Tuberculosis, a severe airborne disease transmitted by the bacterial intracellular pathogen *Mycobacterium tuberculosis* (*Mtb*), is second only to HIV/AIDS in infectious disease mortality worldwide. As a very successful pathogen *Mtb* has spread intensively across the globe, infecting one-third of the entire human population. In 2013, 9 million new cases were diagnosed and 1.5 million people died because of tuberculosis. The incidence of tuberculosis is worsened by the emergence and rapid spread of multi-drug resistant (MDR), extensively-drug resistant (XDR) and totally drug-resistant (TDR) strains of *Mtb* that cannot be cured with standard anti-tuberculosis drugs. Furthermore, the raising number of active tuberculosis cases is also associated with the increased incidence of *Mtb* infections in immune-compromised individuals such as patients with AIDS and diabetes. Despite a century of extensive research and public health efforts, effective treatment of tuberculosis still remains a great challenge. What is also disquieting, we are still far from full understanding of the complex mechanisms used by tubercle bacilli to successfully gain access into, survive and replicate within hostile environment of targeted innate immune cells, namely macrophages. Such knowledge is urgently necessary for the search and selection of new therapeutic targets and, for the development of modern anti-tuberculosis drugs and vaccines. It is also vital in order to avoid the danger of tuberculosis becoming an incurable disease and to effectively control tuberculosis.

Mycobacterium tuberculosis is one of the most evolutionarily successful intracellular pathogens that invade humans worldwide. This pathogen possesses outstanding adaptive properties and, during long lasting co-existence with a human host, has developed a plethora of sophisticated mechanisms to subvert the host defense. The pathogenic mechanisms of *Mtb* relay mainly on the complex interactions with the host innate immunity molecules and processes that are induced in response to the infection. The invading and survival strategies used by tubercle bacilli lead to the manipulations of host innate immunity mechanisms and even to hijacking them from their original defense role in order to ensure the entry, dissemination and persistence of the pathogen. After intrusion into the pulmonary alveoli, the invading *Mtb* initiates the host innate defense that begins with pattern recognition of the pathogen-associated molecular patterns (PAMPs) performed by conserved group of the host membrane-bound and soluble molecules, the so-called pattern recognition receptors (PRRs). Since the successful establishment of cellular invasion by pathogens requires adhesion to host cells, the interplay between *Mtb* cell wall components and host recognition molecules plays a crucial role not only in the mounting of an appropriate host first-line innate immune defense but is also of major importance in the tubercle bacilli entry into the target cells, their intracellular multiplication and survival. **Interactions between *Mtb* cell wall components and the host innate recognition molecules within the alveolar microenvironment are considered crucial in determining the outcome of the pathogen invasion. Therefore, the study of these binding interactions represents a key opportunity to identify potential candidates for improved antimycobacterial therapy. Modern anti-*Mtb* therapeutic agents interrupting or facilitating binding events, that determine tubercle bacilli invasion or contribute to the pathogen clearance respectively, would functionally disrupt *Mtb* entry into its host cell niche.** Herein we hypothesize that *Mtb* possesses a ligand/ligands engaged in binding of human major acute phase protein, namely serum amyloid A (SAA), and that this interaction could pose an extra mechanism influencing the pathogen entry into the host macrophages, which are the primary cells infected by tubercle bacilli after inhalation.

Our preliminary data suggests the existence of both the presumed interaction of *Mtb* with SAA and specific mycobacterial effectors responsible for the binding of this acute phase protein. The analysis of binding interaction between *Mtb* and human SAA revealed that *Mtb* specifically binds human SAA in concentration dependent manner. Furthermore, application of complex methodology allowed us to select and identify six potential mycobacterial ligands, namely Rv2477c, Rv1308, Rv0423c, Rv3881c, Rv0009 and Rv2140c, as candidate pathogen effectors interacting with SAA. Of these six candidates, we focused on two only, namely Rv2477c and Rv1308, in the preliminary experiments. Binding of SAA was confirmed for these two *Mtb* proteins by Western blot and surface plasmon resonance. In order to determine contribution of Rv2477c and Rv1308 protein to the early events of *Mtb* infection we constructed tubercle bacilli mutant strains overproducing these ligands separately. **The important goal of this project is farther analysis of binding interaction between *Mtb* and human SAA and its impact on the mycobacterial entry into host macrophages and functional responses of the host target cells and tubercle bacilli.** We plan to develop recombinant forms of Rv0423c, Rv3881c, Rv0009 and Rv2140c *Mtb* proteins to deeply analyze their ability to bind human SAA. The mutant *Mtb* strains unable to synthetize and/or overproducing the selected bacilli effectors responsible for the pathogen-SAA interplay will be constructed and their ability, including previously constructed Rv2477c and Rv1308 mutants, to invade human blood monocyte-derived macrophages will be compared with “wild type” strain of the pathogen. The above experiments will exhibit engagement of *Mtb* ligands recognizing human SAA in early events of invasion of host macrophages. Furthermore, study of the impact of SAA on tubercle bacilli entry into targeted human macrophages will be a concern of this project also.