Molecular mechanisms of T-cell alloreactivity to mismatched HLA-DPB1 in cellular therapy of leukemia

Leukemia is frequently treated by allogeneic hematopoietic stem cell transplantation (HSCT) as immunotherapy. Matching of the HLA-DPB1 (DP) locus is not commonly considered in unrelated HSCT, although DP mismatches are frequent and target of T-cell alloreactivity mediating not only beneficial graft-versus-leukemia effect but also harmful graft-versus-host disease. Specific DP mismatch combinations have been shown to be clinically well tolerated, i.e. permissive, but the molecular basis is not fully elucidated. Two mutually non-exclusive models propose structural similarity of DP T-cell epitope (TCE) groups or differential DP expression levels genetically encoded by single nucleotide polymorphisms (SNPs) in the 3'untranslated region (UTR). The aim of this project is to investigate both models by a) structural TCE analysis of the impact of key amino acid polymorphism in the DP peptide binding groove on T-cell alloreactivity; for this we will comparatively use wild-type and site-directed mutants of DPB1*03:01, *04:01 and *02:01; and b) differential expression analysis; for this we will divide the complete DP 3'UTR into 100bp fragments and screen for regulatory SNPs by means of the luciferase assay. The expected new insights into the genetic basis of permissive DP mismatches will lead to improved strategies for a rational use of alloreactivity to harness the power of T cell immunotherapy against leukemia. The project is funded by the Deutsche José Carreras Leukämiestiftung (DJCLS) and will be carried out in collaboration with the Institute of Transfusion Medicine (Prof. Peter Horn) and the Department for Bone Marrow Transplantation at UK-Essen (Prof. Dietrich Beelen).

25.04.2017