Project DE-2

The impact of the MBL pathway on the outcome of infection with representative mycobacterial strains of the *Mycobacterium tuberculosis* complex

(Supervisors: Dr. Christoph Hölscher, Prof. Stefan Niemann, Prof. Peter Garred)

Tuberculosis (TB) is the leading cause of death from a single infectious agent which are strains of the *Mycobacterium tuberculosis* complex (Mtbc). After inhalation, mycobacteria are recognized by the innate immune system which initiates and shapes the adaptive immunity. In general, the immune response of the host is characterized by a balance between protection and pathology.

Complement evasion strategies of Mtbc strains have been inadequately investigated so far. Mannose binding lectin (MBL) recognizes specific cell surface carbohydrates such as mannosylated lipoarabinomannan of the mycobacterial cell wall. MBL can act as an opsonin or activate the lectin pathway of the complement cascade and thereby modulate the innate and adaptive immune response. Besides host factors that are important for the outcome of infection also the genetic diversity of mycobacteria has a significant influence on the pathogenesis of TB. The Hölscher lab could demonstrate that strains of the ancient Mtbc lineage *M. africanum* bind MBL to a higher extend than strains of modern lineages e.g. Euroamerican and that a specific human *MBL2* variant confers protection against TB caused by *M. africanum*. In humans, several *MBL2* gene polymorphisms exist which result in a great variation of circulating MBL levels. By exploiting MBL-null mice, host-pathogen interactions which are influenced by this receptor can be investigated in a controlled setting. So far, the role of MBL in TB infection has not been analyzed in the experimental mouse model of infection. Therefore, the aim of this PhD thesis project is the detailed characterization of the MBL mediated modulation of host-pathogen interaction during Mtb infection.

To achieve this goal, first, the binding of MBL to the cell wall of strains of different ancient and modern mycobacterial lineages will be determined *in vitro* (RCB). The interaction of different Mtbc complex proteins with MBL and other complement activating molecules will be explored at the University of Copenhagen. The impact of MBL on susceptibility to TB will be investigated *in vivo* by infecting *Mbl1/2-deficient* $^{(-/-)}$ mice infected with well characterized strains ofancient and modern mycobacterial lineages at the RCB. The course of infection will be compared with wild-type mice by analyzing the bacterial burden in different organs, histopathology, immunophenotyping and transcription profiling at defined time points after infection.

General description of your individual PhD-schedule:

- Your main university will be University of Lübeck (Germany). Supervision will be shared by Dr. Hölscher (RCB) and Prof. Niemann (University of Lübeck). You will mainly work at RCB.
- You will have a 6-months research secondment at University of Copenhagen (Denmark) with Prof. Garred as supervisor, where you continue to scientifically work on your thesis project.
- You will have a further 6-months research secondment at RCB (Germany) where you will investigate the impact of MBL on the course of experimental tuberculosis.
- You will have a 1-month clinical training at University Hospital Helsinki (Finland).
- You will have a 1-month entrepreneur training at RCB.
- You will finally receive a PhD issued by University of Lübeck and University of Copenhagen if you fulfil the respective requirements.

Application

The position is advertised from 10.09.2019 – 10.11.2019 on **www.corvos.eu**. Please apply via this homepage during that time.