Summary

Adoptive T cell therapy is a promising approach for the treatment of cancer. Donor lymphocyte infusions in patients with cytomegalovirus-mediated disease, Epstein-Barr virus-positive B cell lymphomas, and chronic myelogenous leukaemia have proven the efficacy of transferred T cells to kill infected or malignant cells. The main hindrance of using this approach for the cure of other tumour entities is the often unsuccessful isolation and amplification of tumour-reactive T cells from patients. A potential method to circumvent this problem is the transfer of anti-tumour specificity to peripheral blood lymphocytes by retroviral T cell receptor (TCR) gene transfer. In this thesis I have compared several retroviral vectors regarding their gene transfer potential. For this purpose the green fluorescent protein (GFP) was cloned into vectors containing different *cis*-regulatory elements. Promoter and enhancer elements of two different long terminal repeats (LTR) and a cellular gene were compared. The LTR originating from the myeloproliferative sarcoma virus (MPSV) was shown to be superior to the Moloney murine leukaemia virus (MoMLV) LTR and a truncated MoMLV LTR/CD2 enhancer combination. Furthermore, the impact of a modified leader sequence and the Woodchuck hepatitis virus post-transcriptional regulatory element (PRE) was analysed. These elements showed an enhancing effect on transgene expression and retroviral titre, respectively. Taken together, the MP71 retrovirus containing the MPSV LTR, the modified leader, and the PRE demonstrated strong and durable transgene expression in murine and human T lymphocytes. High transduction rates were obtained when using retroviruses pseudotyped with an ecotropic MoMLV or the amphotropic 10A1 MLV envelope for murine or human cells, respectively. The same results were obtained after exchanging GFP with TCR α and β-chain genes, linked by an internal ribosomal entry site. The redirected primary human T lymphocytes showed the same specificity as the tumour infiltrating lymphocyte (TIL)-26 from which the TCR originated. Furthermore, the intensity of anti-tumour reactivity, measured as cytokine release and tumour cell lysis, was comparable for both the TCR-26-grafted T cells and the TIL-26. The TCR expression, analysed for a period of 100 days, remained stable. This approach enables us to generate functional renal cell carcinoma (RCC)-specific T lymphocytes by TCR gene transfer. These data provide the rationale for adoptive T cell therapy for RCC.