Name of PI:

Prof. Dr. Stefanie Scheu

Title of Ph. D. Project:

Identifying the Immunological Properties of Natural Products and their Derivatives for the Treatment Optimization of Chemoresistant Tumors and Bacterial Pathogens

Abstract:

The development of resistances against cytostatic drugs or antibiotics is currently one of the major challenges in the treatment of cancer and infectious diseases. The aim of this project is to identify and to functionally characterize new lead structures from natural products that harbor the capacity to modulate immune effector functions in addition to a cell autonomous toxicity against tumors or bacterial pathogens. The synergism between immune activation on the one hand and a tumoricidal and/or bactericidal activity on the other hand reduces the risk of development of resistances and might even be able to actively prevent these. Several leads (amongst these the fungal compound Phomoxanthone A) that have the specific capacity to activate immune cells and are cytotoxic against tumor cell lines and/or are bactericidal at the same time were identified already from a library of natural products derived from marine invertebrates or fungal endophytes. The immunological activation mechanisms of Phomoxanthone A and other selected structures will be defined using fluorescence-labeled and epitope-tagged compound variants in confocal microscopy, protein biochemistry, next generation sequencing, and proteome analyses. Promising candidates will be tested in tumor and bacterial infection mouse models in vivo. In close cooperation with other groups of the Research Training group further natural compounds or derivatives will be screened for immune modulatory activities.

Suggested Reading:

Bauer J, Dress RJ, Schulze A, Dresing P, Ali S, Deenen R, Alferink J, Scheu S (2016) Cutting Edge: IFNβ expression in the spleen is restricted to a subpopulation of pDCs exhibiting a specific immune modulatory transcriptome signature. The Journal of Immunology 196: 4447-51.

Frank M, Niemann H, Böhler P, Stork B, Wesselborg S, Lin W, Proksch P (2015) Phomoxanthone A - from mangrove forests to anticancer therapy. Current Medicinal Chemistry 22: 3523–3532.

Rönsberg D, Debbab A, Mándi A, Vasylyeva A, Böhler P, Stork B, Engelke L, Hamacher A, Sawadogo R, Diederich M, Wray V, Lin W, Kassack MU, Janiak C, Scheu S, Wesselborg S, Kurtán T, Aly AH, Proksch P (2013) Pro-apoptotic and immunostimulatory tetrahydroxanthone dimers from the endophytic fungus Phomopsis longicolla. The Journal of Organic Chemistry 78: 12409-25.

Scheu S, Dresing P, Locksley RM (2008) Visualization of IFN beta production by plasmacytoid versus conventional dendritic cells under specific stimulation conditions *in vivo*. Proceedings of the National Academy of Sciences of the United States of America 105: 20416-21.