



Innovative Medicines Initiative

8th Call for proposals 2012

Innovative Medicines Initiative

Version 1

All information regarding IMI's 8th Call for proposals is indicative and subject to change. Final information about IMI's 8th Call will be communicated after approval by the IMI Governing Board.

TABLE OF CONTENTS

GENERAL PRINCIPLES	2
COMBATTING ANTIBIOTIC RESISTANCE: NEWDRUGS4BADBUGS (ND4BB).....	6
ND4BB TOPIC 1: INNOVATIVE TRIAL DESIGN AND CLINICAL DRUG DEVELOPMENT¹ SUBTOPIC 1C WP6: CONDUCT OF CLINICAL STUDIES SUPPORTING THE DEVELOPMENT OF MEDI4893, A MONOCLONAL ANTIBODY TARGETING STAPHYLOCOCCUS AUREUS ALPHA TOXIN.....	14
ND4BB TOPIC 3: DISCOVERY AND DEVELOPMENT OF NEW DRUGS COMBATTING GRAM – NEGATIVE INFECTIONS.....	28
DEVELOPING AN AETIOLOGY-BASED TAXONOMY OF HUMAN DISEASE.....	45
EUROPEAN INDUCED PLURIPOTENT STEM CELL BANK.....	51



¹ 6th Call for proposals launched in May 2012 (<http://www.imi.europa.eu/content/6th-call-2012>)

GENERAL PRINCIPLES

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is a unique pan-European public private partnership between the European Commission and EFPIA² driving collaboration between all relevant stakeholders including large and small biopharmaceutical and healthcare companies, regulators, academia, and patients.

The aim of IMI is to propose a coordinated approach to overcome identified research bottlenecks in the drug development process, in order to accelerate the development of safe and more effective medicines for patients, by fostering collaboration between all stakeholders such as industry, public authorities (including regulators), organisations of patients, academia and clinical centres, and enhancing Europe's competitiveness.

The revised IMI Scientific Research Agenda <http://www.imi.europa.eu/content/research-agenda> describes the research bottlenecks in the drug development process and identifies new and established research priorities correlated to at least one of the seven IMI Areas of Research Interest.

The IMI 8th Call 2012 for proposals includes topics covering the following key research priorities:

- Infectious diseases (correlated to the area of interest: Disease Drug Efficacy)
- Pharmacogenetics and Taxonomy of Human Diseases (correlated to the area of interests: Patient, Diseases, Knowledge)
- Stem Cells for Drug Development and Toxicity Screening (correlated to the area of interests: tools)

The 8th Call topics are:

Two topics under the Theme *Combatting Antimicrobial Resistance: NewDrugs4BadBugs (ND4BB)*

- ND4BB Subtopic 1C (as part of Topic 1³): Conduct of clinical trials supporting the development of MEDI4893, a monoclonal antibody targeting S. aureus alpha toxin
- ND4BB Topic 3: Discovery and development of new drugs combatting Gram-negative infections

Three topics under the Theme *Developing an aetiology-based taxonomy for human diseases*

- Topic A: Approaches to develop a new classification for Systemic Lupus Erythematosus (SLE) and related connective tissue disorders and Rheumatoid Arthritis (RA).
- Topic B: Approaches to develop a new classification for neurodegenerative disorders with a focus on Alzheimer's disease and Parkinson's disease.
- Topic C: Approaches to develop a new classification for Chronic Obstructive Pulmonary Disorders (COPD).

and:

² European Federation of Pharmaceutical Industries and Associations – www.efpia.eu

³ 6th Call for proposals launched in May 2012 (<http://www.imi.europa.eu/content/6th-call-2012>)

- European induced pluripotent stem cell bank

Applicant Consortia are invited to submit expressions of interest to one of the topics (or subtopics in case of ND4BB Topic 3).

The expressions of interest should address all aspects of the topic (or subtopic in case of ND4BB Topic 3) to which the Applicant Consortia are applying.

The size of each consortium should be adapted to the scientific goals and the expected key deliverables.

Further information can be found under the section 'Synopsis of Call and evaluation processes'.

Before submitting an expression of interest, the various Call Documents, such as *IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals, Rules for Participation, the IMI Intellectual Property Policy*, etc., shall be considered carefully. These documents are published on the IMI website www.imi.europa.eu at the time of the 8th Call 2012 launch.

Synergies and complementarities with other EU funded projects should be explored in order to avoid overlaps and duplications and to maximize European added value in health research.

DURATION OF THE PROJECTS

The indicative duration of the project is between 5 years and 6 years.

FUNDING OF THE PROJECTS

For this Call, the total available financial contribution from the IMI JU to participants eligible for funding will be maximum EUR 150 300 000.

The indicative EFPIA 'in kind'⁴ contribution will be EUR 106 400 000.

The Applicant Consortia shall keep in mind that the budget of each expression of interest is to be adapted to the scientific goals and the expected key deliverables of the project.

SYNOPSIS OF CALL AND EVALUATION PROCESS

The IMI JU supports research activities following open and competitive Calls for proposals, independent evaluation and the conclusion of Project and Grant Agreements.

The Topics included in the 8th Call are associated with a group of pharmaceutical companies that are members of EFPIA (hereafter called the 'EFPIA Consortia') and which are committed to collaborate with public and private organisations eligible for funding by the IMI JU. The EFPIA members will provide 'in kind' contributions to support their activities within the research projects.

The IMI JU applies a two stage Call process. In the first stage, 'Applicant Consortia' (i.e. formed by academia, small and medium sized enterprises (SMEs), patient organisations, non EFPIA companies, etc.) are invited to submit, to the IMI JU, an expression of interest (EoI) in response to a Call Topic.

⁴ In kind contribution is e.g. personnel, clinical research, equipment, consumables.

In preparing their EoIs, the Applicant Consortia should carefully consider the research contribution that an EFPIA Consortium will make to a given project as well as the expectations from the Applicant Consortia, as outlined in the topic texts below.

Each EoI submitted will be reviewed by independent experts according to predefined evaluation criteria.

The Applicant Consortium with the highest ranked EoI for each topic will be invited to jointly develop a full project proposal together with the EFPIA Consortium. However in case of ND4BB Topic 3, the Applicant Consortium with the highest ranked EoI for each of the subtopic will be invited to jointly develop a full project proposal together with the EFPIA Consortium.

For each topic, the full project proposal will then be subject to a final review by independent experts according to predefined evaluation criteria.

Only a full project proposal that has been favourably reviewed in the evaluation process can be selected for funding. This project will then be invited by the IMI JU to conclude a Grant Agreement governing the relationship between the selected project consortium and the IMI JU.

For full details, applicants should refer to the *IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals* published on the IMI JU website www.imi.europa.eu at the launch of the 8th Call.

ELIGIBILITY TO PARTICIPATE IN PROJECTS AND TO RECEIVE FUNDING FROM THE IMI JU

Criteria of eligibility to participate in IMI projects and the criteria to receive funding from the IMI JU are specified under the *Rules for participation* in the IMI JU collaborative projects published on the IMI JU website www.imi.europa.eu.

The IMI JU financial contribution will be based on the reimbursement of the eligible costs. The following funding rates apply to the legal entities eligible for funding: For research and technological development activities, up to 75% of the eligible costs and for other activities (including management and training activities) up to 100% of the eligible costs charged to the project are eligible for funding. For the indirect costs (overheads), the legal entities eligible for funding may opt for one of the following indirect costs methods: the actual indirect costs; or the simplified method which is a modality of the actual indirect costs for organisations which do not aggregate their indirect costs at a detailed level, but can aggregate them at the level of the legal entity; or a flat rate of 20% of total eligible direct costs (excluding subcontracting costs and the costs of resources made available by third parties which are not used on the premises of the beneficiary).

For full details, Applicant Consortia are invited to refer to the *Rules for Participation* in the IMI JU collaborative projects (www.imi.europa.eu).

The research based companies that are members of EFPIA shall not be eligible to receive financial contributions from the IMI JU.

IMI INTELLECTUAL PROPERTY POLICY

The IMI Intellectual Property Policy (IMI IP policy, www.imi.europa.eu) has been developed to be aligned with the objectives of the IMI JU to ensure knowledge creation, together with the swift dissemination and exploitation of knowledge, and fair reward for innovation.

The IMI IP Policy sets out *inter alia* basic principles regarding ownership of Background and Foreground, access rights depending on the entity and the purpose, and dissemination.

In submitting an EoI, the Applicant Consortia fully understand the principles laid out in the IMI IP policy that will apply to all research projects conducted under the IMI JU.

The IP policy does not foresee all details and does not aim to answer to all possible practical situations participants may be faced with. Flexibility is provided for participants to establish the most appropriate agreements (e.g. the project agreement) serving each individual project's objectives, and considering the wider IMI objectives.

Applicant Consortia are invited to read carefully the Guidance Note on the IMI IP Policy (www.imi.europa.eu), whose purpose is to explore ways to handle related issues and pitfalls that participants may encounter during the preparation, negotiation and completion phases of the Grant Agreement and Project Agreement.

PROJECT AGREEMENT

The Project Agreement is a private agreement which the participants of an IMI project conclude amongst themselves to implement the provisions of the Grant Agreement and to regulate internal issues related to work organisation and objectives for each participant, consortium governance, IP, financial and other matters.

All participants of a selected IMI project are requested to start negotiation on the project agreement between them in parallel to the preparation of the full project proposal.

The Full Consortium shall ensure that the negotiation of the project agreement is completed no later than the finalisation of the full project Description of Work.

COMBATTING ANTIBIOTIC RESISTANCE: NEWDRUGS4BADBUGS (ND4BB)

BACKGROUND

Antimicrobial resistance (AMR) is a major global public health threat. Infections caused by resistant bacteria are increasing and are associated with increases in mortality, morbidity, and length of hospitalization.⁵ In Europe 25,000 deaths were reported in 2007 as a result of AMR, with two-thirds of these deaths being due to Gram-negative bacteria. This clinical burden is associated with soaring treatment and societal costs, with the cost of AMR being estimated at around € 1.5 billion per year in Europe (see ECDC/EMA joint technical report "The bacterial challenge: time to react," 2009). The European Commission (EC) is committed to combating AMR, as outlined in its recent communication to the European Parliament and Council, entitled 'Action plan against the threats from antimicrobial resistance' (COM (2011) 48) (http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf). The European Federation of Pharmaceutical Industries and Associations (EFPIA) shares the views of the EC and recognizes that, although a number of activities have already been undertaken at the European Union (EU) (including FP7 funded activities) and international levels, including the Trans-Atlantic Task Force on Antimicrobial Resistance, more concrete actions need to materialize to make a meaningful change.

The ND4BB programme represents a core element of the "Action plan against the rising threats from Antimicrobial Resistance" adopted by the European Commission in answer to the Council Conclusions and European Parliament resolution to "establish an EU-wide plan to combat AMR". Action 6 of this action plan reads:

To promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antibiotics to patients by:
– *Launching rapidly with EFPIA, within the IMI-Joint Undertaking, a program for research on new antibiotics aimed at improving the efficiency of research and development of new antibiotics through unprecedented open sharing of knowledge.*

The ND4BB programme began with IMI JU 6th Call for proposals launched in May 2012 with and including two Topics: Innovative Trial Design and Clinical Drug Development, and Learning From Success and Failure & Getting Drugs Into Bad Bugs (see (http://www.imi.europa.eu/sites/default/files/uploads/documents/6th_Call/1_Anne%20x%201%20%206th%20Call%20for%20Proposals_2012%2005%2024.pdf))

PROBLEM STATEMENT FOR ND4BB

Despite the recognized need for new antimicrobials for clinical use, only two new classes of antibiotics have been brought to market in the last 30 years, and many drug developers have left the field.

There are key barriers to the development and delivery of effective antibiotics:

- Discovery and development of novel antibacterial agents is scientifically challenging. For example, many traditional screening approaches have failed to unearth novel chemical starting points, and Gram-negative pathogens have many inherent barriers and mechanisms preventing penetration of antibiotic agents.
- There are substantial regulatory challenges to the introduction of novel antibacterial agents.

⁵ Cosgrove, SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis. 2006; Jan 15;42 Suppl 2:S82-9.

Antibiotics have a low return on investment relative to other medicines, making it an unattractive area for drug developers, therefore limiting the future antibiotic pipeline.

To date, there have not been sustained efforts to explore novel avenues in fighting antimicrobial resistance outside of the antibiotic paradigm. Thus, the role of monoclonal antibodies (mAbs) in antibacterial drug development has not been thoroughly evaluated. Because mAbs do not bind to the same bacterial targets as antibiotics, they may complement antibiotics in the management of difficult-to-treat infections. In addition, mAbs have relatively long half-lives and are not expected to contribute to antibiotic resistance due to a different mechanism of action, and therefore may offer opportunities in the prevention of serious bacterial infections.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most important cause of antibiotic-resistant healthcare-associated infections (HAIs) worldwide. Infections with MRSA result in prolonged hospital stays and increased mortality rates. Although some European countries have reported decreasing trends for MRSA in recent years, the opposite trend is observed in other countries, and the proportion of invasive *S. aureus* isolates that are methicillin-resistant remains above 25% in more than one quarter of EU countries (European Centers for Disease Control and Prevention [ECDC] data). Given that at least 10 years are required to develop a new antibiotic such that it is available to patients, it is crucial that research delivers agents able to address any future unpredictable epidemiology changes in Europe, such as increases in the prevalence of MRSA, increase in resistance to currently available anti-MRSA agents, and the emergence of other drug resistances in *S. pneumoniae* (eg, quinolone resistance).

The incidence of multi-drug resistant Gram negative infections continues to rise (especially the Gram-negative ESKAPE pathogens: *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *E. coli*) and it is clear that new antibiotics are needed to address this rising unmet need. One of the major challenges in antibiotic discovery is not the identification of new targets, but the generation and optimisation of novel molecular starting points (Hit and Leads) with appropriate mechanism of action and sufficient activity against a range of key pathogens with sufficient selectivity (i.e. therapeutic index) over eukaryotic mechanisms.

Both the nature of the targets and the inherent difficulties in penetrating the outer and inner membranes of Gram-negative bacteria provide significant challenges in identifying novel antibacterials directed at the Gram-negative ESKAPE pathogens.

A general challenge in many areas of drug development is a lack of mechanisms through which investigators, drug developers, and clinicians can share data and experiences from the development of both failed and successful drug candidates. This leads to duplication of effort and ultimately inefficiencies in the drug development process. A common element across ND4BB is to drive the sharing of data and knowledge to increase the probability of success in the development of novel agents, thus accelerating the delivery of quality medicines to patients.

NEED FOR PUBLIC-PRIVATE PARTNERSHIP

The effort required to significantly impact the challenges facing the discovery and development of novel antibacterial agents is too great for any single entity; collaboration is essential. Furthermore the diversity of skill sets required to tackle the challenges faced requires contribution from a number of key stakeholders. For example, the lack of a robust pipeline illustrates the scientific challenges that the industry faces; consequently, a framework for sharing knowledge and resources across distinct companies, small and medium sized enterprises (SMEs), and academia is needed to increase the success of antibiotic research and development (R&D). It is essential that the antibiotic research community works together to ensure that societal needs for novel and effective antibiotics are fulfilled for the foreseeable future.

OVERALL OBJECTIVES OF ND4BB

The goal of the ND4BB research programme is to create an innovative and collaborative public-private partnership (PPP)-based approach that will positively impact all aspects of AMR, from the discovery of novel Leads and Development Candidates to Phase 1, Phase 2, and Phase 3 clinical studies. These activities will increase the probability of success in the development of new and effective antibiotics and biologics for the treatment or prevention of infections caused by resistant pathogens as well as the consequences of those infections.

The focus of the ND4BB programme is the discovery and development of new agents targeting the treatment, prevention, or management of the sequelae of infections due to resistant priority bacterial pathogens (eg, one or more of the following: Enterobacteriaceae [specifically *E coli*, *K pneumoniae* and *Enterobacter* species], *Acinetobacter*, *Pseudomonas aeruginosa*, *Clostridium difficile*, or methicillin-resistant *Staphylococcus aureus* [MRSA]).

Another important goal of ND4BB is to develop a data repository that is sustainable beyond the life of the current programme, providing a key information base for research projects focused on antibiotic resistance. All consortia participating in studies conducted under the ND4BB research programme will be expected to contribute data to the ND4BB data hub and collaborate to share data and experience as widely as possible amongst all programme members and the antibiotic research community as a whole.

Finally, ND4BB will establish a network of investigators that will exist beyond the life of the current IMI Calls.

ND4BB PROGRAMME ARCHITECTURE

In the current 8th Call for proposals, the ND4BB programme is expanded with the addition of the following:

- **Subtopic 1C: WP 6A-D**, which is part of Topic 1: Innovative Trial Design & Clinical Drug Development

Total indicative budget for Subtopic 1C WP 6: € 25.4M EFPIA/€ 26.4M IMI JU)

- **Topic 3: Discovery and development of new drugs combatting Gram-negative infections**

Total indicative budget for ND4BB Topic 3: € 26.0M EFPIA/€ 58.9M IMI JU)

- Subtopic 3A: WP1-3, WP5A, WP6-8
Total indicative budget for Subtopic 3A: € 24.5M EFPIA/€ 47.5M IMI JU
- Subtopic 3B: WP4+5B
Total indicative budget for Subtopic 3B: € 1.5M EFPIA/€ 11.4M IMI JU

A summary diagram of the ND4BB programme is presented in Figure 1.

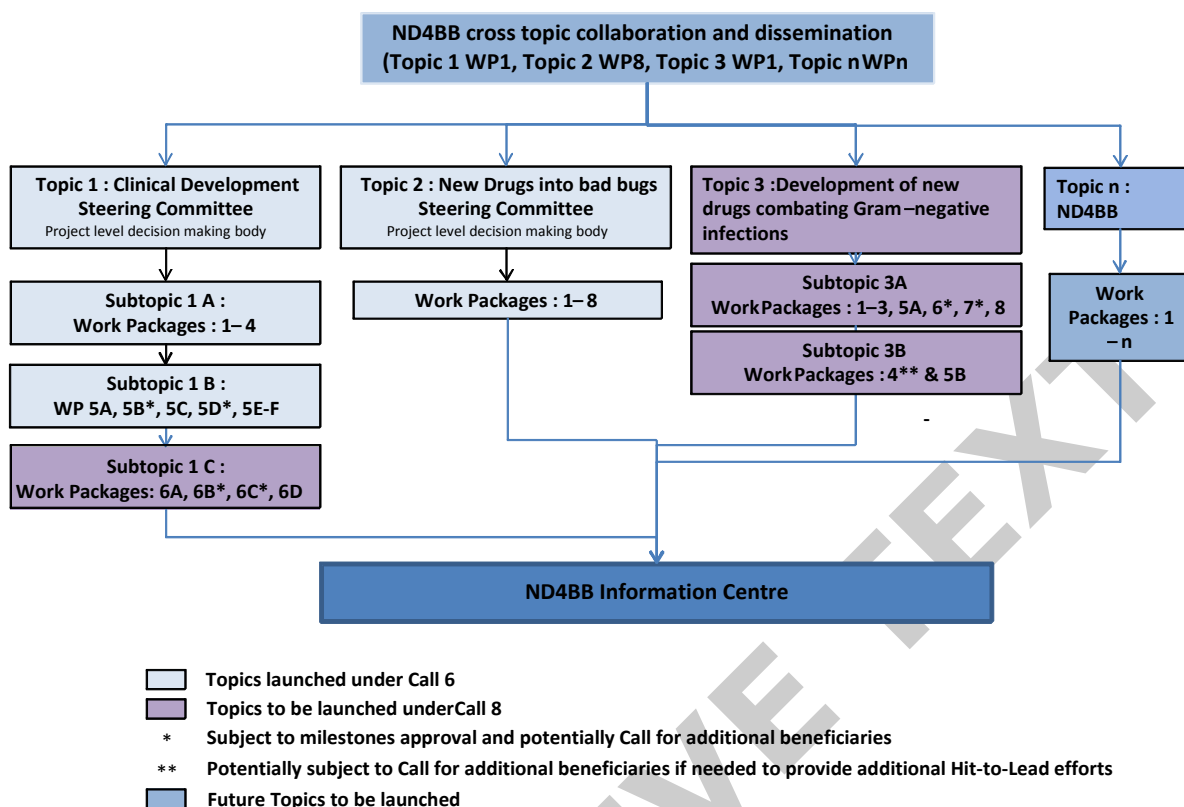


Figure 1 Summary diagram of the ND4BB programme

The ND4BB programme may also be expanded in future Calls to include future topics, including clinical drug development with novel anti-infectives.

POINTS OF NOTE:

- An Applicant Consortium may submit an expression of interest (EoI) either for Subtopic 1C or for one or both of the Subtopics (3A and/or 3B) of Topic 3 and is not obliged to apply for more than one Subtopic. For Topic 3, the Applicant Consortium with the highest ranked EoI for each of the two subtopics will be invited to jointly develop a full project proposal together with the EFPIA Consortium.
- Current Consortium participants in ongoing Topic 1 and Topic 2 may apply to Subtopic 1C and/or Topic 3.
- Funding for certain activities as described in some WPs will be allocated after milestone review in a stepwise manner. If after milestone reviews it is decided that additional expertise will be required, for instance for the implementation of clinical studies, open and competitive Calls for selecting additional beneficiaries will be organized by the Consortium, according to the Call process hereafter described.
- All Applicant Consortia are expected to provide plans and resources to support collaboration among projects funded under ND4BB. It is envisaged that this will be a shared activity across the projects generated by the current Call and existing ND4BB projects.
- All Consortia participating in topics conducted under the ND4BB research programme will be expected to contribute data to the ND4BB Information Centre, as developed in ND4BB Topic 2, and to participate in cross-project team meetings as appropriate to ensure learnings, knowledge, and skill sets are maximized

across the ND4BB teams.

SPECIFIC APPROACH FOR ACCEPTING NON-EU CONTRIBUTION EFPIA IN-KIND CONTRIBUTION (SPECIAL CLAUSE 13B)

Given the current low level of drug development activity to combat antibiotic resistance, the fact that the majority of drug development activities are being conducted outside of the EU and the gravity of the health threat that antibiotic resistance offers, acceptance of non-EU EFPIA in-kind contributions as part of the EFPIA in-kind contribution has been agreed by the Founding Members under the following conditions:

For topics of interest for EU citizens that will benefit European academics and SMEs, where there are few EFPIA research capacities in Europe while academic research is strong or substantially developed in Europe and, in particular research into rare diseases or disease areas of high public interest where creation of a critical mass of research is needed: For these projects a global cap of 30% at programme level of the actual committed EFPIA in-kind contribution to research activities, with no limit per IMI collaborative research project, may apply when agreed at the time of the Call definition and confirmed at the time of the selection decision of full project proposals.

The benefit to Europe of implementing this Special Clause

For the patient and society as a whole: Antibiotic resistance is an increasing threat to health across Europe and action is urgently required to support the development of new antibiotic agents. Without a joint and urgent action from public and private sectors, society will no longer have access to effective antibiotic agents to combat these resistant infections.

For public investigators and SMEs: All IMI funding will be directed to investigators and SMEs located within the EU.

Investigators will have a unique opportunity to gain funding to support the development of new and innovative approaches, while at the same time gaining invaluable insight into the complexities of drug development as well as access to learnings and experience from all partners involved in ND4BB. It gives partners the opportunity to build relationships with EFPIA companies participating (and also those outside of ND4BB) to strengthen their ability to identify partnering opportunities for further development of promising new drugs. It is anticipated that the opportunity to build a network of investigators through which academics, pharmaceutical and biotechnology companies can advance the pre-clinical and clinical development of new assets will attract future drug discovery efforts and future clinical trials to Europe. Investigators will also become part of the broader ND4BB research community through regular joint symposia and sharing of experiences through the ND4BB Information Centre.

Having the opportunity for collaboration has already actively encouraged companies developing new antibiotic agents to focus on running clinical trials within the EU rather than outside of the EU where typically it is easier to recruit subjects with the appropriate resistant infections. This will bring revenue directly to hospitals, universities and SMEs through the ongoing studies as well as establishing a network of European investigators with the expertise and resources required to participate in global trials.

For pharmaceutical and biotechnology companies developing antibiotic agents : The opportunity to work with leading experts in all fields required for successful drug discovery in order to tackle major challenges in drug discovery and development.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Data and learnings generated in the first two ND4BB Topics, in particular Topic 2 (“Learning from Success and Failure & Getting Drugs into Bad Bugs”), should be incorporated into the current project whenever possible. Further, valuable synergies should be considered with the Lead Factory and K4DD IMI projects, and with the portfolio of IMI Knowledge Management projects.

In addition, complementarities and potential synergies with other initiatives on AMR should be taken into account, in particular:

- Joint Programming Initiative on AMR
- EARS-net: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/about_EARS-Net/Pages/about_network.aspx
- ESAC-NET: <http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net/Pages/index.aspx>
- HAI-Net: ECDC Healthcare-associated Infections Surveillance Network <http://www.ecdc.europa.eu/en/activities/surveillance/HAI/Pages/default.aspx>
- AO Trauma Foundation, Davos, Switzerland, Bone Infection Registry <https://www.aofoundation.org/Structure/pages/newsdetail.aspx?newslist=https://aotrauma.aofoundation.org/News/Lists/News+Common&newsid=13>
- National Institutes of Health (NIH)/Infectious Diseases Society of America (IDSA) initiative to set up a clinical research network on antimicrobial resistance (“Bad Bugs No Drugs – 10 by 20” to support the development of 10 new antibiotics by 2020.) <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-019.html> and <http://cid.oxfordjournals.org/content/50/8/1081.full>
- Potential synergies may be developed with existing IMI projects such as RAPP-ID. This project deals with the development of rapid point-of-care test platforms for infectious diseases and will tackle the problem of early diagnosis of microbial resistance. The work of RAPP-ID will bring important contributions to the testing of new antibiotics in clinical trials.
- Portfolio of FP7-funded projects in the area (see: http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/index_en.html, for instance:
 - AEROPATH: Identification, characterisation and exploitation of novel Gram-negative drug targets
 - AntiPathoGN: Identification and validation of novel drug targets in Gram-negative bacteria by global search: a trans-system approach
 - DIVINOCELL: Exploiting Gram-negative cell division targets in the test tube to obtain antimicrobial compounds
 - Three FP7 Cooperation Work Programmes, Health-2013 (HEALTH.2013.2.3.1-1, HEALTH.2013.2.3.1-2 and HEALTH.2013.3.1-1), KBBE-2013 (KBBE.2013.1.3-05) and NMP-2013 (NMP.2013.1.2-2) which include Call topics for proposals supporting the aims of the recently launched Action Plan Against the Rising Threats from Antimicrobial Resistance by the European Commission

Expressions of interest should clearly outline the unique properties of the proposed plan of work and how potential interaction with these initiatives would be managed, while avoiding the potential for duplication or overlap of activities.

THE OPEN CALL PROCESS FOR ADDITIONAL BENEFICIARIES TO PERFORM TASKS

- When open Calls from within the existing consortium are required to engage additional beneficiaries, these will be handled by the consortium with guidance from the IMI JU. The consortium will propose procedures for implementing an open and

competitive Call(s) in order to recruit investigators for the conduct of clinical trials as required in response to protocol requirements. The procedures will be based on the guiding principles provided below and will comply with the conditions established in the IMI model grant agreement⁶:

- The selection shall be based on openness, transparency, efficiency and equal treatment.
- Each open and competitive Call shall explicitly describe:
 - the activities to be carried out, the required capacities and the related dedicated budget;
 - the rules for participation (eligible entities);
 - the applicable evaluation, submission and selection procedures.
- Each open and competitive Call shall be subject to wide advertising and publication by the consortium, to ensure appropriate communication to any potential interested parties in Member States and associated countries. In order to achieve this, the consortium shall publish the competitive call at least in one international journal and in three different national newspapers in three different Member States or Associated countries. It shall also be responsible for advertising the call widely using specific information support, particularly the IMI Internet site and Internet sites on the Seventh Framework Programme, the specialist press and brochures and through the national contact points set up by Member States and Associated countries. In addition, the publication and advertising of the Call shall conform to any instructions and guidance notes established by the IMI JU Executive Office. The consortium shall inform the IMI JU Executive Office of the Call and its content at least 30 days prior to its expected date of publication.
- The competitive Call shall remain open for the submission of proposals by interested parties for a period of at least five weeks.
- The proposals' evaluation shall be carried out by the consortium:
 - According to the criteria that governed the IMI JU's original evaluation and selection of the project. In case additional criteria are to be set up by the consortium considering the specific features of the open and competitive Call, these shall receive prior approval by the IMI JU;
 - With the assistance of at least two independent experts appointed by the consortium on the basis of the criteria described in the 'IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals'. Experts shall be independent of any project's participant and any applicant to the open and competitive Call.
- The consortium shall notify the IMI JU Executive Office of the proposed accession of a new beneficiary(ies) in accordance with Article II.35 of the IMI model grant agreement. At the same time, it will inform the IMI JU Executive Office of the means by which the competitive call was published and of the names and affiliation of the experts involved in the evaluation. The IMI JU Executive Office may object to the accession of any new beneficiary within 30 days of the receipt of the notification. Based on evaluation outcome the consortium will submit a report to IMI providing evidence that the principles of openness, transparency, efficiency, and equal treatment have been fulfilled. The costs incurred by the consortium in relation to each open and competitive Call may be reimbursed or considered as in-kind contribution provided that

⁶ The IMI model grant agreement (IMI-GB-DEC-2012-8) will be amended in order to introduce the specific provisions establishing the process for launching open and competitive calls for the selection of additional beneficiaries.

the eligibility criteria laid down in the IMI grant agreement are fulfilled special clause for non-EU contribution (special clause 13b).

INDICATIVE TEXT

ND4BB TOPIC 1: INNOVATIVE TRIAL DESIGN AND CLINICAL DRUG DEVELOPMENT⁷

SUBTOPIC 1C WP6: CONDUCT OF CLINICAL STUDIES SUPPORTING THE DEVELOPMENT OF MEDI4893, A MONOCLONAL ANTIBODY TARGETING *STAPHYLOCOCCUS AUREUS* ALPHA TOXIN

The overall objectives of Topic 1 are:

- To increase the efficiency of antibiotic R&D through analysing shared preclinical and clinical data sets and making recommendations for the development of novel antibiotic agents and making the development of antimicrobial products more feasible.
- To establish investigator networks and surveillance programmes to support antibacterial clinical development
- To conduct prospective clinical studies with novel trial designs to deliver safety, pharmacology, and proof of efficacy data for novel agents directed towards the treatment or prevention of infections due to priority pathogens.

The overall expected deliverables of topic 1 are:

- Phase 1, Phase 2, and/or Phase 3 clinical studies demonstrating the pharmacology, safety, and efficacy of new antibiotics against priority pathogens
- Global surveillance and epidemiological data relevant to the future use and development of novel products
- Good Clinical Practice (GCP)-qualified investigational centers (with a focus on European regions reporting high levels of AMR) with all necessary training, test materials, and instrumentation to conduct clinical studies of drugs and diagnostic devices
 - Functioning investigator network(s) for the conduct of antibacterial clinical and non-interventional trials
 - Novel clinical trial design proposals
 - Novel diagnostics and/or endpoints

Indicative duration of the project

The indicative duration of the entire Topic 1 is 7 years; its duration may be shorter depending on the study designs implemented. Current estimates for WP start dates and durations under Subtopic 1C are provided below.

EFPIA participants

GlaxoSmithKline, AstraZeneca, Janssen R&D, Sanofi

TOPIC 1, SUBTOPIC 1C WP6: CONDUCT OF CLINICAL STUDIES SUPPORTING THE DEVELOPMENT OF MEDI4893, A MONOCLONAL ANTIBODY TARGETING *STAPHYLOCOCCUS AUREUS* ALPHA TOXIN

SPECIFIC POINTS OF NOTE FOR SUBTOPIC 1C WP6

- An Applicant Consortium is expected to address all WPs of Subtopic 1C (WPs 6A through 6D)
- The successful Applicant Consortium for Subtopic 1C will join the existing Topic 1 Full Consortium selected under the 6th Call for proposals. Since all Topic 1 participants (ie, Subtopics 1A, 1B, and 1C participants) will be part of the same Grant Agreement, the

⁷ 6th Call for proposals launched in May 2012 (<http://www.imi.europa.eu/content/6th-call-2012>)

successful Applicant Consortium of Subtopic 1C will be required to adhere to the Project Agreement agreed by the existing Topic 1 Full Consortium, especially with regard to the provisions related to governance and intellectual properties (IP). Some adaptations might nonetheless be considered to accommodate the peculiarities of Subtopic 1C.

- The leading EFPIA company for this WP6 is AstraZeneca.

OVERALL OBJECTIVES

- To increase the probability of success and efficiency of clinical development of MEDI4893 through a stepwise approach: first, evaluation of burden of disease and potential target population, utilizing targeted active surveillance, followed by interventional Phase 1b/2 studies in the populations of interest, using study designs informed by the data collected from the epidemiology surveillance studies.
- To establish population-specific surveillance programmes to support the clinical development of anti-*S aureus* therapies
- To conduct prospective clinical studies with novel trial designs to deliver safety, pharmacology, and proof of efficacy data for MEDI4893, a novel mAb directed toward the prevention of *S aureus* disease.

OVERALL EXPECTED DELIVERABLES

- Prospective epidemiology surveillance of surgical site infections (SSIs) and intensive care unit (ICU) pneumonia attributable to *S aureus* (WP 6A).
- Epidemiologic data collected from WP 6A will subsequently be used to define populations at high risk of *S aureus* infection, eg, intubated patients in the ICU and patients undergoing complicated surgeries. These populations will comprise the target patient populations for Phase 1b/2 studies of MEDI4893 (Subtopic 1C WPs 6B and 6C).
- Phase 1b/2 studies of MEDI4893 to prevent *S aureus* disease in surgical and ICU patients in Europe (WP 6B and WP 6C)
- Development of novel diagnostics and biomarkers aligned with the overall objectives and endpoints of Subtopic 1C, WP 6

INDICATIVE DURATION

The indicative duration of Subtopic 1C is 6 years; the duration may be less, depending on the study designs implemented. Estimated start dates and WP durations are provided within the description for each WP.

INDICATIVE BUDGET

The indicative in-kind contribution from EFPIA is €25.4M, and from IMI JU is €26.4M.

The total budget is to be divided among the 4 WPs, along the following indications:

- WP 6A: The indicative in-kind contribution from EFPIA company is €6.2M, and from IMI JU, €10.3M.
- WP 6B: The indicative budget for WP 6B is €7.2M EFPIA; €9.2M IMI JU
- WP 6C: The indicative budget for WP 6C is, €9.3M EFPIA; €5.6M IMI JU
- WP 6D: The indicative budget for WP 6D is €2.7 M EFPIA; €1.3 M IMI JU

ALLOCATION OF FUNDING AND MILESTONE PROGRESSION DECISIONS FOR SUBTOPIC 1C, WP 6

The Applicant Consortium should apply with EOIs that address all WPs and include suggestions for biomarkers relevant to study endpoints. Approximately € 3M is available for biomarker research for each of WP 6A, WP 6B, and WP 6C and is included in the

indicative budget figures provided above. Applications for biomarker research must align with the proposed endpoints for the studies, must not deter from the successful conduct of the programme, and should aim to inform the clinical development pathway for MEDI4893.

The success of drug discovery is uncertain; only a small percentage of those drug candidates entering clinical trials enter the marketplace. Funding for the clinical studies described in WP 6B and WP 6C will therefore be allocated in a stepwise manner based on milestones review, with the inclusion of the EFPIA sponsor company governance process. In particular, funding of these studies will be subject to a successful outcome of the surveillance study described by WP 6A, ie, identification of surgical and ICU patients at risk for developing *S aureus* disease, as potential candidates for intervention with MEDI4893.

The study results from WP 6A, as well as guidance of regulatory agencies, are expected to impact plans for the conduct of WP 6B and WP 6C.

If required, open Calls as described in the overall introduction will be launched from within the Consortium to identify additional beneficiaries to ensure the successful delivery of WPs 6B and 6C. The budget for the additional partners to be recruited through an open Call will be taken from the overall budget agreed at the time of the Grant Agreement signature.

OVERVIEW OF THE DEVELOPMENT OF MEDI4893

Staphylococcus aureus causes significant morbidity and mortality in diverse patient populations worldwide. *S aureus* is also one of the primary causes of nosocomial infections. Patients in the intensive care unit (ICU) are at high risk for developing severe *S aureus* (including MRSA) infections, such as pneumonia, bacteraemia, and sepsis. Patients undergoing complicated surgeries are also at substantial risk of developing serious *S aureus* infection.

Treatment with antimicrobial agents has driven the emergence of *S aureus* strains resistant to methicillin (MRSA) and glycopeptides (glycopeptide-intermediate *S aureus* [GISA], heterogeneous glycopeptide-intermediate *S aureus* [hGISA], and glycopeptide-resistant *S aureus* [GRSA]), thus limiting antimicrobial therapeutic options. The limitations of available antibiotics combined with the continued emergence of new resistance mechanisms require new approaches to prevent or treat *S aureus* disease.

Virulence factors play an important role in the tissue and organ damage that occur in disease caused by *S aureus*. Alpha toxin (AT), encoded by the *hla* gene and also known as alpha haemolysin, is a key *S aureus* virulence factor that leads to tissue invasion and necrosis. It induces cell injury by forming transmembrane pores in cell membranes. *S aureus* isolates lacking AT have been shown to be less virulent in animal models of dermonecrosis, pneumonia, sepsis, endocarditis, and mastitis,^{8,9,10,11,12,13} and the

⁸ Bramley AJ, Patel AH, O'Reilly M, Foster R, Foster TJ. Roles of alpha-toxin and beta-toxin in virulence of *Staphylococcus aureus* for the mouse mammary gland. *Infect Immun*. 1989 Aug;57(8):2489-94.

⁹ Bayer AS, Ramos MD, Menzies BE, Yeaman MR, Shen AJ, Cheung AL. Hyperproduction of alpha-toxin by *Staphylococcus aureus* results in paradoxically reduced virulence in experimental endocarditis: a host defense role for platelet microbicidal proteins. *Infect Immun*. 1997 Nov;65(11):4652-60.

¹⁰ Kernodle DS, Voladri RK, Menzies BE, Hager CC, Edwards KM. Expression of an antisense *hla* fragment in *Staphylococcus aureus* reduces alpha-toxin production in vitro and attenuates lethal activity in a murine model. *Infect Immun*. 1997 Jan;65(1):179-84.

¹¹ Bubeck Wardenburg J, Bae T, Otto M, Deleo FR, Schneewind O. Poring over pores: alpha-hemolysin and Pantone-Valentine leukocidin in *Staphylococcus aureus* pneumonia. *Nat Med*. 2007 Dec;13(12):1405-6

¹² Bubeck Wardenburg J, Palazzolo-Ballance AM, Otto M, Schneewind O, DeLeo FR. Pantone-Valentine leukocidin is not a virulence determinant in murine models of community-associated methicillin-resistant *Staphylococcus aureus* disease. *J Infect Dis*. 2008 Oct 15;198(8):1166-70.

presence of anti-AT antibodies in patients with bacteraemia, sepsis, and endocarditis has been associated with improved outcomes.^{14,15,16} Consequently, targeted inhibition of AT might be expected to prevent or limit *S aureus*-related disease.

MEDI4893 is a human immunoglobulin G1 kappa (IgG1 κ) mAb directed against *S aureus* AT. MEDI4893 is being developed for immunoprophylaxis in individuals at high risk for *S aureus* infections. Three amino acid substitutions (known as YTE) were introduced into the heavy chain CH2 constant region of the fragment crystallizable (Fc) domain of MEDI4893 to increase the serum half-life ($t_{1/2}$) and exposure in humans.

MEDI4893 binds with high affinity and specificity to AT and blocks AT-induced pore formation in target cell membranes. The epitope on AT recognized by MEDI4893 is highly conserved and is expressed by 94 of 105 (90%) *S aureus* clinical isolates tested. In in vitro studies, MEDI4893 inhibited AT-mediated rabbit red blood cell and human lung epithelial, monocytic, and keratinocyte cell line lysis. Prophylaxis with anti-AT mAb resulted in reduced disease severity in the murine infection models of dermonecrosis and pneumonia. In the dermonecrosis model, anti-AT mAb significantly reduced skin lesion sizes, limited tissue damage, modulated inflammatory cytokine response, and caused reduced bacterial load at the site of infection.¹⁷ In the lethal *S aureus* pneumonia model, anti-AT mAb significantly improved survival, preserved lung integrity, and reduced both bacterial load in lungs and bacterial dissemination to the kidneys. These findings suggest that MEDI4893 may provide broad coverage against a variety of serious *S aureus* diseases in humans.

Anti-infective mAbs that are specific for pathogens and not human antigens, are anticipated to have relatively few off-target toxicities. In addition, the long serum half life of human IgG offers an advantage over small-molecule antibacterials in a prophylactic setting. Passive administration of mAbs also offers certain advantages over active vaccination for protection against disease caused by *S aureus*. Unlike active vaccination, passive immunoprophylaxis does not require an active immune response and thus could be utilized in populations with impaired immune systems. In addition, unlike vaccines, the passive protection from mAbs is immediately available. Therefore, MEDI4893 offers a novel opportunity to fight *S aureus* disease in individuals with high-risk conditions.

WP 6A: EPIDEMIOLOGIC SURVEILLANCE OF HEALTHCARE-ASSOCIATED INFECTIONS AMONG SURGICAL AND INTENSIVE CARE UNIT PATIENTS IN THE EUROPEAN UNION

Estimated Start: 1Q 2014

Estimated Study Duration: 24-30 months

Recruitment will focus on potential sites within the European Union (EU), ie, those sites eligible for IMI JU funding.

Study preparation: **3Q 2013-4Q 2013**

¹³ Kobayashi SD, Malachowa N, Whitney AR, Braughton KR, Gardner DJ, Long D, et al. Comparative analysis of USA300 virulence determinants in a rabbit model of skin and soft tissue infection. *J Infect Dis*. 2011 Sep 15;204(6):937-41.

¹⁴ Adhikari RP, Ajao AO, Aman MJ, Karauzum H, Sarwar J, Lydecker AD, et al. Lower antibody levels to *Staphylococcus aureus* exotoxins are associated with sepsis in hospitalized adults with invasive *S. aureus* infections. *J Infect Dis*. 2012 Aug 6. [Epub ahead of print].

¹⁵ Jacobsson G, Colque-Navarro P, Gustafsson E, Andersson R, Mollby R. Antibody responses in patients with invasive *Staphylococcus aureus* infections. *Eur J Clin Microbiol Infect Dis*. 2010;29:715-25.

¹⁶ Ruotsalainen E, Karden-Lilja M, Kuusela P, Vuopia-Varkila J, Virolainen-Julkunen A, Sarna S, et al. Methicillin-sensitive *Staphylococcus aureus* bacteraemia and endocarditis among injection drug users and nonaddicts: host factors, microbiological and serological characteristics. *J Infect*. 2008;56:249-56.

¹⁷ Tkaczyk C, Hua L, Varkey R, Shi Y, Dettinger L, Woods R, et al. *Clin Vaccine Immunol*. 2012; 19(3):377-85

Site recruitment: **1Q 2014-4Q 2014**

Study close-out and report generation: **2Q 2016**

Study Rationale

Healthcare-associated infections (HAIs) cause considerable morbidity and mortality among hospitalized patients. Surgical site infections (SSIs) and pneumonia acquired by patients admitted to intensive care units (ICU) contribute significantly to the financial burden of the healthcare system.

The epidemiology of SSI and ICU pneumonia in the EU has not been fully described, in part due to variation in the case definitions and surveillance systems utilized by EU Member States. Efforts to standardize assessments of disease measures in hospitals across different countries are hampered by temporal and geographic variation in disease risk.

The overarching goal of the proposed study is to systematically assess the impact of patient-related and contextual factors on the incidence of SSI and ICU pneumonia in the EU and to identify the patient subgroups that bear a disproportionate disease burden. These subgroups will be the target population for MEDI4893, which is being developed for the prevention of SSIs in patients undergoing specific high-risk surgeries and pneumonia attributable to *S aureus* in patients in the ICU.

Study Objectives

The objectives of the proposed study are:

- 1) To estimate the incidence of SSI and ICU pneumonia attributable to *S aureus* infection and to describe their temporal distribution
- 2) To ascertain patient-related and contextual factors independently associated with SSI and ICU pneumonia attributable to *S aureus*
 - a. To assess the independent association between baseline serum antibody levels against *S aureus* AT and the risk of *S aureus* infection
 - b. To assess the independent association between *S aureus* colonization and risk of *S aureus* infection
 - c. To assess *S aureus* isolates associated with *S aureus* colonization or SSI/ICU pneumonia cases for gene sequence and gene expression of *S aureus* virulence factors
- 3) To assess the prevalence of SSI and ICU pneumonia attributable to specific etiologic agents (eg, *S aureus*, *Pseudomonas aeruginosa*) and the antimicrobial susceptibility of these agents by susceptibility patterns (eg, methicillin-susceptible [MS] *S aureus* and MRSA)
- 4) Biomarkers:
 - a. To explore the role of antibodies against *S aureus* virulence factors as potential biomarkers associated with *S aureus* disease severity and outcome
 - b. To explore the role of antibodies against Gram-positive and Gram-negative bacterial virulence factors as biomarkers among surgical and ICU patients

Study Population

This study will enroll two separate patient populations:

- 1) Patients undergoing surgical procedures that are associated with high rates of SSI (eg, cardiothoracic, neurosurgery/spine, or orthopaedic procedures); and
- 2) Patients admitted to participating ICUs who, upon admission, do not show signs or symptoms of an acute bacterial infection and are expected to stay in the ICU for at least 2 days.

Study Design

The proposed study is a prospective, 24-month, active-surveillance study to identify and characterize SSI among patients undergoing surgeries of interest and ICU pneumonia among eligible patients admitted to the ICU in participating sites.

Study Details

The proposed study is planned to include **10 to 20 hospital networks in 6 to 12 EU countries** (no sites outside Europe).

The first 12 months of study data collection will be defined as the exposure period. Data will be captured from a minimum of **50,000 patients undergoing surgeries of interest and 5,000 patients admitted to the ICU** without signs or symptoms of an acute bacterial infection. These data will include de-identified patient-specific data (eg, demographics, co-morbidities, procedure details, mechanical ventilation, APACHE IV score, American Society of Anesthesiologists (ASA) score, *S aureus* colonization status) and hospital data (eg, annual number of surgeries performed by procedure type, infection control surveillance protocol details, SSI rates). Routinely collected pre-surgery and pre-ICU nasopharyngeal specimens from patients will be tested on site to assess *S aureus* colonization.

The outcome assessment period will span the first 24 months of study data collection, which includes a maximum post-discharge surveillance period of 12 months. Patient-specific, de-identified clinical diagnosis and confirmatory microbiologic test results regarding the etiology and date of an infection will be linked to patient-specific data collected during the exposure period. The case definitions for SSI and ICU pneumonia will be finalized in collaboration with participating partners; however, it is expected that standard European Centers for Disease Control and Prevention (ECDC) definitions will be used. In addition, routinely collected pre-surgical or pre-ICU serum specimens will be stored on site and subsequently tested at a central participating laboratory for the presence of antibodies to Gram-positive and Gram-negative bacteria, including innate antibodies against *S aureus* AT.

If collection of nasopharyngeal specimens and/or serum specimens prior to surgery or ICU admission is not a part of routine clinical care or infection control surveillance protocols of participating sites, then a prospective observational study will be nested within the surveillance effort. For this study, a representative sample of approximately 11,000 patients, including approximately 10,000 surgical and 1,000 ICU patients who consent to additional testing and linkage of test results to their patient-specific data, will be enrolled. The sampling methodology employed to select patients for additional testing will be determined by the participating sites' volume of procedures.

Should informative data be available from 2010-2012 as part of network databases, preliminary analyses may be performed to help inform and finalize the design of this prospective surveillance study.

The cost for the proposed study is estimated to be €16.5 M (external and internal costs).

EFPIA contribution: All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics). Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%) incurred by public partners ensuring that 100% of these costs will be reimbursed. Serology assays developed by the sponsoring EFPIA company will be transferred under a technology transfer agreement to a laboratory within the Consortium, which may serve as the central laboratory resource for the WP6 Consortium. Characterization of *S aureus* virulence factors by gene sequencing and gene expression will be performed by the sponsoring EFPIA company as an in-kind contribution. The results of these studies will be shared with Topic 1 Consortium members.

WP6B: PHASE 1B/2A RANDOMIZED, PLACEBO-CONTROLLED, SINGLE-DOSE, DOSE-RANGING STUDY TO EVALUATE THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF MEDI4893 FOR THE PREVENTION OF STAPHYLOCOCCUS AUREUS (INCLUDING MRSA) VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

Estimated Start: 4Q 2014

Estimated Study Duration: 30 months

Recruitment will focus on potential sites within the EU, ie, those sites eligible for IMI JU funding. An estimated **390 subjects /25 sites** will be recruited for this study. Sample size and study specifics will be updated after the results of the WP 6A study and a Phase 1 safety and pharmacokinetics (PK) study, as well as scientific advice from regulatory agencies, are available.

Study preparation: **2Q 2014**

Site recruitment: **4Q 2014-1Q 2016**

Study close-out and report generation: **2Q 2019**

Study Objectives

The objectives of the proposed study are:

- 1) To evaluate the safety and tolerability of MEDI4893 administered to mechanically ventilated ICU patients
- 2) To evaluate the pharmacokinetics (PK) of MEDI4893 in serum
- 3) To evaluate the effect of MEDI4893 on the incidence of *S aureus* pneumonia in mechanically ventilated ICU patients
- 4) To evaluate measures of *S aureus* disease severity in patients with *S aureus* pneumonia
- 5) To evaluate biomarkers associated with *S aureus* disease severity and outcome

Study Population

The proposed study population consists of subjects admitted to the ICU, who can be identified prior to infection to be at increased risk (to be determined) of developing *S aureus* (including MRSA) pneumonia, and who require mechanical ventilation.

Study Design

The proposed study is a Phase 1b/2a, randomized, placebo-controlled, dose-escalation study in mechanically ventilated ICU patients.

Study Details Summary

Key efficacy endpoint: Reduction in the incidence of *S aureus* ventilator-associated pneumonia

Key safety endpoints: Safety, PK, and anti-drug antibody (ADA)

EFPIA contribution: All study implementation-related expertise (clinical, regulatory support, project management, data management, biostatistics, pharmacovigilance). Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%) incurred by public partners ensuring that 100% of these costs will be reimbursed.

WP6C: PHASE 1B/2A RANDOMIZED, PLACEBO-CONTROLLED, SINGLE-DOSE, DOSE-RANGING STUDY TO EVALUATE THE SAFETY, EFFICACY, AND PHARMACOKINETICS, OF MEDI4893 FOR THE PREVENTION OF SURGICAL SITE INFECTIONS (SSIS) ATTRIBUTABLE TO STAPHYLOCOCCUS AUREUS

Estimated Start: 4 Q2014

Estimated Study Duration: 30 months

An estimated **300 subjects/24-30 sites** will be recruited for this study. For one half of sites, recruitment will focus on potential sites within the EU, ie, those sites eligible for IMI JU funding; the other **150 subjects /12-15 sites** will be recruited in the rest of the world, with funding directly from AstraZeneca. Sample size and study specifics will be updated after the results of the WP 6A study and a Phase 1 safety and PK study, as well as scientific advice from regulatory agencies, are available.

Study preparation: **2Q 2014**

Study recruitment: **4Q 2014-1Q 2016**

Study close-out and report generation: **2Q 2019**

Study Objectives

The objectives of the proposed study are:

- 1) To evaluate the safety and tolerability of MEDI4893 administered to surgical patients at high risk for *S aureus* SSI
- 2) To evaluate the pharmacokinetics (PK) of MEDI4893 in serum
- 3) To evaluate the effect of MEDI4893 on the incidence of *S aureus* SSI in surgical patients at high risk for *S aureus* SSI
- 4) To evaluate measures of *S aureus* disease severity in patients with *S aureus* SSI
- 5) To evaluate biomarkers associated with *S aureus* disease severity and outcome

Study Population

The proposed study population consists of surgical patients considered at high risk for developing *S aureus* surgical site infections (to be determined), with a recent history of a prior *S aureus* SSI. Individuals at high risk of *S aureus* SSI include those with a *S aureus* SSI rate of 20% or higher; eg, orthopaedic patients undergoing a 2-stage procedure, with history of implant/device *S aureus* infection, and who are candidates for reimplantation. To be eligible for current study enrollment, subjects will be required to be free of any clinical and laboratory signs of active *S aureus* disease.

Study Design

The proposed study is a Phase 1b/2a randomized, placebo-controlled study in surgical patients who are at high risk for *S aureus* SSI and are free of *S aureus* disease at the time of study enrolment. Subjects will be evaluated for safety, PK, and efficacy.

WP 6C Study Details Summary

Key efficacy endpoint: Reduction in incidence of *S aureus* surgical site infection

Key safety endpoints: Safety, PK, and ADA

EFPIA contribution: All study implementation-related expertise (clinical, regulatory support, project management, data management, biostatistics, pharmacovigilance). Direct financial contribution by the sponsoring EFPIA company to supplement the study

costs (up to 25%) incurred by public partners ensuring that 100% of these costs will be reimbursed.

WP6D: ND4BB PROJECT MANAGEMENT, COLLABORATION, AND DISSEMINATION

Estimated Start: 3Q 2013

Estimated Study Duration: 72 months

Purpose

The overall purpose of WP 6D is:

- 1) to ensure effective Programme Management
- 2) to contribute to the overall scientific coordination of Topic 1, including programme governance
- 3) to manage the process for additional Calls from within the Consortium, and
- 4) to ensure adequate training and qualifications of investigators within the Consortium conducting WP 6A, WP 6B, and WP 6C.

Activities

A dedicated team within the Consortium will collaborate with members of other Topic teams to ensure effective communication and collaboration among projects funded under the ND4BB programme. The activities of this team will include:

- Development of standard communication tools for all projects funded under the AMR research area/ND4BB programme, eg, standard templates, externally facing website, etc
- A strategy for the dissemination of ND4BB-related communications to the broader scientific community that is coherent and aligned across all projects
- Provision for ensuring that data from all projects are deposited into the ND4BB Information Centre in accordance with the ND4BB framework
- Arrangement of training meetings among all WP6 investigators; at least one face-to-face training prior to initiation of the project, and subsequently follow-up training (possibly via webcast, teleconference, etc)
- Coordination of clinical trial operations and management, including data management, as appropriate
- Development of processes for the effective integration of the WP6 Consortium investigators into the Topic 1 investigator network.

Experienced clinical investigators, in collaboration with EFPIA partners, will function as coordinators and mentors within the consortium, facilitating information-sharing among the Consortium investigators and providing training to new investigators. Training will align when appropriate with the certification and training programme for the emerging Topic 1 investigator network.

EFPIA Partner Contribution: Project/Alliance Management personnel, meeting facilities, communication expertise. Provision of workshops/seminars/Q&As. Providing training and oversight for ensuring GLP standards for Consortium laboratories, especially those serving as central laboratories for WP 6B and WP 6C. Providing training and oversight to ensure clinical and laboratory sites remain "audit ready." Sharing of learning from clinical networks and the conduct of clinical trials in emerging economies. Information/expertise in clinical trial design, epidemiologic methods, infectious disease surveillance, regulatory requirements, quality assurance monitoring, clinical microbiology requirements and data quality standards.

APPLICANT CONSORTIUM

(To be selected on the basis of the submitted EoI)

Overall, the successful Applicant Consortium for Subtopic 1C must document in the EOI the capability for conducting active-surveillance, observational epidemiology **and** clinical studies in ICU and surgical patient populations. Applicants should be able to fulfil within the indicated time frame the patient recruitment and study personnel resourcing requirements of all studies (WP 6A, WP 6B, and WP 6C) described under Subtopic 1C.

Participating sites must conduct studies in accordance with the ethical principles in the Declaration of Helsinki, and consistent with ICH GCP and the applicable local regulations.

Other requirements of successful Applicants include:

- Expertise in current standard of care for patients undergoing surgeries and those requiring ICU care
- Expertise in epidemiologic surveillance and observational study design and conduct
- Expertise in providing clinical project management, including cross-functional collaborations, budget/timeline management, and regular status reporting
- Expertise in establishing and complying with standards for data extraction, data recording, database architecture, data analysis, and data privacy principles
- Ability to provide bacterial isolates and associated microbiological and epidemiologic data to a central regional laboratory
- Experience in supplying on-site training to ensure compliance with clinical study protocols
- Expertise in statistics and preclinical PK/PD modeling approaches
- Data from existing clinical studies to contribute to the ND4BB Information Centre
- Expertise in GCP and local and global regulations as they pertain to clinical trial design
- Expertise in bacterial, especially *S aureus*, virulence factors and in developing and performing relevant serologic assays on samples from clinical subjects, preferably under GLP conditions¹⁸
- Proposals for novel diagnostics/biomarkers to be utilized in clinical trial designs. Relevant diagnostics should be close to validation and with sufficient turnaround time (< 60 minutes) to identify subjects for enrollment and/or biomarkers which can be incorporated into the trial design with little or no impact on the collection of study data required for regulatory submissions.

Laboratory Requirements

Minimum local and central regional microbiology laboratory requirements include:

- Expertise in performing microbiologic testing, including standardized Gram stain and *in vitro* MIC (minimum inhibitory concentration) testing
- Ability to perform microbiology testing on a variety of patient samples, eg, nasopharyngeal, skin, deep surgical, blood, respiratory including sputum, endotracheal aspirate, bronchoalveolar lavage, or protected brush
- Documentation of appropriate quality control/quality assurance programme
- Laboratory accreditation by a country-specific agency

Minimum local and central regional serology laboratory requirements include:

- Ability to perform standardized serologic assessments of antibacterial antibody responses on samples from clinical subjects. The lab should provide evidence of expertise in developing or adopting and, subsequently, validating new serologic assays, and in providing the assays to clinical and/or epidemiology surveillance research under Good Laboratory Practice (GLP) conditions.
- Ability to perform enzyme-linked immunosorbent assays (ELISAs) using rabbit red blood cells under GLP conditions as recommend by the Medicines and Healthcare Products Regulatory Agency (MHRA) or other comparable regional guidance for

¹⁸ Special consideration will be given to laboratories capable of acting as a central regional laboratory to provide serologic testing support to other member sites

laboratories testing samples from clinical studies.

- Documentation of appropriate quality control/quality assurance programme
- Laboratory accreditation by a country-specific agency

Requirements Specific to WP 6A

- Member sites that have either participated in the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) and/or the Healthcare Associated Infections Surveillance (HAI-Net) networks (or other networks or consortia), **or** have demonstrated the ability to implement **patient-based** modules of similar surveillance protocols. Applicant Consortia should provide recent reports/analyses of HAI (or comparable) data both from individual sites and collectively from across the Consortium.
- The demonstrated ability to collect and report surveillance data on ≥ 1000 surgical procedures of interest (for SSI reporting) and ≥ 1000 patients admitted to the ICU (for ICU pneumonia reporting) per year per member site/network, by providing recent data collected in the two populations at member sites and collectively across the consortium.
- Surveillance experts to create study protocols and to determine the relevant pathogens, antimicrobial agents, clinical correlates, and analyses.
- Ability to collect nasopharyngeal and serum samples from patients prior to surgery or admission to the ICU, preferably as standard practice

Requirements Specific to WP 6B and WP 6C

- Clinical study experience with antibacterial or mAb treatments, preferably with the capability of administering parallel infusions to maintain double-blinding of studies and with the ability to follow patients upon discharge, and the ability to track recurrences or new disease onset requiring outpatient or inpatient management.
- Expertise in immunointervention or prophylaxis for infectious diseases, particularly in the surgical and intensive care unit populations.
- 24-hour availability of an unblinded pharmacist/third party for preparation and dispensing of IV infusions and trained blinded staff to administer IV infusions.

Requirements Specific to WP 6B

- Investigators with research and clinical backgrounds in intensive care and pulmonology, or with an established track record of conducting research in pneumonia, ventilator-associated pneumonia, or infections in the ICU. Investigators are expected to provide summary data on the number of ICU infections at their site; in particular, the number of pneumonia infections in the ICU, ideally by etiologic agent. Sites should have a patient load capable of supporting enrollment of 10-20 study subjects per site over a 12-month period.
- Investigators with experience in obtaining informed consent in patients requiring mechanical ventilation and/or sedation.
- Investigators with track record of performing research involving risk factors for ICU infections and/or pneumonia.
- Applicants are expected to propose ICU patient population(s) that have an increased risk for developing ICU pneumonia due to *S aureus*.

Requirements Specific to WP 6C

- Investigators with research and clinical backgrounds in general surgery, orthopaedic surgery, trauma surgery, neurosurgery, cardiothoracic surgery, and vascular surgery, or with an established track record of conducting research in surgical patients or research focused on surgical site infections (SSIs). Investigators are expected to provide site-specific summary data on the number of SSIs and nonsurgical infections within the surgical population, in particular, the number of SSIs

with and without device or implant, ideally by etiologic agent. Sites should have a patient load capable of supporting the enrollment of 10-15 study subjects per site over a 12 month period.

- Investigators with experience in obtaining informed consent in patients requiring urgent or trauma surgeries.
- Investigators with a track record of performing research involving risk factors for surgical infections and/or infections in the surgery population.
- Applicants are expected to propose surgical population(s) that have a 20% or higher rate of *S aureus* infection.

GENERAL PRINCIPLES FOR ALL STUDIES CONDUCTED UNDER ND4BB

Study Management

All clinical studies conducted in ND4BB will be conducted to Good Clinical Practice (GCP) standards to ensure that no process or data quality issues arise to jeopardize the outcome of the studies. In the case of the clinical trials, protocol compliance data quality and data integrity are essential to avoid the risk of a failed regulatory process. Noncompliance can severely jeopardise regulatory approval and pose ethical issues related to informed consent agreements with patients.

Due to the complexities of designing a global clinical trial to support regulatory submissions, it is common for both industry-funded and FP7 projects that a clinical research organization (CRO) is engaged to implement the study design and monitor clinical sites to ensure compliance. While this is the preferred approach, in some instances it may be preferable for a SME/CRO in collaboration with the sponsoring company's internal operations groups to implement these clinical trials.

There are two possible scenarios for the selection of the CRO:

- 1) The public entities recruit subcontractors under full respect of all applicable rules and regulations. In order to make up the funding gap arising out of the maximum 75% reimbursement of research activities, EFPIA companies foresee to provide a direct financial contribution to concerned beneficiaries.
- 2) In the event that the EFPIA fund the CRO in its entirety as part of their contribution in kind, the CRO will be appointed directly by the sponsoring EFPIA company according to normal internal procurement practices. The EFPIA company must be able to demonstrate 'value for money' to satisfy external auditors; otherwise, this cannot be counted as contribution in kind.

The criteria for the selection and identification of the CRO will be agreed upon during the formation of the full project proposal and project negotiation phase in accordance with the applicable rules, with the intention of having the contract with the CRO in place as soon as the project agreements are completed. This CRO will be accountable for delivering the operation of the clinical trial, including monitoring of all investigational sites operating under Good Clinical Practice (GCP) standards. This CRO will be responsible for ensuring coordination across all clinical trial sites (ie, those funded directly by the sponsoring EFPIA company as well as those engaging as part of the Applicant Consortium). This relationship will be governed through a specific Clinical Trial Agreement among the sites, Sponsor and CRO. Where CRO activities reside outside of the EU, this will be funded directly by the EFPIA Sponsor. In some clinical trials it may be possible that the EFPIA Sponsor may also recruit a CRO to manage non-EU based sites as part of a global study; in these situations an agreement between the EFPIA CRO and the consortium CRO will be established to ensure effective overall management of the trial. In all circumstances, only those hospital and healthcare institutions shown via site visits to be sufficiently compliant to be able to fulfill all aspects of the protocol to GCP standards will be permitted to recruit patients into the study.

Monitoring

Site Compliance

The EFPIA company that owns the asset will act as study trial Sponsor and as such will remain accountable for regulatory filings, pharmacovigilance, and all aspects of trial conduct. If a CRO is used, it will be responsible for ensuring effective monitoring of all sites with respect to medical governance, data management, and GCP requirements.

Trial-related decision making

Standard decision-making processes will apply to progression of clinical trials and will be the responsibility of the Sponsor. As the sponsoring company is legally accountable for the safety of all patients on the trial all decisions regarding trial progression or termination due to emerging safety issues will remain the responsibility of the sponsoring company. The Topic 1 Steering Committee will be notified of any decisions to terminate or change a study in response to emerging safety data.

In accordance with the requirements of the trial sponsor, the CRO will perform site inspections of investigator sites as needed to confirm the ability of the site to function up to GCP standards and to be capable of processing microbiology and serology specimens to laboratory certification requirements. Should a site fail to pass this inspection they would not be allowed to participate in the study, unless corrective measures can be taken by the site to address all critical insufficiencies.

Data Sharing in ND4BB

Data sharing is paramount to the success of ND4BB. The framework supporting this data sharing (ie, the type of data to be shared and the access governing data sharing) will be established during the preparation of the full project proposal in line with IMI IP Policy.

Clinical Trial Data

Disclosure of data from all ND4BB clinical trials supporting regulatory filings is subject to specific regulatory requirements with which EFPIA partners must comply. These regulations ensure that all data are presented and communicated in a responsible way by ensuring that efficacy data are presented with a balanced understanding/communication of the adverse event profile or other safety risks. Strict adherence to these regulations also ensures that data sharing activities will not be misrepresented as 'promotional activities,' as the conduct of such activities is prohibited prior to drug approval. While respecting these strict regulations, Sponsors of clinical trials conducted under ND4BB intend to disseminate results from trials conducted under the ND4BB programme as broadly as possible.

The goal of data sharing is to disseminate knowledge that is generally useful for others planning clinical trials. Examples of data sharing might include:

- Issues with specific inclusion criteria or endpoints
- Techniques for facilitating rapid enrolment of subjects at study sites
- Insights regarding pharmacodynamic markers/drivers of efficacy

Conversely, some data are very compound specific, may have special handling and reporting requirements due to regulatory concerns, and do not provide generalized insight useful for other development programmes. The most obvious such data are the safety and adverse event data for a particular product.

To address all of these concerns, ND4BB-related work will be shared in several ways. First, protocols and summary results from studies conducted under the ND4BB programme will be posted on internet registers, and clinical trial Sponsors will aim to publish results as journal manuscripts in searchable, peer-reviewed scientific literature, ensuring the accurate and balanced presentation of data. As such, for all clinical trials conducted under the ND4BB programme, Sponsors will ensure that:

- Protocols and informed consent documents clearly outline the intent to post a protocol summary on a publicly available protocol register and the clinical trial summary results on a publicly available results register, and to publish the results in searchable, peer-reviewed scientific literature.

- Primary publication of the study results, whether positive or negative, preferably as a journal manuscript (including primary and secondary efficacy endpoints and safety results and, when medically informative, exploratory analyses) will be mandatory. Publication of trial results will also be accompanied by public disclosure of the full study protocol (which may be redacted for proprietary content) on the Sponsor's Clinical Study Register.
- Proposals for additional analyses and reporting of either aggregate or subject-level data pre- or post-approval are assessed for scientific merit, impact, and reporting concerns by the Topic 1 Steering Committee and EFPIA Sponsor and will only be undertaken following final approval by the Sponsor. As noted above, reporting is legally required to be presented and communicated in a responsible way such that efficacy data are presented with a balanced understanding and communication of the adverse event profile or other safety risks. Such work is generally undertaken as collaborations between the clinical trial Sponsor and the proposer, with all analyses being reviewed and approved by the Sponsor prior to publication to ensure Sponsor policies regarding responsible communication are regarded (i.e. to ensure that the data is being used for appropriate scientific purposes in line with the original informed consents in addition to all local and national data privacy and data transparency policies).

In general, summary data from all clinical trials conducted under the ND4BB programme must be publicly posted within a reasonable period following study completion (typically considered the date of the last subject's last visit) or completion of the clinical study report. Once a clinical trial has been completed and the database locked for subsequent statistical analyses and reporting, data collected from study subjects at a specific investigator site can, at the Sponsor's discretion, be disclosed only to that specific investigator. Broad dissemination of any clinical trial data to investigators or other public entities will occur only as outlined above, as such data dissemination conducted "pre-approval" is considered as promotional and violates regulatory statutes.

ND4BB TOPIC 3: DISCOVERY AND DEVELOPMENT OF NEW DRUGS COMBATting GRAM – NEGATIVE INFECTIONS

BACKGROUND

One of the major challenges in antibiotic discovery is not the identification of new targets, but the generation and optimisation of novel molecular starting points (Hit and Leads) with a novel mode of action and sufficient activity against a range of key pathogens with sufficient selectivity (i.e. therapeutic index) over eukaryotic mechanisms. Due to the nature of the targets and the inherent penetration barrier of both the outer and inner membranes, this challenge is increased further for Gram-negative ESKAPE pathogens (*Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *E. coli*).

The identification of Hits is often the starting point for small molecule drug discovery. A Hit is usually defined as a molecule that binds to a target which has been identified to be important in the disease of interest. However while many Hits prove to be invaluable tool molecules few Hits are suitable for the development of new drugs. In order to ensure potential for drug development, such Hits would generally be expected to have a data package similar to what is outlined in Figure 1.

Once there is sufficient confidence in the Hit, this Hit then needs to be developed into a Lead series (i.e. clusters of molecules with high affinity to the target and 'drug-like' properties). Development of such a Hit into a Lead is an iterative process which can involve novel approaches (e.g. structure-based design, fragment approaches, combinatorial chemistry) in addition to traditional medicinal chemistry, in close cooperation with experts and platforms in microbiology, biochemistry, drug metabolism and others. Inherent to this process there is significant risk that the next milestone (e.g. 'Lead declaration') will not be obtained due to poor tractability of the series, challenging chemistry, off-target activities, etc. For novel antibiotic agents, a Lead would be expected to have properties similar to what is outlined in Figure 1.

Further, the development of a Lead into a Development Candidate is generally an even more challenging and lengthy process. Similar to the Hit-to-Lead stage, this 'Lead-to-Candidate' stage is an iterative process where the Lead compounds are further optimised, but in addition other attributes are considered, providing a compound with a profile similar to what is outlined in Figure 1.

Indeed the hurdles a compound must pass become greater the further into this process a programme goes. Thus, the optimisation of a Lead is a highly collaborative science where novel thinking must go hand in hand with high quality execution in a constantly revised iterative process to ensure the biological activity can be maintained while generating a molecule with the properties required of a useful drug for the indication of choice. Once all of these attributes appear to be appropriate for further testing Candidate selection can be declared.

With a Candidate molecule in hand a number of additional tests need to be performed to prepare the drug Candidate for clinical testing in human volunteers. Although some aspects will depend on the actual profile of the compound and the development strategy the team selects, much of the work in this phase is clearly dictated by regulatory authorities (e.g. assessment of toxicity in two species, assessment of genotoxicity, pharmaceuticals to ensure appropriate delivery of drug, extensive *in vivo* efficacy profiling, etc). In addition in this phase there is often time to bolster the scientific package of the drug candidate to clarify the development path and/or differentiate from existing

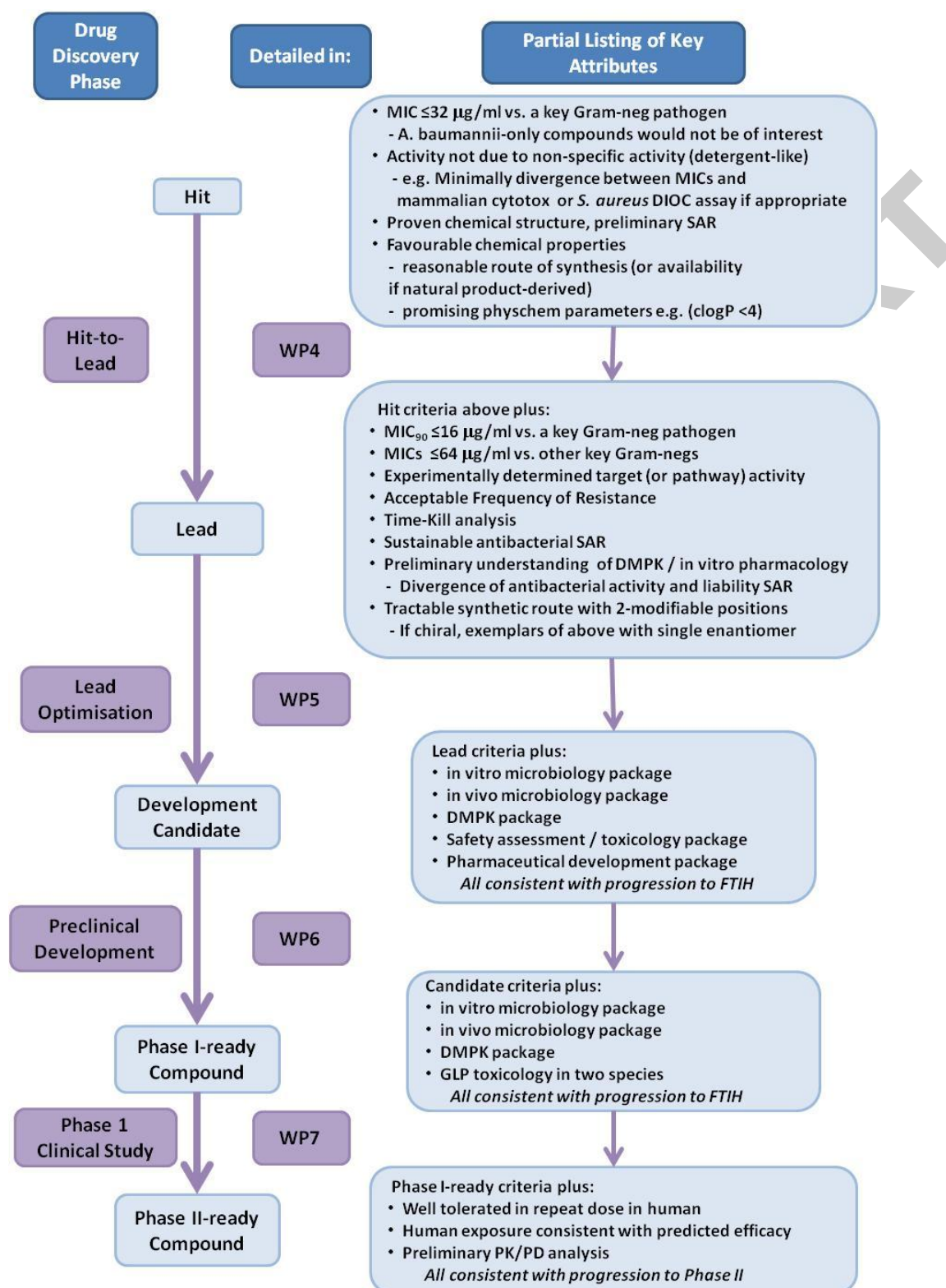
medicines (additional *in vivo* efficacy models, fundamental biology related to the target, better characterisation of resistance risks, etc.).

Phase 1 clinical trials are designed to study initial pharmacokinetics and tolerability of new, experimental medicines. Similar to the preclinical characterisation, much of the work in this phase is directed by guidance from regulatory authorities, although there are still potential opportunities for additional basic science characterisation of the drug and/or target, in addition to novel approaches to demonstrate that success has been obtained (e.g. *in vivo* efficacy models with human recreated pharmaco-kinetic (PK), etc).

Clearly successful drug discovery requires significant innovation combined with knowledge of drug discovery and also sufficient screening, chemistry, biology and pharmacokinetic capacity to deliver high quality molecular entities with high probability of success of generating a medicine. Historically however academics, SMEs and industry partners have competed with each other in the quest to develop the next antibiotic leading to duplication of effort and in many occasions failing to benefit from skills, knowledge and expertise available across these different sectors. The current Topic aims to break down these barriers to create a vibrant, collaborative drug discovery community where learnings and experience are shared for the benefit of all partners and the patients.

INDICATIVE ONLY

Figure 1: Summary of the Drug Discovery Flow and Key Compound Criteria for ND4BB Topic 3.



Abbreviations: MIC = Minimum Inhibitory Concentration; DIOC = 3-ethyl-2-[3-(3-ethyl-2(3H)-benzoxazolylidene)-1-propenyl]-benzoxazolium iodide; SAR = Structure Activity Relationship; DMPK = Drug Metabolism and Pharmacokinetics; FTIH = First Time in Human; GLP = Good Laboratory Practice; PK/PD = pharmacokinetic / pharmacodynamic

ND4BB TOPIC 3: GENERAL OUTLINE

The focus of the work in the current topic will be to establish a vibrant drug discovery hub across Europe with the resource, skills and expertise to generate a pipeline of "Leads" and "Development Candidates" originating from private or public partners targeting the systemic treatment of infections due to resistant Gram-negative bacterial pathogens (e.g. Enterobacteriaceae especially *E. coli*, *K. pneumoniae* and *Enterobacter* species, *Acinetobacter* species and *Pseudomonas aeruginosa*).

The core of Topic 3 will be a Drug Discovery Platform (WP3). This work package will effectively bring together scientists and leaders with a diverse set of skills to create a fully functional antibacterial drug discovery unit, capable of prosecuting multiple targets in both Hit-to-Lead and Lead-to-Candidate phases in parallel. Proposals for 'Hit-to lead' and 'Lead-to-Candidate' programmes will be invited from academic and SME investigators to utilise the resource and expertise available in WP3. Likewise, EFPIA partners will also benefit from the resources available in WP3 to advance certain Lead-to-Candidate programmes under ND4BB. A Portfolio Management Committee (WP2) will be responsible for critically evaluating all programmes and managing the resources in the Drug Discovery Platform (WP3) acting on behalf of the consortium. A further group will cover cross-topic communication with other ongoing ND4BB projects and overall project management (WP1).

Molecules or series with a novel mode of action from public and SME partners will enter the Hit-to-Lead phase as part of WP4. Note that herein novel mode of action could include action at a novel target, a novel mechanism of action against a known target or, a known mechanism of action against a known target so long as activity against target-based resistant strains and management of known liabilities are appropriate. Each of these modalities offers advantages and disadvantages.

Hit-to-Lead programmes of WP4 will utilize efforts of the Drug Discovery Platform (WP3), but will also be supplemented by target or programme specific efforts funded directly via WP4. Once a programme has entered into WP4 clearly defined screening activities, milestones and go/no go criteria will be established (in collaboration with EFPIA partners) and approved by the Portfolio Management Committee acting on behalf of the consortium. The Portfolio Management Committee will be responsible for managing the delivery of the overall portfolio of programmes such that if programmes in WP4 fail to meet pre-determined go/no-go criteria (including a maximum working period of 18 months) the programme might be terminated. It is envisaged that a maximum of 4 Hit-to-Lead programmes and 2 Lead-to-Candidate programmes will be ongoing at any one time. In the event that a Hit-to-Lead programme either is terminated or successfully transitions to Lead-to-Candidate there will be an opportunity to bring forward a new Hit-to-Lead programme. In the event that a new Hit-to-Lead programme cannot be identified from within the consortium, open Calls may be launched to allow additional Hit-to-Lead programmes to enter WP4. If a programme in WP4 meets pre-determined Lead criteria (as judged by the Portfolio Management Committee on behalf of the consortium), then it will progress to Lead-to-Candidate phase in WP5B and be eligible for additional resources from the Drug Discovery Platform Team to bring the programme to Development Candidate stage.

In addition to applicant programmes, GSK and Sanofi have agreed to share portions of their discovery portfolio and will begin working on the Lead optimisation of novel topoisomerase inhibitors as part of WP5A (for clarity, this will constitute one of the proposed three Lead-to-Candidate programmes which will be supported by the Drug Discovery Platform Team). As with WP4, the programmes in WP5A and WP5B will need to meet pre-determined go/no-go criteria for funding to continue. Any molecule(s) from WP5A or WP5B meeting Development Candidate status (as assessed by the Portfolio

Management Committee on behalf of the consortium) may transition to preclinical development as part of WP6 and, if successful, may transition to Phase 1 clinical trials as part of WP7. It is anticipated that the Topic 3 consortium shall identify and propose to the IMI JU the participation of new beneficiaries following an open and competitive Call to assemble the skills and resources needed to complete these later phases of Topic 3.

OBJECTIVES

The ND4BB project '**Discovery and Development of new drugs combatting Gram-negative infections**' will seek to:

- 1) Provide a unique platform to foster collaboration and exchange between private and public partners.
- 2) Establish a vibrant drug discovery hub across Europe with the resource, skills and expertise to generate a pipeline of "Leads" and "Development Candidates" (see Figure 1) originating from private or public partners. This group should be large enough to prosecute four Hit-to-Lead (WP4 programmes) and two Lead-to-Candidate (WP5A and WP5B programmes) efforts simultaneously;
- 3) identify three high quality, novel mode of action antibacterial Leads (see Figure 1) for the treatment of systemic Gram-negative infections;
- 4) identify two high quality, novel mode of action Development Candidate molecules for the treatment of systemic Gram-negative infections;
- 5) progress at least one novel mode of action Development Candidate into preclinical and Phase 1 clinical studies.

DELIVERABLES

- Three novel mode of action Gram-negative antibacterial Leads. Some key attributes of a Lead are laid out in Figure 1 above.
- Two novel mode of action Gram-negative antibacterial Development Candidates. Some key attributes of a Development Candidate are laid out in Figure 1 above.
- 1-2 novel mode of action Gram-negative antibacterial ready for Phase 1 clinical trials, e.g. a Development Candidate with microbiology including PK/PD studies to define target exposure to be achieved in Phase 1 studies, pharmaceutical development/CMC, DMPK/ADMET and safety assessment data packages to support progression to Phase I studies in human volunteers.
- 1-2 Gram-negative antibacterial agent which has been demonstrated to be sufficiently safe and well-tolerated at a dose and exposure that is predicted to be efficacious based on animal models of infection to progress to clinical trials in patient populations, and for which a viable dosage form for further progression has been identified.

EFPIA PARTICIPANTS

GlaxoSmithKline R&D, Sanofi, AstraZeneca, Basilea

INDICATIVE DURATION OF THE PROJECT

The indicative duration of this Topic will be 6 years.

INDICATIVE BUDGET

The in-kind contribution from the EFPIA participants is estimated at approximately €26M and the IMI JU contribution at €58.9M.

This budget is anticipated to be allocated in a staged manner, as exemplified under the specific work package section further down this document.

PROPOSED PROJECT ARCHITECTURE

The ND4BB Topic 3 consists of two subtopics as described below and as shown in Figure 2. Applicants are invited to submit an expression of interest to any of the subtopics. There is no obligation to apply for both subtopics. The expression of interest should address all WPs of the subtopic to which the applicant consortium is applying. Should an applicant consortium want to apply to both subtopics, then two separate expressions of interest shall be submitted.

The two successful applicant consortia from Subtopic 3A and Subtopic 3B will merge with the EFPIA consortium to prepare a Full Project Proposal. All participants working under Topic 3 will be part of the same Grant Agreement.

Subtopic 3A: Management and resource hub (Indicative EFPIA budget: €24.5M; IMI JU: €47.5)

In short, Subtopic 3A will combine project management aspects, project governance, and the resources and expertise required to move portfolio programmes forward. For a more detailed description of the subtopic, please refer to the information provided further down under each work package. Subtopic 3A is divided into the following seven work packages:

WP1: ND4BB Project Management, Collaboration and Dissemination (Indicative EFPIA budget: €1.5M; IMI JU: €0.3M)

WP2: Portfolio Management Committee (Indicative EFPIA budget: €0.6M; IMI JU: €0.6M)

WP3: Establishment of the ND4BB Drug Discovery Platform (Indicative EFPIA budget: €10; IMI JU: €29.1M)

WP5A: Delivery of Development Candidates for Gram-negative Infections, GSK/Sanofi Collaboration (Indicative EFPIA budget: €7.4M; IMI JU: €2.5M)

WP6: Delivery of Phase 1-Ready Antibacterials for Gram-negative Infections (Indicative EFPIA budget: €1.5M; IMI JU: €4.5M)

WP7: Phase 1 Trial of Novel Antibacterials for Gram-negative Infections (Indicative EFPIA budget: €3.5M; IMI JU: €10.5M)

WP8: Partnering Outreach (Indicative EFPIA budget: €0.5M; IMI JU: €0M)

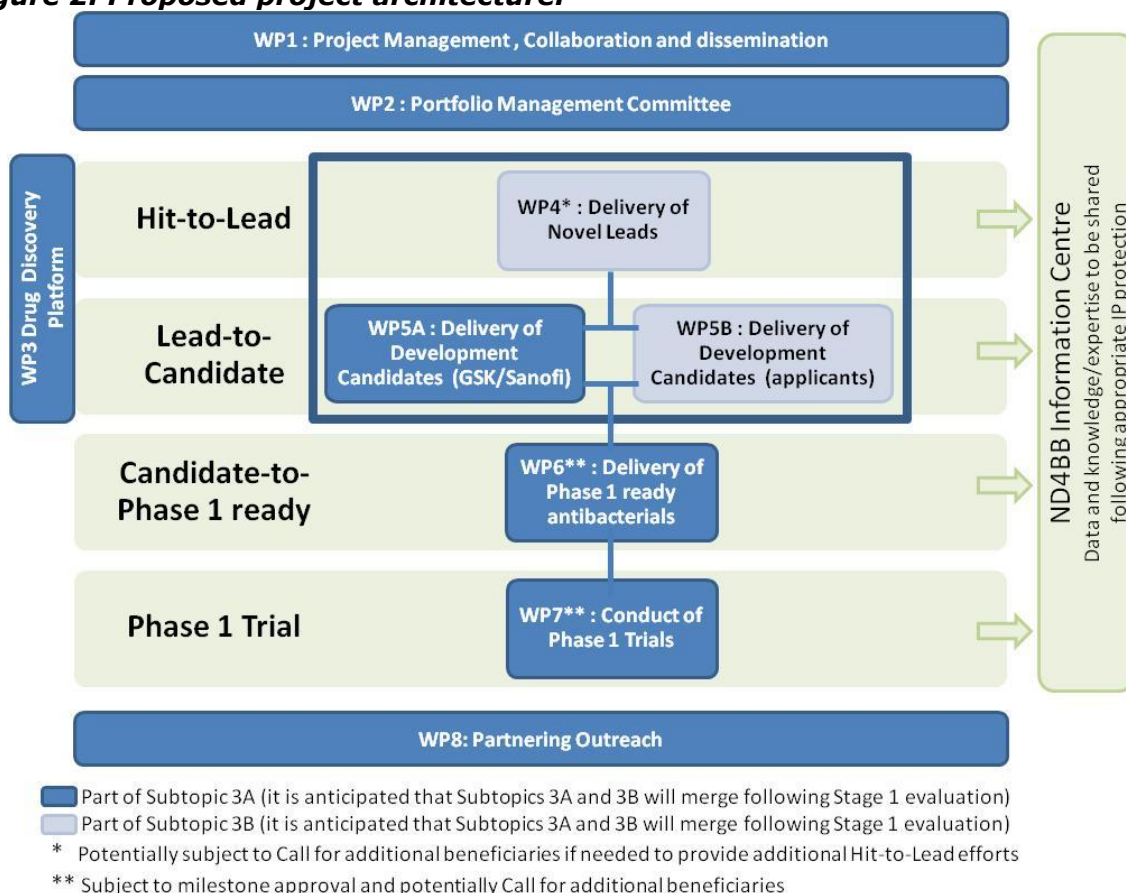
Subtopic 3B: Hit-to-Lead and Lead-to-Candidate portfolio (Indicative EFPIA budget: €1.5M; IMI JU: €11.4M)

In short, Subtopic 3B invites Hit-to-Lead and Lead-to-Candidate programmes into the project. For more detail please refer to the specific description provided further down under each work package. Subtopic 3B comprises the following two work packages:

WP4: Delivery of Novel Leads (Indicative EFPIA budget: €1.5M; IMI JU: €6.4M)

WP5B: Delivery of Development Candidates for Gram-negative Infections (Indicative EFPIA budget: €0.0M; IMI JU: €5.0M)

Figure 2: Proposed project architecture.



POINTS OF NOTE

The applicant consortium should:

- for Topic 3B include at least 2-4 potential Hit-to-Lead programmes (with Hits in hand as defined in Figure 1)—proposed budget should be in line with the number of programmes proposed. At least four research programmes will be selected to enter into WP4 initially. In accordance with the “IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals”, any arrangements for clustering or merging expressions of interest may be dealt with at the stage of the Full Project Proposal.
- propose research plans for each WP as outlined in the WP descriptions with associated resource requirements and indicative budgets. It is expected that the details of the screening and optimisation activities, milestones and go/no-go criteria (with associated resource) for each of the drug discovery programmes will be fine-tuned by the consortium within the first 1-2 months after the project has started. During the entire course of the project, plans and budgets may be refined and endorsed by the Portfolio Management Committee (WP2) on behalf of the consortium.
- be aware that since drug discovery is a highly risky business with only few potential Hits or Leads making it all the way through clinical development, funding should be released based on pre-determined milestones. These milestones will be pre-agreed by the Portfolio Management Committee on behalf of the consortium at the beginning of the project;

- be aware that in the event that any programme fails to progress to the next milestone, or if progress does not meet pre-determined criteria as outlined in WP2, programmes will be terminated. If this occurs, partners will have the opportunity to work on a new Hit-to-Lead or Lead-to-Candidate programme either available within their own institution or from one of the EFPIA partners in accordance with the provisions of the IMI Model Grant Agreement. Similarly in the event that a Hit-to-Lead programme successfully transitions to Lead-to-Candidate there will be an opportunity to bring forward a new Hit-to-Lead programme. In the event that a new Hit-to-Lead programme cannot be identified from within the consortium, open Calls may be launched to allow additional Hit-to-Lead programmes to enter WP4. A maximum of 8 Hit-to-Lead Programmes will be funded through the lifetime of the project;
- be willing to adhere to the progression criteria established by EFPIA and ratified by the Portfolio Management Committee on behalf of the consortium and the resourcing and prioritisation decisions made by the Portfolio Management Committee on behalf of the consortium;
- envision that additional beneficiaries might be required to ensure successful delivery of WPs 6-7. To that end applicants for Topic 3A should already outline plans to address WP6 & WP7 tasks in their expression of interest;
- note that when open Calls from within the existing consortium to engage additional beneficiaries are required, either to welcome additional Hit-to-Lead programmes into WP4 or to recruit expertise needed to conduct WP6 and/or WP7, these will be handled by the consortium with guidance from the IMI JU and shall follow the rules as outlined in the introductory section of the ND4BB programme; the budget for the additional partners to be recruited through an open Call will be taken from the overall budget agreed at the time of the Grant Agreement signature.
- aim to ensure that it remains attractive for public partners to bring in novel programmes into the ND4BB initiative and take full advantage of the flexibilities offered by the IMI IP policy (http://www.imi.europa.eu/content/documents#ip_policy);
- acknowledge that confidentiality needs to be preserved within the Portfolio Management Committee and adequate arrangements will be made during the development of the Full Project Proposal to ensure this. Applicants should propose a mechanism by which the Portfolio Management Committee can perform their required tasks while protecting proprietary information;
- be aware that final agreement on tasks to be conducted and budget to be allocated will be made following endorsement of the drug discovery plan by the Portfolio Management Committee by Month 2 of the project in accordance with the IMI rules.

ND4BB TOPIC 3: WORK PACKAGES

WP1 (part of subtopic 3A): ND4BB Project Management, Collaboration and Dissemination (Indicative EFPIA budget: €1.5M; IMI JU: €0.3M).

The main purpose of this WP will be to conduct administrative tasks of the Project, including annual scientific and financial reporting, project planning, managing the process for open Calls, ensuring collaboration between Topic 3 investigators and those in other ND4BB consortia and ensuring coherent dissemination of ND4BB results to the broader scientific community. **A similar WP is part of all projects launched under the ND4BB programme to ensure a close collaboration between all ND4BB projects.**

In WP1, a dedicated team, led and supported by experienced project management resource within EFPIA will work to:

- Disseminate ND4BB activities to the external community through a coherent strategy aligned across all projects (website etc.)

- Work out a plan to ensure that data from all projects is deposited in the ND4BB Information Centre (created in ND4BB Topic 2, WP6)
- Participate in the arrangement of annual meetings between all ND4BB investigators
- Participate in the ND4BB Scientific Advisory Board consisting of leading academics, key stakeholders and industry experts
- Create educational materials to be shared with the broader community.

Note that most of these activities will have already been established as part of the deliverables of the ND4BB Topic 2 project.

EFPIA Partner Contribution: Project/Alliance Management personnel, meeting facilities, communication expertise

WP2 (part of subtopic 3A) : Portfolio Management Committee (Indicative EFPIA budget: €0.6M; IMI JU : €0.6M)

In order to efficiently and objectively resource Topic 3 activities a Portfolio Management Committee will be created with equal representation from EFPIA and public partners and will, on behalf of the consortium:

- 1) Endorse the criteria that each molecule will have to meet in order to be declared a "Lead", "Development Candidate", "Phase 1 ready" or "Commit to Clinical Development". For each programme this will be tailored based on a set of broad criteria agreed by the consortium based on input provided by the EFPIA partners. Ensure all drug discovery programmes running under Topic 3 have well defined screening cascades, with timelines and resource requirements clearly aligned with each activity.
- 2) Review and approve critical path and screening activities proposed by the programme team ensuring focus on critical path activities with clearly defined go/no-go criteria and timelines.
- 3) Establish a business model and framework to objectively resource the ND4BB Discovery Portfolio and ensure that the portfolio is managed effectively based on these pre-defined go/no-go criteria, i.e ensuring the most promising programmes are resourced as a priority, terminating programmes which reach a no-go decision point, approve milestone achievements i.e. Lead Declaration, Candidate Selection, and Phase I ready, and release funding to partners and making the decision to invite new programmes to join ND4BB as appropriate in accordance to the provisions of the IMI model grant agreement.
- 4) Conduct regular reviews of the ND4BB Drug Discovery Portfolio to ensure programmes with highest probability of success are resourced adequately;
- 5) Propose an appropriate mechanism to ensure effective review while maintaining confidentiality.

It is envisaged that the consortium will engage external advisors to support the Portfolio Management Committee. These external advisors would be experts in antibacterial drug discovery and would provide additional, independent feedback and opinions on the progress and resourcing of the ND4BB Topic 3 portfolio. The Portfolio Management Committee will plan to meet e.g. quarterly to review the portfolio and discuss / decide on prioritisation, though provision for ad hoc discussion or recommendations will be possible if the need arises.

EFPIA Partner Contribution: Committee Co-chair, experts in drug discovery, well defined lead and candidate declaration criteria and experts in project management, portfolio management and business development. Educational materials and training on the principles of drug discovery.

WP3 (part of subtopic 3A): Establishment of the ND4BB Drug Discovery Platform (Indicative EFPIA budget: €10; IMI JU: €29.1)

WP3 aims to establish a pool of resources and expertise from SMEs, academia, and EFPIA in many different fields that are all related to, and important for antibacterial drug discovery. The aim of this work package will be to focus on establishing a clustered drug discovery group for the support of all drug discovery programmes conducted in ND4BB Topic 3. Therefore, initially within WP3 there will be no focus on specific targets or compounds, rather this WP will gather all the expertise and resource required to establish screening cascades and optimisation strategies for specific programmes in WP4, WP5A and WP5B.

This work package will focus on:

- Working in partnership with the Programme leaders from WP4 and WP5A/WP5B and the Portfolio Management Committee created in WP2 to establish the screening cascades for the Hit-to-Lead and Lead-to-Candidate programmes entering into ND4BB.
- The establishment of the resource and expertise to support all drug discovery efforts conducted under ND4BB Topic 3 i.e.:
 - Expertise and resource in medicinal chemistry including specific experience in bringing programmes through both the Hit-to-Lead phase and to the Candidate Selection phase [indicative capacity ~ 32-36 FTEs]
 - Expertise and resource in drug metabolism and pharmacokinetics (e.g. CYP p450 inhibition / induction; *in vitro* metabolism and metabolite identification; solubility and pKa / logP / logD measurement; plasma protein binding; permeability measurements; rodent and non-rodent *in vivo* pharmacokinetics, IV, SC, IP or PO dosing) [indicative capacity ~ 6 FTEs]
 - Expertise and resource in *in vitro* and *in vivo* microbiology, specifically with the key Gram negative pathogens listed above (e.g. routinely running a primary panel of MICs to support Hit-to-Lead and Lead-to-Candidate programmes; determination of MIC₉₀s for key organisms; time-kill analysis, frequency of resistance determination, animal infection models in mice and rats; preliminary PK/PK studies) [indicative capacity ~16-20FTE]
 - Project Management for individual drug discovery programmes
- Ideally the effort in WP3 should be appropriate to support four Hit-to-Lead and two Lead-to-Candidate programmes in parallel. For guidance purposes only, the following efforts are suggested, though final efforts will need to be balanced between available budget and resource needs for a given programme
 - Indicative effort for Hit-to-Lead programmes to include 2-3 medicinal chemistry and 2-3 biology and 0.3 DMPK FTE
 - Indicative effort for Lead-to-Candidate programmes to include 12 medicinal chemistry and 4 biology and 2 DMPK FTE

Guidelines (not requirements) as to the potential breakdown and staging of the IMI JU budget for individual efforts from WP3 are shown below:

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
4 x Hit to Lead : €4.8M					
GSK/Sanofi Lead-to-Candidate : €6.5M					
		4 x Hit-to-Lead : €4.8M			
		2 x Lead-to-Candidate : €13M			
				2 x Phase 1 ready* : €4.5M	
					2 x Phase 1* €10.5M

* maximum of 2 programmes (assuming 1 partnered with EFPIA)

EFPIA Partner Contribution: Educational materials and training on the principles of drug discovery, well defined Lead and Candidate Declaration criteria. Advice in all areas of drug discovery (for example: computational modelling, *in vitro* and *in vivo* microbiology, medicinal chemistry, pharmacokinetics, pharmaceutical development, safety assessment), project management.

WP4 (part of subtopic 3B): Delivery of novel "Leads" (Indicative EFPIA budget:€1.5; IMI JU: €6.4M)

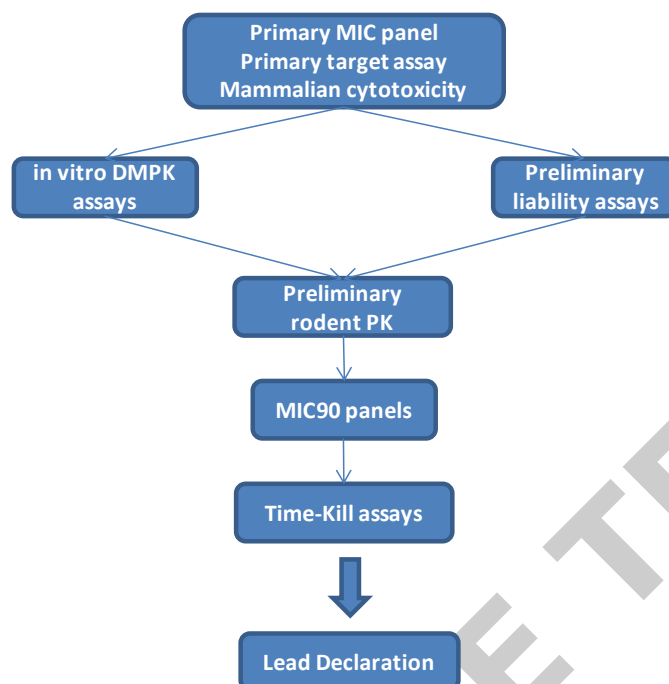
This work package will focus on the study and development of novel small molecule antibacterial Hits into Leads which can then progress into WP5B. Efforts could include conducting more detailed mechanism of action studies; broader antibacterial screening, establishing assays and generating reagents and iterative Hit-to-Lead medicinal chemistry that would be required prior to initiating a full Lead optimisation programme (e.g. transition to WP5B). These efforts would be conducted by the Drug Discovery Platform team, with additional programme specific efforts funded directly via WP4. The role of EFPIA in this WP will be to provide expertise in antibacterial drug discovery to help guide the programmes to a successful endpoint.

Proposals should therefore include details of

- a programme of work including a proposed screening cascade with go/no-go criteria (similar to the example below).
- Expertise and resource required from the Drug Discovery Platform (WP3). Funding available in WP4 should be utilized to conduct activities that cannot be conducted by the Drug Discovery Platform.

A high level view of a potential screening cascade is shown in Figure 3, though the cascade for any particular programme should be tailored to address the key needs and risks for any given programme. It is acknowledged that this plan will vary over time, but applicants should provide a cascade that reflects their current thinking given the stage of their individual programmes.

Figure 3: Potential screening cascade for a Hit-to-Lead program.



The overall aim of this work package will be to identify two-three molecules / series that fulfill the 'Lead' criteria for entry into the Lead-to-Candidate phase. This "Lead" criteria will be guided by EFPIA's current standards and will be fully defined during the development of the Full Project Proposal, but would be expected to include the criteria as laid out in Figure 1.

Please note that it is envisaged that four Hit-to-Lead programmes will initially be selected and funded under this WP. Therefore each Hit-to-Lead programme proposed should assume a total budget of €2.0M, of which €1.2M are available from WP3: The Drug Discovery Platform and €0.8 M can be planned in directly through this WP should programme-specific resources be required (for activities that cannot be supported by WP3). All efforts will be initiated at the start of the project i.e. Month 1 and will run until a "Lead" is identified, or pre-determined no-go criteria are reached (see WP2) or for a maximum of 18 months. Note that an additional €8M will be available for 4 new Hit-to-Lead programmes once the first 4 programmes have transitioned/Terminated (€3.2M from WP4 and €4.8M from WP3). A certain flexibility around the allocation of budget depending on the needs of a specific programme is anticipated.

Applicant consortia should propose efforts to develop "Hits" into Leads i.e.: the proposal should outline a drug discovery programme built around Hits that already have datapackages consistent with the Hit criteria as shown in Figure 1.

Guidelines (not requirements) as to the potential breakdown and staging of the IMI JU budget for individual efforts from WP4 are shown below.

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
4 x Hit-to-Lead : €3.2M WP4 + €4.8M WP3					
		4 x Hit-to-Lead : €3.2M WP4 + €4.8M WP3			

EFPIA Partner Contribution: Advice and expertise in all areas of drug discovery (for example: computational modelling, *in vitro* and *in vivo* microbiology, medicinal chemistry, pharmacokinetics, pharmaceutical development, safety assessment), project management. In the event that several WP4 programmes fail to generate high quality Leads EFPIA may, pending further discussion, also contribute Hit-to-Lead programmes to bolster the overall probability of success of the programme.

WP5A (part of subtopic 3A): Delivery of Development Candidates for Gram-negative Infections: GSK/Sanofi Collaboration (Indicative EFPIA budget: €7.4M; IMI JU: €2.5M)

This work package will focus on the development of novel Leads originating from the Sanofi/GSK collaboration into development candidates ready for preclinical profiling. To this end GSK and Sanofi have agreed to share portions of their early discovery portfolios and in collaboration, provide "Leads" to WP5A. These Leads will have a data package consistent with the Lead criteria as described above.

The bacterial topoisomerases (DNA gyrase and topoisomerase IV) are the clinically validated targets of the fluoroquinolone class of antibiotics. These drugs clearly demonstrate that inhibition of gyrase function can result in rapid, cidal and highly efficacious antibacterial agents. However, the quinolone class is significantly compromised by widespread target resistance and therefore any new antibacterials targeting the topoisomerases needs to be unaffected by these target mutations. The current work package will focus on the development of Leads proposed by GSK/Sanofi which target the topoisomerases via a novel mechanism of action, binding to a site that has not lead to a marketed drug yet or has never been previously identified in the literature. As such, these Leads are unaffected by current target-based quinolone resistance and therefore offer a very attractive starting point for Lead optimisation of a novel antibacterial agent. In addition, the complex and rich biochemistry and structural biology of these targets that has recently emerged following the public disclosure of high quality gyrase crystal structures unlocking the 40 year mystery of the detailed molecular mechanism of quinolones offers multiple avenues for innovative thinking which can directly affect the optimisation of these agents. These points are coupled with GSK's and Sanofi's significant historical expertise in this target area.

In depth knowledge of molecular and structural biology of the type II topoisomerase enzymes and detailed enzymology to determine the mechanism of action of Lead compounds will be extremely helpful for rational drug design. In addition, the development of innovative approaches to understand the frequency of resistance risk, both *in vitro* and *in vivo* would be of interest. This is expertise that normally resides primarily within academia.

Therefore, this WP is inviting applicants to, for example:

- provide proposals to study the molecular basis of action and enzymology of lead compounds against bacterial type II topoisomerases. This may include a structural biology component, provided that it is comparable to or better than the platform already developed within GSK to support structure based drug design for this crystallographically challenging target system (Bax et al., 2010, Nature, 466, 935-940; Wohlkonig et al., 2010, NSMB, 17, 1152-1153).
- propose innovative approaches to understand the frequency of resistance risk, either *in vitro* and/or *in vivo*.
- Note that the applicants should have flexible enough skills to work on other targets if need arises.

It is envisaged that one Lead-to-Candidate programme from the GSK/Sanofi collaboration will be funded under this WP. Guidelines (not requirements) as to the potential breakdown and staging of the IMI JU budget for individual efforts from WP4 are shown below. There will therefore be a total resource of €9.0 M per Lead-to-Candidate programme split €6.5M to the Platform group and €2.5M to the work conducted here.

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
GSK/Sanofi Lead-to-Candidate : €6.5M					

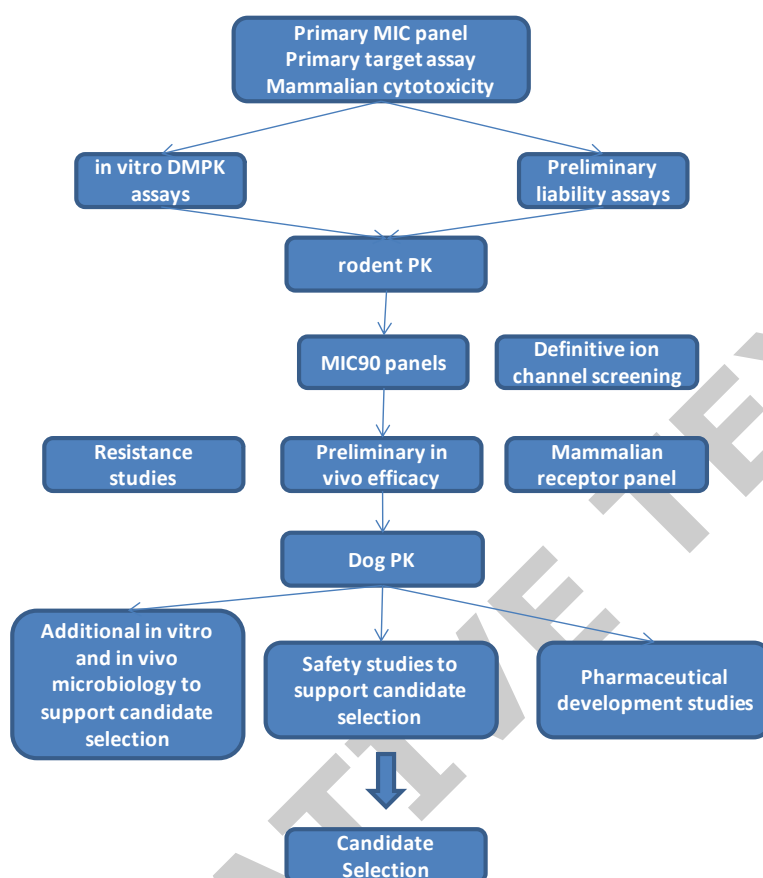
EFPIA Partner Contribution: Lead series, expertise and capacity in all areas of drug discovery (for example: computational modelling, *in vitro* and *in vivo* microbiology, medicinal chemistry, pharmacokinetics, pharmaceutical development, safety assessment, protein crystallography, enzymology), project management.

WP5B (part of subtopic 3B): Delivery of Development Candidates for Gram-negative Infections (Indicative EFPIA budget: €0.0M; IMI JU: €5.0M)

This work package will focus on the study and development of the novel small molecule antibacterial Leads arising from WP4 into development candidates which can progress into WP6. Efforts could include - depending on the nature of the Leads - more detailed mode of action studies, biochemical characterization of the target, characterization of potential resistance mechanisms and iterative Lead optimisation that would be required to provide a development candidate (e.g. transition to WP6). These efforts would be conducted by the Drug Discovery Platform team, with additional programme specific efforts funded directly via WP5B. The role of EFPIA in this WP will be to provide expertise in antibacterial drug discovery to help guide the programmes to a successful endpoint.

A high level view of a potential screening cascade is shown in Figure 4; though the cascade for any particular programme should be tailored to address the key needs and risks at the time and will likely vary over the course of a programme. Such changes would be brought to the Portfolio Management Committee, acting on behalf for the consortium, for approval.

Figure 4: Potential screening cascade for a Lead optimisation programme.



Potentially, if molecules from the applicant consortium already fulfill “Lead” criteria then these applicants may build a proposal including the following:

- a full data package supporting a Lead declaration proposal
- The remainder of the proposal should then focus on the plans for the Lead-to-Candidate phase including
 - the proposed programme of work including a proposed screening cascade with proposed go/no-go criteria (similar to the example below).
 - Expertise and resource required from the Drug Discovery Platform. Funding available in this work package should be utilized to conduct activities that cannot be conducted by the Drug Discovery Platform.

The programme would initially enter WP4 but would be able to transition directly into WP5B during the project implementation following approval by the Portfolio Management Committee.

It is envisaged that up to two Lead-to-Candidate programmes will be funded under this WP. Guidelines (not requirements) as to the potential breakdown and staging of the IMI JU budget for individual efforts from WP4 are shown below. There will therefore be a total resource of €2.0 M per Lead-to-Candidate programme split €6.5M to the Platform group and €2.5M to the work conducted here.

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
		2 x Lead-to-Candidate : €5M WP4 + €13M WP3			

EFPIA Partner Contribution: Expertise and advice in all areas of drug discovery (for example: computational modelling, *in vitro* and *in vivo* microbiology, medicinal chemistry, pharmacokinetics, pharmaceutical development, safety assessment, protein crystallography, enzymology), project management.

WP6 (part of subtopic 3A): Delivery of Phase 1-Ready Antibacterials for Gram-negative Infections (Indicative EFPIA budget: €1.5M; IMI JU: €4.5M) Estimated start: year 5.

This work package will focus on building a robust body of data to support Phase 1 clinical trials for novel antibacterial candidates developed under ND4BB. It is anticipated that WP6 efforts will follow on from successful WP5A and/or WP5B campaigns, thus this WP will start after the initiation of WP1-5. It is envisaged that 1-2 molecules from WP5A and/or WP5B will be progressed to this stage in the programme. The selection of the asset(s) will be made by the Portfolio Management Committee on behalf of the consortium using pre-determined criteria. The activities conducted in this WP will vary with the actual target and profile of the compound selected, but will include large scale synthesis, characterization and formulation of drug substance appropriate for clinical study, acceptable safety profile in GLP rodent and non-rodent species, evaluation of genetic toxicology potential, metabolism and pharmacokinetic characterization, large scale microbiological profiling, etc.

It is envisaged that some activities will be fulfilled by existing project participants; however the tasks and budget will be defined and allocated following successful completion of WP5A and/or WP5B. **In addition is it likely that this WP will be subject to an open Call for additional beneficiaries if the required skill sets are not already present within the consortium.** Guidelines (not requirements) the breakdown of the IMI JU budget assumes total cost per programme of €3M. Budget breakdown assumes one EFPIA partnered programme where costs are shared 50:50 with the IMI JU and one programme fully funded by the IMI JU.

EFPIA Partner Contribution: expertise in all areas of drug discovery and preclinical development (for example: computational modelling, *in vitro* and *in vivo* microbiology, medicinal chemistry, pharmacokinetics, pharmaceutical development, safety assessment, process chemistry, regulatory, clinical), project management.

WP7 (part of subtopic 3A): Phase 1 Trial of Novel Antibacterials for Gram-negative Infections (Indicative EFPIA budget: €3.5M; IMI JU: €10.5M) Estimated start: year 6.

It is anticipated that WP7 efforts will follow on from successful WP6 efforts, thus this WP will start after the initiation of WP1-6. This work package will focus on the planning, execution and interpretation of the human volunteer pharmacokinetics studies performed on the compound derived from WP6 of this Topic. The expectation is for an initial investigation of single dose pharmacokinetics in a dose escalation format, followed by investigation of pharmacokinetics with repeated dosing based on the single dose pharmacokinetics and the intended clinical treatments relevant to the compound's spectrum of antibacterial activity. Once the initial single and repeat dose investigations establish an expectation of acceptable safety, tolerability and exposure in a range predicted to deliver clinical efficacy, additional human investigations will be conducted to investigate relevant changes in drug exposure in specific subpopulations (varied age, gender, impaired hepatic or renal function, exposure in lung epithelial lining fluid). Other investigations will also be conducted that explore the absorption, distribution, metabolism and excretion of the compounds along with an assessment of any effect on the human cardiac conduction system.

It is envisaged that some activities will be fulfilled by the initial project participants; however the tasks and budget will be defined and allocated following successful completion of WP6. **In addition is it likely that this WP will be subject to an open Call for additional beneficiaries if the required skill sets are not already present within the consortium.** Guidelines (not requirements) the breakdown of the IMI JU budget assumes total cost per programme of €7M. Budget breakdown assumes one EFPIA partnered programme where costs are shared 50:50 with the IMI JU and one programme fully funded by the IMI JU.

EFPIA Partner Contribution: If the molecule arises from EFPIA, knowledge and expertise on the novel antibacterial drug being studied. All study implementation-related processes for EFPIA-partnered programmes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise, statistical analysis, etc).

WP8 : Partnering Outreach (Indicative EFPIA budget: €0.5M; IMI JU : €0M)

This work package will focus on supporting partners with potential novel antibiotics generated within ND4BB in developing attractive packages to support them in seeking partnering opportunities. EFPIA member companies have Business Development functions which specialise in partnering with external organisations, and have access to a wide range of potential partners and will directly support the facilitation of partnering discussions.

INDICATIVE EXPECTATIONS FROM THE APPLICANTS

The applicant consortium applying for this project should offer the following:

Subtopic 3A

- Scientific and media communications expertise
- Project management expertise
- Expertise in antibacterial drug discovery and portfolio management
- Expertise and capacity in synthetic and medicinal chemistry and drug discovery with a demonstrated track record of bringing programmes to Candidate Selection phase
- Expertise and capacity in pharmacokinetics and drug metabolism
- Expertise in process or scale-up chemistry
- Expertise in *in vitro* and *in vivo* microbiology (preferably with expertise in the key Gram-negative pathogens listed above); including *in vitro* capacity for routine profiling, MIC₉₀ profiling and applied microbiology studies (e.g. time kill analysis, frequency of resistance, and *in vivo* capacity for both profiling and Candidate Selection datapackage workup);
- Expertise in biochemistry and enzymology for target work and liability screening
- Expertise in the target / pathway work related to WP5A beyond the scope available in WP3

Subtopic 3B

- Hit-to-Lead programmes with a novel mode of action
- Potentially programmes already fulfilling Lead criteria
- Ability to carry forward novel antibacterial small molecule direct antibacterial activity Hits with indications of tractable mode of action
- Expertise in the targets / pathways being targeted beyond the scope available in WP3, potentially including protein crystallography

DEVELOPING AN AETIOLOGY-BASED TAXONOMY OF HUMAN DISEASE

This call theme in this IMI call consists of 3 topics:

- Topic a: approaches to develop a new classification for systemic lupus erythematosus (sle) and related connective tissue disorders and rheumatoid arthritis (RA).
- Topic b: approaches to develop a new classification for neurodegenerative disorders with a focus on Alzheimer's disease and Parkinson's disease.
- Topic c: approaches to develop a new classification for chronic obstructive pulmonary disorders (COPD).

An Applicant Consortium applying for one of the topics of the Call Theme will not be obliged to apply for the other two topics. It is foreseen that the three projects will strictly collaborate and coordinate their respective activities by sharing data, and information, by providing access rights to foreground and by establishing a joint governance structure under the umbrella of the taxonomy call theme.

New diseases areas will be added to the call theme in future IMI calls.

BACKGROUND

Current classification of disease is built upon a hierarchical structure with subdivisions of morbid entities assigned based on consensus criteria.

The Classification is grouped into:

- Epidemic diseases
- Constitutional or general diseases
- Local diseases arranged by anatomical site
- Developmental diseases
- Injuries

The origin of the current classification of diseases dates back to William Farrs work in 1855. A major part of the criteria is based on anatomical foci of the disease, symptomatological and epidemic patterns of the disease and very little, if any, is based on molecular mechanisms which are likely to more closely reflect the effects of medicines.

Major issues with this taxonomy are that the criteria are based on the effects of the disease process rather than aetiological mechanisms. As a consequence of this, the current disease classification contains both aetiologicaly heterogenous disorders and misclassification of other aetiologicaly similar conditions. This significantly impedes the development of molecularly directed and potentially more effective medicines.

There are early and non-complete attempts to reclassify disorders based on molecular findings e.g. classification based on hereditary patterns and genetic findings within the current taxonomical system.

A novel taxonomy of disease may require a multi-axial approach for example using mutations and polymorphisms within a genetic axis, gene expression data on a genomics axis, protein modifications and protein expression patterns on a proteome axis, protein interactions on a biological system axis, clinical data and imaging data and so forth.

PROBLEM STATEMENT

The success rate in drug development is far below that of other industries, on an average at 11%, in some therapeutic areas even below that figure. In parallel, the development timelines are long and increasing and consequently, the costs are high and increasing. New approaches must be sought to improve the success rates. In parallel, unmet medical need is very high for many diseases and curative treatments are lacking.

Current disease taxonomy is based on effects of the disease process rather than aetiological mechanism. As a result of this, several disease entities overlap, the identification of specific and objective diagnostic criteria are hampered, and consequently, the development of more molecularly directed and thereby more effective medicines is delayed. The lack of a clear relationship between molecular pathogenesis and disease classification means that:

- Currently patients are being exposed to novel and approved agents with little chance of benefit due to the heterogeneity of molecular mechanisms resulting in the same "disease class".
- Patients are being denied access to potentially beneficial novel and approved agents due to misclassification to a different "disease class" despite a similar aetiological mechanism.
- In immunoinflammatory disorders the conditions are classified by the end organ phenotype. This is especially the case for rheumatoid arthritis (RA) where it is the active inflammation of joints which is the key feature. However the cause of the inflammation may be different and there are multiple patterns of joint inflammation observed and non-joint manifestations. The heterogeneity of the disease can also be observed in the variable response to different therapies. Systemic lupus erythematosus (SLE) is a second immunoinflammatory disorder with a very variable phenotype driven by a range of autoantibodies. Despite having the autoantibodies in common the phenotype observed in patients is very heterogenous in terms of both organ involvement and severity. The current phenotypic classification results in neither condition being well served with current therapies. The large number of potential targets for these conditions currently in development based on our developing understanding of immune biology will require a more sophisticated understanding of disease biology and hence disease classification for successful approval.
- The development of chronic neurodegenerative conditions is widely recognized as one of the major societal health problems of the 21st century. To date the focus of therapies for these conditions e.g. Alzheimer's disease and Parkinson's disease has been on symptomatic relief and efforts to develop disease modifying treatments have been unsuccessful. The traditional method of classifying neurodegenerative diseases is based on the original clinico-pathological concept supported by 'consensus' criteria and data from molecular pathological studies. Current problems in this classification

results from the coexistence of different classificatory schemes, the presence of disease heterogeneity and multiple pathologies, the use of 'signature' brain lesions in diagnosis, and the existence of pathological processes common to different diseases. Over the last decade, several autosomal dominant and recessive genes causative of Parkinson's (PD) and dementia including Alzheimer's disease (AD) have been identified. The functional studies on their protein products and the pathogenic effect related to their mutations have greatly contributed to understand the many cellular pathways leading to neurodegeneration. On the other hand it has also emerged that mutation in the same gene can be found in different neurodegenerative conditions and the same pathogenic mechanisms are seen in neurodegenerative diseases currently classified as separate entities. For example recently, a hexanucleotide repeat expansion in C9orf72 was identified as a major cause of both sporadic and familial frontotemporal dementia and amyotrophic lateral sclerosis, suggesting that these disorders are part of a disease continuum. The microtubule-associated protein tau is the major component of the paired helical filament of Alzheimer's disease. Similar filamentous deposits are also present in a number of other diseases, including progressive supranuclear palsy, corticobasal degeneration and Pick's disease. The broad move from improving symptoms to disease modification will require a more sophisticated understanding of disease pathogenesis and hence disease taxonomy.

- Chronic Obstructive Pulmonary Disease (COPD) is a condition characterized by obstructive lung defects with smoking being the most common aetiological factor. However the pathology is variable with approximately 1/3 of subjects having a predominantly bronchiectatic pathology causing productive cough, 1/3 of subjects predominantly emphysematous and 1/3/ mixed. These pathologies result from chronic lung damage but do not necessarily represent different or homogenous molecular aetiologies. There are no good disease modification therapies for COPD and the lack of an ability to identify homogenous disease groups based on molecular pathologies is stopping the rational application of potential therapies focusing on disease mechanisms.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The magnitude of the issue of reclassifying disorders is so large that it can only be addressed by a major Public-Private-partnership involving a variety of stakeholders including those primarily involved in understanding molecular mechanisms of disease, biopharmaceutical companies which endorse the approach and have a complimenting experience and expertise and the regulators.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Synergies may be sought from other IMI initiatives, in particular those already focusing on the relevant disease areas and those on knowledge management (in particular ETRIKS). Furthermore synergies will be sought with other European (e.g. Joint Programming on Neurodegenerative Diseases and other ongoing and planned FP7 projects) and non-European (e.g. CAMD) Initiatives.

OVERALL OBJECTIVES

To evaluate the scientific status and initiate a new taxonomical approach to classification of human diseases which is based on objective data-driven aetiologically relevant

molecular evidence related to a syndrome (a disease) rather than based on anatomical foci, and/or symptomatological and epidemic patterns.

This Call Theme will include three Topics in this IMI Call. The first topic will be for approaches to develop a new classification for SLE and related connective tissue disorders and RA. The second topic will focus on neurodegenerative disorders with a focus on Alzheimer's disease and Parkinson's disease. The third topic will be on COPD. All of these disorders are recognized as being heterogeneous according to ICD-10 diagnostic criteria.

The successful consortium within each topic area will merge with the EFPIA consortium to prepare a Full Project Proposal, evaluating the use of molecular criteria to stratify associated syndromes/diseases into more homogenous segments based on underlying aetiological mechanism.

In future Calls the scope of the initiative will be widened to include other disease areas.

It is expected that the projects originated by this Call Theme will deliver in an open access spirit, tools and resources for the benefit of the whole biomedical community, to foster their exploitation and validation beyond the lifetime and framework of the IMI projects.

EXPECTED KEY DELIVERABLES

Within its 5 year lifetime each project should aim to deliver a proposal for a new aetiologically based taxonomy of common SLE and related disorders and RA (Topic A), Dementia and PD or a subset thereof (Topic B) and COPD and related respiratory disorders (Topic C) that will provide the foundation for the taxonomy of other disorders. The approach should be data driven (based on both existing data from private and public partners and newly generated data) and multidisciplinary.

For each Topic Key deliverables to be achieved, adapting when necessary to the need of the specific disease area, are:

- A new disease classification able to provide the basis for patient selection and stratification to facilitate clinical trials and speed up the development of new more effective medicines. The development of a new taxonomy of disease should be based on molecular aetiology by combining
 - a. Clinical data
 - b. Molecular data
 - c. Imaging data
- The basis for a more efficient and improved drug development process.
- The basis for the identification of novel targets or pathways for future therapeutic interventions.
- Standardized and harmonized databases and biobank for data-mining from the whole biomedical community.
- A rationale for more specific diagnostic tools.
- A close collaboration and involvement of regulatory authorities to ensure alignment of the project scope with the regulatory requirements to facilitate qualification and validation of results.
- Sustainability of project results should be addressed.
- Community wide dissemination of project results should be one of the project's priorities.

- As the intent is to create a new more rational taxonomy of disease for biomedical research and practice it is not expected that this call will generate specific IP. The new taxonomies and underlying data should be put into the public domain for additional validation as soon as is practicable.

EFPIA PARTICIPANTS

Leading company representative(s): UCB S.A.

Participating company representative(s):

Lundbeck, MerckSerono, Pfizer, Hoffman La Roche, Servier, Eli Lilly, Bayer.

INDICATIVE DURATION OF THE PROJECTS

5 years

INDICATIVE BUDGET OF THE PROJECTS

The above described project contribution of EFPIA participants is in-kind, this means that EFPIA companies input is non-cash. The current total indicative value of this non-cash contribution for the 3 Topics of the Call Theme is 25 million Euros. The IMI JU financial support to this project will approximately match the cash equivalent of the EFPIA companies' in-kind contribution. The budget is divided per Topic as below:

Topic A: Approaches to develop a new classification for Systemic Lupus Erythematosus (SLE) and related connective tissue disorders and Rheumatoid Arthritis (RA) (EFPIA 9M EUR; IMI JU 9M).

Topic B: Approaches to develop a new classification for neurodegenerative disorders with a focus on Alzheimer's disease and Parkinson's disease (EFPIA 8M EUR; IMI JU 8M).

Topic C: Approaches to develop a new classification for Chronic Obstructive Pulmonary Disorders (COPD) (EFPIA 8M EUR; IMI JU 8M).

APPLICANT CONSORTIUM

(To be selected on the basis of the submitted EoI)

An Applicant Consortium applying for one of the topics of the Call Theme will not be obliged to apply for the other two topics. However, to insure integration at the level of the Call Theme each consortium shall take in consideration this dimension of overarching collaboration and integration of activities among the topics in the preparation of the EoI. A novel taxonomy of disease may require a multi-axial approach for example using mutations and polymorphisms within a genetic axis, gene expression data on a genomics axis, protein modifications and protein expression patterns on a proteome axis, protein interactions on a biological system axis, clinical data and imaging data and so forth.. The approach will be driven by research as well as existing data review and analysis. The desired areas of expertise include omics technologies, genetics, clinical research, preclinical research, imaging, informatics, epidemiology and modeling among others.

PROPOSED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium for each Topic is expected to address all the research objectives and make key contribution to the defined deliverables in synergy with the EFPIA consortium.

In designing their expression of interest the applicant consortium should take in consideration:

- 1) The Theme Call will be led by a steering committee (SC) having one chair and a co-chair. Reporting to this SC will be one project team (PT) per Topic/Project. The applicant consortium for each Topic has to take this in consideration in the design of its governance structure.
- 2) Data basing, harmonization, standardization and sharing are key activities that have to be addressed at the level of each Topic/disease area and for integration at the level of the Theme Call.
- 3) It is expected that approximately the first 3 years will be spent generating a proposed new taxonomy and the final 2 years starting to validate the taxonomy using prospective pilot studies.

INDICATIVE TEXT

EUROPEAN INDUCED PLURIPOTENT STEM CELL BANK

BACKGROUND

The ability to reprogram terminally differentiated adult cells to produce induced pluripotent stem (iPS) cells is a tremendous breakthrough and was the basis for the 2012 Nobel Prize in Medicine awarded to Shinya Yamanaka and John Gurdon. Once generated, iPS cells can be differentiated into cells of interest including all three cell lineages required to form the body's organs, nervous system, skin, muscle and skeleton (Takahashi et al 2007; Takahashi & Yamanaka, 2007; Phillips & Crook, 2010). Since their discovery 7 years ago, there have been rapid advances in iPS cell related research resulting in new approaches to: developing a personalised medicine approach for patients, efficacy and toxicity testing of new therapies using iPS cells differentiated from disease relevant populations, and other drug discovery enabling techniques (see figure below).

Drug discovery	Structure Activity Relationships (SAR) and target validation
Clinical validation	Understanding genetic variation for precision medicine
Post drug launch	Addressing safety issues following rare event reporting

There is a high expectation that these scientific advancements will only come to fruition if the generation, genotyping, phenotyping and banking of iPS cells is available without constraint for use in the academic, biotech and pharma communities. Consequently, this is a unique opportunity to create an industrial scale, not-for-profit, storage and distribution Centre for iPS cells across Europe, which will be of lasting value within the EU.

PROBLEM STATEMENT

The number of stem cell lines created worldwide is likely in the low thousands but increasing rapidly; although the quality and consistency varies greatly (Loser et al, 2010) and, in fact, many may not be pluripotent. In addition, many iPS cell lines do not come with a complement of clinical data and/or supporting genotypic or phenotypic data. Therefore, it is important to generate an iPS cell bank that consistently provides research scientists with quality reagents within a defined time frame. This has been both underestimated and undervalued.

Both public and private stem cell banks exist, but the international availability and access to stem cells, particularly iPS cells derived from patients with genetic mutations, for research purposes has been limited with the majority only available to those labs which generated them or closely associated collaborators. With the continued exponential rise in interest in stem cell research, demand for access to such reagents now far outstrips their provision.

Current proposals for providing banking services are small sections of much larger iPS cell proposals, whose aims are to further our scientific understanding of the utility of stem cells in the progression human disease. A bespoke service provider is required to undertake the cell banking element, whose focus is on cell quality and delivery. The two activities require very different skills sets: motivation and drive to deliver an efficient cell provision service should therefore ultimately be spun out and run as a bespoke service with appropriate funding to go with it. Without this a new bottleneck in iPS cell provision will occur, with access to all these newly generated cell lines still being the limiting factor. The unique attributes of the European iPS cell bank will therefore be the ability to provide patient derived iPS cell cultures which are quality assured and established within defined

timelines at scale to support academic researchers, private-public partnerships, biotech's & "pharma" for research, early drug discovery and safety assessment. The iPS cell bank will be run on a not-for-profit basis, thereby keeping costs to a minimum and making outsourcing of company's stem cell lines an attractive proposition.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

Access to well-defined iPS cell lines for research purposes is poor which limits scientist's ability to utilise iPS cells for efficacy and toxicity testing. The concept of the European iPS cell bank is, therefore, to respond to this rapidly increasing demand for well defined iPS cells from disease relevant populations, whilst utilising the expertise, facilities and scientific experts across the EU, to set-up a bespoke not-for-profit specialist storage and distribution centre for iPS cells across Europe. The vision for the bank is that it would be devoted entirely to consistent and high quality characterisation, banking, differentiation and distribution of iPS cell lines. This resource would provide drug discoverer's, academic scientists, and non-profit foundations with an enormous leap forward by enabling them to link disease properties with the physiology of defined cells (from phenotype differentiated cell types derived from patient specific iPS cells) and to explore the genetic linkage between patient and disease.

The focus of this cell centre would be on iPS cell lines derived from carefully genotyped and phenotyped patients. A number of EU Research Funders are now considering establishing various banks of iPS cells, so it is timely to establish a central supply facility to generate standardised processes, efficiency, consistency of product, as well as scale. Of the various cell banks/repositories that do exist, all have some limitations:

- Academic – usually good characterisation, but access and supply can be limited
- Pharma – no/limited access for outside parties, internal maintenance costs
- Biotech – cost of access, often US-based
- Public service collections – limited funding to accommodate needs of large number of iPSC lines
- All – range of disease areas covered is often limited

It is critical that iPS cell lines are linked to as much relevant information as is available, such as information that outlines its genotype, lineage, and phenotypic characteristics and would allow a decision to be made as to whether they are the correct tool for the specific scientific experiment, drug discovery effort, or clinical/safety study being conducted. To-date such detailed information is not always available, highlighting the need for a consistent and uniform European approach which could provide worldwide leadership and guidance. Clear differences in production requirements and documentation are required for clinical grade iPS cells versus those to be used for research purposes only: to-date the current intention of the iPS centre is to focus solely on provision of iPS cells for research purposes.

It is an ideal time in Europe, where the iPS cell repositories are still in their infancy, to introduce a consortium led approach to an iPS cell bank with the objective to generate a harmonised framework of best practices that are globally agreed. Demand for iPS cells is rising rapidly and so the need for sustainable access to iPS cells is growing in parallel. Feedback from the US banking field has demonstrated that multiple small funded cell banks is not the way to go, with many struggling to remain viable, reinforcing the importance of a single centralised European initiative that has a well developed operating plan and evidence that it could be self funding within a defined period.

Creating a successful European iPS cell banking centre will require a unified adoption of the proposal by all research institutions, whether from the academic, biotech or pharma

environment. There must be a single goal to have the best international iPS cell banking centre, thereby maximizing the ability of stem cell research to promote our understanding of human pathophysiology to tackle key disease issues within the next six years and beyond. It also creates a unique environment in which scientists can share data/learning from their iPS cell lines, with the aim to accelerate understanding and minimising duplication.

OVERALL OBJECTIVES

1. Identification of key cohorts of patients that are useful for research purposes within the wider scientific community
 - a. Covering a broad range of therapeutic areas/patient diseases
 - b. Provision of support for academics who have key patient cohorts to generate the full complement of pheno or genotypic data (or missing iPS cells)
 - c. Upon completion iPS cells generation they will be banked in a central repository - open access to all
2. Creation of a large single European iPS cell repository that will provide a :
 - a. Sustainable supply of iPS cells at low cost for IMI consortium members, academics, biotech's, and patient advocacy groups
 - b. Consistent, high quality provision of iPS cells in a defined time frame to the bioscience sector
 - c. Partnership with key iPS banks around the world to create a consistent approach to banking
 - d. Strengthening of the European Bioscience base
 - e. Financially self-sustaining bank within 6 years of founding
3. Generation of Centre of scientific excellence for standardisation and optimisation in cryopreservation, retrieval and differentiation methods for iPS cell lines
 - a. Standardisation of methodologies for generating iPS lines and/or differentiation protocols
 - b. Provision of laboratory space and training facilities in iPS cell culture
 - c. Sharing of information generated on iPS cell lines

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Synergies and complementarities with other ongoing FP7 activities should be explored in order to avoid overlaps and duplications and to maximise European added value in health research e.g. SEURAT-1 Research Initiative, SC4SM & the European partnership on alternatives to animal testing.

A coordinated effort should be pursued among ongoing IMI projects to remove the burden of cell banking from these publically funded iPS cell projects through the creation of a centralized repository for all existing consortia. This should lead to a reduction in cell banking infrastructure costs for subsequent IMI calls and the sustainability for IMI of iPS cell lines from past and previous calls either pre or post the end of each funded project.

IMI Call	Project
IMI Call 4	StemBancc: Stem cells for Biological Assays of Novel drugs and predictive toxicology
IMI Call 3	MIP- DILI: Mechanism-Based Integrated Systems for the Prediction of Drug-Induced Liver Injury
IMI Call 3	EU-AIMS: "European Autism Interventions - A Multicentre Study for Developing New Medications"

Exchange of protocols for differentiation and maintenance of cell lines, and for the scalability of protocols & assays development would be of great advantage. A unique and essential component will also be the coordination and partnership with already existing biobanks, SME's and NGO's to create a harmonized framework of best practice and as a consequence a high quality resource centre. In addition, this iPS cell bank should be a leader in partnering with other iPS banks globally to create a single network with consistent standards and quality.

The iPS cell bank proposal would be strengthened by partnering with researchers in the stem cell field to ensure:

- Access to the widest & most diverse patient derived iPS cell lines (including support to patients groups to have an influential role)
- Implementation of the International Stem cell banking guidelines
- Efficient routine generation of human iPS cells
- A strong network of stem cell researchers & providers
- Access to the latest established peer reviewed differentiation protocols

Such partnerships allow scientists to focus on evaluating the methodologies to generate and characterise iPS cells, rather than on routine banking procedures for which they are not specialists. In return the iPS cell bank would provide the expert operational management knowledge (speed, cost, dependability, quality and flexibility), facilities and subject matter experts to set-up this bespoke specialist production, storage and distribution centre for iPS cells. This is a clear unmet need and an opportunity to create a much stronger return on investment (ROI).

EXPECTED KEY DELIVERABLES

BIO-BANK AND CENTRAL TEST FACILITY

Infrastructure, laboratory space will be required, where operations are efficiently run within budget but independent of any Pharma company. Access to road, rail and air freight services across Europe is key. Strong ties to research institutions generating iPS cells are essential, although close proximity is not a prerequisite. Expandable space/capacity within the iPS centre or closely associated facilities would be an advantage to encourage partnerships with engineer/automation/equipment specialist and to facilitate training for the next generation of stem cell scientists. A single European central banking and distribution site is preferred, but a limited additional distributed model could be considered. It is expected the bank will need to store in the order of tens of thousands of diverse iPS cell lines from a range of diseases, genetic background, age, gender etc to ensure that a broad range of therapeutic areas are well supported.

Tissue/somatic cell collection and the generation and differentiation of iPS cells are expected to take place at the academic, pharma or biotech facilities throughout Europe. The primary source cells, phenotyped iPS and differentiated cells will also initially be kept at these institutions. A sample of each iPS line and when available, expandable differentiated cells, would be transported to the iPS cell centre to form the daughter bank from which an 'on-demand' European shipping service will be managed. Seamless electronic access to clinical, genotypic and phenotypic data associated with each deposited cell line will be required, although may not necessarily be required to be stored on servers at the bank. IP will need to be resolved prior to the start up. A prioritisation process for iPS cell lines entering the bank will be drawn up, with EFPIA members participating to this process.

Once at the bank it is expected that the iPS cells will be catalogued and banked in a searchable format with a standardised nomenclature, with the ability to trace the lineage

of the cell back to the source cell. Cell donor origin will be anonymised, but both phenotype (healthy, disease, drug treatment) and genotype (source tissue, pluripotency status, gene expression profiles) data will be recorded where available. These iPS cell lines should then be made available for wider dissemination, within a defined time line and with a standardised growth protocol for each iPS cell line.

The bank would be expected to start generating revenue within its first year of operation, although there is an appreciation that revenue will rise exponentially toward the backend of the call as the 'value' of the bank, in terms of diversity and number of iPS cell lines available, also increases. A two tiered pricing structure should be in place to reflect those who are participants of the call and those who are not. Although cell banking will be central to revenue generation, other related activities such as storage of tissue or somatic cell lines through to iPS cell generation will also need to be considered. Furthermore it's anticipated that automation projects will yield some FTE savings by year 3. In summary the bank revenue generation should mean that between years 5-6 the bank should become self-sustaining and not require further cash contributions from IMI.

KEY DELIVERABLES

Scientific	Operational
<ul style="list-style-type: none"> • Generation of a full complement iPS cells with geno- & phenotypic data for key patient cohorts that would be useful to the scientific community • Research and implementation of current gold standard best practises for the generation and differentiation of iPS cells • Development of automatable processes for iPS cell culture and banking • Application of best practise in cryopreservation & biobanking in order to develop a 'commercial standard' state of the art iPS facility • Provision of quality protocols and training in iPS cell growth & development 	<ul style="list-style-type: none"> • Leadership, HR systems and recruitment of top talent • Set-up of a sustainable, not-for-profit, specialist production, storage and distribution centre for iPS cells across Europe • Provision of patient derived iPS cells to a defined quality and within a defined time from placing an order • Supply an iPS differentiation service during the latter half of the call • Provide searchable anonymized geno-, phenotypic & clinical data associated with each iPSC line

CONSORTIUM

It is anticipated that up to 10 pharmaceutical companies together with academics, biobanks with existing expertise in the area, patient advocacy groups, biotech's & public partners will participate in the overall program of work highlighted in this call, demonstrating true collaboration and desire to increase the availability of iPS cells for research purposes. In general terms it is envisaged that those companies, academics or biotech's involved will contribute through the donation of their iPS cell lines for banking. In return they will benefit from access to iPS cells from a greater range of patient interest groups such as:

- Genetic mutations associated with disease
- Specific clinical phenotypes of disease
- Responders and non-responders to drug treatment
- Ethnically diverse populations with unique drug metabolism

EFPIA PARTICIPANTS

- Pfizer (coordinator)
- Sanofi
- NovoNordisk
- Servier
- Lundbeck
- Astra Zeneca
- Novartis
- Lilly
- UCB

The EFPIA participants will contribute:

- Business model and financial expertise
- Legal and patenting expertise. This will include the participation of legal and IP experts to facilitate discussions among the partners, with other stake holders (e.g. IP owners, patient organisations, regulatory authorities)
- Scientific background on disease biology and expertise in stem cell biology and clinical practise to support and guide academic collaborators and SMEs
- Experimental support (FTE costs) for the generation & characterisation of iPS cell lines and missing genotypic or phenotypic data
- Contribution of iPS lines made by companies during the call
- The accessing of iPS cells from the bank and subsequent generation of valuable shareable data sets
- Cash

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 6 years. It is expected that the iPS cell bank will become self sustaining within this time frame such that the bank would generate sufficient revenue to cover all costs and become a long-term viable entity. The goals in year one and two should be to put the infrastructure and people in place, while also beginning to bank cells. From the outset the Centre should look to operate at a significant scale with the ability to receive, expand, bank and retrieve cell lines in the hundreds to thousands within 6 years and with the aim to expanded operations such that at the end of year 6 it has the ability to ship >1,000 iPS cell lines/annum, on demand and in multiple formats.

INDICATIVE BUDGET FOR THE PROJECT

Indicative EFPIA in kind contribution is up to €30 million.

The established bank will have the remit to generate revenue from the selling of cells and services to academics and companies (both EFPIA and non-EFPIA) and would be focused on becoming self funding by the end of the call. The generation of revenue over time would be expected to build significantly from year 1 as the bank begins to operate both at scale and high efficiency. In addition, the number of lines available for inclusion in the bank should increase considerably as the science continues to improve for making iPS lines.

As the iPS cell bank builds its revenue generation over time, it is expected that the contribution of cash from IMI will decrease on a sliding scale i.e. the bank would be cost neutral by the end of the call.

Indicative IMI JU contribution is up to €40 million.

APPLICANT CONSORTIUM

(TO BE SELECTED ON THE BASIS OF THE SUBMITTED EXPRESSION OF INTEREST)

It is an ideal time to underwrite/support the research community with a sustainable platform who has expertise in cell culture, cryopreservation and quantitative analysis in cell biology. In turn this should open up the access to iPS cell lines from a wide variety of patient cohorts to the European and International scientific community. It is expected that the winning consortia will have identified a broad and useful cohort of patient derived iPS cell lines i.e. ensuring the bank will be successful in attracting pharma, biotech's and academics to purchase cells from the beginning.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all of the objectives and make key contributions towards the defined deliverables in synergy with the EFPIA consortium. The architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

EFPIA Contribution for each work package could include:

- Business model knowledge (WP1)
- Vision development (WP1)
- Data governance expertise (all WP)
- Legal, compliance (WP1, WP2, WP5)
- Scientific expertise (WP2, WP3, WP4, WP6)
- Program management (all WP)
- Contribution of analytical data (WP1, WP3, WP4)
- Contribution of cell lines and technical expertise around iPS generation (WP1, WP2, WP3, WP5, WP6)
- Cash (all WP)

WORKPACKAGE 1: GOVERNANCE/POLICY

A central governing body (akin to a board of directors) will be developed to oversee and coordinate the strategy as well as all activities of the iPS bank and ensure efficient collaboration between the service layers. Key to this will be insuring a sustainable business model is developed, which outlines the path and milestones required for sustainability:

- Recruit the right leadership to enable bank success
- Develop the business strategy that will lead to sustainability
- Build the financial model that supports the strategy and goal of sustainability
- Develop the appropriate HR /financial support systems required for sustainability
- Develop the legal framework of the bank
- Develop guidance for biological material depository
- Develop governance policies and structure related to data, security, standards
- Develop ethical and confidential policy and strategies to handle bank ethical/consent, issues with patients, the scope and limits of informed consent and harmonization across existing structure
- Develop guidance to Intellectual Property rights, commercialization and benefit
- Develop a strategy to link to already established organisations and banks around the world
- Develop a strategy to adapt to changes and additions in key elements in step with scientific advances

WORK PACKAGE 2: SUSTAINABILITY OF IPS LINES

iPS Cell Line Procurement

A key element for success of the bank is insuring a substantial number of lines are banked and available for purchase. The bank will be required to procure iPS cell lines and provide evidence that the sample comes with consent to allow multiple establishments to use the cells for research purposes. This should include research in pursuit of identifying a clinical drug candidate.

iPS cell lines should be deposited with a completed set of paperwork that shows the cell line meets the basic acceptance criteria/standards set out in the field. It is expected that most, if not all, cell characterisation will have been conducted by the provider of the iPS cell line.

Partnership with on-going European funded stem cell initiatives (e.g., STEMBANCC) must be created to remove the burden of cell banking from their projects, reducing their costs and ensuring sustainability of their iPS cell line post the closure of their project.

The inclusion of patient derived iPS cell lines that cover a breadth of disease areas, address areas that have a high unmet medical need or address rare and neglected diseases, will be seen to have significant value to the bank.

Finally, identifying the various projects across the EU that will generate significant numbers of iPS lines and be willing to bank them in the IMI bank is critical for bank sustainability.

WORK PACKAGE 3: MAXIMISING IPS COLLECTIONS

iPS Cell Collections

The bank must provide access to a wide and diverse range of patient derived iPS cell lines with associated genotypic, phenotypic and clinical data: for key patient cohorts this may require the generation of missing genotypic or phenotypic data.

Database

All incoming data (clinical, genotypic and phenotypic) associated with each iPS cell line deposited in the bank should be delivered in a pre-defined standard format determined by the bank (WP4). The data may or may not be stored within the banks database, and in the latter case seamless links will be provided to other databases where this information will be stored.

Emerging Reprogramming Technologies

The bank will remain abreast of the emergent reprogramming technologies, adopting those accepted by the wider scientific community. Rapid in-depth characterisation will occur using these adopted best practise technologies and new iPS cells lines developed for key patient cohorts already within the bank. In vitro assay systems predicting the propensity of pluripotent stem cells for differentiation will also be explored.

WORK PACKAGE 4: BIO-ENGINEERING AND AUTOMATION

The generation of iPS cells is technically demanding and extremely manual in terms of process. The amount of cell culture required limits the number of iPS cell lines any researcher can handle and, hence, there is a clear need for the bank to facilitate the identification and implementation of automation methods for iPS cell culture and biobanking whilst maintaining the strict quality and consistency required. Focusing on automation of the process can not only improve the bank's path to sustainability, it will also benefit the broader community as the systems could be replicated elsewhere.

WORK PACKAGE 5: ETHICS, IP & TRAINING CONSIDERATIONS

Ethics

The bank will be responsible for ensuring the human tissue/somatic cells are acquired ethically and supplied in accordance with customer companies' corporate policies (in collaboration with WP1 regarding appropriate consenting). A license to store and hold human tissue will be required if any tissue biopsy/somatic cells are stored. The cell donor must remain anonymised at all times. Policies will need to be developed to ensure all patient data is handled appropriately under EU law.

Intellectual Property

It is also imperative that iPS cells received by the bank are not deposited with unacceptable IP constraints, including reach-through rights. Streamlined agreements for deposit and release of cells should be implemented and ready at the outset of the project. IP associated with iPS cell reprogramming technologies may result in the need for licenses or royalty payments to the creators when the cells are used in commercial drug discovery projects. A process of direct payment by the bank to the IP holders on all cells purchased from the bank could be considered (as done by companies such as Invitrogen for their recombinant assay kits) could be one way of enabling drug discovery to continue for every company without IP infringements. Putting in place an appropriate, flexible, cost effective IP framework (in collaboration with WP1) is critical to the bank's sustainability.

Dissemination of Learning's/Training

The iPS cell bank should provide facilities for training/education workshops on stem cell biology and cryopreservation that can be run independently or in partnership with institutions such as the UKSCB and ECACC. An appropriate oversight mechanism should be implemented to ensure balanced input from the research community and other key stakeholders.

Public interest in the bank may be high given the debates around the use of stem cells as therapies. External communications of the banks value to the science community in the EU should therefore be proactive from day 1; clarity should be provided in these communications that the bank is not about stem cell therapy and that patient anonymisation is paramount. Within the consortium internal communications will also be a priority to ensure strong interactions and sharing of knowledge.

WORK PACKAGE 6: BANKING INFRASTRUCTURE AND MANAGEMENT SYSTEMS

Wide scale adoption of human iPS cells as tools within the pharmaceutical industry has been limited because of the procedural complexity of generating reproducible batch sizes large enough for meaningful research to be conducted. In addition the availability of iPS cells from a variety of patient groups has been poor. The aim of the bank should be to provide rigorous, standardized, scalable processes with clear documentation for cell freezing, revival and continued culture.

Quality Control and Characterisation

iPS cells should be banked and resuscitated following good scientific practice (GSP) guidelines i.e. to ensure the uniformity, consistency, reproducibility and quality required for research work. For each iPS cell line a defined, scalable quality protocol will be provided on how to thaw and grow the iPS cell line. An electronic repository will be produced containing the standard operating and quality control procedures: these protocols will reflect best practice amongst scientists and regulatory authorities and the bank should encourage widespread dissemination amongst the stem cell community.

When iPS cell lines are generated from the same individual it is not uncommon for there to be a significant variability in different iPS cell lines from the same donor. It is therefore imperative to investigate multiple iPS cell lines per individual; a true disease-related defect should be present in all 'disease' iPS cell lines and absent from all 'healthy' iPS cell lines.

The bank will also be expected to provide information on:

- The method(s) by which they will demonstrate that the iPS cells are free from most prevalent adventitious agents.
- The cryopreservation methods they plan to use
- The degree to which equipment (from pipettes through to automation) will be monitored in terms of quality control (accuracy of use), as well as contamination
- Any genetic or phenotypic abnormalities or unusual features of the cell
- Any specialised maintenance conditions required

Depositor User Interface.

The bank will provide an IT infrastructure that has the capability to link large data sets of information associated with each iPS cell vial in a way that complies with EU legal and ethical requirements. It should include items such as:

- an intuitive web based ordering system from which the client can easily review what cells are available to purchase and clear instructions as to how to order it
- a data repository containing all the information provided with the incoming iPS cell line i.e. access to clinical, genotypic, phenotypic and microbiologic information
- a tracking system showing a seamless link through an iPS cells history and a link back to its lineage
- a standardised data sheet outlining how the data needs to be structured for incorporation within the banks database

Additional aspects of the user interface may need to be developed as the scale increases and this list should only serve to provide examples of the wide ranging complexity of the IT infrastructure. In addition, consideration should be given for potential interoperability of systems with other cell banks akin to the umbilical cord blood networks.

Both technical advice and customer service should be offered.

Distribution

Applicants are to describe the sales and distribution supply chain they will use, along with their shipping procedures. It is envisaged that initially the focus should be on European supply, but could extend globally over time.