Projekt 6 (P6): Studies on essential enzymes involved in the biogenesis of α-glucan derivatives in *Mycobacterium tuberculosis*

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Mycobacterium tuberculosis (*Mtb*), the etiologic agent of tuberculosis, is the most important bacterial human pathogen on a global perspective. Due to the unrestricted global spread of multi drug-resistant strains, the identification of potential targets as basis for the rational development of novel antitubercular chemotherapy is of utmost importance. We have identified a hypothetical protein from *Mtb* that exhibits homology to α-glucan synthases utilizing ADP-glucose and/or UDP-glucose as activated donor substrates for the biosynthesis of α-1,4-glucan oligo-/polymers. Due to these homologies, we hypothesize that this protein might utilize related nucleotide-activated sugars as substrates for the synthesis of yet-unknown α-glucan derivatives. The pathway products appear to be of critical importance for viability of *Mtb*, as we have demonstrated strict essentiality of the coresponding gene by means of site-specific conditional mutants of *Mtb* and other mycobacteria. Sublethal silencing in conditional mutants resulted in an altered colony morphology, indicative of direct or indirect participation in cell wall biogenesis. Inhibition of cell wall biogenesis is generally a highly efficient way to kill bacteria, and some clinically used antitubercular antibiotics such as isoniazid and ethambutol work this way. Thus, the essential protein might represent an interesting novel potential drug target as there is no human counterpart. Having demonstrated strict essentiality, this project now aims at the characterization of the enzymatic activity and elucidation of the identity and biological relevance of the pathway products using bioinformatic, molecular genetical and biochemical approaches. Additionally, further potentially essential genes that might be involved in α-glucan metabolism will investigated as well.