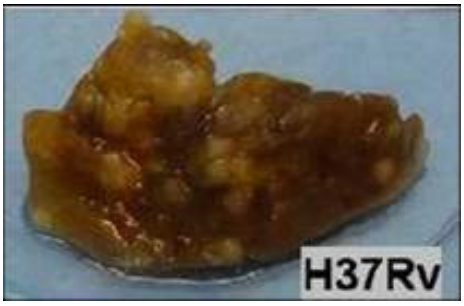

Associated project K10: Functional analysis of a conserved essential gene cluster in *Mycobacterium tuberculosis*

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Project summary

Multi-drug resistance is a major force causing the exacerbation of the global tuberculosis pandemic, caused by the bacterium *Mycobacterium tuberculosis*. Strains of *M. tuberculosis* are emerging worldwide at an alarming rate which are resistant to most available antitubercular drugs and which are very difficult to control. Thus, it is undoubted that new drugs as well as new molecular targets for the rationale development of selective chemotherapy are urgently needed for the fight against drug-resistant *M. tuberculosis* strains.

Our laboratory employs reverse genetic approaches in the quest of identifying novel antitubercular drug targets. A conditional gene silencing system has been developed allowing the facilitated generation of conditional mutants and regulated expression of target genes in *M. tuberculosis* both *in vitro* and in animal models. This enables us to study potentially essential gene candidates, most of which are of unknown function. Phenotypical characterization of sublethally silenced cells of conditional mutants allows us to draw inferences on gene functions. Furthermore, controlled silencing of selected *M. tuberculosis* candidate genes in infected macrophages and in mice determines their vulnerability *in vivo* in the context of infection and validates their drug target potential.

In this project, we are analyzing the function of a conserved mycobacterial gene cluster of unknown function which is exclusively present in mycolic acid producing actinobacteria. Silencing of several genes from this cluster in conditional *M. tuberculosis* mutants confirmed their essential role for viability. Sublethal silencing of some genes resulted in drastically altered colony morphology, indicative of impaired cell wall biosynthesis. We thus hypothesize that this gene cluster plays a direct or indirect role in construction of the mycobacterial cell wall. Comparison of the lipid profiles of fully induced and partially silenced cells of the conditional *M. tuberculosis* mutants shall shed light on the physiological function and biochemical properties of these essential gene products.