DMSC staff seminar 2009.
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A short review of 2009
in the Danish Multiple Sclerosis Center

In 2009 the number of patients in the Danish Multiple Sclerosis Center (DMSC) increased to 1777. To meet the challenge of providing care of an increasing number of MS patients referred for diagnosis and therapy, in particular for treatment with Tysabri infusions, we employed an additional staff neurologist, MS nurse and secretary to the MS Clinic. By the end of 2009 approximately 300 patients were receiving monthly infusions of Tysabri and it has been a challenge to organize the treatments due to the limited space in the MS Clinic facilities.

In 2009 we completed two multi-center, international trials organized and directed from DMSC. These trials showed that it is possible to achieve significant improvement in the efficacy of interferon-beta by giving monthly pulses of methylprednisolone as add-on therapy.

We have expanded our international research collaboration in clinical research, neurogenetics, neuroimmunology and MS pathology. We have published a series of scientific papers on response of the immune system to various treatments. These papers have extended our understanding of the deleterious effects of antibodies to interferon-beta and a paper has reported the first series of patients treated with Tysabri outside a clinical trial setting. We have published papers together with Austrian collaborators showing that compartmentalized central nervous system inflammation is closely related to neurodegeneration giving us the hope that therapies able to eliminate the inflammation in the central nervous system will stop the degenerative processes in the brain and spinal cord.

I hope that you will enjoy reading the annual report of DMSC.

Per Soelberg Sørensen
DMSC missions and aims

The mission of Rigshospitalet is to be the leading hospital in Denmark for patients in need of highly specialized treatment

The missions of the Danish Multiple Sclerosis Center (DMSC) are:

- To be the leading multiple sclerosis (MS) center in Denmark
- To be at the forefront of highly specialized management of MS
- To carry out research and development in MS at an advanced international level
- To collaborate scientifically and exchange knowledge in MS research
- To educate staff to a highly specialized level in their relevant fields
- To contribute with professional advice on MS to the healthcare community
- To meet people with MS at their terms with openness and respect

The aims of the DMSC are:

- To provide the optimal interdisciplinary patient care to all MS patients in the region and to patients from other regions in need of highly specialized therapy
- To carry out high quality research in MS with focus on clinical research, new therapies, MS genetics, neuroimmunology and MS pathology
- To teach undergraduate students and PhD-students and stimulate their interest in MS research
- To educate post docs, MS physicians, nurses, secretaries and other professionals to a high level of knowledge of MS in their relevant expert fields
- To lead the national research in Denmark in partnership with other Danish researchers and to establish a broad international collaboration with MS research groups in Europe and from overseas.
About
The Danish Multiple Sclerosis Center
The Danish Multiple Sclerosis Center (DMSC) is composed of the MS Clinic and the MS Research Unit.

The MS Clinic is located on the 8th floor of the main complex of Rigshospitalet. The MS Clinic comprises offices of the professor and consultants, the reception desk and secretary office, the nurses’ offices, the consultation rooms as well as the facilities for intravenous therapy with Tysabri and rooms for invasive procedures. The MS Clinic provides a multi-disciplinary care for almost 1800 MS patients of whom the majority receive disease-modifying therapy dispensed by the MS Clinic. Apart from disease modifying therapy patients are offered symptomatic therapy for spasticity, bladder and bowel disturbances, pain and cognitive symptoms. The medical staff comprises a professor, 4 consultants and 3 staff neurologists; there is one leading nurse and 6 MS specialist nurses, 3 secretaries, a neuropsychologist, a physiotherapist and a medical social counselor.

Approximately half of the patients in the MS Clinic are from our local Copenhagen region and the other half are patients referred for highly specialized therapy from the neighbouring regions all over Zealand. The MS Clinic has been appointed by the National Board of Health to perform highly specialized therapy such as strong immunosuppression and Tysabri therapy. In addition patients are referred for experimental therapy with highly specific monoclonal antibodies. Further, the MS Clinic provides highly specialized treatment of spasticity with an intrathecal baclofen pump. In collaboration with pediatricians children and adolescents with MS from Eastern Denmark are also treated at the MS Clinic.

It is the aim of the MS Clinic to provide high quality multi-disciplinary care for all our patients with openness and respect.

The MS Research Unit is partly located in the proximity of the MS Clinic and partly in the Michaelsen Building 63. Clinical research has to be performed in close proximity to the MS Clinic and offices for 3 research nurses and 1 research secretary are embedded in the MS Clinic. The remaining part of the MS Research Unit with the Neuroimmunology Laboratory is located on the first floor in the Michaelsen building 63 and in the basement of building of 93. The facilities contain offices for the research staff and laboratories. The laboratories contain an 8-color flow cytometer, facilities for doing real-time polymerase chain-reaction (PCR), a neurogenetics laboratory for DNA preparation and facilities for making routine laboratory tests. The focus of the research is clinical research including neuroimaging, neuroimmunology, neurogenetics and neuropathology of MS.
Organization

**Director:** Professor Per Soelberg Sørensen

**MS clinic**

**NEUROLOGISTS**
Professor Per Soelberg Sørensen
Consultant Morten Blinkenberg
Consultant Finn Sellebjerg
Consultant Annette Oturai
Consultant Karen Schreiber
Staff neurologist Ana Voldsgaard
Staff neurologist Lars Pindborg
Staff neurologist Melinda Magyari
Staff neurologist Henrik Mathiesen

PhD student Stephan Bramow
PhD student Lars Børnsen
PhD student Jeppe Romme Christensen
PhD student Dan Hesse
PhD student Rikke Ratzer
Junior physician Morten Møller

**MS NURSES**
Leading nurse Anne Hansen
Dorte Stauning Rasmussen
Anette Husted Pedersen
Lene Almind
Julie Yoon S. Moberg
Louise Nathalie Christiansen
Maj Daac Christensen
Sidsel Nielsen

**SECRETARIES**
Annette Larsen
Malene Møllersøe
Maria Brændbjerg
Helle Vilhelmsen

**NEUROPSYCHOLOGIST**
Agnete Jønsson

**PHYSIOTHERAPIST**
Lis Albrechtsen

**MEDICAL SOCIAL COUNSELOR**
Keld Nissen

**MS Research Unit**

**CLINICAL RESEARCH**
Professor
Per Soelberg Sørensen
Consultant Karen Schreiber
Staff neurologist Ana Voldsgaard
Staff neurologist
Melinda Magyari
Neuropsychologist
Agnete Jønsson

Research nurses
Vibeke Jespersen
Joan Pietraszek
Sidsel Nielsen

Research secretary
Annette Larsen

**NEUROIMMUNOLOGY RESEARCH**
Ass. professor Finn Sellebjerg
Senior research fellow
Helle Bach Søndergaard

PhD students
Dan Hesse
Lars Børnsen
Jeppe Romme Christensen
Rikke Ratzer

Junior research fellow
Marianne Hansen

**NEUROPATHOLOGY RESEARCH**
Professor
Per Soelberg Sørensen

Ph.d. student
Stephan Bramow

**NEUROIMMUNOLOGY LABORATORY**
Laboratory leader
Poul Erik Hylgaard Jensen

Laboratory technicians
Leading Laboratory technician
Joy Mendel-Hartvig
Marie Koefoed
Anne Mette Hedegaard Nielsen
Michael Jensen
Vibeke Fuglholt
Professor
Per Soelberg Sørensen

Ass. professor
Finn Sellebjerg

Consultant
Morten Blinkenberg

Consultant
Annette Oturai

Consultant
Karen Schreiber

Staff neurologist
Ana Voldsgaard

Staff neurologist
Henrik Mathiesen

Staff neurologist
Melinda Magyari

Laboratory leader
Poul Erik Hyldgaard Jensen

Senior research fellow
Helle Bach Søndergaard

Leading laboratory technician
Joy Mendel-Hartvig

Leading nurse
Anne Hansen
Research activities 2009
Clinical research

- Clinical research
- Neuroimaging
- Neurogenetics
- Neuroimmunology
- Neuropathology
- Routine analyses in Neuroimmunology Laboratory
Clinical research

CLINICAL RESEARCH GROUP:
Per Soelberg Sørensen, Morten Blinkenberg, Finn Sehliebjerg, Annette Oturai, Ana Voldsgaard, Karen Schreiber, Henrik Mathiesen, Melinda Magyari, Dan Hesse, Stephan Bramow, Lars Børnøn, Jeppe Romme Christensen, Agnete Jønsson, Vibeke Jespersen, Joan Pietraszek, Sidsel Walther Nielsen, Anne Hansen, Annette Larsen

Therapeutic trials
The results of two international multi-center clinical trials managed by DMSc using monthly pulse therapy of methylprednisolone tablets as add-on therapy to interferon-beta were presented at major MS congresses in 2009. The NORMIMS trial showed that in patients with breakthrough disease on interferon-beta 1a treatment add-on therapy with methylprednisolone tablets 5 days a month reduced the monthly relapse rate by 62% compared to add-on of placebo and reduced the accumulation of lesions on MRI. These results were corroborated in the MECOMBIN study of previously untreated patients showing that the combination of interferon-beta 1a and methylprednisolone tablets 3 days monthly reduced the relapse rate by 38% and showed beneficial effect in MRI outcomes compared to interferon-beta and placebo.

Two other large combination trials are currently directed from DMSc. The SIMCOMB study is a Nordic multi-center study of Simvastatin as add-on therapy to interferon-beta in de novo treated patients with relapsing-remitting MS. More than 300 patients have been recruited and the trial will be completed by the end of April 2010. The RECYCLINE study is a European multi-center study exploring the effect of Minocycline as add-on therapy to interferon-beta in de novo treated patients. Recruitment of 320 patients has been completed and the results will be available in 2012.

We are currently performing three single-center studies: A study of erythropoietin (EPO) in patients with progressive MS; a small safety study of treatment with eggs of the pig whipworm (Trichuris suis); and we have as the first center initiated an exploratory trial of natalizumab (Tysabri) in patients with progressive MS.

Neutralizing antibodies (NAb) against biological therapies
In a study using affymetrix gene chips we showed that interferon-beta treated NAb-positive patients, in whom MxA could not be induced by interferon-beta, had no residual bioactivity present and were virtually untreated.

DMSc collaborates with an EU supported European study of neutralizing antibodies against interferon-beta (NABINMS study). We are currently analyzing data from population-based cohorts of patients from Denmark, Spain, The Netherlands and The Czech Republic. Further, the NABINMS study has introduced a new assay for neutralizing antibodies based on a Luciferase reporter gene under control of interferon-beta, and this assay has been adapted for routine measurements of neutralizing antibodies in DMSc.

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PET
During the last decades, functional imaging have improved our understanding of the neurodegenerative processes in MS.

Former positron emission tomography (PET) studies, carried out in the Danish Multiple Sclerosis Center, have shown that cerebral activation in MS patients, is severely reduced as a consequence of disease progression.

Our current PET studies focuses on the early relapsing remitting phase of the disease and the corresponding changes in cerebral activation. Preliminary results show, that reductions in PET is associated with neuronal dysfunction or loss, measured by magnetic resonance spectroscopy (MRS). In this way there seem to be a close relationship between these two measures of cerebral neuronal integrity in MS.

MRI
In collaboration with Danish Research Centre for Magnetic Resonance (DRCMR), Hvidovre Hospital we have previously shown, that measurements of MRS correlate with cognitive dysfunction in MS. This cohort has now been re-evaluated and analyzed for longitudinal changes in MRS. Preliminary data show, that MRS decrease in the early stage of MS, predicts disease progression after 5 years. MRS may therefore be used as a clinical tool, to determine disease course in MS.

Another study focuses on the pathophysiological mechanisms underlying changes in cerebral activation in MS patients. Resting-state fMRI is a new approach to assess functional brain connectivity by measuring the synchronous fluctuation in the blood-oxygen-level dependent signal between remote brain regions at rest. DRCMR uses this method to study, whether changes in functional connectivity of the motor network, reflect disease severity in patients with MS. Brain functional connectivity is investigated in a cross-sectional study of 42 patients and furthermore in a longitudinal study of 12 patients evaluating the temporal dynamics during a relapse and clinical remission. Patient recruitment has been completed during year 2009 and elaborated statistical analysis is ongoing.
The ultimate cause of multiple sclerosis (MS) is still unknown. The probable cause is thought to be a combination of hereditary factors, an environmental trigger and a defect in the immune system. From family studies we have known for many years that genes play a role.

Identifying the involved genes is a complex challenge, because no single Mendelian locus causes MS. Through decades scientists have worked to find gene variations tied to MS. Genome linkage screens have failed finding major genes except genes of the HLA-complex, where linkage to DR2 (HLADRB1*15) is strongest in Northern Europeans. The HLA-DR2 association to MS was already identified back in 1973. A break-through took place in the summer 2007, when three new studies showed that the IL7 receptor and IL2receptor genes were important risk genes of MS. Both genes are important for the T cell regulation, and thus the immune system. Since then, several new genes have been confirmed. Presently, the Wellcome Trust Case Control Consortium is investigating the largest set of MS cases and controls (11,000/11,000) by a 500,000 SNPs chips. Results are expected later this year. We are taking part in this large international genetic collaboration through our membership of the IMSGC (International Multiple Sclerosis Genetic Consortium).

For more than 15 years the MS Genetic Group at Rigshospitalet have collected DNA, and today we have DNA from more than 1800 Danish MS patients and 1200 controls, all kept in the “Danish Multiple Sclerosis Biobank” located at our department at Rigshospitalet. In order to increase the sample size for genetic testing, we have participated in the “Nordic MS Genetic Network” since 1994, and today the Nordic material consists of 5000 MS cases and 5000 controls. Local research is focused on the candidate gene approaches and the genetic influence on the differences in treatment response.
Research activities 2009

Neuroimmunology

NEUROIMMUNOLOGY RESEARCH GROUP: Finn Sellebjerg, Helle Bach Søndergaard, Poul Erik Hylgaard Jensen, Dan Hesse, Jeppe Romme Christensen, Lars Børnsen, Rikke Ratzer, Per Soelberg Sørensen

Immunological studies
The interplay between the different types of immune cells in relapsing-remitting MS is only incompletely understood. Furthermore, the role of immune cells in the pathogenesis of the slowly developing deterioration in chronic progressive MS is a matter of debate. Some researchers consider immune activation to be of crucial importance in the pathogenesis of progressive MS, others consider progressive MS to result from slowly developing, neurodegenerative processes that are initiated by previous, inflammatory insults rather than by active inflammation.

We are using a combination of immunological studies, addressing the reactivity of subsets of T cells to autoantigens expressed in the brain and spinal cord, studies addressing the role of other leukocytes in the activation of T cells, and studies of the effect of immunomodulatory treatment to further our understanding of the role of immune activation in different disease stages in MS. Initial studies using these techniques, conducted in collaboration with the Institute for Inflammation Research at the Copenhagen University Hospital Rigshospitalet, have provided evidence that active MS is associated with the activation of a recently discovered subtype of T cells termed Th17 cells. We are now studying the nature of these cells in more detail.

In other studies we use flow cytometry, which is a method that allows the analysis of the phenotype of individual, circulating lymphocytes by measuring the binding of fluorochrome-coupled, monoclonal antibodies to distinct molecules. This technique is well suited for studying the activation status of subsets of lymphocytes. By combining the analysis of different molecules expressed on the cell surface, these cells can be divided into a large amount of functionally relevant subtypes, which can be quantitated both in relative and absolute terms. We have previously reported that flow cytometry can detect changes in the activation of circulating T cells and monocytes that differ in relapsing-remitting and secondary progressive MS. We are now exploring the extent to which such changes can be observed in other lymphocyte subsets, and whether they are associated with changes in the expression of cytokines and intrathecal immune activation that may reflect disease activity in progressive MS.

Molecular biology
The functional activation of immune cells requires complex interactions between different immune cells and coordinated, tightly regulated expression of numerous different molecules within single cells. DNA arrays provide a platform for unbiased studies of gene expression in different disease states and for studying the effect of treatment on gene expression. Using Affymetrix GeneChips®, we have found that even in clinical remission, circulating immune cells from MS patients show profound changes in gene expression compared to healthy control subjects. Furthermore, we have identified a gene expression pattern that appears to reflect the activity of endogenous interferon-beta, and is associated with the expression of factors that control disease activity in MS.

Gene expression is controlled by the activity of transcription factors that are either constitutively expressed in active forms, expressed in forms that require activation by other signals, or are inducible on cellular activation. The transcription
factors direct the expression of messenger RNA (mRNA) from the genes encoded by the DNA sequence, and after export from the nucleus the mRNA provides a template for protein synthesis on ribosomes in the cytosol. Within the last decade it has become apparent that endogenous, small RNA molecules termed microRNA (miRNA) have a key role in regulating the translation of protein from mRNA in the cytosol. MiRNA can either induce the degradation of mRNA, or can inhibit the translation of mRNA into protein by binding to the 3’ untranslated region of mRNA molecules. Recent studies have identified miRNA molecules that are differentially expressed in MS patients and healthy controls, and it has been suggested that pathogenic immune activation in MS may, indeed, reflect changes in miRNA expression. We have studied miRNA expression in MS, and have found that even patients with MS in clinical remission show clear changes in the expression of miRNA compared to healthy control subjects. Furthermore, we have identified miRNA molecules that are specifically regulated by treatment with interferon-beta.

As miRNA have profound effects on the translation of protein within the cell, studies of miRNA molecules that are differentially expressed in MS, may provide the key to understanding the regulatory mechanisms involved in MS pathogenesis. Indeed, as miRNA can now be therapeutically introduced into specific human cells, treatment with miRNA or with molecules blocking the effect of individual molecules may by a feasible avenue for the future treatment of MS. In ongoing studies, we are analysing the functional relevance of the changes in miRNA expression observed in our previous studies.

Biomarker studies
The term biomarker is used for, e.g., a gene product or protein, that can be measured in blood or other body fluids, and reflects a pathogenetically or therapeutically relevant in vivo process. Immunological and molecular biology studies provide the platform for the development of biomarkers, but the validation of these also requires access to collections of well characterized samples from MS patients with well characterized disease subtypes, who are followed prospectively. Such biomarker studies are important both for improving our understanding of the pathogenesis of MS and for understanding the therapeutic effects of immunomodulatory and immunosuppressive treatment strategies.

Our group has been active in studying the immunological effects of treatment with interferon-beta. These studies have resulted in the identification of novel markers that may reflect the therapeutic effect of treatment better than the currently used biomarkers. Furthermore, we have used systematic DNA array biomarkers studies to show that the development of neutralizing anti-interferon-beta antibodies results in complete abolishment of the biologic effects of treatment. These studies have also resulted in the identification of a gene expression pattern that appears to be associated with disease protection, and may identify patients that are more likely to remain in clinical remission on treatment with interferon-beta.

Cerebrospinal fluid is well suited for studying biomarkers that reflect pathogenic processes within the intrathecal compartment. Although cerebrospinal fluid is more difficult to obtain on a routine basis than blood samples, studies of such biomarkers have yielded important information about the dynamics of immune cell infiltration, immune regulation and tissue damage in MS. Most recently, we have studied changes in cerebrospinal fluid in patients treated with natalizumab (Tysabri), and have identified an apparently central role for the chemotactic factor (chemokine) CXCL13 in controlling the recruitment of immune cells to the brain and spinal cord in MS.

The development of biomarkers that may serve as surrogate outcomes in clinical trials is an important aim of the ongoing biomarker research at our center. We assess changes in cerebrospinal fluid biomarkers in patients with progressive MS that participate in ongoing treatment trials, and analyse the relationship between the different types of biomarkers and clinical and magnetic resonance imaging measures of disease activity and disease severity. These studies provide the platform for the design of future phase 2 studies of new MS treatments that may be conducted more rapidly, requiring a lower number of patients than the current protocols for phase 2 studies in MS.
In close collaboration with Dr. Henning Laursen, Laboratory of Neuropathology, Rigshospitalet and Professor Hans Lassmann, Director of Institute for Brain Research in Vienna, we have studied the pathological correlates in brain and spinal cord of patients with long-standing MS disease. We have been able to show that inflammation and neurodegeneration are closely associated. We identified a group of patients without any active or slowly expanding demyelination in the brain, and these patients did not show any signs of acute axonal injury apart from confounding pathology unrelated to MS such as Alzheimer disease.

Planimetric analysis of brain and spinal cords from patients with clinically well characterized primary progressive or secondary progressive MS showed that at total demyelination was more profound in brains of secondary progressive patients compared to primary progressive patients, whereas demyelination in the spinal cord was similar. Active demyelination correlated with shorter survival in patients with secondary progressive MS.

We also demonstrated that remyelinated areas had increased vulnerability and recurrent demyelination in the remyelinated areas were more frequent than appearance of new demyelinating plaques. This could explain why patients often develop recurrence of symptoms in new relapses. We also showed that diffuse inflammation in the white-matter outside plaques correlated with the load of active demyelination elsewhere in the brain. The correlation between diffuse new inflammation and active focal demyelination emphasizes the necessity of an action on both sides of the blood-brain-barrier for new treatments of progressive MS.
Routine analysis in neuroimmunology laboratory

NEUROIMMUNOLOGY LABORATORY RESEARCH GROUP:
Poul Erik H. Jensen, laboratory technicians: Joy Mendel-Hartvig, Marie Koeofoed, Michael Kolbjørn Jensen, Vibeke Fuglholm

Diagnostic evaluation
The presence in CSF of oligoclonal IgG-bands is of interest in the diagnosis of Multiple Sclerosis (MS). In 2009 we have analyzed 624 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 2009 we analyzed 1233 patient samples.

Measurement of neutralizing antibodies
Subgroups of MS patients, treated with interferon-beta or Tysabri, generate neutralizing antibodies, which diminish the therapeutic effects. Interferon-beta 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 neutralization of interferon-beta by antibodies in new cell-culture assay based on luciferase-induced expression, and further by the MxA mRNA-expression as a biological response to treatment with interferon-beta. In 2009 we have analyzed 244 patient samples for neutralizing antibodies, and 131 patient samples for MxA mRNA expression. Furthermore, we have screened 36 patient samples for interferon-beta binding antibodies using an ELISA-assay.

The action of Tysabri differs from interferon-beta, 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 2009 we analyzed 634 blood samples for the presence of antibodies to Tysabri by ELISA.
Scientific publications, prizes, collaboration, acknowledgements

- Scientific publications 2008-2009
- Prizes
- Honorary offices
- Scientific collaboration
- Acknowledgements
Scientific publications

Publications 2008

Peer reviewed original papers


Ravnborg M, Bendtzen K, Christensen O, Jensen P, Hesse D, Tovey M, Sorensen PS. Treatment with azathioprine and cyclic methylprednisolone has little or no effect on bioactivity in anti-interferon beta antibody-positive patients with multiple sclerosis. Mult Sci 2008.

Other publications


Peer reviewed original papers


Koch-Henriksen N, Sorensen PS, Bendtzken K, Flach EM. The clinical effect of neutralizing antibodies against interferon-beta is independent of the type of inter-


Ravnborg M, Bendtzen K, Christensen O, Jensen PE, Hesse D, Tovey MG, Sørensen PS. Treatment with azathioprine and cyclic methylprednisolone has little or no effect on bioactivity in anti-interferon beta antibody-positive patients with multiple sclerosis. Mult Scler 2009;15(3):323-8.


Other publications


Prizes and honorary offices

Prizes

 ANNETTE OTURAI
“Henry Hansen and wife’s grant”: 400,000 kr, donated for many years of scientific working within multiple sclerosis, 2009.

Honorary offices

 ANNETTE BANG OTURAI has held the following honorary offices:

A: National
Board member of the Danish Society for Multiple Sclerosis (DAReMuS)

FINN SELLEBJERG has held the following honorary offices:

A: National
Chairman of the Danish Society for Research in Multiple Sclerosis (MS) and chairman of the research board of the Danish MS Society.

B: International
Chairman of the task force on treatment of MS relapses and member of the scientist panel on demyelinating disease of the European Federation of Neurological Societies.

PER SOELBERG SORENSEN has held the following honorary offices:

A: National
Chairman of the Foundation for Research in Neurology, 1986-
Chairman of the Scientific Advisory Committee of the Danish MS Society, 2004-2010
Chairman of the 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-
Executive Board Member of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 2009-
Scientific collaboration

National

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The Danish Multiple Sclerosis Register, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark (Nils Koch-Henriksen, MD)

Department of Clinical Immunology, Copenhagen University Hospital Rigshospitalet, Denmark (Jacob Larsen MD, Lars Ryder, Klaus Rieneck, MD, Hans O. Madsen, MD)

Institute for Inflammatory Research, Copenhagen University Hospital Rigshospitalet, Denmark (Christian Enevold-Johansen MD, Professor Klaus Bendtzen)

Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (Trine Rasmussen Nielsen, MD, Henrik Hjalgrim, MD, professor Mads Melbye, Peter Michael Bager, ph.d.)

Department of Human Genetics, Aarhus University, Denmark (Bjørn Andersen Nexø)

Laboratory of Neuropathology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark (Hennig Laursen, MD)

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Department of Neurology, Lund University Hospital, Lund, Sweden (Professor Magnhild Sandberg-Wolfheim)

Department of Neurology, Gothenburg University Hospital, Gothenburg, Sweden (Professor Olaf Andersen)

Institute for Molecular Medicine Finland, University of Helsinki, Finland (Janna Saarela)

University of Cambridge, Neurology Unit, Addenbrooke’s Hospital, Cambridge, United Kingdom (Stephen Sawcer, MD, Professor Alastair Compston)

“International Multiple Sclerosis Genetic Consortium” (IMSG): collaboration between 20 countries from Europe, USA, Canada and Australia

Department of Immunopathology, Brain Research Center, Medical University of Vienna, Vienna, Austria. (Professor Hans Lassmann and Josa Frischer, MD)

Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA (Professor Claudia F. Lucchinetti)

VU Medical Centre, Amsterdam, The Netherlands (Professor Chris Polman)

Utrecht University, Utrecht, The Netherlands (Professor Hub Schellekens)

Heinrich-Heine-University, Düsseldorf, Germany (Professor Hans-Peter Hartung)

Ospedale Universitario San Luigi, Torino, Italy (Professor Auturio Bertolotto)

Queen Square, London, The United Kingdom (Professor Gavin Giovannoni)

Innsbruck Medical University, Innsbruck, Austria (Professor Florian Deisenhammer)

General Charles University, Prague, Czech Republic (Professor Eva Havrdova)

International

Nordic MS Genetic Network: Collaboration between the Nordic countries: Sweden (Huddinge, Lund, Gothenburg, Stockholm), Norway (Oslo, Bergen), Finland (Helsinki) and Denmark (Copenhagen)

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 (Professor Kjell-Morten Myhr)

Department of Neurology, Huddinge University Hospital, Karolinska Institute, Huddinge, Sweden (Professor Jan Hillert, Eva Åkesson, MD, Helena Modin, MD)
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
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Octapharma, Austria
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Genzymes, Holland
BioMS
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