

Project description

THE NORWEGIAN MULTIPLE SCLEROSIS REGISTRY AND BIOBANK

1. RELEVANCE

The Norwegian Multiple sclerosis Registry and Biobank project is within the NevroNor call for proposals "Epidemiological research of central nervous system diseases" and will become an unique platform for high quality multiple sclerosis (MS) research within specialities such as epidemiology, clinical neurology, neurogenetics, neuropathology, neuroimmunology as well as biochemistry. The main goal for establishing this unit is to contribute to research aiming to identify exogenous and genetic risk factors for MS as well as detect specific markers for diagnosis and evaluation of treatment effects. The unit will also facilitate establishment and maintenance of research networks between national and international MS research groups and will make Norwegian MS researches highly attractive for international collaborative projects.

2. BACKGROUND AND STATUS OF KNOWLEDGE OF MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an immune-mediated, inflammatory disease of the central nervous system (CNS) in genetically susceptible patients. It is largely a disease of young adults, with the mean age of onset at about 30 years. Most patients (80–85%) have an initially relapsing-remitting course (RRMS) that begins with subacute attacks of neural dysfunction and tends to remit spontaneously. Subsequent relapses then occur, with the development of permanent nervous system impairment in most patients. The patients with an initial primary progressive course (PPMS) (15–20%) have an older age of onset and usually present with slowly indigenus development of motor dysfunction.

2.1 Epidemiology of MS

The frequency of the disease is unevenly distributed throughout the world. In the Northern Hemisphere, a diminishing north-south gradient for MS prevalence has been described, and the reverse, a south-north gradient, has been reported in the Southern Hemisphere. Norway is a high risk area with a prevalence of 120-150 per 100.000 inhabitants and an incidence of 5-7 new patients per 100.000 inhabitants each year (Myhr 2006).

2.2. Diagnosis of MS

No single symptom, sign or test provides a diagnosis of MS. The diagnosis is based on disease history, clinical evaluation and para clinical tests including magnetic resonance imaging (MRI) cerebrospinal fluid (CSF) analysis and in some cases evoked potentials (Polman 2005).

The clinical evaluation includes thorough disease history and neurological examination. The typical history is subacute attacks, separated in time (dissemination in time), of nervous system dysfunction that tends to remit spontaneously. Subsequent relapses then occur, with the development of permanent neural impairment in most of the patients. The neurological examination reveals evidence of two or more lesions from different parts of the CNS (dissemination in space). Patients with PPMS often present motor symptoms progressing slowly over at least 12 months.

MRI has a high sensitivity for MS lesions. The standard approach is to do axial T2-weighted scans that show high-intensity (white) lesions in the CNS. The lesions are usually located around the lateral ventricles or in the corpus callosum (seen best on sagittal scans) but are also seen in the brainstem, cerebellum, spinal cord, optic nerve and cortex. T1-weighted

MRI scans using contrast agents (Gd-DTPA) detect blood-brain barrier (BBB) disruption, which is a sign of new lesion formation.

Isoelectric focusing electrophoresis of CSF is also a very sensitive test, as oligoclonal bands (OCB) can be detected in more than 95% of patients with a clinically definite diagnosis. The OCB are predominantly of the IgG class and are restricted to the CSF, thus indicating abnormal intrathecal IgG production (Andersson et al. 1994).

2.3. Treatment of MS

No curable treatment is available for MS. MS relapses may, however, be treated with glucocorticosteroids (methylprednisone) that speed up remission, but do not improve remission or prevent new relapses. When repeated relapses occur, immunomodulatory treatment (interferon-beta or glatirameracetate) is used to reduce disease activity. In addition various symptomatic treatments are available for different symptoms such as pain, spasticity, bladder and sexual dysfunction.

2.4. Pathogenesis of MS

MS is characterised by multifokal inflammatory demyelination in the CNS with loss or removal of myelin and oligodendrocytes, and various degree of axonal damage. The pathogenesis of the lesions has been extensively characterized, but there is still a controversy regarding the initial events of lesion formation. There is inflammation in MS lesions, containing macrophage and lymphocyte infiltration, but it is not known whether this is a primary event. The MS inflammation may be an immunological attack on previously normal myelin and oligodendrocytes, or a secondary response to an initial damage of oligodendrocytes and/or myelin. Lucchinetti et al. (2000) suggested four distinct pathological subtypes of MS, which do not directly correspond to clinical subgroups. She hypothesized a pathogenetical heterogeneity, with initial autoimmune demyelination in some patients (~ 70%) and initial oligodendrocyte damage and death in others (~ 30%). Others have indicated that pathological heterogeneity may reflect different lesion stages, and that inflammation in white matter MS lesions is due to a primary damage to oligodendrocytes (Barnett 2005). It is therefore not clear what constitutes the initial events of MS lesion pathogenesis, what changes are primary and what changes are secondary to tissue damage, and whether there is heterogeneity of MS pathogenesis. The complexity is further complicated by studies indicating location-dependent lesion heterogeneity. Inflammatory MS lesions are typically located in brain white matter, but recent studies have also shown widespread grey matter/ cortical lesions as well, but with relative absence of inflammation (Bø 2003a, b). Thus the only known common denominators of MS lesions in all locations are demyelination and axonal loss.

2.5. Etiology of MS

The cause of MS is largely unknown, but evidence suggests that the disease is immune mediated in genetically susceptible individuals in response to environmental factors (Compston 2002, Noseworthy 2000).

The most widely discussed *environmental factors* are various viral infections, nutrition factor such as fatty acids and vitamins and climate related to temperature and sun exposure. However, no single infectious agent other exogenous factor has been confirmed to be associated to the disease.

The *genetic susceptibility* has been shown from family studies of twins, adoptees, half-siblings and conjugal pairs all indicating that a substantial part of family clustering seen in MS is a result from shared genetic factors. Association of MS with human leukocyte antigen (HLA) genes is firmly established (Olerup 1991) but as yet no other candidate gene has been

firmly implicated. Several whole genome linkage screens in MS have been performed, each implicating multiple chromosome regions, but none succeeding in demonstrating statistically unequivocal linkage (The Transatlantic Multiple Sclerosis Genetics Cooperative 2001). The limited power of linkage in the analysis of complex diseases like MS is well known. This has led to a shift towards association based studies employing large collections of well characterised cases and controls, which are expected to be more powerful (Risch 1996).

2.6. The Norwegian MS Registry and Biobank – a resource for improved MS research

There is growing knowledge of several aspects within MS. However, the etiology is still unknown, the pathogenesis is unclear and there is an urgent need for diagnostic markers and improved treatments. This relative lack of break through findings in MS calls for improved fundamentals for future research. It is a need for representative patient materials in studies within epidemiology, genetic, pathology, and evaluation of long-term treatment. By establishing large population based patient materials, we could contribute to high-impact MS research. *The Norwegian MS registry* that was established in 2001 aims for registering all MS patients in Norway (Myhr 2006). Increasing numbers of patients are included, and at the present time about 50-60 % of all patients are registered (n ~ 3500). A broad national research group has put forward a proposal for establishing a biobank unit linked to the registry. The project has been approved by the Regional Ethical Committee, the Norwegian Data Inspectorate and The Ministry of Health and Care Services/The Directorate for Health and Social Affairs. The new unit is called *The Norwegian Multiple Sclerosis Registry and Biobank*, and consists of a registry unit (former Norwegian MS registry) and three biobank units for collection and storage of DNA, serum, CSF and CNS tissue. The main goal for this unit is to offer high quality patient materials to MS research projects for identifying exogenous and genetic risk factors for the disease as well as detect specific markers for diagnosis and evaluation of treatment effects.

3. ADVANTAGES & POSSIBILITIES FOR NORWEGIAN MS RESEARCH

3.1. Productive Norwegian Multiple Sclerosis Research Groups

The main MS research groups in Norway are located in Bergen at Haukeland University Hospital and University of Bergen and Oslo at Ullevål University Hospital and University of Oslo. The Bergen group has a longstanding production in epidemiology and clinical neurology, immunology and pathology (Myhr 2006). The Oslo group has focused on epidemiology, immunology and genetics. During several decades, the research groups have contributed with important MS research. *Epidemiological studies* have defined Norway as high risk area for MS (Grytten 2006, Celius 1998), shown adolescence as a possible critical period in life for exposure from exogenous factors (Riise 1992), defined the clinical course and natural history of the disease (Myhr 2001) and complication rates of MS pregnancies (Dahl 2005). *Immunological studies* have shown important aspects in the immunopathogenesis of the disease implicating microglia activation (Ulvestad 1994), immune activation molecules (Bø 1994) and inflammatory substances (Bø 1994) as well as intrathecal T-cell responses (Holmøy 2003). *Studies in MS genetics* have confirmed the HLA association (Spurkland 1991, Harbo 2004), identified candidate chromosome regions for MS susceptibility genes by genome wide screening (Harbo 2003) and indicated possible disease modifying genes (Myhr 1999). *Studies of MS pathology* have identified important characteristics of the MS brain lesions such as axonal damage (Trapp 1998) and widespread grey matter and cortical lesions (Bø 2003a, b).

Several other departments in other counties have also contributed with some MS research activity; Troms and Finnmark, Møre and Romsdal, Rogaland, Akershus, Buskerud, Nord-Trøndelag, Nordland and Rikshospitalet/Oslo.

3.2. The MS National Competence Centre and Registry

The Norwegian Multiple Sclerosis National Competence Centre was established at the Department of Neurology, Haukeland University Hospital in 1996. The main responsibility for the Centre is promotion of research, supervision and education to doctors and other health care professionals in Norway. The Centre has through different projects established extended national and international networks both in clinical neurology and research, as well collaboration with the Norwegian MS Society (Myhr 2006). The National (Norwegian) Multiple Sclerosis Registry was established at the Centre in 2001 and includes at the present time about 50-60 % of all MS patients in Norway. The Registry organises a network of MS-neurologists at hospital departments of neurology in all the 19 Norwegian counties, and will be the core unit of the new The Norwegian MS Registry and Biobank.

3.3. Unique Norwegian Possibilities to promote high quality MS research

Norway has a stable and a relatively homogenous population that is included in several national health registries such as the Medical Birth Registry, Infectious Disease Registry, Vaccination Registry, Prescription Registry, Cancer Registry and Cause of Death Registry. Most of these registries are organized by the Norwegian Institute of Public Health that is also responsible for Biohealth Norway. This is a biobank platform, chaired by Division Director Camilla Stoltenberg, providing access to biological materials and data from large Norwegian health surveys including The Norwegian Mother and Child Study and Cohort of Norway. By linking information from the different registries and biobanks to a fully established Norwegian MS Registry and Biobank, a population based MS patient material can be generated for high quality MS research. Based on this unique potential and the fact that Norway is a high risk area for MS, we also have a certain responsibility to make this happen.

4. THE NORWEGIAN MS REGISTRY AND BIOBANK

Norwegian MS Registry and Biobank will be organized in four units with the Norwegian MS Registry as the coordinating unit. A biobank unit for collection and storage of DNA will be established at the Norwegian Institute of Public Health, Oslo, a biobank unit for collection and storage of CSF and serum at the Department of Neurology, Haukeland University Hospital, and a biobank unit for collection and storage of CNS Tissue at the Department of Pathology, Haukeland University Hospital, Bergen.

4.1. Target population

All MS patients included in the National/Norwegian MS registry will be asked for giving consent for collecting and storage of biological materials. Samples from parents (DNA and serum) and siblings (serum) will be included as controls. Thus they will also be asked, through their family member with MS, for giving consent for collecting and storage of biological materials.

4.1. The Norwegian MS Registry

The registry (see also section 3.2) is located at Haukeland University Hospital and is chaired by associated professor Kjell-Morten Myhr. The registry is financed by Western Norway Regional Health Authority and aims to register all MS-patients in Norway. The registry includes demographic and clinical in addition to treatment variables. The registry is based on written informed consent and the patients are recruited by their local neurologist. The registry has been given the approval from The Regional Ethical Committee, the Norwegian Data Inspectorate and The Ministry of Health and Care Services/The Directorate for Health and Social Affairs to link a biobank to the registry.

4.2. MS biobank unit for DNA

This unit will be localized at the Norwegian Institute of Public Health, Oslo and chaired by Dr. Hanne Flinstad Harbo. The National Institute of Public Health has great experience in establishing biobanks linked to population-based registries. The Institute is responsible for the FUGE biobank platform, BIOHEALTH NORWAY, financed by the Norwegian Research Council. By localizing MS DNA biobank Unit at the Institute, we will take advantage of scientific and technological resources already established at the Institute. Harbo will in collaboration with Division Director Camilla Stoltenberg at the National Institute of Public Health be responsible for establishing DNA biobank unit.

4.3. MS biobank unit for CSF and serum

This unit will be localized at the Department of Neurology, Haukeland University Hospital and chaired by Professor Christian A Vedeler. The Routine Laboratory at the Department is responsible for the majority of CSF analyses in MS diagnostics in Norway. It performs isoelectric focusing to detect oligoclonal bands in the CSF, which is the preferred method for CSF analyses in multiple sclerosis (Polman 2005). Professor Vedeler will be responsible for establishing the CSF and serum biobank unit.

4.4. MS biobank unit for CNS tissue

This unit will be localized at the Department of Pathology, Haukeland University Hospital and chaired by Professor Sverre Mørk. He has for several decades been working with characterization of MS-lesions in MS brain and spinal cord. In collaboration with Dr Lars Bø he has established several international collaborations for MS tissue studies. Mørk will be responsible for establishing the CNS tissue biobank.

4.5. Norwegian MS Registry and Biobank working committee

A working committee consisting of the leaders of the four units will be established. The committee will be chaired the leader of the Norwegian MS Registry, p.t. associate professor Kjell-Morten Myhr, and will have the responsibility for coordinating activity between the different units and prepare received project applications that will be evaluated by the board.

4.6. Norwegian MS Registry and Biobank board

A board for the Norwegian MS Registry and Biobank will be established and will include members from the Regional Health Authorities and the National Institute of Public Health as well as an observational member from the Norwegian MS society. The board will be responsible for establishing guidelines for access to data and biological materials from the Norwegian MS Registry and Biobank. The board will be responsible for evaluation all applications.

5. PROCEDURES FOR THE NORWEGIAN MS REGISTRY AND BIOBANK

5.1. Informed consent

All responders/donors to the biobank units have to give informed consent prior to donation and the documents will be received and stored at the MS registry unit, Department of Neurology, Haukeland University Hospital.

5.1.1. *The patients that already have been included* in the Norwegian MS registry have previously given informed consent. These patients will be asked to expand their consent to include collecting and storage of biological material (DNA, serum and CSF).

5.1.2. *Patients that prospectively are included* will be asked for informed consent including both registry data and biological materials (DNA, serum and CSF).

5.1.3. Parents and siblings of MS patients will be asked for informed consent for collecting and storage of biological materials (DNA and serum).

5.2. DNA samples

When informed consents are received at the MS registry unit, the patients are given a unique ID number in the Norwegian MS registry and biobank, a letter will be sent to the responder/donor including appropriate tubes for blood sampling (DNA and serum). The blood sampling will be performed by the local GP or neurologist and the tubes will be sent to the Norwegian Institute for Public Health. DNA extraction will be performed and the samples will be stored at minus 20°C in appropriate volumes. Serum samples will be prepared and stored at minus 80°C in appropriate tubes for later transfer to the biobank unit for spinal fluid and serum at the Department of Neurology, Haukeland University Hospital.

5.3. CSF and serum samples

5.3.1. CSF. When informed consents (together with the register forms) are received at the Norwegian MS registry unit, a letter will be sent to the routine laboratory for CSF analysis at the Department of Neurology Haukeland University Hospital and/or the patients local hospital asking for transfer of any stored CSF (from the primary diagnostic analysis) from the patients. Any stored CSF samples will be transferred to the biobank unit for CSF and serum at the Department of Neurology, Haukeland University Hospital. Samples will be prepared and stored at minus 80°C in appropriate volumes.

5.3.2. Serum. Any serum samples that are stored together with CSF samples will be collected along with those. Serum samples will also be collected as described in paragraph 5.2.

5.4. CNS tissue samples

A separate information brochure describing the Norwegian MS registry and biobank, focusing on the tissue unit and its purpose, will be made and distributed in collaboration with the Norwegian MS society. Through this brochure the patients will be given the opportunity to give their informed consent to donate tissue post mortem. They will then receive a specific ID-card and the donation procedure will be activated post mortem. A detailed description including procedures for tissue preparation and storage will be distributed to collaborating departments of pathology. Collected tissues will be transferred, according to detailed procedures, to the biobank unit for CNS tissue samples at the Department of Pathology, Haukeland University Hospital, Bergen.

6. CLINICAL AND SCIENTIFIC IMPACT OF THE PROJECT

The Norwegian MS registry and biobank will be a resource for MS research, and will give Norwegian MS researchers a unique position to establish high impact MS projects that also will be attractive for international collaboration. The scientific impact will be illustrated by publication of original papers in preferable high-impact journals in the field of clinical neurology, epidemiology, genetics, immunology and pathology. Results will also be presented at the leading international conferences as well as to Norwegian researchers, practising neurologists and to the patients and the Norwegian MS society.

Three main projects, that immediately can take advantage of the Norwegian MS registry and biobank, have already been established.

6.1. Identification of genetic susceptibility factors in Multiple Sclerosis (ES369017).

This is a project, chaired by Dr. Hanne F. Harbo, aiming to identify genetic factors determining the development of multiple sclerosis. Major sub goals in the project are to

characterise the HLA associated disease susceptibility and fine-mapping of candidate chromosome regions by single-nucleotide polymorphisms (SNP)-studies.

6.2. Gene Expression studies in Multiple Sclerosis Brains (ES366494).

This is a project, chaired by Dr. Lars Bø, aiming to identify unique gene expression changes contributing to demyelination and axonal loss in MS. Major sub goals in the project are to characterise gene expression changes specific for active demyelination in MS brain white matter and in cortical grey matter.

6.3. A Proteomic and Bioinformatic search for novel Diagnostic Biomarkers in Multiple Sclerosis (ES375052).

This is a project, co-chaired by Professor Rune Ulvik and associate Professor Kjell-Morten Myhr, aiming to identify disease specific biomarkers in the proteoms of cerebrospinal fluid (CSF) and serum of patients with MS by mass spectrometric and bioinformatic technology.

We expect the projects to come up with new results of clinical importance regarding exogenous and genetic factors related to MS etiology and possible also related to disease course and prognosis. MS specific disease markers will become important diagnostic markers that also may be used for evaluation of treatment response.

7. RESEARCH GROUP

A national research group that includes experienced researchers within clinical neurology, epidemiology, genetics, immunology, pathology as well as biochemistry has been established. The members represent clinical neurology departments and research groups from all university hospitals in Norway, as well as the Norwegian institute of public health.

7.1. Project leader:

Kjell-Morten Myhr, MD, PhD. Associated professor and consultant, Department of Clinical Medicine, University of Bergen and The Multiple Sclerosis National Competence Centre, Department of Neurology, Haukeland University Hospital. Myhr is head of the Multiple Sclerosis National Competence Centre and Registry, and have long experience in MS research. The centre has available resources for secretary and IT-technician work, as well as laboratory technician for handling of samples in the CSF/serum and the CNS tissue biobank units.

7.2. Core research group:

7.2.1. Hanne F. Harbo, MD, PhD. Consultant and post doc, Department of Neurology, Ullevål University Hospital and Institute of Immunology, University of Oslo. Harbo has previously organized large collaborative MS genetic projects. Her group has available technician resources for handling DNA samples in the DNA biobank unit.

7.2.2. Christian A. Vedeler, MD, PhD. Professor and consultant, Department of Clinical Medicine, University of Bergen and, Department of Neurology, Haukeland University Hospital. Professor Vedeler is head of the laboratory unit at the Department that offer several neuroimmunological analyses for diagnostics purposes. He has long experience in neuroimmunology research and will be responsible for establishing the CSF and serum biobank unit.

7.2.1. Sverre J. Mørk, MD, PhD. Professor and consultant, The Gade Institute, University of Bergen and Department of Pathology, Haukeland University Hospital. Professor Mørk is head of the neuropathology unit at the Department and has for several decades been working with characterization of MS-lesions in MS brain and spinal cord. He has established several

international collaborations for MS tissue studies. Mørk will be responsible for establishing the CNS tissue biobank.

7.2.1. Camilla Stoltenberg, MD, PhD. Division Director, Norwegian Institute of Public Health, Oslo. Stoltenberg is the Director of the The Division of Epidemiology at the Norwegian Institute of Public Health that includes six departments and approximately 200 employees in Oslo and Bergen. The division is responsible for several large population based cohorts, national health registries and biobanks. She is co-principal investigator of the *Autism Birth Cohort*, and leads the Norwegian part of the study. The Autism Birth Cohort is conducted in collaboration with Columbia University in New York, and funded by the National Institutes of Health, USA. She is principal investigator of *Biobanks for Health*, a functional genomics platform based on a network of population based biobanks and health studies in Norway.

7.3. National cooperation:

- Jan H Aarseth, PhD. Head Statistician, The Norwegian MS registry, Department of Neurology, Haukeland University Hospital, Bergen.
- Rune Midgard, MD, PhD. Associated professor, and consultant, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, and Department of Neurology, Molde Hospital.
- Svein Ivar Mellgren, MD, PhD. Professor and consultant, Department of Neurology, University Hospital of North Norway and the University of Tromsø.
- Harald Hovdal, MD. Consultant, Department of Neurology and Clinical Neurophysiology, St Olavs Hospital, Trondheim
- Elise Tandberg, MD PhD. Consultant, Department of Neurology, Stavanger University Hospital.
- Elisabeth G. Celius, MD. Consultant and Head of Department of Neurology, Ullevål University Hospital, Oslo.
- Christian Lund, MD, PhD. Consultant, Department of Neurology, Rikshospitalet University Hospital, Oslo.
- Antonie G Beiske, MD. Consultant, Department of Neurology, Akershus University Hospital, Lørenskog.
- Anne Spurkland, MD, PhD. Professor, Department of Anatomy, University of Oslo.
- Lars Bø, MD, PhD. Consultant and post doc, Department of Clinical Medicine, University of Bergen and Department of Neurology, Haukeland University Hospital, Bergen.
- Rune Ulvik, MD, PhD. Professor and consultant, Department Internal Medicine, University of Bergen and Laboratory of Clinical Biochemistry, Haukeland University Hospital.
- Professor Olav Kvalheim, PhD. Professor Department of Chemistry, University of Bergen

7.4. International collaboration.

Through ongoing projects within genetics, pathology and CSF studies we have established collaboration several international experts in the field:

- Professor Jan van der Greef, University of Leiden and TNO, The Netherlands. van der Greef is a highly respected international scientist in liquid chromatography with mass spectrometers (LC-MS) technology.
- Dr. Marco Gaspari, Univ. di Catanzaro, Italy is an expert in capillary-LC-MS and nano-LC-MS.
- Dr. Stephen Sawcer, MD, Ph D, The Cambridge University Neurology unit Multiple Sclerosis Genetics, Department of Clinical Neurosciences, Addenbrooke's Hospital,

University of Cambridge, UK, is one of the leading scientists in the field of MS genetics and has been one of the leaders of the Genetic Analysis of Multiple sclerosis in Europe (GAMES) and International Multiple Sclerosis Genetics Consortium (IMSGC) projects.

- Professor Jan Hillert, Karolinska institutet, Stockholm, Sweden, has for several years been the leading MS-genetic researcher within the Nordic countries and he has recently chaired the Nordic Group of MS Genetics, an EU funded Nordic collaborative project.
- Professor Paul van der Valk, VU University Medical Center, Amsterdam, The Netherlands who is responsible for the neuropathological unit at the MS centre in Amsterdam.

8. AVAILABLE RESOURCES AND BUDGET

The biobank units have equipment and some laboratory technician resources available for handling of samples. The amount included in the application cover the cost related to collection, preparation and storage of samples and meetings as well as a technician (50% for 3 yrs) at the DNA unit and technician (50% for 3 yrs) at the tissue unit:

Application to the Research Council		
1. Total cost for collection, preparation and storage of samples		3.143.775
2. Meetings (3 research group + 1 national)		150.000
3. Technician, 50% for 3 yrs, l.tr. 35 (275 000)	DNA unit	602.250
4. Technician, 50% for 3 yrs, l.tr. 35 (275 000)	Tissue unit	602.250
Total		4.498.275

Own funding:		
Personnel cost	Location	Total
1. Secretary, 50% for 3 yrs, l.tr. 35 (275 000)	Register	602.250
2. IT expert 50% for 2 yrs, l.tr. 45 (323 200)	Register	471.900
3. Technician, 50% for 3 yrs, l.tr. 35 (275 000)	DNA unit	1.204.500
4. Technician, 50% for 3 yrs, l.tr. 35 (275 000)	CSF unit	602.250
Total		2.278.650

See also separate attachment with detailed information

9. ETHICAL CONSIDERATIONS

The Norwegian MS registry and Biobank has been approved by the Regional Ethical Committee, the Norwegian Data Inspectorate and The Ministry of Health and Care Services/The Directorate for Health and Social Affairs. All projects that will get access to data and materials from the unit have to be improved by all relevant bodies. Any linkage between registries, between registries and other patient information, and any other linkage of patient-related information will strictly depend on the approval of all relevant bodies, and be undertaken according to their advice. All studies will be in full conformity with the last revision of the Declaration of Helsinki. All results obtained will be published in referee-based international journals, irrespective of research outcome. Patient representatives will be sought for advice when appropriate.

10. REFERENCES

- Andersson M et al. Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. *J Neurol Neurosurg Psychiatry* 1994;57:897-902.
- Barnett et al. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. *Ann Neurol* 2004;55:458-68.

- Bø L et al. Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *J Neuropathol Exp Neurol* 2003a;62:723-32.
- Bø L et al. Intracortical multiple sclerosis lesions are not associated with increased lymphocyte infiltration. *Mult Scler* 2003b;9:323-31.
- Bø L et al. Detection of MHC class II-antigens on macrophages and microglia, but not on astrocytes and endothelia in active multiple sclerosis lesions. *J Neuroimmunol* 1994a;51:135-46.
- Bø L et al. Induction of nitric oxide synthase in demyelinating regions of multiple sclerosis brains. *Ann Neurol* 1994b;36:778-86.
- Celius EG. Multiple sclerosis in Oslo, Norway: prevalence on 1 January 1995 and incidence over a 25-year period. *Eur J Neurol* 2001;8:463-9.
- Compston A et al. Multiple sclerosis. *Lancet* 2002;359:1221-31. *Lancet* 2002;360:648
- Dahl J et al. Pregnancy, delivery, and birth outcome in women with multiple sclerosis. *Neurol* 2005;65:1961-3.
- Harbo HF et al. Two genome-wide linkage disequilibrium screens in Scandinavian multiple sclerosis patients. *J Neuroimmunol* 2003;143:101-6.
- Harbo HF et al. Genes in the HLA class I region may contribute to the HLA class II-associated genetic susceptibility to multiple sclerosis. *Tissue Antigens* 2004;63:237-47.
- Holmoy T et al. T cells from multiple sclerosis patients recognize immunoglobulin G from cerebrospinal fluid. *Mult Scler* 2003;9:228-34
- Grytten N et al. A 50-year follow-up of the incidence of multiple sclerosis in Hordaland County, Norway. *Neurol* 2006;66:182-6.
- Lucchinetti et al. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol* 2000;47(6):707-17.
- Myhr KM et al. Immunoglobulin G Fc-receptor (FcγR) IIA and IIIB polymorphisms related to disability in MS. *Neurol* 1999;52:1771-6.
- Myhr KM et al. Disability and prognosis in multiple sclerosis: demographic and clinical variables important for the ability to walk and awarding of disability pension. *Mult Scler* 2001;7:59-65.
- Myhr KM et al. The Norwegian Multiple Sclerosis National Competence Centre and National Multiple Sclerosis registry – a resource for clinical practice and research. *Acta Neurol Scand* 2006;113(suppl 183):37-40.
- Noseworthy JH et al. Multiple sclerosis. *N Engl J Med* 2000;343:938-52.
- Olerup O et al. HLA class II-associated genetic susceptibility in multiple sclerosis: a critical evaluation. *Tissue Antigens* 1991;38:1-15.
- Polman CH et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005;58:840-6.
- Riise T et al. Relationship between the degree of individual space-time clustering and age at onset of disease among multiple sclerosis patients. *Int J Epidemiol* 1992;21:528-32.
- Risch N and Merikangas K. The future of genetic studies of complex human diseases. *Science* 1996; 273: 1516-17.
- Spurkland A et al. HLA-DQA1 and HLA-DQB1 genes may jointly determine susceptibility to develop multiple sclerosis. *Hum Immunol* 1991;30:69-75.
- The Transatlantic Multiple Sclerosis Genetics Cooperative. A meta-analysis of genomic screens in multiple sclerosis. *Mult Scler* 2001;7:3-11.
- Trapp BD et al. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med* 1998;338(5):278-285.
- Ulvestad E et al. Reactive microglia in multiple sclerosis lesions have an increased expression of receptors for the Fc part of IgG. *J Neurol Sci* 1994;121:125-31.