Drug Evaluation in Guinea Pig Model

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**FACTS AND FIGURES**

**Start date:** 01/05/2012  
**End date:** 31/10/2017  
**Contributions:**  
**IMI funding:** 14 778 855 €  
**EFPAR in kind:** 9 296 106 €  
**Other:** 4 478 125 €  
**Total Cost:** 28 553 866 €  
**Project website:** www.predict-tb.eu

**Social media:**  
- @PreDiCT_TB

**Work Packages:**  
- WP1: in vitro models  
- WP2: in vivo models:  
  - Selection: mouse models that span multiple aspects of TB disease, guinea pigs, non-human primates.  
- WP3: Developing technologies  
- WP4: Clinical Data:  
  - Clinical patient datasets from relevant clinical trials.  
- WP5: in silico modeling:  
  - Translation of pre-clinical and clinical data into mathematical models.  
- WP6: Project management  
- WP7: Data management

**CHALLENGE**

Tuberculosis is a global health problem with approximately 10.8 million people each year contracting the disease (1). The standard first line drugs used to treat tuberculosis (TB) are a combination of isoniazid, rifampicin, ethambutol and pyrazinamide. Although relatively successful, the emergence of Multi-Drug Resistant (MDR) and Extensively Drug resistant (XDR) TB, due to lack of patient adherence to the drug regimen, the expense of the drugs and the ability of Mycobacterium tuberculosis (Mtb) to enter into a latent state, has made it essential that new drugs are developed (2).

The overall goal of PreDiCT TB was to develop and enhance an integrated set of pre-clinical in vitro and in vivo models that provide critical data for the purpose of identifying decision criteria for the progression of novel drug and combinations to innovative early phase drug development and clinical trials. The specific role of PIP and IP, under work package 2 (WP2), is to perform drug evaluation studies in guinea pigs to inform the consortia on preclinical PK/PD data from new and existing drugs. This collaboration between the two sites will ensure that as many drug regimens as possible are evaluated in the guinea pig. The guinea pig model is used due to the high susceptibility of these animals to aerosol infection by Mtb, as well as being morphologically resembling humans in the pathogenesis of TB and in the development of necrotic granulomas.

**APPROACH AND METHODOLOGY**

**Pharmacokinetics:**  
- PK sampling conducted prior to PK/PD studies with the aim of obtaining human like exposure levels from the dose groups.  
- PK sampling has proved problematic due to the coagulation of guinea pig blood.

**Approach:**  
- Analysis has shown unusual results lead to refined methodology as well as novel sampling schemes.

**Study Specific Aims:**  
- Comparing PK/PD of multiple monotherapy, triple therapy and bedaquiline monotherapy in the guinea pig model.

**Study Specific Approach:**  
- Evaluate PK/PD of standard drug combination regimens in the guinea pig model.

**PK/PD of single drugs in the guinea pig model:**  
- Harnomatization of data between PHE and IP.

**PK/PD of standard drug combination regimens in the guinea pig model:**  
- Evaluate PK/PD of R monotherapy and Z monotherapy in the guinea pig model.

**PK/PD of round two drug combination regimens in the guinea pig model:**  
- Evaluate PK/PD of round two drug combination regimens in the guinea pig model.

**Study Specific Aims:**  
- Novel Combination Drug Evaluation PK/PD Studies

**Study Specific Approach:**  
- Evaluate PK/PD of multiple monotherapy, triple therapy and bedaquiline monotherapy in the guinea pig model.

**Study Specific Approach:**  
- Evaluate PK/PD of round two drug combination regimens in the guinea pig model.

**Study Specific Aims:**  
- Novel Combination Drug Evaluation PK/PD Studies

**Study Specific Approach:**  
- Evaluate PK/PD of round two drug combination regimens in the guinea pig model.

**VALUES OF IMI COLLABORATION**

- Innovative study designs and data analyses in collaboration with WP7:  
  - Reducing number of animals and length of experiments  
  - Minimum sample volumes required for analysis.

**EFPAR has provided access to all clinical and trial data (WP4):**  
- Improved reproducibility of animal data, 18 different animal models including guinea pig, mice and NHPs.  
- Data on clinical and trial data trial (WP4), may improve productivity of preclinical data package.

**Collaboration with partners developing novel technologies (WP7):**  
- Enhance in vivo models and provide validation of novel assays.

**IMPACT AND TAKE HOME MESSAGE**

**PreDiCT TB Project**

- **PreDiCT TB**

**Clinical studies:**  
- Tuberculosis is a global health problem addressed by PreDiCT TB.

**REFERENCES AND ACKNOWLEDGMENTS**

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