

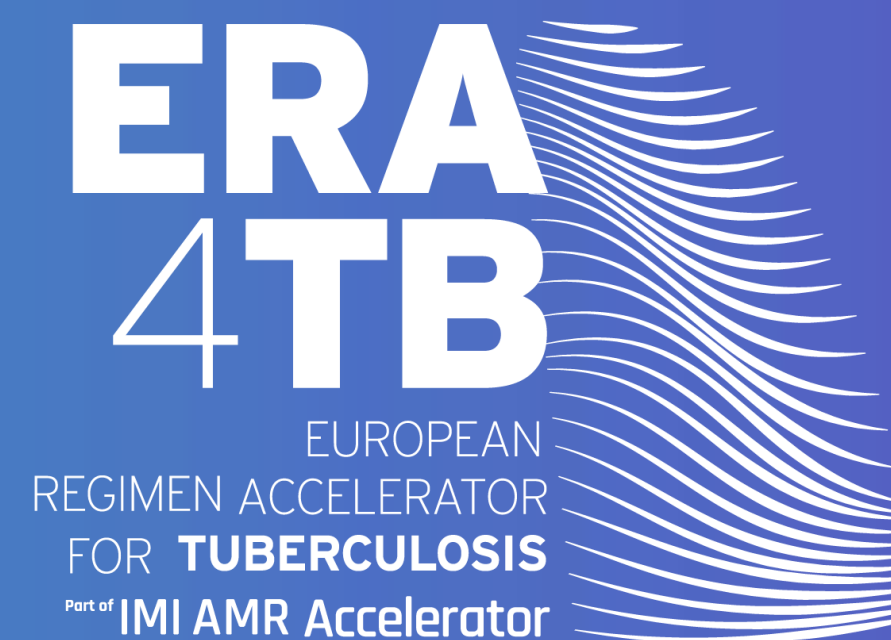


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Antitubercular effects of TBAJ-587 a new diarylquinoline derivative on sub-populations of *M. tuberculosis* and prediction of early bactericidal activity in humans

Silvia Grandoni ^{1,2}, Jerry Nedelman ³, Tian Yang ³, Paul Bruinenberg ³, Almari Conradie ³, Oscar Della Pasqua ^{1,2}

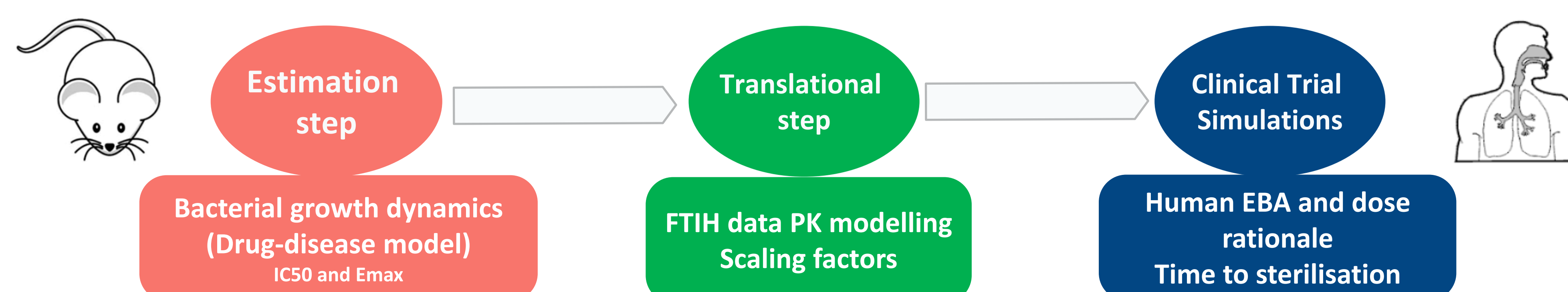
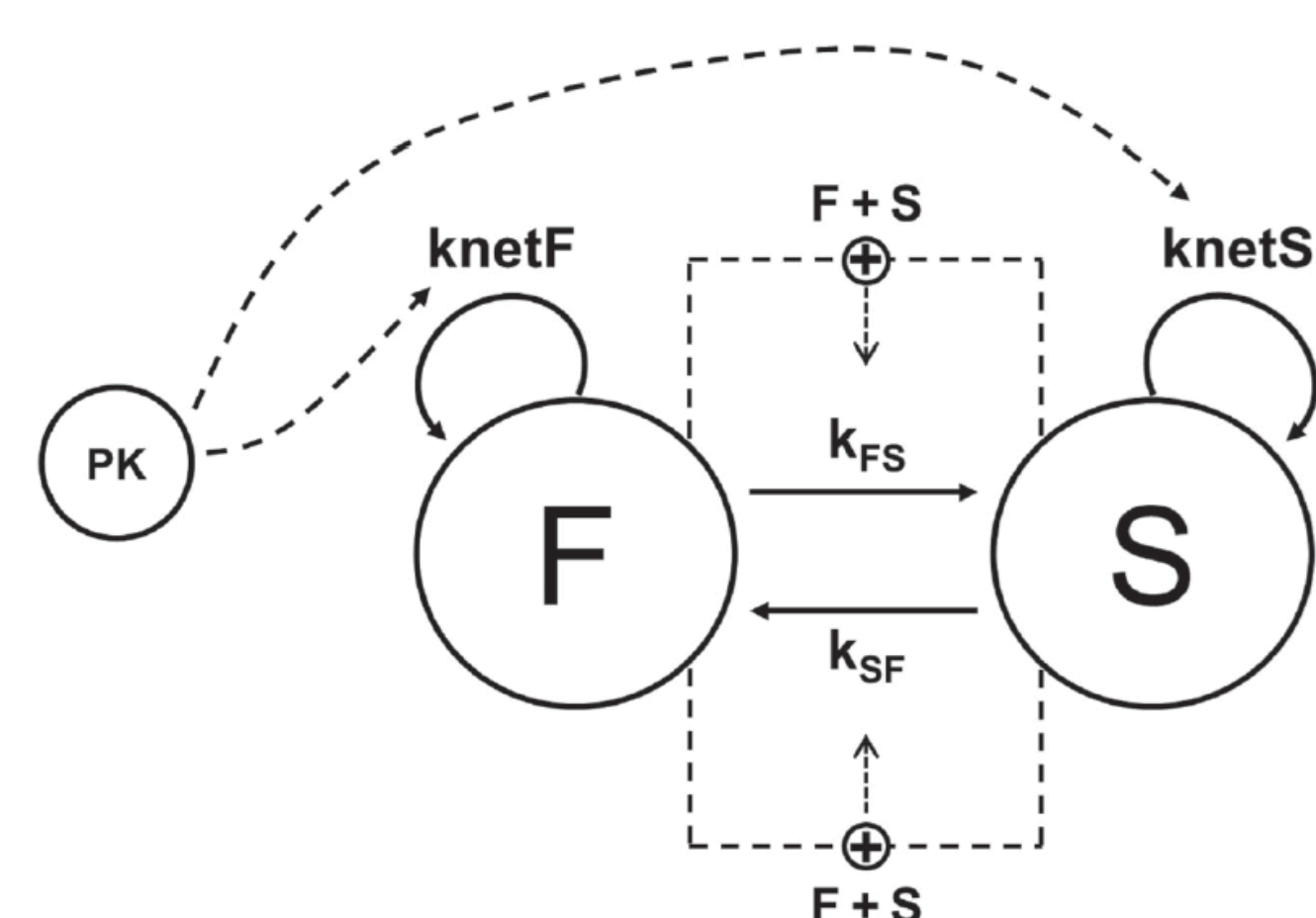
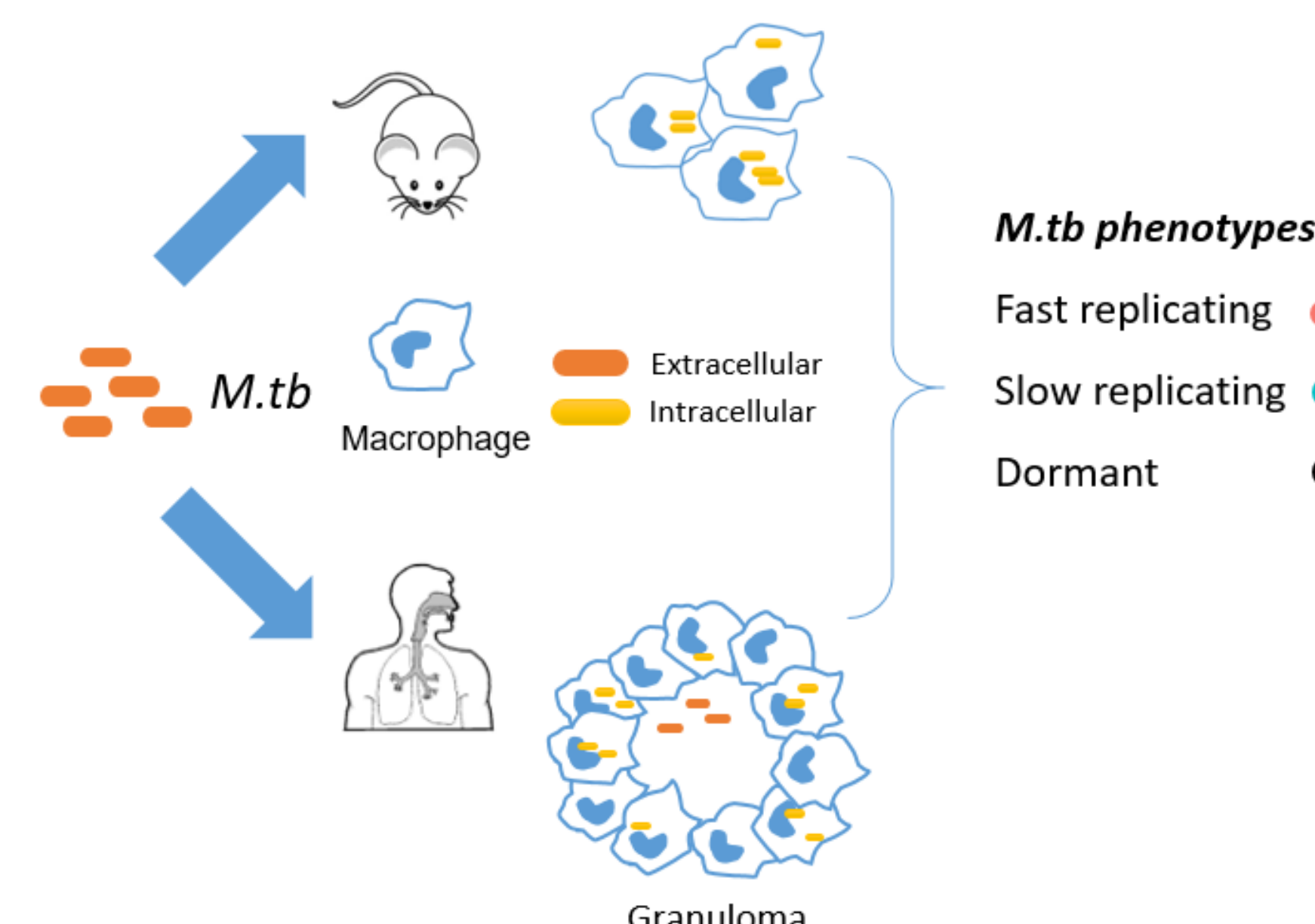
(1) Consiglio Nazionale delle Ricerche (CNR), Rome, Italy (2) University College London (UCL), School of Life and Medical Sciences, London, UK
(3) TB Alliance, New York, USA



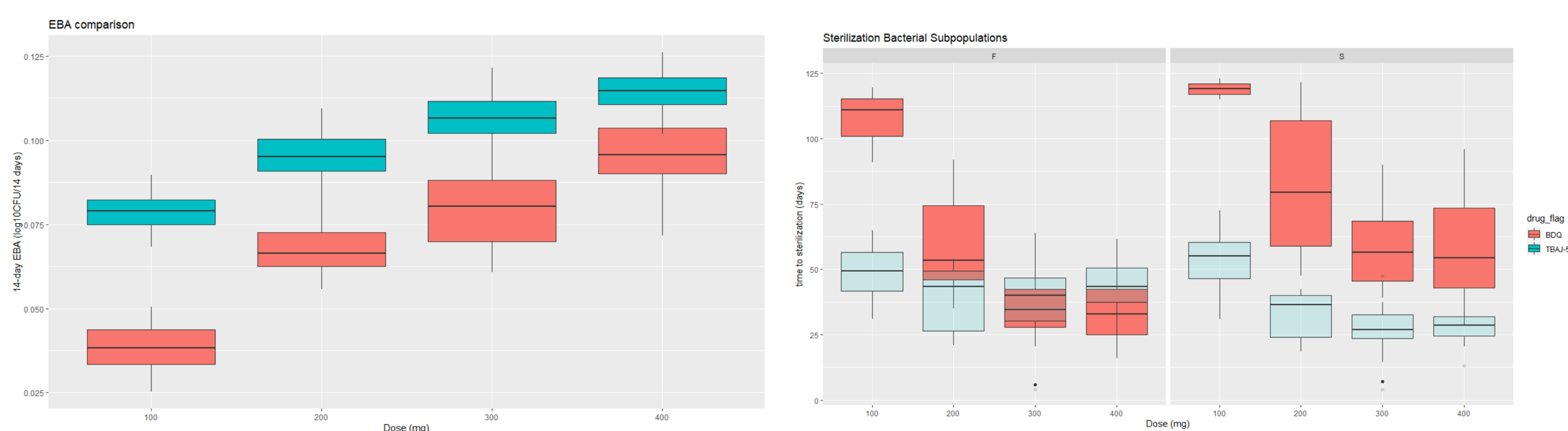
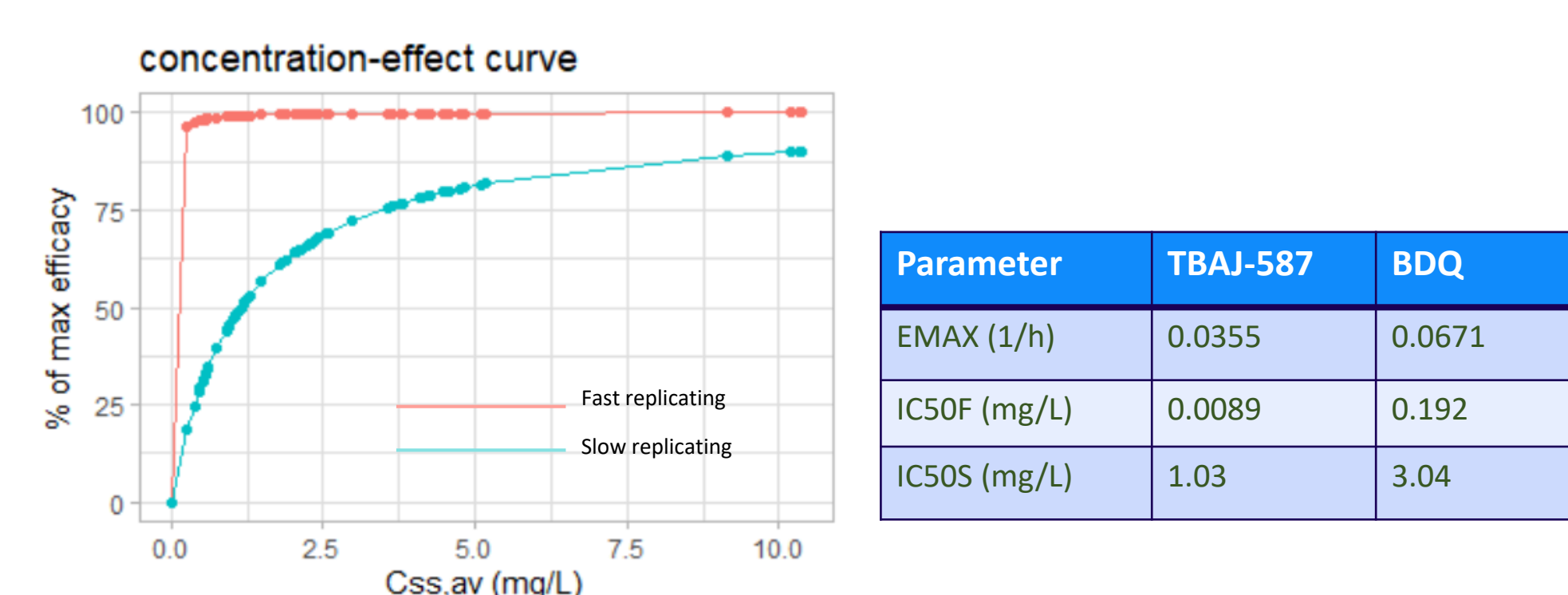
Introduction: Tuberculosis (TB) is a complex disease in which the heterogeneity of pathological lesions, and the presence bacterial phenotypes with different drug susceptibilities, make the selection of compounds and dosing regimens for use as combination therapy very challenging. Currently, one of main goals of anti-TB drug development is to identify drug combinations and regimens that allow treatment shortening [1]. In this context, model-based approaches offer an opportunity to assess treatment performances in a systematic manner. A bacterial growth dynamics model has been proposed that enables the evaluation of the contribution of companion drugs to the antibacterial activity of anti-TB combinations in mice [1]. It includes fast-(F) and slow-(S) growing bacterial subpopulations, which represent the log-growth and stable phase of *Mycobacterium tuberculosis* (*M.tb*) infection [1, 2]. This framework has been embedded within the ERA4TB consortium [3], which aims to identify new combination regimens with treatment-shortening potential and fast progression into Phase II clinical evaluation.

Objectives: TBAJ-587 is a new diarylquinoline developed by TB Alliance, part of the ERA4TB portfolio [4]. In preclinical studies, it demonstrated the potential for being more efficacious and safe than the diarylquinoline bedaquiline (BDQ). Here we characterise the antibacterial activity of TBAJ-587 using the previously developed bacterial growth dynamics model and clinical trial simulations (CTS) to predict its early bactericidal activity (EBA) and compare treatment performance using BDQ as benchmarking. In addition, we illustrate how a model-based approach can be applied to assess the minimum treatment duration required to achieve eradication of different bacterial phenotypes.

Methods: As a first step, a PK model was developed to describe the systemic exposure of TBAJ-587 at steady state ($C_{ss,avg}$) in Balb/c mice. Predicted $C_{ss,avg}$ was then used to characterise the antibacterial activity on F and S bacteria using the bacterial growth dynamics model and data from a chronic infection model in Balb/c mice. Drug effects were parameterised in terms of potency and maximum antibacterial activity. Subsequently, system-specific parameters were scaled from mice to humans to predict EBA in TB patients assuming comparable potency and maximum effect. Predicted $C_{ss,avg}$ levels in TB patients were derived using a pop-PK model built on phase I data, taking into account the effect of drug-food interaction. CTS describing a 14-day EBA study were implemented in NONMEM v7.5 using a virtual cohort of patients with baseline characteristics similar to the one previously used for the evaluation of BDQ [5]. The simulated EBA₀₋₁₄ for TBAJ-587 for a range of doses (100, 200, 300, 400 mg q.d.) was compared to that of BDQ at 400 mg q.d. [5]. In addition, to assess sterilising properties of TBAJ-587 relative to BDQ, simulation scenarios were evaluated in which different doses of each drug were used as monotherapy up to four months. Log CFU counts over time were summarised for each bacterial subpopulations and the time to sterilisation was computed using a sterilization threshold of 10 CFU/mL, taking into account the detection limit for sputum samples.



Results: IC50 estimates for F and S bacteria were 0.0089 and 1.03 mg/L, respectively, whereas the maximum inhibitory effect on the net growth rate constant (Emax) was 0.0355 1/h. These values reveal that TBAJ-587 has a higher potency than BDQ (IC50F = 0.192 mg/L, IC50S = 3.04 mg/L), despite a lower Emax (BDQ = 0.0671 1/h). Scaling and prediction of a 14-day EBA in patients suggest greater treatment effect relative to BDQ when comparing results from TBAJ-587 doses between 200 and 400 mg (i.e. EBA 0.096, 0.106 and 0.113 log10CFU/14 days) to the approved dose of 400 mg BDQ (i.e. 0.097 log10CFU/14 days). Moreover, based on a q.d. regimen of 400 mg, the time to achieve the sterilisation threshold for the less susceptible subpopulation (S) was 27 days for TBAJ-587 and 58 days for BDQ.



Conclusions: implications of EBA results for dose selection for subsequent progression of compounds in combinations have been overlooked. Compared to empirical approaches, the use of a bacterial growth dynamics model provides a robust basis for quantifying the antibacterial activity on different metabolic phenotypes of *M.tb*. These findings offer an opportunity to minimise the risk of relapse in future study protocols aimed at treatment shortening.

References:

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