and inflammatory cytokines, resulting in reduced overall activation and expansion immediately following infusion. These observations provide a rationale for the simultaneously reduced incidence and severity of aGvHD and intact GvL responses previously observed in preclinical animal models. ProTmune is currently undergoing clinical testing in PROTECT, an ongoing Phase 1-2 clinical trial in adult patients with hematologic malignancies.

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The Role of S1PR1 Agonism in Thymus-Dependent T-Cell Regeneration and Graft-vs.-Tumor Activity Following Experimental Allogeneic Hematopoietic Stem Cell Transplantation

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Allogeneic hematopoietic stem cell transplantation (alloHSCT) can be used as immunotherapy that exploits a graft-vs-tumor (GVT) effect to contain hematological malignant diseases. Pretransplantation cytoreductive therapy, however, elicits deficits in adaptive T-cell immunity. Restoration of a normal peripheral T-cell pool post-HSCT is a slow process that requires the *de novo* production of naïve T cells in a functionally competent thymus. Using murine models of alloHSCT we had previously shown, however, that transferred alloreactive T cells can gain access to the host thymus and affect T-cell development, thereby further intensifying posttransplantation immune deficiency (Dertschnig et al., Blood 2013;122:837 and 2015;125:2720). In a parallel study to the present one, we found that donor T-cell trafficking to the thymus could be constrained by pharmacological modulation of the sphingosin-1-phosphate receptor 1 ($S1PR_1$) signalling pathway with the synthetic $S1PR_1$-specific agonist KRP203 (a gift from Novartis Inc.). Here, we tested its effect on long-term thymus-dependent T-cell regeneration following alloHSCT. In lethally irradiated mice receiving fully mismatched, but T-cell depleted alloHSCT, prophylactic $S1PR_1$ administration (3 mg/kg/day; starting on day -1 before alloHSCT and then injected continuously until the end of the study) was found to allow for normal intrathymic T-cell maturation and the development of a sizeable peripheral T-cell pool in the absence of aGVHD. Our data did hence not confirm a previously published finding that thymic export is negatively affected by S1P modulation using FTY720. KRP203 was, however, not able to fully inhibit thymic injury when mice received alloreactive donor T cells. In the aGVHD setting, KRP203 did accordingly not suffice to improve the thymus-dependent peripheral T-cell pool with regard to its numerical size. Our investigations revealed, however, an advantage with regard to the functional capacity of this cell pool as there were fewer autoreactive T cells present (as demonstrated in our parallel study). Moreover, a GVT response against A20 lymphoma cells (10,000 cells injected directly into the lymph nodes) was sustained even in a less than efficiently reestablished thymus-dependent T-cell pool. Our data confirmed that $S1PR_1$ receptor agonism may retain induction of immune responses in lymphoid tissues and is thus expected to maintain the capacity to reject hematopoietic tumors that are retained in these sites. If S1P receptor agonism is used as a principle for aGVHD prophylaxis, this contention should in the future be addressed in clinical practice.

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In Vivo Characterization in Non-Human Primates of the New Immune Suppressive Anti Human CD83 Monoclonal Antibody 3C12C That Prevents Graft Versus Host Disease

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Aims: CD83 is expressed on activated dendritic cells (DC) and other immune cells. We developed a potential therapeutic human monoclonal antibody to CD83 (3C12C) and showed it prevents graft versus host disease in a human PBMC mouse xenograft model. Having established that 3C12C binds to non-human primate (NHP, baboon Papio Hamadryas) cells, we tested 3C12C *in vivo* in NHPs before a first in man, first in class, Phase I clinical trial.
Methods: Five baboons received 3C12C (1, 5, 10 mg/kg) or human IgG 10 mg/kg on d0, 7, 14 and d21. Peripheral blood and serum were collected weekly (x4) then every 4 weeks (x2). Bone marrow and lymph node (LN) biopsies were taken at d28. Blood counts and biochemistry were monitored. Flow cytometry analysis followed the PBMC DC subsets, B cells and T cells and bone marrow haematopoietic stem cells. Immune histological studies were performed on LNs.
Results: All 5 animals remained well following anti-CD83 antibody injection. 3C12C did not change blood counts or liver function. CD4 + T, CD8 + T and B cells remained normal to d84. 3C12C injection increased peripheral Treg transiently at d21. 3C12C reduced blood CD1c + DC in a dose dependent manner. CD1c + DC were reduced in LN. 3C12C had no influence on bone marrow hematopoietic stem cell numbers.
Conclusion: Our results demonstrate that 3C12C is safe in NHPs and that it reduced activated DC numbers. This data will facilitate our planned Phase I trial of 3C12C in allogenic hematopoietic stem cell transplantation.

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Immunohistological Detection of P16, Ki67 and ß-Catenin in Gut Mucosa of Allografted Patients with Symptoms of Gastrointestinal (GI) Acute Graft Versus Host Disease (aGVHD)

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Introduction: Persistent DNA-damage response (DDR) signaling in reaction to severe genotoxic stress induces permanent cell cycle arrest—cellular senescence, which is associated with robust pro-inflammatory secretion. Some senescent cells express markers of cell cycle arrest (p16) and are absent for markers of proliferation (Ki67). Production of reactive-oxygen species is a known trigger of Wnt/ß-cat