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Anti-TB Medication Development

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Introduction

Tuberculosis (TB) is a terrible infectious disease that kills around two million people each year and causes nine million new cases, wreaking havoc on global health and development. The pathogen *Mycobacterium tuberculosis* is latently infecting one-third of the world's population. Treatment for drug-resistant strains is excessively long, complex, expensive, and toxic, and many MDR-TB patients die as a result. Unfortunately, there is no viable treatment for XDR/TDR-TB. To combat medication resistance and latent bacilli, new medicines with novel mechanisms of action are urgently needed. Validating a single medication for a new TB regimen involves much more time and effort in resource-constrained laboratory settings. As a result, there is an urgent need for a continuous pipeline of new inhibitors to treat drug-resistant and latent TB on a global scale. Three essential interdisciplinary research approaches in preclinical drug development include validation of a novel therapeutic target, target-based discovery of novel leads, and whole-cell evaluation of novel chemical entities [1-5].

Many firms cannot afford to participate in these initiatives due to the significant expenditure required for TB drug development, which is almost usually deemed a non-profit making programme for big Pharma. To address these unmet medical needs, we recently reported that academic networks' integration and collaboration have yielded considerable results from university-based wet laboratories at the early stages of drug development.

Novel therapeutic targets in *Mycobacterium tuberculosis* validation

TB bacilli that are viable but non-replicating (VBNC) can live for an indefinite period. When the host's immune system is compromised, VBNC-bacilli are more likely to convert into actively dividing cells, resulting in TB symptoms. The "bacterial cytokine" Resuscitation-promoting factor (Ruff) was first discovered in Micrococcus lutes and allows the bacterium to re-emerge from hibernation. Ruffs has five sequence homologues in M. tuberculosis. These proteins are peptidoglycan degrading (hydrolase) enzymes, according to bioinformatics and structural investigations. The Rpfs are secretory products that awaken bacilli from their persistent (dormant) state, but their regulatory mechanism and endogenous substrates have yet to be discovered.STPKs are engaged in a variety of metabolic processes in mycobacteria, including cell division, macrophage survival, stress responses, and hostpathogen interactions, although there is no direct evidence for their role in dormancy. Understanding the physiology of *Mycobacterium tuberculosis* during metabolic transition between active and dormantreactive stages is a fascinating topic of anti-TB medication development [2,3].

The complex cell walls of tuberculosis-causing bacteria are made up of an uncommon mycolyl-arabinogalactanpeptidoglycan (MAGP) complex. The bacterial cell's form and structural stability are provided by peptididoglycan. With the exception of Archea, virtually all bacteria have this innermost layer of the bacterial cell wall. The glycosyl backbone of peptidoglycan (PG) is made up of alternating N-acetyl glucosamine (NAG) and N-acetyl muramic acid (NAM) residues linked by -(1,4)-glycosidic linkages, with the muramic acid residues carrying a polypeptide side chain (N-glycolyl muramic acid is also present in M. tuberculosis). Mur enzymes (MurA-F) are involved in the early stages of PG production in the cytoplasm. MurC, D, E, and F belong to the family of ATP-dependent ligases. Through a sequential peptide-ligase reaction involving UDP-MurNAc, ATP, and various amino acid substrates, these enzymes contribute to the synthesis of UDP N-acetyl muramoyl pent peptide. In E. coli, the crystal structures of recombinant Mur ligases have been determined.

In a variety of pathogenic bacteria, all of these Mur ligases have been discovered to be necessary. However, sequence alignments at the gene and amino acid levels reveal considerable differences between these Mur ligases from M. tuberculosis and those from other microbes, such as E. coli. To date, the mur C, D, E, and F genes have been cloned from M. tuberculosis H37Rv and the recombinant Mtb-Mur proteins purified from the soluble fraction have been shown to be functional in order to characterise the key biochemical pathway involved in the initial cytoplasmic stages of mycobacterial PG biosynthesis. Mtb-MurC was discovered to be capable of more than just adding l-Ala [4,5].

Predictive model for whole-cell phenotyping with high throughput

While a large number of novel chemical libraries await comprehensive phenotypic evaluation in the preclinical stage of TB drug development, the search for novel chemotherapeutics against drug-resistant TB is hampered by the slow growth of this organism and the requirement to work in highly stringent and expensive biosafety level-3 laboratories, as well as the need for additional health and safety training for researchers. This creates significant roadblocks in the way of substantial drug screening studies, such as difficult handling, high setup costs, and particular training requirements. Surrogates have been used in the drug discovery process to address these essential concerns, with non-pathogenic, fast-growing Mycobacterium aurum being one of the most useful and closely related surrogate strains. This is due to its cell wall composition, drug sensitivity profile, and drug-resistance mechanisms being identical to M. tuberculosis.

The wholecell high-throughput screening (HTS) platform, a fast but gold-standard assay for characterising anti-tubercular drugs, is always useful for successfully choosing potential hits at an early stage of the TB drug discovery programme. As a first step toward discovering new anti-TB molecules in a faster and more efficient assay method, a high throughput intracellular screening model for both actively dividing and dormant Mycobacterium sp. must be developed and characterised as a gold standard to replace the highly virulent, extremely slow-growing M. tuberculosis in the early stages of an anti-TB screening programme. Articulated translational and cooperative research interventions from interdisciplinary research laboratory settings offer rays of hope in the fight against M. tuberculosis, a long-time menace to human health and well-being [1,2].

Conclusion

When there is a high eosinophil count, multisystem involvement, and skin eruptions, DRESS syndrome is always taken into account. With some medications and infectious agents, it can be a potentially fatal illness in people

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who are prone to it. It is essential to stop using the harmful medicine and to stay away from new exposure.

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Conflict of Interest

The author reported no potential conflict of interest.

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