Improving the preclinical models and tools for tuberculosis medicines research

Martin Pan
EFPIA Coordinator
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

- Preclin
- Ph I-II
- Ph III
- Reg

Cost in millions of dollars:
- $1000 M
- $750 M
- $500 M
- $250 M
- $0

Years:
- 0
- 4
- 8
- 12
- years
IMI TB Tools topic impacts on cost & development times
IMI TB Tools topic impacts on cost & development times

$1000 M

$750 M

$500 M

$250 M

0

0 4 8 12 years

Preclin Ph I-II Ph III Reg
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.

In vitro models

In vivo models

Integrated PK/PD modeling

Predictive pre-clinical tools

Predictive mathematical tools

Estimates of critical parameters

Design of optimal clinical trials
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

WP5: Project Management

WP1: *In vitro* and *ex vivo* models

WP2: *In vivo* models

WP3: Enabling technologies

WP4: Mathematical modeling

Clinical input
Expected impact on the R&D process

R&D Cycle

Continuum: learn/confirm/predict

Registration

Phase I
Preclinical

Phase II
Preclinical

Phase III
Preclinical

Phase IV
Registration

Academia, literature, regulatory agencies

Translational research - Knowledge integration

Open Information Day – 22 October 2010 - Brussels
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

Regulatory Agencies

Pharma industry

Funding Institutions

Open Information Day – 22 October 2010 - Brussels
Key deliverables of full project

Drug Development Organizations

Regulatory Agencies

Open Information Day – 22 October 2010 - Brussels
"No one can whistle a symphony. It takes an orchestra to play it"
• **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


• **Pharmacokinetic-Pharmacodynamic relationships for Rifampicin in an aerosol infection model of tuberculosis.** Jayaram, R, AAC 2003,47: 2118-2124.
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
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 \textit{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 \textit{in vitro} bactericidal response to treatments
  
  - imaging technologies for non-invasive measurement of \textit{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