Neuro-SysMed

Annual report 2019

A centre for clinical treatment research
on neurological diseases

Multiple Sclerosis • ALS • Parkinson's disease • Dementia

Annual report for Neuro-SysMed 2019

Introduction

Neuro-SysMed - a major investment for brain health in Norway

One in three people will develop a brain disease during their lifetime - and the proportion of people living with a brain disease increases dramatically with increasing life expectancy and age composition in the population. Correspondingly, the society impacts of these challenges are also increasing, both in terms of costs, as well as healthcare personnel resources.

Neuro-SysMed is the first research centre of excellence for clinical treatment in Norway. This is a new initiative from the Research Council of Norway, that is clinical medicine's parallel to Norwegian Centres of Excellence that usually have more basic research approach. The centre aims to use a systems medicine approach on accumulating data from clinical trials to identify accurate markers for early diagnosis and sub-classification of diseases, predict prognosis and treatment response.

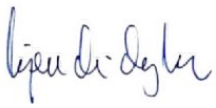
Neuro-SysMed will focus on four diseases; multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and dementia.

MS is an inflammatory disease of the central nervous system (CNS), typically affecting young adults that usually can be treated by therapies by anti-inflammatory mechanism of action. Neuro-SysMed aims to further improve treatment strategies of existing therapies and develop new ones - especially for those with progressive disease courses with very limited available therapy options.

PD, ALS, and dementia are all classified as neurodegenerative diseases of the CNS, with a progressively disease course, that most often affect patients in higher age groups. These diseases are characterized by numerous subgroups, and hardly any therapy that substantially slows the progression of disability is available. Obvious goals for Neuro-SysMed are therefore identification of markers for precise sub-classification of diagnosis, as well as contributing to the development of novel therapies that can slow disease progression.

Neuro-SysMed has further an overall aim to facilitate the conduction of randomized clinical trials in collaboration with the pharmaceutical industry, to provide Norwegian patients access to new therapies in an early stage of the development. We also aim to improve symptom management and rehabilitation, as well as the general care provided to patients and their families.

In this annual report, we present activities of the first months of Neuro-SysMed. Taking advantage of a close and active collaboration with our national and international research network, highly skilled advisory board members, and patient user organisations, we hope to fulfil our goals in the coming years and make a difference for people living with brain diseases.



Kjell-Morten Myhr
Director of Neuro-SysMed

Summary

Neuro-SysMed is a Norwegian Centre of Excellence for clinical research into diseases of the brain, focusing on multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and dementia. The Centre is hosted by Haukeland University Hospital in collaboration with the University of Bergen and Haraldsplass Deaconess Hospital in Bergen, Norway, and Lawson Health Research Institute, in London, Ontario, Canada.

Vision / goals

The overarching objective of Neuro-SysMed is to improve the treatment of multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and dementia. To achieve this goal, the Centre is establishing a state-of-the-art clinical trial unit and conducting ground-breaking clinical and translational studies involving health care institutions across Norway and international partners.

Research plan / strategy

Neuro-SysMed will organize and conduct randomized clinical treatment trials to evaluate the efficacy and safety of therapies, novel or established drugs with new indications, that may delay or even arrest disease progression, ameliorate symptoms or optimize care for affected individuals.

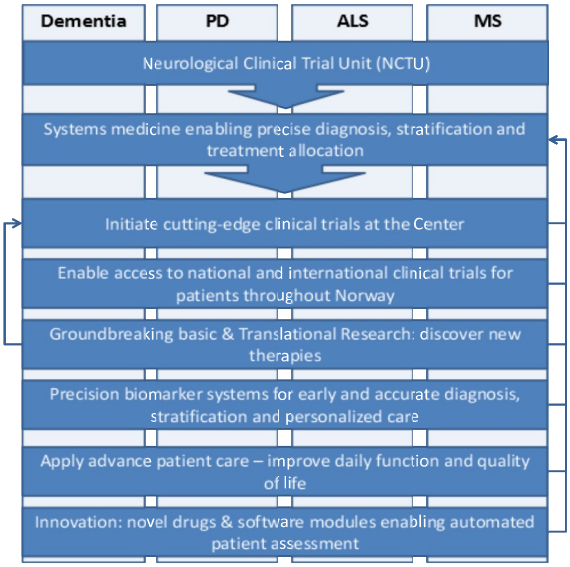


Figure 1: Research plan

While each study will have its own scientific questions and efficacy endpoints, all projects running under the centre will contribute data, such as clinical scorings, DNA, blood and cerebrospinal fluid analyses, and brain images, to a common Neuro-SysMed database. Using this database, we will integrate the vast amount of information collected at the Centre, in order to define biomarkers that enable early and precise diagnosis, subgrouping of patients within each disease, accurate prognosis and tailored treatment choices for individual patients (i.e. personalized medicine). Thus, Neuro-SysMed aims to development early and improved treatment strategies for patients with serious diseases of the central nervous system.

Randomized clinical trials are the backbone of the centre activities, and cannot be started at a meaningful scale with the NRC funding alone. Consequently, the centre staff made a large effort during 2019 to secure addition external funding for trials.

Organization

The project owner and host institution of the centre is Haukeland University Hospital (HUH), but the work of the centre, both financially and in terms of research activity, is split equally between Haukeland and the University of Bergen (UiB). At the hospital, the centre is attached to the clinic for neurology and neurosurgery (Neurology Clinic), while at the university, the corresponding attachment is to the Department of clinical medicine at the Faculty of Medicine (MED). Additional partners are, Haraldsplass Deaconess Hospital (HDH) in Bergen and Lawson Health Research Institute (Lawson) in Ontario, Canada.

Organizational structure

The Centre is led by Professor Kjell-Morten Myhr (Centre Director and Head for Multiple Sclerosis), Professor Charalampos Tzoulis (Vice Centre Director and Head for Neurodegeneration), and Magnus Alvestad, Head of administration.

The centre has a board with representation from all the partners, and Professor Per Bakke, Dean of Medicine (MED), UiB, as chair. The other board members are Eivind Hansen, Director of HUH, Torhild Næss Vedeler, Director of Neurology Clinic, HUH, Helge Ræder, Vice Dean for innovation, MED, UiB, Kjerstin Fyllingen, Director of HDH, and Dr. David Steven, Lawson.

User council

The council was established and had their first meeting in late 2019. It has representation from all the relevant patient organizations.

Members:
Lise Johnsen (Chair) – MS-forbundet
Trine Lise Corneliussen (vice-Chair) – Parkinsonforbundet
Berit Orheim – Nasjonalforeningen
Gry Caroline Aarnes – Nasjonalforeningen
Gudrun Østhassel – MS-forbundet
Ragnhild Støkket – Parkinsonforbundet
Lise Stousland – ALS Norge
Gry Lien – Alltid Litt Sterkere

Scientific advisory board

A scientific advisory board was established, but did not have a meeting in 2019. Their first meeting was planned during a scientific seminar during the spring of 2020 – but has been postponed due to the Covid-19 pandemics.

Members:
Professor Kailash Bathia, Queen Square Institute, UCLH, London, UK – neurodegeneration
Professor Albert Ludolph, University Hospital of Ulm, Germany – ALS
Professor Xavier Montalban, University of Toronto, Canada – multiple sclerosis
Professor Raymond Koopmans, Radboud University, Netherlands – dementia

Cooperation between the partners

The work is more or less fully integrated at the University of Bergen and Haukeland University Hospital. Many researchers have positions in both institutions, and even those that only have a position at one institution, use resources at the other. Similarly, researchers at other faculties than MED at UiB, are also closely integrated in the centre research-activity

Haraldsplass Deaconess Hospital are focusing on dementia research, in close cooperation with the other institutions, i.e. several PhD candidates at UiB will be doing all of their research at Haraldsplass.

Lawson Health Research Institute are most closely involved in the research related to Parkinson's disease, and cooperate with the other partners in that area. Multiple studies are planned in close cooperation between the partners.

Neuro-SysMed research groups

Improved and tailored therapies for patients with multiple sclerosis

Kjell-Morten Myhr

Myhr is consultant and professor in Neurology, and has since 2001, directed the multiple sclerosis (MS) research group at Haukeland University Hospital and the University of Bergen (https://www.uib.no/fg/kgj-ms). He has previous chaired the first KG Jebsen centre for medical research, focusing on MS-biomarkers (2011-2016), and has since 2019 been the director of the first Norwegian centre for clinical treatment research, Neuro-SysMed.

The MS research group at Haukeland University Hospital and the University of Bergen has a long-standing tradition, since the early 1970s, for clinical epidemiology and immunology research in MS. This include studies of incidence and prevalence, and risk factors in MS, as well as immunological and genetic analysis of blood, cerebrospinal fluid (CSF) or brain tissue. The focus has been on aetiology, prognosis and pathogenesis of the disease.

Along with the introduction of disease modifying therapies in the early 1990s, we have increasingly organized and participated in national and international multicentre randomized clinical trials. This has naturally led into additional research activity focusing on symptom identification and therapy, rehabilitation, patients reported outcome measures, as well as health economy to evaluate the consequences of the disease to the patients, their families and society. Biomarker detection for early diagnosis, prognosis and treatment response for tailored therapy for individual patients is yet another research topic of the group.

The MS research group is highly dedicated for translational research to improve MS care, with a strong focus on treatment trials and biomarker detection.

The group is currently organizing a randomized clinical trial to evaluate the efficacy and safety of autologous haematological stem cell transplantation (HSCT) compared to standard high-efficacy therapies in MS. Haukeland University Hospital is the national centre for such MS-therapy in Norway, and we have recently reported efficacy and safety data from patients that received HSCT prior to the study start.[1]

Another focus of our group has been B-cell depletion as early high-efficacy therapy in MS. Years before B-cell therapy was approved for MS, off label rituximab has been offered MS patients at Haukeland University Hospital. Based on this experience, a non-inferiority study comparing low-cost rituximab to the approved high-cost ocrelizumab is now underway. We have recently reported real world clinical experience of high efficacy and safety from rituximab therapy in relapsing-remitting MS (RRMS).[2]

Other important contributions from our group are milestone articles on axonal transection and cortical pathology in MS.[3-4] Moreover reports of modifiable risk factors in MS, including

vitamin D,[5-6] and bodyweight.[7-8] Importantly, vitamin D and body weight also seem to influence disease progression,[9-11] and therapy response.[12-13]

Biomarkers for prognoses and treatment response are other important contributions from our research group. We, and others, have shown that CSF- and serum levels of neurofilament light chain (NFL) predict long-term prognosis,[14] and ongoing disease activity[15] in MS. More recently, we have presented data indicating that receptor occupancy may influence outcome of the high-efficacy natalizumab therapy in MS.[13]

Symptomatic therapy, rehabilitation, patients reported outcomes measures and health economy have likewise been a prioritized area of research. This will further be integrated in the Neuro-SysMed research activity. We were pioneers in quality of life (QoL) research in MS.[16-17] Reports on physiotherapy rehabilitation,[18] as well as MS-symptoms related to fatigue,[19] sleep disturbances,[20] depression,[21] cognition[22-23] and bladder & sexual dysfunction[24] have been important contributions from our group. Moreover, knowledge of long-terms consequences of the disease for the patients and their family, related to health economy and prognosis are important in the planning of the healthcare services.[25-29]

STAFF

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Trond Riise – MSc, PhD
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Frode S Berven – MSc, PhD

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Hildegunn Gjerald – RN, Urotherapist

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Espen Benjaminsen – MD
Alok Bhan – MD

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Liesbeth Kroondijk – MSc

MS-Registry associates
Håvard Nyhagen Henriksen – MSc
Lars Martin R Skår – Medical student

SELECTED KEY PUBLICATIONS

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Biomarkers and tailored therapies for Parkinson's disease

Charalampos Tzoulis, MD, PhD

Charalampos Tzoulis is Professor of Neurology and Neurodegeneration and Consultant of Neurology at the University of Bergen and Haukeland University Hospital, Norway. He is the Director of the Neuromics Research Group, Head of Neurodegeneration Research and Vice Centre Director at the Neuro-SysMed Centre of Excellence for Clinical Research in Neurological Diseases.

Prof. Tzoulis' clinical expertise includes neurodegeneration, movement disorders, mitochondrial medicine and neurogenetics. His main research focus is neurodegeneration and in particular Parkinson's disease (PD). His research group, "Neuromics" (http://www.neuromics.org/#research), comprises more than 20 members and integrates molecular, computational and clinical neuroscience with the single overarching goal to combat neurodegeneration.

Prof. Tzoulis' work has provided novel insights into the clinical spectrum and molecular pathogenesis of mitochondrial diseases[1–9] and advanced the understanding of how dysfunction in mitochondria, the powerhouses of the cell, is involved in the pathogenesis of Parkinson's disease and other neurodegenerative disorders[10–16]. For Tzoulis, the transition from mitochondrial disorders to PD came with the 2013 discovery that impaired mitochondrial DNA (mtDNA) homeostasis caused by mutations in the mitochondrial DNA polymerase (*POLG*) causes severe degeneration of the dopaminergic *substantia nigra pars compacta* (SNc), similar to that observed in individuals with PD[2,17].

Subsequent work by the Neuromics team showed that mtDNA homeostasis does indeed play a central role in idiopathic PD. They showed that dopaminergic SNc neurons of healthy individuals compensate for the accumulation of age-dependent somatic mtDNA damage, by increasing their total mtDNA copy number. This essential protective mechanism fails in persons with PD resulting in gradual loss of their healthy mitochondrial DNA population. This, in turn, could predispose to energy deficiency, leakage of dangerous by-products and neuronal damage[10]. Further work by Tzoulis' team suggested that aberrant mtDNA homeostasis in PD may be partly mediated by a polygenic risk conferred by rare genetic variation in the genes encoding the mtDNA "homeosome" (i.e. proteins involved in mtDNA replication and repair)[12].

While being an important piece of the puzzle, aberrant mtDNA maintenance is but one of many facets of mitochondrial dysfunction in PD. In 2017, the Neuromics team discovered that deficiency of the mitochondrial respiratory complex I, an established feature in the SNc of individuals with PD, is a widespread - nearly global - phenomenon in the PD brain. Intriguingly, complex I deficiency does not correlate with mtDNA damage suggesting it has a different (mtDNA independent) origin. Moreover, an inverse association between complex I deficiency and α-synuclein pathology suggested that these two pathological hallmarks of PD may be linked.[11]

These findings, along with rapidly accumulating additional evidence by others in the field, place mitochondria at the very centre of the molecular pathogenesis of PD and highlight a central need to increase our understanding of the underlying processes. Inspired by this growing body of evidence, Tzoulis' team has now turned to mitochondria as a therapeutic target in PD.

Indeed, registry-based retrospective epidemiological studies by Tzoulis' team and others show that drugs stimulating mitochondrial biogenesis and function reduce the risk for Parkinson's disease[18–20]. Encouraging as these findings may be, a clinical trial using one of the aforementioned targeting mitochondria failed to produce a clinical effect. Tzoulis believes that this may be due to the vast biological heterogeneity of PD. Preliminary findings by the Neuromics group, suggest that mitochondrial dysfunction may be a central feature in some, but not all, individuals with PD. Thus, it is plausible that only a subgroup of patients would benefit from therapies targeting mitochondria. Detecting subgroup-specific effects in heterogeneous populations requires very large samples, which are typically not feasible in early phase clinical trials. There is therefore an unmet need for biomarkers enabling selection of PD patients with mitochondrial (and other) molecular defects for targeted trials.

Developing and testing mitochondrial therapies as well as biomarkers for patient selection is a central aim of the Neuro-SysMed work led by Prof. Tzoulis. A detailed description of the ongoing and planned work can be found in the section for Parkinson's disease below.

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Motion biomechanics and biomarkers in Parkinson's disease

Mandar S. Jog, MD, FRCPC, FAAN

Mandar S. Jog, MD, FRCPC, is the Director of the National Parkinson Foundation Centre of Excellence in Parkinson Disease and Movement Disorders Program at London Health Sciences Centre, Professor of Neurology at Western University, both in London, Ontario, Canada and one our PIs at the Neuro-SysMed Centre. He is also one of the Associate Directors of the Lawson Health Research Institute.

Prof. Jog trained in Neurology in Toronto and completed a fellowship in movement disorders with Dr. Anthony Lang, followed by a post-doctoral fellowship in Computational Neuroscience at the Massachusetts Institute of Technology (MIT) and a visiting professorship at Stanford Research Institute, CA, USA.

Prof. Jog is an internationally renowned expert in movement disorders, including dystonia, tremor, ataxia and Parkinson's disease, and runs a state-of-the-art centre dedicated to the diagnosis and treatment of patients with these common and debilitating disorders. He is also widely acknowledged as a leader in research and innovation in the fields of movement disorders and neurodegeneration. Prof. Jog's early research advanced the understanding of how neuronal networks function in animal models. He then transferred these findings to the clinic and translated them into novel therapeutic approaches as well as smart technologies to objectify clinical assessment and treatment of patients. His seminal scientific work has made outstanding contributions to improving the care and quality of life of patients with movement disorders.

Prominent examples of Prof. Jog's work include using spinal cord stimulation for gait dysfunction treatment in Parkinson's disease[21], with impressive results, which justifiably attracted the attention of international media:

https://www.lawsonresearch.ca/news/revolutionary-research-helping-patients-parkinson%E2%80%99s-walk-again

In another major scientific and clinical contribution, Prof. Jog and his team established innovative machine learning algorithms improving the outcome of injection therapy for patients with cervical dystonia and tremor[22]. Moreover, Prof. Jog's lab has recently discovered that brain injections with botulinum toxin (a drug that is already in clinical use for other indications) holds potential as a novel treatment alternative for patients with Parkinson's disease and potentially other movement disorders[23]. Furthermore, Prof. Jog's work has led to substantial innovation and commercial value generation, including the establishment of several start-up businesses.

Since 2019, Prof Jog has been a Principal Investigator at our Centre. At Neuro-SysMed, Prof. Jog has a key role in the design and implementation of clinical cohort studies as well as randomized clinical trials for PD, such as the ongoing NO-PARK (ClinicalTrials.gov Identifier: NCT03568968) and NAD-PARK (ClinicalTrials.gov Identifier: NCT03816020) studies. These trials employ innovative approaches for objective patient assessment, which are enabled by technologies developed by Prof. Jog's lab, such as wireless whole-body wearable sensors with accompanying computational algorithms. Moreover, together with Prof. Jog, we are now initiating STRAT-PARK, a large prospective study across London, Ontario and Norway, aiming to stratify PD according to underlying biological mechanisms, so that tailored therapies can be applied. Moreover, we are currently developing a joint fellowship training program in movement disorders across London and Norway.

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Dr. Farid Moshgelani PhD Research Associate
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Dr. Mohammed Almotiri MD Clinical Fellow
Yokesh Tamilselvam (PhD candidate)
Greydon Gilmore (PhD candidate)
Olivia Samotus (PhD candidate)

SELECTED KEY PUBLICATIONS

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2. Samotus, O., Lee, J. & Jog, M. Personalized botulinum toxin type A therapy for cervical dystonia based on kinematic guidance. J. Neurol. 265, 1269–1278 (2018).
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Clinical treatment for ALS

Professor Ole-Bjørn Tysnes

Ole-Bjørn Tysnes is Consultant neurologist in the Department of Neurology at Haukeland University Hospital, and Professor in Neurology at the University of Bergen. He has for many years focused on research in ALS and Parkinson's disease and is PI of the ongoing ParkWest project.

ALS is a fatal neurodegenerative disorder of unknown etiology for which there is no effective treatment. Progressive denervation of neuromuscular synapses in the peripheral nervous system (PNS) and degeneration of upper and lower motor neurons in the central nervous system (CNS) result in muscle weakness, atrophy, paralysis and ultimately death within 2-3 years from the onset of symptoms. Initial presentation of ALS varies between affected individuals, and typically presents as spinal-onset disease (muscle weakness of the limbs), or bulbar-onset disease (difficulty with speech and swallowing). Sporadic ALS (sALS) accounts for 90% of cases and has no clear aetiology, while familial ALS (fALS) accounts for 10% of cases and contains an underlying genetic component. However, while these two forms differ in causation, they appear pathologically and clinically indistinguishable. There is no known cure for ALS. There are two approved medications to treat ALS, riluzole (a glutamate blocker) and edaravone (a free radical scavenger), but with limited efficacy. Riluzole, approved in 1995, is administered orally twice daily and delays time to tracheostomy or death in patients with ALS (Riluzole package insert 2016), prolonging survival by 2-3 months (Miller et al. 2012). Edaravone, approved in the US in 2017, is administered in courses intravenously and shows efficacy in only a small subset of patients with ALS.

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Research group
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Tina Taule, PhD, researcher

National collaborators
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Hilde Nilsen, PhD, professor
Evandro Fei Fang, PhD, researcher

SELECTED KEY PUBLICATIONS

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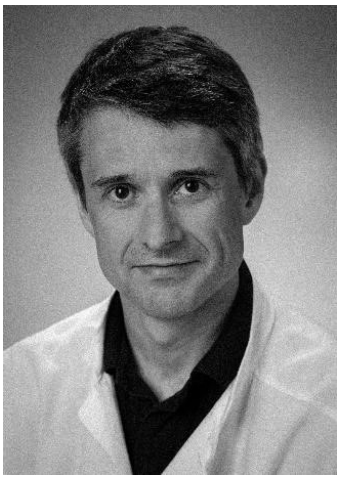
Bergen Dementia Research Group

Kristoffer Haugarvoll



Dr. Kristoffer Haugarvoll is principal investigator (PI) in Bergen Dementia Research Group and consultant neurologist at the Department of Neurology at Haukeland University Hospital.
Dr. Haugarvoll clinical expertise includes neurodegeneration, movement disorders, dementia, and neurogenetics. His main research focus is dementia and neurodegeneration in particular dementia related to the Alzheimer's disease, Dementia with Lewy bodies and Parkinson's disease dementia (PDD) spectrum.

Bergen Dementia Research Group is located at Haraldsplass Deaconess Hospital and Haukeland University Hospital. The group aims at identifying novel biomarkers for dementia and stratifying dementias according to underlying molecular patterns. The research group has a particular focus on Alzheimer's disease and Dementia with Lewy bodies. Furthermore, the group will participate in, and initiate clinical trials on dementia.

GROUP MEMBERS _____

Lasse Giil, MD, PhD – postdoc
Ragnhild E. Skogseth, MD, PhD – physician
Research nurse – being hired
PhD-student – advertised

SELECTED KEY PUBLICATIONS

1. Gaare JJ, Nido GS, Sztromwasser P, Knappskog PM, Dahl O, Lund-Johansen M, MD, Maple-Grødem J, Alves G, Tysnes OB, Stefan Johansson S, Haugarvoll K, Tzoulis C. Rare genetic variation in mitochondrial pathways influences the risk for Parkinson's disease. Mov Disord. 2018 Oct;33(10):1591-1600. PMID: 30256453.
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Elderly and Nursing Home Medicine

Bettina Husebø

Husebø is a professor at the University of Bergen (UiB), Norway, and head of the Centre for Elderly and Nursing Home Medicine (SEFAS) at the Department of Global Public Health and Primary Care (IGS). She is a specialist in anaesthesiology, intensive care, palliative care and nursing home medicine. In 1999, she established (to the best of our knowledge) the first palliative care unit located in a European nursing-home, Bergen Red Cross Nursing Home, aimed to integrate palliative care for the dying old.

In 2012, she initiated SEFAS, UiB, to make education and research in elderly care available for students in medicine, nursing, pharmacology, nutrition, odontology, etc. Her PhD degree (2004-2008) was based on "The Assessment of Pain in People with Dementia;" followed by the postdoctoral project (2008-2011) on "The Effect of Treating Pain on Behavioural Disturbances in People with Advanced Dementia." Currently, she has the responsibility for 18 multidisciplinary researchers at SEFAS. Her research covers epidemiology; method development; placebo-controlled RCT, stepped-wedge or cluster RCTs, and multicomponent intervention studies at home and in the nursing home. The RCN finances most of her projects. Husebø is member of the group for Artificial Intelligence and Machine Learning, UiB and responsible for Innovation at IGS. She is related to EU-COST-Action TD1005 "Pain in People with Dementia". She developed, tested and implemented the Mobilization-Observation-Behaviour-Dementia (MOBID-2) Pain Scale, an international recognized pain tool for people with dementia. Ground-breaking results by the PAIN.BPSD Trial demonstrates that individual treatment of pain significantly improve dementia related neuropsychiatric symptoms. Results are published in *BMJ* and *Nature Neurol Rev*.

Using Norwegian registry data, her team demonstrates in the "HomeDeath" project that almost 40% of home-dwelling patients are sent to hospitals 13 weeks before their death, in Norway. Results from the REDIC trajectory of dying nursing home patients show that staff is unable to identify imminent dying, leading to inadequate treatment, pain and distressing symptoms. The multidisciplinary, multicentre studies (COSMOS and LIVE@Home.Path), are multi-component interventions conducted in nursing homes and at home. Collaboration is established with researchers from UK, Romania, Germany, NL, and oversee. She is working together with Prof Ipsit V. Vahia, Harvard University, McLean; Prof. Rich Fletcher, Massachusetts Institute of Technology (MIT); Prof Heather Allore, Yale University, and Prof Ryuta Kawashima, Tohoku, Japan. Vahia, Nouchi, Achterberg have a visiting professorship at SEFAS. She was invited speaker at TIPS2019 conference, Harvard, on the topic "Re-think Elderly Care in Norway". She is related to the *Lancet Commission for 'Revaluing death'* and regularly invited speaker on national and international congresses. Recently, she published a comprehensive textbook on Elderly Care (Eldreboken ISBN 978-82-450-2178-3) which is textbook for eight different studies (e.g. medicine, nursing, odontology, psychology, nutrition, pharmacy).

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Neuroimmunology – biomarkers

Professor Christian Vedeler

Prof. Christian Vedeler is professor and consultant neurologist. He is an expert in neuroimmunology and is the Director of the Section for Neuroimmunology at Haukeland University Hospital and the research group on paraneoplastic neurological diseases. His team will contribute essential expertise and infrastructure for assessment of biomarkers such as neurofilaments and immune cell profiling at the Mass Cytometry unit at the University of Bergen.

The group is working on a set of important protein, called cerebellar degeneration proteins (CDR1, CDR2, CDR2L) which they have localized to important cell organelles, which are essential for neuronal functions. These proteins are further characterized as potential biomarkers for neurodegenerative diseases.

The group is also working on established biomarkers, such as neurofilament light chain (NF-L) which can be measured in serum samples from patients. NF-L will be used to monitor treatment response and disease progression in neurodegenerative diseases. In collaboration with Department of Medical Biochemistry and Pharmacology the group is now establishing a very sensitive capillary gel electrophoresis method that will be used to further increase the sensitivity and specificity of oligoclonal immunoglobulins in cerebrospinal fluid of patients with multiple sclerosis and other neuroinflammatory diseases. They are also aiming to establish this method to test pharmacological profiles (concentrations and neutralizing antibodies) of biological medications, such as anti-CD20 antibodies, being used to treat patients with multiple sclerosis.

Furthermore, the group works on immune cell profiling (Cytof) and have developed a sensitive method to measure the effect of biological medications used in multiple sclerosis, such as natalizumab. This method can also be employed in the study of other biological medications and to measure their clinical effect, and possible side effects. The group is also investigating the role of microglia activation in neurodegenerative diseases using imaging mass cytometry. This is important to further understand the immunological processes that contributes to neuronal cell death.

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Kristin Nielsen Varhaug, MD
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SELECTED KEY PUBLICATIONS

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Mitochondrial Medicine and Neurogenetics (MMN) group

Professor Laurence Bindoff

Laurence Bindoff is professor and consultant neurologist and leader of the Mitochondrial Medicine and Neurogenetics (MMN) research group. His clinical focus has been within neurogenetics (particularly mitochondrial), muscle disease and neurodegeneration. The MMN group is a clinical and basic research unit primarily devoted to the investigation of mitochondrial disease such as those caused by mutations in POLG, the gene encoding the catalytic subunit of the mitochondrial DNA polymerase, polymerase gamma. We are also interested in the involvement of mitochondria in amyloid-beta homeostasis from our studies focused on PITRM1, a mitochondrial metallopeptidase we showed was involved in a spinocerebellar ataxia/dementia syndrome.

We have established a robust model system to investigate mechanisms involved in disease related to changes in mitochondrial function. Using patient skin cells (fibroblasts) reprogrammed to induced pluripotent stem cells (iPSC), immortal cells with the ability to differentiate into any cell type, we have generated neuronal lineages including dopaminergic neurons, astrocytes and oligodendrocytes and cardiomyocytes.

Our studies show that we can replicate findings such as respiratory chain complex 1 deficiency and mtDNA depletion in neural stem cells (NSC), cells that have been started on the path to neuronal lineage but which retain the ability to divide. Using astrocytes derived from NSC, we have also shown that these cells actively participate in the disease process caused by mitochondrial DNA disease.

Our role in Neuro-SysMed will be to provide expertise in generating stem cell models of disease in appropriate cell lineages (e.g. neuronal or glial). Since mitochondrial pathology is so clearly linked with neurodegeneration, we will continue to focus on mechanisms involved in primary and secondary mitochondrial disease.

GROUP MEMBERS _____

PIs and Senior Researchers
Laurence A Bindoff, MD, PhD
Kristina Xiao Liang, MSc, PhD

Postdoctoral fellow
Yu Hong, Post-doctoral fellow

PhD students
Omar Hikmat, MD
Kristin Nielsen Varhaug, MD
Sepideh Mostafavi, MSc
Cecilie Kristensen, MSc
Anbin Chen, MSc

Master Student
Atefeh Kianian

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Drug screening to identify factors influencing disease risk

Trond Riise

Dr. Riise has a background in mathematics/statistics and works as a professor in epidemiology at the University of Bergen, Norway. His research has been related to epidemiological studies of neurological diseases including Parkinson's disease and Multiple Sclerosis. The focus has been to identify environmental factors that, by their own or in combinations, significantly change the disease risk.

Dr. Riise has an extensive collaboration with researchers at Harvard University, where he was a visiting professor in 2008/09. He is also currently a core Investigator of the Centre for Parkinson Precision Neurology at Brigham and Women's Hospital and Harvard University. Riise has also been a visiting professor at the Universities of Ferrara (2000/01) and Bologna (2014/15), Italy. Riise's international collaborators are key researchers in this Neuro-SysMed project.

GROUP MEMBERS _____

Kjell-Morten Myhr, MD, professor
Jannicke Igland, associate professor
Anne Kjersti Daltveit, professor
Anders Engeland, professor
Julia Romanowska, PhD, bioinformatician
Magne Solheim, statistician, PhD-candidate
Kari Juul, technical staff
Three PhD-candidates (PD, ALS, MS)
Postdoc (Artificial Intelligence) under announcement

National collaborators
Kari Furu, PhD, Senior Researcher, Norwegian Prescription Database, Norwegian Institute of Public Health.
Trygve Holmøy, MD, Professor, Institute of Clinical Medicine, UiO

International collaborators
Clemens Scherzer, MD, Associate Professor of Neurology, Harvard Medical School and Director of the Precision Neurology Program, Brigham's & Women's Hospital and Harvard University.
Xianjun Dong, PhD, Director of Computational Neuroscience, Harvard Medical School, Brigham & Women's Hospital
Alberto Ascherio, MD, Professor, Harvard School of Public Health
Kjetil Bjørnevik, MD, PhD, Research Fellow, Harvard School of Public Health

SELECTED KEY PUBLICATIONS

1. Antonazzo IC, Poluzzi E, Forcesi E, Riise T, Bjørnevik K, Baldin E, Muratori L, De Ponti F, Raschi E. Liver injury with drugs used for multiple sclerosis: A contemporary analysis of the FDA Adverse Event Reporting System. Multiple Sclerosis 2019;25:1633-40.
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Molecular Bioenergetics and Signalling

Mathias Ziegler

Professor Ziegler is a world leading expert on mitochondrial biology and NAD-metabolism and leads the NAD group at the UiB Department of Biomedicine. Metabolic alterations are a hallmark of many diseases. Perturbations of energy metabolism are particularly critical in neurodegenerative processes owing to the impairment of mitochondrial functions often caused by altered mitochondrial DNA homeostasis. Decreased oxidative phosphorylation leads to ATP deficiency, accumulation of reactive oxygen species and depletion of neuronal NAD^+, one of the most critical molecules for bioenergetic conversions and signalling in human cells. Modulation of mitochondrial bioenergetics may be an effective therapeutic strategy to counteract neurodegeneration and drugs boosting mitochondrial biogenesis and function have indeed been associated with decreased incidence of Parkinson's disease and dementia in various independent studies. Based on these findings, we propose that therapies promoting mitochondrial function via replenishing the NAD^+ pool can shield neurons against the neurodegenerative processes and delay disease progression. Nicotinamide riboside (NR) is a well-established precursor, which effectively elevates NAD^+ synthesis and is non-toxic in animals and humans. It is fully approved for human use, has good oral bioavailability, crosses the blood-brain barrier and has been shown to extend lifespan in yeast and to have strong neuroprotective effects in animals. Therefore, we believe that NR is an excellent candidate for correcting NAD^+ deficiency and rectifying the metabolic impairment in neurodegeneration.

Using various cell systems and state-of-the-art metabolomics approaches, we are studying the impact of NAD+ deficiency on major cellular bioenergetics and signalling systems. Recently, we have been able to set up the analytical technologies to measure the NAD^+ metabolome and its dynamics in biological samples. We have established cellular NAD^+ turnover rates in human cell lines and identified metabolic adjustments evoked by chronic NAD^+ deficiency. These measurements require the use of stable isotope-labelled NAD^+ precursors and high-resolution mass spectrometry. We will now extend our efforts and use the developed methodology to analyse the potential metabolic effect of NR supplementation in patients with Parkinson's disease as part of the NAD-PARK and NOPARK clinical studies.

GROUP MEMBERS _____

Høyland, Lena Elise - MSc
Jensen Sverkeli, Lars - MSc
Megias Perez, Roberto - PhD
Niere, Marc - PhD
Strømland, Øyvind - PhD

SELECTED KEY PUBLICATIONS

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Biorecognition

Aurora Martinez

Professor Aurora Martinez leads the Martinez lab, Biorecognition Unit. She is an expert in biophysical investigations of biomolecular interactions and protein stability, applied to inborn errors of metabolism with neurological impairment, mainly parkinsonisms and phenylketonuria. The projects combine biophysical and structural studies of isolated proteins and protein complexes, and assays in appropriated cellular and animal models. The group is also increasing research- and innovation focus on drug discovery and development, and contributes to Nor-Openscreen and EU-Openscreen (Eric and Drive) infrastructure projects for high capacity screening, chemical biology and drug design.

Within Neuro-SysMed the research of the group is integrated in translational projects with the clinical partner groups, focusing on the effect of misfolding mutations on selected targets associated with neurometabolic and neurological disorders, and evaluation and development of specific mechanistic-based therapies.

In the Centre, our group will contribute to the molecular and neuronal level characterization of disease models, investigating phenotypic markers related to proteostasis dysfunction and metabolic and neurotransmitter defects. Specific mechanistic-based therapies will be evaluated and developed. The use of our screening methods and facilities are essential in these projects.

GROUP MEMBERS _____

Ming Ying, MD, PhD. Senior Technician,
Marte I Flydal, PhD, Researcher
Tie-Jun Sten Shi, PhD, Postdoc
Helene Bustad Johannessen, PhD, Postdoc
Svein I Støve, PhD, Postdoc
Fredrik G Johannessen, PhD student
Kunwar Jung KC, PhD student

SELECTED KEY PUBLICATIONS

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Bioinformatics

Inge Jonassen

Inge Jonassen is a professor at the Department of Informatics and head of the Computational Biology Unit, an inter-disciplinary centre for bioinformatics at the University of Bergen. He is also Head of ELIXIR Norway - the Norwegian node of the pan-European infrastructure ELIXIR for biological data. Jonassen has broad expertise within bioinformatics with a focus on methods for the automatic discovery of patterns and regularities in molecular biology data. In the context of Neuro-SysMed, the group will contribute to management and analysis of omics data, and in particular integrated analysis of multi-omics data and application of machine learning approaches. We will apply and develop methods able to integrate and utilize in a joint manner data on multiple levels including genomics, epi-genetics, gene transcription and proteomics to aid in finding sub-classes of patients with similar alterations on the molecular level - and to develop biomarkers that can be used for prognosis and potentially personalized medicine. The focus is initially on Parkinson's disease, but it will also be explored if the methodology that is developed can be applied successfully also to other neurodegenerative diseases studied in the centre.

GROUP MEMBERS _____

Kjell Petersen, senior researcher and technical coordinator ELIXIR Norway
Fatemeh Ghavidel, post-doc
Lilah Toker, post-doc
Dimitrios Kleftogiannis, post-doc
Korbinian Bösl, data management expert (ELIXIR Norway/Digital Life Norway)

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Philosophy of Neurodegeneration

Jan Reinert Karlsen

Jan Reinert Karlsen works as an associate professor at the Centre for the Study of the Sciences and the Humanities, an inter-disciplinary and inter-faculty research unit at the University of Bergen. Through 25% of his position, he is affiliated with Neuro-SysMed. Karlsen is trained as a philosopher (Cand. Philol. (philosophy, 2003) from the University of Bergen, and Ph.D. (medical ethics, 2011) from the University of Oslo).

During the last decade his work has focused on developing and delivering an interdisciplinary teaching and learning design for addressing complex societal questions. The prizewinning work has resulted in the course portfolio 'Major Questions in Research and Society', which currently encompasses seven different course topics (e.g. climate change, artificial intelligence, global health). Karlsen is also heading an interdisciplinary research seminar about suffering which focuses on the reflexive, epistemological and methodological difficulties in theorizing suffering, disease, and health.

The Philosophy of Neurodegeneration group will expand on this work, conducting theoretical and empirical work on the problems of suffering as they emerge and become framed within different perspectives, contexts, and levels of analyses – from the micro-level of disease constructs in research and the clinic, via the lived experience and burdens of patients and next of kin, to the macro-level of neurodegeneration as a complex societal question. Our research will build on and challenge extant theoretical frameworks on suffering within the philosophical tradition of neurology (e.g. Cassell (2004), Canguilhem (1991), Goldstein (1994), Frankl (1959)). Rather than to analyse these levels in isolation from each other, including the theoretical level, we will attempt at connecting them into more holistic approaches by "cross-fertilizing" insights across the different perspectives, contexts, and levels of analyses. While philosophy has a history of building comprehensive perspectives, we believe that the complexity of the issues of neurodegeneration and the degree of specialisation in the sciences studying it, favours a more inclusive approach to its philosophy.

GROUP MEMBERS _____

Caroline Benedicte Nitter Engen, MD, Ph.D.

Berge Osnes, Cand. Psychol., Ph.D.

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Ongoing and planned research

Multiple Sclerosis

Head of research: Kjell-Morten Myhr

About multiple sclerosis (MS)

Multiple sclerosis (MS) is an immune mediated disease of the central nervous system (CNS) characterized by accumulation of widespread inflammatory lesions with demyelination and axonal damage. The disease has huge impact on patients function and quality of life, as well as financially, both for patients and society.

Most patients (85-90%) experience a relapsing-remitting (RRMS) course with repeated episodes of CNS-dysfunction, followed by partial or fully remissions. Nevertheless, if not effectively treated, accumulating disability will usually appear along the disease course, and a substantial proportion will convert to a secondary progressive course (SPMS). The most disabling disease course, primary progressive MS (PPMS), affects about 10-15 % with gradually increasing disability without remission.

Although several genetic and environmental risk factors of MS are identified, the exact pathogenesis of the disease is not yet fully understood. No cure for MS is available, but acute relapses are shortened by courses of high dose methylprednisolone. Increasing numbers of disease-modifying therapies reduce the relapse-frequency and disability progression, most effectively in the early inflammatory phase of the disease. With the development of more effective treatments, the aim of treatment has changed dramatically during the last decades, from simply reducing relapse rates and slowing of disability progression to preventing all evidence of new disease activity.

Early initiation of highly effective therapy may be one way to avoid permanent disability in relapsing MS. Careful risk stratification among the increasing numbers of treatment options, minimize the risk of serious side effects associated to the highly effective drugs. The aim should therefore be that most patients receive the most effective therapy option from onset of the disease.

Tailored symptomatic therapy and rehabilitation to reduce potential disabling symptoms such as spasticity, pain, bladder and bowel dysfunction, depression and improve overall functioning are important as well.

Ongoing MS research at Neuro-SysMed

The aim of Neuro-SysMed related to MS is to improve MS care by;

- Optimize or develop new treatment strategies in MS
- Make new therapies early available for Norwegian patients, preferably through participation in randomized clinical trials
- Define and evaluate biomarkers for early diagnoses, disease classification, prognosis and treatment response to offer tailored treatment for the individual patients

Trial: Autologous hematopoietic stem cell transplantation (HSCT) in MS

Principal Investigator: Lars Bø

A randomized clinical trial for comparing autologous hematopoietic stem cell transplantation (HSCT) versus alemtuzumab in MS (The RAM-MS study)

HSCT is a promising therapy in MS, but limited data from randomized clinical trials (RCTs) are available. A Norwegian HTA confirmed this challenge, and concluded that further studies are needed (https://nyemetoder.no/metoder/autolog-stamcelletransplantasjon). Haukeland University Hospital has been the national centre for such MS-therapy in Norway, and are currently organizing a multicentre, international randomized clinical trial to evaluate the efficacy and safety of autologous HSCT compared to standard high-efficacy therapies in MS (https://clinicaltrials.gov/ & NCT03477500). The trial is multidisciplinary and involves a close collaboration between the department of haematology (investigators Anne Kristine Lehmann and Aymen Ahmed), department of transfusion medicine and immunology (investigator Einar Kristoffersen) and the department of neurology (investigator Øivind Torkildsen).

The objective is to study whether HSCT is a safe and effective therapy in highly active multiple sclerosis compared to standard high-efficacy therapies, and to establish sufficient evidence to support routine use of HSCT in MS.

The primary endpoint of the study is the proportion of patients with no evidence of disease activity (NEDA) after 2 year (96 weeks) and further after 5 year (240 weeks).

Currently, about 40 patients have been enrolled in the study, and during the next years, more patients will be included to a maximum of n=100. Patients from all over Norway are included for screening and randomization at Haukeland University Hospital (HUS). Patients randomized for HSCT are treated at HUS, and those for standard highly active MS-therapy are treated at their local hospitals. Blood sampling, imaging and clinical scoring of the Norwegian patients are performed at HUS. The patients are primarily followed for two years and further for another 3 years in the extension phase of a total of 5 years. Patients are also be recruited at centres in Sweden, Denmark and The Netherlands.

Norwegian web-page: https://helse-bergen.no/ram-ms

SUPPORT _____

Participating Centres

Norway
Haukeland University Hospital, Bergen
Akershus University Hospital, Lørenskog
St Olav's Hospital, Trondheim
The University Hospital Nord-Norge, Tromsø

Sweden
Sahlgrenska University Hospital, Gothenburg,
Uppsala University Hospital, Uppsala

Denmark
Copenhagen University Hospital, Rigshospitalet, Copenhagen
Aarhus University Hospital, Aarhus
Odense University Hospital, Odense
The Netherlands:
VU University Medical Centre, Amsterdam

Funding
KLINBEFORSK
The Regional Health Authority of Western Norway
Norwegian research council, Neuro-SysMed
Haukeland University Hospital

Trial: B-cell depletion therapy in early onset MS

Principal Investigator: Øivind Torkildsen

The Ocrelizumab VErsus Rituximab off-Label at the Onset of Relapsing MS Disease; The OVERLORD-MS study;

B cell depletion therapies (rituximab, ocrelizumab, ofatumumab) are proven highly effective in MS. A very recent Norwegian HTA indicate similar treatment effects from rituximab and ocrelizumab – but clearly, state that more data, preferably from a RCT is needed (https://nyemetoder.no/Documents/Rapporter/disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab-hta-rapport-2019.pdf). Rituximab has been used for the treatment of rheumatologically diseases and haematological cancers since 1998, and due to patency expire, costs only a fraction of ocrelizumab. If rituximab proves to have similar effects as ocrelizumab, it may therefore reduce the annual cost for MS-therapy by several hundred million NOK in Norway alone, and give MS-patients access to highly effective treatment at an earlier time point. In this study, we therefore aim to compare the efficacy and safety of rituximab to ocrelizumab for early treatment in MS.

The objectives of this non-inferiority study are to evaluate if rituximab has comparably efficacy and safety as ocrelizumab in the treatment of newly diagnosed patients with multiple sclerosis.

The primary endpoint of the study is the proportion of patients free of new T2 magnetic resonance imaging (MRI) lesions between month 6 and month 24 (two years).

Currently, the study is evaluated by the Regional Committees for Medical and Health Research Ethics Western Norway, and the application to the Norwegian Medicines Agency is about to be submitted. Scheduled study start is August/September 2020.

SUPPORT

Participating Centres	**Funding**
Haukeland University Hospital, Bergen	KLINBEFORSK
Oslo University Hospital, Oslo	Norwegian research council, Neuro-SysMed
Akershus University Hospital, Lørenskog	Haukeland University Hospital
Stavanger University Hospital, Stavanger	University of Bergen
St Olav's Hospital, Trondheim	Participating hospitals
The University Hospital Nord-Norge, Tromsø	

Trial: Rituximab dose-extension study in relapsing-remitting multiple sclerosis

Principal Investigator: Øivind Torkildsen

B-cell depletion therapy his highly effective in relapsing-remitting MS. Rituximab seems to have similar efficacy and safety profile as ocrelizumab, but data on optimal dosing is limited and largely based on various off-label regimes. The most used dosing regimen in Norway is a single starting dose of 1000 mg infusion, followed by 500 mg infusions every six months for an undefined time. The therapy seems safe, and limited side effects are reported, but neutropenia, hypogammaglobulinemia and infections are the most frequent adverse events. Real world experience indicate that B-cells may be depleted for a longer period of time, even for at least 12 months, and longer dosing intervals than 6 months (i.e. due to intercurrent illness or pregnancy planning) seems safe.

Based on these observations, we aim to investigate if extended dosing interval from 6 to 12 months is safe in relapsing-remitting MS.

We aim to enrol clinical stable patients that have received a standard dose of rituximab in six months intervals for two years. The patients should have CD19 and CD27 cell counts less than 5 % prior to the scheduled 6 months dosing interval during the first two years period. The patients will be randomized for further therapy with the same dose (500 mg) at either 6 months or 12 months intervals.

The objectives of the study are to evaluate if the efficacy of extended dosing of rituximab is similar to the standard six months interval, and if the frequency of neutropenia, hypogammaglobulinemia and infections are reduced.

The primary endpoint of the study is proportion of patients with no evidence of disease activity (NEDA) after 2 years.

Currently, the study protocol is under preparation for submission to the Regional Committees for Medical and Health Research Ethics Western Norway, and the Norwegian Medicines Agency autumn 2020. Estimated study start; Q1, 2021

SUPPORT

Participating Centres
Haukeland University Hospital, Bergen
Other centres in Norway are to be decided

Funding
Norwegian research council, Neuro-SysMed
Haukeland University Hospital
University of Bergen
Participating hospitals

Trial: Mesenchymal Autologous stem cells in progressive multiple sclerosis

Principal Investigator: Lars Bø

Study of Mesenchymal Autologous stem cells as Regenerative Treatment for Multiple Sclerosis (SMART-MS)

There is currently no effective treatment available to promote repair of damage to the central nervous system (CNS), caused by multiple sclerosis (MS), and thereby reverse neurological disability. Mesenchymal stem cells (MSCs) have the potential to induce neuronal repair through multiple neuro-regenerative mechanisms, including remyelination, immunomodulation and stimulation of endogenous cerebral stem cells. In this study, we aim to investigate the potential of regenerative stem cell treatment with MSCs in MS and to increase the understanding of the underlying mechanisms of action.

The objectives of the pilot project are to study if treatment with autologous bone marrow derived MSCs is feasible, safe and promotes neural repair in patients with progressive MS.

Currently, the study is under preparation for submission of the protocol to the Regional Committees for Medical and Health Research Ethics Western Norway, and the Norwegian Medicines Agency autumn 2020. Optimizing of protocols for expanding human MSC in vitro and production (GMP) of MSCs for clinical studies will be performed during autumn 2020. Estimated study start; Q1-2, 2021.

SUPPORT _____

Participating Centres
Haukeland University Hospital, Bergen
Akershus University Hospital, Lørenskog
St Olav's Hospital, Trondheim
The University Hospital Nord-Norge, Tromsø

Funding
KLINBEFORSK
The Regional Health Authority of Western Norway
Norwegian research council, Neuro-SysMed
Haukeland University Hospital
University of Bergen

Trial: Nicotinamide Riboside in Progressive Multiple Sclerosis

Principal investigator: Kjell-Morten Myhr

Evidence suggests that mitochondrial dysfunction occurs in the brain of patients with MS, and may play a particularly important role in the neurodegenerative processes underlying progressive multiple sclerosis (PMS). This mitochondrial dysfunction is predicted to compromise neuronal metabolism and survival, including ATP deficiency and decreased rate of mitochondrial NADH oxidation, leading to depletion of neuronal NAD, one of the most essential molecules for bioenergetic conversion and signalling in human cells. We propose that increase of neuronal NAD levels may improve mitochondrial function and rescue neuronal dysfunction and death in PMS. We therefore aim to investigate if oral nicotinamide riboside (NR), a NAD precursor, can improve neuronal NAD deficiency and mitochondrial dysfunction in patients with PMS.

See section "Therapies targeting mitochondrial dysfunction" below, for more detailed information about mitochondrial dysfunction and nicotinamide riboside (NR)

The objectives are to study if oral nicotinamide riboside (NR) reduce disability progression in PMS, and thus is a novel therapy for this devastating MS disease course.

Currently, the study protocol is under preparation for submission to the Regional Committee for Medical and Health Research Ethics Western Norway, and the Norwegian Medicines Agency autumn 2020. Estimated study start; Q1-2, 2021.

SUPPORT _____

Participating Centres
Haukeland University Hospital
Stavanger University Hospital, Stavanger
Haugesund Hospital, Haugesund
Førde Hospital, Førde

Funding
The Regional Health Authority of Western Norway
Norwegian research council, Neuro-SysMed
Haukeland University Hospital
University of Bergen
Participating hospitals

Research: Genetic susceptibility in multiple sclerosis

Principal Investigator: Stig Wergeland

MS-SEQ - elucidating the genetic susceptibility of multiple sclerosis by whole exome sequencing

The cause of multiple sclerosis (MS) is unknown, but there is strong evidence for involvement of both genetic and environmental factors. There is a clear heritability in MS, but the genes and variants involved are largely unknown. GWAS studies have provided some insight by identifying genetic markers (> 200) associated with a modified risk for MS. These have generally small effects and mark loci rather that specific genes. Therefore, the genes and biological pathways involved remain largely unmapped. To overcome this limitation, we aim to sequence the complete coding genome (exome) of a large cohort of patients and controls and apply sensitive analyses methods to understand the role of common and rare genetic variation in MS. Unlike GWAS studies, our design will allow the direct identification of genes and molecular pathways involved in the disease and therefor help identify novel therapeutic targets. We therefore aim to map the entire coding genome (exome) of 2500 MS patients and 3500 controls to elucidate the heritability of MS
The objectives are to identify novel genetic risks of MS and possible biomarkers for diagnosis and disease progression, and further exploit the obtained insight of disease mechanisms to identify novel therapeutic targets.

DNA samples from about 2500 MS patients in the Norwegian MS Registry and about 3000 controls, mainly from the HUSK-study (https://husk-en.w.uib.no/) will be analysed by whole exome sequencing and data will be available for analyses from Q4 2020. We will then analyse the data for possible novel genetic risks of MS or possible biomarkers for diagnosis and disease progression, and further exploit the obtained insight of disease mechanisms to identify possible novel therapeutic targets.

Currently, the study is approved by to the Regional Committee for Medical and Health Research Ethics Western Norway, and contract for collaboration with HUSK and the exome sequencing providers is finalized.

SUPPORT

Participating Centres
The Norwegian MS Registry
Haukeland University Hospital
University of Bergen

Funding
The Norwegian MS Registry
Norwegian research council, Neuro-SysMed
Haukeland University Hospital
University of Bergen

National and international collaborators in MS

Years of successful MS research have been dependent on extensive local, national and international collaboration. Our network is also important for further research in Neuro-SysMed, and some of our collaborators are listed below:

Professor Jan Lycke, Sahlgrenska University Hospital, Sweden. **Associate Professor Joachim Burman**, Akademiska sjukhuset, Uppsala. **Dr. Morten Blinkenberg**, Copenhagen University Hospital, Denmark. **Professor. Joep Killestein**, VUmc, Amsterdam, Netherlands. **Professor Frederik Barkhof,** VU Medical Center, Amsterdam, Netherlands and University College London, UK. **Professor Minoru Ueda**, University of Nagoya, Japan. **Professor Hubert Schrezenmeier** Institute for Clinical Transfusion Medicine and Immunogenetics Ulm, Ulm, Germany. **Professor Anders Svenningsson,** Karolinska Institutet, Stockholm, Sweden, **Dr. Jeppe Romme Christensen,** Copenhagen University Hospital, Denmark. **Professor Alberto Ascherio**, Harvard School of Public Health, Boston USA. **Dr. Kjetil Bjørnevik**, Harvard School of Public Health, Boston USA. **Professor Maura Pugliatti**, University of Ferrara, Ferrara, Italy. **Professor Christina Wolfson**, McGill University, Montreal, QC, Canada.

Professor Trygve Holmøy, Akershus University Hospital, Lørenskog, **Dr Gro Owren Nygård**, Oslo University Hospital. **Dr. Cecilie Jacobsen**, Stavanger University Hospital. **Dr. Kathrine Lian**, St. Olavs University Hospital, Trondheim. **Associate Professor Margitta Kampman**, University Hospital of North Norway (UNN), Tromsø. **Dr Kritin Lif Breivik**, Førde Hospital, Førde. **Dr Ineke HogenEsch**, Haugesund Hospital, Haugesund.

Parkinson's disease

Head of research: Charalampos Tzoulis

About Parkinson's disease

Parkinson's disease (PD) affects ~1-2% of the population above the age of 65 and its prevalence increases dramatically as the population ages. Available treatments are purely symptomatic and have no effect on disease progression. Thus, patients confront a future of progressive disability, early institutionalization and premature death. PD has a devastating global socioeconomic impact. In Europe alone, PD affects an estimated 1.2 million people and has a cost of €14 billion per year. Since demographic studies show that patient numbers will continue to grow, effectively doubling by 2040, our failure to make any significant impact to halt or delay disease progression means that PD is now a major challenge to health care and society.

Ongoing PD research at Neuro-SysMed

Our PD research at Neuro-SysMed has three primary aims:

- Advance the mechanistic understanding of PD so that new therapeutic targets can be developed
- Address the disorder's vast clinical and biological heterogeneity and develop biomarkers enabling patient stratification for tailored therapies
- Develop and test novel therapies targeting specific molecular pathways

Therapies targeting mitochondrial dysfunction

Mitochondrial dysfunction plays an important role in the pathogenesis of both familial and idiopathic forms of PD. Previous work by the Tzoulis group showed that impaired regulation of neuronal mitochondrial DNA (mtDNA) copy number, partly mediated by polygenic inherited risks, contributes to the injury of dopaminergic neurons in PD. Moreover, mitochondrial respiratory chain deficiency, preferentially affecting the mitochondrial respiratory complex I, is a global event, affecting neurons throughout the brain of patients with PD. This widespread complex I deficiency is predicted to have profound effects on neuronal metabolism and survival, including ATP deficiency and decreased rate of mitochondrial NADH oxidation, leading to a decrease in neuronal NAD^+, one of the most essential molecules for metabolism and signalling in human cells.

NAD exists in an oxidized (NAD^+) and reduced (NADH) form and is the central redox coenzyme in cellular metabolism and critical supplier of energy equivalents to the respiratory chain. Furthermore, NAD^+ acts as a co-substrate for several essential non-redox reactions, including: 1) ADP-ribosylation, playing a central role in signalling and DNA-repair, 2) synthesis of the second messenger cyclic ADP-ribose, involved in the regulation of calcium homeostasis, and 3) acetyl group removal by the sirtuin family of NAD^+-dependent protein deacetylases. By modulating histone acetylation, via the sirtuins, NAD provides a direct link between mitochondrial function, cell metabolism and regulation of gene expression. Moreover, an overall decline in NAD content is observed with age and NAD deficiency has been strongly

linked to a broad spectrum of age-related diseases, including neurodegeneration, inflammation and cancer.

An altered NAD redox ratio with decreased levels of NAD^+ and diminished cellular NAD content can compromise neuronal function and survival, due to a combination of ATP deficiency, impaired DNA repair, altered signalling and dysregulation of histone acetylation leading to aberrant control of gene expression. While NAD levels cannot be reliable measured in *post mortem* brain, ongoing breakthrough research by our group showed that genome-wide histone hyper-acetylation associated with altered sirtuin levels and impaired transcriptional control do indeed occur in the PD brain.

Taken together, these findings nominate NAD supplementation as a potential neuroprotective therapy for PD. In humans, NAD is either produced *de novo* from tryptophan or via salvage pathways from three NAD precursor compounds: nicotinamide, nicotinic acid and nicotinamide riboside (NR). Nicotinic acid is effective in increasing NAD levels and used to treat hyperlipidemias, but its use is limited by painful flushing. Nicotinamide is non-toxic, but inhibits sirtuins and other NAD^+-dependent signalling reactions at high doses. NR is the only known precursor that both effectively boosts NAD synthesis, increases sirtuin activity and is non-toxic in animals and humans. NR may thus have potential as NAD-supplementation therapy in PD and other neurodegenerative disorders.

Inspired by these findings, we are currently conducting a randomized clinical trial, known as the NAD-PARK and NO-PARK studies, to determine whether increasing NAD^+ levels via oral supplementation of nicotinamide riboside in patients with newly-diagnosed Parkinson's disease can ameliorate the disease and/or delay disease progression.

Trial: NAD-PARK

Principal Investigator: Charalampos Tzoulis

We recently completed the NAD-PARK study, a trial of tolerability and cerebral bioavailability of NAD supplementation therapy with NR in PD (ClinicalTrials.gov: *NCT03816020*). A total of 30 individuals with newly diagnosed, drug naïve PD were randomized to NR 500 mg x2/day or placebo for 30 days. The study showed excellent compliance, tolerability and no signs of toxicity or adverse side effects. Intriguingly, phosphorus magnetic resonance spectroscopy (31P-MRS) of the brain showed a highly significant increase in NAD levels in the treatment group compared to the placebo group. Data analyses are ongoing. The current conclusion of the study is that NR is a safe and well-tolerated therapy in PD and leads to substantial NAD supplementation in the brain, the target organ of the disease. Moreover, these results are highly encouraging for the larger NO-PARK study (see next section).

SUPPORT

Participating centres
Haukeland University Hospital

Funding
The Regional Health Authority of Western Norway
Norwegian research council, Neuro-SysMed
Haukeland University Hospital

Trial: NO-PARK

Principal Investigator: Charalampos Tzoulis

To test the potential of NR as a neuroprotective therapy for PD, we will perform NO-PARK (ClinicalTrials.gov: *NCT03568968*), a multi-centre, phase II randomized double-blinded clinical trial, comparing NR to placebo in individuals with early stage PD. The central hypothesis of NO-PARK is that oral administration of the NAD precursor NR can boost neuronal NAD levels and ameliorate mitochondrial dysfunction in PD. This, in turn, will rectify neuronal metabolism and inhibit neurodegeneration, resulting in amelioration of clinical symptoms and delayed PD progression.

Individuals with PD (n = 400) will be recruited starting 01/10/2020 from eight centres across all four health regions of Norway: 1) Haukeland University Hospital (HUS, leading site), Bergen; 2) Akershus University Hospital (AHUS), Akershus, Oslo; 3) Ullevål University Hospital (UUH), Oslo; 4) Rikshospitalet (RH), Oslo; 5) Drammen Hospital (DH), Drammen; St. Olavs University Hospital (St. Olavs), Trondheim; 6) University Hospital of North Norway (UNN), Tromsø; 7) Dr Karen Herlofson Practice and Arendal Hospital (AH), Arendal; 8) Førde Central Hospital (FCH), Førde

After the initial assessment, participants will be randomly assigned to either NR 500 mg x 2/day, or placebo and followed with regular clinical examination, brain imaging and blood tests for a total period of one year. This work aims to discover and develop a therapy with the potential to delay the progression of PD.

The primary objective is **to** determine whether high dose oral NR delays disease progression in PD measured by MDS-UPDRS**. Secondary objectives** include to determine whether high dose oral NR: **a)** Improves and/or prevents specific clinical symptoms in PD (e.g. motor and non-motor symptoms, cognitive symptoms, activity of daily living), **b)** Delays nigrostriatal degeneration (DAT-scan) **c)** Rectifies NAD metabolism and mitochondrial function, **d)** Corrects histone hyperacetylation and gene expression profile

SUPPORT _____

Participating centres/partners

Haukeland University Hospital, Bergen
Akershus University Hospital, Akershus, Oslo
Ullevål University Hospital, Oslo
Rikshospitalet, Oslo
Drammen Hospital, Drammen
St. Olavs University Hospital, Trondheim
University Hospital of North Norway, Tromsø
Dr Karen Herlofson and Arendal Hospital Arendal
Førde Central Hospital, Førde

Funding

The Regional Health Authority of Western Norway
Norwegian research council, Neuro-SysMed
Haukeland University Hospital
Participating hospitals

DECODE-PD – a research initiative to stratify PD and develop tailored therapy

A major bottleneck hindering breakthroughs in PD research is the disorder's biological heterogeneity. Although PD is commonly referred to as a single entity, evidence suggests that it is, in fact, an umbrella term, comprising a spectrum of disorders with overlapping clinical symptoms, but diverse molecular mechanisms. Proposed PD subtypes are defined by largely subjective clinical observations and lack accuracy and reproducibility[14,15]. Without objective molecular markers, drug trials are being conducted on clinically selected PD populations, which are heterogeneous in terms of underlying molecular mechanisms and, therefore, also in their response to treatment.

The main objectives of this bulk of work are to:

1) Resolve the heterogeneous clinical syndrome of PD into molecular subclasses of disease
2) Develop clinically applicable biomarkers for patient subgroup identification and
3) Identify therapeutic targets tailored to each of the emerging disease subclasses.

Towards these goals, we are developing **DECODE-PD**, an integrated translational concept combining and integrating clinical and multi-omic molecular signatures from large patient cohorts with cutting-edge computational methods and artificial intelligence. Being less susceptible to human "mislabelling", **DECODE-PD** has the potential to mitigate the problem of heterogeneity and enable us to identify molecular subclasses of PD. The DECODE-PD research program comprises two major projects: the translational study "ParkOme" and the cohort study "STRAT-PARK" (see detailed description below).

Research: The ParkOme - a multidimensional molecular atlas of PD

Principal Investigator: Charalampos Tzoulis, Inge Jonassen, Kristoffer Haugarvoll

We are currently in the process of establishing the **ParkOme** database, a multidimensional molecular atlas of PD at unprecedented resolution. We are mapping the molecular landscape of PD in key-regions of fresh-frozen *post-mortem* brain (n > 1,000). In each bulk-tissue sample, we are constructing a multilayer molecular map combining the genome, DNA-methylation, selected histone modifications, chromatin accessibility, transcriptome and proteome. To mitigate the confounder of cellular heterogeneity, we are conducting additional studies in single cells using a dual strategy: ***1) High-throughput single-cell analyses***, using our 10X Genomics platform. ***2) Pathology-guided single-cell transcriptomics*** to elucidate the selective neuronal vulnerability to PD-associated pathology such as α-synuclein aggregation, mitochondrial or lysosomal dysfunction.

We will interrogate the ParkOme using a combination of powerful supervised and unsupervised computational analyses (including artificial intelligence). Molecular signatures defining PD and its subclasses will be identified and translated into: **1) Disease models** recapitulating subclasses of human disease. These will be developed and characterized in our cell model workflow (section 2.4), **2) Precision biomarkers** for patient stratification in clinical practice and **3) Therapeutic targets** tailored to the molecular profile of patients. Biomarkers and therapies emerging from this work will trigger clinical studies at the Neuro-SysMed Centre. The ParkOme data analyses are being carried out by the bioinformatics unit of the Tzoulis group in collaboration with Prof. Inge Jonassen and Dr Kjell Petersen at the computational Biology Unit (CBU) of the UiB, and Microsoft.

SUPPORT _____

The Regional Health Authority of Western Norway
Norwegian research council, Neuro-SysMed
Norwegian research council, FRIPRO
Trond Mohn Foundation
Haukeland University Hospital
University of Bergen

Research: Cohort study STRAT-PARK

Principal Investigators: Charalampos Tzoulis, Mandar Jog

The heterogeneity of Parkinson´s disease (PD) is a major obstacle preventing the development of patient-tailored therapies. Here, we aim to stratify PD by identifying and characterizing subgroups of patients with distinct clinical and/or molecular characteristics. Moreover, we aim to develop biomarkers enabling patient stratification in clinical practice.

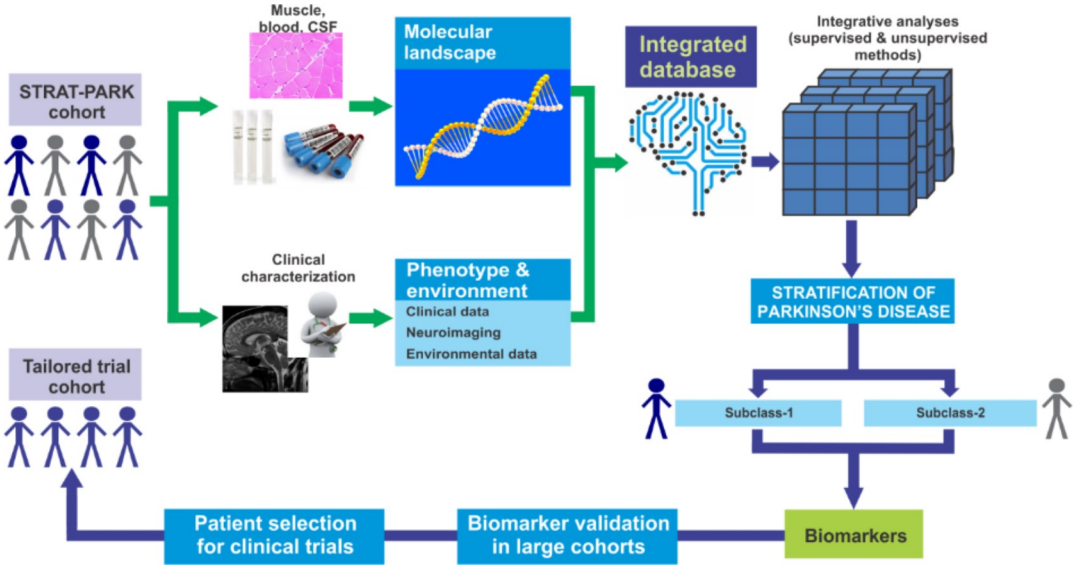


Figure 2: STRAT-PARK

We will establish a population-based cohort from three centres across Norway and Canada. We will follow the cohort yearly and map the longitudinal change of the molecular landscape in clinically accessible tissues of patients and controls. This will elucidate molecular processes implicated in disease initiation and progression and provide an early, crude clustering of patients according to molecular background. Subsequently, we will apply state-of-the-art computational analyses to perform multidimensional integration of our database and identify biomarkers for molecular stratification of PD. Biomarkers will be validated in other appropriate cohorts and assessed for innovation and commercialization potential. Successful biomarkers will enable patient selection for participation in tailored trials.

The STRAT-PARK study represents a vast clinical endeavour, co-led by Neuro-SysMed PIs **Charalampos Tzoulis** in Norway and **Mandar Jog** in Canada. A total of 1,500-2,000 patients and controls will be recruited from three clinical centres: Haukeland University Hospital (HUS) in Bergen, St. Olavs University Hospital in Trondheim and The London Movement Disorders Centre (LMDC), Ontario, Canada. Subjects will be followed at yearly visits with repeated clinical investigations, neuroimaging, blood and cerebrospinal fluid sampling and muscle biopsy. We are particularly interested in the muscle specimens as this is a post mitotic tissue that may express epigenetic, mitochondrial and other molecular markers of disease that are undetectable in blood. As part of our clinical characterization, we will implement novel methods of objective motor assessment using body suits with integrated movement sensors,

implemented in collaboration with co-PI **Prof. Mandar Jog**, who is leading world expert in motion biomechanics for PD and related movement disorders.

SUPPORT _____

Participating centres/partners
Haukeland University Hospital, Bergen
St. Olavs University Hospital, Trondheim
The London Movement Disorders Centre (LMDC), Ontario, Canada

Funding
Trond Mohn Foundation
The Regional Health Authority of Western Norway
Haukeland University Hospital
University of Bergen
Norwegian research council, Neuro-SysMed

Research: Impaired mitochondrial homeostasis as a cell model for neurodegeneration

Principal Investigator: Laurence Bindoff

In projects led by Prof. Bindoff, we have generated cell and mouse models of impaired mtDNA homeostasis. Impaired mtDNA homeostasis due to *POLG* mutations results in the same pattern of mitochondrial dysfunction as seen in the brain with aging and multiple CNS disorders including PD, dementia, ALS and MS. We have induced pluripotent stem cells (iPSC) derived neurons and astrocytes from patients with POLG mutations. By co-culturing these, we will construct a cell model of mtDNA damage in the CNS and use it to screen for compounds that reverse/slow the development of mtDNA abnormalities. Outcome measures will include mitochondrial membrane potential and the amount of TFAM (which reflects the amount of mtDNA/cell) in flow-based assays. In addition to iPSC, we have a mouse model with a neurological phenotype and impaired neuronal mtDNA maintenance due to *POLG* mutations.

Research: User involvement and user-initiated research

Principal Investigators: Magnus Alvestad, Charalampos Tzoulis

The "end-users" in our research are the patients with PD, their families and the health services, all of who will directly benefit from a positive study outcome. Patients/families are regularly updated on the progress of our research and are recruited for our studies via our website, popular and social media, and regular open meetings organized in collaboration with the Norwegian PD association. Together with our head of administration, Magnus Alvestad, our PD team ensures that the projects adhere to the Responsible Research and Innovation (RRI) framework laid down by the Research Council of Norway (as outlined by Stilgoe et al.) and have a major focus on inclusion and active user participation.

A user panel has been assembled comprising a representative of the PD patient association (Ellen Tove Lindblom), and convenes regularly with the following agenda: **1)** Sharing of latest research findings and potential impacts; **2)** Information on upcoming studies and call for participant recruitment; **3)** User input on prioritization of research directions and ethics; **4)** User-initiated research.

Standardized care pathway for PD diagnosis, follow-up and treatment

The project will develop a care pathway that will become active at first contact with the neurology department at Haukeland. It will be built on interviews with patient, family members, and representatives of all the different disciplines involved at the hospital.

The standard care pathway will be based on evidence, but with an opportunity to adjust for the clinical needs and preferences of individual patients. This approach will optimize healthcare for PD by ensuring every task is done efficiently, and without redundancy, and it will create better opportunities for networking and cooperation within and across healthcare institutions and other related assets including the industry.

National and international collaborators in PD research

We are privileged to have an extensive network of national and international collaborators contributing to our PD research. A few of these are listed below:

Prof. Kailash Bathia, Sobell Department of Movement Neuroscience at the Institute of Neurology, UCL, Queen Square, London, UK. **Prof. Nikolaos P. Daskalakis**, McLean Hospital/Harvard Medical School, Massachusetts, USA. **Dr Lara Kular**, Karolinska Institute, Stockholm. **Prof. Leonidas Stefanis,** University of Athens, Greece. **Prof. Gabor G. Kovacs** currently works at the University of Toronto, Canada.

Prof. Mathias Toft, Oslo University and Ullevål University Hospital. **Prof. Christofer Lundqvist**, Akershus University Hospital (AHUS), Oslo. **Dr. Kari Anne Bjørnarå**, Drammen Hospital (DH), Drammen. **Prof. Jan Aasly**, St. Olavs University Hospital (St. Olavs), Trondheim. **Prof. Hallvard Lilleng**, University Hospital of North Norway (UNN), Troms. **Dr Karen Herlofson** private practice and Arendal Hospital (AH), Arendal. **Dr Stig Hegrestad**, Førde Central Hospital (FCH), Førde.

ALS

Head of research: Ole-Bjørn Tysnes

Amyotrophic lateral sclerosis (ALS) is a devastating progressive neurological disorder with a mean survival of only 3 years from symptom onset. With the exception of Riluzole, there is no effective treatment and patients face a future of progressive disability and premature death. In Norway the yearly cost in advanced ALS is 4-8 mill NOK/patient.

Recent research by us and others indicates that boosting the activity of the histone deacetylate enzymes known as sirtuins, via a combination of nicotinamide riboside (NR) and pterostilbene, has neuroprotective effects in ALS and may delay clinical disease progression. Based on these preliminary findings, we hypothesize that oral administration of combination therapy with NR and pterostilbene will inhibit neurodegeneration and increase survival and quality of life in patients with ALS.

Trial: NO-ALS

Principal Investigators: Ole-Bjørn Tysnes, Charalampos Tzoulis

To test the potential of NR as a neuroprotective therapy for ALS, we will perform NO-ALS, a multi-centre, phase II randomized double-blinded clinical trial, comparing combined oral NR and pterostilbene to placebo in early ALS. Based on power estimations, a total of 180 patients will be recruited nation-wide.

This project is entirely novel and has the potential to discover a therapy modulating disease activity and progression in ALS, thus vastly improving patient care and prognosis.

We plan to start inclusion of patients from September 2020.

SUPPORT _____

Participating Centres
Haukeland University Hospital, Bergen
Akershus University Hospital, Lørenskog
Other Norwegian hospital

Funding
The Regional Health Authority of Western Norway
Norwegian research council, Neuro-SysMed
Haukeland University Hospital
University of Bergen
Participating hospitals

Dementia

Head of research: Kristoffer Haugarvoll

About dementia research

Alzheimer's disease causes 50-70% of all dementias and is a leading cause of mortality. The prevalence of Alzheimer's disease is about one percent at age 65 and increases dramatically to between 20-50% in those older than 85 years. The pathological hallmarks of Alzheimer's disease are extracellular accumulation of amloid β (Aβ) peptide in the brain ("senile plaque" SP) and by intraneuronal accumulation of hyper-phosphorylated tau protein in neurofibrillary tangles (NFT). This is accompanied by synaptic and neuronal losses. Neuropathological criteria of Alzheimer's disease are based on density and distribution of SP and NFT in the brain. Thus, the pathological diagnosis is Alzheimer type pathology, while the diagnosis of dementia relies on clinical information. Lewy body disease are other common dementias, which present themselves clinically as Dementia with Lewy bodies or Parkinson disease dementia (PDD). There is commonly a large degree of overlapping Alzheimer's disease and Lewy body pathology in demented individuals.

Research – Cohort study: STRAT-DEM

Principal Investigator: Kristoffer Haugavoll

Key knowledge gaps both nationally and internationally are our limited understanding of the etiology and molecular pathogenesis of dementia. These mechanisms need to be elucidated in order to identify novel therapeutic targets that can prevent disease progression. Furthermore, better biomarkers dementia diagnosis and progression need to be identified. Biomarkers would be of particularly high value in dementia as neurodegeneration is already advanced at the time of clinical diagnosis. Furthermore, biomarkers are necessary to provide surrogate endpoints to evaluate the clinical efficacy of new neuroprotective therapies. Hence, biomarkers are pivotal to identify patients with prodromal dementia that may be ideal candidates for neuroprotective therapies.

The dementia cohort study will start during 2020 and aims at identifying molecular processes that are relevant across sub-groups of dementia and processes that can help stratify dementia into sub-groups that reflect underlying biology. The central hypothesis in this project is that converging molecular pathways exist across subtypes of dementia, but also that there are underlying subtypes that may not be fully reflected in the current classification system of dementia. We will identify biological overlap and disease subtypes, based on a transdisciplinary approach integrating cognitive testing, clinical investigations, neuroimaging and molecular biomarkers. Thus, this approach will enable us to reclassify and stratify Dementia according to underlying biological patterns. Our overarching objective is to establish a cohort with multidimensional data that can be integrated in order to the complex clinical and biological spectrum of in Dementia and stratify it into subclasses with homogeneous biology and prognosis. This knowledge will then be used to develop diagnostic and prognostic biomarkers and identify novel therapeutic targets. Secondary objectives include: 1) Establish and characterize the Dementia cohort, a population-based dementia cohort focusing on AD

and DLB; 2) Elucidate genome-wide epigenetic and transcriptomic signatures associated with Dementia; 3) Establish an objective molecular classification system for Dementia; 4) Develop precision biomarkers for accurate molecular diagnosis and patient stratification in clinical practice. Professor Dag Årsland is a collaborator in this study.

FUNDING _____

The Regional Health Authority of Western Norway
Norwegian research council, Neuro-SysMed
Haraldsplass Deaconess Hospital
Haukeland University Hospital
University of Bergen

Bergen Dementia Research Group will also be a partner in the planned ANeED Study, headed by Associate Professor Arvid Rongve at Helse Fonna. This is a phase IIa multicentre randomized controlled double blind clinical trial to demonstrate clinical efficacy on cognitive, neuropsychiatric and functional outcomes of Ambroxol in New and Early patients with prodromal and mild Dementia with Lewy bodies.

Drug screening to identify factor influencing disease risks and to nominate novel therapies

Head of research: Trond Riise

The "drug-screening" project involves screening of all prescriptions given to all Norwegians since 2004. These prescriptions (about 800 mill) are linked to the incidence of Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). The overall objective of the project is to evaluate whether existing drugs (molecules) can be repurposed as effective treatment of PD, ALS and MS.

The commonly used model when developing new medical treatment is the so-called translational research approach where findings in basic science experiments are transferred to clinical medicine by combining resources, expertise and techniques within various fields in a highly interdisciplinary manner. A limitation to this approach is that it is dependent on existing hypotheses and knowledge on disease mechanisms for the first phase in basic sciences experiments. Furthermore, findings in animal models may not be directly relevant for human disease, and studies comparing the representativeness of animal models for human disease show overall poor results. We are addressing these limitations by introducing an initial screening phase in humans that will form the basis for new hypotheses that in a second phase will be tested and validated in mechanistic experiments using human iPSC-derived neurons and animal models. This approach might be referred to as "inverse translational research" and represents a novel use of Norwegian health registries.
We are currently evaluating whether use of any of the 1600 drugs used in Norway are associated with a decreased – or – increased risk of developing PD, ALS or MS. In a second phase of the study, we will perform several sub-studies of the most promising drugs including studying the effect of doses and time between the use of these drugs and time of diagnosis of PD, ALS or MS. The aim of these analyses is to disclose whether the associations we find are caused by these patients using these drugs because of their neurological disease or whether the association reflects a real change in risk for developing the diseases. Finally, for the resulting list of candidate drugs we want to do a validation study using experimental models at a molecular level in collaboration with world leading basic research environments.
Drugs that are validated in all three phases of the study are likely to represent reliable and plausible biological mechanisms relevant for the disease. As these drugs have a known safety profile, the results from this study could form a direct basis for phase-II clinical studies in humans. This could lead to novel treatment that may benefit those affected by diseases in considerable shorter time than in a more traditional drug development approach.

FUNDING _____

Norwegian research council, Neuro-SysMed
University of Bergen
Michael J. Fox foundation
Norwegian Research Council, FRIPRO

Systems Medicine

Head of research: Charalampos Tzoulis

Participating PIs: Charalampos Tzoulis, Kjell-Morten Myhr, Mandar Jog, Kristoffer Haugarvoll, Ole-Bjørn Tysnes, Christian Vedeler, Laurence Bindoff, Inge Jonassen, Mathias Ziegler, Aurora Martinez, Trond Riise.

The concept of systems medicine in neurology is the backbone of the Centre. As we are collecting a wealth of data from our ongoing clinical studies, we are gradually constructing a **clinical pipeline** to: 1) screen, recruit and systematically assess patients, 2) assign patients to appropriate experimental treatment protocols that most closely matches their disease profile, and 3) precisely monitor treatment effects and outcomes. This will enable patients, and their caregivers, to receive tailored/personalized treatment as well as the opportunity of participating in cutting-edge clinical research. Using machine-learning models, we will develop specific and sensitive biomarker systems to enable and refine early and precise diagnosis, stratification and prediction of treatment response. The concept is schematically represented in Figure 3.

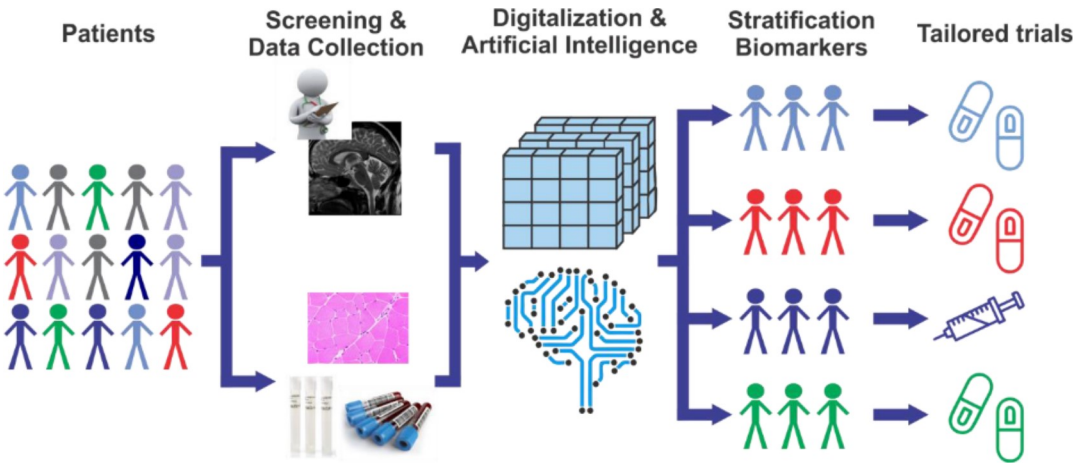


Figure 3: Neuro-SysMed pipeline

(1) Patients from all of Norway will enter via our neurological clinical trial unit (NCTU). Our Neuro-SysMed pipeline will systematically characterize patients using routine and experimental examinations. **(3)** Based on the initial assessment, patients are nominated for standard or experimental intervention (trial of therapy or care-based study). These will be implemented either locally at the Centre, the patient's local or regional hospital, or abroad as appropriate. **(4)** Screening packages will be performed at inclusion, during follow-up and after study period. **(5)** Trial outcomes are registered and fed into the Neuro-SysMed database. **(6)** Machine learning algorithms are trained and validated against our database in order to generate future biomarkers for patient stratification, treatment selection and monitoring. The systems medicine unit is highly integrated with our one-stop-shop NCTU. Together these tasks support the clinical trials and biomarker discovery.

Early in the process of planning the centre, it became clear that the IT tools to realize the centre's vision within systems medicine was not available. To meet this essential need, an innovation project was initiated by Neuro-SysMed in collaboration with the regional IT department, Microsoft and CAP Gemini, to establish a platform for storage and high throughput data analysis in the Azure cloud. This platform will host the wealth of data generated by Neuro-SysMed as well as the tools required for basic and advanced computational analyses and high-dimensional integration of data. We are planning to publish both our methodological approach and our results in this work, and encourage others to apply similar solutions in the management of other complex diseases. This work has already attracted substantial attention from other research groups and the Research Council of Norway.

The Neuro-SysMed Laboratory

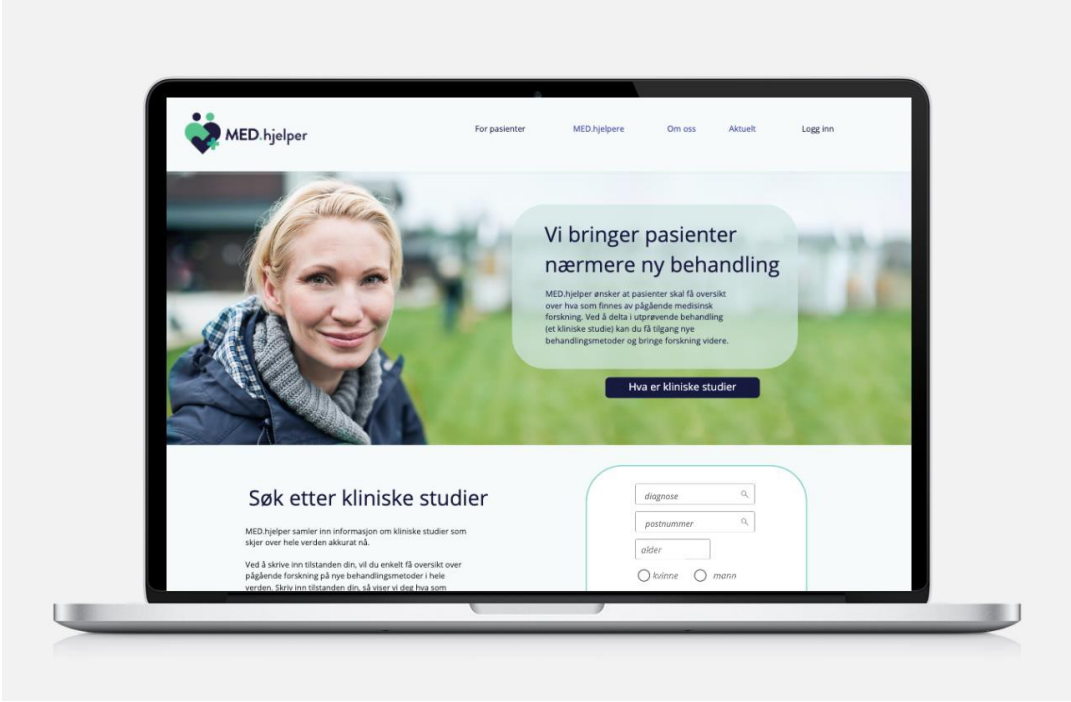
Head: Charalampos Tzoulis
Manager: Hanne Linda Nakkestad

Haukeland University Hospital has invested major resources into establishing a brand-new laboratory for the exclusive use of the centre. The Neuro-SysMed lab comprises state-of-the art facilities for biobanking, biosa mple processing, neuropathology, genomics, single-cell analyses, cell-culture, biomarker identification and development. A dedicated bioinformatic unit provides cutting edge in house computational analyses with a major focus on multi-omics. The area also includes office space and meeting rooms for research group members. When open, in early 2020, the lab will support and accelerate our work, especially related to genomics and cell models.






Innovation



Project manager: Tone Skår

In cooperation with the technology transfer office of western Norway (VIS), the centre has worked on designing MED.hjelper, an online solution to make it easier for patients and their supporters to identify and join appropriate clinical trials. This will be useful for the centre to improve our recruitment to trials, but we are building a solution that will work for all trials and all diseases.

In 2019, we presented the project a number of times, to different audiences:

- The Neuro-SysMed User council
- The Haukeland Open Innovation Day
- The CCBIO course “Clinical Trials in Cancer Research”
- Bergen Design Festival, under the “Design for better health” topic
- Alrek Health Cluster, topic group for “e-health and innovation”
- Nansen NeuroScience Network
- LMI (Legemiddelindustriforeningen)

In addition to funds from the centre, external funding has already been secured for this project, from VIS and Sparebanken Vest, and we expect to have a business case and further financing in place during 2020. In December, we started preparing an application to DAM Stiftelsen in cooperation with Nasjonalforeningen.

International cooperation

Lawson Health Research Institute in Canada is the centres only foreign partner. Lawson contributes with their competence, especially in the centre work on Parkinson's disease. Additionally, the cooperation gives the centre the opportunity to recruit Canadian patients to our studies. In 2020, we will apply for external financing to expand our cooperation with Lawson.

Recruitment

Beyond the applicants and the PIs, some key personnel were recruited in 2019:

Magnus Alvestad – administrative manager
Christian Dölle – senior molecular scientist with a focus on mitochondrial metabolism in neurodegeneration

The centre also started recruiting for a number of positions in 2019, where contracts will be signed during 2020:

- Research advisor
- Data manger
- 3 Study nurses
- Study coordinators
- Several PhD and Post Doc positions
- Several Researchers

Communication / dissemination

The opening of the centre was widely covered, both in general media and in the medical specialist press. We have registered at least 24 articles. Centre researchers published 19 articles, reports, conference presentations etc. as well as 2 scientific publications, in 2019. The centre also established a presence on Facebook, Twitter and other social media, and published a number of shorter articles there, relating to issues with public interest. Over 500 people follow the centre on Facebook.

Institutions

- Helse Bergen: https://helse-bergen.no/nasjonal-kompetansetjeneste-for-multippel-sklerose-ms/millioner-til-nytt-forskningssenter-for-klinisk-behandling-av-hjernesykdommer-neuro-sysmed
- Norges parkinsonforbund: https://parkinson.no/aktuelt/nytt-forskningssenter-i-hordaland
- UiB: https://www.uib.no/med/130503/åpning-av-neuro-sysmed og https://www.uib.no/med/130743/åpnet-nytt-hjerneforskningssenter
- Haraldsplass: https://www.haraldsplass.no/om-haraldsplass/nyheter/nytt-forskningssenter-for-nevrologiske-sykdommer
- VIS: https://www.visinnovasjon.no/2018/11/norways-first-research-center-for-clinical-trials/
- Regjeringen: https://www.regjeringen.no/no/aktuelt/helseministeren-apner-neuro-sysmed/id2673748/ og https://www.regjeringen.no/no/aktuelt/nytt-hap-for-flere/id2674657/
- Helsebiblioteket: https://www.helsebiblioteket.no/omsorgsbiblioteket/nyheter-og-aktuelt/apnet-neuro-sysmed-i-bergen
- Helse Stavanger: https://helse-stavanger.no/seksjon/NKB/Documents/Move_1-19_Digitalt.pdf

Organizations

- Hjernerådet: http://www.hjerneradet.no/?page_id=27043 and http://www.hjerneradet.no/?page_id=27891
- Parkinson-foreningen: https://www.youtube.com/watch?v=R-ih_u-YFcA og https://parkinson.no/aktuelt/nytt-forskningssenter-i-hordaland
- ALS Norge: https://www.alsnorge.no/2019/08/26/24-08-2019-nytt-forskningssenter-neuro-sys-med-bergen-apner-offisielt-17-oktober-2019/
- Mohn Foundation: https://www.mohnfoundation.no/gratulerer-charalampos-tzoulis/
- Stiftelsen K G Jebsen: https://stiftkgj.no/2019/10/21/gratulerer-kjell-morten-myhr/
- Uniforum (UiO): https://www.uniforum.uio.no/notert/2018/uib-far-nasjonalt-senter-for-hjernesykdommer.html
- MS-foreningen: https://www.ms.no/nyheter/nytt-forskningssenter-for-kliniske-forsoek as well as references in the yearly reports of both 2018 and 2019

Media

- Dagens Medisin: https://www.dagensmedisin.no/artikler/2019/10/17/apnet-neuro-sysmed-i-bergen/ and https://www.dagensmedisin.no/blogger/anette-storstein/2019/10/16/apningen-av-neuro-sysmed-er-viktig-for-hele-hjerne-norge/
- VG: https://www.vg.no/nyheter/i/rA5ddR/aapner-nytt-forskningssenter-i-bergen-slik-skal-de-loese-als-gaaten
- NRK Hordaland: https://www.nrk.no/hordaland/nytt-senter-skal-forske-pa-demens-1.14745602
- Wikipedia: https://no.wikipedia.org/wiki/Neuro-SysMed
- Bergens Tidende: https://www.bt.no/nyheter/lokalt/i/qLEM0L/nytt-hjernesenter-gir-cathrine-haap
- På Høyden (UiB): https://pahoyden.no/demens-forskningsradet-klinisk-forskningssenter/uib-far-nasjonalt-senter-for-hjernesykdommer/383456
- Forskning.no: https://forskning.no/aldring-om-forskning-sykdommer/slik-forsoker-forskere-a-lose-als-gaten/1574322

Opening

The opening of the centre was a two-day event. The morning-session of the 17th of October, included a seminar with the user organizations focusing on research prioritization. The formal opening of the Neuro-SysMed by the Norwegian Minister of Health followed the lunch. The second day, 18th of October, focused on research plan discussions with participation from Neuro-SysMed researchers, national research collaborators and representatives from the user organizations (see detailed program below).

Åpning 17. og 18. oktober 2019

Scandic Hotel Norge, Bergen

Vi samles i konferanseområdet, gå inn hovedinngangen og opp trappen til venstre

17. Oktober 2019 -- før lunch: samtale med brukerorganisasjonene om forskningsprioritering

09:00	**Praktisk om senterets organisering** Kjell-Morten Myhr Charalampos Tzoulis Magnus Alvestad
09:15	**Senterets prosjekter, kompetanse, erfaring og infrastruktur** Kjell-Morten Myhr Charalampos Tzoulis Ole-Bjørn Tysnes Christian Vedeler Kristoffer Haugarvoll Bettina Husebø Laurence Bindoff
10:15	Pause
10:30	**Tilbakemeldinger og spørsmål fra brukerorganisasjonene**
11:00	Lunsj (egen påmelding)

17. Oktober 2019 -- etter lunch: formell åpning

12:15	Uformell prat i konferanseområdet
12:30	**Velkommen** Kjell-Morten Myhr, direktør Neuro-SysMed
12:50	**Kunstnerisk innslag**
13:05	**Innledning om behov og forventninger fra et brukerperspektiv** Magne Wang Fredriksen, generalsekretær Norges Parkinsonforbund
13:15	**Åpning** Bent Høie, helseminister
13:25	**Neuro-SysMed** Kjell-Morten Myhr og Charalampos Tzoulis, direktør og vise-direktør Neuro-SysMed
13:40	**Hva ønsker og hva forventer Forskningsrådet?** Anne Kjersti Fahlvik, områdedirektør, Norges forskningsråd
13:50	PAUSE
14:05	**Sykehuset som vertskap** Eivind Hansen, administrerende direktør Haukeland Universitetssjukehus
14:15	**Universitetet som hovedpartner** Dag Rune Olsen, rektor Universitetet i Bergen
14:25	**Nærhet til det kliniske arbeidet** Torhild Vedeler, klinikkdirektør Nevroklinikken, Haukeland Universitetssjukehus
14:35	**Senterets betydning for medisinsk forskning ved UiB** Per Bakke, dekan Det medisinsk fakultet, Universitetet i Bergen
14:45	**Haraldsplass som partner i demens-forskningen** Kjerstin Fyllingen, administrerende direktør Haraldsplass Diakonale Sykehus
14:55	**Hjerneforskning i et nasjonalt hjernehelse-perspektiv** Anette Storstein, styreleder Hjernerådet
15:05	PAUSE
15:20	**Universitetssykehusenes samarbeid med senteret (5 min hver)** Hanne Flinstad Harbo, avdelingsleder Nevrologisk avdeling, Oslo Universitetssykehus Tormod Flatby, avdelingsleder Nevroklinikken, Akershus Universitetssykehus Geir Bråten, klinikksjef Nevroklinikken, St. Olavs Hospital Margitta Kampman, overlege Nevrologisk avdeling, Universitetssykehuset i Nord-Norge Elisabeth Farbu, klinikksjef klinikk for Hode-hals og rehabilitering, Stavanger Universitetssjukehus
15:45	**Brukerorganisasjonenes deltagelse i senteret** Mina Gerhardsen, generalsekretær nasjonalforeningen for folkehelsen
15:55	**Kunstnerisk innslag**
16:10	**Avslutning** Kjell-Morten Myhr, direktør Neuro-SysMed
18:00	Uformell prat i barområdet i hotellets 3. etasje
19:00	Middag i hotellets restaurant (egen påmelding)

18. Oktober 2019 – faglig seminar

09:00	**Velkommen** Charalampos Tzoulis
09:10	**Innledning multippel sklerose** Kjell-Morten Myhr
09:30	**Uløste utfordringer ved MS - hvordan kan vi bidra?** Trygve Holmøy, seksjonsoverlege Nevroklinikken, Akershus Universitetssykehus
09:50	**RAM-MS** Øivind Torkildsen, overlege Nevrologisk avdeling, Haukeland Universitetssjukehus Lars Bø, leder, Nasjonal kompetansetjeneste for MS
10:00	**Brukermedvirkning MS** Lise Johnsen, styreleder MS-forbundet
10:10	**Diskusjon**
10:30	PAUSE
10:45	**Innledning Parkinson's Sykdom** Charalampos Tzoulis
11:05	**Innlegg om forskningsstatus for Parkinson's Sykdom** Mathias Toft, professor og overlege, Oslo Universitetssykehus
11:25	**NAD-PARK** Brage Brakedal, lege Nevrologisk avdeling, Haukeland Universitetssjukehus
11:35	**Brukermedvirkning Parkinson's Sykdom** (navn kommer), Parkinsonforbundet
11:45	**Diskusjon**
12:05	Lunsj
12:50	**Innledning ALS** Ole-Bjørn Tysnes, overlege og professor, Neuro-SysMed
13:10	**ALS – hva kan genene fortelle oss?** Helle Høyer, overingeniør Seksjon for medisinsk genetikk, Sykehuset Telemark
13:30	**NO-ALS** Ole-Bjørn Tysnes, overlege og professor, Neuro-SysMed
13:40	**Brukermedvirkning ALS** Lise Stousland, forfatter og nestleder ALS Norge Cathrine Nordstrand, styremedlem ALS - Alltid Litt Sterkere Gry Lien, styremedlem ALS – Alltid Litt Sterkere
13:50	**Diskusjon**
14:10	PAUSE
14:25	**Demens** Kristoffer Haugarvoll, overlege, Neuro-SysMed
14:45	**Dementia Disease Initiation** **Nasjonalt initiativ for tidligdiagnostikk og intervensjon ved demens** Tormod Fladby, avdelingsleder Nevrologisk avdeling, Akershus universitetssykehus
15:05	**Studie** Bettina Husebø, professor Institutt for global helse og samfunnsmedisin, Universitetet i Bergen
15:15	**Brukermedvirkning Demens** Gry Caroline Aarnes, prosjektleder Nasjonalforeningen for folkehelsen
15:25	**Diskusjon**
15:45	**Avslutning** Kjell-Morten Myhr

Appendix 1: Personnel

Administration
Magnus Alvestad
Liv-Rebecca Arnedatter Aae
Beate Flood

Key researchers
Kjell-Morten Myhr
Charalampos Tzoulis
Ole-Bjørn Tysnes
Laurence Bindoff
Christian Vedeler
Kristoffer Haugarvoll
Bettina Husebø
Trond Riise
Inge Jonassen
Kjell Petersen
Jan Reinert Karlsen
Aurora Martinez
Christian Dölle
Lilah Toker

Other researchers
Lars Bø
Øivind Torkildsen
Stig Wergeland
Jan Aarseth
Tori Smedal
Sonia Gavasso
Anne Britt Runhovde Skår
Randi Haugstad

Postdoctoral researchers with external financial support
Gonzalo Nido
Irene Flønes
Birgitte Berentsen
Nina Grytten Torkildsen

PhD students with external financial support
Gia Tuong Thi Tran
Thomas Schwarzlmuller
Brage Brakedal
Johannes Jernqvist Gaare
Nelson Osuagwu
Romain Guitton
Fiona Dick
Janani Sundaresan
Gerd Haga Bringeland
Hilde Torgauten
Ellen Skorve
Hilde Norborg
Kristin Wesnes
Silje Stokke Kvistad

Appendix 2: Funding and expenses

Funding

In 2019, the centre received 2 303 359 NOK in funding from the Norwegian Research Council. The contribution from Haukeland University Hospital was 1 613 101 NOK, from the University of Bergen 1 013 931 NOK and Lawson 51 900 NOK. Haraldsplass Deaconess Hospital did not contribute to the funding in 2019. Total funding was 4 395 724 NOK.

Expenses

Haukeland University Hospital spent 1 463 996 NOK on personnel, 300 365 NOK on buying research services, 251 762 NOK on equipment and 682 126 NOK on other costs running the centre, in total 2 698 249 NOK. The University of Bergen spent 1 150 806 NOK on personnel, 310 455 NOK on other running costs, in total 1 461 261 NOK. Lawson spent 236 214 NOK on personnel costs. Haraldsplass Deaconess Hospital did not have expenses in 2019. Total expenses were 4 395 724 NOK.

Appendix 3: Publications and presentations

Lectures-2019

Lecture presentation by Kjell-Morten Myhr and Charalampos Tzoulis at Nevrodagene 2019: "Use of system medicine to change Norwegian neurology"

Lecture presentation by Kjell-Morten Myhr at Post ECTRIMS Seminar, Oslo 2019: "Preparing for clinical MS studies in Norway"

Lecture presentation by Kjell-Morten Myhr at MS HINAS LIS-MS meeting 2019: "The Rituximab vs Ocrelizumab trial"

Lecture presentation by Kjell-Morten Myhr at Brain health conference 2019: "How to ensure national recruitment in clinical trials"

Lecture presentation by Ole-Bjørn Tysnes at ALS NO-AGE conference 2019: "NO-ALS: a randomized clinical trial of nicotinamide riboside "

Lecture presentation by Charalampos Tzoulis at NO-AGE conference 2019: "NO-PARK: a randomized clinical trial of nicotinamide riboside for Parkinson's disease"

Lecture presentation by Charalampos Tzoulis at the Scandinavian-German meeting for Parkinson's disease: "Aberrant histone acetylation and decoupling from transcription in Parkinson's disease"

Lecture presentation by Inge Jonassen at the 4th Disease Maps Community Meeting (DMCM2019): «Analysis of multi-omics data to improve the understanding of Parkinson's disease»

Articles - 2019

Nystad AE, Lereim RR, Wergeland S, Oveland E, Myhr KM, Bø L, Torkildsen Ø. Fingolimod downregulates brain sphingosine-1-phosphate receptor 1 levels but does not promote remyelination or neuroprotection in the cuprizone model. J Neuroimmunol 2020;339:577091. doi: 10.1016/j.jneuroim.2019.577091. Epub 2019 Oct 31. PubMed PMID: 31739156.

Olberg HK, Eide GE, Vedeler CA. Can serum GAD65 antibody levels predict neurological disease or cancer? J Neuroimmunol 2019;336:577025. doi: 10.1016/j.jneuroim.2019.577025. PubMed PMID: 31472399.

Kråkenes T, Herdlevaer I, Raspotnig M, Haugen M, Schubert M, Vedeler CA. CDR2L Is the Major Yo Antibody Target in Paraneoplastic Cerebellar Degeneration. Ann Neurol 2019;86:316-321. doi: 10.1002/ana.25511. PubMed PMID: 31148214.

Osuagwu N, Dölle C, Tzoulis C. Poly-ADP-ribose assisted protein localization resolves that DJ-1, but not LRRK2 or α-synuclein, is localized to the mitochondrial matrix. PLoS One 2019;14:e0219909. doi:10.1371/journal.pone.0219909. eCollection 2019. PubMed PMID: 31323073; PubMed Central PMCID: PMC6641658.

Varhaug KN, Torkildsen Ø, Myhr KM, Vedeler CA. Neurofilament Light Chain as a Biomarker in Multiple Sclerosis. Front Neurol 2019;10:338. doi:10.3389/fneur.2019.00338. eCollection 2019. PubMed PMID: 31024432; PubMed Central PMCID: PMC6460359.

Centre management and researchers meeting with patient organizations in October of 2019

Haukeland University Hospital

UNIVERSITY OF BERGEN

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Diakonale Sykehus

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