

Name of PI:

Prof. Dr. Rainer Kalscheuer

Title of Ph. D. Project:

Elucidation of the antimicrobial mode-of-action of the natural compounds Sceptrin and Chlorflavonin against *Mycobacterium tuberculosis*

Abstract:

Representing one of the most serious infectious diseases at a global perspective, chemotherapy of tuberculosis is increasingly complicated by the spread of multi-drug resistant isolates. Novel antibiotics with modes-of-action different from those of currently used antituberculosis drugs are urgently required for controlling the world-wide tuberculosis pandemic. In this project, we will focus on the characterization of the mode-of-action, molecular targets and resistance mechanisms of two natural compounds, whose antibacterial activity has recently been discovered in our group. Sceptrin has been isolated from a marine sponge, whereas Chlorflavonin is produced by an endophytic fungus. Due to their potent activity against *Mycobacterium tuberculosis* and their low cytotoxicity against human cells, both natural compounds are promising lead structures for further development. Complementary molecular biological, microbiological and genetic approaches will be followed to uncover the molecular principles underlying the antituberculosis activity. These studies comprise the characterization of resistant mutant strains, site-specific overexpression and depletion of putative target candidates, transcriptome analysis of the elicited stress profiles as well as biochemical characterization of potential target proteins. This project will include handling of pathogenic *Mycobacterium tuberculosis* strains in a biosafety level 3 facility.

Suggested Reading:

Koliwer-Brandl H, Syson K, van de Weerd R, Chandra G, Appelmeik B, Alber M, Ioerger TR, Jacobs Jr. WR, Geurtsen J, Bornemann S, Kalscheuer R (2016) Metabolic network for the biosynthesis of intra- and extracellular α -glucans required for virulence of *Mycobacterium tuberculosis*. PLoS Pathogens **12**, e1005768.

Daletos G, Kalscheuer R, Koliwer-Brandl H, Hartmann R, de Voogd NJ, Wray V, Lin WH, Proksch P (2015) Callyaerins from the marine sponge *Callyspongia aerizusa*: cyclic peptides with antitubercular activity. Journal of Natural Products **78**: 1910-1925.

Kalscheuer R, Syson K, Veeraraghavan U, Weinrick B, Biermann KE, Liu Z, Sacchettini JC, Besra G, Bornemann S, Jacobs WR, Jr. (2010) Self-poisoning of *Mycobacterium tuberculosis* by targeting GlgE in an alpha-glucan pathway. Nature Chemical Biology **6**: 376-384.