



**Marie Curie Host Fellowships for Early Stage Research Training:**

Interdisciplinary, international PhD-program of the  
Center for Systems Neuroscience Hannover  
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Project No. 2:

**Autoreactive T cells and activation-induced apoptosis and detection of target genes by gene expression profiling in a murine model for multiple sclerosis**

Supervisors: Prof. Bäutigärtner, W., Dr. Beineke, A.

Institute of Pathology, School of Veterinary Medicine, Hannover

**Aim of the project**

Theiler's murine encephalomyelitis virus (TMEV) infection induces a chronic demyelinating disease in susceptible mouse strains (SJL) and serves as a viral model for multiple sclerosis in humans (Oleszak et al., 2004). The present study will focus on the regulation of apoptosis and co-stimulation of autoreactive lymphocytes in the central nervous system and lymphoid organs during TMEV infection in SJL-mice. Up- and down-regulation of target genes will be detected by gene expression profiling using DNA microarray techniques. Genes of interest and the localization of expressing cells will be further characterized by additional techniques, such as quantitative reverse transcription polymerase chain reaction, in situ hybridisation and immunohistochemistry. Obtained results will give insight in the regulation of peripheral tolerance for further therapeutic application in this murine model for human demyelinating diseases.

**Current state of research**

In unaffected individuals autoreactive T cells will be eliminated by a lack of co-stimulatory signals (anergy), suppression by regulatory T cells or activation-induced apoptosis (Pender, 2002). Break down of this peripheral tolerance leads to the exacerbation of several autoimmune diseases, such as multiple sclerosis. In this regard, inhibition of lymphocyte apoptosis is associated with increased expression of inhibitors of apoptosis (IAP) in clinically

active multiple sclerosis (Sharief et al., 2002a). Additionally, the therapeutic success of interferon-beta in multiple sclerosis is based on its immunoregulatory effects and elimination of autoreactive T cells by the down-regulation of anti-apoptotic molecules (Sharief et al., 2002b; Özenci et al., 2000). Decreased induction of apoptosis in lymphocytes has been detected in the chronic demyelinating phase in the central nervous system of TMEV infection in mice. However, the exact mechanisms of inhibition of programmed cell death in this viral disease remains unknown (Oleszak et al., 2003).

### **State-of-the-art**

In previous studies a murine model for autoimmune demyelinating diseases has been established at the institute of pathology of the University of Veterinary Medicine Hannover (Division of neuropathology). Due to intracerebral injection of TMEV a biphasic course of disease can be induced in susceptible mouse strains (SJL mice). While the first phase of the disease is dominated by acute inflammatory lesions in the CNS, the second phase is characterized chronic demyelinating processes, resembling multiple sclerosis in humans. In preliminary investigations, fresh-frozen tissues of the CNS (brain, spinal cord) and lymphoid organs (thymus, spleen, lymph nodes) of infected and control mice have been collected for gene expression profiling using DNA microarray and other molecular techniques. Furthermore, formalin-fixed, paraffin-embedded samples has been collected for histology and immunohistochemistry.

### **Cited literature**

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Sharief MK, Noori MA, Zoukos Y. Reduced expression of the inhibitor of apoptosis proteins in T cells from patients with multiple sclerosis following interferon-beta therapy. *J Neuroimmunol.* 2002 Aug;129(1-2):224-31.

Özenci V, Kouwenhoven M, Huang YM, Kivisakk P, Link H. Multiple sclerosis is associated with an imbalance between tumour necrosis factor-alpha (TNF-alpha)- and IL-10-secreting blood cells that is corrected by interferon-beta (IFN-beta) treatment. *Clin Exp Immunol.* 2000 Apr;120(1):147-53.

Oleszak EL, Hoffman BE, Chang JR, Zaczynska E, Gaughan J, Katsetos CD, Platsoucas CD, Harvey N. Apoptosis of infiltrating T cells in the central nervous system of mice infected with Theiler's murine encephalomyelitis virus. *Virology.* 2003 Oct 10;315(1):110-23.

The Project belongs to the main topic of ZSN: Movement Disorders