International Journal of Infectious Diseases 56 (2017) 253–257

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

A tuberculosis biomarker database: the key to novel TB diagnostics

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ARTICLE INFO

Article history:
Received 10 October 2016
Received in revised form 18 January 2017
Accepted 22 January 2017
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Biomarkers
Database
Pipeline

SUMMARY

New diagnostic innovations for tuberculosis (TB), including point-of-care solutions, are critical to reach the goals of the End TB Strategy. However, despite decades of research, numerous reports on new biomarker candidates, and significant investment, no well-performing, simple and rapid TB diagnostic test is yet available on the market, and the search for accurate, non-DNA biomarkers remains a priority. To help overcome this 'biomarker pipeline problem', FIND and partners are working on the development of a well-curated and user-friendly TB biomarker database. The web-based database will enable the dynamic tracking of evidence surrounding biomarker candidates in relation to target product profiles (TPPs) for needed TB diagnostics. It will be able to accommodate raw datasets and facilitate the verification of promising biomarker candidates and the identification of novel biomarker combinations. As such, the database will simplify data and knowledge sharing, empower collaboration, help in the coordination of efforts and allocation of resources, streamline the verification and validation of biomarker candidates, and ultimately lead to an accelerated translation into clinically useful tools.

Contents

Introduction

"Scarcely four years have elapsed since the important discovery of the tubercle-bacillus by Koch was announced. Many then thought that the key to the various problems of pulmonary consumption was close at hand, if not in our actual possession" W N, 1886.[1]

More than a century after Koch's discovery and the hopes that answers would quickly follow,[1] tuberculosis (TB) continues to kill 4000 people per day,[2] and we are still searching for 'the key' as envisioned in the 1880s. An array of diagnostic and treatment solutions is required to control and prevent the complex medical and socio-economic problems caused by TB. In countries experiencing the worst TB epidemics, i.e., high-burden, low- and middle income settings, the continuing dependence on slow diagnostic tools with limited performance allows epidemics to persist. Despite the advent of molecular diagnostic tests such as Xpert MTB/RIF,[3] limited access and affordability prevent people with TB symptoms from accessing services. Within this context,

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http://dx.doi.org/10.1016/j.ijid.2017.01.025

intensified research and innovation towards the discovery, development, and rapid implementation of new diagnostic tools have been identified as important components of the End TB Strategy of the World Health Organization (WHO).[4,5]

Recent efforts to identify the highest priorities in the field of TB diagnostics have revealed the urgent need for biomarker-based assays that will enable more efficient, affordable, and accessible diagnosis for those in need.[6,7] Table 1 lists the target product profiles (TPPs) that will likely rely on non-DNA biomarkers. The highest priority is a rapid biomarker-based, non-sputum test for detecting active TB with the purpose of initiating treatment.[6,7] The second highest priority is a triage test, also probably biomarker-based and with high sensitivity, that can rule out disease and be used to refer patients to the more expensive and accurate molecular testing for confirmation.

Unfortunately, despite decades of research, significant investment, and numerous reports on new biomarker candidates, few biomarkers have been independently validated for specific use cases and translated into new diagnostic tests.[8,9] This problem is not unique to TB; it is true for biomarker research in general, with very few of the biomarkers discovered having advanced to the clinic in the form of approved diagnostic tests.[10–12] Preliminary data from our ongoing systematic review of biomarker studies reporting on the detection of active TB confirm this lack of validation: for the majority of biomarkers ($n = 399$), diagnostic performance is not reported (161 biomarkers), or is based on testing of a non-blinded, usually retrospective set of conveniently obtained samples (170 biomarkers), or on blinded testing in a single study (68 biomarkers) (Figure 1). Only 12 biomarkers have been confirmed in prospectively designed studies and, to date, only one urine biomarker-based test has been endorsed by the WHO (Determine LAM; Alere, Waltham, MA, USA);[13] however, none of the biomarkers identified has so far led to a diagnostic test that meets the performance requirements of any TPP.

Key issues that limit the impact and translation of biomarker research include: (1) a lack of coordination of similar research activities and limited knowledge-sharing between researchers; (2) an often limited assessment of a biomarker to one or two exploratory studies and a lack of well-designed validation studies; (3) the lack of standards and frameworks for biomarker validation, as well as generally low reporting quality; (4) the failure of many studies to clearly articulate the intended use case and benchmark a biomarker towards it; and (5) optimism and publication bias, which result in a lack of confirmation of initially promising findings. Concerns over intellectual property (IP) rights are common, incentives to share data in the current publishing system

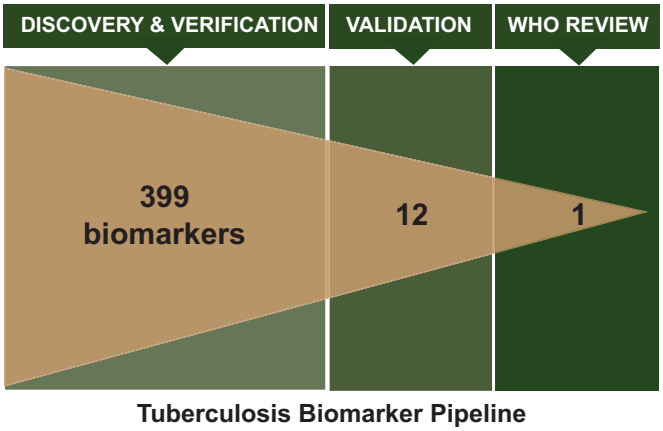

Figure 1. TB biomarker pipeline based on the evidence from 763 studies on TB biomarkers published between 2010 and 2015. A systematic search was employed to find studies in PubMed, Embase, and Web of Science reporting either statistical significance or diagnostic performance of TB biomarkers for the detection of active TB. In total, the 763 included studies reported on 413 (non-DNA) biomarkers or biomarker signatures. The 'discovery and verification' category includes 399 biomarkers for which only statistical significance was reported ($n = 161$), or data were based on testing of a non-blinded sample (usually retrospective set of conveniently obtained samples) ($n = 170$), or performance was based on blinded testing in an initial study ($n = 68$). Only 12 biomarkers were validated in a prospectively designed study in a blinded manner (category 'validation') and only one biomarker-based test has been reviewed by the World Health Organization (lipoarabinomannan in urine, category 'WHO review').

are limited, and easy-to-use tools for in-depth analysis of datasets are unavailable. Moreover, independent validation studies are laborious and costly, as they require larger sample sizes than discovery studies to ensure sufficient statistical power. This discouraging (and expensive) reality prevents researchers from moving from discovery to further stages of development. Additionally, some biomarkers are repeatedly 'discovered' or probed with retrospective, discovery-level studies based on whatever haphazard specimens can be obtained conveniently. This represents an avoidable waste of financial resources as well as patient and researcher time.

Combining resources and evaluating multiple biomarkers side-by-side could be a way to surpass these hurdles, but the lack of communication and coordination among scientists and funding bodies often impedes such possibilities. The end result is the poor translation of biomarkers into urgently needed, fit-for-purpose diagnostic solutions. Poste proposed replacing "this dismal

Table 1
World Health Organization endorsed priority target product profiles (TPP) for the detection of active TB for which non-DNA biomarkers may play a key role.[7]

Priority TPP	Description	Diagnostic sensitivity	Diagnostic specificity
Rapid biomarker-based non-sputum-based test for detecting TB	The majority of pulmonary TB cases are diagnosed by sputum smear microscopy. However, smear microscopy has suboptimal sensitivity, and children and HIV-infected individuals often have difficulties providing a good quality sputum sample. The unmet need is a rapid point-of-care test detecting characteristic biomarkers or biosignatures in non-sputum samples. The requirement is a very high specificity and moderate to high sensitivity for the purpose of initiating treatment.	Minimal: ≥65% overall Optimal: ≥80% overall (≥98% sputum smear-positive and ≥68% in sputum smear-negative patients)	≥98% ≥98%
Community-based triage or referral test for identifying people suspected of having TB	Two weeks of cough is a widely used symptomatic indicator to identify individuals with presumed active pulmonary TB who require diagnostic testing. Since most individuals with suspected TB do not have TB, a triage test can help to narrow down the population that needs more costly and complex confirmatory testing. The needed point-of-care test has a high overall sensitivity and moderate specificity.	Minimal: ≥90% overall Optimal: ≥95% overall	≥70% ≥80%