



Investigating the Virulence Determinants of *Mycobacterium tuberculosis*

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World Health Organization's (WHO) 2010 global infectious disease estimates rank India as the number ONE nation in tuberculosis (TB) burden. Annually, around 5 lakh people die of this "wasting" disease. WHO recommends at least three different lines of antibiotics for TB treatment and classifies it under "CURABLE" diseases. If tuberculosis (TB) is curable, why is it still a major infectious disease? What is the key to its success? To establish infection, *Mycobacterium tuberculosis* (Mtb), the causal agent of human TB, hijacks alveolar macrophages and builds a protective niche within the early phagosomal compartments. At a simplistic level, Mtb accomplishes such a task by secreting a sleuth of "virulence" molecules that interact with host molecules and modulate their host cellular functions. One mechanism by which Mtb accomplishes host modulations is by utilizing specialized secretion systems such as ESX-1. The prevailing hypothesis for ESX-1 function(s) is that it directly secretes a cache of virulence "effectors" into host environment to promote virulence. However, my current work on ESX-1 suggests an alternate model for ESX-1's role. Secondly, I will discuss if and how Mtb might exploit outer-membrane like vesicles for delivering its toxins and virulence effectors. This is a more common strategy exploited by several Gram negative pathogens to deliver their virulent substrates. Lastly, I will discuss strategies I am undertaking to perform an unbiased ORFeome-based screen that would aid in identification of virulence proteins that get secreted/delivered into host environment. Identifying this virulent stockpile and defining their host-specific functions utilizing genetic, biochemical and proteomic tools would be the drive force of my lab.