2 Objective

The occurrence of acute GVHD is one of the major determinants of the short- and long-term outcome of allogeneic hematopoietic stem cell transplantation. Although many cell types, inflammatory mediators and signaling molecules are involved in the development of GVHD, allogeneic donor T cells remain the sine qua non for the induction of disease. Most current regimens for the prophylaxis or treatment of GVHD have significant and sometimes deleterious side-effects. Their potent but relatively unspecific immunosuppression increases the risk of infections and graft rejection and most importantly reduces GVT activity. Therefore, a more specific therapy which is able to ameliorate GVHD without affecting T cell alloreactivity and GVT effect is needed. Inhibition of T cell migration into GVHD target organs while confining their alloresponse to the lymphohematopoietic system might be a novel approach towards this goal.

CCR2 and its main ligand CCL2 are among the chemokine receptor-ligand pairs that control leukocyte migration during inflammatory processes. In GVHD, the expression of CCL2 in the gut, liver, skin and lung coincides with the increase of inflammatory cytokines early after transplant and the time course of CCL2 levels correlates with the severity of cellular infiltrates. Blockade of CCL2 with a monoclonal antibody results in reduced severity of IPS after allogeneic HSCT. CCR2 is expressed on effector, memory and activated T cells and can be upregulated after exposure to IL-2. CCR2 is required for the control of T cell migration towards CCL2 *in vitro* and might also be involved in the control of T cell migration *in vivo* but this has not been convincingly demonstrated in any disease model so far.

In the present study, it is hypothesized that CCR2-deficient $CD8^+$ T cells induce less GVHD morbidity and mortality than wild type $CD8^+$ T cells while their GVT activity stays intact. It is further assumed that this effect is due to an organ specific migratory defect of CCR2-deficient $CD8^+$ T cells and not due to other functional defects such as reduced proliferation, activation or cytotoxicity.

In this context the following questions will be addressed in well-established murine bone marrow transplantation models:

1) Are CCR2-deficient alloreactive donor $CD8^+$ T cells less potent to induce GVHD morbidity and mortality than wild type $CD8^+$ T cells?
2) If yes, are the observed differences organ-specific or due to reduced overall alloreactivity of CCR2-deficient $CD8^+$ T cells?

3) Is the possible organ specificity mediated by a migratory defect of CCR2-deficient $CD8^+$ T cells as suggested by previous *in vitro* studies?
4) Are there any additional functional defects of CCR2-deficient $CD8^+$ T cells?
5) And finally, is the GVT activity of alloreactive donor $CD8^+$ T cells affected by the absence of CCR2 signaling?

It is hoped that answering these questions will contribute to a better fundamental understanding of the role of CCR2 for $CD8^+$ T cell function during inflammation and will provide new data for the development of specific strategies to separate GVHD from GVT activity. Ultimately, data from this study might support the initiation of clinical trials employing the novel concept of chemokine receptor inhibition for GVHD prophylaxis and therapy.