In the 20th century, organ transplantation has evolved from a highly experimental treatment into the standard treatment for end-stage organ failure. However, although immunosuppressive drugs have greatly augmented early kidney allograft survival rates, long-term allograft surival has changed little due in large part to chronic rejection. For this reason there has been a long-standing intrest in the induction of transplantation tolerance which would obviate the use of immunosuppressive agents for prolonged periods after transplantation and, hence, prevent the complications associated with these drugs (malignancies and opportunistic infections) while also preventing rejection.

The induction of mixed chimerism through hematopoietic stem cell transplantation represents one possible approach to induce tolerance. Based on extensive studies in both rodents, non-human primates and combined HLA-identical related kidney/bone marrow transplantation (CKBMT) in patients with renal failure due to multiple myeloma (1), the group of Megan Sykes et al. recently extended CKBMT to a group of patients who had renal failure without malignancy in an attempt to induce transplantation tolerance (NKDO3-study). Four of 5 patients treated with CKBMT became tolerant and have accepted their renal allografts for several years without immunosuppressive therapy (2) providing proof of principle that this approach can be used to induce tolerance across HLA barriers in humans. A new trial has now been initiated that involves treatment of 15 additional patients with a similar protocol.

A limited number of *in vitro* studies were performed in the NKDO3-study demonstrating the development of specific unresponsiveness to the donor. The applicant's work will consist of detailed mechanistic studies on samples from patients on the new trial to address several hypotheses generated from NKDO3 in order to obtain a comprehensive understanding of the tolerance achieved through CKBMT. The specific aims of this project are as follows: 1) Assess tolerance of directly and indirectly donor alloreactive T cells in recipients of HLA-mismatched CKBMT. Indirect responses to both hematopoietic and renal tubular cell-derived antigens will be measured; 2) Assess the role of regulatory cells in the development of donor-specific tolerance in recipients of CKBMT. We will assess the phenotype and function of regulatory cell populations obtained from patient PBMC and expanded from renal biopsy specimens.

References:

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