



M. Stangel

#### **Martin Stangel**

1989	B Med Sci, University of Melbourne, Australia
1992	MD and Dr. med., Georg-August-University Göttingen, Germany
1992 - 1994	Junior Resident (AIP), Dept. of Neurology and Clinical Research Group for Neuroimmunology, Julius-Maximilians-University Würzburg, Germany
1994 - 2002	Resident, clinical training in Neurology, Dept. of Neurology, Free University Berlin, Germany
1997 - 1999	Postdoctoral research, Brain Repair Centre and Neurology Unit, University of Cambridge, U.K.
2002	Habilitation
since 2002	Consultant, Dept. of Neurology, Medical School Hannover, Germany

#### **Current Research**

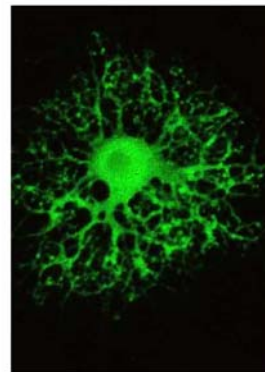
The main interest of our group are repair mechanisms in demyelinating diseases of the central nervous system (CNS) like multiple sclerosis (MS). MS is a chronic disease that develops spontaneously usually in young adults and is the most common reasons for neurological disability in this age group. The neuropathological hallmark is immune mediated demyelination in the CNS, but other features like astrogliosis, microglial activation and axonal damage are also found. Current views on the pathophysiology of MS assume the development of an autoimmune reaction that is triggered by a yet unknown environmental factor in individuals with a genetically determined susceptibility. Repair mechanisms may occur in MS lesions, however, they are usually incomplete and the molecular mechanisms are only poorly understood. To better understand remyelination and why it fails in MS patients, we study remyelination in an animal model, investigate molecular mechanisms in vitro in cell cultures of glial cells, and participate in treatment studies in patients with MS.

#### **1. In vitro studies on oligodendrocytes and microglia**

Glial cells play an important role in the pathophysiology of MS. Microglia, the main resident immune cell in the CNS, participate in the immune reaction. In vitro studies allow the investigation of both factors involved in the pathophysiology of MS as well as potential therapeutic agents on the effector functions of microglia, like production of cytokines, nitric oxide, phagocytosis, and migration.

Oligodendrocytes manufacture the myelin sheath in the CNS and are thus the target of the immune attack. However, remyelination is achieved by the proliferation, migration, and differentiation of oligodendrocyte precursor cells. Using in vitro cultures of oligodendrocyte precursor cells (Fig. 1) we investigate the functional role of chemokine receptors expressed on these cells. Understanding the regulation of oligodendrocyte precursor cells will help to identify potential therapeutic strategies to improve remyelination and repair mechanisms in MS. The hypotheses generated by the in vitro findings can then be tested in vivo in an animal model.

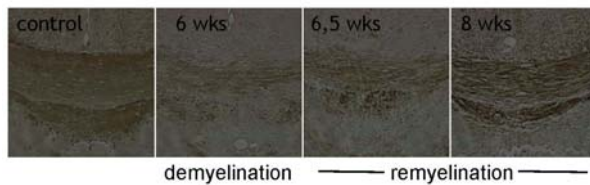
**Fig. 1:  
Oligodendrocyte in  
vitro, MBP staining.**



## 2. Animal model

In order to better understand the myelin system, we study the mechanisms of remyelination in a mouse model. Demyelination in the CNS is induced by the copper chelator cuprizone added to the diet of the animals. Focal demyelination in the corpus callosum occurs after 5 to 6 weeks, followed by remyelination when cuprizone is withdrawn (see Fig. 2). This model allows the study of factors required for a successful remyelination. Furthermore, the contribution of a single factor can be investigated by the use of transgenic animals deficient in this factor.

**Fig. 2: Demyelination and remyelination of the corpus callosum in the cuprizone model. Immunohistochemical staining for the myelin protein MOG.**



## 3. Clinical studies

Current treatments of MS include immunomodulatory and immunosuppressive therapies. Although it has been shown in controlled clinical trials that these treatments can suppress disease progression, there is no regenerative treatment available that could restore neurological deficits. We have conducted treatment trials on MS patients exploring the regenerative potential of intravenous immunoglobulins. Furthermore we are a participating centre for various new treatments in phase II and III trials. Accompanying these trials we conduct immunological studies on the mechanisms of immunomodulating treatments.

## Future projects and goals

Current projects are investigating the role of chemokines and chemokine receptors on oligodendroglial cells and their potential to improve remyelination in the CNS. Future projects will involve the use of transgenic animals to further characterise the factors involved in remyelination and repair mechanisms in the CNS. Understanding the regulatory mechanisms will open new treatment strategies for diseases like MS. Ultimately, the goal is to translate these experimental findings into clinical therapies.

## Selected publications

[1] Stangel M, Boegner F, Klatt CH, Hofmeister C, Seyfert S. A placebo-controlled pilot trial to study the remyelinating potential of intravenous immunoglobulins in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000;68:89-92

[2] Stangel M, Compston A, Scolding NJ. *Oligodendroglia are protected from antibody mediated complement injury by normal immunoglobulins ("IVIg")*. *J Neuroimmunol* 2000;103:195-201

[3] Stangel M, Compston A. *Polyclonal immunoglobulins ("IVIg") modulate nitric oxide production and microglial functions in vitro via Fc receptors*. *J Neuroimmunol* 2001;112:63-71

[4] Stangel M, Bernard D. *Polyclonal IgM influence oligodendrocyte precursor cells in mixed glial cell cultures: implications for remyelination*. *J Neuroimmunol* 2003;138:25-30

[5] Nguyen D, Höpfner M, Zobel F, Henke U, Scherübl H, Stangel M. *Rat oligodendroglial cell lines express a functional receptor for the chemokine CCL3 (macrophage inflammatory protein-1alpha, MIP-1alpha)*. *Neurosci Lett* 2003;351:71-74

## Group Structure

Group leader:	Martin Stangel
Postdoctoral fellows:	Corinna Trebst Sandra Heine,
Graduate students:	Maren Lindner, Samaneh Maysami Refik Pul
Undergraduate students:	Jens Ebnet Caroline Pitz
Technicians:	Karin Fricke

## Contact

PD Dr. med. Martin Stangel  
Dept. of Neurology  
Medical School Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover  
Ph.: +49-511-532 2391  
Fax: +49-511-532 3115  
E-mail: Stangel.Martin@MH-Hannover.de