Establishment of a marmoset preclinical model for antituberculosis treatment evaluation

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FACTS & FIGURES

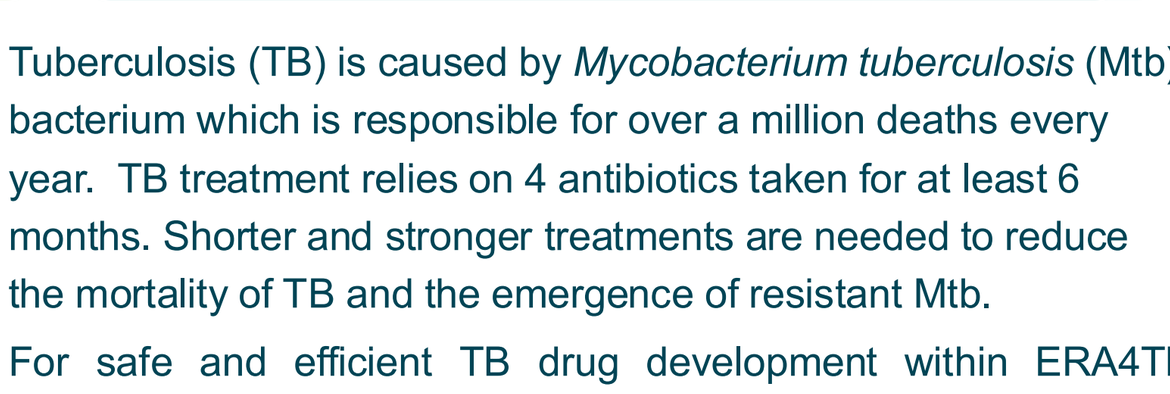
Start date:	01/01/2020
End date:	31/12/2026
IMI funding:	89 815 600 €
EFPIA in kind:	118 148 291 €
Total Cost:	207 963 891 €
Project website:	https://era4tb.org/
Social media:	https://www.linkedin.com/company/era4tb/

CHALLENGE

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (Mtb) bacterium which is responsible for over a million deaths every year. TB treatment relies on 4 antibiotics taken for at least 6 months. Shorter and stronger treatments are needed to reduce the mortality of TB and the emergence of resistant Mtb.

For safe and efficient TB drug development within ERA4TB program, CEA-IDMIT and its partners contributed to the establishment of the marmoset preclinical model which recapitulates the pathophysiology of human TB. To predict the clinical outcome of a new treatment, we developed PET-CT imaging, clinical, immunological, pharmacological, and microbiological tools.

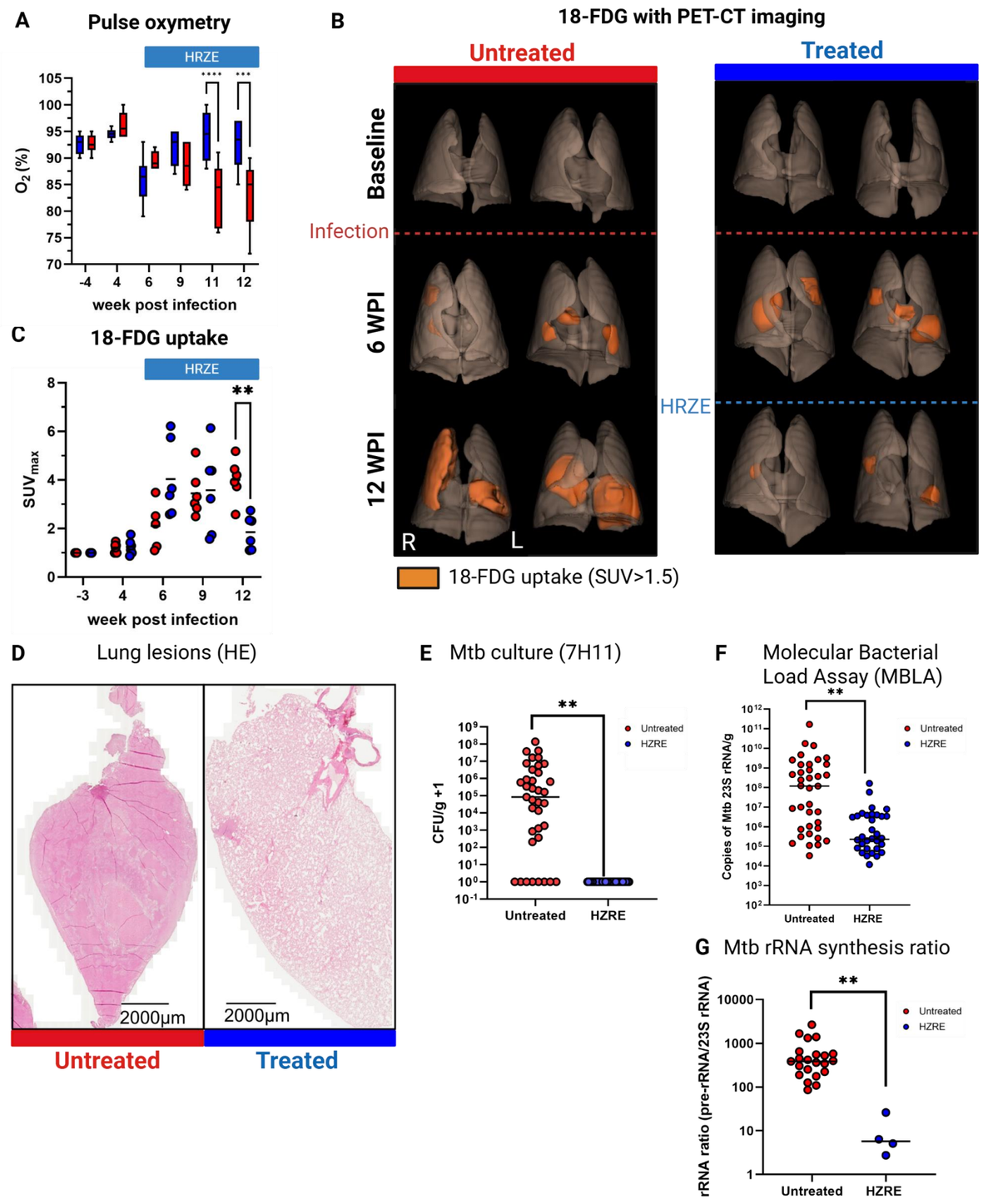
APPROACH & METHODOLOGY



Study design with 3R approach:

- **A**. *In silico* and *in vivo* PK for dose optimization in marmosets.
- **B.** For HRZE treatment evaluation, 12 marmosets were infected with Mtb H37Rv. Longitudinal follow-up was performed with PET-CT imaging, blood RNAseq, blood PK, and clinical monitoring. Tissues were harvested for bacteriology, pharmacology, and histology.

RESULTS



Evaluation of HRZE regimen in Mtb-infected marmosets: A. Evolution of pulse oximetry in infected animals. **B-C.** 3D reconstruction of longitudinal lungs PET-CT depicting hypermetabolic lesions in orange and SUVmax values. **D.** Representatives' images of lung sections from untreated and treated animals. **E-G.** Bacterial culture (E), molecular bacterial load assay (F) and ribosomal RNA ratio (G) in lung lesions.

- HRZE treatment restores lung function, reduces lung lesions, and bacterial loads.
- HZRE totally inhibits Mtb culture from lesions.
- MBLA and RS-ratio identify lesions with low metabolism of Mtb, which can be a source of TB relapse.

VALUE OF IMI COLLABORATION

- Enables the development of a translational preclinical model to evaluate new drug candidates.
- The marmoset model was developed through collaboration with Laura Via at NIAID.
- Opportunity to collaborate with CNR for advanced PK/PD analyses, ALIRI for MALDI-MSI analyses, Institut Pasteur Paris and Lille for bacteriology, UC3M for PET-CT analyses and molecular assays, and FZB for whole blood transcriptomics.

CAREER IMPACT

- Building strong collaborations with both private and public partners
- Understanding of the scientific and economic challenges of anti-TB drug development
- Learning from experts in the field on TB
- Establish a network for my future research
- Perspectives for new programs on immunotherapies and vaccines

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