Innovative Medicines Initiative

Improving the preclinical models and tools for tuberculosis medicines research

Martin Pan
EFPIA Coordinator

efpia

Need for public-private collaboration

- Tuberculosis as a paradigm for pre-competitive research and public-private partnership

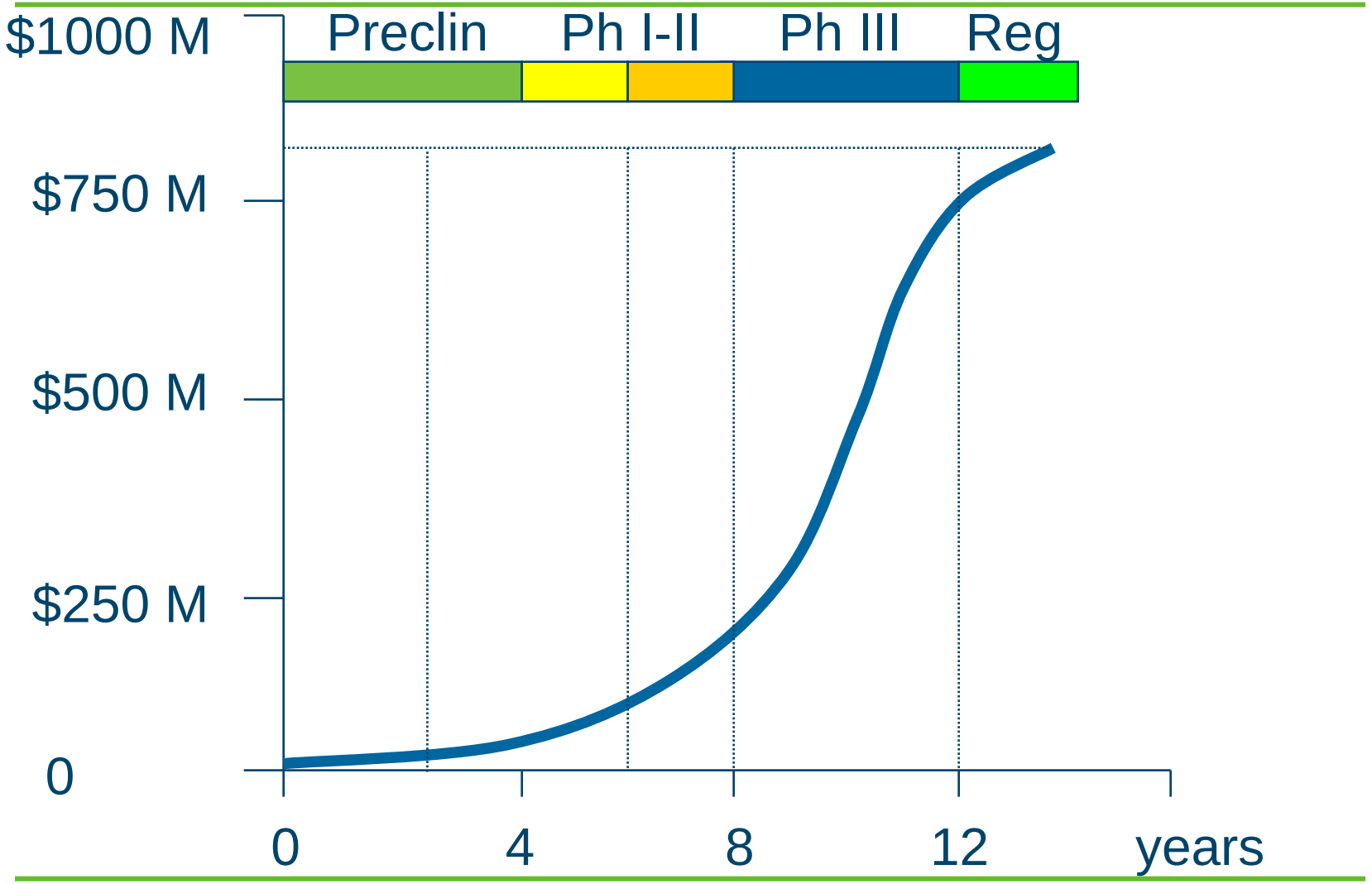
- Major global health threat:
  - *Poverty-related disease, public health emergency, global dimension of the problem*
  - *Neglected area in main stream drug research*
  - *Disease burden represent a major scientific challenge*

- No single organisation can be successful: joint collaborative public and private efforts are critical

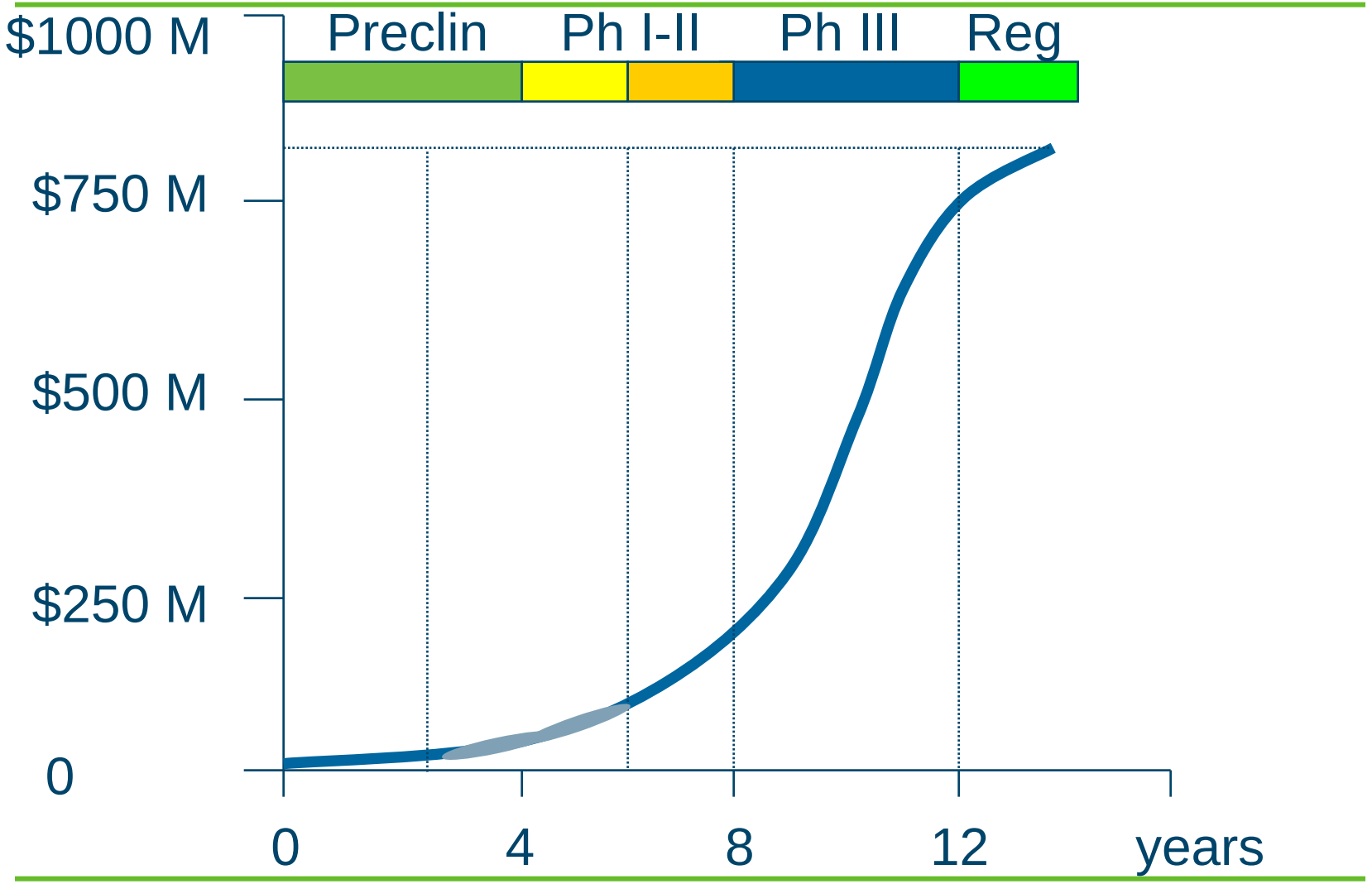
Objectives of the full project

- To define an integrated set of criteria for the assessment of drug properties in pre-clinical *in vitro* and *in vivo* models that:
  - improve the design of early clinical studies (phase I and Proof of Concept) in TB patients

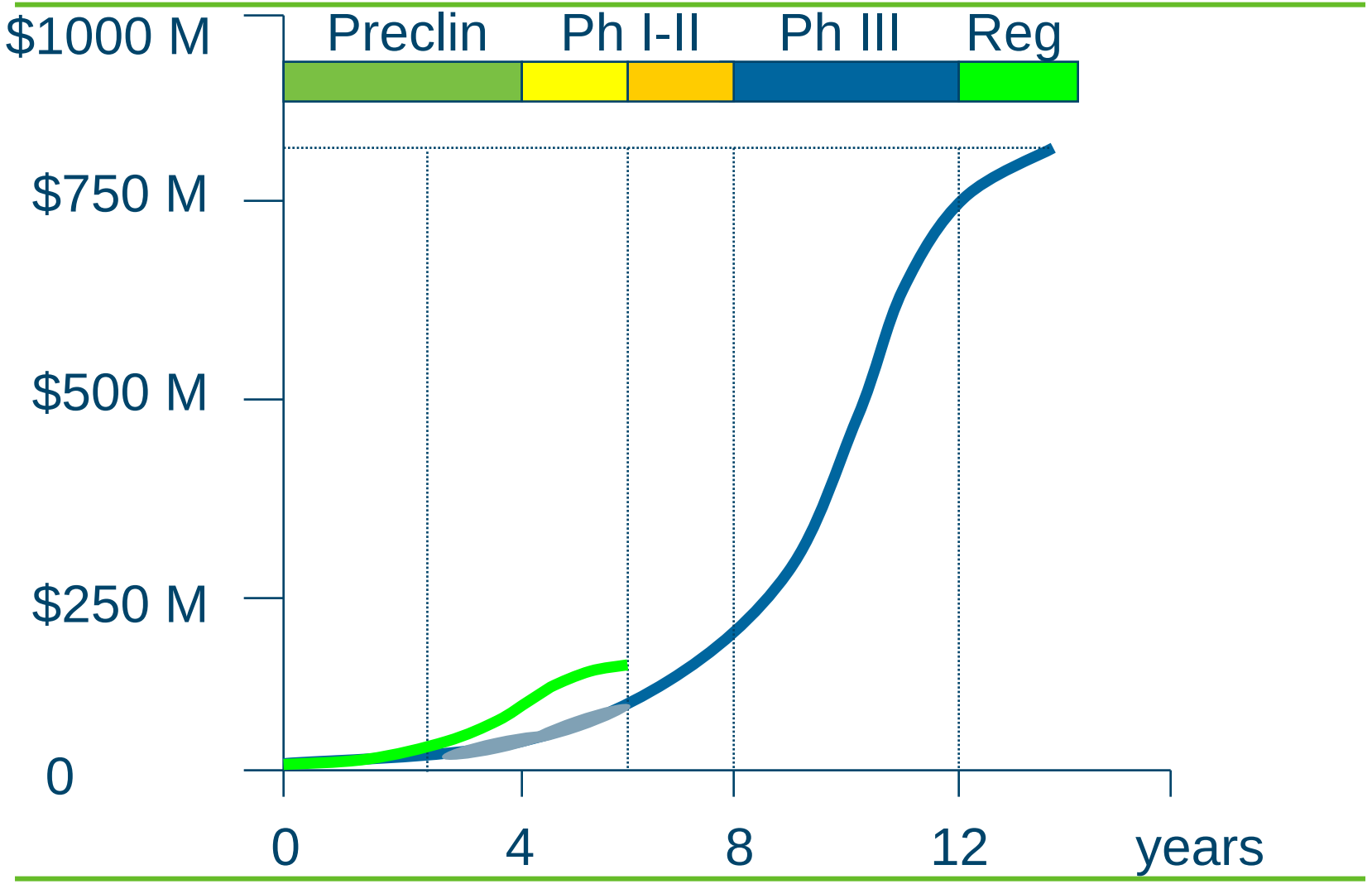
IMI TB Tools topic impacts on cost & development times



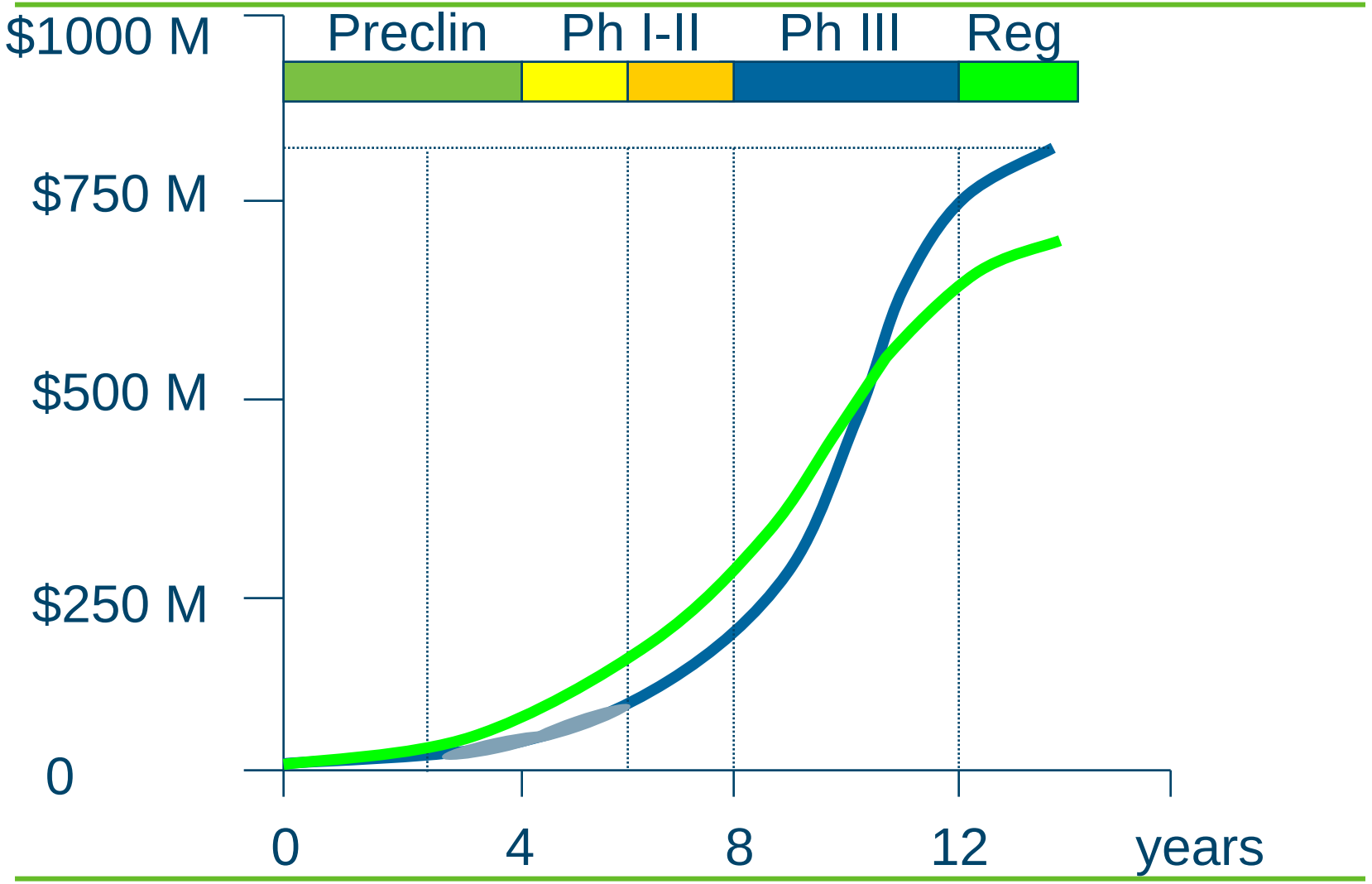
IMI TB Tools topic impacts on cost & development times



IMI TB Tools topic impacts on cost & development times

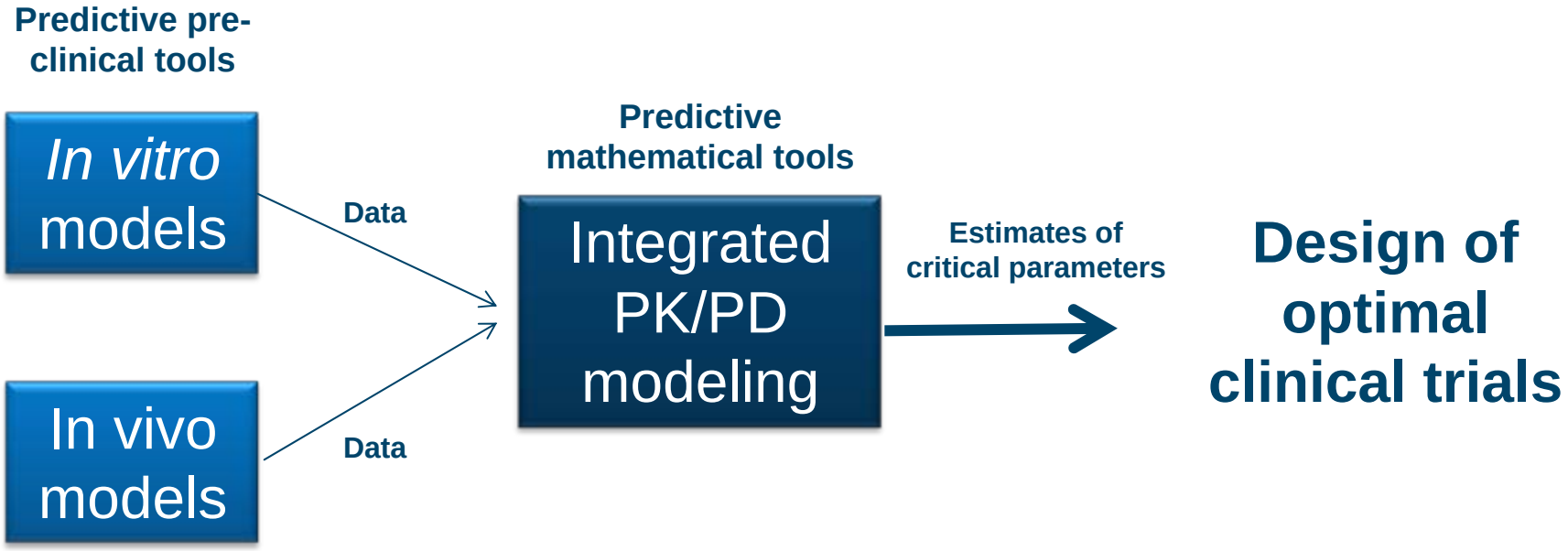


IMI TB Tools topic impacts on cost & development times



Objectives of the full project

- To define an integrated set of pre-clinical in vitro and in vivo models that provide critical data to design optimized clinical studies in TB patients



Pre-competitive nature

- Magnitude of the problem:
  - A single player cannot address the problem of drug development in tuberculosis
- Industry priorities are not focused on the development of research tools or basic science
- IMI is an opportunity to engage key players into a concerted effort aimed at solving critical bottlenecks
- Industrial consortia are key for development of new combinations of drugs

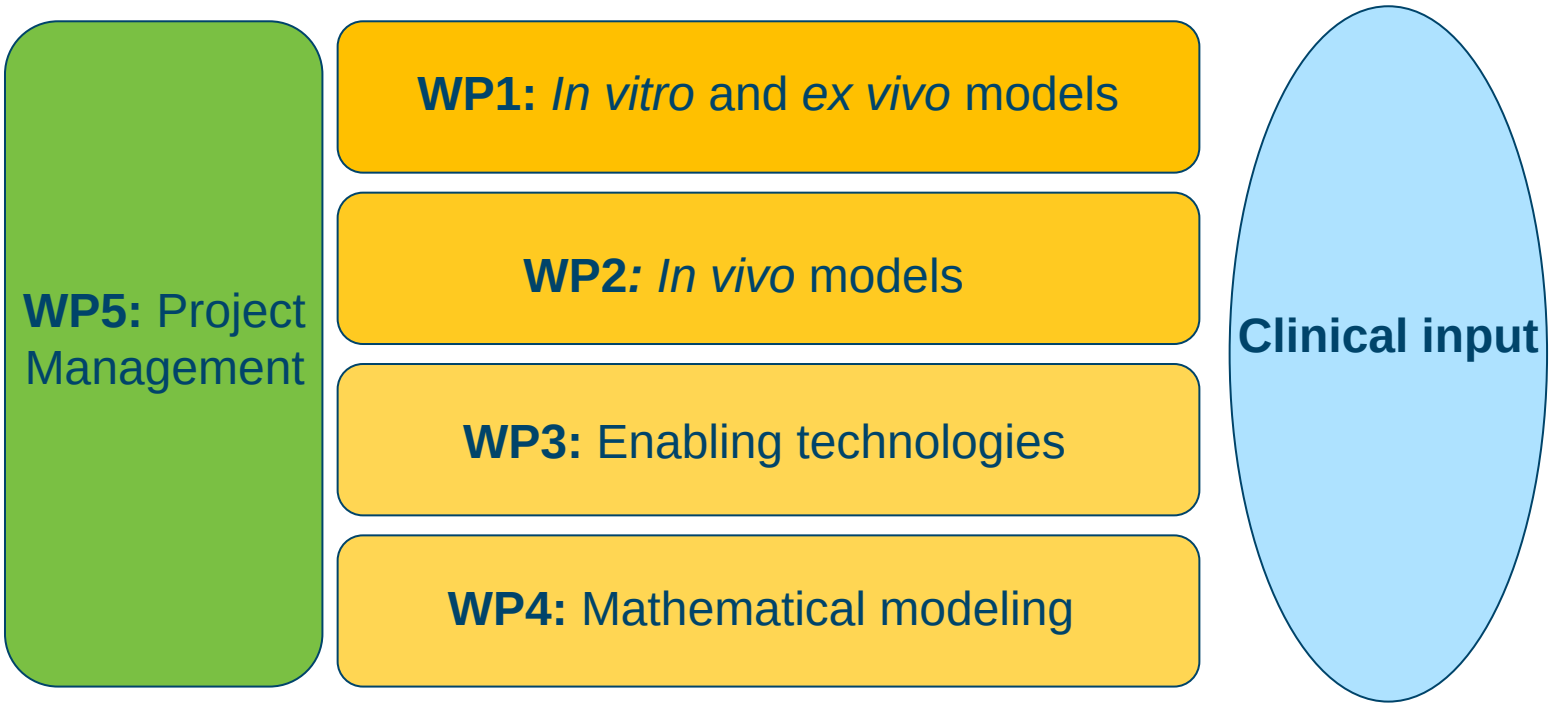
Expected contributions of the applicants

- The Applicant Consortium is expected to have ability for interdisciplinary and to cover the following critical fields:
  - Microbiology of TB. Cellular Biology and Immunology related with TB
  - *In vitro*, *in vivo*, *in silico* models
  - Enabling technologies (e.g. imaging, biomarkers)
  - Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation

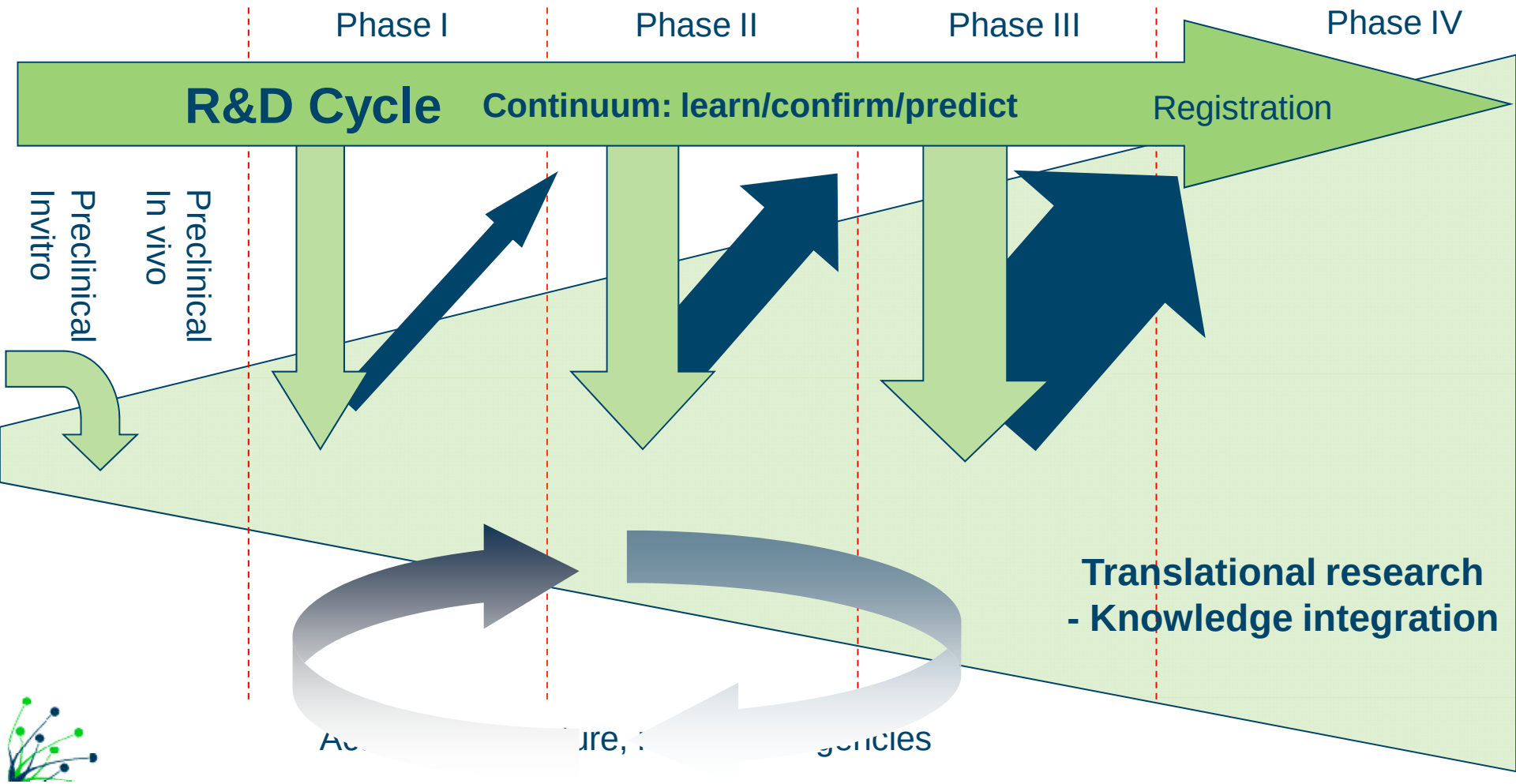
Expected (in kind) contributions of EFPIA members

- **GSK:** in vitro models, PK/PD studies in animal models, PK/PD modelling & simulation, chemical library, OpenLab
- **Sanofi-aventis:** Zebrafish model and imaging
- **AstraZeneca:** intracellular PK/PD of TB drugs, expertise in microbiology & animal models, PK/PD modelling & simulation
- **Pfizer:** expertise in whole blood assay and candidate approaches for its modification; candidate strategies and compounds for evaluation
- **Tibotec / J&J:** expertise in animal models & predictive biomarkers, PK/PD modelling & simulation, Project Management

Suggested architecture of the project



Expected impact on the R&D process



Key deliverables of full project

Overall objective is to develop in Europe a set of preclinical *in vitro* and *in vivo* models which provide data allowing optimization of the design of clinical studies in tuberculosis

- Identify, optimize, standardize and validate drug discovery models
- Develop mathematical models predictive of efficacious and safe exposures in humans

Key deliverables of full project

Drug Development Organizations

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Regulatory Agencies

FDA U.S. Food and Drug Administration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharma industry

efpia

Pfizer

gsk

sanofi aventis

AstraZeneca

Johnson&Johnson

tibotec

IMPROVING THE PRECLINICAL MODELS AND TOOLS FOR TUBERCULOSIS MEDICINES RESEARCH

Funding Institutions

BILL & MELINDA GATES foundation

Key deliverables of full project

Drug Development Organizations

Regulatory Agencies

Pharma indus

Critical Path to TB Drug Regimens

"No one can whistle a symphony. It takes an orchestra to play it"

References

- **Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice.** Robert S Wallis et al., The Lancet (series), 375, 1-18
- **Biomarkers for tuberculosis disease activity, cure, and relapse.** Robert S Wallis, The Lancet, 9, 162-172
- **Fast standardized therapeutic-efficacy assay for drug discovery against tuberculosis.** Rullas J, García JI, Beltrán M, Cardona PJ, Cáceres N, García-Bustos JF, Angulo-Barturen I, AAC 2010 May; 54(5):2262-4
- **Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against Mycobacterium tuberculosis: Evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy.** Shandil, RK, AAC 2007, 51(2): 576-82.
- **Pharmacokinetic-Pharmacodynamic relationships for Isoniazid in an aerosol infection model of tuberculosis.** Jayaram, R, AAC 2004, 48: 2951-2957.
- **Pharmacokinetic-Pharmacodynamic relationships for Rifampicin in an aerosol infection model of tuberculosis.** Jayaram, R, AAC 2003,47: 2118-2124.

Backup slides

OpenLab: inviting scientists to work with us

- *GSK - A possible framework for collaborative work:*

DDW Medicines Development Campus (Madrid, Spain)

  - Up to 60 scientists from R&D institutions, universities, charities or research councils
  - The Open Laboratory: Enabling access to:
    - Resources
    - Compounds and data
    - IP (Knowledge Pool)

- *AZ and other companies* will allow members of the Applicant consortium to work at their facilities


SENER

Key deliverables of full project

Workpackage 1: *In vitro and ex vivo models.*

- This workpackage should aim to the development and validation of innovative culture systems that can assess *in vitro* dose-response relationships for measuring activity against:

- intra- and extracellular bacteria either actively growing or in non-growing state.

- bacteria found in histological lesions from human patients (e.g. artificial human granulomas).

- *ex vivo* system to assess the antibacterial activity of drug combinations in the presence of human effector cells (e.g. ex vivo whole blood bactericidal assays).

Key deliverables of full project

Workpackage 2: Animal models of tuberculosis.

- This workpackage should aim to the development and validation of innovative animal models to estimate curative drug exposure in animals against *M. tuberculosis* in different physiological and histological conditions:

- *in vivo* models showing human-like granulomas

- *in vivo* models for actively replicating intracellular bacteria

- *in vivo* models for assessment of compounds capable of killing non-growing *M. tuberculosis.*

Key deliverables of full project

Workpackage 3: Standardized enabling technologies.

- This workpackage should contribute to the development of new standardized enabling technologies to measure biological effects of treatments with combinations of antitubercular drugs *in vitro and in vivo,* using the models developed in the previous WPs and leading the way to translation in the clinic. Possible candidate technologies and tools are:

- imaging technologies for *in vitro bactericidal response to treatments*

- imaging technologies for non-invasive measurement of *in vivo* therapeutic response in animal models

- novel biomarkers to predict cure (e.g., absence of relapse).

Key deliverables of full project

Workpackage 4: Mathematical PK/PD model for prediction of efficacious dose regimens in patients.

- This workpackage should deliver statistical support and new mathematical PK/PD models that, using the data generated by the set of selected standardized techniques, provide accurate estimates of clinically efficacious exposures of drug combinations.

Work Package 5: Project management and communication.

- The workpackage should cover all aspects of project management and coordination, including dissemination and communication strategy.

For Further information

infodesk@imi.europa.eu

www.imi.europa.eu