DKMS Stiftung Leben Spenden

Project Summary

DKMS Mechtild Harf Research Grant 2019

Investigating the role of the microbiota in chronic GvHD and immune reconstitution after HCT

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The proposed project will investigate the relationships between the gastrointestinal microbiome and patient outcome after allogeneic hematopoietic stem cell transplantation (HCT), by focusing on 2 key areas: chronic GvHD (cGvHD) and immune reconstitution.

Chronic GVHD is an often debilitating late-complication of HCT that resembles some autoimmune conditions where the role of the gastrointestinal microbiota has been established. We will investigate the relationship between gastrointestinal microbiota and the auto- and allo-immune dysfunction that characterizes cGvHD, with the goal of identifying biomarkers for cGVHD risk, and gaining mechanistic insights into pathogenesis, and designing rational microbiota-focused therapies.

Failure of robust immune reconstitution has serious consequences for stem cell transplant recipients. We have identified that early domination of the gastrointestinal microbiota with Enterococcus species is associated with poor transplant outcome. We propose that certain groups of immune cells with roles in GVHD protection (the so called MAIT cells) are dependent on microbial diversity for both development and maintenance. However, the mechanism underlying this is unclear.

We want to demonstrate that: 1) Pre-transplant T cell populations (particularly MAIT cells) will predict future microbial imbalance and transplant outcome, and 2) patients who experience early domination of their gastrointestinal microbiome with Enterococcus have aberrant reconstitution of the microbe-dependent unconventional T cells, like MAIT cells and gamma-delta T cells and this will be associated with poor transplant outcome.

Examining the relationship of immune reconstitution to the microbiota will lead to new biological discoveries both readily testable in pre-clinical models, and translatable into strategies for clinical microbiota-focused therapies.