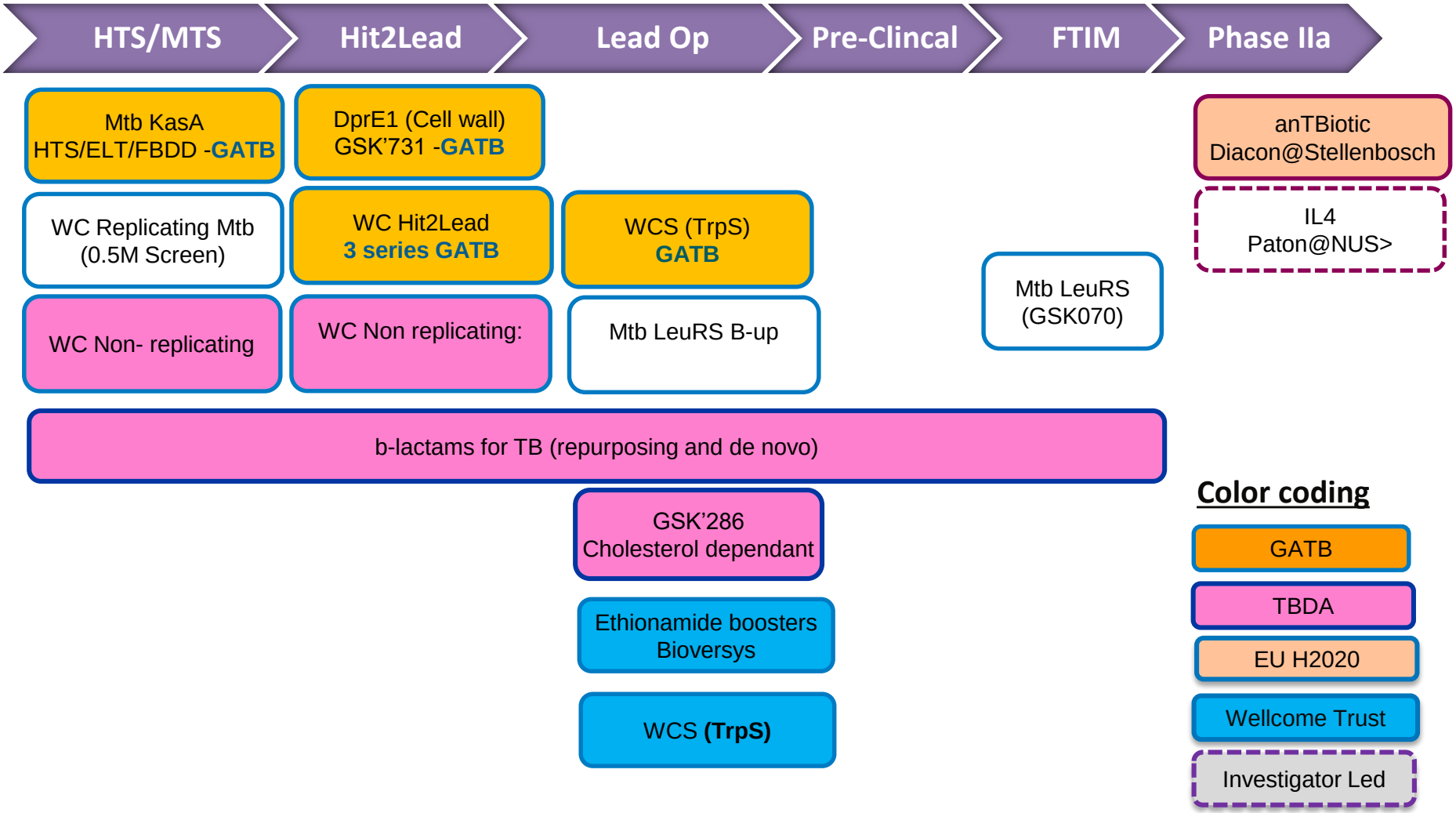
GSK DDW
Tuberculosis DPU portfolio

TB DPU, Tres Cantos GSK DDW

TB DPU

Global portfolio of Projects: GSK+ External Collaborations

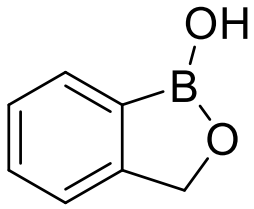


TB Pipeline: Advanced Projects

From Repurposing old drugs to the discovery of new chemical entities

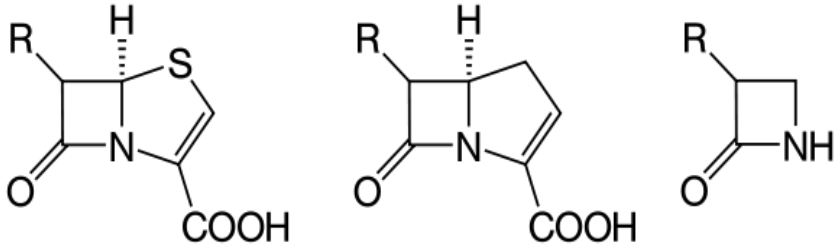
- Focused on the discovery of new clinical candidates for the treatment of multidrug resistant TB
- In house expertise on novel imaging techniques and animal models
- Source of projects: phenotypic hits, target based and new mechanisms of action

Discovery of a NCE for TB



New, oral and low dose

Repositioning b-lactams for MDR-TB



Rapidly cytocidal, safe and approved for children

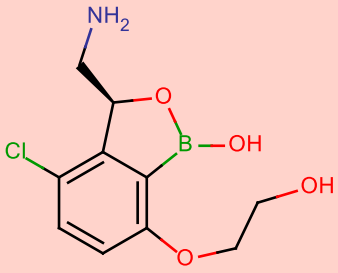
FTIM (2Q 2017)

AnTBiotic Consortium
Clinical repurposing (2017-2021)

GSK070 Mtb LeuRS inhibitor

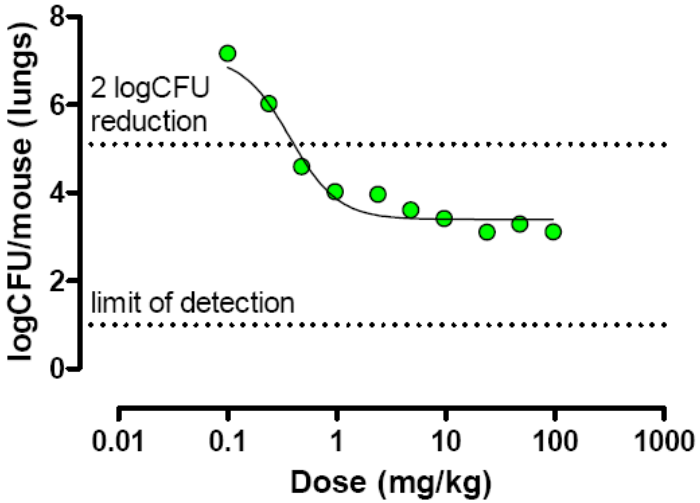
A novel protein synthesis inhibitor with a new MoA

GSK070

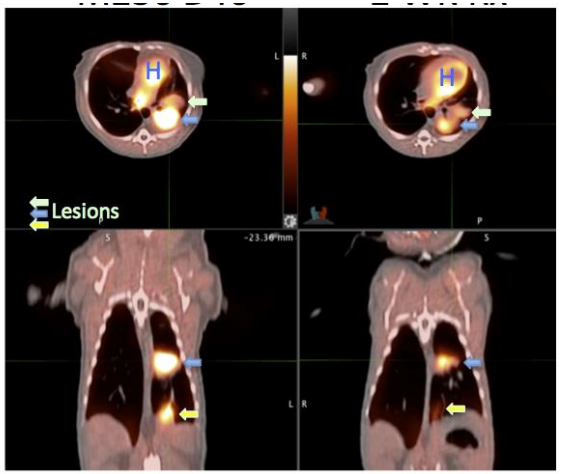


- Mtb MIC H37Rv < 0.1 uM
- THP-1 Mtb MIC < 0.1 uM

Acute Murine model (8 days Rx)



Chronic Marmoset model (8w Rx)



NIH National Institute of Allergy and Infectious Diseases

- 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-tuberculars

Successful progression of b-lactam combination to clinical POC

CORRESPONDENCE

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

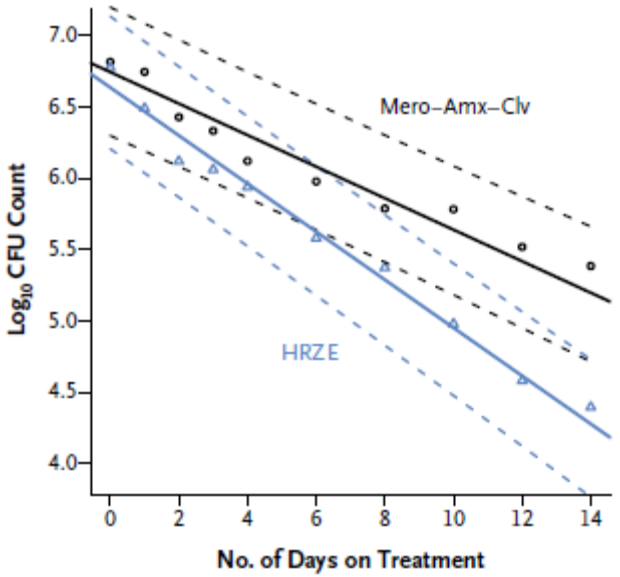


Figure 1. Estimated Mean Log_{10} CFU Counts per Treatment over Time.

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).

Andreas H Diacon, Lize van der Merwe, Marinus Barnard, Florian von Groote-Bidlingmaier, Christoph Lange, Alberto L García-Basteiro, Esperança Sevene, Lluís Ballell and David Barros-Aguirre. **New England Journal of Medicine 15-13236**

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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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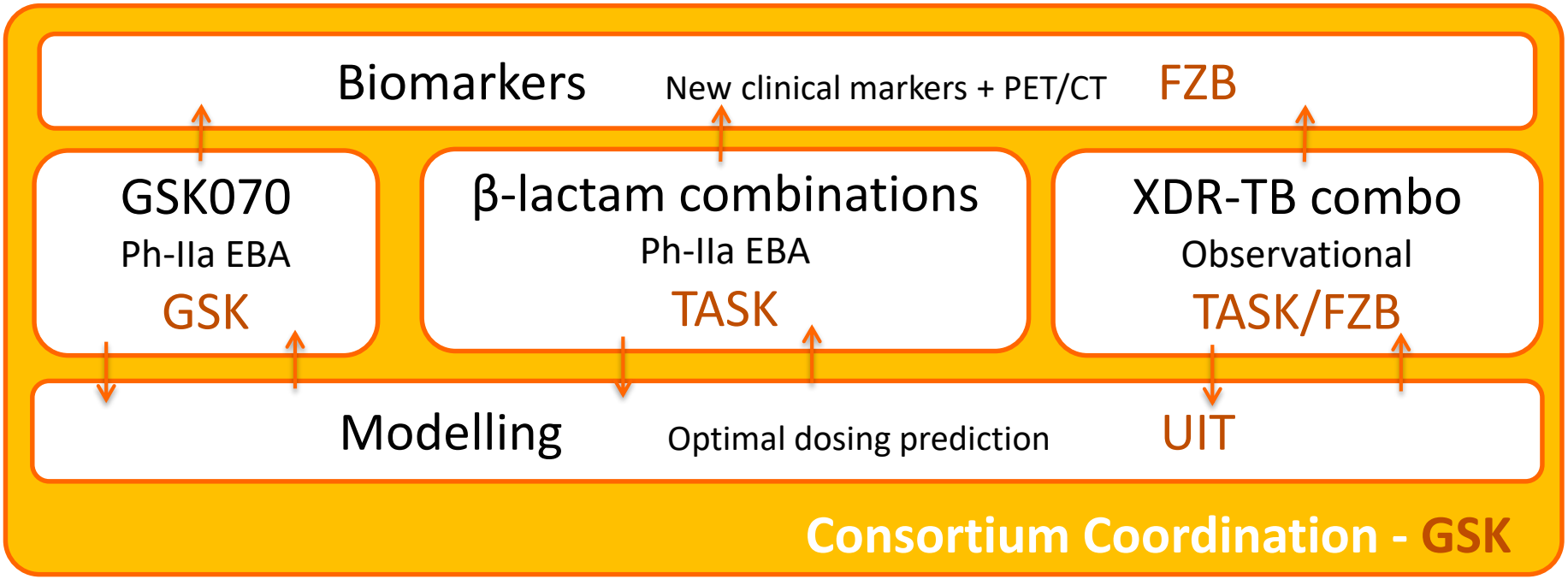
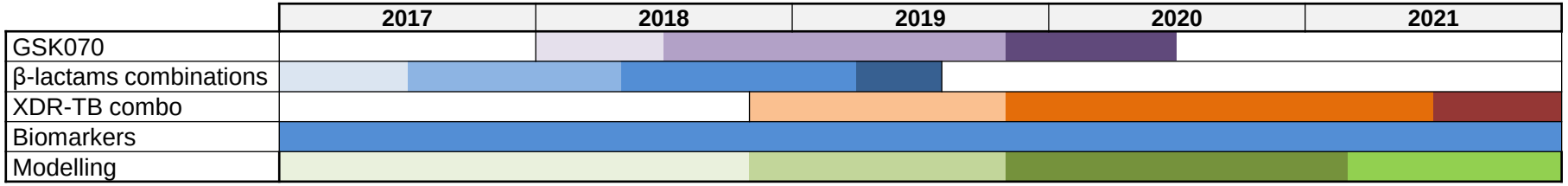
Project plan



GSK	GSK DDW	UCT	UNIVERSITY OF CAPE TOWN	FZB	RESEARCH CENTRE BORSTEL
UIT	ARTIC UNIVERSITY OF NORWAY	TASK	TASK FOUNDATION		



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