**LITERATURE SURVEY**

**Acharya, B., Acharya, A., Gautam, S., Ghimire, S.P., Mishra, G., Para- juli, N. and Sapkota, B., 2020. Advances in diagnosis of Tuberculosis: an update into molecular diagnosis of Mycobacterium tuberculosis. Molecular biology reports, 47, pp.4065-4075.**

Tuberculosis (TB) is a major cause of deaths by a single infectious agent and has now been a global public health problem due to increasing numbers of drug-resistant cases. Early and effective treatment is crucial to prevent the emergence of drug-resistance strains. This demands the availability of fast and reliable point-of-care (POC) diagnostic methods for effective case management. Commonly used methods to screen and diagnose TB are clinical, immunological, microscopy, radiography, and bacterial culture. In addition, recent advances in molecular diagnostic methods including MTBDRplus, loop-mediated isothermal amplification (LAMP), line probe assay (LPA), GeneXpert, and whole genome sequencing (WGS) have been employed to diagnose and characterize TB. These methods can simultaneously identify Mycobacterium tuberculosis (MTB) and mutation(s) associated with routinely used anti-TB drugs. Here, we review the use of currently available diagnostic methods and strategies including conventional to recently implemented next-generation sequencing (NGS) methods used to detect MTB in clinical perspective.

**Ranjitha, J., Rajan, A. and Shankar, V., 2020. Features of the bio- chemistry of Mycobacterium smegmatis, as a possible model for My- cobacterium tuberculosis. Journal of infection and public health, 13(9), pp.1255-1264.**

Objective Actinomycetes have been known to be the great natural sources to explore antibiotics for the treatment of tuberculosis (TB). The isolation of actinomycetes from the samples in Vietnam followed by the screening of their antimycobacterial activity was performed in this study. The metabolites isolated from the most active strain were further evaluated for their antimycobacterial, antimicrobial and cytotoxic activity. Methods Actinomycetes were growth in culture media, isolated and identified by colony, spore chain morphology and 16S rRNA gene sequencing. Agar diffusion assay was used for the screening of the isolated strains against Mycobacterium smegmatis, a safety surrogate for Mycobacterium tuberculosis. The metabolites produced from the most active strain were investigated by actinomycete fermentation, extraction and isolation from biomass and cultures. The structures of the isolated compound were elucidated by spectral data and comparison with the reported literatures. Results 181 strains were isolated from nine regions along the north to central Vietnam. The five most active strains against Mycobacterium smegmatis were detected. Following the bioassay-guided result, the strain A121 (Streptomyces alboniger) was selected for further isolation of the bioactive metabolites. As a result, obscurolide B2β (1) and chartreusin (2) were obtained and evaluated for their antimycobacterial activity against M. smegmatis. Compound 2 displayed potential antimycobacterial activity, antimicrobial effect against the Gram positive bacteria Staphylococcus aureus, Bacillus subtilis, Lactobacillus fermentum and cytotoxicity against four cancer cell lines KB, HepG-2, Lu-1 and MCF-7. Conclusions Five strains possessing potential antimycobacterial activity were identified from the samples collected in Vietnam. Two compounds including obscurolide B2β (1) and chartreusin (2) were isolated from the most active strain A121 (Streptomyces alboniger). This is the first time these compounds have been isolated from this strain. Chartreusin (2) exhibited notable antimycobacterial, antimicrobial and cytotoxic activity, making its worthy attention for further drug development, particularly for antituberculosis therapeutic agents.

**Ernest, J.P., Strydom, N., Wang, Q., Zhang, N., Nuermberger, E., Dar- tois, V. and Savic, R.M., 2021. Development of new tuberculosis drugs: translation to regimen composition for drug-sensitive and multidrug- resistant tuberculosis. Annual review of pharmacology and toxicology, 61, pp.495-516.**

Tuberculosis (TB) kills more people than any other infectious disease. Challenges for developing better treatments include the complex pathology due to within-host immune dynamics, interpatient variability in disease severity and drug pharmacokinetics-pharmacodynamics (PK-PD), and the growing emergence of resistance. Model-informed drug development using quantitative and translational pharmacology has become increasingly recognized as a method capable of drug prioritization and regimen optimization to efficiently progress compounds through TB drug development phases. In this review, we examine translational models and tools, including plasma PK scaling, site-of-disease lesion PK, host-immune and bacteria interplay, combination PK-PD models of multidrug regimens, resistance formation, and integration of data across nonclinical and clinical phases.We propose a workflow that integrates these tools with computational platforms to identify drug combinations that have the potential to accelerate sterilization, reduce relapse rates, and limit the emergence of resistance.

**Singh, V. and Chibale, K., 2021. Strategies to combat multi-drug resis- tance in tuberculosis. Accounts of chemical research, 54(10), pp.2361- 2376.**

*Drug resistance is an unavoidable consequence of the use of drugs; however, the emergence of multi-drug resistance can be managed by accurate diagnosis and tailor-made regimens.*"Antimicrobial resistance (AMR), is one of the most paramount health perils that has emerged in the 21st century. The global increase in drug-resistant strains of various bacterial pathogens prompted the World Health Organization (WHO) to develop a priority list of AMR pathogens. *Mycobacterium tuberculosis* (*Mtb*), an acid-fast bacillus that causes tuberculosis (TB), merits being one of the highest priority pathogens on this list since drug-resistant TB (DR-TB) accounts for ∼29% of deaths attributable to AMR. In recent years, funded collaborative efforts of researchers from academia, not-for-profit virtual R&D organizations and industry have resulted in the continuous growth of the TB drug discovery and development pipeline. This has so far led to the accelerated regulatory approval of bedaquiline and delamanid for the treatment of DR-TB. However, despite the availability of drug regimes, the current cure rate for multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) treatment regimens is 50% and 30%, respectively. It is to be noted that these regimens are administered over a long duration and have a serious side effect profile. Coupled with poor patient adherence, this has led to further acquisition of drug resistance and treatment failure. There is therefore an urgent need to develop new TB drugs with novel mechanism of actions (MoAs) and associated regimens.This Account recapitulates drug resistance in TB, existing challenges in addressing DR-TB, new drugs and regimens in development, and potential ways to treat DR-TB. We highlight our research aimed at identifying novel small molecule leads and associated targets against TB toward contributing to the global TB drug discovery and development pipeline. Our work mainly involves screening of various small molecule chemical libraries in phenotypic whole-cell based assays to identify hits for medicinal chemistry optimization, with attendant deconvolution of the MoA. We discuss the identification of small molecule chemotypes active against *Mtb* and subsequent structure-activity relationships (SAR) and MoA deconvolution studies. This is followed by a discussion on a chemical series identified by whole-cell cross-screening against *Mtb*, for which MoA deconvolution studies revealed a pathway that explained the lack of in vivo efficacy in a mouse model of TB and reiterated the importance of selecting an appropriate growth medium during phenotypic screening. We also discuss our efforts on drug repositioning toward addressing DR-TB. In the concluding section, we preview some promising future directions and the challenges inherent in advancing the drug pipeline to address DR-TB.

**Jamal, S., Khubaib, M., Gangwar, R., Grover, S., Grover, A. and Hasnain, S.E., 2020. Artificial Intelligence and Machine learning based prediction of resistant and susceptible mutations in Mycobacterium tuberculosis. Scientific reports, 10(1), p.5487.**

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis* (*M.tb*), causes highest number of deaths globally for any bacterial disease necessitating novel diagnosis and treatment strategies. High-throughput sequencing methods generate a large amount of data which could be exploited in determining multi-drug resistant (MDR-TB) associated mutations. The present work is a computational framework that uses artificial intelligence (AI) based machine learning (ML) approaches for predicting resistance in the genes *rpoB*, *inhA*, *katG*, *pncA, gyrA* and *gyrB* for the drugs rifampicin, isoniazid, pyrazinamide and fluoroquinolones. The single nucleotide variations were represented by several sequence and structural features that indicate the influence of mutations on the target protein coded by each gene. We used ML algorithms - naïve bayes, k nearest neighbor, support vector machine, and artificial neural network, to build the prediction models. The classification models had an average accuracy of 85% across all examined genes and were evaluated on an external unseen dataset to demonstrate their application. Further, molecular docking and molecular dynamics simulations were performed for wild type and predicted resistance causing mutant protein and anti-TB drug complexes to study their impact on the conformation of proteins to confirm the observed phenotype.