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Blood-based tuberculosis precision medicine: transcriptomic model shortens therapy duration

Keywords: tuberculosis (TB), MDR-TB, XDR-TB, transcriptomic analysis, whole blood, therapy monitoring, end-of-therapy, relapse-free cure

INVENTION NOVELTY

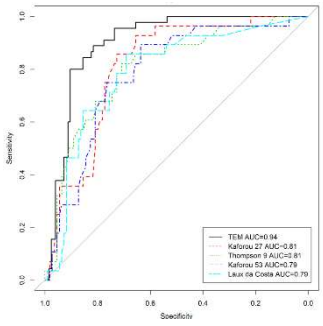
Tuberculosis (TB) remains a major global health problem that is further aggravated by the emergence of drug-resistant strains of *Mycobacterium tuberculosis*. Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are associated with very high treatment costs, frequently occurring severe adverse events, and discouragingly poor outcomes. Current guidelines recommend a standardized duration of treatment (in case of MDR-/XDR-TB: 18 months or more), although it is known that individual success and duration of anti-TB therapy to achieve relapse-free cure varies widely depending on e.g., patient's immune status, extent of disease, pathogen's virulence, drug-resistance, and active drugs available for treatment. The innovation concerns a transcriptomic model for blood-based precision medicine that enables prediction of therapy response, treatment outcome and cure-related end-of-therapy not only for drug-sensitive TB (DS-TB), but, for the first time, also for MDR/XDR-TB.

VALUE PROPOSITION

The innovative transcriptomic model represents a versatile and valuable tool for blood-based TB precision medicine. It enables reliable prediction of therapy response, therapy success, and therapy end in DS-TB and – most importantly – MDR/XDR-TB. Using the model, therapy duration can be drastically reduced (e.g., by three to four months on average in MDR/XDR-TB), ultimately leading to better treatment adherence, fewer side effects, lower costs, and a reduced risk of resistance development.

TECHNOLOGY DESCRIPTION

The transcriptomic model is based on prospective analysis of whole-blood RNA transcripts in healthy controls and two patient cohorts (DS-TB vs. MDR/XDR-TB). Study visits included assessment of clinical parameters and collection of blood samples and were performed prior to initiation of treatment and at specific time points until guideline-designated end-of-therapy. Blood-based RNA microarrays were used to identify genes that are significantly up- or down-regulated between healthy controls and therapy naïve TB patients. Analysis revealed a six-gene and a nine-gene signature that predict the outcome of therapy and the remaining days of therapy in both DS-TB and MDR/XDR-TB patients, respectively. Furthermore, genes differentiating between ongoing therapy and completed therapy were identified. The entire set of 22-genes was combined to a single transcriptomic model that allows to determine successful completion of therapy with outstanding high accuracy. In comparison to known published approaches, the innovative transcriptomic model allows to determine individual therapy response and duration for both, DS-TB and MDR/XDR-TB, as confirmed by established clinical endpoints.



ROC curves for therapy end detection. *Proprietary transcrisptomic model (TEM): black, known published models: colored (from Heyckendorf et al., 2021)*

COMMERCIAL OPPORTUNITY

The transcriptomic model is available for co-development and in-licensing.

DEVELOPMENT STATUS

The transcriptomic model was validated on three independent cohorts of TB patients. The model showed superior performance when compared to state-of-the-art methods, reliably determining e.g., therapy duration in patients with DS-TB and MDR/XDR-TB, as confirmed by smear and culture status, radiological findings, and other strict outcome criteria. Based on the proprietary model, treatment duration for most patients enrolled in the validation cohorts (especially those suffering from MDR/XDR-TB) could have been significantly shortened (e.g., from 638 days to 420 days). Further clinical validation is in progress.

PATENT SITUATION

The technology is protected by international PCT application PCT/EP2021/054288.

FURTHER READING

Heyckendorf et al. (2021) Prediction of anti-tuberculosis treatment duration based on a 22-gene transcriptomic model. European Respiratory Journal; https://doi.org/10.1183/13993003.03492-2020.

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