DKMS Stiftung Leben Spenden

Project Summary

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Defensis as a Potential Treatment Option for Acute Graft-versus-host Disease

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Acute graft-versus-host disease (GVHD) is a major cause of morbidity and mortality in patients undergoing allogeneic hematopoietic cell transplantation. During acute GVHD, epithelial tissues of the patient, most frequently the skin, liver and gastrointestinal tract, are damaged by allogeneic donor immune cells. Despite of significant side effects, corticosteroid therapy remains the gold standard for acute GVHD therapy. However, only a fraction of patients responds to steroids and patients developing steroid refractory acute GVHD have a dismal prognosis with only 5-30% overall survival. The intestinal microbiome plays a crucial role for immune homeostasis under steady state conditions and in many diseases. Acute GVHD is characterized by complex deficiencies of the mucosal antimicrobial barrier and intestinal microbial imbalance, which contribute to disease pathogenesis.

Defensins are endogenous antimicrobial peptides, which can modulate immune responses, protect epithelial barrier integrity and shape the intestinal microbiota composition. The first objective of this study is to analyze whether acute GVHD affects defensin production at different time points after transplantation. In a second step, we will test if treatment with defensins has a therapeutic effect in acute GVHD, with respect to disease severity and survival. To further delineate the immunomodulatory effects of defensins in GVHD, we aim to analyze whether defensins influence immune cell function, activation and migration to GVHD target organs as well as the beneficial graft-versus-leukemia (GVL) effect. Furthermore, we will assess how defensins affect the intestinal microbiome and intestinal barrier integrity during acute GVHD. Taken as a whole, this project aims to elucidate the role of defensins in the pathogenesis of acute GVHD and to develop a potential novel treatment approach that may target GVHD at multiple different levels. Given both their multifaceted mode of action and endogenous nature, defensins might be able to modulate the allogeneic immune response, improve intestinal barrier integrity and increase intestinal microbiome diversity, representing a possible promising tolerable therapeutic option for acute GVHD.