PERIODIC REPORT
Publishable summary

AN TB IOTIC

Context and overall objectives of the project

anTBiotic aims to fuel the Tuberculosis (TB) clinical pipeline while also immediately offering new options to clinicians when confronted with drug-resistant (DR)-TB.

TB is the second leading cause of death from infectious diseases after COVID. The number of patients has never been higher and the growing proportion of DR-TB and the COVID-19 pandemic effects is threatening control strategies. Effective drugs are urgently needed to build new regimens that can improve outcomes and potentially shorten treatment.

The project objectives are to:

1. Establish proof of concept of a first-in class low-dose oxaborole compound in an Early Bactericidal Activity (EBA) Phase IIa study. GSK3036656´656 is an exciting new molecule, with a novel mechanism of action and no pre-existent resistance in the field.

2. Identify a combination of β-lactam antibiotics (meropenem or ertapenem in combination with amoxicillin/clavulanate) suitable for the treatment of DR-TB orally or as a once daily intravenous or intramuscular application, in a second EBA study. This repurposing strategy is based on a positive proof of concept generated within FP7 and EDCTP-funded projects.

3. Explore personalized treatment duration by comparing therapy outcomes of DR-TB patients with biomarker defined therapy durations vs. standard of care. This approach has the potential to significantly shorten drug-exposure whilst also reducing adverse events and costs and enabling the identification of patients at risk for therapy failure.

4. Identify improved pathways through early TB drug development using biomarkers and in-silico dose modelling approaches:

- Explore the predictive potential of Positron Emission Tomography (PET) integrated with computed tomography (CT) as a non-invasive approach to complement the more traditional CFU (colony forming units) and TTP (time to culture positivity) EBA sputum markers. Should a correlation between early PET/CT signals and the sterilizing potential of drugs or regimens be confirmed, this would impact future clinical trial design, shortening clinical development timelines and lowering the associated uncertainties.

- Identify biomarkers that reflect the early therapy-induced immunological and bacteriological changes as surrogates for treatment outcome that could lead to improved treatment monitoring, better prediction of treatment response and better classification of patients demanding longer treatments.

- Develop and validate in silico predictions able to shorten the drug development cycle. Mathematical models can inform optimal dosing strategies from preclinical data and address bottlenecks between early clinical development and phase III, where TB relapse is assessed. A new in silico approach connecting processes within single bacteria with the dynamics of entire bacterial populations within patients would enable the extrapolation of basic molecular mechanisms of drug action into response signals to treatment.

Work performed and main results achieved

Both 2-week EBA clinical studies planned have been completed at project end:

- The EBA study with β-lactam antibiotics meropenem and ertapenem in combination with amoxicillin/clavulanate, aimed to identify a once daily regimen for drug resistant TB that could be administered intravenously or intramuscularly (WP2), completed enrolment in 2020. During the last period the team focused on compilation and analysis of results, clinical study report writing and preparation for publication (expected late 2022).

- The EBA study of a low-dose oxaborole drug (WP1) aimed to establish proof of concept of anti-TB activity in humans completed enrolment of the last 2 cohorts during the last period. The clinical study report was finalised in June 2022. Topline study results was presented at the Keystone Symposia on Molecular and Cell Biology in August 2022 and the study manuscript is in preparation for submission later this year.

PET/CT scan images from participants in these trials, as well as blood and urine samples, have been collected and analyzed with the objective of validating biomarkers that accurately reflect the early therapy-induced immunological, radiological and bacteriological changes (WP4). The human biological samples were sourced ethically and their research use is in accordance with the terms of the informed consents under the approved protocols.

PET/CT scan images have been analyzed both manually and computationally and "cubes" (unit of measurement) categorised into 3 types describing presence of TB-related lesions at baseline, day 14 or both. Statistical analysis showed that the computational model detected a dose effect on reduction in lesion volume and FDG uptake (WP1 study).

For immunological biomarkers, main results are 1) a novel urine trDNA assay developed and validated on a WP2 study cohort, 2) the identification of clusters of immune response within the first 14 days of therapy in EBA trials via RNA transcriptomic analysis, 3) the development of an RNA based model predicting TTP results during the EBA trial, 4) the correlation of this model with PET/CT readouts, and 5) the identification of a set of potential biomarkers (cytokines, chemokines, and growth factors) for monitoring treatment response in 14-day EBA studies. Research will continue after project end to enable uptake for use in clinical studies.

Finally, in WP5, a meropenem model was developed to investigate the relationship between EBA and PK measures as well as the target occupancy of different dosing regimens, as part of the modelling work aimed to find optimal treatment strategies for carbapenem antibiotics. A two-drug mathematical model was developed based on binding kinetics to simulate the drug interaction and investigate the possibility of synergy or antagonism between the drugs.

Status of expected results at project end

- A novel chemical entity ready for progression to Phase IIb clinical trials. Status at project end: molecule ready for PhIIb combination studies, funding secured and legal framework in place.
- Optimised drug regimen options for the treatment of resistant TB with currently available and out of patent protection drugs. Status at project end: optimised dosing recommendations can be made for meropenem and ertapenem for DR-TB, publication in planning.
- A defined set of biomarkers to guide individualized treatment duration able to improve patient outcomes by enabling personalized treatment-shortening. Status at project end: Biomarkers identified, further work needed for use in clinical research.

Expected impact

anTBiotic contributes to address major challenges in the TB field, namely:

- Address the large mortality and morbidity associated with drug resistant TB by providing drugs for new combination therapies
- Contribute to the TB treatment shortening agenda, one of the main goals pursued by major TB stakeholders
- Shorten TB drug development cycles by identifying biomarkers with the potential to predict clinical endpoints at earlier phases.
- Contribute to the Sustainable Development Goals of the United Nations on TB.

This project has received funding form the European Union´s Horizon2020 research and innovation programme under Grant Agreement No. 733079