Poster abstract submission

Approval Status Not Started

Presenting author Susanne Mirold-Mei

Presenting author's email susanne.miroldmei@med.uni-muenchen.de

Further authors (if any)

Bailo, Rebeca2; Cirillo, Daniela7; Ezquerra, Jose Manuel 2; Galizia, Jordana2; Gaudin, Cyril8; Ghodousi, Arash7; Hoelscher, Michael1; Hoffmann, Eik8; Maci, Ludovica4; Niemann, Stefan5; Parbhoo, Trisha5; Pasca, Maria Rosalia4; Rabodoarivelo, Sylvianne2; Ramon-Garcia, Santiago3, Recchia, Deborah4; Saluzzo, Francesca7; Sanz-García, Fernando2, Sonnenkalb, Lindsay5; Spitaleri, Andrea6 and Dreisbach, Julia1on behalf of the ERA4TB and the UNITE4TB Consortia*

Affiliation(s)

1Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Germany
2Department of Microbiology, University of Zaragoza, C/ Domingo Miral s/n 50009-Zaragoza, Spain
3Research & Development Agency of Aragón (ARAID) Foundation, Zaragoza, Spain.
4Department of Biology and Biotechnology “Lazzaro Spallanzani”, University of Pavia, Pavia, Italy
5Molecular and Experimental Mycobacteriology, Research Center Borstel Leibniz Lung Center, 23845 Borstel, Germany
6Department of Medical Biotechnology and Translational Medicine, L.I.T.A / University of Milano, Italy
7IRCCS San Raffaele Scientific Institute, Milan, Italy
8Center for Infection and Immunity of Lille, Institute Pasteur Lille, Lille, France
*www.era4tb.org; www.unite4tb.org

Country Germany

Type of organization Academic / research institution

Poster title

Rv0678-dependent BTZ-043 low level resistance in M.tuberculosis – understanding how to overcome it with improved combination therapies

Poster abstract

Tuberculosis (TB) remains a significant global health challenge, exacerbated by the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. Rv0678 encodes a transcriptional regulator of the MmpL5/S5 efflux pump. Mutations in this gene are known to cause resistance to bedaquiline (BDQ) and clofazimine as well as reduced susceptibility to BTZ-043, resulting in a 4- to 8-fold increase in minimum inhibitory concentrations (MICs) due to overexpression of the efflux pump (Ghodousi et al). Evolution experiments of Mycobacterium tuberculosis (Mtb) using BTZ-043 also selected mutations in the Rv0678 gene (Ghodousi et.al.).
To understand the impact with regard to treatment options and resistance prevention, a cascade of in silico, in vitro and in vivo experiments was designed.
Computational docking shows BDQ and BTZ-043 binding to overlapping sites within the accessory pocket of the MmpL5/S5 efflux pump, exhibiting similar docking scores. Importantly, co-docking of the two compounds yields a more favorable score compared to single-ligand docking, suggesting potential cooperative effects.
In vitro checkerboard assays indicate synergism between BTZ-043 and BDQ as MICs decrease when

exposing Rv0678 mutants to a combination of both. This was confirmed in a high throughput time-kill assays (TKA) using GFP-labelled H37Rv Mtb.
To evaluate and visualize a hypothesized competitive inhibition of BDQ and BTZ resulting in a pump saturation, efflux experiments using BDQ and BTZ-043 is being performed.
For clinical regimens consisting of 4-5 drugs, designed to overcome the Rv0678 mediated resistance, contribution of each drug needs to be demonstrated.
An innovative stepwise approach will be applied to deconvolute the individual contribution within the complex 4-5 drug regimen using Time Kill Assays (TKA).
Monotherapy TKA for each combination drug (dose-response curves) will be applied, followed by assessment of individual contribution in a three-drug combination. The three-drug combination core will be combined with drug 4 and/or 5.
Results will be subjected to translational modelling.
Hollow fibre system (HFS) is even more sophisticated in assessing individual drug contribution, mimicking human pharmacokinetics (PK) profiles. Applying human PK profiles shows whether the regimens can overcome the low-level resistance.
Whole genome sequencing will be applied to assess the risk of newly emerging resistances.

Research topic

Microbiology