PreDiICT-TB
Model-based preclinical development of antituberculosis drug combinations

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2 billion latent infections

8.8 million new cases/yr

1.5 million deaths /yr

26% of avoidable adult deaths in developing world
2 billion latent infections
1.5 million deaths /yr
8.8 million new cases /yr

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Challenges in TB Drug Development

Preclinical

- In vitro
- In vivo

Clinical

1. Phase I
   - N=20
   - Unrepresentative growth conditions
   - No emphasis on synergy

2. Phase IIA
   - N=30-50
   - Lack of human-like pathology, destructive sampling
   - No available PD biomarker
   - EBA poorly predictive and irreversible, no crossover designs

3. Phase IIB
   - N=100-500
   - Incompletely validated bacteriological biomarkers based on growth

4. Phase III
   - N=1500
   - Lack of power of relapse endpoint

Years: 1 2 3 4 5 6

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PreDiCT-TB Priorities

- Work with regimens as unit of development from the earliest possible stage

- Capitalise on interdisciplinarity (experimentalists, modellers and trialists)

- Enhanced understanding and monitoring of pharmacodynamics through novel technologies

- Integrated modelling approach and framework
PreDiICT-TB Workplan

WP3 Enabling Technologies

WP1 In vitro systems

WP2 In vivo systems

WP4 Clinical Trials

In vitro models

In vivo models

Clinical models

Integrated modelling framework

Optimised Preclinical Protocol

Prediction of Efficacy

Optimized Trial Design

WP5 PK-PD Modelling

WP7 Data Management

WP6 Project Management

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PreDiCT-TB Strategy

Combinations of existing drugs

Round 1

Initial assay panel & pre-existing data
Development & Data
Modelling
Simulation & Evaluation

Refined assay panel & modelling framework

Months: 6

Combinations of novel drugs

Round 2

Development & Data
Design & selection
Modelling
Simulation & Evaluation

Optimised development pathway & modelling framework

Months: 24

Total: 54

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WP1-in vitro/ex vivo systems

- Elaborate current pharmacodynamic model
- Reflect diversity of target states
- Focus on lethality not growth
WP2- in vivo systems

- Reflect range of tractable species in hierarchical strategy

- Intensified PK and PD sampling using cannulated, non-invasive and improved bioanalytical approaches

- Primate and immunologically “humanised” mouse models
WP3- enabling technologies

- Support intensified non-invasive sampling
- Improve precision of pharmacodynamic monitoring
- Biomarkers that reflect heterogeneity in PD and cell death independently of culture
WP4- clinical trials

- Assemble database of existing IPD clinical trial data
- Provide context for evaluation of preclinical modelling predictions
- IP policy to facilitate public use of database
WP5-PKPD modelling

- Optimal design consulting with experimentalists
- Flexible approach incorporating mechanistic information where available
- Clinical trial simulation and innovative design
WP7-Data management

- TranSMART relational database system
- Assist in ensuring flow and governance of data between partners and WPs
- Cloud-based with open source interface for diverse datasources
Summary

- Model-based approach to preclinical development of combinations
- New technologies to enhance pharmacodynamic model
- Strong emphasis on interdisciplinarity
- Open model of collaboration with wider impact
- Multiple points of contact with allied external groups such as CPTR, TB Alliance and other EU consortia

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