TABLE OF CONTENTS

Annual report 2007

Danish Multiple Sclerosis
Research Center

Department of Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
WWW.MS-Research.dk

ANNUAL REPORT 2007

It is a pleasure to present the 2007 annual report from the Danish Multiple Sclerosis Research Center (DMSC), Department of Neurology, Neuroscience Center, Copenhagen University Hospital Rigshospitalet.
The annual report reviews the activities in the MS Clinic and the MS Research Unit during 2007. In 2007 both the clinical and research staff has expanded and the activities in the MS Clinic and the research unit have increased considerably. New treatments have been established for the benefit of people with multiple sclerosis and promising new research results have been achieved in the core areas of research in DMSC: Clinical research, immunology, genetics and pathology of MS.

Morten Blinkenberg
Per Soelberg Sørensen,
Editors

A short review of 2007 in the Danish Multiple Sclerosis Research Center

Per Soelberg Sørensen
Professor
Chairman DMSC

In 2007 the Danish Multiple Sclerosis Research Center (DMSC) entered its second decade. From a modest start in 1996 the growth has been almost exponential to the position today as one of the European MS Centers of excellence. The MS Clinic provides care for more than 1500 patients of whom 800 are treated with disease modifying drugs.
In 2007 DMSC was one of two Danish centers appointed by the National Board of Health to launch treatment with the new effective MS drug natalizumab (Tysabri). More than 150 patients from all over Zealand have started treatment with natalizumab. During recent years the therapeutic armamentarium against multiple sclerosis has expanded and includes now the 4 approved drugs: Interferon-beta, glatiramer acetate, mitoxantrone and natalizumab, and in addition non-licensed drugs as methotrexate, azathioprine, high-dose methylprednisolone and rituximab are used.
Another specialized task of DMSC is treatment of severe spasticity with intrathecal Baclofen pumps.
Due to the increased activities the staff has been increased and additional space has been included in the MS Clinic. Two new positions as consultant and one new position as senior registrar were established in 2007 together with one MS nurse and one secretary. In 2007 DMSC began to implement the principle of assignment of one MS neurologist and one MS nurse to each patient. The process will continue in 2008.

A major goal of the MS Clinic is to involve as many patients as possible in clinical trials and try to attract trials with new therapeutic drugs to Denmark. A number of multicenter investigator driven randomized trials are organized and directed by DMSC. In addition the MS Clinic has enrolled patients in a number of clinical trials sponsored by the pharmaceutical industry. Among these have been treatment of patients with clinically isolated syndromes with glatiramer acetate, an extension study of natalizumab treatment in patients with relapsing-remitting MS, a placebo controlled trial of the anti-metabolite cladribine and a trial in secondary progressive MS patients with a myelin basic protein residue for induction of immunotolerance.

The activities at the MS Research Unit located in the Michaelsen Building 63 have been expanded due to generous donations. The laboratory is fully equipped with a new flowcytometer and equipment for research in molecular biology. The staff has been increased with a molecular biologist and a laboratory technician.
The research has focused on clinical immunology and biomarkers of disease activity and treatment response, MS genetics, and pathology of MS.
The Research Unit has established a new analysis of antibodies against natalizumab and all patients in Denmark treated with natalizumab are routinely tested for antibodies. Further, the Neuroimmunology Laboratory offers examination of cerebral spinal fluid for oligoclonal bands, antibodies against acethylcoline receptors, antibodies against interferon-beta and in vivo test for interferon-beta activity.
The National MS Biobank at DMSC has now been established and material from the Biobank has been used for genetic and immunological research projects.

FACILITIES, ORGANIZATION AND STAFF

The MS Clinic is located within the Department of Neurology on the 8th floor of the main complex of Rigshospitalet at sections N2082 and N2084. The MS Clinic comprises a secretariat, offices for the professor and consultants, nurse's offices, three consultation rooms and a room for intravenous infusions, and a procedure room for invasive procedures.
The MS Research Unit and the Neuroimmunology Laboratory is located in the Michaelsen Building 63 in which the Research Unit resides at the first floor. The facilities contain offices for the research staff and the Neuroimmunology Laboratory.

In 2007 the staff of DMSC consisted of:

Chairman of DMSC:

Professor Per Soelberg Sørensen, MD, DMSc

Senior physicians:

Morten Blinkenberg, MD, PhD, consultant

Annette Oturai, MD, PhD, consultant

Finn Sellebjerg, MD, DMSc, consultant

Ana Voldsgaard, MD, staff specialist

Neuropsychologist:

Chief neuropsychologist Agnete Jønsson

MS-nurses:

Anne Hansen, leading nurse

Merete Mogensen

Sidsel Walther Nielsen

Annette Husted Pedersen

Dorthe Stauning Rasmussen

Lene Almind

Research nurses:

Vibeke Jespersen

Joan Pietraszek

Physiotherapist:

Lis Albrechtsen

Medical social counselor:
Keld Nissen

Secretaries:
Malene Møllesøe
Annette Larsen

RESEARCH ACTIVITIES 2007

CLINICAL RESEARCH

Clinical research group:
Per Soelberg Sørensen*, Finn Sellebjerg, Annette Oturai, Ana Voldsgaard, Morten Blinkenberg, Dan Hesse, Stephan Bramow, Lars Börnsen, Pourang Mataji, Mads Ravnborg, Vibeke Jespersen, Joan Pietraszek, Annette Larsen*

Therapeutic trials
A number of trials of new combination trials of immunomodulatory drugs have been directed from the DMSC in 2007.
The NORMIMS study is a Scandinavian multi-center double-blind randomized placebo-controlled trial of monthly pulse therapy with methylprednisolone as add-on treatment to interferon-beta 1a (Rebif) in relapsing-remitting MS patients, who have suffered a relapse during the last year on treatment with Rebif. The study has been concluded and data submitted to statistical analysis. The results will be available in the fall of 2008.
The MECOMBIN trial is a multicenter double-blind randomized placebo-controlled trial of monthly pulse therapy with methylprednisolone as add-on to treatment with interferon-beta 1a (Avonex) in relapsing-remitting MS. The trial will be completed in 2008.
The SIMCOMBIN study is multi-center double-blind randomized placebo controlled trial of Simvastatin as add on treatment to interferon-beta 1a (Avonex) as de novo therapy in patients with relapsing-remitting MS. The inclusion of 380 patients will be terminated by the end of 2008.
The RECYCLINE trial is a multi-center double-blind randomized placebo-controlled trial of Minocycline as add-on therapy to interferon-beta 1a (Rebif) as de novo therapy for relapsing-remitting MS performed in the Nordic countries and France. It is planned to include 320 patients through 2008 and Q1 in 2009.

Long-term effects of disease-modifying drugs
Under the auspices of the Danish Multiple Sclerosis Group a study of long-term immunomodulatory therapy is conducted in all patients who started immunomodulatory therapy in Denmark from 1996 to 2003. The primary outcome would be to access the effect of interferon-beta therapy on disability progression in relapsing-remitting MS by comparing the patient cohort with historical controls.

Neutralizing antibodies against interferon-beta
As a part of the Danish Interferon-beta Project all patients have measurements of neutralizing antibodies (NAbs) against interferon-beta performed routinely. In collaboration with the Institute for Inflammation Research at Rigshospitalet we have published a series of articles showing that NAbs reduce the therapeutic effect of interferon-beta. Lately, we have performed 2 controlled trials that attempted to reduce neutralizing antibodies and established the bioactivity of interferon-beta in patients who have developed neutralizing antibodies:
The REVERS study has been performed under the auspices of the Danish Multiple Sclerosis Group and disclosed that treatment with monthly high dose methylprednisolone had none or little effect on the neutralizing antibody levels and bioactivity. Results have been submitted for publication.
The AZATYL trial studied the effect of immunosuppression with azathioprine and monthly high-dose methylprednisolone on neutralizing antibody titers and interferon-

beta bioactivity. The study has been completed and the results will be published in 2008.
Within the EU6 framework programme, lifesciences, genomics and biotechnology for health DMSC has been one of 5 core centers in the NABINMS (neutralizing antibody on interferon-beta in multiple sclerosis project). At DMSC we had the responsibility for a study of the correlation between NAbs and response to interferon-beta using prospectively collected data from population base cohorts from Denmark, Spain, The Netherlands and Czech Republic. The study will run through 2008.

NEUROIMMUNOLOGY

Studies of immune activation and MS therapy

Immunology group:
Finn Sellebjerg*, Poul Erik H. Jensen, Helle Bach Søndergaard, Signe Limborg, Dan Hesse, Martin Krakauer, Per Soelberg Sørensen, Joy Mendel Hartvig, Marie Kofoed*

Therapies that deplete immune cells or inhibit their migration from the blood stream to the CNS are highly efficacious in relapsing-remitting MS. The targeted immune cells include T cells, which are thought to orchestrate an autoimmune response against CNS myelin and axons, and antigen-presenting cells, which control the activation and function of the T cells. The secretion of cytokines associated with T helper (Th)1 and Th17 immunity is believed to be detrimental in MS whereas Th2 T cell activation and activation of different types of regulatory T cells may have beneficial effects. Activation of these cells is reflected by changes in gene expression and changes in surface phenotype at the single cell level that are detectable by flow cytometry. Treatment with interferon (IFN)-β and glatiramer acetate (Copaxone®) influences the activation and effector functions of T cells and antigen presenting cells.

Immune activation in untreated MS patients
We have used Affymetrix Gene Chip® technology to study the expression of approximately 9,000 genes in blood mononuclear cells in collaboration with the Tissue Typing Laboratory, Dept. Of Clinical Immunology, and have observed remarkable changes in gene expression in untreated MS patients compared with gene expression in healthy controls. Bioinformatics methods have revealed that

these changes are likely to reflect an increase in protein synthesis, cellular survival, and active cytokine signaling. Increased cytokine activity has been confirmed by *in silico* analysis of the promoter region of genes with altered expression levels in MS and by directly measuring cytokine mRNA expression in blood cells and cerebrospinal fluid (CSF) cells from patients with MS.

Additional gene expression studies have shown that treatment with IFN-β also results in marked changes in gene expression in MS patients treated with IFN-β, especially within the first 24 hours of administration. In contrast, a much lower number of genes are influenced by treatment with glatiramer acetate. There is only little overlap between genes with altered expression in MS and genes induced or repressed by treatment with IFN-β or glatiramer acetate.

Flow cytometry studies revealed only minor changes in circulating T cells in untreated MS patients in clinical remission. Nevertheless, the activation level of T cell subsets thought to be pathogenetically important decreased upon treatment with IFN-β and glatiramer acetate. The activation level of two important subtypes of antigen-presenting cells, monocytes and dendritic cells, differed markedly in MS and healthy controls, and to varying degrees this was normalized by treatment with IFN-β or glatiramer acetate.

Ongoing studies are aimed at understanding the molecular mechanisms of the systemic immune dysregulation in MS and the effects of immunomodulatory treatment. In addition, our aim is to develop biomarkers that allow the clinician to monitor the disease course and the individual response to therapy in a single blood sample.

Immune activation and interferon-β treatment
In 2007 Martin Krakauer defended his PhD thesis, entitled "Immune activation in multiple sclerosis and interferon-β therapy".
The thesis addressed changes in blood leukocyte cytokine gene expression in patients treated with interferon-β. Treatment resulted in induction of the regulatory cytokine interleukin (IL)-10 but no deviation from Th1 to a less detrimental Th2 cytokine expression profile. IL-23 mRNA, belonging to the recently discovered pro-inflammatory Th17 axis of T lymphocyte activation, was increased in untreated MS patients and was not suppressed by IFN-beta treatment.

The thesis also focused on chemokines, which are chemotactic cytokines, with direct tissue-specific migration of leukocytes. In this regard we focused on chemokines and CD4+ T cell chemokine receptors in MS patients before and during treatment with IFN-beta. We found that CD4+ T cell expression of the T helper type 2 (Th2)-related chemokine receptor CCR4 was decreased in untreated MS patients compared with healthy controls, and that IFN-beta therapy normalized the expression. Furthermore, IFN-beta treatment increased CCR5 and CCR7, suggesting altered lymphocyte trafficking during IFN-beta therapy. The Th1-related CXCR3 was only transiently decreased after an IFN-beta injection.

Flow cytometry was used to study subsets of CD4+ memory T lymphocytes that are related to disease severity and disease activity in MS. The subset of CD4+ memory T lymphocytes that express CD45R0 and high levels CD26 appears to consist of effector cells that may be relevant in the pathogenesis of MS, as a high proportion of such cells express several molecules related to disease activity and a Th1 cytokine secretion profile in MS. Treatment with IFN-beta resulted in changes in the general

activation status of many subsets of CD4+ T lymphocytes, some of which were more pronounced in the CD45R0+ CD26hi subset. Treatment with IFN-beta affected the expression of the apoptosis-controlling molecules Fas and Fas-ligand on CD4+ T cells, and increased plasma concentrations of soluble Fas and Fas-ligand. This suggests that the effects of IFN-beta may at least partly be mediated by apoptosis of pathogenic CD4+ T lymphocytes.

The combined conclusion to the findings of the studies is that MS patients show aberrant immune activation, and that IFN-beta therapy modulates cytokine secretion, T lymphocyte activation and trafficking, but does not induce a clear deviation from a Th1 phenotype to a Th2 phenotype. Furthermore, we have identified a subset of memory CD4+ lymphocytes which may be of special interest in the search for a surrogate marker of disease severity and, possibly, the risk of imminent clinical relapse in MS. Further studies are needed to substantiate these findings, especially studies including functional data, clinical, and paraclinical (such as MRI) measures of disease activity.

In vitro studies of interferon-beta
Signe Limborg has conducted studies of the *in vitro* effects of treatment with IFN-β. Mononuclear cells and T cells were stimulated with IFN-β at a concentration simulating *in vivo* conditions. Subsequently gene expression, the phenotype of CD4+ and CD8+ T cell subsets and proliferation and cytokine secretion after activation was studied.

The *in vitro* experiments showed, that after treatment of the cells with IFN-beta, an increased percentage of T cells expressed the cell surface activation markers: CD69 and CD71 and gene expression assays showed a 4 -fold increase in expression of the cell cycle inhibitory gene p21 in cells treated with IFN-beta compared to controls. A reduction in proliferation of approximately 50 % was observed when IFN-beta was present throughout the period of stimulation whereas no reduction in proliferation was observed in cells pre-treated with IFN-beta. Neither did we observe any effect of IFN-β on activation-induced Th1 and Th2 cytokine secretion. Increased expression of the p21 molecule induced by IFN-β has been confirmed in samples obtained from IFN-treated patients with MS. Furthermore, we have observed an increase in the expression of the immunoregulatory transcription factor Foxp3 *in vitro* and *in vivo* in MS patients treated with IFN-β.

These studies show that IFN-beta has complex effects on mononuclear cells. Both activating and inhibitory effects of the drug are seen, and it is still a challenge to understand which of these mechanisms are responsible for the positive disease modifying effect of IFN-beta.

IFN-ß treatment - neutralizing antibodies and other biomarkers
Disease-modifying treatment with IFN-ß reduces the risk of MS relapses by approximately one third. A major problem associated with IFN-ß is the occurrence of neutralizing antibodies (NAbs), which abrogate the biological response to IFN-ß and decreases the clinical response.

As initial combination therapy of IFN-ß with methylprednisolone (MP) may reduce the frequency of NAb+ patients, Dan Hesse has addressed the hypothesis that immunosuppression with MP in patients already NAb+ could affect NAb status and IFNβ bioactivity after cessation of IFNβ. In an open label trial, we compared changes

in NAbs and IFNβ bioactivity in NAb+ patients with immeasurable bioactivity, which after discontinuation of IFNβ, were either treated with monthly high-dose pulsed MP treatment for six months or, as a control group, were followed six months after switching to glatiramer acetate or stopping any disease-modifying treatment. This study showed that monthly pulsed MP treatment in NAb+ patients had no beneficial effect on NAb status or IFNβ bioactivity as assessed by the biomarker MxA gene expression.

Finally, Dan Hesse is studying a panel of biomarkers for disease activity in MS in a serial and a cross-sectional study of 85 patients treated with IFN-ß or GA, where we collected blood samples and conducted MRI scans to identify biomarkers of treatment response and disease activity. In these studies we have identified a potentially protective role of an endogenous IFN-like gene signature in untreated MS patients. We hope that it will also be possible to identify biomarkers that can discriminate patients with a sufficient response to treatment with these first-line immunomodulatory treatments from patients with an insufficient response, who are in need of more efficacious therapy.

Regulation of proteinases and cytokines by α2-Macroglobulin and Analysis of binding antibodies generated towards interferon-β
α2M is a proteinase inhibitor which also binds various growth factors and cytokines. This has importance for regulation of the immune system, and changed concentrations are found in CSF and blood of MS-patients. It is of interest to determine the balance between proteinase and cytokine concentrations and correlate them to the concentrations of α2M forms in MS-patients and controls. Previously, we have found increased amounts of transformed α2M in plasma from MS patients, which suggest increased inhibition of proteinases. In that respect we further analyze defects or modifications in α2M, such as carbohydrate structures. It is interesting, that α2M participate in the neutralization of the cytokines, which may lower the available concentrations of the cytokines, but also extend their presence in the circulation due to non-covalent binding to native α2M, which circulates for days. We study the correlation between α2M and the proteinases MMP's –1, -2, -3, and –9 in CSF and plasma from MS-patients and controls. Determination of the concentrations of α2M, Il-8, Il-10, TGF-β and TNF-α in plasma and CSF from MS-patients will furthermore be performed.

Oligodendrocytes are the source of myelin, and apoptosis is induced in a human oligodendrocyte cell line (MO3.13) by toxic effects of increased concentrations of the cytokines TNF-α and INF-γ. These effects may indicate that in MS-patients, oligodendrocytes can be damaged by direct attack of the increased concentrations of the cytokines TNF-α and IFN-γ. Synergistic effects of both cytokines result in increased cytotoxicity and more apoptosis. We will examine the effects of α2M on the apoptotic regulation of the cells by different concentrations of cytokines (TGF-β, TNF-α and IFN-γ). Further the effects of α2M on IL-6 and IL-10 will be analyzed. These cytokines have positive effects on the survival of oligodendrocytes. It is our goal to demonstrate the effects of α2M by binding and neutralizing the cytokines and thereby changing the cell-responses of the cytokines in question by studies of apoptosis in the cell-line.

Interferon-β (IFN-b)
MS-patients treated with IFN-β may generate antibodies against the drug, which can reduce the clinical efficacy by neutralization of IFN-β. In this regard we have

introduced a feasible method to analyze the generation of binding antibodies, using a standard ELISA technique. Our intention is to compare these results with the existing technique of measuring neutralizing antibodies, using cytopathic effect assay, as well as MxA mRNA generation, in approximately 300 MS-patients treated with IFN-β.

Routine analyses in Neuroimmunology Laboratory

***Poul Erik H. Jensen**, Joy Mendel-Hartvig, Marie Kofoed, Anne Mette H. Nielsen*

Diagnostic evaluation:
The presence in CSF of oligoclonal IgG-bands is of interest in the diagnosis of Multiple sclerosis (MS). In 2007 we have analyzed 460 patient samples, using isoelectric focusing of CSF and corresponding plasma samples for the characterization of IgG bands.

In the autoimmune disease Myasthenia gravis (MG), autoantibodies against the acetylcholine receptor (AChR) may cause a diminished binding of ACh on muscular surfaces and thereby a reduced impulse transmission to the postsynaptic membrane of the neuromuscular endplate occurs. For diagnostic and therapeutic purposes, we measure the concentrations of these autoantibodies from patient serum samples, using a radio-immunoassay kit, and in year 2007 we analyzed 1083 patient samples.

Measurement of neutralizing antibodies:
Subgroups of MS patients, treated with IFN-β or Tysabri, generate neutralizing antibodies, which diminish the therapeutic effects. IFN-β molecules bind to leucocytes and a specific up-regulation of MxA mRNA in the cells occur. Neutralizing antibodies may abolish this effect, and therefore we measure the MxA mRNA-expression as a biological response to treatment with IFN-ß. In 2007 we have analyzed 145 patient samples for MxA mRNA expression. Furthermore, we have screened patient samples for IFN-ß binding antibodies using an ELISA-assay.
The action of Tysabri differs from IFN-β, since it blocks mononuclear cell binding to endothelial cells. In this way Tysabri inhibits mononuclear cells from entering the central nervous system. The generation of neutralizing antibodies to Tysabri in MS-patients, block the biological effects of Tysabri. In 2007 we analyzed 264 blood samples for the presence of antibodies to Tysabri by ELISA.

NEUROGENETICS

Identification of genes involved in Multiple Sclerosis

MS Genetics group:
Annette Bang Oturai*, Helle Bach Søndergaard, Finn Sellebjerg, Per Soelberg Sørensen, Anne Mette H. Nielsen*

Even though we know genes are important in multiple sclerosis (MS), identifying the involved genes has proven to be a complex challenge. Our group and other scientists have worked for decades to find gene variations tied to MS. Genome linkage screens have failed finding major genes except genes of HLA-complex. A break-through took place in the summer 2007, when three new studies showed that the IL7R (receptor) gene is important as a risk gene for developing MS. One of these studies performed the world largest genome-wide association screen in MS. Apart from the IL7R, the study revealed the IL2R (receptor) as an important risk gene of developing MS. Both genes are important for the T cell regulation, and thus the immune system, but its precise role in MS is not clear yet. Variations in both the IL7R and IL2R genes are common, but they are more common in people with MS. These findings are important, and may eventually lead to new treatments for MS. All in all, the three studies included more than 14,000 people. Two of the studies were published in the journal *Nature Genetics*. The third study, and a related editorial, appeared in *The New England Journal of Medicine.* The three studies constitute the first replicated associations to MS apart from the HLA-DR2 association found back in 1973.

For more than 10 years we have collected DNA, and today we have DNA from more than 900 Danish MS patients and 1200 controls; all kept in the *"Danish Multiple Sclerosis Biobank"* located at Rigshospitalet and organized by our group. The sources of biological material (DNA, mRNA and CSF) in this bank include all patients treated with immune modulating drugs in Denmark. In order to increase the sample size for genetic testing, we have participated in the "Nordic MS Genetic Group" since 1994, and today the Nordic material consists of 4000 MS cases, 4000 controls, 1000 trio families (one MS patient and both parents), and 177-affected sib pairs. Since 2000 we have participated in ***GAMES (G****enetic* ***A****nalysis of* ***M****ultiple Sclerosis in*

E**uropean**S)**,* and recently we have become a part of the ***IMSGC (***I**nternational **M**ultiple **S**clerosis **G**enetic **C**onsortium*).

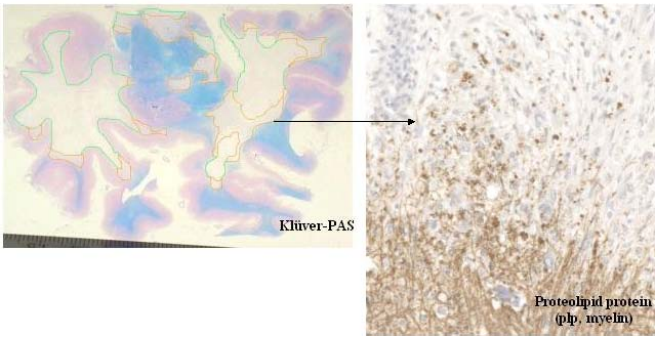
The main focus for our group is identification of genes and their biological effects, especially genes involved in the different immune treatment response.

PATHOLOGY

Inflammation and remyelination in progressive MS

MS pathology Group:
***Stephan Bramow**, Henning Laursen, Per Soelberg Sørensen*

In relapsing-remitting MS (RRMS), relapses result from inflammatory, actively demyelinating plaques in the CNS. These plaques cause a conduction block and are characterized by myelin laden macrophages, lymphocytic infiltrates and acute axonal damage. The recovery phase is believed to be associated with remyelination and resolution of inflammation.



In contrast, in the progressive forms of the disease, the cause of the gradual clinical decline is less clear. Active plaques and remyelination are regarded rarer than in RRMS, instead degenerative loss of axons and atrophy has been suggested as pathological substrates. However, diffuse white matter inflammation and so-called slowly expanding plaques, characterized by intermediate microglial inflammation at the edge, have recently been described. In addition, we have found inflammation and active plaques in sensitive areas of the brain stem that could possibly accelerate respiratory failure and cell death.

One aim of our study is to quantify areas of active and slowly expanding demyelination in progressive MS, and relate them to neurodegeneration, cause of death and rate of progression. If these types of inflammatory demyelination correlate with clinical progression, it would have importance for the design of future treatment options in MS.

Remyelination can be identified as sharply demarcated areas with uniformly thin myelin stain. Animal studies have shown that remyelination rely on oligodendrocyte precursor cells (OPC's) that proliferate and mature, to form new myelin in response to stimulation by microglia. Hence, microglia is a pivotal cell type involved in

destruction as well as remyelination. The cause of remyelination failure in progressive MS remains unknown but speculations focus on OPC depletion or maturation failure. Therefore we wish to quantify remyelination in progressive MS and relate these findings to inflammatory demyelination. If remyelination only occurs when inflammation is absent, it emphasizes the importance of inflammation control in progressive MS.

NEUROIMAGING

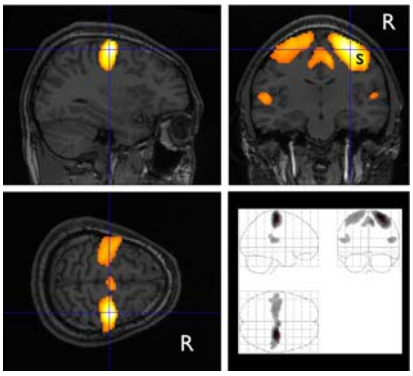
Positron Emmision Tomography and Magnetic Resonance Imaging in MS

Morten Blinkenberg

PET

Previous positron emission tomography (PET) studies, carried out in Danish Multiple Sclerosis Research Centre, have shown that cerebral activation is severely reduced in MS patients. This was illustrated by measuring global and regional cerebral metabolic rate of glucose (CMRglc) and it was furthermore demonstrated, that these measures correlate with cognitive dysfunction as well as MRI lesion burden.
A prospective study has revealed that CMRglc is significantly reduced over a two-year period, as a consequence of the progressive disease.
These studies included MS patients with different disease course and duration, and in this way the approach was general and explorative.

Our current PET studies focus on the early relapsing remitting phase of the disease (RRMS) and the corresponding changes in CMRglc. Our hypothesis is that changes in cerebral activation are present in very early disease, and affect neural networks of importance for cognitive dysfunction.
We have already examined 21 RRMS patients using PET, MRI and neuropsychological evaluation. The patients have primarily been examined in a cross-sectional study, and unpublished data have so far shown a significant reduction of CMRglc in the early phase of the disease. Further data-analysis is ongoing, including MRI data of lesion volume and MR spectroscopy.
A subgroup of these patients has been followed prospectively and the last examinations have been conducted and await data-analysis.



The figure shows the result from a functional connectivity MRI experiment we have performed on a healthy subject. It demonstrates correlation in spontaneous neuronal activity observed when using a seed region (S) in the right (R) motor cortex. In agreement with previous studies we observe significant correlation with left motor cortex, supplementary motor area (bilaterally) and secondary somato-sensory cortex (bilaterally).

MRI

In collaboration with Danish Research Centre for Magnetic Resonance we have initiated two functional imaging studies in 2007.
We have previously shown that measurements of MR Spectroscopy (MRS) correlate with cognitive dysfunction in MS.
This cohort is to be re-evaluated in and analyzed for longitudinal changes in MRS and cognitive function.
Another study focuses on the pathophysiological mechanisms underlying changes in cerebral activation in MS patients.

There is increasing evidence that the severity of the clinical manifestations of MS does not result simply from the extent of tissue destruction, rather it represents a complex balance between tissue damage, tissue repair and cortical reorganization. Magnetic resonance imaging (MRI) has been employed as a valuable tool to detect and characterize MS lesions and is routinely used for diagnosis and evolution monitoring. However, conventional MRI provides low pathological specificity and sensitivity. It is hypothesized that this methodological limitation is in part responsible for missing correlation between structural MRI measures and clinical symptoms.

Functional MRI (fMRI) provides information regarding the extent and nature of brain plasticity following MS-related structural injury, with the potential to limit the clinical manifestations of the disease. Functional connectivity MRI (fcMRI) is a new method of assessing neuronal connectivity in the human brain by mapping brain regions with synchronous, regional fluctuations in cerebral blood oxygenation. fcMRI in combination with fMRI might allow us to obtain a deeper insight into the functional alterations that lead to neurological disability in MS.

The aim of our study is to describe MRI changes in cerebral activation and neural connectivity during an acute MS relapse and following treatment with IVMP. Further to explore if neural connectivity could be used as a surrogate marker to predict functional activation and clinical recovery after an acute relapse in different stages of MS.

SCIENTIFIC PUBLICATIONS 2006 - 2007

Peer reviewed original papers 2006

Jorgensen SH, Storm N, **Jensen PE**, Laursen H, **Sorensen PS**. IVIG enters the central nervous system during treatment of experimental autoimmune encephalomyelitis and is localised to inflammatory lesions. Experimental Brain Research, Epub ahead of print Nov 8, 2006

Jønsson A, Andresen J, Storr L, Scherning T, **Soelberg Sørensen P, Ravnborg M**. Cognitive impairment in newly diagnosed multiple sclerosis patients: A 4 year follow-up study. J Neurol Sci 2006:245;77-85

Sørensen PS, Jønsson A, Mathiesen HK, **Blinkenberg M**, Andresen J, Hanson LG, **Ravnborg M**. The relationship between MRI and PET changes and cognitive disturbances in MS. J Neurol Sci 2006; 245:99-102

Krakauer M, Sørensen PS, Khademi M, Olsson T, **Sellebjerg F**. Dynamic T-lymphocyte chemokine receptor expression induced by interferon-beta therapy in multiple sclerosis. Scand J Immunol 2006; 64:155-163

Krakauer M, Sørensen PS, Sellebjerg F. CD4+ memory T cells with high CD26 surface expression are enriched for CD4+ Th1 markers and correlate with clinical severity of multiple sclerosis. J Neuroimmunol 2006; 181:157-164

Sorensen PS, Tscherning T, Mathiesen HK, Langkilde AR, Ross C, **Ravnborg M**, Bendtzen K. Neutralizing antibodies hamper IFNbeta bioactivity and treatment effect on MRI in patients with MS. Neurology. 2006 Nov 14;67(9):1681-3

Sorensen PS. Neutralising antibodies to interferon-beta-measurement, clinical relevance, and management. J Neurol. 2006 Nov;253 Suppl 6:vi16-vi22

Sorensen PS, Koch-Henriksen N, Bendtzen K. Are ex vivo neutralizing antibodies against IFN-β always detrimental to therapeutic efficacy in multiple sclerosis? Mult Scler 2006;12:1-6

Sorensen PS, Koch-Henriksen N, **Ravnborg M**, Frederiksen JL, Jensen K, Heltberg A, Schaldemose H, Deth S, Kristensen O, Worm M, Stenager E, Hansen HJ, Sivertsen B, Torring J; Danish Multiple Sclerosis Study Group. Immunomodulatory treatment of multiple sclerosis in denmark: a prospective nationwide survey. Mult Scler. 2006 Jun;12(3):253-64

Petersen B, Bendtzen K, Koch-Henriksen N, **Ravnborg M**, Ross C, **Sorensen PS**; Danish Multiple Sclerosis Group. Persistence of neutralizing antibodies after discontinuation of IFNbeta therapy in patients with relapsing-remitting multiple sclerosis. Mult Scler. 2006 Jun;12(3):247-52

Storr LK, Sorensen PS, Ravnborg M. The efficacy of multidisciplinary rehabilitation in stable multiple sclerosis patients. Mult Scler. 2006 Apr;12(2):235-42

Storr LK. Rehabilitation of People With Multiple Sclerosis in Denmark. Diss. Own publish company, 2006

Lundmark F, Harbo HF, Celius EG, Saarela J, **Datta P, Oturai A**, Lindgren CM, Masterman T, Salter H, Hillert J. Association analysis of the LAG3 and CD4 genes in multiple sclerosis in two independent populations. J Neuroimmunol. 2006 Nov;180(1-2):193-8. Epub 2006 Oct 3

Mathiesen HK, **Jonsson A, Tscherning T**, Hanson LG., Andresen J, **Blinkenberg M**, Paulson OB, **Sørensen PS**. Correlation of Global N-Acetyl Aspartate with Cognitive impairment in Multiple Sclerosis. Arch Neurol 2006: 63;533-6

Patrikios P, Stadelmann C, Kutzelnigg A, Rauschka H, Schmidbauer M, Laursen H, **Sorensen PS**, Bruck W, Lucchinetti C, Lassmann H. Remyelination is extensive in a subset of multiple sclerosis patients. Brain. 2006 Dec;129(Pt 12):3165-72. Epub 2006 Aug 18

Nieuwenhuis MM, Van Tongeren H, **Sorensen PS, Ravnborg M**. The six spot step test: a new measurement for walking ability in multiple sclerosis. Mult Scler. 2006 Aug;12(4):495-500

Andersen PB, **Blinkenberg M**, Lassen U, Kosteljanetz M, Wagner A, Poulsen HS, **Sorensen PS**, Paulson OB. A prospective PET study of patients with glioblastoma multiforme. Acta Neurol Scand. 2006 Jun;113(6):412-8

Koch-Henriksen N, **Sorensen PS**, Christensen T, Frederiksen J, **Ravnborg M**, Jensen K, Heltberg A, Kristensen O, Stenager E, Petersen T, Hansen T; Danish Multiple Sclerosis Group. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology. 2006 Apr 11;66(7):1056-60. Epub 2006 Mar 1

Ross C, Clemmesen KM, **Sorensen PS**, Koch-Henriksen N, Bendtzen K. Measuring and evaluating interferon beta-induced antibodies in patients with multiple sclerosis. Mult Scler. 2006 Feb;12(1):39-46

The Games Collaborative Group, Ban M, Booth D, Heard R, Stewart G, Goris A, Vandenbroeck K, Dubois B, Laaksonen M, Ilonen J, Alizadeh M, Edan G, Babron MC, Brassat D, Clanet M, Cournu-Rebeix I, Fontaine B, Semana G, Goedde R, Epplen J, Weber A, Infante-Duarte C, Zipp F, Rajda C, Bencsik K, Vécsei L, Heggarty S, Graham C, Hawkins S, Liguori M, Momigliano-Richiardi P, Caputo D, Grimaldi LM, Leone M, Massacesi L, Milanese C, Salvetti M, Savettieri G, Trojano M, Bielecki B, Mycko MP, Selmaj K, Santos M, Maciel P, Pereira C, Silva A, Silva BM, Coraddu F, Marrosu MG, Akesson E, Hillert J, **Datta P, Oturai A**, Harbo HF, Spurkland A, Goertsches R, Villoslada P, Eraksoy M, Hensiek A, Compston A, Setakis E, Gray J, Yeo TW, Sawcer S. Linkage disequilibrium screening for multiple sclerosis implicates JAG1 and POU2AF1 as susceptibility genes in Europeans. J Neuroimmunol. 2006 Oct;179(1-2):108-16.

Peer reviewed original papers 2007

Datta P, Harbo HF, Ryder LP, Akesson E, Benedikz J, Celius G, Andersen O, Myhr KM, Sandberg-Wollheim M, Hillert J, Svejgaard A, **Sorensen PS**, Spurkland A, **Oturai A**. A follow-up study of Nordic multiple sclerosis candidate gene regions. *Multiple Sclerosis 2007;13:584-9*

Lundmark F, Duvefelt K, Iacobaeus E, Kockum I, Wallstrom E, Khademi M, **Oturai A**, Ryder LP, Saarela J, Harboe HF, Celius G, Salter H, Olsson T, Hillert J. Variation in interleukin 7 receptor alpha chain (IL7R) influences risk of multiple sclerosis. *Nat Genet. 2007;39(9):1108-13*

Knudsen GP, Harbo HF, Smestad C, Celius EG, **Oturai A**, Ryder LP, Spurkland A, Ørstavik KH. X chromosome inactivation in females with multiple sclerosis. *Eur J Neurol. 2007;(12):1392-6*

Sellebjerg FT, Sørensen PS. Behandling af multipel sklerose - nu og i fremtiden. *Ugeskr Læger 2007;169:1121*

Hartung H-P, Polman C, Bertolotto A, Deisenhammer F, Giovannoni G, Havrdova E, Hemmer B, Hillert J, Kappos L, Kieseier B, Killestein J, Malcus C, Comabella M, Pachner A, Schellekens H, **Sellebjerg F**, Selmaj K, **Sorensen PS**. Neutralizing antibodies to interferon-β in multiple sclerosis. *Expert panel report. J Neurol 2007;254:827-37*

Sellebjerg F, Datta P, Larsen J, Rieneck K, Alsing I, **Oturai A**, Svejgaard A, **Sørensen PS**, Ryder LP. Gene expression analysis of interferon-beta treatment in multiple sclerosis. *Mult Scler. In press*.

Krakauer M, Sorensen PS, Khademi M, Olsson T, **Sellebjerg F**. Increased IL-10 mRNA and IL-23 mRNA expression in multiple sclerosis - interferon-beta treatment increases IL-10 mRNA expression while reducing IL-23 mRNA expression. *(In press)*

Mathiesen HK, **Ravnborg MH**, **Sørensen PS**. [Diagnosis of multiple sclerosis: revision of the McDonald criteria]. Ugeskr Laeger. 2007 Nov 5;169(45):3853-6. Danish.

Giovannoni G, Barbarash O, Casset-Semanaz F, Jaber A, King J, Metz L, Pardo G, Simsarian J, **Sørensen PS**, Stubinski B; RNF Study Group. Immunogenicity and tolerability of an investigational formulation of interferon-beta1a: 24- and 48-week interim analyses of a 2-year, single-arm, historically controlled, phase IIIb study in adults with multiple sclerosis. Clin Ther. 2007 Jun;29(6):1128-45.

Hesse D, **Sørensen PS**. Using measurements of neutralizing antibodies: the challenge of IFN-beta therapy. Eur J Neurol. 2007 Aug;14(8):850-9.

Sorensen PS, Koch-Henriksen N, Bendtzen K. Are ex vivo neutralising antibodies against IFN-beta always detrimental to therapeutic efficacy in multiple sclerosis? Mult Scler. 2007 Jun;13(5):616-21. Epub 2007 Feb 9.

Sørensen PS. Resource allocation to brain research in Europe. Eur J Neurol. 2007 Jun;14(6):597.

Kutzelnigg A, **Faber-Rod JC**, Bauer J, Lucchinetti CF, **Sorensen PS**, **Laursen H**, Stadelmann C, Brück W, Rauschka H, Schmidbauer M, Lassmann H. Widespread demyelination in the cerebellar cortex in multiple sclerosis. Brain Pathol. 2007 Jan;17(1):38-44.

Beiske AG, Naess H, Aarseth JH, Andersen O, Elovaara I, Farkkila M, Hansen HJ,

Mellgren SI, Sandberg-Wollheim M, **Sorensen PS**, Myhr KM; Nordic SPMS study group.
Health-related quality of life in secondary progressive multiple sclerosis. Mult Scler. 2007 Apr;13(3):386-92.

Fazekas F, **Soelberg-Sorensen P**, Comi G, Filippi M. MRI to monitor treatment efficacy in multiple sclerosis. J Neuroimaging. 2007 Apr;17 Suppl 1:50S-55S.

Sorensen PS. The gap between effect of drugs and effectiveness of treatments. J Neurol Sci. 2007 Aug 15;259(1-2):128-32. Epub 2007 Mar 23.

Hensiek AE, Seaman SR, Barcellos LF, Oturai A, Eraksoi M, Cocco E, Vecsei L, Stewart G, Dubois B, Bellman-Strobl J, Leone M, Andersen O, Bencsik K, Booth D, Celius EG, Harbo HF, Hauser SL, Heard R, Hillert J, Myhr KM, Marrosu MG, Oksenberg JR, Rajda C, Sawcer SJ, **Sørensen PS**, Zipp F, Compston DA. Familial effects on the clinical course of multiple sclerosis. Neurology. 2007 Jan 30;68(5):376-83.

Nielsen TR, Rostgaard K, Nielsen NM, Koch-Henriksen N, Haahr S, **Sørensen PS**, Hjalgrim H. Multiple sclerosis after infectious mononucleosis. Arch Neurol. 2007 Jan;64(1):72-5.

Jorgensen SH, Storm N, Jensen PE, Laursen H, **Sorensen PS**. IVIG enters the central nervous system during treatment of experimental autoimmune encephalomyelitis and is localised to inflammatory lesions. Exp Brain Res. 2007 Apr;178(4):462-9. Epub 2006 Nov 8.

Sørensen PS. Tysabri. Månedsskr Prakt Lægegern 2007;85:199-207.

SCIENTIFIC PRESENTATIONS AND ABSTRACTS 2007

Simsarian JP, Pardo G, Barbarash O, Casset-Semanaz F, Giovannoni G, Jaher A, King J, Metz L, **Sorensen PS**, Stubinski B. Safety and immunogenicity of Rebif ® new formulation (RNF) a new subcutaneous formulation of interferon beta-1a 44 mcg three times weekly: 1-year results of a phase IIIb study in patients with relapsing multiple sclerosis. NEUROLOGY, 68(12):A274-A274, Suppl. 1, March 20, 2007. American Academy of Neurology Meeting, Boston, May 2007

Sorensen PS, Koch-Henriksen N, Bendtzen K. Low affinity ex vivo neutralizing antibodies may enhance the therapeutic effect of IFN beta in multiple sclerosis. NEUROLOGY, 68(12):A116-A116, Suppl. 1, March 20, 2007. American Academy of Neurology Meeting, Boston, May 2007

Koch-Henriksen N, **Sorensen PS**. The Danish multiple sclerosis registry and the Danish multiple sclerosis treatment register. EUROPEAN JOURNAL OF NEUROLOGY, 14:307-307, Suppl. 1, August 2007. European Federation of Neurological Societies Congress, Brussels, August 2007

Giovannoni G, Comi G, Cook S, Beelke M, Rieckmann P, **Sorensen PS**, Vermersch P. CLARITY Study Group. The CLARITY study (CLAdRIbine tablets treating multiple sclerosis orally): design of a Phase III trial of oral cladribine in relapsing multiple sclerosis. MULTIPLE SCLEROSIS, 13:S245-S245, Suppl. 2, October 2007. ECTRIMS Congress, Prague, October 2007

Mataji P, Sorensen PS, Frederiksen JL, **Sellebjerg F**. Increased concentrations of the B-cell chemokine CXCL13 correlates with intrathecal inflammation and B cell recruitment to the CSF in multiple sclerosis. MULTIPLE SCLEROSIS, 13:S157-S157, Suppl. 2, October 2007. ECTRIMS Congress, Prague, October 2007

Limborg SW, Krakauer M, Hedegaard CJ, Nielsen CH, **Sorensen PS, Sellebjerg F**. Anti-proliferative effects of interferon beta associated with increased expression of p21. MULTIPLE SCLEROSIS, 13:S64-S64, Suppl. 2, October 2007. ECTRIMS Congress, Prague, October 2007

Giovannoni G, Barbarash O, Casset-Semanaz F, King J, Metz L, Pardo G, Sinisarian J, **Sorensen PS**, Stubinski B. RNF Study Group. Safety and immunogenicity of interferon beta-1a (Rebif ® New Formulation) in a phase IIIb study in patients with relapsing multiple sclerosis: 48-week results. MULTIPLE SCLEROSIS 13:S53-S54, Suppl. 2, October 2007. ECTRIMS Congress, Prague, October 2007 (foredrag)

Hesse D, Krakauer M, Lund H, Ryder LP, Alsing I, Svejgaard A, **Sorensen PS, Sellebjerg F**. Spontaneous MxA mRNA expression is associated with low MRI disease activity in multiple sclerosis. MULTIPLE SCLEROSIS, 13:S37-S38, Suppl. 2, October 2007. ECTRIMS Congress, Prague, October 2007

Sellebjerg F, Krakauer M, Ryder LP, Alsing I, Lund H, Svejgaard A, **Oturai A, Sorensen PS**. Gene expression analysis suggests involvement of specific transcription factors and biochemical processes in relapsing-remitting multiple sclerosis. MULTIPLE SCLEROSIS, 13:S27-S28, Suppl. 2, October 2007. ECTRIMS Congress, Prague, October 2007

Sorensen PS, Frederikson IL, Lycke J, **Sellebjerg F**. Does simvastatin antagonise the effect of interferon beta? Interim safety analysis of the ongoing SIMCOMBIN study. MULTIPLE SCLEROSIS, 13:S25-S25, Suppl. 2, October 2007. ECTRIMS Congress, Prague, October 2007

Hesse D, Frederiksen JL, Koch-Henriksen N, **Schreiber K**, Stenager E, Heltberg A, **Ravnborg M, Sellebjerg F**, Bendtzen K, **Sorensen P**S. Effect of methylprednisolone on high-titre neutralising antibodies after discontinuation of interferon beta treatment. MULTIPLE SCLEROSIS, 13:S8-S8, Suppl. 2, October 2007. ECTRIMS Congress, Prague, October 2007

HONORARY OFFICES

Per Soelberg Sorensen have held the following honorary offices:

A: National

- Chairman Foundation for Research in Neurology, 1986-
- Chairman of the Scientific Advisory Committee of the Danish MS Society, 2004-
- Chairman Danish Multiple Sclerosis Group, 1996-

B: International

- Executive Board Member of the European Charcot Foundation for Research in Multiple Sclerosis, 1994-
- Member, Medical Advisory Board of the International Federation of Multiple Sclerosis Societies, 1998-
- Member, US National Multiple Sclerosis Society Advisory Committee on Clinical Trials, 2000-
- Chairman, Scientist Panel on Multiple Sclerosis, European Federation of Neurological Societies, 2003-
- Chairman, Publication Committee, European Federation of Neurological Societies, 2003-

OTHER ACTIVITIES

Editorial boards

Per Soelberg Sorensen has been member of Editorial Board:

- European Journal of Neurology
- Therapeutic Advances in Neurological Disorders

Pre- and postgraduate teaching

Sellebjerg F. Supervisor for OSVAL student Viki Hoé: IVIG treatment of MS post partum.

SCIENTIFIC COLLABORATION

National

Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet (Profesor Olaf Paulson, Professor Gitte Moos Knudsen, Claus Svarer, MSc)
Danish Research Center for Magnetic Resonance, Copenhagen University Hospital Hvidovre, Denmark. (Henrik Kahr Mathiesen MD, Lars G. Hanson, Physicist, professor Olaf Paulson, Henrik Lund, MSc, Kirsten Nielsen, MD)
The Danish Multiple Sclerosis Register, Copenhagen University Hospital, Rigshospitalet,
Copenhagen, Denmark (Nils Koch-Henriksen, MD)
Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet (Jacob Larsen MD, Lars Ryder , Klaus Rieneck, MD, Hans O. Madsen, MD)
Institute for Inflammatory Research, Copenhagen University Hospital, Rigshospitalet (Christian Enevold-Johansen MD, professor Klaus Bendtzen)
Laboratory of Neuropathology, Copenhagen University Hospital (Henning Laursen, MD)
Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (Trine Rasmussen Nielsen , MD, Henrik Hjalgrim, MD, professor Mads Melbye, Peter Michael Bager, ph.d.)
Danish Centre for Experimental Parasitology, Department of Veterinary Pathobiology, Faculty of Life Sciences, University of Copenhagen (Professor Christian Kapel, Professor Allan Knud Roepstorff, Professor Stig Milan Thamsborg)

International

Institute of Immunology, Rikshospitalet, University Hospital, Oslo, Norway (Anne Spurkland, MD, , Hanne F. Harbo, MD, professor Frode Vartdal)
Department of Neurology, Ullevål University Hospital, Oslo, Norway (Elisabeth G Celius, MD)
Department of Neurology, Haukeland Hospital, Bergen, Norway (Kjell-Morten Myhr, MD)
Department of Neurology, Huddinge University Hospital, Karolinska Institute, Huddinge, Sweden (professor Jan Hillert, Eva Åkesson, MD, Helena Modin, MD)
Department of Neurology, Lund University Hospital, Lund, Sweden (Magnhild Sandberg-Wollheim, MD)
Department of Neurology, Gothenburg University Hospital, Gothenburg, Sweden (professor Oluf Andersen)
University of Cambridge, Neurology Unit, Addenbrooke's Hospital, Cambridge, United Kingdom (Stephen Sawcer, MD, professor Alastair Compston)
Department of Neurology, Tromsø University Hospital, Tromsø, Norway (professor Svein Ivar Mellgren)
Department of Neurology, Sentral Sykehuset i Akershus, Nordby Hagen, Norway (Antonie Beiske, MD)
Neuroimmunology Unit, Karolinska Hospital, Stockholm, Sweden (professor Tomas Olsson)
Department of Neurology, Umeå Hospital, Sweden (Anders Svenningson, MD,)
Department of Neurology, Helsinki University Hospital, Helsinki, Finland (professor Markus Färkkilä)
The London, Ontario Multiple Sclerosis Database and the Department of Clinical Neurology, University of Oxford, England (professor George C. Ebers)
Department of Neurology, Duesseldorf University Hospital, Duesseldorf, Germany (professor Hans-Peter Hartung, professor Bernd Kieseier)

Department of Radiology and Neurology, Vrije Universiteit Hospital, Amsterdam, The Netherlands (professor Frederik Barkhof, Bernd Uidtehaag, MD)
Department of Neurology, Karl-Franzens-University, Graz, Austria (professor Franz Fazekas)
VU Medical Centre, Department of Neurology, Amsterdam, The Netherlands (professor Chris H Polman, Joep Killestein, MD)
Utrecht University, Faculty of Pharmaceutical Sciences, Central Lab Animal Institute, Utrecht, The Netherlands (professor H. Schellekens)
Ospedale Universitario San Luigi, Centro di Riferimento Sclerosi Multipla (professor Antonio Bertolotto)
Queen Square, University College London, Institute of Neurology, London, UK (professor Gavin Giovannoni)
Innsbruck Medical University, Dept. of Neurology, Innsbruck, Austria (professor Florian Deisenhammer)
General Charles University, Dept. of neurology, Prague, Czech Republic (professor E. Havrdova)
Hospital Universitari Vall d'Hebron, Unitat de Neuroimmunologie Clinica, Barcelona, Spain (Manuel Comabella, MD, professor. Xavier Montalban)
Austrian Academy of Sciences, Vienna, Austria (Professor Hans Lassmann)
Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, UK (Professor Lars Fugger)

Collaboration with pharmaceutical companies on clinical trials
Novartis, Denmark
Merck Serono Nordic, Denmark, Norway and Sweden
Biogen Idec, Denmark and USA
Teva/Aventis, Israel and Denmark
Sanofi-Aventis, Denmark
Bayer Schering, Germany
Octapharma, Austria
Talecris, Germany and USA
Genmab, Denmark
Genzymes, Holland
BioMS

ACKNOWLEDGEMENTS

Danish Multiple Sclerosis Research Center has received generous support from a number of public and private research funds:

Danish Medical Research Council
Danish MS Society
Warwara Larsen Foundation
Rigshospitalets Scientific Board
H:S Hovedstadens Sygehusfællesskab
Johnsen Foundation
EU Sixth Framework Programme
Ludvig & Sara Elsass Foundation
Brdr. Røjne Holding
Jeppe Juel Memorial Legacy