GSK DDW
Tuberculosis DPU portfolio

TB DPU, Tres Cantos GSK DDW
**TB Pipeline: Advanced Projects**

*From Repurposing old drugs to the discovery of new chemical entities*

- Focused on the discovery of new clinical candidates for the treatment of multidrug resistant TB
- In house expertise on novel imaging techniques and animal models
- Source of projects: phenotypic hits, target based and new mechanisms of action

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**Discovery of a NCE for TB**

New, oral and low dose

**Repositioning β-lactams for MDR-TB**

Rapidly cytocidal, safe and approved for children

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**FTIM (2Q 2017)**

**AnTBiotic Consortium Clinical repurposing (2017-2021)**
GSK070 Mtb LeuRS inhibitor
A novel protein synthesis inhibitor with a new MoA

- Selective antitubercular Mtb MIC= 0.08uM vs MIC> 32uM (other bacteria)
- Active in vivo in acute and chronic TB models (murine and marmosets)
- Projected low human dose <<200mg/day (oral)
- GLP tox completed (1mo rat &dog): Good Therapeutic Index
- Excellent drug partner in combo studies at JHU (ongoing relapse studies)

Next Milestone(s): FTIM 2Q2017 (UK), Ph-IIa EBA 3Q2018 (South Africa, EU H2020)
β-lactams as a source of novel anti-tuberculcurs

Successful progression of β-lactam combination to clinical POC

CORRESPONDENCE

β-Lactams against Tuberculosis — New Trick for an Old Dog?

Figure 1. Estimated Mean Log_{10} CFU Counts per Treatment over Time.

The figure shows mean Log_{10} colony-forming unit (CFU) counts at each time point as symbols (triangles and circles) and superimposed treatment activities as lines, with 95% confidence intervals shown as dashed lines, as derived from a linear mixed-effects model. The estimated daily decline in Log_{10} CFUs for meropenem combined with amoxicillin-clavulanic acid (Mero-Amx-Clv) and isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE) was 0.11 (95% confidence interval [CI], 0.09 to 0.13) and 0.17 (95% CI, 0.15 to 0.19), respectively, over 14 days (P<0.001 for both groups, as compared with no effect; P<0.001 for the comparison between groups).

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Objectives

- **Renew the anti-TB pipeline for the treatment of TB**
  
  Establish the proof of concept of anti-TB efficacy in humans of a pioneering, first-in-class, low-dose GSK oxaborole clinical drug candidate (GSK070).

- **Repurpose and re-establish marketed β-lactam drugs to treat MDR-TB**
  
  Identify a combination of β-lactam antibiotics suitable orally or as a once daily intravenous or intramuscular application.

  Incorporate the best β-lactam combination into an explorative salvage regimen for untreatable patients with extensively drug-resistant (XDR)-TB.

- **Establish new EBA clinical surrogates**
  
  Use of clinical imaging such as Positron Emission Tomography (PET) and a variety of immunological response biomarkers as surrogates for activity in longer-term drug combination trial.

- **Introduce mathematical modelling**
  
  Use pharmacokinetic-pharmacodynamic (PK/PD) modelling approaches to predict optimal dosing, validate translational value of preclinical data and refine these models with experimental data generated in those trials.
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Project plan

Biomarkers
GSK070
Ph-IIa EBA
GSK

β-lactam combinations
Ph-IIa EBA
TASK

XDR-TB combo
Observational
TASK/FZB

Modelling
Optimal dosing prediction
UIT

FZB

GSK

Consortium Coordination - GSK

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