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Tuberculosis Research: One *Mycobacterium Tuberculosis* Bacilli for All

Diane J. Ordway*

Department of Microbiology, Immunology and Pathology, Mycobacteria Research Laboratories, Colorado State University, Fort Collins, Colorado, 80523, USA

Robert Koch elegantly demonstrated in March of 1882 that the tuberculosis bacilli was the causative agent of the disease in humans by isolating the bacilli from tuberculosis patients which had died and subsequently infecting various animal models which succumbed to the disease [1]. More than a century later, the landscape of tuberculosis disease has worsened with around 9.4 million people becoming infected per year, 1.7 million deaths and 4,500 deaths per day [2]. This catastrophic landscape has been fueled by HIV disease, emergence of highly virulent strains and steadily increasing rates of multidrug-resistant and extensively drug resistant strains of tuberculosis [3]. Are our preclinical animal model methodologies for testing new drug and vaccine candidates failing to meet the needs of the ever changing tuberculosis landscape?

It is becoming evident that a significant percentage of new clinical isolates of *M. tuberculosis* are of extremely high virulence [4-6]. Amongst these, the W-Beijing family of *M. tuberculosis* is globally distributed and is being increasingly documented as a cause of major outbreaks of infection worldwide that involve multidrug-resistant strains [7-11]. Increasing evidence suggests that the Beijing genotype family can induce distinctly different host immune responses compared to other *M. tuberculosis* strains, and amongst these is the newly emerging idea that this family induces the generation of regulatory T cells [12]; an event that could allow evasion of both innate and acquired immunity [13,14].

This concern was highlighted by the NIH document "Recommendations for Priority Research in MDR/XDR-TB" ["NIAID Research Agenda; Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis"] issued by the NIAID Tuberculosis Working Group on June 6th, 2007 [15]. One element this document highlighted was the fact that we do not as yet know to what degree our current vaccine, BCG and drug treatment will be effective against the newly emerging strains of TB including MDR/XDR strains.

Despite the obvious high virulence of these newly emerging clinical strains, the majority of research on screening new drugs and vaccines has used the "laboratory adapted strains" H37Rv and Erdman [16,17]. It is well known that continued growth and passage of laboratory strains leads to reduced virulence, and alteration of the cell wall properties of the bacilli may occur. This is of concern, because it has already been noted in the mouse and guinea pig models that such strains are of far less potency in terms of their capacity to induce regulatory T cell responses. [12,18].

Recent studies have begun to address the question of single-strain *Mycobacterium tuberculosis* studies in tuberculosis research. Proponents of single laboratory strains for screening new vaccine and drug candidates have clearly demonstrated some highly virulent clinical isolates. Unfortunately, they have also evaded the protective efficacy of BCG vaccination [19] as well as standard drug treatment compared to the laboratory adapted strain which confers efficacy [20]. In addition, a large Bill and Melinda Gates Foundation-funded study comparing various preclinical animal models used by both industry and academia (determining differences in infection routes, inoculant, bacterial strain, animal strain, timing of the start and length of drug treatment) clearly demonstrated the only factor that impacted the outcome of drug efficacy was the bacterial strain utilized [17].

Recent studies demonstrate how emerging *Mycobacterium tuberculosis* strains of today have become highly virulent in the host. They modulate host-protective immunity and are able to evade BCG vaccine and drug efficacy. This raises a serious question: Have the current screening procedures used to test and prioritize new vaccine and drug candidates based almost exclusively on the use of the "laboratory strains" H37Rv and Erdman become a yet-unrecognized serious impediment to the success of new tuberculosis vaccine and drug candidates?

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***Corresponding author:** Dr. Diane Ordway, Assistant Professor, Department of Microbiology, Immunology and Pathology, Mycobacteria Research Laboratory, Colorado State University, 1682 Campus Delivery, 200 West St , Fort Collins, CO 80523-1682, USA, Tel: +970-491-4117; Fax: +970-491-1815; E-mail: D.Ordway-Rodriguez@ColoState.EDU

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