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Review article

MULTIOMICS INTEGRATION IN ANTI-TUBERCULOSIS DRUG DISCOVERY

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Abstract: Despite intensive global efforts, tuberculosis remains one of the leading global health burdens, with antimicrobial resistance being a significant challenge to managing the disease. In addition, the current drugs used to treat tuberculosis suffer from limitations, such as prolonged therapeutic duration and toxicity. Therefore, the development of new anti-tuberculosis drugs is a priority. However, this process faces several challenges. The introduction of a multiomics approach could serve as an ideal platform to accelerate drug development by addressing these challenges. This article reviews the potential role of multiomics in anti-tuberculosis drug development and briefly discusses the associated challenges in utilizing multiomics for drug discovery.

Keywords: tuberculosis, drugs, proteomics, multiomics, *Mycobacterium tuberculosis*, transcriptomics, metabolomics, genomics.

INTRODUCTION

Tuberculosis remains one of the leading global public health issues, with a significant disease burden. In 2024, approximately 10.8 million new cases were reported, 10% of which occurred in children, while 12% were linked to co-infection with human immunodeficiency virus (HIV) (1). Although the World Health Organization (WHO) has approved effective therapeutic regimens with an estimated 85% cure rate, around 1.6 million deaths were reported (2). Among the newly diagnosed cases, drug resistance was identified in 6.4 million, and 662,000 cases involved co-infection with HIV.

Multidrug resistance remains a major obstacle to global tuberculosis control efforts. Treating drug-resistant tuberculosis requires between 6 and 9 months, presenting significant challenges. The increasing prevalence of drug resistance adversely affects treatment strategies, prolonging therapy and complicating regimens compared to drug-susceptible tuberculosis. This highlights the urgent need for novel antimicrobial compounds effective against *Mycobacterium tuberculosis* (M. tb). Despite international efforts, only three new tuberculosis drugs—pretomanid, delamanid, and bedaquiline—have been introduced in recent years (3, 4).

Several logistical and physiological factors have hindered the development of new drugs using existing technologies, including the ability of drugs to penetrate the lungs, the lipid-rich nature of the bacterial cell wall, and intrinsic mechanisms of drug resistance. The introduction of multiomics technology offers a promising solution to these challenges (4). Multiomics aims to integrate and analyze combined molecular entities based on their biological classification, elucidating the roles of individual components. This approach can play a crucial role in identifying novel drug targets. When applied to tuberculosis research, multiomics can be utilized throughout the entire drug discovery process—from initial phases to preclinical and clinical stages—helping to define mechanisms of action (MoA), derivatives, and formulations for M. tb.

This review will evaluate the role of multiomics technology in the development of anti-tuberculosis drugs by analyzing key components of multiomics approaches, including genomics, metabolomics, proteomics, and transcriptomics (Table 1). It will also explore their potential in identifying and validating novel anti-tuberculosis drug targets and biomarkers for both efficacy and toxicity.

***Table 1**. Multi-omics strategies and the processes in reading (Sources: Ref No 4)*

Multi-omics approach	Molecular read-outs	Technology
Genomics	Genes (DNA)	Sequencing, exome
Epigenomics	Alteration of DNA	Modification-sensitive PCR and qOCR-next-generation sequencing, mass spectrometry
Transcriptomics	RNA and/or cDNA	RT-PCR and RT-qPCR, gene arrays, RNA-sequencing
Proteomics	Proteins	Mass spectrometry, western blotting, and ELISA
Metabolomics	Metabolites	Mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy and HPLC
Lipidomics	Lipids	Mass spectrometry, Bioinformatics data mining, and Ionization techniques
Microbiomics	Microbes	16S profiling
Omic imaging	Tissues and biofluids	Functional and structural magnetic resonance imaging (fMRI and sMRI)

Multiomics Approach

Omics is a systems biology field that integrates different sets of biomolecules, such as RNA or metabolites, to enhance our understanding of molecular complexity in both health and disease states. Advances in omics technology have enabled the integration of multiple omic data types, collectively referred to as **multiomics**. This integrated approach provides a holistic understanding of biological processes by combining genomics, proteomics, microbiomics, metabolomics, transcriptomics, and other multiomics techniques (Table 1).

Multiomics approaches have been instrumental in healthcare and beyond. For example, omics technology enhances our understanding of disease pathogenesis. Additionally, multiomics aids in the identification of novel biomarkers. In terms of disease prevention, multiomics can help uncover genetic and molecular mechanisms that inform preventive strategies, improving both patient classification and clinical outcomes. Furthermore, omics technology plays a crucial role in identifying molecular targets for developing new therapeutic agents. In diseases such as infectious diseases and cancer, targeting specific proteins or mutations is a highly effective strategy for drug development and diagnostics.

The advent of artificial intelligence (AI) has further advanced multiomics by facilitating computational techniques such as bioinformatics, which can significantly enhance drug development and predict drug responses—essential for designing personalized treatment plans. Multiomics is also valuable in clinical trials, where multiomic data can be used to stratify trial participants and evaluate therapeutic interventions. Moreover, statistical analyses in multiomics research can help identify the risk of developing certain diseases, further expanding its role in predictive medicine.

These applications highlight the vast potential of multiomics technology in advancing healthcare and beyond (5).

***Table 2.** Different types of multiomics techniques (Source: Ref No 4)*

• Genomics: Use to study of genome sequences and DNA sequences variants (e.g. single nucleotide variations, insertion-deletions, copy number changes, structural changes
• Transcriptomics: Evaluate or measure complete set of RNA transcripts and their quantity in a cell or population of cell
• Proteomics: Use to quantify all protein identity and abundance in a sample such as serum, plasma, post-mortem samples. Also useful in analysing altered level of immune system-regulating proteins such as apolipoprotein
• Epigenomics: Use to identify chemical changes to DNA and proteins in cell that control gene expression. An epigenome is made of chemical compounds that change or highlight the genome is such as wat that it instruct it what to do, where to do it, and when to it. Cells have different epigenetic markers
• Metabolomics: Study of small molecules in the body. Four type of metabolomics: target metabolomics- identifying and quantifying small subsets of metabolites. It is ideal for identification of novel biomarkers; untargeted metabolomics- used to characterized all possible number of metabolites; fluxomics- monitors the movement of isotopic labels through metabolic intermediates and used to measure the reaction rates of metabolites; metabolites imaging- involves the detection and visualization of metabolites in tissues

Currently, different types of omics approaches are being used. Multi-omics sequencing allows the simultaneous evaluation of multiple molecular layers from a single sample, leading to a detailed elucidation of the biological system. It plays a significant role in combining complex data, which is essential for understanding biological matrices and pathways.

In single-cell multi-omics, a series of omic data are evaluated at the single-cell level to study complex diseases. Single-cell multi-omics can help develop an understanding of how different cell types in pathogens or tumors respond to therapies.

Spatial multi-omics utilizes multi-omics data by combining it with spatial information about the surrounding tissues or cells.

The Role of Innovative Technologies in Drug Development

The development of drugs is a complex process that begins with identifying novel targets and ends with introducing a drug into clinical settings. This process is typically long and expensive, with most drugs tested failing in clinical trials. The ultimate aim of drug development is to identify novel molecules that have an effect in the human body and establish an effective and safe profile that benefits patients.

The US Food & Drug Administration (FDA) estimates that it takes more than 12 years for an experimental drug to advance from the bench to the market (6). More than $20 billion is expended on a single drug discovery, with approximately 20% used in screening assays and toxicity testing (7). Furthermore, long administrative processes play a significant role in the high failure rates associated with new drug development.

While the cost of new drug development continues to rise, there is still a need for new drugs, especially for infectious diseases such as tuberculosis, malaria, and HIV/AIDS, where antimicrobial resistance (AMR) has become a global public health burden. The utilization of novel technologies can facilitate the development of new drugs. The use of genomics, metabolomics, proteomics, and other omics will be essential in facilitating drug development and contributing to more effective treatment regimens.

In tuberculosis medicine, new drugs are urgently needed to address both AMR and the duration of treatment. Different approaches to multi-omics data integration can be used for anti-tuberculosis drug discovery (8, 9). Among these is conceptual integration, in which databases and existing information are connected to various omics data according to measurable concepts or entities, such as genes or proteins. This method is useful for formulating theories and finding connections between various omics datasets. Two platforms for comparing omics data are STATegra and OmicsON (10, 11).

Combining statistical techniques to compare various omics datasets using quantitative metrics such as regression and correlation is known as statistical integration. This method is crucial for identifying trends and differences in omics data. It can also be used to determine whether drug response and gene expression are related. However, causal relationships between the omics data cannot be established using this technique (12).

Using mathematical or computational models to forecast a biological system's behavior based on various omics data is known as model-based integration. Drug absorption, distribution, metabolism, and excretion in various biological models can be assessed using pharmacokinetic/pharmacodynamic models (13, 14). This technique helps in understanding the biological system's dynamics and regulation (5). However, a limitation of this approach is that it requires prior knowledge and assumptions about the parameters and structure of the system.

Network and pathway data integration involves using networks or pathways that depict the composition and operation of a biological system, derived from various omics data. Pathways refer to biological processes that occur under specific conditions, while networks are graphically represented as nodes and interactions within the system (13). Omics data can vary in complexity and format, and this method allows for their integration. For example, it can be used to assess protein-protein interactions. However, this approach is not useful for understanding the system's geometric or temporal details.

Role of Multi-omics in Tuberculosis Drug Development

Multi-omics is a promising technology in the development of anti-tuberculosis agents (Figure 1), as it provides a platform to untangle the pathogenic mechanisms of TB infection, drug resistance, and the host's response to infection (15). Data generated from multi-omics can be utilized to address key research questions. One of the primary applications of multi-omics is the identification and validation of drug targets for therapeutic interventions. These drug targets are molecules that can be modified during the disease state. Targets may include genes, proteins, metabolites, or transcript markers associated with the pathogenic mechanisms of specific diseases, such as tuberculosis, COVID-19, and Dengue fever (5).

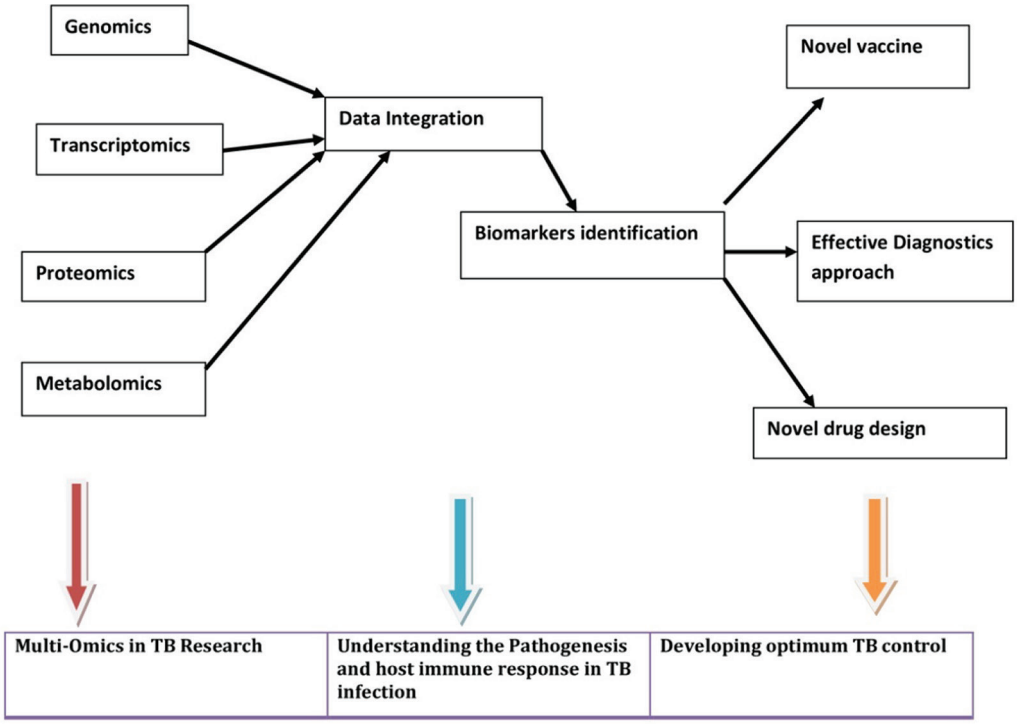

Figure 1. *Multi-omics flow in TB research (Source: Based on protocol of the AHRO small drug molecules development portfolio)*

In TB drug discovery, like in other disease states, multi-omics can be utilized for discovering and validating drug targets. It helps elucidate the disease profile or molecular signature, as well as the potential drug response, by integrating omics data from various levels of biological molecules. Multi-omics data can identify genes, proteins, metabolites, and transcript markers that are differentially expressed or regulated in diseased samples compared to healthy ones, or in individuals who respond to a drug versus those who do not (16). This approach enables the characterization of potential drug targets based on their role in the disease's pathogenic process and their response to drugs, ranking them based on differential expression, disease correlation, and other relevant criteria (5). Drug targets can then be validated using experimental models that assess the effects of modulating these targets in disease versus non-disease states. Multi-omics can also guide studies on gene knockdown, mutation, inhibition, and activation of drug targets (17).

Building molecular networks that integrate omics data—such as the correlations among genes, proteins, metabolites, and transcript markers—can help identify connections to the disease's pathogenic mechanisms and the drug's mechanisms of action (5).

Beyond discovery and validation, multi-omics is valuable for predicting and improving drug responses in various disease states. It can be used to identify markers of drug efficacy, safety, resistance, and other relevant indicators. In TB drug development, multi-omics can help identify genetic variants, such as single nucleotide polymorphisms (SNPs), protein and gene expression levels, and metabolites and transcript markers that influence individual responses to anti-TB drugs. Additionally, it can be used to predict optimal drug dosages during the discovery and formulation phases. Multi-omics can also categorize individuals based on their drug response, which can aid in predicting the efficacy, toxicity, safety, and duration of drug response, as well as other important markers (18, 19, 20).

Although no research specifically evaluates the role of multi-omics in TB drug research, several studies have explored its role in mycobacterial research. Wei et al. used multi-omics to investigate resistance mechanisms in folylpolyglutamylsynthetase-dihydrofolate synthetase gene (folC)-mutated and unmutated *M. tb* strains resistant to p-Aminosalicylic acid (PAS). They found that S-adenosyl-methionine (SAM)-dependent methyltransferases were upregulated, while PAS uptake was downregulated through the inhibition of certain drug transport pathways. These findings suggest that these pathways could serve as novel drug targets for PAS-resistant *M. tb* strains (21).

Krishnan et al. employed multi-omics to identify serum markers of tuberculosis in individuals with advanced HIV infection (22). In a case-control study using a multi-country, open-label randomized controlled trial, they compared a four-drug standard TB treatment with isoniazid preventive therapy among people living with HIV (PLWHIV) initiating antiretroviral therapy. The

study identified several indicators (microRNAs, metabolites, and cytokines/chemokines) associated with newly diagnosed TB among PLWHIV. They found that TNFα and CXCL10 levels were higher in cases than controls, while macrophage-derived chemokine (MDC, also known as CCL22) was higher in controls. This study highlighted the potential of multi-omics in identifying TB among severely immunocompromised PLWHIV.

Cui et al. used a multi-omics approach to evaluate the role and mechanism of DosR (dormancy survival regulator) in *Mycobacterium bovis* Bacillus Calmette-Guerin (BCG). Their study showed that DosR significantly impacted the transcription of 104 genes and 179 proteins, suggesting its involvement in amino acid synthesis and metabolism. These findings suggest that DosR may serve as a novel drug target against M. tb (23).

One of the problems of global health is AMR. Zhao et al. evaluated resistance to capreomycin (CAP), a cyclic peptide that is considered the best second-line treatment for tuberculosis, using multi-omics analysis (24). They evaluated CAP resistance (CAPr) using tlyA-Mtb strains (CAPr1) and tlyA point mutation CAPr M. tb strains (CAPr2), utilizing genomics, proteomics, and metabolomic techniques. They found that compared to CAPr2 strains, CAPr1 bacteria exhibited greater resistance to CAP. Additionally, CAPr1 strains showed greater drug tolerance than CAPr2 strains, which was associated with deficient S-adenosyl-L-methionine-dependent methyltransferase and abnormal membrane metabolism. Their research identified a novel drug resistance mechanism in M. tb in CAP therapy, which may help in understanding other resistance mechanisms in M. tb. Moreover, multi-omics was used to elucidate the correlation between drug similarities and drug efficacy in type 2 diabetes (19). Si et al. identified new targets for chronic kidney disease (CKD) using multi-omics. They discovered thirty-two new therapeutic targets in a thorough analysis of CKD patients' plasma using proteomics and transcriptomics. These included centrosomal protein of 170 kDa, liver-expressed antimicrobial peptide, fibroblast growth factor 5, oromoduline, and others. As a result, the researchers concluded that these new potential therapeutic targets might be used to develop new immunotherapy drugs, targeted medications, and CKD combination treatments (20). Bai et al. used data-based Mendelian randomization (MR) techniques to find a novel therapeutic target for Sjögren's syndrome (SS). Three proteins were shown to be associated with the risk of SS. TNFAIP3, PLAU, and BNT3A1 were among them. They therefore suggested novel drug targets for SS (25). All these studies show that multi-omics has potential in TB drug development, as outlined briefly below.

Novel pharmacological targets can be identified through genomics. Different microenvironments that provide beneficial routes for M. tb can be identified by inactivating genes through experimental mutation using genomics. These may be effective methods for discovering new targets. Genomics can also be crucial in clarifying the MOA of new medications. Whole genome sequencing (WGS) can be used to identify possible mutations that could impact a drug's mode of action. The MOA of bedaquiline was described by Kundi et al. in a study, which demonstrated that the medication works by targeting the bacterial F-ATP synthase's epsilon subunit (26). To enable the innovative use of licensed medications in TB treatment, WGS can also be used to determine the MOA of repurposed medications in TB. In an intracellular model of infection, Rybniker et al. found that lansoprazole protected against lung fibroblasts. This medication was found in the Prestwick Library pool, which included 1280 FDA-approved medications (7, 27).

Understanding M. tb transcriptomics is also crucial in identifying novel pharmacological targets for TB infection, as it links crucial genomic data to protein expression targets, revealing new target pathways and M. tb's response to exposure to that novel drug. Transcriptomics is an essential tool for understanding the biology of M. tb, the pathogenic mechanism of the bacteria, gene function, and the identification of new therapeutic targets (4). The drug mechanisms, including the metabolism of fatty acids, cholesterol, and the glyoxylate shunt of M. tb replicating within macrophages, were clarified by Schnappinger et al. and Rienksma et al. using transcriptomics (28, 29). Additionally, purimidine-imidazole detection during whole-cell screening of M. tb was reported by Pethe et al. (30). This lends more credence to the claim that WGS in transcriptomics is the ideal platform for discovering new, potentially effective therapeutic targets. As a result, using transcriptomics in conjunction with gene mining datasets may be an essential multi-omics tool for TB drug development. The MOA of a novel medicinal molecule can also be better understood with the aid of transcriptomics. According to a study by Wilson et al. using DNA microarray to clarify gene expression caused by isoniazid, exposure to the drug led to upregulation of five genes encoded by synthesis-type II fatty acid enzymes and other genes linked to isoniazid MOA (31). In addition, Boshoff et al. quantified the effect of various inhibitors that affect M. tb transcriptional responses (32) by characterizing TB metabolism utilizing various therapeutic agents, growth environments, and drug combinations. They were able to classify different medications according to their MOA. As a result, they used whole-cell data to predict novel MOA for the medications under study.

Drug discovery for tuberculosis may also benefit from a proteomics approach (33). Changes in protein levels indicate that proteomics may offer a valuable platform for characterizing the physiological response of M. tb and expression of novel targets. Although it has not yet attained the same potential as transcriptomics and genomics, both in vitro and in vivo data from certain research have suggested new pharmacological targets. Understanding the mechanism of virulence can facilitate the development of a cure for tuberculosis. By distinguishing the proteome profiles of virulent strains of intracellular and extracellular M. tb and BCG from infected macrophages, Liu et al. elucidated the virulence mechanism of M. tb. They discovered 1557 proteins linked to the pathogenicity of M. tb (34). These proteins were associated with particular pathways, including metabolic pathways, which can be targeted for therapeutic intervention. A database called ProteomicsDB has been created with several molecular resources to support proteomics research. For example, analysis of the database showed that GSK986310C is a candidate that is effective as a spleen tyrosine kinase (SYK) inhibitor (35). These resources will therefore be helpful in TB drug discovery research and may lead to the identification of inhibitors for TB infection. In a review study, Bisht et al. suggested that proteomics can be a useful platform for the discovery of biomarkers for TB and other diseases (36). It can also be useful in vaccine development and in providing a platform for developing a rapid test for diagnosing tuberculosis.

Finally, just as discussed with other "omics," metabolomics is another powerful approach that can facilitate drug discovery and development. As highlighted earlier (Table 2), it evaluates the metabolite profile in a biological system, providing insight into therapeutic targets in M. tb drug discovery by identifying metabolic pathways essential for the survival of the bacteria. In a review discussion, Yu et al. highlighted the role metabolomics can play in the identification of TB biomarkers (37). These biomarkers can be important in elucidating the MOA of drugs and also play a significant role in evaluating drug resistance and responses. The proteomics approach will be essential in TB drug development as it can help elucidate MOA and induced drug resistance during drug development. It can also play a role in predicting drug toxicity and treatment outcomes (38). With the advent of more omics approaches, multi-omics techniques can be critically used in identifying novel drugs for many disease conditions.

Challenges in Multiomics

Although multiomics holds great potential for use in human medicine, the technology faces several challenges. One major difficulty is the integration of data generated during the multiomics workflow. This is not an easy task due to the diversity of omics data produced. Each omics workflow generates different types of data, which complicates the analytical process. The vast volume of data produced by these high-throughput techniques further complicates matters. Transforming and combining the different sets of data is a challenge that must be addressed. Another issue is related to space. Spatial multiomics assays aim to image hundreds or thousands of genes and proteins together. This often results in many fluorophores occupying the same area in the cell, making it difficult to resolve individual genes or proteins (8). Establishing standardized protocols is another challenge. These protocols should outline how data are collected, evaluated, and interpreted. Finally, while multiomics has immense potential in research, research partnerships and collaborations are crucial for its advancement.

Future Prospects and Conclusion

The multi-omics approach is an exciting development in tuberculosis and infectious disease research, offering the potential to transform the discovery of anti-tuberculosis agents that could significantly improve the efficacy, safety, and specificity of novel drugs. Multi-omics can be incorporated into every phase of the drug discovery process, including genomics, proteomics, transcriptomics, and metabolomics. Despite the immense potential of omic technology, several challenges remain. Ethical considerations pose a significant challenge, as multi-omics data could reveal personal health information. This information might be used to stigmatize, discriminate against, or exploit individuals. Therefore, multi-omics data must be assembled with the privacy and confidentiality of the subjects in mind. Stringent protocols are needed to address these challenges, but these should not stifle scientific progress.

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Sažetak

MULTIOMIKS PRISTUPI U OTKRIVANJU LEKOVA PROTIV TUBERKULOZE

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Uprkos intenzivnim globalnim naporima, tuberkuloza i dalje predstavlja jedan od najvećih globalnih zdravstvenih problema, s antimikrobnom rezistencijom koja predstavlja značajan izazov u lečenju bolesti. Takođe, trenutni lekovi za lečenje tuberkuloze imaju ograničenja, kao što su produženo trajanje terapije i toksičnost. Zbog toga je razvoj novih lekova protiv tuberkuloze prioritet. Međutim, ovaj proces se suočava sa brojnim izazovima. Uvođenje multiomiks pristupa može poslužiti kao idealna platforma za ubrzanje razvoja lekova, rešavajući ove izazove. Ovaj članak istražuje potencijalnu ulogu multiomiks pristupa u razvoju lekova protiv tuberkuloze i ukratko razmatra izazove u korišćenju ovog pristupa za otkriće lekova.

Ključne reči: tuberkuloza, lekovi, proteomiks, multiomiks, Mycobacterium tuberculosis, transkriptomiks, metabolomiks, genomiks.

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