8 Summary

Due to degenerate peptide recognition self reactive T cells are a part of the normal T cell repertoire. Autoreactive CD8+ T cells have been associated with autoimmune diseases including diabetes, rheumatoid arthritis and multiple sclerosis. Since hsp expression is induced during an infection in both the host and the pathogen and because of their high degree of evolutionary conservation hsp have been implicated in the crossrecognition of bacterial and self antigen during an immune response to bacterial infection.

The goal of this work was the characterization of a TCR from a CD8+ T cell clone that crossreacted with defined epitopes of both mycobacterial and murine hsp60 and induced an autoimmune intestinal pathology.

TCR analysis of this T cell clone revealed the productive in-frame rearrangement of one *TCRb* and two *TCRa* genes. The question was addressed whether hsp60 crossrecognition was directly linked to the surface expression of two TCR by the same cell or if a single TCR αβ combination was sufficient for the crossrecognition of the mycobacterial and murine hsp60. Therefore, the potentially dual TCR of the hsp60 reactive T cell clone was dissected into single TCR by double retroviral transduction of TCR deficient cell lines. Our data show that only one of the two TCR α/β combinations could constitute a functional cell surface TCR and that posttranslational allelic exclusion of the second α chain was achieved by its inability to pair with the TCR β chain. In conclusion, a single TCR is not only sufficient for crossrecognition with peptides that share minimal sequence homology, moreover this promiscuous TCR reactivity accounts also for the immunopathology of the original T cell clone.

Consequently, the rearranged α8 and the β8 chain genes of the functional hsp-crossreactive single TCR were employed for the generation of TCR transgenic mice. In spite of their self-reactive potential, the αβ chain double transgenic T cells were not negatively selected during thymic maturation. Like the parental T cell clone, the transgenic αβ T cells displayed the CD8 T cell coreceptor and were specific for mycobacterial hsp60 peptides. So far, the TCR transgenic mice do not show any signs of autoimmune disease and the transgenic T cells were not spontaneously

activated by self hsp60 peptides. Thus the hsp specific TCR transgenic mice represent a valuable tool to study the potentially harmful activation of selfreactive T cells *in vivo*, e.g. by mycobacterial infection and thereby may provide new information about the link between infection and autoimmunity.
In addition, using MHC class I tetrameters, the recognized mycobacterial hsp60 peptide was shown to be a relevant CD8 epitope during an immune response to mycobacterial infection. Hence, these transgenic mice may serve to study CD8+ T cell responses against mycobacterial infections.

Transgenic expression of the second in-frame rearranged but non-pairing TCR α7 chain in TCR $\alpha^{-/-}$ mice unveiled that this TCR α chain was generally unable to form a normal αβ TCR. Surprisingly, augmented frequencies of unconventional CD4+ TCR $\alpha^{-}\beta^{+}$ T cells were found in these mice. This unusual CD4+ TCR $\alpha^{-}\beta^{+}$ T cell population is associated with the development of IBD resembling human UC in TCR $\alpha^{-/-}$ mice. However, the significance of CD4+ TCR $\alpha^{-}\beta^{+}$ T cells in immunocompetent individuals remains unclear. We found that an in-frame rearranged but non-pairing TCR α chain stabilizes newly synthesized TCR β chains in TCR $\alpha^{-/-}$ mice. This lead to increased frequencies of CD4+ TCR $\alpha^{-}\beta^{+}$ T cells and exaggerated the course of IBD. Furthermore, it was shown that CD4+ TCR $\alpha^{-}\beta^{+}$ T cells are chronically activated. In this model, physiological TCR α chain rearrangement can promote the formation of chronically activated CD4+ TCR $\alpha^{-}\beta^{+}$ T cells. Thus, we conclude that these T cells are present under physiological conditions and play a role in the etiology of UC.