabling studies such as synthesis (up-scales, fermentation), optimisation of lead molecules, computational chemistry, profiling in in vitro and in vivo models (marmoset and murine models, cell & lesion penetration, PKPD profiling and Modelling, metabolomics), access to enzymology platform (biochemical and biophysical assays and crystallography) and toxicology of novel precandidates[6] from TB portfolios from EFPIA and associated partners (DDU and TB Alliance) for further analysis;
- perform preclinical development studies7 (e. g. GLP toxicity studies, formulation, synthesis of material of clinical degree);

[6] Precandidate studies: discovery activities from Lead optimisation to selection of a molecule as Preclinical candidate
[7] Preclinical development: studies performed between Pre clinical candidate and First Time in Human.

- where appropriate provide compounds to support and/or validate the development of assays or approaches including potentially the generation of new natural products (fermentation, extract purification);
- share historical TB drug discovery and development data where appropriate;
- provide knowledge and expertise in TB drug discovery and development including:
  - capacity for multi-gram scale up synthesis of non-GMP grade of selected pre-candidates (500g), to assess therapeutic index of preclinical pre-candidates (non GLP toxicity and in vivo profiling into advanced TB models);
  - pharmaceutical development techniques to maximize the evaluation of the therapeutic index of novel compound;
  - capacity for scale up synthesis of selected candidate compounds of GMP grade (1-5 kg) of active product ingredients of GMP grade to perform GLP toxicity studies;
  - if additional throughput is needed, ability to undertake first into human studies (FTIH) on heathy volunteers to determine key pharmacokinetic parameters in humans (half-life, volume of distribution, clearance and potential for accumulation under extensive repeated doses) and to asses an indication of adverse effects (standard for any new IND with special focus on cardiovascular and hepatotoxicity).
- generate and share data, samples, and information from industry-sponsored clinical trials (Phase 1-3) in the field of TB including drug sensitive, drug resistant, and multidrug resistant tuberculosis, of compounds (e.g. Sirturo (Bedaquiline), Pretomanid, Delamanid, Sutezolid, Leu-tRNA synthetase inhibitor, Mtb cholesterol dependent inhibitor and Mtb DprE1 inhibitors and others), including enabling studies (e.g. synthesis, profiling, and toxicology of novel precandidates from TB portfolios from EFPIA and associated partners (DDU and TB Alliance) for further analysis;
- assist in the analysis of the output of clinical trials in the TB space, e.g. efficacy, safety, translation of preclinical data with respect to safety, tolerability, dose prediction, animal models of infection and efficacy.

The TBDDN project will include activities from industry-sponsored studies in Phase 1-3 generating data to be shared by EFPIA within the AMR accelerator consortium partners. Studies will be sponsored and funded by the respective contributing partner including the cost of FTEs and other expenses to run the studies, including but not limited to CRO costs, laboratory costs, and investigator and institutional grants based on respective site contracts. Payments will be based on respective agreements with trial related sites and/or trial related scientific advisory groups.

Indicative duration of the action

The indicative duration of the action is 72 months.

Applicant consortium

The applicant consortium will be selected on the basis of submitted short proposals. The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full project proposal for stage 2.

To achieve the scientific objectives of the TBDDN, the applicant consortium is expected to mobilise, as appropriate, expertise and capabilities in the following areas:

- analysis of preclinical and clinical trial data in the TB space in relation to e.g. efficacy, safety, translation of preclinical data with respect to safety, tolerability, dose prediction, animal models of infection and efficacy;
- collection, collation and curation of TB-specific data sets and identifying, implementing, maintaining IT systems (e.g. information sharing portals or databases) across large collaborative projects or PPPs, for example datasets could include:
  - Clinical trial data;
  - Microbiology data;

- Preclinical screening / profiling data;
- Chemical structures and descriptors;
- Animal infection model data;

- development of assays that can rapidly measure the efflux, outer membrane penetration, of both mycobacteria, infected macrophages, and caseum to enable rational design of novel pan-active anti-TB drug candidates;
- translation of PK/PD and regulatory knowledge to support the development of limited use/accelerated pathways for anti-tubercular drugs;
- conducting and analysing TB-animal infection models for single drugs and combinations;
- imaging platforms to measure pharmacodynamic responses at the sites of action;
- translational PBPK-PD models fed with preclinical data in the TB space (PBPK, PD and disease progression integrative models, expertise in preclinical and clinical TB biomarkers;
- drug discovery optimisation activities, e.g. medicinal chemistry, microbiology, scale up, DMPK, toxicology, etc;
- development of in vitro and in vivo tools to identify, characterize and progress molecules from host-defence or virulence approaches;
- multi-gram scale up synthesis of non-GMP grade of selected pre-candidates (500g), to assess therapeutic index of preclinical pre-candidates (non GLP toxicity and in vivo profiling into advanced TB models);
- pharmaceutical development techniques to maximize the evaluation of the therapeutic index of novel compound;
- scale up synthesis of selected candidate compounds of GMP grade (1-5 kg) of active product ingredients of GMP grade to perform GLP toxicity studies;
- ability to conduct in parallel several first into man studies (FTIH) on heathy volunteers to determine key pharmacokinetic parameters in humans (half-life, volume of distribution, clearance and potential for accumulation under extensive repeated doses) and to asses an indication of adverse effects (standard for any new IND with special focus on cardiovascular and hepatotoxicity).

Note that most day-to-day management such as: rigorous project, programme, and alliance management (including but not limited to, supporting the coordinator in management of scientific and financial reporting, prosecution of legal agreements such as CDA, MTA, meeting facilitation and secretariat) of projects across the Accelerator will be supported by the operational group within the CBN, therefore only minimal project and financial management capabilities will be required from the applicant consortium in the TBDDN.

In addition, representatives from the selected project 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 operations 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 consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. These strategies should be aiming to ensure access and uptake in high TB burden countries to secure maximum impact on the TB epidemic. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure e.g. qualification advice on the proposed methods for novel methodologies for drug development.

Note that overall plans and go/no-go milestones for progression of different molecules or approaches in the project will need to be established during the full project proposal phase of the application and should be included in full proposals. These milestones will then assist in the decision-making process to help ensure that the overall TBDDN portfolio remains dynamic and work on compounds is prioritized across the portfolio appropriately. Therefore, applicants should be aware that resource dedicated to a specific phase or piece of work may increase or decrease during the project.

Decision making: Following the first stage of the IMI2 JU call process and selection of partners to receive IMI2 JU funding, it is expected that the consortium preparing the full proposal for the second stage of the IMI2 JU call process will agree on a robust decision-making process (including escalation procedures) for progression of different molecules or approaches. Such decisions would be made by a committee that includes representatives from all project partners, e.g. including from the Associated Partners, the contributing EFPIA partners, and the public partners (to be detailed and agreed by all partners in the Consortium Agreement). A fair and efficient decision making process will be presented in the full proposal at the second stage of IMI2 JU call process. This committee will track progress of the project against its own internal milestones and will be empowered (to be outlined in the Consortium Agreement) to make progression/termination decisions based on pre-agreed go / no go milestones in a e.g. quarterly, streamlined, single-meeting process. For the avoidance of doubt, any decisions directly impacting an existing compound asset (such as an investigational medicinal product from one of the Participants), shall always require consent of the Participants who owns such existing compound asset. Of note, such mechanism must be established in full compliance with the IMI2 JU Model Grant Agreement.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, it is envisaged that IMI2 proposals and projects may allocate a leading role within the consortium to an EFPIA beneficiary/large industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted at stage 2, it is expected that one of the EFPIA beneficiaries/large industrial beneficiaries may elect to become the coordinator or the project leader. Therefore to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities therein. Until the roles are formally appointed through a Consortium Agreement the proposed project leader shall facilitate an efficient negotiation of project content and required agreements.

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