Neuro-SysMed

ANNUAL REPORT 2023

Centre for
Clinical Treatment
Research

CONTENT

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DIRECTORS' COMMENTS

As in previous years, 2023 has been a highly successful and productive year for Neuro-SysMed. We successfully hosted our first annual international Neuro-SysMed Symposium at Solstrand, featuring an inspiring program that covered topics within and across our four focus diseases. More than 120 participants from our Centre, along with several international partners and key opinion leaders in our research areas, actively participated. Additionally, we held our first on-site scientific advisory board meeting, providing valuable discussions and advice on our research strategies and the organisation of our Centre. We are already planning the next symposium for early October 2024.

2023 marked a significant milestone for our Centre, as we secured our first Horizon Europe funding as coordinators for an international project on Epstein-Barr virus (EBV) infection in multiple sclerosis (MS). Professors Myhr (University of Bergen) and Torkildsen (Haukeland University Hospital) are coordinating this project, which includes high-profile collaborators from Sweden, Belgium, Italy, Spain, and the USA. The project aims to define environmental, immunological, and genetic factors involved in the development of MS, following a primary EBV infection. Additionally, perhaps the most exciting part of the project is that we are initiating clinical trials of antiviral therapy to investigate its impact on chronic EBV infection and its potential to reduce MS disease activity and disability progression. If successful, antiviral therapy for MS will be a paradigm shift in MS therapy – and open perspectives for primary prevention of the disease by antiviral therapies or even vaccination.

Another milestone achieved in 2023 was securing funding and launching the NADAPT study, Norway's first disease-modification trial for atypical parkinsonism syndromes, including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal syndrome (CBS). The study will test whether high-dose nicotinamide adenine dinucleotide (NAD) replenishment therapy can delay disease progression and will include patients from all of Norway, as well as the UK and France. Most of all, we are excited to be able to offer experimental therapy to a group of individuals who have traditionally had virtually no options of standard healthcare and no opportunities to participate in trials.

Moreover, in 2023 we reported further evidence on the safety and metabolic effects of high-dose NAD therapy with nicotinamide riboside (NR), in the NR-Safe study. These results are important for our Centre, as we are currently investigating NR in trials across all four focus diseases of Neuro-SysMed.

On the innovation side, we are delighted to have received our first commercialisation grant from the RCN (KOMMERSFORSK program) to further develop and commercialise NAD-replenishment therapy for neurodegenerative parkinsonisms. The grant was received by Professor Tzoulis and Dr Dölle, together with our technology transfer office (VIS).

Our flagship trials made significant progress during 2023. The OVERLORD-MS trial comparing rituximab to ocrelizumab is showing an extremely low relapse rate across the treatment arms (blinded data), and we expect to present exciting results in Q2-2025. The NO-PARK phase III trial of NAD-replenishment therapy in PD is nearly fully enrolled and is set to complete in March 2025. This will be the world's first phase III efficacy trial of NAD-replenishment therapy for a neurodegenerative disease, and the results are highly anticipated. The NO-ALS and N-DOSE_AD trials of NR in ALS and Alzheimer's disease have also made great progress in patient recruitment and are expected to reach their target numbers in 2024/2025. Thus, Neuro-SysMed is approaching inclusion of 1600 patients across more than 30 interventional and observational trials, and more than 15 pharmaceutical industries sponsored trials. Considering Norway's population approaching 5.6 million, this represents an extraordinarily high trial activity and recruitment rate by global standards. The key to this success is the excellent infrastructure our team has built and the incredible dedication and hard work of all our colleagues at Neuro-SysMed. However, we can only claim half the credit for this – the rest belongs to the Norwegian people for their unparalleled support and commitment to advancing medical treatment.

Neuro-SysMed is continuously recruiting and educating young researchers and health care personnel through our research activity. Our research school organises monthly seminars, quarterly junior symposiums, and specific courses. We are particularly proud of our success in establishing research school collaboration with the other research centres for clinical treatment research, including NorHEAD (St. Olav's Hospital, Trondheim), Matrix (Oslo University Hospital, Oslo), and REMEDY (Diakonhjemmet Hospital, Oslo).

Reflecting on 2023, we are proud of our achievements and look forward to the future with excitement and optimism, ready to tackle the ongoing challenges of improving healthcare for brain diseases.

Kjell-Morten Myhr
Neuro-SysMed Director

Charalampos Tzoulis
Neuro-SysMed Co-Director

VISION AND GOALS

Neuro-SysMed is a Norwegian Centre of Excellence for Clinical Treatment Research focusing on four neurological diseases: multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and dementia disorders, including Alzheimer's disease and dementia with Lewy bodies.

The overarching aim of Neuro-SysMed is to develop new and/or improved treatments and treatment strategies. The Centre facilitates early access to such new therapies for patients across Norway through participation in national and international randomised clinical trials. Our ultimate goal is to lower the burden of disease.

We have established a comprehensive novel support framework to address the unmet treatment needs of Norwegian patients within the four diseases. In doing so, we are continuing to enable patients from all over Norway access to cutting-edge treatment trials and to develop precision medicine. More specifically, Neuro-SysMed continues to work towards:

- Discovering novel therapeutic targets by both nominating (in silico and in vitro screening) and testing new therapies in novel disease models
- Performing cutting-edge clinical trials (mainly investigator-initiated)
- Developing biomarkers for disease detection, patient stratification and ultimately precision medicine
- Enabling and applying advanced patient care by improving daily function and quality of life
- Introducing systems medicine into Norwegian neurology

RESEARCH PLAN AND STRATEGY

Neuro-SysMed clinical trials are at its core, with samples and data from the trials feeding the Centre's translational research activities. Research goes across research groups and expertise, and involves large interdisciplinary efforts to achive its goals.

Neuro-SysMed is organising and conducting randomised clinical treatment trials to evaluate the efficacy and safety of therapies, by novel or established drugs with new indications that may delay or even arrest disease progression, ameliorate symptoms or optimise care for affected individuals. While each study has its own scientific questions and efficacy endpoints, all projects running under the Centre contribute with data, such as clinical scorings, DNA and RNA data, blood and cerebrospinal fluid analyses, tissue sample analyses, and brain images, to a common Neuro-SysMed database. Using this database, the vast amount of information collected by the Centre is integrated to define biomarkers that enable early and precise diagnosis, to subgroup patients within each disease (stratification), and achieve accurate prognosis and tailored treatment choices for individual patients.

In terms of systems medicine, our Parkinson's disease (PD) team is setting up the path for others to follow, with the ParkOme project having mapped molecular profiles from tissue samples from more than 1,300 brains of deceased patients with PD and other neurodegenerative diseases – the largest brain omics database for PD in the world. From this study, a new subtype of PD has been identified based on mitochondrial deficiency. Work to develop clinical biomarkers is ongoing in all four diseases. Several cell models have been developed and are being used to screen and discover new treatments. We are also well underway with our in-silico drug screening, based on the national Norwegian registries.

To better visualise the activities going across the numerous research groups involved in Neuro-SysMed, we have organised these into 9 research nodes as described from page 40.

ORGANISATION OF THE CENTRE

The Centre is hosted by Haukeland University Hospital (HUH) in partnership with the University of Bergen (UiB) and Haraldsplass Deaconess Hospital (HDS) in Bergen, Norway, and the Lawson Health Research Institute in London, Ontario, Canada. Neuro-SysMed is funded by The Research Council of Norway (RCN) and the host and partner institutions.

Organisational structure

The Centre is led by Professor Kjell-Morten Myhr (Centre Director and Head of the Multiple Sclerosis Program) and Professor Charalampos Tzoulis (Centre Co-Director and Head of the Neurodegeneration Program). At the implementation level, the Directors, supported by the Neuro-SysMed administrative team, manage the Centre's personnel, financial plans, communication, and dissemination activities, and coordinate annual and financial reporting to the Norwegian Research Council. This is further supported by the host and partners' own administrative departments.

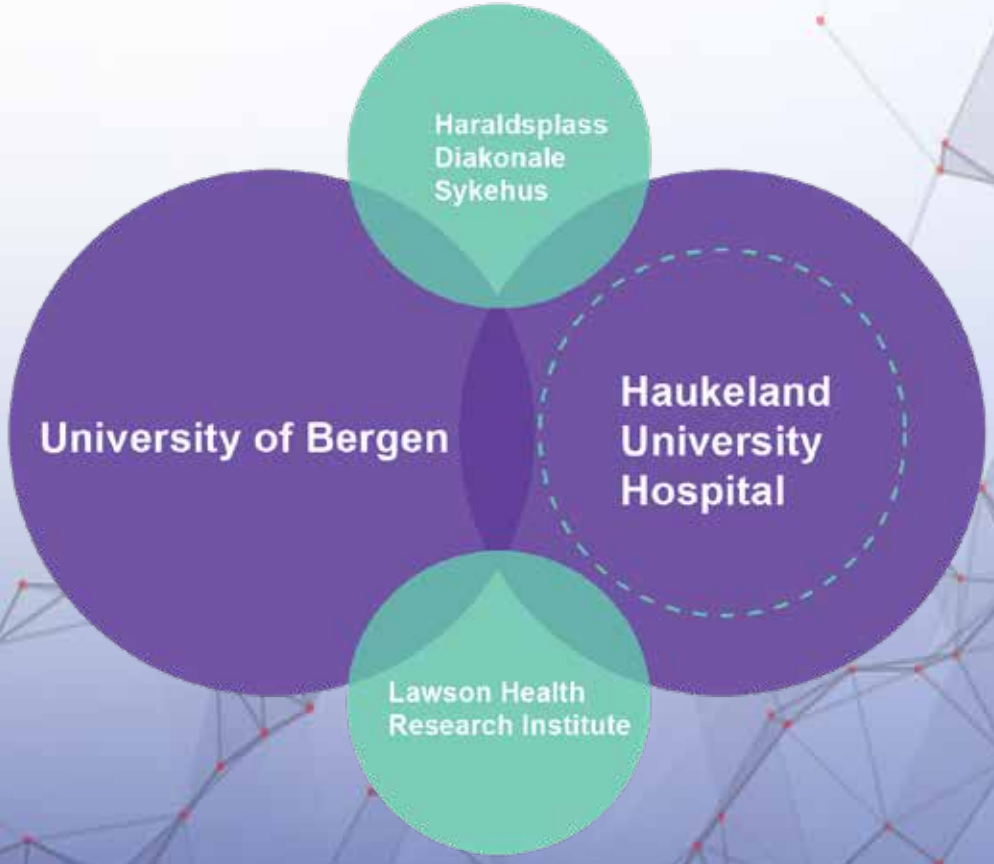
The **Centre Board** includes members from the host and partner institutions. The board is chaired by Professor Per Bakke, Dean of the Medical Faculty, UiB, and the other board members are Eivind Hansen, Chief Executive Officer (CEO) of HUH, Torhild Næss Vedeler, Director of the Neurology Clinic, HUH, Helge Ræder, Vice Dean for Innovation, MED, UiB, and Kjerstin Fyllingen, CEO of HDS, Linda Haugland, Chair of the User Committee at HUH, Reidun Tjønn Rinde, member of the User Committee, HUH, Lise Johnsen, Norwegian MS Society and Chair of the Neuro-SysMed User Council, Trine Lise Corneliussen, Norwegian Parkinson's Association, and Vice Chair of the Neuro-SysMed User Council. The Centre Board members meet bi-annually and facilitate cooperation between the consortiums, give advice on overarching Centre strategies, and aid the Centre leadership with administrative challenges. The Board ensures that the Centre follows the planned work as specified in the agreement with the Norwegian Research Council

and that this happens within the agreed budget and schedule. The Centre is also supported by a Scientific Advisory Board, providing scientific guidance and feedback, and a **User Council.**

Cooperation between partners

Most of the work is physically located at the Haukeland medical campus (HUH, UiB, HDS). The Neuro-SysMed researchers work across departments and institutions using their resources and facilities. The Neuro-SysMed laboratory, administration, most offices, and most of the clinical work are located at the Neurology Clinic, HUH. In addition, resources such as imaging, bio-banking, stem cell facilities, core facilities at The Medical Faculty, including animal facilities, and biostatisticians, among others, are available for Neuro-SysMed at all three institutions in Bergen. This close co-localisation allows for close interactions between the research groups to work towards shared projects and goals. Each research group has weekly meetings and often invites members from other groups to take part in scientific discussions, often pertaining to the different research nodes. In 2023, we have continued organising our monthly seminar series, and a larger symposium organised in September with all Neuro-SysMed members and invited international speakers. These activities have provided crucial meeting points for scientific discussions and cooperation for all Centre members, students and interested collaborators.

The Lawson Health Research Institute is involved in the research related to Parkinson's disease and cooperates with the other partners in that field. Regular digital meetings have been carried out with the teams at Lawson.



CORE CENTRE PERSONNEL AND FACILITIES

Neuro-SysMed provides the foundation for supporting its ongoing clinical and translational projects and for the development and establishment of new projects. This includes dedicated personnel and infrastructure, as described below.

The Neuro-SysMed laboratory

The Neuro-SysMed laboratory provides critical infrastructure required to support the clinical and translational research taking place at the Centre. The offices and the laboratory benches of the Neuro-SysMed laboratory currently host more than 40 people, including laboratory engineers and researchers at all levels, from master-level students to senior scientists. The Neuro-SysMed laboratory comprises a state-of-the-art wet-lab and computational facilities. We have a dedicated *Lab Manager* in charge of the day-to-day management of the facilities, in addition to *technicians* assisting with both the sample processing from the clinical trials and translational research.

The ***wet-lab facilities*** include the following functional units:

- General purpose molecular biology laboratory
- Tissue processing and morphology/microscopy laboratory
- Cell-culture facilities including induced pluripotent stem cell work
- Biomarker facility including a Simoa Quanterix digital biomarker detection platform
- Genomics facility including a dedicated 10X Chromium platform for high-throughput parallel single-cell analyses
- Ultra-freezer facility hosting a human brain and tissue bank

The ***computational unit*** comprises expert bioinformaticians who perform a complete range of big data analyses – from raw-data pre-processing to sophisticated supervised and unsupervised analytical approaches.

Clinical Trials Unit

At the heart of Neuro-SysMed are the clinical trials. In 2023, the Centre had 31 investigator-initiated clinical trials in addition to more than 15 industry sponsored trials. To administer this substantial number of trials, we have two trial coordinators as part of our core team, in addition to our twelve research nurses. Practical planning of the clinical trials (including protocols, ethics approvals, site recruitment, monitoring, etc.), patient recruitment and execution, data monitoring and analysis are coordinated by our clinical trials unit together with the PI of each study.

We have a dedicated medicine room, administered by our trial coordinators for the storage, packaging, and labelling of trial medications. The unit plans trials initiated by Neuro-SysMed PIs in collaboration with external investigators or the industry, enabling patient participation in national and international multi-centre trials. The Research and Development Department at Haukeland University Hospital assists in coordinating and negotiating industry-sponsored clinical studies.

The role of the trial coordinators

Our two trial coordinators work full time in the clinical treatment trial teams and play a vital part in planning and executing of the clinical trials across diseases. They monitor the clinical trials from planning to completion and provide support for the management and PIs.

Their job is to ensure that our clinical trials comply with current national guidelines and within the guidelines from Haukeland University Hospital, and the University of Bergen. They help with contracts and financial agreements with other sites and departments. In addition, they provide the study teams on the different sites with the essential documents and ensure that team members have the correct training and certificates.

The importance of Neuro-SysMed's research nurses

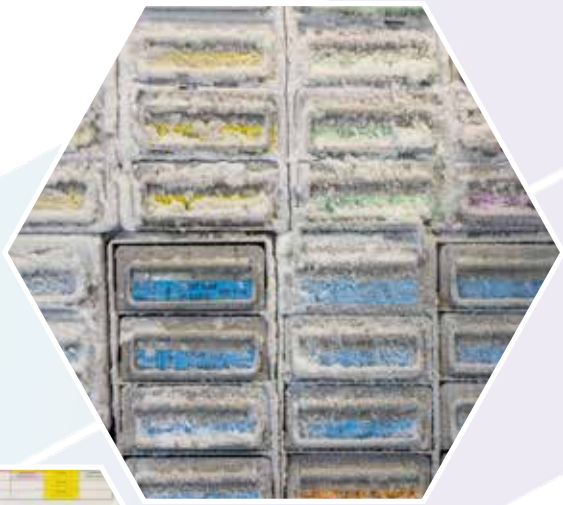
Neuro-SysMed has a team of nurses, nurse specialists and staff with master degrees in nursing working as research nurses. They work in clinical treatment trial teams and are specialised in MS, PD, ALS and dementia. Thus, participants in our studies meet a highly trained and specialised team of highly skilled nurses that has specialised knowledge and experience in the different diseases, contributing to patient safety and helping to make the participant feel well cared for.

The research nurses plan the logistics for the clinical studies, perform testing and clinical assessments, gather data, maintain essential documents, and provide therapy in the different trials. They also provide input throughout the planning process with focus on feasibility and the patients.

There are many different departments and professions working together in a clinical treatment trial, and the nurses are often the ones that link them all together. In our multicentre studies, the nurses at Neuro-SysMed also provide support for nurses at other sites. It is crucial to have dedicated nurses with expertise in neurology facilitating patient recruitment, patient satisfaction and secure efficient study logistics.

Neuro-SysMed administration

During 2023, our Research Advisor, Yamila Torres Cleuren, has been also acting as Centre Coordinator, taking care of both pre- and post-award phases of our external funding. In addition to the personnel actively involved with the lab, data, and clinical trials coordination and management, Neuro-SysMed has a Communications Officer (Eli Vidhammer), and a Research School Coordinator (Nina Grytten Torkildsen). The administration is further supported by administrative teams from the host and partner institutions regarding economy, HR, and general administration.



RESEARCH ADVICE AND PROJECT DEVELOPMENT

During 2023, Neuro-SysMed has continued a high level of research activity at the Centre, and this has benefitted not only the research output, but also the successful development of new projects, resulting in excellent external funding recruitment throughout the year.

Responsible for this support function: Senior Advisor Yamila Torres Cleuren

The Centre has continued to build scientific collaborations and consortia, and we are now starting to see the results in the shape of increased collaborations (both national and international) and increased funding for our projects. Our highly interdisciplinary set-up allows us to design projects across the research groups, taking advantage of the different expertise available. An asset for our Centre is the work across the diseases; findings from one disease are being translated into the others (e.g., from PD to ALS, dementia, and MS), and we have developed new laboratory and clinical trial projects thanks to the interactions between the research groups. In addition, big efforts have gone towards European grants, which we see as long-term aims of the research at the Centre, as well as towards increasing the visibility of the Centre. This is crucial for the success of our clinical trials, and to ensure that our projects go beyond national borders, increasing not only our national but also international collaborations. As a result, Neuro-SysMed now coordinates a new project "EBV-MS", which received 7 million euros from the Horizon Europe program, which had its official start in December 2023. Getting this funding is a great boost for our teams and a sign of Neuro-SysMed research reaching the international stage.

In 2023, we have continued to receive external funding from our Regional Health Authorities (Helse Vest) in PhD projects, postdocs, a clinical fellowship grant and open project support for our clinical and translational projects; from KLINBEFORSK, we have secured funding for our first atypical parkinsonism trial; from the Norwegian Research Council we have

received commercialisation funding; and funding from private donors, patient organisations and foundations, providing invaluable support for our projects especially in the start-up phase, and for equipment.

Support for early career researchers

In previous years, we have organised workshops, individualised follow-up, research project conceptualisation and development and grant writing support for our postdoctoral researchers. We are continuing this targeted approach and further developing it to the needs of our researchers. We are seeing a high number of research grants going to our younger researchers, and they are in a higher degree (co-) supervising students, gaining independence, and taking on more senior roles.

– Yamila Torres Cleuren, Senior Advisor

"I think the main reason that we got this funding was the time we spent on planning the project and establishing the international research network. We had an idea for a project on EBV and MS, and we found that it fitted very well within the scope of the EU-call. This work started almost a year before we submitted the application, we had weekly meetings with our collaborators to refine the project, and the ideas and enthusiasm from all participants made this into a very strong application. We also had an excellent research advisor (Yamila) leading the application and good help from the University of Bergen with preparing the application."

- Øiving Torkildsen, about the EBV-MS Horizon Europe grant.

THE SCIENTIFIC ADVISORY BOARD

Neuro-SysMed is advised by a Scientific Advisory Board (SAB), and the Centre had its first in-person meeting with the three SAB members Kailash Bhatia, Raymond Koopmans and Xavier Montalban in September 2023, during the first Annual Symposium.

Professor Kailash Bhatia is a Professor of Clinical Neurology at the Clinical and Movement Neuroscience Department at the UCL Queen Square Institute of Neurology, London and an Honorary Consultant Neurologist at the affiliated National Hospital for Neurology (NHNN), Queen Square, UK. Professor Bhatia's main research interest is in movement disorders, merging clinical, electrophysiological and genetic methods to study the pathophysiology of conditions like dystonia and Parkinson's disease.

Professor Raymond Koopmans is a Professor of Nursing Home Medicine studies at the Faculty of Medical Sciences at Radboud University, The Netherlands. Professor Koopmans studies the course of dementia in nursing home patients.

Professor Xavier Montalban is the Chair of the Department of Neurology and Director of the Multiple Sclerosis Center of Catalonia (Cemcat) at the Vall d'Hebron University Hospital, Barcelona, Spain, and Professor of Neurology at the Autonomous University of Barcelona. He is a key opinion leader in the field of multiple sclerosis, and has been a PI in more than 150 clinical trials.

Neuro-SysMed's principal investigators for MS, PD and dementia met with their relevant SAB members to discuss their projects, planned activities, and how they work with the rest of the Centre. This led to fruitful discussions and insightful feedback into the individual projects. In general, the SAB members were very impressed with the high volume of investigator-initiated trials and their quality. All agreed that more focus was needed into radiology and imaging. Thinking of the future of the Centre beyond the funding period, it was also commented how a larger emphasis should be placed on visibility of our activities and potentially more collaborations with industry.

The SAB members also contributed with scientific talks at the Neuro-SysMed Annual Symposium.

Internal midway evaluation

It was initially planned that the Research Council of Norway (RCN) would carry out a midway evaluation of the centre in 2023. However, due to changes at the RCN, it was cancelled and Neuro-SysMed was confirmed to have funding for the entire 8-year period. As the central administration of the Centre was well on the way to prepare for such a process, we decided to carry out our own internal midway evaluation following the standard forms from the RCN and in addition carry out workshops with most of the Centre to get feedback on how the Centre is working at all levels. This feedback has been used to further make improvements and changes to how we work and we will continuously evaluate each year. Due to this process and the feedback from the SAB, efforts are being made to strengthen imaging at the Centre through new collaborations and positions, more meeting points for staff to have scientific discussions, and improved internal and external communications.

THE USER COUNCIL

Neuro-SysMed's User Council was established in the early phase of the Centre (2019), serves as an advisory body with representatives from all the relevant patient organisations, with two representatives for each disease group.

The importance of the user voice in research

User participation and user involvement in research and innovation processes is about letting those who know the needs be part of shaping the agenda. There is an explicit expectation that research projects should take advantage of the experience and knowledge built by those who live with or near the patient. User involvement is an approach for making certain that this competence and this perspective has a natural place and voice in the research projects. The user perspective can be useful in strategic decisions when planning and establishing projects, as well as when planning the small but essential details that ensure projects are aligned to the requirements and challenges of the people living with the disease. When funding research and innovation projects, the government expects user experience and knowledge to be part of the projects. This makes it more likely that new knowledge will reflect user requirements, and that it will be implemented and used. We in the User Council find this to be an important and appropriate goal for our engagement in the Neuro-SysMed activities.

The assignment of the User Council

The User Council provides advice to the Neuro-SysMed management and contributes towards:

- development of research ideas and in discussions on clinical research;
- recruitment of user representatives to the Centre's research;
- equal access to participation in clinical trials;
- design of user-friendly information from Neuro-SysMed;
- communication of research results;
- bringing attention to the work of the Centre.

Further, the User Council works to:

- be a link between users and the Centre;
- attend various relevant events;
- work for political attention to the work of the Centre and increased funding of research related to neurodegenerative diseases in general;
- contribute towards good principles for user involvement.

The User Council wishes to contribute to increased awareness of the opportunities for patients and caregivers to participate in clinical trials. Many are still not aware of this as a treatment option. Additionally, we emphasise the importance of user representatives in research projects. We see that users for example can:

- identify current topics or challenges;
- contribute to improved research design;
- contribute to better recruitment of patients and their participation in the trials;
- contribute to the dissemination of research results;
- give feedback on language, how to present the message, and on dissemination channels;
- bring in new perspectives on the analysis of results.

Status in the collaboration with Neuro-SysMed

The cooperation with the researchers and the administrative group is well-functioning. We experience that all parties are aiming at the best possible collaboration. Together, we have established processes and a structure that facilitate successful collaborations between the Centre's administration, researchers and user representatives. We have also developed procedures and checklists for use in user participation in research. Our hope is that these can also be used by other environments and beyond the Centre's duration.

Meetings in 2023

In 2023, there were two meetings with the User Council. The April meeting was a one-day meeting, while the autumn meeting was held over two days as a workshop. The participants were very pleased with this meeting format, allowing them time to get to know each other and the researchers, as well as more time to discuss more complex issues. The User Council also contributed to ideas for the Neuro-SysMed events at Arendalsuka in August.

– Lise Johnsen, User Council Chair

Members of the User Council in 2023

- **Lise Johnsen, Norwegian MS Society (Chair)**
- **Mirjeta Emini, National Association for Public Health (Vice-Chair)**
- **Kjell Grorud, Norwegian Parkinson Association**
- **Magne Wang Fredriksen, Norwegian MS Society**
- **Ragnhild Stenshjemmet Støkket, Norwegian Parkinson Association**
- **Kristin Reimers Kardel, National Association for Public Health**
- **Marit Stensen, ALS Norway**
- **Lise Stousland Flesjå, Alltid Litt Sterkere"**
- **Ditte Staldgaard, National Association for Public Health (deputy)**
- **Betty Bakken Kleppe, ALS Norway (deputy)**
- **Gry Lien, Alltid Litt Sterkere (deputy)**

NEURO-SYSMED IN NUMBERS

In 2023, we had a large increase in activities due to new externally funded trials starting up, new international projects in addition to the ongoing work. This has resulted in a total of 107 million NOK spent on Neuro-SysMed related projects.

Neuro-SysMed funding

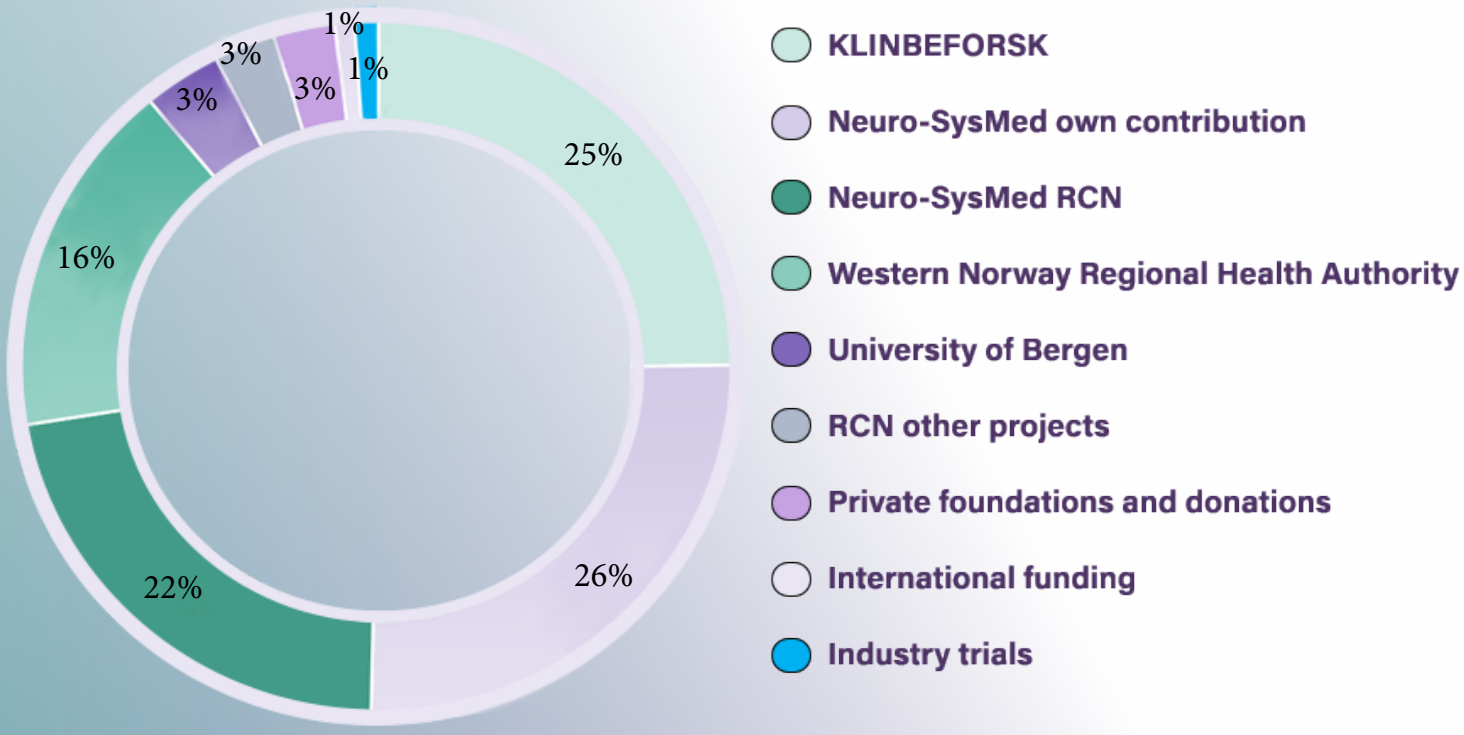
The core activities of Neuro-SysMed are funded through the Research Council of Norway (RCN)'s FKB scheme. In 2023, this amounted to 27.5 MNOK as own contribution from the consortium institutions and 23.9 MNOK from the RCN. The large volume of investigator-initiated clinical trials requires large resources in terms of personnel, infrastructure and running costs, and therefore additional funding has been crucial to reach this level of activity.

The KLINBEFORSK program, funded by the regional health trusts, is the largest external funding contributor with over 26 MNOK spent, followed by the Western Norway regional health authority. In addition, we have several University of Bergen funded PhD positions, innovation projects, EU and US-funded projects, other RCN funded research and commercialisation projects, private foundations and donations (including patient organisations), and income from industry trials.

Neuro-SysMed in numbers

We have researchers from over 26 different countries, spanning from Master-level and medical research students, PhD students, postdoctoral fellows, senior researchers, clinicians, research technicians, research nurses, clinical trial coordinators, and administrative staff. Approximately 60% of our staff are female, but there is an overrepresentation of men in scientific leadership positions. However, we have been actively recruiting and training women to take on more senior roles. This is reflected in a continuous increase of publications with female senior/last authorship, increased successful research funding, and an increase of supervisory roles. We are continuing to support their careers via research project grant applications and mentoring

Total funding in 2023 for Neuro-SysMed projects



INNOVATION

Innovation is a central part of Neuro-SysMed's activities, not just in implementing modern technologies but also in our approach, build-up of infrastructure, and our way of working inter- and trans-disciplinarily.

We have integrated innovative approaches to our clinical trials and translational research. This is reflected in the activities we have been organising for our students (a 4 ECTS PhD course in health innovation in collaboration with CCBIO, started in 2021) and a Symposium on Clinical Trials Design in 2022, aimed at encouraging new methodological and design approaches to overcome the obstacles hampering therapeutic breakthroughs in neurological diseases. This was a big topic of discussion during the 2023 Neuro-SysMed Annual Symposium and continues to be at the centre of project design.

Our Research Advisor, together with the innovation advisors in our host and partner institutions, works closely with our PIs and researchers in mapping out their activities and plans, to identify potential new projects and ideas. Part of our strategic planning is to support their project development with research applications, commercialisation, and Intellectual Property strategy discussions (together with our technology transfer office VIS), or support to develop proof-of-concept ideas. We currently have 5 active projects with VIS, directly stemming from Neuro-SysMed project findings. A large innovation endeavour currently running at our Centre, aims to develop and commercialise specific forms of nicotinamide adenine dinucleotide (NAD) replenishment as medical treatments for Parkinson's disease and other parkinsonisms. This ambitious project, led by Professor Tzoulis and Dr. Dölle, received significant support from the KOMMERSFORSK program of the RCN in 2023, and is progressing fast both on the science and exploitation fronts.

Another example of innovative projects includes the DIGI.PARK project in which sensor and tracking technologies are used to better understand Parkinson's disease, bringing together mathematicians, clinicians, patients, and other experts. This is representative of Neuro-SysMed's approach to work with projects

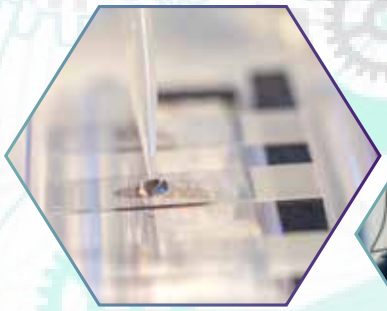
across disciplines and to involve users directly in the development of new tools.

Neuro-SysMed has strong collaborations with the industry. Two such examples would be the projects with Otivio and Gilead Sciences.

The Norwegian company Otivio has developed a medical device that increases blood circulation in the lower extremities, called “FlowOx”. Based on anecdotal reports of pain and spasticity relief in MS by using the device, the Centre has, together with Otivio, performed a pilot study showing that about one-third of the patients benefited from the intervention. These positive results were further extended into a larger international randomised placebo-controlled trial that was completed during the fall of 2023, and data will be presented during 2024.

The Horizon Europe funded EBV-MS project has generated collaboration with Gilead Sciences that supply for free the project drug tenofovir alafenamide fumarate (TAF). This is a randomised double-blind, placebo-controlled clinical trial (RCT) including MS-patients for receiving the antiviral drug TAF 25 mg once daily (n=25) or placebo (n=25) for six months of therapy. The primary outcome is safety, and the key secondary outcome is EBV-shedding in saliva.

A further larger RCT of the same drug is planned with MS-disease activity as measured by MRI-activity. Proven effective, antiviral therapy in MS will represent a paradigm shift in MS-therapy – that would open up for perspectives of primary prevention of the disease.



FROM THE NEURO-SYSMED CENTRE BOARD

Text by Per Bakke (Dean in 2023 for Faculty of Medicine, University of Bergen) and Eivind Hansen (CEO of Haukeland University Hospital)

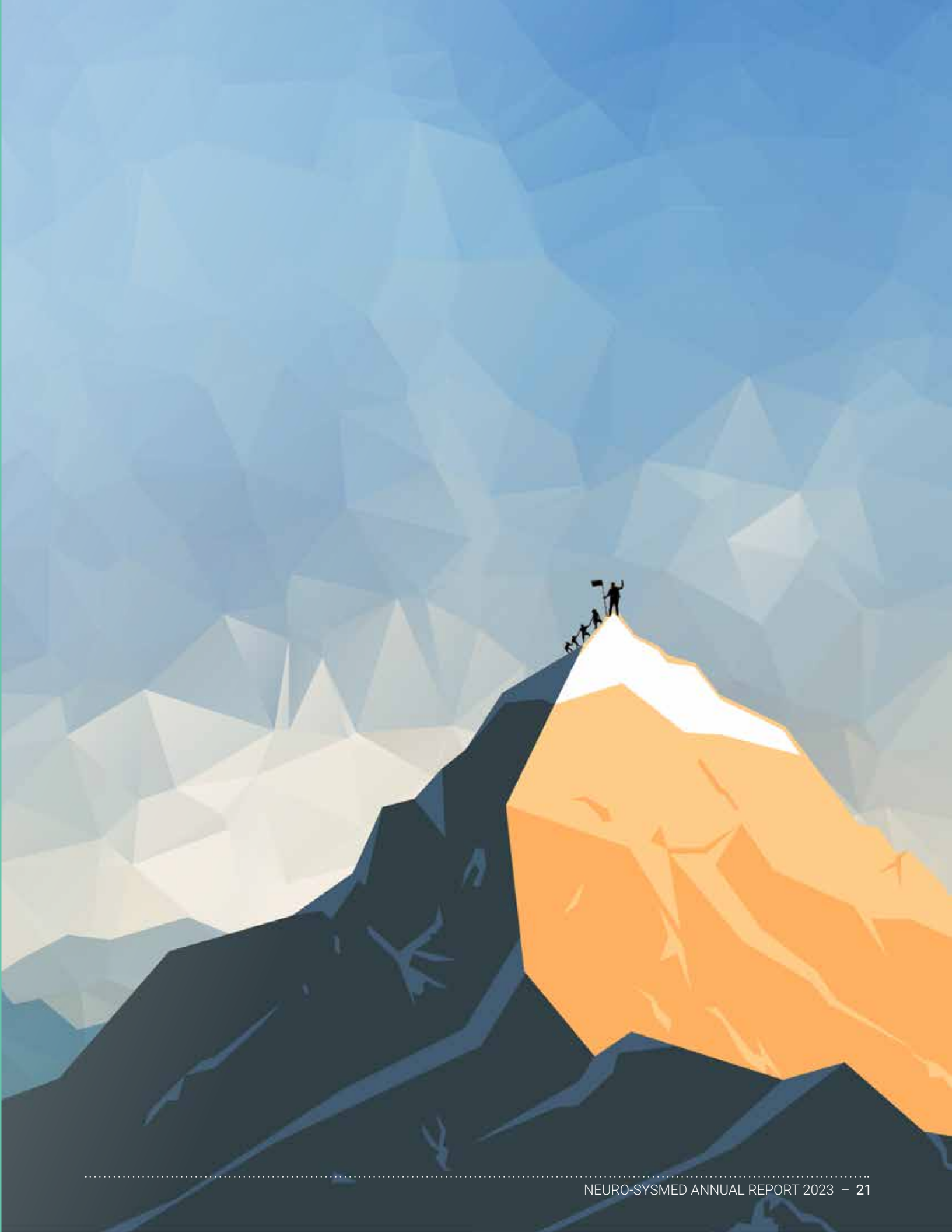
COLLABORATION IS A KEY FACTOR FOR SUCCESS IN RESEARCH

If you want to go fast, go alone; if you want to go far, go together. This is an old African saying - which is also highly applicable in research. Short and limited projects can be carried out in your own research group, but if you have ambitions for large and long-term projects, you need collaboration partners across institutions locally, nationally but also often internationally. Fruitful cooperation must be based on trust and must be developed over time. One likes to start out with smaller limited projects which can then be developed into larger and long-term projects.

The Faculty of Medicine at the University of Bergen and Haukeland University Hospital recently prepared evaluation reports of medical research for the Research Council of Norway. In this work, it became clear that the large and most productive research groups are characterised by close collaboration across the institutions locally - but also nationally and internationally.

Nevro-SysMed illustrate this in a nice way. The research centre is based on collaboration across several departments and faculties at the University of Bergen, as well as collaboration across several departments at Haukeland University Hospital and Haraldsplass. This was crucial to succeed in the application to the Research Council of Norway for funding of the centre. Later, the research groups in the centre have established projects based on national collaboration with all neurological departments in the country. This is crucial for the implementation of projects, but also for securing funding for the projects. Several of the centre's research groups have also succeeded in securing international funding in collaboration with several Norwegian, European, and American partners. Strategic thinking is important to succeed with such research applications. What competence is needed to be able to carry out a project must be clarified early on and provide guidance for the establishment of collaboration. Early and clear inclusion and involvement of partners in the development of the project is also important for success.

Our institutions work systematically to facilitate collaboration in both research and teaching. This is crucial for advanced research and facilitates recruitment for both research and clinical work. Agreements on cooperation have been established and investments have been made in equipment and core facilities, often with contributions from both institutions, which facilitate advanced research. In this venture, it is necessary to build up complementary resources - which can be used across the institutions and with the aim of strengthening and promoting collaboration. This also contributes to the research groups becoming attractive collaboration partners both nationally and internationally.



NEURO-SYSMED VIEWPOINT

Text by Marianna Cortese, Department of Nutrition, Harvard T H Chan School of Public Health, Boston, Massachusetts, USA

PREVENTION OF NEUROLOGICAL DISEASE - TOWARDS A HOPEFUL FUTURE

Neurological diseases are disorders of the brain and spinal cord affecting millions of people around the world. These conditions are among the most feared, as many neurological diseases are incurable, progress over time, and can lead to severe disability. The treatments that are available can only prevent or alleviate symptoms and are at best modestly contributing to slowing disease progression. There is often uncertainty surrounding prognosis, the effectiveness of treatments, and the possibility of disease progression. Moreover, neurological diseases can drastically reduce an individual's quality of life, with conditions such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis leading to significant physical and cognitive impairment, affecting the ability to carry out daily activities independently.

The ideal scenario would be to prevent these diseases before they even start, but this may be the most difficult goal to achieve. Prevention requires a thorough understanding of what causes a neurological disease, which is complicated by the fact that many neurological diseases have a long phase of silent progression prior to the onset of typical neurological symptoms. Parkinson's disease, for example, may begin up to 15 years before the classic motor symptoms appear, and affected individuals can show a combination of seemingly unrelated other symptoms first, which are difficult to identify.

> "Despite these challenges, the prevention of neurological diseases is possible."

Despite these challenges, the prevention of neurological diseases is possible. One success story is the prevention of poliomyelitis, a rare complication of an infection with the poliovirus, which leads to paralysis and limb deformity. With the widespread vaccination of children, it has been eradicated from many countries worldwide.

Hope around the possibility of prevention of neurological diseases was also created by the recent breakthrough in understanding the cause of multiple sclerosis (MS). Research could finally show that MS is caused by an infection with the Epstein-Barr virus

(EBV), which also causes infectious mononucleosis, otherwise known as “kissing disease”. For decades, EBV was a prime suspect in MS, but it was difficult to prove a direct link as most adults are infected with EBV and do not develop MS. However, a large study conducted in the US military tracked individuals who were not infected with EBV, finding that their risk of developing MS was only dramatically increased after they got infected with EBV. MS is now considered a rare complication of an infection with EBV, opening the door to the possibility that preventing EBV infection through vaccination could, in theory, prevent MS. Researchers are also focusing on understanding the mechanisms more in detail in the hope of identifying also other preventive strategies.

Viruses are also a key area of interest and investigation as potential causes of other neurological conditions. For instance, herpesvirus 1, known for causing cold sores, as well as other pathogens, are being investigated as potential causes of Alzheimer’s disease. Acute flaccid paralysis, a serious spinal cord disease in children characterised by limb weakness, has been linked to infections with certain types of enteroviruses, which are subject of extensive investigation.

As we learn more about the viral causes of neurological diseases, there is hope that we may enter an era where preventing these conditions is as straightforward as administering an antibiotic for a bacterial infection.

This would represent a monumental shift in our approach to and our view of these devastating diseases.

NEURO-SYSMED VIEWPOINT

Text by Frank Riemer and Peder Lillebostad, Neuro-SysMed and the Mohn Medical Imaging and Visualization Centre (MMIV)

CURRENT AND POTENTIAL USES OF AI IN NEUROLOGICAL RESEARCH AND MEDICINE

Current and potential applications of AI in neurological research and medicine have captured both public and professional imaginations, stirring excitement and scepticism in equal measure. Amidst a landscape teeming with AI-generated art and deepfake videos, the question arises: how can AI meaningfully contribute to neurological research and medicine beyond the sensational headlines?

The evolution of AI technology has seen a shift from the early fascination with computer vision, particularly in radiology, to the current buzz around generative large language models (LLMs) like Chat-GPT. Deep convolutional networks, for instance, have demonstrated capabilities in automatically identifying anatomical structures and lesions from medical images, bypassing the need for manual and laborious work. News headlines promised a future where algorithms could outperform doctors in diagnosing conditions such as skin cancer by simply looking at your latest holiday pictures, if access to plentiful, high-quality training data is provided.

In 2016, the AI pioneer Geoffrey Hinton proclaimed that AI would soon make radiologist training obsolete, however as of yet, the anticipated domination of AI in medicine has not materialised. According to research by Health Imaging, by mid-2023, 527 out of 692 of FDA-approved AI applications were in radiology, with less than 20 approved in neurology. Worth noting is that none of these are based on the generative models dominating the current news headlines. This might be due to the inherent lag in bench-to-bedside transition and equally bureaucratic hurdles and general scepticism towards new technology.

> "The anticipated dominiation of AI in medicine has not yet materialised."

A more fundamental problem however stems from the challenge of achieving true generalisation in AI applications. AI models, reflective of their training data, can struggle with accuracy across diverse populations and diagnostic imaging hardware. The phenomenon of AI "hallucinating" - fabricating details with unwarranted confidence - further complicates their reliability.

Peder Lillebostad draws from personal experiences with AI, where for example an algorithm mistakenly identified medical conditions in unrelated scans.

Peder underscores the importance of recognising and addressing these limitations.

Recognising these flaws requires the realisation that AI is not magic, and these flaws may go unnoticed unless explicitly tested for.

Among the thousands of academic articles published in medical AI, it is still uncommon to publish pretrained models along with the articles, due to the absence of incentives to do so. This might also be part of the explanation of the discrepancy between fantastic research results and the relatively few real-world deployments.

Frank Riemer does research into AI algorithms to count, measure and classify multiple sclerosis lesions. Having trained a model with local data coming from the same MRI scanner, the algorithm is able to let us know if a patient's disease presentation on imaging data remains stable or improves in between visits.
But direct clinical tools like diagnosis and treatment monitoring is not the only benefit AI can provide. Sorting and filtering through vast databases and automating trivial tasks can make the clinicians workflow more efficient, freeing up more time for actual clinical work. To realise AI's full potential in medicine, it is crucial to maintain clinicians in the decision-making loop. An important prerequisite to this is to educate medical professionals in how these tools work and sometimes don't work.

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NEURO-SYSMED VIEWPOINT

Text by Tale Litlere Bjerknes, Neuro-SysMed

THE IMPACT OF LONG-TERM MECHANICAL VENTILATION ON THE QUALITY OF LIFE OF ALS PATIENTS AND THEIR FAMILIES

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterised by gradual muscle wasting and paresis due to death of motor neurons[1]. In Norway, there is around 400 patients living with ALS at any given time[2]. The progression of symptoms is often rapid, and patients die of respiratory failure on average 2-3 years after the time of diagnosis, some within the first year[1].

In later years, it has become increasingly common that patients are offered treatment with long-term mechanical ventilation support (LTMV) when they display symptoms of respiratory failure, either non-invasively using a mask or through tracheostomy. In the period of 2015-2020, 256 ALS patients started treatment with LTMV in Norway[3]. When planning ALS patient care, clinicians always consider whether the treatment offered provides the patients with more benefit than challenges or possible harm. In addition to physical parameters and survival, quality of life is an especially important parameter to consider when deciding on treatment options such as LTMV.

Quality of life is broadly defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[4].

"Overall quality of life is especially important in the ALS patient group, where the physical health will deteriorate over time as a consequence of the illness, but other factors may still make life worth living."

Instruments measuring quality of life can have questions that are only meaningful to a patient group with a specific illness (disease-specific quality of life), they can measure more general health-parameters, or the overall quality of life that also take into consideration existential and social dimensions of life. Overall quality of life is especially important in the ALS patient group, where the physical health will deteriorate over time as a consequence of the illness, but other factors may still make life worth living. There are indications that some ALS patients are able to maintain a good overall quality of life during most of the disease course, even as the physical function declines5. This is most likely due to a so-called response-shift, where patients are able to reprioritise which factors in life that are important even as the disease progresses[5].

One of the most challenging topics in ALS care is whether to extend ventilatory support into the stages of disease that require treatment both day and night.

This will extend the life of the patient, and may sustain quality of life, but the burden of caregiving for both family and caregivers is huge as the patients in this disease stage require extensive support and often has communication difficulties. While prolongation of life may be an obvious goal for some patients, it also entails the possibility or need to actively withdraw treatment at some future point in time, i.e. when the disadvantages outweigh the benefits, and the treatment is no longer perceived meaningful by the patient. This decision can be difficult for both the patient, next of kin and health personnel. There is currently limited knowledge on how families deal with this situation, but a small study found that 30 % of caregivers of ventilated patients had lower quality of life than the patients[6]. Other studies in earlier disease stages find that the caregivers' quality of life falls over time whereas the patients' quality of life remain stable[7,8]. There is no data regarding how young and adult children of ALS patients on ventilation support are coping with the parent's illness, but it is well-known among clinicians that the situation also has a huge impact on children and young adults in the affected families.

Based on these challenges, the ALS group at Neuro-SysMed has initiated the ALS-LTMV study, where we aim to increase the knowledge on how life-sustaining ventilation support with non-invasive or invasive mechanical ventilation affects quality of life of ALS patients, life partners and children in Norway. Quality of life will be measured around the time when the decisions about life-prolonging therapy is made, and longitudinally throughout the disease course. The ALS-LTMV study started in February 2023, and we plan to include 200 ALS families across Norway. Knowledge from this study will provide crucial information about one of the most difficult ethical issues in ALS treatment that can help patients, relatives and clinicians in the decision-making process.

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NEURO-SYSMED VIEWPOINT

Text by Ragnhild Eide Skogseth and Kristoffer Haugarvoll, Neuro-SysMed

A GROWING POPULATION OF OLDER ADULTS AND IMPACT ON NEUROLOGICAL DISEASES

Thanks to advances in hygiene, nutrition, healthier lifestyles, improved health care and reduced child mortality, we can expect to live significantly longer than just decades ago. This is certainly a good thing! However, age is the most important risk factor for several diseases, including neurodegenerative diseases. In 2020 it was estimated that there were more than 100,000 individuals suffering from dementia in Norway, and this number is expected to more than double by 2050 (https://demenskartet.no/). A similar increase is expected in the number of individuals affected by Parkinson's disease.

Dementias are already the costliest disease group in Norway with about 10% of total health spending. Almost 80 percent of the health spending related to dementias was incurred at nursing homes.

"We lack insights into the mechanisms that underlie neurodegeneration. In addition, neurodegenerative diseases are complex and current clinical classification does not sufficiently capture the biology involved."

Neurodegenerative disease is one of the last frontiers in medicine. While great strides have been made in other fields such as cardiovascular diseases and cancer, we still lack effective therapies to prevent, delay or cure neurodegenerative diseases. The major explanation for this is probably the number of limitations regarding our understanding of these diseases. We lack insights into the mechanisms that underlie neurodegeneration. In addition, neurodegenerative diseases are complex and current clinical classification does not sufficiently capture the biology involved. Thus, there is an urgent need to invest in research on neurodegenerative diseases.

Future research must address key questions related to neurodegeneration, such as how do human brain cells die? The pattern and sequence of neurodegeneration need to be mapped. We also need better insights into how brain cells are connected in the human brain, i.e. mapping the human connectome. To achieve this, we need to invest in fundamental studies on the human brain, including postmortem brain tissue donated to research.

Medical treatments have traditionally been designed as

a one-size-fits-all-approach. This may be beneficial for some patients but not for others. Precision medicine is aiming to tailor disease prevention and treatment, taking into account interindividual differences in people's genes, environments, and lifestyles. The goal is to target the right treatments to the right patients at the right time.

To enable precision medicine against neurodegenerative diseases, biomarkers are needed. Biomarkers are markers that reflect the biological state or condition. The biomarker field has been making important progress during the last decade; however, we still lack good markers of several important neuropathologies. Autopsy unfortunately remains the only way to map out the underpinning of cognitive impairment in the individual patient with dementia. Biomarkers must be further developed and verified against neuropathology so that neuroimaging and blood tests can guide more precise diagnosis that better reflect biology. Blood based biomarkers are of particular importance, as they can be implemented broadly, including in primary health care, to ensure an improvement in diagnostic accuracy for all patients in the future. This is pivotal in order to offer the best treatment at the individual level.

We must improve care for individuals suffering from neurodegenerative diseases and their families. This field of research must be advanced and measures to capture frailty must be implemented to improve quality of life and enable independent living. Education is crucial! Health professionals, patients, caregivers, and the public must be educated on how to meet individuals suffering from dementia. This is of fundamental importance to create a better society for us all!

RESEARCH SCHOOL IN TRANSLATIONAL NEUROSCIENCE

Since the launch of the Neuro-SysMed Research School in Translational Neuroscience, a broad range of PhD courses has been established. All research groups from the different fields are responsible for organising the courses, promoting high quality education to PhD candidates and other students, aiming at building a strong foundation for their research.

The Research School aims at providing PhD candidates with relevant courses to fulfil mandatory credit points for the PhD training program at the University of Bergen. Another important objective is to provide an ambitious and inspiring environment to motivate future research among junior scientists as well as established senior researchers, and to help them in developing their scientific network for future career development. The Neuro-SysMed Research School in Translational Neuroscience is coordinated by Nina Grytten Torkildsen in collaboration with the Neuro-SysMed director and co-director.

Currently, we have 7 established courses providing PhD candidates with a total of 19 ECTS:

- NEUROSYSM910, the Neuro-SysMed Junior Scientist Symposium, 3 ECTS (started 2023, running continuously)
- NEUROSYSM940, The Nature of Disease and Suffering and the Goals of Precision Medicine, 2 ECTS (started 2023, next course in 2024)
- NEUROSYSM920, Neuro-SysMed Seminars and Symposium, 3 ECTS (started 2022, running continuously)
- NEUROSYSM930, Applied Bioinformatics and Data Analysis in Medical Research, 3 ECTS (started 2022, running annually)
- CCBIONEUR910, Patient and Public Involvement in Medical and Health Research, 2 ECTS (started 2021, next course in 2024)
- CCBIONEUR911, Clinical Trials, 2 ECTS (started 2021, next course in 2024)
- CCBIONEUR912, Health Innovation, 4 ECTS (started 2021)

2023 course activities

In 2023, we hosted the established courses NEUROSYSM920 and NEUROSYSM930 as well as launched the new courses NEUROSYSM910 and NEUROSYSM940.

NEUROSYSM920, Neuro-SysMed Seminars and Symposium

This 3 ECTS course is organised with monthly seminars and an annual 2-day international Neuro-SysMed symposium. The objective is to provide knowledge on research of the Neuro-SysMed focus fields of MS, Parkinson's disease, dementia, and ALS, and treatment strategies for these diseases. The participants gain knowledge about the affiliated diseases, learn how clinical trials and treatment strategies are conducted, get acquainted with terminology and methods used in a broad range of scientific conduct, and learn to evaluate «state-of-the-art» scientific breakthroughs at Neuro-SysMed. The course is open for researchers, postdocs, PhD candidates, master students, students enrolled in the Medical Student Research Program, and others interested in the topics. See separate chapters on the seminars and the 2023 Annual Symposium.

NEUROSYSM930, Applied Bioinformatics and Data Analysis in Medical Research

This 3 ECTS course focuses on practical aspects and methodological considerations necessary when dealing with human derived data, such as data sensitivity, limited sample sizes, sample misclassification, choice of appropriate statistical models, and covariates, and tissue heterogeneity. The course is highly beneficial for participants with a research interest in bioinformatics, biology, medicine, or clinical research in general. It is open to researchers, postdocs, PhD students, master students, students enrolled in the Medical Student Research Program and others interested in the topic. This course was organised for the second time in November 2023.

"We have established the research school courses to accommodate the needs of our junior researchers. The positive evaluations from the PhD candidates illustrate that the research school is meeting their requirements and expectations, laying a strong foundation for its success and impact in our academic community".

Nina Grytten Torkildsen, Research School coordinator

NEUROSYSM910, Neuro-SysMed Junior Scientist Symposium

This 3 ECTS course aims to provide the PhD candidates and other students with valuable skills in oral presentation techniques, presenting their own research as well as giving feedback to other young researchers. The course kick-off was in January 2023. See separate chapter on the Junior Scientist Symposium.

NEUROSYSM940, The Nature of Disease and Suffering and the Goals of Precision Medicine

This 2 ECTS course in Precision Medicine (PM) provides valuable knowledge and understanding about key features and concepts related to PM, suffering, disease, and health in different research traditions. Through a broad scope of literature, seminars, and cases brought from the participants' own research projects, the aim of this course is to facilitate reflection and deliberation on central philosophical and normative issues in the social organisation and practices of PM. Key concepts are utilised to open up the PM paradigm for philosophical criticism and reflection, thus contributing to a knowledge culture of PM where central philosophical, societal, and ethical issues, dilemmas, ambiguities, and controversies are addressed. The course is open for researchers, postdocs, PhD students, master students, students enrolled in the Medical Student Research Program and others interested in the topic. The course was launched in April 2023.

NEURO-SYSMED SEMINARS

Neuro-SysMed Seminars

The overarching aim of the Neuro-SysMed Seminars is to share knowledge between the research groups and the different research disciplines within Neuro-SysMed, as well as providing professional update from invited scientists. The seminar series started in May 2022 with monthly events where PIs at Neuro-SysMed invite local, national or international speakers to provide talks on Neuro-SysMed topics.

The seminars start with an informal lunch, facilitating social interactions, networking and discussions between all members of the different research groups. The seminars are also open to other research environments and visitors.

The seminar series is part of the Neuro-SysMed Research School of Translational Neuroscience under the subject code NEUROSYSM920, covering both the Neuro-SysMed Seminars and the Annual Symposium. Participation provides 3 ECTS for PhD candidates.

The following list of seminars covering a wide range of topics were organised during 2023, including additional special seminars.

JAN 18

Laura Airas, Professor in Neurology at the University of Turku, Finland.
Title of the talk: *Microglia in multiple sclerosis – pathogenesis and imaging*

FEB 15

Christian Dölle, Neuro-SysMed researcher on Parkinson's Disease and NAD-metabolism at Haukeland University Hospital, Norway.
Title of the talk: *Cell models for Parkinson`s Disease*

MAR 22

Ole-Bjørn Tysnes, Neuro-SysMed PI for ALS research, senior consultant neurologist at the Department of Neurology, Haukeland University Hospital, and professor at the University of Bergen, Norway.
Title of the talk: *The NO-ALS study: the first Norwegian experimental treatment study against ALS*

APR 26

Aurora Martinez, Neuro-SysMed PI for drug screening, professor at the Department of Biomedicine, and leader of the Biorecognition Unit, University of Bergen, Norway.
Title of the talk: *Compound screening and drug discovery in Parkinson's disease*

MAY 24

Alberto Ascherio, Professor of Epidemiology and Nutrition at the Harvard T. H. Chan School of Public Health and a Professor of Medicine at the Harvard Medical School, USA. This was a joint event with the UiB Medical Faculty, presenting the Falch Lecture 2023.
Title of the talk: *The Epstein-Barr virus as the leading cause multiple sclerosis and the possible viral etiology of other neurodegenerative diseases*

JUN 21

Gonzalo Sanchez Nido , Neuro-SysMed Neuro-SysMed researcher on bioinformatics and Parkinson's Disease at the University of Bergen, Norway.
Title of the talk: *Decoding neurodegeneration - one cell at a time*

SEP 1

David Eidelberg, Head of the Center for Neurosciences at The Feinstein Institute for Medical Research, Manhasset, NY, USA. Special seminar.
Title of the talk: *Metabolic Networks as Functional Biomarkers of Parkinson's Disease*

SEP 13

Mathias Ziegler, Neuro-SysMed PI for metabolomics, professor and leader of the Molecular Bioenergetics and Signaling Group at the Department of Biomedicine, University of Bergen, Norway.
Title of the talk: *Key roles of NAD metabolism in neurodegeneration*

OCT 18

Trond Riise, Neuro-SysMed PI for drug screening and professor in epidemiology at the Department of Global Public Health and Primary Care, University of Bergen, Norway. He leads the DRONE group – Drug RepurpOsing for NEurological diseases.
Title of the talk: *Drug-wide prospective study associates thirty-one drug classes with the risk of Parkinson's disease*

NOV 22

Christopher Elnan Kvistad, neurologist researcher on treatment with mesenchymal stem cells in MS, PI in the Neuro-SysMed SMART-MS study and holds a clinical career grant from Helse Vest within the field of stem cell based neuroregeneration.
Title of the talk: *A brief history of the (failing) neural regeneration in the human CNS*

DEC 5

NeuroDialogues, a Special Seminar on *Reconstructing Identity – Navigating Neurological Changes*. Workshop initiative from the Neuro-SysMed RRI/PPI node, with the aim to foster discussions and debates on a wide spectrum of topics at the intersection of severe neurological conditions, technology, and the human mind. It serves as a space for exploring the profound questions raised by the integration of cutting-edge technologies and medical practices in the field of neurology.

DEC 13

Mathias Toft, Head of the Department of Neurology, Oslo University Hospital and Professor of neurology at the University of Oslo, Norway.
Title of the talk: *Insights into Parkinson's disease: From genetic associations to functional mechanism*

THE NEURO-SYSMED ANNUAL SYMPOSIUM

The very first Neuro-SysMed Annual Symposium took place at the historic Solstrand Hotel outside of Bergen, September 25-26, 2023, with more than 120 participants from the Neuro-SysMed environment.

Besides being the Neuro-SysMed event of the year and open to all, the annual symposium is part of the course NEUROSYSM920 - Neuro-SysMed seminars and symposium, at the Neuro-SysMed Research School for Translational Neuroscience.

The 2023 program covered sessions on treatment trials in neurodegeneration and in multiple sclerosis, NAD replenishment as a strategy for neuroprotection, and statistics for clinical trials. International speakers including professors Kailash Bhatia (UK), Raymond Koopman (the Netherlands), Marie Vidailhet (France), Suvankar Pal (UK), Xavier Montalban (Spain), Fredrik Piehl (Sweden), Vilhelm Bohr (USA/Denmark), Tim Friede (Germany), Fan Li and Tong Guangyu (both USA) shared from their vast experience, and local senior and junior researchers added to the program with ongoing Neuro-SysMed research.

The Neuro-SysMed Director Kjell-Morten Myhr and Co-Director Charalampos (Haris) Tzoulis opened the talks by presenting the Neuro-SysMed origin, visions, and goals. The following talks highlighted challenges related to diagnosis as well as to treatment and clinical inclusion of atypical Parkinson's disease. Research on young onset dementia showed the importance of adapting the follow-up related to age and the need for the patient and families, quite different from older onset dementia. These presentations were followed by talks on multiple sclerosis treatment options and optimalisation, as well as mechanisms of action of B-cell therapies, and new potential trials and research from imaging and biomarkers.

The NAD session provided an excellent review of the basic concepts and rationale for a large number of trials currently being performed at Neuro-SysMed. The Centre is currently running NAD trials across all

four diseases. Professor Vilhelm Bohr provided a comprehensive overview of how it all started, followed up by glimpses of some of the trials happening at the Centre right now.

The statistics session by professors Tim Friede, Fan Li and Tong Guangyu was followed by a plenum discussion together with Professors Bettina Husebø and Charalampos Tzoulis, facilitating a fruitful discussion.

> "One size doesn't fit all. For instance, when something is developed for Parkinson's, you cannot take for granted that you can apply the same for MS. We need to be very aware of the designs we use for clinical trials."
> – Charalampos Tzoulis

The program also included a successful poster session where junior researchers could present their projects. Twenty high quality posters were discussed and evaluated. An evaluation committee did their rounds to evaluate the PhD candidates among the poster presenters, as well as selecting a winner for Best Poster among all 20. The audience also digitally elected the Best Poster winner through voting on their cell phones. Both winners received great applause during the closing remarks on the last day: Elise Førsund for Best Poster by the evaluation committee, and Yola Gerking for Best Poster by audience voting.

Neuro-SysMed used the opportunity to have strategy meetings with the Scientific Advisory Board (SAB), consisting of Kailash Bhatia, Raymond Koopman and Xavier Montalban. The SAB expressed clear support for Neuro-SysMed's research and provided valuable advice for further developments.

The 2nd Neuro-SysMed Annual Symposium will take place September 30 - October 1, 2024, also this time at Solstrand.

SCIENTIFIC PROGRAM

Day 1: Monday September 25, 2024

Neuro-SysMed
Annual Symposium

08:00-09:20	Registration and coffee
09:20-09:30	Welcome by the Neuro-SysMed Director Kjell-Morten Myhr and Co-Director Charalampos Tzoulis

SESSION 1: THEURAPEUTIC TRIALS IN NEURODEGENERATION, chair: Charalampos Tzoulis

09:30-10:25	Keynote Lecture by Professor Kailash Bhatia, Sobell Department of Movement Neuroscience at the Institute of Neurology, UCL, London, UK and the National Hospital for Neurology and Neurosurgery, London. Talk title: Atypical atypical parkinsonism
10:25-10:50	Professor Raymond Koopmans, Radboud University Medical Center, the Netherlands. Talk title: Palliative care in people with young onset dementia
10:50-11:10	Professor Bettina Husebø, Neuro-SysM ed and the Centre for Elderly and Nursing Home Medicine, University of Bergen. Talk title: Visualization of pain in people with dementia by system analysis algorithms
11:10-11:30	Associate Professor Line Iden Berge, Neuro-SysMed and the Department of Global Public Health and Primary Care, University of Bergen. Talk title: Virtual darkness and digital phenotyping in specialized and municipal dementia care: The DARK.DEM randomized controlled trial
11:30-12:30	Lunch break

SESSION 1 CONTINUED, chair: Kristoffer Haugarvoll

12:30-13:05	Keynote lecture by Professor Marie Vidailhet, the Movement Disorders and Parkinson's Disease Department at the Salpêtrière Hospital, Sorbonne University, Paris, France. Talk title: Markers of atypical parkinsonism - from diagnosis to treatment evaluation
13:05-13:40	Professor Suvankar Pal, the Centre for Clinical Brain Sciences, University of Edinburgh, UK. Talk title: MND SMART - Delivering innovation for trials in motor neuron disease (MND)
13:40-14:00	PhD Candidate Julia Tuominen, Neuro-SysMed and the Department of Global Public Health and Primary Care, University of Bergen. Talk title: Medication use after diagnosis and Parkinson's disease survival: A target trial approach
14:00-14:30	Coffee break

SESSION 2: THERAPEUTIC TRIALS IN MULTIPLE SCLEROSIS, chair: Kjell-Morten Myhr

14:30-15:25	Keynote lecture by Professor Xavier Montalban, Multiple Sclerosis Centre of Catalonia (CEMCAT)/ Neurology Department, Vall d'Hebron University Hospital (HUVH), Neuroimmunology Research Group at the Vall d'Hebron Research Institute (VHIR), Barcelona, Spain. Talk title: New mechanistic framework for MS. Therapies in clinical practice and future treatments for progressive MS
15:25-15:50	Professor Fredrik Piehl, Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden. Talk title: B-cell depletion in multiple sclerosis; mode of action and optimisation of long-term benefit-risk balance
15:50-16:15	Professor Øivind Torkildsen, Neuro-SysMed and Department of Clinical Medicine, University of Bergen, and Department of Neurology, Haukeland University Hospital, Bergen. Talk title: Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease - The OVERLORD-MS trial, and TAF-1 - Tenofovir antiviral therapy in multiple sclerosis
16:15-16:30	Dr. Frank Riemer, Neuro-SysMed and Mohn Medical Imaging and Visualization Centre (MMIV), Department of Radiology, Haukeland University Hospital, Bergen, Norway. Talk title: Microstructural changes precede depression in patients with relapsing-remitting multiple sclerosis
16:30-16:45	PhD Candidate Akash Kapali, Neuro-SysMed and the Department of Global Public Health and Primary Care, University of Bergen. Talk title: Dietary vitamin D and the risk of multiple sclerosis in the Norwegian Mother, Father and Child cohort
16:45-18:00	Break
18:00-19:30	**POSTER SESSION & Aperitif, same room as the talks, chairs: Ragnhild Skogseth and Christian Dölle**
19:30	Dinner

Day 2: Tuesday September 26, 2024

Neuro-SysMed
Annual Symposium

SESSION 3: NAD REPLENISHMENT AS A STRATEGY FOR NEUROPROTECTION, chair: Mathias Ziegler

09:00-09:55 Keynote Lecture by Professor Vilhelm Bohr, Department of Cellular and Molecular Medicine, University of Copenhagen, Denmark. Talk title: DNA damage signaling to mitochondria in neurodegeneration and aging

09:55-10:15 Professor Mathias Ziegler, Neuro-SysMed and the Department of Biomedicine, University of Bergen. Talk title: NR – how and why it works. Sometimes.

10:15-10:25 Coffee break

10:25-10:45 Dr. Christian Dölle, Neuro-SysMed and the Department of Clinical Medicine, University of Bergen. Talk title: NAD replenishment therapy for Parkinson's disease

10:45-11:00 Dr. Suraj Sharma, Neuro-SysMed and the Department of Biomedicine, University of Bergen. Talk title: Predicting metabolic alterations in human metabolism using a genome-scale network analysis approach

11:00-11:15 PhD Candidate Haakon Berven, Neuro-SysMed, University of Bergen. Talk title: NR-SAFE: a randomized, double-blind safety trial of high dose nicotinamide riboside in Parkinson's disease

11:15-11:30 Associate Professor Ragnhild Eide Skogseth, Neuro-SysMed and the Department of Clinical Science, University of Bergen. Talk title: N-DOSE-AD: a dose optimization study of nicotinamide riboside in Alzheimer's disease

11:30-13:00 Check out of rooms for those leaving on the 26th, and lunch

SESSION 4: BIOSTATISTICS FOR CLINICAL TRIALS, chair: Bettina Husebø

13:00-13:25 Professor Tim Friede, Department of Medical Statistics, University Medical Center Göttingen, Germany. Talk title: Multiple treatment arms, design stages and endpoints: Methods and their applications in neurodegenerative diseases

13:25-13:50 Dr. Fan Li, Department of Biostatistics, Yale University, USA. Talk title: Current developments in stepped wedge cluster randomized trials

13:50-14:15 Dr. Tong Guangyu, Yale School of Medicine, Yale University, USA. Talk title: A Bayesian approach for estimating the survivor average causal effect when outcomes are truncated by death in cluster-randomized trials

14:15-15:00 Workshop/Discussion - Challenges in the field, discussion with all.

15:00-15:15 Closing remarks and prizes for best poster

JUNIOR SCIENTIST SYMPOSIUM

This symposium series was established in 2023, aiming to provide the PhD candidates and other students with valuable skills in oral presentation techniques, giving them an arena to present their own research as well as give feedback to their peers.

The symposia are organised 4 times annually, twice every semester. The program kick-started in January 2023 with the opening lecture by Professor Lars A. Akslen, Director at CCBIO, University of Bergen, explaining how the young CCBIO researchers have benefitted from the CCBIO Research School for Cancer Studies, giving an example from another Center of Excellence.

Since then, every symposium has included an inspirational talk from other senior researchers, as well as PhD candidates and postdoctoral researchers presenting their work. We are happy to see that the participants engage in scientific discussions and take advantage of peer reviews and comments. The aim is that this will strengthen the scientific quality of their work and boost their scientific thinking.

Neuro-SysMed

Junior Scientist Symposium SCIENTIFIC PROGRAMS

JANUARY 18, 2023

Auditorium in Bikuben
Academic responsible: Shamundeeswari Anandan
Chair:

13.15-13.30	Introduction
13.30-14.00	Keynote lecture by **Professor Lars A. Akslen**, Director at CCBIO: Our experience of great benefits for students attending the Junior Symposia at CCBIO
14.00-14.15	*Coffee break*
14.15-14.40	**Simon Ulvenes Kverneng**: Respiratory chain integrity in Parkinson's disease skeletal muscle
14.40-15.05	**Andrea Habbestad**: Towards older age at Multiple Sclerosis onset?
15.05-15.20	*Coffee break*
15.20-15.45	**Haakon Reithe**: Wearable sensing technology in research for Parkinson's disease: experience from the field
15.45-16.05	**Ingrid Anne Lie**: Research stay abroad. My experiences from Amsterdam
16.05-16.20	Concluding remarks

APRIL 28, 2023

Auditorium 4, BB-Building
Academic responsible: Shamundeeswari Anandan
Chairs: Ida Herdlevær and Sepideh Mostafavi

09.00-09.10	Welcome and introduction
09.10-09.40	Keynote lecture by **Katrin Kleinmanns**: Disease modelling – challenges and opportunities
09.40-10.10	**Christopher Kvistad**: SMART-MS – Can mesenchymal stem cells promote regeneration in multiple sclerosis?
10.10-10.30	*Coffee break*
10.30-10.55	**Katarina Lundervold**: Parkinson's disease and the gut
10.55-11.20	**Magne Solheim**: Studying ALS using health registries – An introduction to my PhD project
11.20-12.00	*Lunch (included)*
12.00-12.25	**Brit Ellen Rød**: B-cell depletion therapy in multiple sclerosis
12.25-12.50	**Haakon Berven**: NAD clinical studies in Parkinson's disease
12.50-13.00	Concluding remarks

OCTOBER 20, 2023

Auditorium 4, BB-Building
Academic responsible: Shamundeeswari Anandan
Chairs: Yola Gerking and Fiona Dick

09.00-09.10	Welcome and introduction
09.10-10.10	Keynote lecture by **Cecilie Nordbotten**: Life after PhD: Career guidance and how to build your academic CV
10.10-10.30	*Coffee break*
10.30-10.55	**Magnus Svensen**: Phosphorous MRS in neurodegenerative disorders
10.55-11.20	**Tale Bjerknes**: Mitochondrial dysfunction in amyotrophic lateral sclerosis
11.20-12.00	*Lunch (included)*
12.00-12.25	**Eirik Solheim**: Using multi-omics to discover new pathways controlled by the cerebellar degeneration-related proteins
12.25-12.50	**Anna Rubiolo**: Stratification of idiopathic Parkinson's disease based on mitochondrial dysfunction: the mitoPD subtype
12.25-12.50	Concluding remarks

DECEMBER 1, 2023

Auditorium 4, BB-Building
Academic responsible: Shamundeeswari Anandan
Chairs: Katarina Lundervold and Brit Ellen Rød

09.00-09.10	Welcome and introduction
09.10-09.40	Keynote lecture by **Dr. Paulo Rodrigues Santos,** University of Coimbra, Portugal: Disease modelling – challenges and opportunities
09.40-10.10	Keynote lecture by **Dr. Sonia Gavasso**: University of Bergen, Norway: Neuro-immunological insights from high dimensional analysis
10.10-10.30	*Coffee break*
10.30-10.55	**Peder Lillebostad**: SNceg: automated segmentation of the substantia nigra pars compacta from multiparametric MRI
10.55-11.20	**Karine Eid**: Summary of findings from my PhD thesis: Childhood abuse, adult abuse, and the risk of perinatal depression in women with multiple sclerosis
11.20-12.00	*Lunch (included)*
12.00-12.25	**Yola Gerking**: Application of imaging mass cytometry to compare microglia activation in various brain regions in paraneoplastic cerebellar degeneration
12.25-12.50	**Gard A. S. Johanson**: The N-ADAPT study: a Randomized Double-blind Trial of NAD Replenishment Therapy for Atypical Parkinsonism
12.50-13.00	Concluding remarks

RESEARCH NODES

In previous years, we have reported the work by each principal investigator and their respective research groups separately. During the development of the Neuro-SysMed activities, we have seen a need to improve this presentation to focus on research areas across research groups in the Centre. In addition, during 2023 we had some changes to our principal investigator team: Senior Researcher Xiao Liang has left to start her own research focusing on POLG disease; Dr. Gonzalo Sanchez Nido and Dr. Dimitrios Kleftogiannis have taken over responsibility for the bioinformatics node and infrastructure.

We have now organised Neuro-SysMed into the following nodes:

- **Multiple Sclerosis (MS) Node**, led by **Professor Kjell-Morten Myhr**, coordinating clinical studies in MS
- **Parkinson's Disease (PD) Node**, led by **Professor Charalampos Tzoulis**, coordinating clinical studies in PD
- **Amyotrophic Lateral Sclerosis (ALS) Node**, led by **Professor Ole-Bjørn Tysnes**, coordinating clinical studies in ALS
- **Dementia Node**, led by **Dr. Kristoffer Haugarvoll**, coordinating clinical studies in dementia
- **Care Node**, led by **Professor Bettina Husebø**, coordinating clinical studies in care and palliation
- **Drug Discovery Node**, led by **Professors Aurora Martinez and Trond Riise**, coordinating drug discovery activities for novel and repurposed compounds
- **Cell Models Node**, led by **Dr. Christian Dölle**, coordinating development and characterisation of cell models for the purpose of drug discovery
- **Systems Biology & Bioinformatics Node**, led by **Dr. Gonzalo Sanchez Nido** and **Dr. Dimitrios Klefogiannis**, coordinating data integration, multimodal analyses and bioinformatics – an essential part of our systems medicine activity
- **Responsible Research and Innovation & Patient and Public Involvement (RRI/PPI) Node**, led by **Professor Jan Reinert Karlsen** and **Dr. Caroline Engen**, coordinating RRI/PPI and philosophy of neurodegeneration

THE MULTIPLE SCLEROSIS (MS) NODE

Biomarkers and tailored therapies for patients with multiple sclerosis

The Multiple Sclerosis (MS) Node conducts cutting-edge translational and clinical research with the aim to improve early diagnosis, treatment, and quality of life of individuals with MS. The MS Node has a longstanding and internationally acknowledged research experience spanning from basic immunopathological characterisation of the disease and preclinical animal studies to studies on epidemiology, clinical course, imaging, treatment trials, health economy and patient reported outcome measures.

Node leader: Kjell-Morten Myhr
Myhr is a senior consultant and professor of neurology and has since 2001 chaired the Bergen Multiple Sclerosis (MS) Research Group at Haukeland University Hospital and the University of Bergen. He has previously chaired the Norwegian MS Competence Centre, the Norwegian MS registry and the first KG Jebsen Centre for Medical Research (in MS) and is currently the director of Neuro-SysMed.

The MS Node is focusing on major challenges in MS therapy, aiming at optimising the treatment of relapsing-remitting MS, with early high efficacy therapies and stem cell therapy in patients with breakthrough disease activity. The node is also focusing on the treatment of progressive MS, as well as symptomatic therapy of pain and spasticity, and most recently searching for novel antiviral treatment targets for treatment and disease prevention.

Node activities

The MS Node has broad experience focusing on various topics related to diagnosis and treatment of the disease. Ongoing research projects are aiming at defining the importance of potential risk factors as well biomarkers for prognosis and treatment response to optimise treatment strategies at different disease stages. Overall, the aim is to develop tailored treatment strategies for patients with MS. Major challenges are thus how to improve the use of already available disease modifying therapies, and how to define new disease pathways that can be targeted by novel treatments. The latter is especially needed for the progressive disease courses in MS. Most recently, we are also developing novel treatment strategies for possible prevention of the disease. The MS Node is currently running twelve investigator and nine industry sponsored clinical trials.

Investigator sponsored clinical trials:

• **The RAM-MS study** evaluates the safety and efficacy of autologous hematopoietic stem cell transplantation compared to high-efficacy disease-modifying therapies in relapsing disease activity.

• **The OVERLORD-MS study** is a non-inferiority study evaluating and comparing the efficacy and safety of rituximab (500 mg) and ocrelizumab (600 mg) in newly diagnosed relapsing remitting MS patients.

• **The ocrelizumab to rituximab switch study** is an observational study evaluating the efficacy and safety of switching therapy from ocrelizumab (600 mg) to rituximab (500 mg) after 30 months of therapy. This is an extension of the OVERLORD-MS study.

• **REDUCE-MS** is an observational study investigating extended dosing interval of rituximab therapy. Patients that have been stable on standard 6-months dosing intervals of rituximab for 36 months (during the OVERLORD-MS study) will extend the dosing interval to 12 months for further 24 months.

• **The COVID-19 vaccine response study** evaluates the impact of various disease-modifying therapies on the vaccination response in MS patients, and in addition evaluate the clinical efficacy of vaccination.

• **The SMART-MS study i**s a placebo-controlled, cross-over pilot study evaluating regenerative effects from mesenchymal autologous stem cells in progressive MS.

• **NORSEMAN-MS** is a placebo-controlled add of nicotinamide riboside (NR) to standard care in progressive multiple sclerosis, evaluating effects on disability progression defined by the Expanded Disability Status Score (EDSS), the Nine-Hole-Peg test (9-HPT) or Timed 25 Foot Walking (T25FW).

• **The rituximab versus cladribin study** is a prospective registry-based observational study, comparing the

efficacy of the therapies among previous untreated patients and those that switch from previous therapies due to treatment failure or side effects.

• **TAF-MS 0** is a six-month observational study to evaluate Epstein-Barr virus (EBV) shedding in the saliva of patients receiving natalizumab, rituximab or cladribine for relapsing-remitting MS.

• **TAF-MS 1** is a placebo-controlled add-on proof-of-concept study of tenofovir alafenamide fumarate (TAF) to standard natalizumab infusion therapy. Stable natalizumab treated RRMS patients will receive oral placebo or 25 mg of TAF for six months.

• **A digital therapeutic to improve Insomnia in multiple sclerosis** is a randomised controlled trial to evaluate the efficacy and safety of cognitive behavioural therapy for insomnia in multiple sclerosis.

• **The 3TR – Taxonomi, Treatment, Target and Remisson – study** is an international EU-funded observational study to define treatment response biomarkers for different immune mediated diseases.

The MS Node also serves as the national coordinator for five industry-sponsored multicentre randomised clinical trials in both relapsing-remitting and progressive disease. In addition, they are the national coordinator in one extension study and another five safety studies sponsored by the industry.

In addition, the MS Node is currently immune phenotyping stem cells and immune cells from patients included in the ongoing clinical trials, aiming at identifying biomarkers for tailored dosing or patient selection for the different therapies. They also perform preclinical animal studies to evaluate possible disease pathways of progressive MS and regenerative potentials of stem cell therapy. They also evaluate treatment responses by neurofilament biomarkers in both spinal fluid and serum. In collaboration with the Mohn Medical Imaging and Visualization Centre at Haukeland University Hospital, they evaluate treatment responses by magnetic resonance imaging (MRI).

The MS Node is also running projects for optimising treatment switches if treatment fails, as well as safety studies of therapy during breastfeeding. Further, the node has ongoing studies aiming at identifying modifiable risk factors for the disease that may influence disease progression, or even risk of side effects from therapies. This includes studies of comorbidity, with special focus on cancer, as well as registry projects analysing real world data on treatment compliance and factors influencing discontinuation rates for ongoing therapies.

Selected publications from 2023:

1. **König M, Lorentzen ÅR, Torgauten HM, Tran TT, Schikora-Rustad S, Vaage EB, Mygland Å, Wergeland S, et. al.** Humoral immunity to SARS-CoV-2 mRNA vaccination in multiple sclerosis: the relevance of time since last rituximab infusion and first experience from sporadic revaccinations. J Neurol Neurosurg Psychiatry 2023;94(1):19-22. doi: 10.1136/jnnp-2021-327612. PMID: 34670844
2. **Grytten N, Myhr KM, Celius EG, Benjaminsen E, Midgard R, Vatne A, Aarseth JH, Mannseth J, Torkildsen Ø.** Cancer related mortality in multiple sclerosis. A population based cohort study. Mult Scler Relat Disord 2023;69:104417. doi: 10.1016/j.msard.2022.104417. PMID: 36423459
3. **Lie IA, Rød BE, Kvistad SS, Holmøy T, Myhr KM, Torkildsen Ø, Wergeland S.** Interferon β1a treatment does not influence serum Epstein-Barr virus antibodies in patients with multiple sclerosis. Mult Scler Relat Disord 2023;70:104530. doi: 10.1016/j.msard.2023.104530. PMID: 36701908
4. **Karlowicz JR, Klakegg M, Aarseth JH, Bø L, Myhr KM, Torgauten HM, Torkildsen Ø, Wergeland S.** Predictors of hospitalization due to infection in rituximab-treated MS patients. Mult Scler Relat Disord 2023;71:104556. doi: 10.1016/j.msard.2023.104556. PMID: 36842313
5. **Riemer F, Skorve E, Pasternak O, Zaccagna F, Lundervold AJ, Torkildsen Ø, Myhr KM, Grüner R.** Microstructural changes precede depression in patients with relapsing-remitting Multiple Sclerosis. Commun Med (Lond) 2023;3(1):90. doi: 10.1038/s43856-023-00319-4. PMID: 37349545.
6. **Kalincik T, Sharmin S, Roos I, Freedman MS, Atkins H, Burman J, Massey J, Sutton I, Withers B, Macdonell R, Grigg A, Torkildsen Ø, Bo L, Lehmann AK, et. al.** Comparative Effectiveness of Autologous Hematopoietic Stem Cell Transplant vs Fingolimod, Natalizumab, and Ocrelizumab in Highly Active Relapsing-Remitting Multiple Sclerosis. JAMA Neurol 2023 Jul 1;80(7):702-713. doi: 10.1001/jamaneurol.2023.1184. PMID: 37437240
7. **Kapali A, Daltveit AK, Myhr KM, Bjornevik K, Baldin E, Pugliatti M, Riise T, Cortese M.** Childbirth delivery mode and the risk of multiple sclerosis: a prospective population-based study. J Neurol Neurosurg Psychiatry 2023;95(1):8-13. doi: 10.1136/jnnp-2023-331241. PMID: 37479464
8. **Førde JL, Herfindal L, Myhr KM, Torkildsen Ø, Mollnes TE, Skrede S.** Ocrelizumab and ofatumumab, but not rituximab, trigger complement induction in vitro. Int Immunopharmacol 2023;124(Pt B):111021. doi: 10.1016/j.intimp.2023.111021. PMID: 37816262
9. **van der Linden ML, Kos D, Moumdjian L, Kalron A, Coote S, Smedal T, et al.** Changes in physical activity participation during the COVID-19 pandemic in people with multiple sclerosis: An international survey study. Ann Phys Rehabil Med 2023;66(7):101798. doi: 10.1016/j.rehab.2023.101798. PMID: 37967488.
10. **Habbestad A, Willumsen JS, Aarseth JH, Grytten N, Midgard R, Wergeland S, Myhr KM, Torkildsen Ø.** Increasing age of multiple sclerosis onset from 1920 to 2022: a population-based study. J Neurol 2023. doi: 10.1007/s00415-023-12047-9. Online ahead of print. PMID: 38097800

THE PARKINSON'S DISEASE (PD) NODE

Biomarkers and tailored therapies for Parkinson's disease

The Parkinson's Disease Node conducts cutting-edge translational and clinical research with the aim to improve the diagnosis, treatment, and quality of life of individuals with PD and other parkinsonisms, including dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal syndrome (CBS).

Node leader: Charalampos Tzoulis

Charalampos Tzoulis, MD, PhD, is Professor of Neurology and Neurogenetics at the University of Bergen and Haukeland University Hospital, Bergen, Norway. He is also Director for Neurodegeneration at the Neuro-SysMed, and Director of the DECODE-PD, KG Jebsen Centre for Translational Research in Parkinson's disease. As a clinical neurologist, Professor Tzoulis is an internationally recognised expert on movement disorders and neurodegeneration. His work has made key scientific contributions to the field, especially pertaining to the role of mitochondrial dysfunction and NAD-metabolism in Parkinson's disease. Professor Tzoulis has pioneered trials of NAD-replenishment with NR for degenerative parkinsonisms and is currently a global leader in this field.

Key node partner: Mandar S. Jog

Professor Mandar S. Jog, MD, FRCPC, is a leader in research and innovation in the fields of movement disorders and neurodegeneration, and is Director of the London Movement Disorders Centre, Ontario, Canada. He is the co-PI of the STRAT-PARK initiative, and Head of the study arm in Canada.

The PD Node is globally acknowledged for implementing full-cycle translation – from the laboratory to the bedside and back – and for being world leaders in NAD-replenishment therapy for neurodegeneration. Their work has been acclaimed by the field and has constituted the foundation for multiple clinical trials across neurodegenerative diseases, at the Centre and across the globe.

Node activities

Basic and translational research at the PD Node has nominated mitochondrial function and NAD-metabolism as promising therapeutic targets primarily for PD and, by extension, other neurodegenerative and neuroinflammatory disorders, including Alzheimer's disease, ALS, and MS. Inspired by these findings, the PD Node conducts multiple clinical trials of NAD-replenishment therapy, with a broad range of objectives ranging from establishing safety and pharmacokinetic profiles, to determining the optimal biological dose for brain diseases, and testing efficacy in delaying or preventing PD and other parkinsonisms. Moreover, this research has catalysed several other NAD-replenishment trials at the Centre, targeting Alzheimer's disease, ALS, and MS (see respective sections). In addition, the PD Node is working actively on setting the foundations for individualised medicine in PD, by running an international initiative aiming to stratify PD according to underlying molecular mechanisms and develop biomarkers for patient selection for tailored therapies. Finally, the PD Node runs world-class translational research aiming to identify novel therapeutic targets and candidate therapies for PD and emerging subtypes thereof.

During 2023, the PD Node made key advances in their clinical research projects, which include six clinical trials, and one prospective cohort study:

- **The NR-SAFE study** is a phase I randomised, double blinded trial, with the primary objective to assess the safety and tolerability of high dose NR therapy (3000 mg daily) in PD.
- **The N-DOSE study** is a phase II randomised, double blinded dose-optimisation trial of NR in PD. The primary objective is to determine the optimal biological dose of NR for PD and other brain diseases.
- **The NADbrain study** is a phase I pharmacokinetic study, aiming to assess the blood and brain NAD-kinetics following the consumption of different NAD-precursors. Based on the results of NADbrain, the optimal dosing frequency of NAD replenishment therapy will be determined.

• **The NO-PARK study** is a phase-III randomised, double-blind, multicentre clinical trial, with the primary objective to assess the efficacy of NR as a neuroprotective therapy, delaying the rate of neurodegeneration and clinical disease progression in PD.

• **The NO-PARK extension study** is a phase-III open-label, multicentre clinical trial, with the primary objective of assessing the long-term safety of NR therapy in PD.

• **The NADAPT study** is a phase-II randomised, double-blind, multicentre trial, aiming to assess the efficacy of NR as a neuroprotective, disease-modifying therapy for atypical parkinsonism, including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal syndrome (CBS).

• **The STRAT-PARK initiative** is a longitudinal population-based multicentre cohort study aiming to identify biological subtypes of PD and to develop biomarkers enabling patient stratification in clinical practice.

Selected publications from 2023:

1. **Flønes IH, Toker L, Sandnes DA, Lura N, Shadad O, Nyland H, Sandnes DA, Fernandez-Vizarra E, Painous C, Pérez-Soriano A, Compta Y, Molina-Porcel L, Alves GW, Tysnes OB, Dölle C, Nido GS, Tzoulis C.** Mitochondrial complex I deficiency stratifies idiopathic Parkinson's disease. Accepted, Nature Communications, Dec 2023.
2. **Berven H, Kverneng S, Sheard E, Søgnen M, Af Geijerstam S, Haugarvoll K, Skeie, GO, Dölle C, Tzoulis C.** NR-SAFE: a randomized, double-blind safety trial of high dose nicotinamide riboside in Parkinson's disease. Nat Commun. 2023 Nov 28;14(1):7793.
3. **Neufeld LM, Ho E, Obeid R, Tzoulis C, Green M, Huber LG, Stout M, Griffiths JC.** Advancing nutrition science to meet evolving global health needs. Eur J Nutr. 2023 Dec;62(Suppl 1):1-16
4. **Gaare JJ, Brügger K, Nido GS, Tzoulis C.** DNA methylation age acceleration is not associated with age of onset in Parkinson disease. Mov Disord. 2023 Nov;38(11):2064-2071.
5. **Dick F, Gard J, and Tzoulis C.** Neuronal loss drives differentially expressed protein-pathways in the PSP globus pallidus. Clin Transl Med. 2023 Jul;13(7):e1280.
6. **Toker L, Nido GS, and Tzoulis C.** Not every estimate counts. Genome Med. 2023 Jun 7;15(1):41.
7. **Gaare JJ, Dölle C, Brakedal B, Brügger K, Haugarvoll K, Nido GS, Tzoulis C.** Nicotinamide riboside supplementation is not associated with altered methylation homeostasis in Parkinson`s disease. iScience. 2023 Feb 27;26(3):106278.
8. **Dick F, Tysnes OB, Alves GW, Nido GS, and Tzoulis C.** Altered transcriptome-proteome coupling indicates aberrant proteostasis in Parkinson's disease. iScience. 2023 Jan 4;26(2):105925.

THE AMYOTROPHIC LATERAL SCLEROSIS (ALS) NODE

Clinical studies and stratification of ALS

The ALS Node conducts cutting-edge clinical research on ALS with the aim to improve the diagnosis, treatment options, and care of individuals with ALS.

Node leader: Ole-Bjørn Tysnes
Ole-Bjørn Tysnes is a consultant neurologist at the Department of Neurology at Haukeland University Hospital, and professor of 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 ALS studies at Neuro-SysMed.

The ALS node conducts clinical and molecular research with the aim to improve the diagnosis, treatment, and quality of life of individuals with ALS.

Node activities

Translational and clinical research from our PD Node and other groups has nominated NAD-replenishment therapy as a potential neuroprotective intervention across neurodegenerative diseases. Moreover, one small study suggested that the combination of NR and pterostilbene (a sirtuin activator), may have added benefit in patients with ALS (PMID: 30668199). Encouraged by this evidence, the ALS Node conducts clinical trials to determine whether combination therapy of NR and pterostilbene may inhibit neurodegeneration and increase survival and quality of life in patients with ALS. Another area the ALS Node is particularly active in is evaluating the effect of life-prolonging interventions, such as mechanical ventilation, on the quality of life of patients and their informal caregivers. Finally, the ALS Node conducts research aiming to improve the diagnosis and tailored treatment opportunities for patients.

During 2023, the ALS node made substantial advances in their clinical research projects, which include five clinical trials, including one industry-sponsored trial, and one prospective cohort study.

- **The NO-ALS study** is a phase-II randomised, double-blind, multicentre clinical trial, with the primary objective to assess the efficacy of NR as a neuroprotective therapy, delaying the rate of neurodegeneration and clinical disease progression and increasing patient survival in ALS.
- **The NO-ALS extension study** is a phase-II open label, multicentre clinical trial, with the primary objective of assessing the long-term safety of NR therapy in ALS, actively recruiting patients who have completed the NO-ALS study.
- **The LTMV study** aims at studying the effects of long-term ventilation support in ALS patients on quality of life in patients and their families.
- **STRAT-ALS**: The ALS Node is carrying out a stratification study in ALS (STRAT-ALS), recording detailed clinical data and collecting biological materials including autopsies from ALS patients and controls.

Selected publications from 2023:

1. **Olsen CG, Busk ØL, Holla ØL, Tveten K, Holmøy T, Tysnes OB, Høyer H.** Genetic overlap between ALS and other neurodegenerative or neuromuscular disorders. Amyotroph Lateral Scler Frontotemporal Degener 2023 Oct 17:1-11. doi: 10.1080/21678421.2023.2270705. Online ahead of print.
2. **Taule T, Eide IS, Fjær L, Myrberget MA, Oseland MS, Renså MA, Revheim T, Tysnes OB, Aßmus J, Rekand T.** Norwegian version of the Edinburgh cognitive and behavioural ALS screen: Construct validity, internal consistency, inter-rater, and test-retest reliability. PLoS One. 2023 May 4;18(5):e0285307. doi: 10.1371/journal.pone.0285307. eCollection 2023.PMID: 37141321

THE DEMENTIA NODE

Biomarkers and tailored therapies for dementia

The Dementia Node conducts clinical and translational research aiming to improve the diagnosis and treatment of people with neurodegenerative dementias, such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). The dementia research at Neuro-SysMed depends heavily on our partners at Haraldsplass Deaconess Hospital, the University of Bergen and Haukeland University Hospital.

Node leader: Kristoffer Haugarvoll

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

Key node partner: Bettina Husebø

Bettina Husebø, MD, PhD is a professor and the head of the Centre for Elderly and Nursing Home Medicine (SEFAS) with 12 active researchers. Since 2019, she is also the head of innovation at the Department of Global Public Health and Primary Care (IGS). Her research focus is on care with a special focus on dementia, palliative medicine and care, pain assessment, impact of pain on behavioural disturbances in patients with dementia, psychometrics and algesimetry, sensing technology and smart housing. She is also the leader for Neuro-SysMed's Care Node. In 2023, she received an ERC Consolidator grant (5-D) and a Trond Mohn Centre for Complex Conditions and Ageing (CC.AGE).

Node activities

Motivated by the promising finding of NAD-replenishment therapy in PD, the Dementia Node has initiated clinical treatment studies to assess the neuroprotective potential of NAD-supplementation in Alzheimer's disease. In addition, they conduct state-of-the-art biomarker research aiming at identifying subtypes of individuals with dementia, including AD and DLB, and to develop clinically applicable biomarkers for stratifying the dementias according to underlying molecular patterns.

During 2023, the Dementia Node made key advances in their clinical research projects, which include one clinical trial and one prospective cohort study:

• **The N-DOSE study** is a phase II randomised, double blinded dose-optimisation trial of NR in AD. The primary objective is to determine the optimal biological dose of NR for AD, so that larger trials focusing on efficacy can be designed.

• **The STRAT-COG initiative** is a longitudinal population-based cohort study aiming at stratifying individuals with dementia, such as AD and DLB, according to underlying molecular patterns, and to develop biomarkers enabling patient stratification in clinical practice. The study is employing a comprehensive biomarker panel for dementia combining existing biomarkers for AD pathology with biomarkers for neuronal loss and α-synuclein pathology.

The Dementia Node is a partner in the ANeED study, a phase II trial testing ambroxol in DLB (PI: Arvid Rongve), and in the ongoing Dementia Disease Initiation (DDI) study (PI: Tormod Fladby).

Selected publications from 2023:

1. **Watne LO, Pollmann CT, Neerland BE, Quist-Paulsen E, Halaas NB, Idland AV, Hassel B, Henjum K, Knapskog AB, Frihagen F, Raeder J, Godø A, Ueland PM, McCann A, Figved W, Selbæk G, Zetterberg H, Fang EF, Myrstad M, Giil LM.** Cerebrospinal fluid quinolinic acid is strongly associated with delirium and mortality in hip-fracture patients. J Clin Invest. 2023 Jan 17;133(2):e163472. doi: 10.1172/JCI163472.PMID: 36409557
2. **Helvik, AS., Bergh, S., Šaltytė Benth, J. et al.** Pain and quality of life in nursing home residents with dementia after admission – a longitudinal study. BMC Health Serv Res 23, 1032 (2023). https://doi.org/10.1186/s12913-023-10041-5
3. **Puaschitz NGS, Jacobsen FF, Berge LI and Husebo BS.** Access to, use of, and experiences with social alarms in home-living people with dementia: results from the LIVE@Home.Path trial. Front. Aging Neurosci. 2023, 15:1167616. doi: 10.3389/fnagi.2023.1167616

THE CELL MODELS NODE

The Cell Models Node is tasked with constructing and characterising models reflecting key-aspects of the four disease groups of Neuro-SysMed, with the aims to increase mechanistic understanding of the diseases and to enable the screening of therapies, in collaboration with the Drug Screening Node.

Node leader: Christian Dölle

Dr. Christian Dölle is a senior researcher in Molecular Biology. A biochemist by training, he obtained his PhD in molecular biology/biochemistry in 2008. He is an expert in mitochondrial biology and NAD metabolism and has extensive experience in establishing and studying neuronal cell models.

Node activities

Efforts to develop effective therapies for PD, dementia, ALS and MS are impeded by the lack of models recapitulating fundamental processes involved in the initiation and progression of the neurodegenerative process. The Cell Models Node is establishing models of key processes associated with neuronal dysfunction and death in patients with these diseases, based on findings from the Systems Medicine Node and new discoveries published by the field. The models are then used to: 1) advance the mechanistic understanding of these processes and 2) discover therapies targeting and ameliorating these processes (in collaboration with the Drug Discovery Node).

Several models have been established, including cell models of mitochondrial dysfunction, ribosomal inhibition, and α-synuclein aggregation.

The Cell Models Node will continue to implement mechanistic analyses of these models (including multi-omics characterisation) and initiate high-throughput drug screening in collaboration with the Drug Discovery node.

THE CARE NODE

The global population ages faster than the resources for care can keep up with. In Norway, 1 in 7 employees currently work in healthcare, and this number is estimated to increase to 1 in 3 in 2050. The Care Node is focused on improving the care and quality of life of people with neurodegenerative diseases, both at home and at institutions.

Node leader: Bettina Husebø

Bettina Husebø, MD, PhD is a professor and the head of the Centre for Elderly and Nursing Home Medicine (SEFAS) with 12 active researchers. Since 2019, she is also the head of innovation at the Department of Global Public Health and Primary Care (IGS). Her research focus is on care with a special focus on dementia, palliative medicine and care, pain assessment, impact of pain on behavioural disturbances in patients with dementia, psychometrics and algesimetry, sensing technology and smart housing. She is also the leader for Neuro-SysMed's Care Node. In 2023, she received an ERC Consolidator grant (5-D) and a Trond Mohn Centre for Complex Conditions and Ageing (CC.AGE).

Node activities

The Care Node has highlighted the necessity for a paradigm change in elderly care and argues for digital phenotyping, that is, characterisation of human behaviour by moment-by-moment monitoring with personal digital devices. These are wearable devices to allow for real-time monitoring of function and quality of life, thereby optimising individualised intervention.

Current studies

• **The ActiveAgeing study** investigates digital phenotyping in older adults with and without PD by wearable devices to improve our understanding of the ageing process and PD. For this purpose, two smartwatches (Fitbit Sense and Empatica E4) and a smart ring (Oura Ring) are utilised in the project. These instruments can measure movements, heart rates, and electrodermal activities, which yield information about activity, sleep, and stress, among other. The project duration is four years, and it consists of two sub-projects: DIGI.PARK and ACT.LIVE.

• **The DIGI.PARK study** aims to better understand subtypes and symptoms in people with PD. The study will ascertain whether this technology can help identify, track, and predict symptom associations of PD. It will also investigate new outcome measures for clinical trials in PD. Partners or spouses of people with PD will also be included to explore the impact of the disease in a patient-caregiver dyad.

• **The ACT.LIVE study** takes place at the Helgetun Living Lab. Helgetun is an innovative living environment for seniors located in Bergen, aimed to support social, mental, and physical activities of older adults. The Helgetun residents are encouraged to self-organise and to participate in their favourite activities. For instance, they volunteer in the Eplekarten kindergarten, do gardening, work with the animals on the farm, and support each other whenever needed. The project aims to quantify and understand the effect on this living environment on their ageing process, and to what extent it fosters an active lifestyle. For this purpose, the subjects' daily life will be monitored with wearable devices, and qualitative interviews will be conducted to explore technology acceptance, the social living context, and their experiences with their own ageing process.

• **The DIPH.DEM study** investigates whether digital phenotyping can enhance the objectivity of measuring activity changes during the last period of life, by using sensing-based digital phenotyping combined with validated assessment tools to describe the activity trajectory and associated processes that occur during long-term stay in the nursing home.

• **The DARK.DEM study** investigates chrono-theraphy, i.e., interventions targeting the circadian rhythm. The aim of the study is to develop and evaluate digital phenotyping and virtual darkness therapy to enhance management of behavioral and psychological symptoms of dementia (BPSD) in specialised dementia care and facilitate implementation in municipal dementia care.

Photo by Silje Robinson

• **The 5-D study, Decoding Death and Dying in people with Dementia by Digital thanotyping**, aims to provide methods and tools to diagnose and describe dying to an unprecedented level of accuracy and robustness, within a timespan larger than is possible now, focusing on the case of dying people with dementia as one of the most vulnerable and difficult to study groups.

• **The CC.AGE project, the Trond Mohn Centre for Complex Conditions and Ageing**, explore the efficacy and cost-efficacy of a research-based digital plug-and-play mobile platform (ALIVE) connecting a range of selected technologies for use at home based on a randomised controlled trial design (RCT).

The Care Node has also in 2023 developed an introduction course to algorithms for health researchers, to provide graduate students without engineering or computer sciences background with the basics of algorithmics, scripting and programming. The course is designed to empower health researchers to perform tasks related to advanced data analysis, visualisation techniques, and signal processing in their studies. The course is adapted to the interdisciplinary perspective of a doctorate in health sciences, offering doctoral candidates the skills to perform multiple interpretations and use a variety of outcomes related to advanced data analysis. The first internal proof-of-concept course took place during the fall semester of 2023 and is aiming to achieve ECTS providing status.

Selected publications from 2023:

1. **C. Berceanu, N. Arshad and M. Patrascu.** Contagion Propagation with Rule-Based Reasoning and Decentralized Control in an Agent-Based Susceptible-Infected-Recovered-Susceptible Infodemic Model, 2023 International Conference on Big Data, Knowledge and Control Systems Engineering (BdKCSE), Sofia, Bulgaria, 2023, pp. 1-6, doi: 10.1109/BdKCSE59280.2023.10339741.
2. **Helvik, AS., Bergh, S., Šaltytė Benth, J. et al.** Pain and quality of life in nursing home residents with dementia after admission – a longitudinal study. BMC Health Serv Res 23, 1032 (2023). https://doi.org/10.1186/s12913-023-10041-5
3. **Lobbezoo F, Verhoeff MC, Aarab G, Husebø BS, van der Torre W, Volgenant CMC.** The contribution of palliative oral health care to dying with dignity, The Journal of the American Dental Association, Volume 154, Issue 1, 2023, Pages 3-5, https://doi.org/10.1016/j.adaj.2022.08.015.
4. **Puaschitz NGS, Jacobsen FF, Berge LI and Husebo BS.** Access to, use of, and experiences with social alarms in home-living people with dementia: results from the LIVE@Home.Path trial. Front. Aging Neurosci. 2023, 15:1167616. doi: 10.3389/fnagi.2023.1167616

THE DRUG DISCOVERY NODE

The Drug Discovery Node comprises two research groups employing different methodologies towards the common goal of discovering novel or repurposed drugs targeting the four disease groups of the Centre.

Node leaders: Aurora Martinez and Trond Riise

Aurora Martinez is a professor at the Department of Biomedicine, University of Bergen, and the head of the Biorecognition group. The research group investigates the molecular mechanisms underlying neurometabolic and neurological disorders applying multidisciplinary and translational approaches. The Martinez Lab is a specialised screening site at the NOR-Openscreen and EU-Openscreen networks and has skills in biophysics, structural biology, drug design, cellular biology, and animal models of disease. The methodological expertise brought to Neuro-SysMed includes target identification and compound screening using both biophysical and cellular screens, mechanistic validation of best hits and knowledge on the path from early-stage drug discovery to the identification of best leads towards proof-of concept in patients, aiming to develop preventive and corrective therapies for Parkinson's disease and other parkinsonisms.

Trond Riise is a professor in epidemiology at the University of Bergen. He leads the DRONE group – Drug RepurpOsing for NEurological diseases. The DRONE group harbours world-leading expertise on registry and epidemiology research. They focus on virtual drug screening, employing the Norwegian national registries to identify candidate drugs for repurposing. Riise's research is related to epidemiological studies of neurological diseases including Parkinson's disease and multiple sclerosis. The focus is to identify environmental factors that, on their own or in combinations, significantly change the disease risk.

Node activities

The activities of the Drug Discovery Node in 2023 comprised:

• **Mitochondrial function**. The Drug Discovery Node is optimising screening approaches and assays targeting neuronal respiratory complex I (CI) deficiency and impaired mitochondrial DNA homeostasis, in collaboration with Professor Charalampos Tzoulis. They have established a cell-based screening method and are currently screening libraries, predominantly for drug repurposing. In 2023 they identified an FDA-approved drug with the previously unknown potential to enhance mitochondrial CI protein levels and increase mitochondrial biogenesis. Further investigation is being conducted to identify the mechanisms through which the drug interacts with the cellular components to modulate mitochondrial function, aiming to elucidate the potential therapeutic effects in various disease conditions, such as PD.

• **Tyrosine hydroxylase (TH) as a treatment target in PD and parkinsonisms.** In collaboration with the labs of Angeles García-Cazorla (Hospital Sant Joan de Déu, Barcelona) and Antonella Consiglio (Bellvitge University Hospital-IDIBELL, Barcelona), the node has recently investigated alternative therapeutic options for patients with TH deficiency (THD), a rare disorder associated with parkinsonism and variable response to L-Dopa treatment. Using dopamine-neurons differentiated from iPSCs from healthy subjects and THD patients, they found that supplementation of the TH cofactor tetrahydrobiopterin (BH4) resulted in an increase in the number of TH+ cells and improved motor outcomes in a knock-in THD mouse model. These findings highlight the therapeutic potential of BH4 for specific TH variants (Jung-Kc et al., 2024).

• **The node has also continued their work on the identification of drugs that maintain the proteostatic regulation and intracellular stability of TH**. They have recently identified DNAJC12 as a molecular chaperone that maintains the stability of TH and decreases

its propensity to aggregate, especially in the case of THD-associated variants. The recently solved structure of the complex by Cryo-EM (Tai et al., 2023; preprint; https://doi.org/10.21203/rs.3.rs-3621320/v1) is facilitating the screening and derivatisation of stabiliser drugs of TH and the TH:DNAJC12 complex.

• **VMAT2 as a treatment target in PD.** This project studies the vesicular monoamine transporter 2 (VMAT2) which is responsible for packaging of monoamines such as dopamine into synaptic vesicles for subsequent release into the synaptic cleft. VMAT2 is associated with both TH and α-synuclein, both important targets in PD, but the role of this association in regulation of DA signalling is still not known. In a recent project, Neuro-SysMed researcher Svein Isungset Støve has screened for compounds modulating VMAT2 activity using both biophysical and cellular screenings and has obtained effective inhibitors of VMAT2 that have a potential for treatment of Tardive Dyskinesia. He continues the project in a screening campaign to identify molecular chaperones that can increase VMAT2 expression levels and subsequently dopamine sequestration. The identification of activators or stabilisers of VMAT2 is especially interesting, as high cytoplasmic levels of DA are associated with cytotoxicity, and stimulation of VMAT2 in early stages of PD is a therapeutic approach of increasing interest.

• **Registry-based drug screening**. Riise's group is conducting a comprehensive registry-based drug screening project which 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. A full screen of drugs associated with PD-risk has been completed, and in collaboration with Clemens Scherzer, director of The Neurogenomics Lab at Harvard University, the groups is currently validating 72 promising drugs using neurons from patient stem cells carrying the SNCA triplication linked to autosomal dominant PD. The first epi-screening results are published in Neurology (2023, Romanowska et. al.).

The group has further received new funding from the Michael J. Fox Foundation (USD 300 K) to combine their results with similar studies in Finland and France using meta-analysis.

Selected publications from 2023:

1. **Jung-Kc K, Tristán-Noguero A, Altankhuyag A, Piñol Belenguer D, Prestegård KS, Fernandez-Carasa I, Colini Baldeschi A, Sigatulina Bondarenko M, García-Cazorla A, Consiglio A, Martinez A.** Tetrahydrobiopterin (BH4) treatment stabilizes tyrosine hydroxylase: Rescue of tyrosine hydroxylase deficiency phenotypes in human neurons and in a knock-in mouse model. J Inherit Metab Dis. 2024 Jan 9. doi: 10.1002/jimd.12702. PMID: 38196161.
2. **Thöny B, Ng J, Kurian MA, Mills P, Martinez A.** Mouse models for inherited monoamine neurotransmitter disorders. J Inherit Metab Dis. 2024 Jan 2. doi: 10.1002/jimd.12710. PMID: 38168036.
3. **Alam KA, Svalastoga P, Martinez A, Glennon JC, Haavik J.** Potassium channels in behavioral brain disorders. Molecular mechanisms and therapeutic potential: A narrative review. Neurosci Biobehav Rev. 2023 152:105301. doi: 10.1016/j.neubiorev.2023.105301. PMID: 37414376.
4. **Romanowska J, Bjornevik K, Cortese M, Tuominen JA, Solheim M, Abolpour Mofrad A, Igland J, Scherzer CR, Riise T.** Association Between Use of Any of the Drugs Prescribed in Norway and the Subsequent Risk of Parkinson Disease: A Drug-wide Association Study. Neurology. 2023 Nov 21;101(21):e2068-e2077. doi: 10.1212/WNL.0000000000207899. Epub 2023 Oct 10. PMID: 37816645.
5. **Tuominen JA, Bjørnevik K, Romanowska J, Solheim MH, Grydeland TB, Cortese M, Scherzer CR, Riise T, Igland J.** Beta2-adrenoreceptor agonists and long-term risk of Parkinson's disease. Parkinsonism Relat Disord. 2023 May;110:105389. doi: 10.1016/j.parkreldis.2023.105389. Epub 2023 Mar 31. PMID: 37027994.
6. **Olsen A, Locascio J, Tuncali I, Laroussi N, Abatzis E, Kamenskaya P, Kuras Y, Yi T, Videnovic A, Hayes M, Ho G, Paulson J, Khurana V, Herrington T, Hyman B, Selkoe D, Growdon J, Gomperts S, Riise T, Schwarzschild M, Hung A, Wills A, Scherzer C.** Health phenome of Parkinson's patients reveals prominent mood-sleep cluster. Res Sq. 2023 Dec 22:rs.3.rs-3683455. doi: 10.21203/rs.3.rs-3683455/v1. Preprint. PMID: 38196602
7. **Riise T, Solheim M, Bjornevik K, Igland J, Tuominen J, Mofrad A, Cortese M, Scherzer C, Romanowska J.** Treatment of High Blood Pressure is associated with a Reduced Incidence of Parkinson's disease. Neurology 2023 April 25, 100 (suppl 2). doi.org/10.1212/WNL.0000000000202952.

THE SYSTEMS BIOLOGY & BIOINFORMATICS (SBB) NODE

Addressing the complexity of neurodegenerative and neuroinflammatory diseases requires the ability to analyse and integrate big datasets of multimodal information, encompassing epidemiological, clinical, molecular, and socioeconomic data. The Systems Biology & Bioinformatics Node is coordinating data integration, multimodal analyses and bioinformatics – an essential part of our systems medicine activity. The node is highly integrated with the one-stop-shop clinical trials unit. Together, these tasks support clinical trials and biomarker discovery.

Node leaders: Gonzalo Nido and Dimitrios Kleftogiannis

Dr. Gonzalo Nido is a senior researcher in bioinformatics at the University of Bergen, with more than a decade of experience in the analysis of multiomic datasets, including genomics, epigenomics, transcriptomics, and proteomics, as well as single-cell omics, and data integration. His work has made important advances particularly in the field of Parkinson's disease transcriptomics.

Dr. Dimitrios Kleftogiannis is a senior bioinformatician at the University of Bergen. His work focuses on the development and application of computational approaches to dissect omics datasets from Next Generation Sequencing (NGS), as well as mass cytometry (CyTOF) and imaging mass cytometry (IMC) technologies. He is also interested in the application of machine learning for biomarker discoveries in multiple sclerosis.

Node activities

The concept of systems medicine in neurology is the backbone of the Centre. Based on the wealth of data collected through the clinical and translational activities of the Centre, and using supervised and unsupervised data-analysis models, including artificial intelligence (AI), the node is developing specific and sensitive biomarker systems to enable and refine early and precise diagnosis, stratification, and prediction of treatment response. Our Parkinson's disease (PD) team has jump-started this activity and is paving the way for the other diseases to follow.

During 2023, the Systems Biology & Bioinformatics (SBB) Node made substantial advances:

The ParkOme initiative integrates state-of-the-art multiomics and clinicopathological data, with the aim to advance the mechanistic understanding of PD (and subtypes thereof), and to discover novel biomarkers and treatment targets. To this end, the SBB Node is mapping the genome, epigenome, transcriptome, proteome, and metabolome of multiple tissues from individuals with neurodegenerative parkinsonisms and healthy controls. To mitigate the confounder of cellular heterogeneity, they are conducting additional studies in single cells using a dual strategy: 1) High-throughput single-cell analyses, using the inhouse 10X Genomics platform. 2) Pathology-guided single-cell transcriptomics to elucidate the selective neuronal vulnerability to PD-associated pathology (e.g., as α-synuclein aggregation, or mitochondrial dysfunction). Integration across omics layers and with clinical, pathology, environmental and epidemiological information, enables the team to identify complex molecular interactions, and how these interact with the environment and, in turn, influence the disease phenotype.

Molecular signatures emerging from this work are translated into disease models by the Cell Models Node, therapeutic targets by the Drug Discovery Node, as well as candidate biomarkers for disease diagnosis and stratification, which are tested in the STRAT-PARK cohort.

Funding was in 2023 secured for **the The Mito-ALS study,** investigating mechanisms of cell death in ALS, using pathologic material from the brain banks in Barcelona and the Netherlands. The aim is to study whether complex 1 deficiency is present in ALS.

Several key milestones were reached in 2023. The transcriptome and coding genome sequence of more than 1,300 brain samples were analysed to completion. This constitutes by far the largest transcriptomic repository of neurodegenerative parkinsonism's in the world, including PD, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, dementia with Lewy bodies, Alzheimer's disease, and healthy controls. In addition, we mapped and analysed the proteome of ~500 of the same samples, and single-nucleus transcriptomics using the 10X Genomics technology in 50 individuals. These analyses have revealed multiple novel molecular signatures which characterise neurodegenerative parkinsonism – both associated with and independent of the severity of the proteinopathy – at the level of individual genes/proteins and molecular processes and pathways.

This data has constituted the foundation for several original papers, currently in review or revision in high-impact journals, including Molecular Neurodegeneration and Nature Neuroscience. Moreover, these findings have been presented in several international conferences generation significant interest in the reported discoveries.

THE RESPONSIBLE RESEARCH AND INNOVATION & PATIENT AND PUBLIC INVOLVEMENT (RRI/PPI) NODE

The RRI/PPI Node is developing a model of human suffering. Suffering involves conceptions of human affliction that places disease within a larger frame of burdens and carrying capacities of patients and their caregivers. Such conceptions are crucial for the node's ongoing work on the RRI and PPI of precision medicine (PM).

Node leaders: Jan Reinert Karlsen and Caroline Engen

Jan Reinert Karlsen, is an associate professor at the Centre for the Studies of the Sciences and the Humanities at the University of Bergen. His research includes the RRI of post-genomic medical research and conceptions of suffering across different thought traditions. He has a long track record in interdisciplinary research and teaching.

Caroline Engen is a postdoc (50%) and specialist in training (psychiatry) (50%). She has previous experience from development of personalised molecular therapy for acute myeloid leukaemia and is currently focusing on RRI of precision medicine and philosophy of suffering.

Node activities

The RRI/PPI Node is responsible for four projects:

• A research project entitled "Philosophy of precision medicine in severe chronic neurological diseases (POS-PM)."

• An innovation project entitled "Communicating cognitive decline: Language games with tactile and visual objects (CCD)." The project was a proof of concept to test Amy van den Hooven's visual and tactile tool kit, created during her Master's in Design.

• A teaching subject called "The nature of disease and suffering and the goals of precision medicine (NEUROSYSM940)", which is part of the Neuro-SysMed research school. Initially introduced in the spring of 2023, it is slated for its next iteration in the autumn of 2024.

• An RRI initiative called NeuroDialogues. The NeuroDialogues initiative is a biannual forum dedicated to fostering discussions on severe neurological conditions, the impact of technology, and the intricacies of the human mind. Launched in autumn 2023, NeuroDialogues plans to continue its sessions in the spring and autumn of 2024, providing a platform for critical engagement with these issues emerging from Neuro-SysMed.

During 2023, Engen and Karlsen have continued working on a co-authored monograph (working title: Precision and Suffering). The book will contain the development of a novel model of suffering and its application in RRI engagements with precision medicine. The innovation project (2) was concluded. Although we concluded negatively on the prospect of using van den Hooven's design for the project's intended aim, a number of positive findings and experiences nonetheless were made. These were documented in an extensive report submitted to UiB Ide, Neuro-SysMed, and the Humanistic Faculty. Work on a follow-up project was commenced in cooperation with the Dementia group and the Norwegian Health Association.

Selected dissemination activities from 2023:

1. **Engen C.** (2023) «Å stille diagnose på medisinen – Jubileumsmarkering – 25 år med Filosofisk poliklinikk» (Panel discussion) 04.10.2023. Filosofisk poliklinikk, store auditorium, Haukeland universitetssykehus
2. **Engen C.** (2023) «Evighetsmennesket" – hvilke etiske utfordringer må vi forberede oss på?» 24.05.2023. Digital helse-dager 2023, Hotel Edvard Grieg. https://vimeo.com/haukeland/review/829500989/0a42898503
3. **Karlsen JR., Haugarvoll K., Gissum K.** (2023) «Å leve med demens». Presentation and interactive workshop with members of 'Erfaringspanelet'. Nasjonalforeningen for folkehelsen in Oslo.
4. **Engen C.** (2023) «Responsible clinical trials in the age of personalized medicine» (Panel discussion) 09.05.2023. 11th CCBIO Annual Symposium 2023, Solstrand Hotel. Panel: Linn Getz, NTNU; Caroline Engen, Neuro-SysMed/UiB; Line Bjørge and Karen Rosnes Gissum, CCBIO
5. **Engen C.** (2023) «Presisjonsmedisin - muligheter og utfordringer for psykiatrien» 16.03.2023. Psykiatriveka 2023
6. **Engen C.** (2023) «Lytring: Skal vi bare kvitte oss med kunnskap vi ikke liker?» (Panel discussion) 23.02.2023. Stormen bibliotek, Bodø. https://site.nord.no/lytring/debatt/kunnskap/
7. **Engen C. (2023) «Ansvarlig kreftforskning – hvordan få det til?»** (Panel discussion) 14.02.2023. Litteraturhuset, Berner-kjelleren - Bioteknologirådet og PINpOINT (NFR Digitalt Liv Norge, Oslo universitetssykehus) https://www.youtube.com/watch?v=qz6LqWgSjyw

CLINICAL STUDIES

Clinical studies, or trials, are the backbone of the Neuro-SysMed activities. Two overarching types of clinical trials are performed at the Centre. *Interventional trials* involve testing of a clinical intervention (e.g., a drug, device, or procedure), commonly in a randomised, double-blind setup. *Observational trials* involve following and characterising a cohort, typically to study disease progression and develop biomarkers for diagnosis and stratification. While each study has its own scientific questions and efficacy endpoints, all projects running under the Centre contribute samples and data to a common Neuro-SysMed database. This combined information is integrated to define biomarkers that enable early and precise diagnosis, subgrouping of patients within each disease, accurate prognosis, and tailored treatment choices. We currently have 31 ongoing or planned investigator-initiated clinical studies (our industry-sponsored trials are not described in this report):

MS	The RAM-MS study: a randomised clinical trial for comparing autologous hematopoietic stem cell transplantation (HSCT) versus alemtuzumab, cladribine or ocrelizumab in MS
MS	The OVERLORD-MS study: Ocrelizumab Versus Rituximab Off-Label at the Onset of Relapsing MS Disease
MS	The OR-Switch-MS study: Ocrelizumab to Rituximab Switch Study in Multiple Sclerosis.
MS	The REDUCE-MS study: Rituximab Extended Dose interval in mUltiple sClErosis
MS	The SMART-MS study: Study of Mesenchymal Autologous stem cells as Regenerative Treatment for Multiple Sclerosis
MS	The NORSEMAN Study: Nicotinamide Riboside Supplementation in Progressive Multiple Sclerosis: A Randomised Controlled Trial
MS	The COVAC-MS study: Humoral response and clinical efficacy of COVID-19 vaccination in multiple sclerosis patients receiving various disease-modifying
MS	Long-term safety and efficacy of rituximab and cladribine – A tale of two cities
MS	The TAF-MS 0 study: Epstein-Barr virus shedding in saliva in MS-patients receiving cladribine, natalizumab or rituximab
MS	The TAF-MS 1 study: Tenofovir alafenamide fumarate (TAF) and Epstein-Barr virus infection in multiple sclerosis – a proof of concept study
MS	A digital therapeutic to improve insomnia in Multiple Sclerosis: A randomised controlled trial (NorseMS)
MS	The 3TR - Taxonomi, Treatment, Target and Remisson - study

PD	The NR-SAFE study: a safety tolerability study of high-dose oral NR in Parkinson's disease
PD	The N-DOSE study: a dose optimisation trial of nicotinamide riboside in Parkinson's disease
PD	The NADbrain study: a pharmacokinetic study of NAD-replenishment in human blood and brain
PD	The NOPARK study: a phase III randomised controlled trial of nicotinamide riboside in early Parkinson's disease
PD	The NOPARK extension study: an open label trial of long-term treatment with nicotinamide riboside (NR) in Parkinson's disease
PD	The NADAPT study: A phase II randomised controlled trial of NAD replenishment therapy for atypical parkinsonism
PD	The STRAT-PARK study: a prospective multimodal cohort study to stratify Parkinson's disease and other parkinsonisms
ALS	The NO-ALS study: a phase-II, multi-centre, double-blinded randomised clinical trial of oral NR and pterostilbene in early ALS
ALS	The NO-ALS extension study: an open label study of long-term therapy with NR and pterostilbene in ALS
ALS	The STRAT-ALS study: an initiative to stratify amyotrophic lateral sclerosis
ALS	The ALS LTMV study: effects of long-term ventilation support on the quality of life of ALS patients and their families
DEM	N-DOSE AD: A dose optimisation trial of nicotinamide riboside in Alzheimer's disease
DEM	The STRAT-COG study: a prospective cohort study to stratify dementia
DEM	NADage study: a phase II randomised controlled trial of nicotinamide riboside in aging-related frailty
CAR	The ActiveAgeing study – the Helgetun branch
CAR	The ActiveAgeing study – the DIGI.PARK branch
CAR	The DIPH.DEM study
CAR	The DARK.DEM study
CAR	The 5-D study: Decoding Death and Dying in people with Dementia by Digital thanotyping

The RAM-MS study: a randomised clinical trial for comparing autologous hematopoietic stem cell transplantation (HSCT) versus alemtuzumab, cladribine or ocrelizumab in MS

Disease: Multiple Sclerosis
Type of study: Interventional trial

Coordinating investigators: Øivind Torkildsen & Anne Kristine Lehmann. Study director: Lars Bø

Background: Autologous hematopoietic stem cell transplantation (HSCT) is a promising therapy in MS, but data from randomised clinical trials (RCTs) are limited. Haukeland University Hospital (HUH) is the national centre for such MS-therapy in Norway, and is currently conducting a multicentre, international randomised clinical trial to evaluate the efficacy and safety of autologous HSCT compared to standard high-efficacy therapies in MS.

This is an international multicentre treatment trial, coordinated by HUH in close collaboration with coordinating centres in all Norwegian health regions and international study sites in Sweden (Uppsala and Gothenburg), Denmark (Copenhagen) and the Netherlands (Amsterdam).

The objectives are to investigate the efficacy and safety of HSCT in highly active multiple sclerosis compared to standard high-efficacy therapies, and to establish sufficient evidence to support routine use of HSCT in MS.

Design: This is a randomised controlled open-label trial comparing the efficacy and safety of HSCT (n=50) compared to standard high-efficacy therapies (n=50) in highly active multiple sclerosis with breakthrough disease activity.

The primary endpoint of the study is the difference of HSCT versus comparator in the proportion of patients with no evidence of clinical or MRI disease activity (NEDA) after 2 years (96 weeks) in the main study, and further after 5 years (240 weeks) in the extension study.

Status: By 2023, 90 patients have been included in the study, and enrolment will continue until the target of 100 patients is reached. Patients from all health regions in Norway are screened and randomised at the University Hospital of North Norway (Tromsø), St. Olav's Hospital (Trondheim), Akershus University Hospital (Lørenskog), and Haukeland University Hospital (Bergen). Norwegian patients randomised for HSCT are treated at HUH, and those for standard high-efficacy MS-therapy are treated at their local hospitals. Blood sampling, imaging and clinical scoring of the Norwegian patients are performed at HUH.

Participating centres

Norway
- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- St. Olav's University Hospital, Trondheim
- University Hospital of North Norway, Tromsø

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

Denmark
- Copenhagen University Hospital, Rigshospitalet

The Netherlands
- Amsterdam UMC, Amsterdam

Funding

- KLINBEFORSK
- The Regional Health Authority of Western Norway
- Haukeland University Hospital
- Participating hospitals
- The Research Council of Norway, Neuro-SysMed
- Norwegian MS Society

The OVERLORD-MS study: Ocrelizumab Versus Rituximab Off-Label at the Onset of Relapsing MS Disease

Disease: Multiple Sclerosis
Type of study: Interventional trial

Coordinating investigator: Øivind Torkildsen
Study director: Kjell-Morten Myhr

Background: B-cell depletion therapies (rituximab, ocrelizumab, ofatumumab) are proven highly effective in MS. A Norwegian health technology assessment (HTA) indicate similar treatment effects from rituximab and ocrelizumab – but clearly state that more data, preferably from a randomised double-blinded clinical trial, is needed.

Rituximab has been used for the treatment of rheumatological diseases and haematological cancers since 1998, and due to patency expiration, costs only a fraction of ocrelizumab. If rituximab proves 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 timepoint. In this study, we therefore aim to compare the efficacy and safety of rituximab to ocrelizumab for treatment of newly diagnosed treatment naïve patients with RRMS.

The objective is to evaluate whether rituximab has comparably efficacy and safety as ocrelizumab in the treatment of newly diagnosed RRMS patients.

Design: This is a randomised, double-blinded, controlled non-inferiority trial comparing the efficacy and safety of rituximab to ocrelizumab (3:2) in newly diagnosed RRMS.

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

Status: The first patient was recruited at Haukeland University Hospital in early November 2020 and the study was fully included by November 2022, with 214 patients participating. Altogether, 12 hospitals in Norway and Sweden have recruited patients in the study and participate in the follow-up.

Participating centres

Norway
- Haukeland University Hospital, Bergen
- Oslo University Hospital, Oslo
- Akershus University Hospital, Lørenskog
- Stavanger University Hospital, Stavanger
- University Hospital of North Norway, Tromsø
- Nordland Hospital, Bodø
- Namsos Hospital, Namsos
- Molde Hospital, Molde
- Sørlandet Hospital, Kristiansand
- Telemark Hospital, Skien
- Vestre Viken Hospital, Drammen

Sweden
- Karolinska Institute, Stockholm

Funding

- KLINBEFORSK
- The Regional Health Authority of Western Norway
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals

The OR-Switch-MS study: Ocrelizumab to Rituximab Switch Study in Multiple Sclerosis

Disease: Multiple Sclerosis
Type of study: Interventional trial

Coordinating investigator: Øivind Torkildsen
Study director: Kjell-Morten Myhr

Background: B-cell depletion therapies are proven highly effective in MS. Real world data indicate similar efficacy and safety of rituximab compared to ocrelizumab. Currently several ongoing non-inferiority trials are comparing the two compounds, including the Norwegian OVERLORD-MS study.

According to the OVERLORD-MS study protocol, all patients will be offered routine treatment with rituximab after finishing 30 months of blinded therapy with ocrelizumab or rituximab. Because of limited data available describing the efficacy and safety of a switch from ocrelizumab to rituximab, we will perform a blinded six-month observation of starting on rituximab after finishing the 30 months study period with ocrelizumab or rituximab in the OVERLORD-MS study.

The objective is to evaluate the efficacy and safety of switching therapy from ocrelizumab to rituximab.

Design: This is a blinded observation study evaluating the efficacy and safety of switching therapy from ocrelizumab to rituximab.

The primary endpoint of the study is the proportion of patients free of clinical disease during the following 6 months after switching from ocrelizumab to rituximab (n=85) compared to those that continue rituximab therapy as received during the OVERLORD-MS study (n=129).

Status: All patients in the OVERLORD-MS study consenting for participation are consecutively included when finishing the pre-planned 30 months study period of OVERLORD-MS. The last patient will be included in May 2025 and followed for another six months.

Participating centres

Norway
- Haukeland University Hospital, Bergen
- Oslo University Hospital, Oslo
- Akershus University Hospital, Lørenskog
- Stavanger University Hospital, Stavanger
- University Hospital of North Norway, Tromsø
- Nordland Hospital, Bodø
- Namsos Hospital, Namsos
- Molde Hospital, Molde
- Sørlandet Hospital, Kristiansand
- Telemark Hospital, Skien
- Vestre Viken Hospital, Drammen

Sweden
- Karolinska Institute, Stockholm

Funding

- KLINBEFORSK
- The Regional Health Authority of Western Norway
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals

The REDUCE-MS study: Rituximab Extended Dose interval in mUltiple sClErosis

Disease: Multiple Sclerosis
Type of study: Interventional trial

Coordinating investigator: Øivind Torkildsen
Study director: Kjell-Morten Myhr

Background: B-cell depletion therapy is highly effective in relapsing-remitting MS. Rituximab seems to have comparable efficacy and safety profile to ocrelizumab, but data on optimal dosing is limited and largely based on various off-label regimes. The most frequent used dosing regimen in Norway (until recently) has been 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, where neutropenia, lymphopenia, hypogammaglobulinemia and infections are the most frequent adverse events. Real world experience indicates that B-cells may be depleted for a longer period, even for at least 12 months, and longer dosing intervals than six months (e.g., due to intercurrent illness or pregnancy planning) seems safe. Based on these observations, clinical practice in Norway is changing to extended dosing intervals after at least two years of therapy. In this study, we aim to investigate whether an extended dosing interval from 6 to 12 months is safe in RRMS.

All patients finishing the OVERLORD-MS study that have been stable without new MRI or clinical disease activity for at least two years will be offered an extension of further rituximab (500 mg) dosing interval from 6 to 12 months interval.

The objectives of the study are to evaluate whether the efficacy and safety of 12-months dosing of rituximab is equal to the standard six months interval.

Design: This is a prospective observational open label trial comparing the efficacy and safety of standard interval dosing (SID – of six months) to extended interval dosing (EID – of twelve months) of rituximab in relapsing-remitting MS patients. The patients will be their own controls by comparing previous SID period to later EID period in each patient.

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

Status: The study will prospectively recruit patients that have finished the OVERLORD-MS study period, including the following switch period of 6 months.

Participating centres

- Haukeland University Hospital, Bergen
- All OVERLORD-MS study centres in Norway

Funding

- The Research Council of Norway, Neuro-SysMed
- The Regional Health Authority of Western Norway
- Haukeland University Hospital
- The University of Bergen
- The DAM foundation
- Participating hospitals

The SMART-MS study: Study of Mesenchymal Autologous stem cells as Regenerative Treatment for Multiple Sclerosis

Disease: Multiple Sclerosis
Type of study: Interventional trial

Coordinating investigator: Christopher Elnan Kvistad
Study director: Lars Bø

Background: 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 to reverse neurological disability. Mesenchymal stem cells (MSCs) have the potential to induce neuronal repair through multiple neurodegenerative mechanisms, including remyelination, immunomodulation and stimulation of endogenous cerebral stem cells. In this study, the group aims to investigate the regenerative potential of stem cell treatment with MSCs in MS and to increase the understanding of the underlying mechanisms of action.

The objective of this pilot project is to study whether intrathecal treatment with autologous bone marrow derived MSCs is feasible, safe and promotes neural repair in patients with progressive MS.

Design: This is a randomised placebo-controlled cross-over pilot trial comparing the efficacy and safety of autologous bone marrow derived MSCs (n=9) compared to placebo (n=9) in progressive multiple sclerosis patients.

The primary endpoint of the study is the difference in the change of composite score (CEP) of three neurophysiological measures (somatosensory evoked potentials (SEP), visual evoked potentials (VEP) and motor evoked potentials (MEP)) from baseline between MSC treatment versus placebo.

The study is performed as a collaboration between Haukeland University Hospital, the Tissue Engineering Group at the University of Bergen, the University Hospital in Ulm, Germany, and coordinating centres in all Norwegian health regions, including Akershus University Hospital (Lørenskog), St. Olav's Hospital (Trondheim), and the University Hospital of North Norway (Tromsø).

Status: The first patient was included at Haukeland University Hospital in August 2021 and the study inclusion was completed in 2023. The final study visit will take place in first quarter of 2025.

Participating centres

Norway
- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- St. Olav's University Hospital, Trondheim
- University Hospital of North Norway, Tromsø

Germany
- University Hospital in Ulm

The Netherlands
- Amsterdam University Medical Centre

Funding

- KLINBEFORSK
- The Regional Health Authority of Western Norway
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals
- The Norwegian MS Society
- The Red Cross

The NORSEMAN Study: Nicotinamide Riboside Supplementation in Progressive Multiple Sclerosis: A Randomised Controlled Trial

Disease: Multiple Sclerosis
Type of study: Interventional trial

Coordinating investigator: Kristin Varhaug
Study directors: Kjell-Morten Myhr & Charalampos Tzoulis

Background: 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 the pathogenesis of progression in MS. This mitochondrial dysfunction is suggested 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 bioenergetics conversion and signalling in human cells.

The objective is to study whether oral supplementation with nicotinamide riboside (NR) as add-on to standard care, reduces disability progression in MS.

Design: This is a randomised double-blinded study where 300 patients with disability progression receive oral 500 mg oral nicotinamide riboside (NR) twice daily (n=150) or placebo (n=150) for 30 months. The patients will attend nine visits that include clinical scorings, imaging, blood sampling, questionnaires, and patient reported outcomes.

The primary endpoint is the proportion of patients with 6 months confirmed disability progression, either by worsening of Expanded Disability Status Scale (EDSS), Nine-Hole-Peg-Test (9-HPT) or Timed 25 Foot Walking (T25FW) after two years of therapy.

Status: The first patient was included at Haukeland University Hospital in May 2023 and by end of 2023, altogether 16 patients were included. New study centres across Norway are currently recruited.

Participating centres

- Haukeland University Hospital, Bergen
- Stavanger University Hospital, Stavanger
- Haugesund Hospital Trust, Haugesund
- Førde Hospital Trust, Førde

Funding

- The Regional Health Authority of Western Norway
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals
- Elysium Health, New York
- The Kjell Alme Legacy, Bergen

The COVAC-MS study: Humoral response and clinical efficacy of COVID-19 vaccination in multiple sclerosis patients receiving various disease-modifying therapies

Disease: Multiple Sclerosis
Type of study: Observational trial

Coordinating investigator: Hilde M. Torgauten
Study director: Øivind Torkildsen

Background: Previous studies have shown that vaccination in general is safe for MS-patients. Vaccination is not a risk factor for developing MS, and do not represent a risk for further disease activity or disease progression. Nevertheless, live vaccines are not recommended for patients that receive disease-modifying therapies.

Vaccination response and immunity is another challenge related to vaccination of MS-patients receiving disease-modifying therapies. These medications have immunomodulatory or immuno-suppressive effects and may therefore influence the immune response to various vaccines. Although limited data are available, we have previously shown that interferon-beta therapies do not influence the vaccination response, while fingolimod, and especially mitoxantrone, may influence the humoral vaccination responses. Other studies have shown that rituximab, ocrelizumab, alemtuzumab and teriflunomide, but not dimethyl fumarate, seem to reduce vaccine responses. Based on these limited data on vaccine response in MS patients receiving disease-modifying therapies, and the challenge of COVID-19 vaccination, the MS group have performed a study on efficacy and safety of COVID-19 vaccines in MS-patients.

The objective is to evaluate the efficacy and safety of COVID-19 vaccines in MS-patients with and without disease-modifying therapies, compared to healthy population controls not receiving immunotherapy.

Design: This is a prospective observational trial evaluating vaccination responses of COVID-19 vaccines in MS-patients receiving different disease-modifying therapies.
Primary endpoint: Humoral vaccine response and clinical efficacy of COVID-19 vaccine.

This is a collaborative project, chaired by Professor Rebecca Cox at the Influenza Centre at the University of Bergen. Other participants include researchers at Oslo University Hospital, University of Oslo, and Sørlandet Hospital Trust, as well as the Norwegian MS Registry.

Status: Patients have been recruited for participation at Haukeland University Hospital, Oslo University Hospital and Sørlandet Hospital Trust, as well as through the Norwegian MS Registry.

Results so far have shown that rituximab and fingolimod reduce the humoral vaccination response to COVID-19 vaccines, and that booster vaccines improve this vaccine response (PMID: 35072702; PMID: 34670844). Further studies of COVID-19 vaccination in rituximab treated patients have shown that, despite reduced humoral vaccination response, the vaccine is clinically effective in reducing severe Covid-19 disease (manuscript submitted).

Participating centres

- Haukeland University Hospital, Bergen
- Oslo University Hospital, Oslo
- Sørlandet Hospital, Kristiansand

Funding

- The Research Council of Norway, Neuro-SysMed
- The Regional Health Authority of Western Norway
- Haukeland University Hospital
- Oslo University Hospital
- Sørlandet Hospital, Kristiansand
- The University of Bergen
- The Norwegian MS Registry
- The Kjell Alme Legacy, Bergen

Long-term safety and efficacy of rituximab and cladribine – A tale of two cities

Disease: Multiple Sclerosis
Type of study: Observational trial

Coordinating investigator: Brit Ellen Rød
Study directors: Gro Owren Nygaard (OUH) & Stig Wergeland

Background: Norwegian MS treatment guidelines recommend prompt treatment with high efficacy therapy at the time of diagnosis. Cladribine and rituximab are among the recommended high-efficacy therapy treatment options. Cladribine has not been compared to other active therapies in clinical trials, and the extension of the pivotal placebo-controlled trial indicate return of new clinical and MRI disease activity after standard treatment regimens during the first and second year.

Clinical experience confirms these findings, and based on this background, we aim to compare prospective collected data from patient cohorts from the Departments of Neurology at Haukeland University Hospital (HUH) and Oslo University Hospital (OUH), who started with rituximab or cladribine therapy during 2018 and 2019. At that time point, rituximab was the preferred high-efficacy therapy at HUH for both treatment-naïve patients and for those experiencing breakthrough disease activity on other therapies. At OUH, cladribine was the preferred high-efficacy therapy for the same patient populations.

The objectives of this study are to compare the efficacy and safety of cladribine and rituximab therapy.

Design: This is a prospective observational registry study comparing the efficacy and safety of cladribine and rituximab therapy for treatment naïve RRMS patients and for those switching from other therapies.

The primary endpoint of the study is the proportion of patients who develop new MRI disease activity during up to a four-year observational period.

Status: The study has received all approvals from the ethical committee and the Norwegian MS-Registry. Data has been collected and results from the analyses will be presented at the annual meeting of the Norwegian Neurological Association in March 2024.

Participating centres

- Haukeland University Hospital, Bergen
- Oslo University Hospital

Funding

- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- Oslo University Hospital
- The DAM foundation
- The Norwegian MS Society
- The Torbjørg Hauge Legacy, University of Bergen
- The University of Bergen
- The University of Oslo
- The Kjell Alme Legacy, Bergen

The TAF-MS 0 study: Epstein-Barr virus shedding in saliva in MS-patients receiving cladribine, natalizumab or rituximab

Disease: Multiple Sclerosis
Type of study: Observational trial

Coordinating investigator: Øivind Torkildsen
Study director: Kjell-Morten Myhr

Background: Novel insights from our MS research group indicate that infection with the Epstein-Barr Virus (EBV) is the leading cause of MS. As an EBV infection is persistent for life, the virus could function as a trigger or driver of MS-disease activity. If results from a clinical trial could confirm that targeting EBV reduces MS-disease activity, it would result in a paradigmatic change in our understanding of MS and the management of the disease.

Antiviral therapy targeting the Epstein-Barr virus (EBV) in not available, but evidence suggest that tenofovir alafenamide (TAF) may be an attractive candidate. To further evaluate the efficacy of TAF on EBV infection, EBV shedding in saliva is suggested as a surrogate endpoint of efficacy.

The objective is to establish knowledge of the natural course of EBV shedding in saliva from patients with RRMS receiving disease modifying therapies. This knowledge will be used to further design clinical trials targeting EBV infection in MS patients receiving those disease modifying therapies.

Design: This is an open observational study analysing EBV shedding in saliva samples collected weekly for five weeks from RRMS patients receiving cladribine, natalizumab or rituximab.

The primary endpoint is the frequency of EBV shedding in saliva samples collected weekly for five weeks.

Status: Funding for the trial is secured. Patient recruitment started September 2023 and by the end of 2023, a total of 55 patients are included.

Participating centres

- Haukeland University Hospital, Bergen
- Stavanger University Hospital, Stavanger
- Førde Hospital, Førde
- Haugesund Hospital, Haugesund
- Oslo University Hospital, Oslo
- Akershus University Hospital, Lørenskog
- Stavanger University Hospital, Stavanger
- Vestre Viken Hospital, Drammen

Funding

- The Norwegian MS Society
- The Regional Health Authority of Western Norway
- Horizon Europe
- Meyer Nyquist Legacy
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals

The TAF-MS 1 study: Tenofovir alafenamide fumarate (TAF) and Epstein-Barr virus infection in multiple sclerosis – a proof of concept study

Disease: Multiple Sclerosis
Type of study: Interventional trial

Coordinating investigator: Øivind Torkildsen
Study director: Kjell-Morten Myhr

Background: Novel insights from the MS research group indicate that infection with the Epstein-Barr Virus (EBV) is the leading cause of MS. As an EBV infection is persistent for life, the virus could function as a trigger or driver of MS-disease activity. If results from a clinical trial could confirm that targeting EBV reduces MS-disease activity, it would result in a paradigmatic change in our understanding of MS and the management of the disease. In collaboration with researchers at Harvard University, Boston, USA, we have identified a highly interesting candidate drug targeting EBV, not yet evaluated in MS patients. This trial could lead to a new paradigm in MS therapy, as it will evaluate a drug that may target the underlying cause of the disease.

The objective of this study is to investigate the efficacy and safety of tenofovir alafenamide (TAF) on Epstein-Barr virus infection in patients with RRMS.

Design: This is a randomised double-blinded, placebo-controlled trial comparing the efficacy and safety of tenofovir alafenamide fumarate (TAF) 25 mg daily (n= 25) to placebo (n=25) on EBV viral infection in stable RRMS patients receiving natalizumab therapy.

The primary endpoint is safety and tolerability of the drug, and the key secondary endpoint is change in EBV shedding in the saliva during 6 months of treatment.

Status: Funding for the trial is secured. The study protocol for the trial is approved by the Clinical Trials Information System (CTIS) of the European Medicines Agency. Study medication is provided by Gilead Sciences, USA. Inclusion of patients will start late January 2024.

Participating centres

Norway
- Haukeland University Hospital, Bergen
- Stavanger University Hospital, Stavanger
- Førde Hospital, Førde
- Haugesund Hospital, Haugesund
- Oslo University Hospital, Oslo
- Akershus University Hospital, Lørenskog
- Stavanger University Hospital, Stavanger
- Vestre Viken Hospital, Drammen

Sweden
- Karolinska Institute, Stockholm

USA
- Harvard University, Boston

Funding

- The Norwegian MS Society
- The Regional Health Authority of Western Norway
- Horizon Europe
- Meyer Nyquist Legacy
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals
- Gilead Sciences, USA

The NorseMS study: A digital therapeutic to improve insomnia in Multiple Sclerosis – a randomised controlled trial

Disease: Multiple Sclerosis
Type of study: Interventional trial

Coordinating investigator: Simen B. Saksvik (NTNU)
Study directors: Håvard Kallestad (NTNU) & Lars Bø (HUH/UiB)

Background: Insomnia is prevalent among individuals with multiple sclerosis (MS). Improving sleep is an important therapeutic goal, but there is currently a lack of effective treatment options. Cognitive Behavioural Therapy for Insomnia (CBT-I) has been widely studied in other patient groups and is currently recommended as first-line treatment for chronic insomnia.

Overall, the availability of CBT-I has been limited, as the number of patients in need of treatment far exceeds the number of available therapists. Therefore, fully automated digital adaptations of CBT-I (dCBT-I) have been developed that contain both screening and intervention. Whether this treatment is effective for patients diagnosed with MS, or if improved sleep can lead to reduced daytime fatigue in MS, is however, currently unknown.

The objective of this study is to investigate the efficacy and safety of dCBT-I in patients with MS.

Design: This is a multicentre parallel-group randomised controlled trial of 260 persons with MS with self-reported insomnia allocated 1:1 to either dCBT-I or a digital control-condition consisting of patient education about sleep.

The primary endpoint is to test if dCBT-I is effective in reducing insomnia severity in patients with MS.

Status: Funding for the trial is secured, the protocol is approved by the Ethical Committee, and recruitment of patients started in the fall of 2023.

Participating centres

- St. Olav's Hospital, Trondheim
- Haukeland University Hospital, Bergen
- The Norwegian University of Science and Technology, Trondheim
- The University of Bergen

Funding

- The Norwegian MS Society
- St. Olav's Hospital, Trondheim
- The Central Regional Health Authority of Norway
- Haukeland University Hospital, Bergen
- The Norwegian University of Science and Technology, Trondheim
- The University of Bergen
- The Norwegian MS Society

The 3TR – Taxonomi, Treatment, Target and Remisson – study

Disease: Multiple Sclerosis
Type of study: Observational trial

Coordinating investigator: Kjell-Morten Myhr
Study directors: Luisa María Villar Guimerans, Hospital Universitario Ramón y Cajal, Madrid, Spain, & Marta Alarcon Riquelme, University of Granada, Granada, Spain

Background: Targeted treatment of immune mediated diseases is a general challenge due to heterogenous disease courses and treatment responses. There is a lack of biomarkers to guide treatment decisions and adjustment of therapies due to clinical, laboratory or imaging defined breakthrough disease activity.

The objective of this study is to evaluate the efficacy and safety of different immunomodulatory therapies for different immune mediated diseases, to define treatment response biomarkers to develop personalised therapies within inflammatory bowel diseases, rheumatological diseases, respiratory diseases, and multiple sclerosis.

Design: This is a multicentre observational study of treatment response of immunomodulatory therapies for different immune mediated diseases
The primary endpoint is to define biomarkers for treatment response of immunomodulatory therapies for different immune mediated diseases.

Status: Ten centres in Norway, Germany, Belgium, the Netherlands, Switzerland, Italy, and Spain have included about half of the target population of 350 patients by December 2023. Inclusion target is expected to be met by 2024, and initial biomarkers analyses are in progress.

Participating centres

- Haukeland University Hospital, Bergen
- The University of Bergen
- Hospital Universitario Ramón y Cajal, Madrid, Spain
- Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
- Academic Medical Centre, University of Amsterdam, the Netherlands
- Charité-Universitätsmedizin Berlin, Germany
- Universiteit Hasselt, Belgium
- The University of Basel, Basel, Switzerland
- Hospital Clinic of Barcelona, Barcelona, Spain
- University of Genova, Genova, Italy
- Hospital Reina Sofía, Córdoba, Spain

Funding

- Haukeland University Hospital, Bergen, Norway
- The University of Bergen, Norway
- Horizon 2020 / IMI European Union
- Participating centres

The NR-SAFE study: a safety tolerability study of high-dose oral NR in Parkinson's disease

Disease: Parkinson's disease
Type of study: Interventional trial

Coordinating investigator: Haakon Berven
Study director: Charalampos Tzoulis

Background: While our previous findings nominate NR as therapy for PD, the observed effects were heterogeneous across the study population, raising the question of individualised dose-dependent responses. The optimal NR dose for neurological intervention is unknown, and doses over 2000 mg daily have not been tested in humans. To be able to conduct a dose-optimisation study for NR in PD (see the N-DOSE study), we first must establish the range of safe dosage. Here, we will conduct a safety and tolerability trial of 3000 mg oral NR in PD.

The primary objective of the NR-SAFE study is to determine the safety of oral NR 3000 mg daily for a period of 4 weeks in individuals with Parkinson's disease (PD). Safety is defined as the absence of clinically significant NR-associated moderate or severe adverse events (AE).

Design: NR-SAFE is a randomised double-blinded placebo-controlled trial to assess the safety and tolerability of NR at a dose of 3000 mg per day. Twenty individuals with PD will receive NR 3000 mg or placebo (1:1 randomisation) and followed with frequent laboratory and clinical examinations for 30 days.

Primary endpoint: The Incidence of treatment-associated moderate and severe AEs.

Status: The study was completed and published in 2023. No NR-related adverse events or signs of toxicity were observed. NR-recipients exhibited a pronounced augmentation of the NAD metabolome, with up to 5-fold increase in blood NAD+ levels, and a significant improvement in the total MDS-UPDRS, by 10.7 ± 9.94 points (p = 0.007). These results establish that short-term NR treatment at a dose of 3000 mg daily is safe, induces a pronounced augmentation of the NAD metabolome, and may be associated with a clinical symptomatic improvement in PD. While these findings do not guarantee long-term safety, they allow for a dose range extension of NR employed in clinical trials up to 3000 mg daily, provided appropriate safety monitoring. This will be important for determining potential dose-dependent beneficial effects of NR in PD and other disorders (see the N-DOSE and N-DOSE_AD trials). The study was published in the journal Nature Communications (PMID: 38016950).

Participating centre

- Haukeland University Hospital, Bergen

Funding

- The Research Council of Norway, Neuro-SysMed
- The Regional Health Authority of Western Norway
- Haukeland University Hospital

The N-DOSE study: a dose optimisation trial of nicotinamide riboside in Parkinson's disease

Disease: Parkinson's disease
Type of study: Interventional trial

Coordinating investigator: Haakon Berven
Study director: Charalampos Tzoulis

Background: While our previous findings nominate NR as therapy for PD, the observed effects were heterogeneous across the study population, raising the question of individualised dose-dependent responses. Thus, the optimal NR dose for neurological intervention is unknown. N-DOSE is a dose-optimisation trial of NR in PD, which will address this important knowledge gap.

The primary objective of the N-DOSE study is to determine the Optimal Biological Dose (OBD) for NR, defined as the dose required to achieve maximal cerebral NAD increase (measured by 31P-MRS or CSF metabolomics), or maximal alteration in cerebral metabolism patterns (measured by FDG-PET), or maximal proportion of MRS-responders, in the absence of unacceptable toxicity.

Design: N-DOSE is a randomised double-blinded placebo-controlled trial (RCT) to assess the optimal biological dose for nicotinamide riboside (NR) in PD. Individuals with PD (n = 80) will be randomised in a 1:1:2 ratio to three groups: placebo, 1000 mg NR daily, or a dose escalation group starting with 1000 mg daily and escalate to 2000 mg and 3000 mg at one-month intervals. Measures will include clinical, neuroimaging (31P-MRS, FDG-PET), molecular, and biochemical endpoints. Study duration will be three months.

Primary endpoint: The between-visit change in the following parameters: 1) Cerebral NAD levels (measured by 31P-MRS). 2) Proportion of MRS responders 3) CSF NAD and related metabolite levels (measured by HPLC-MS metabolomics, or the NADmed method) 4) Brain metabolic expression (measured by FDG-PET). The between-visit difference in the placebo group will be assessed to determine the specificity of the findings to the NR-therapy. The between-visit difference in the 1000 mg NR group will be assessed to identify any time effects and differentiate those from dose-effects.

Status: The study crossed its halfway point in 2023 with 42/80 patients enrolled.

Participating centre

- Haukeland University Hospital, Bergen

Funding

- The Research Council of Norway, Neuro-SysMed
- The Research Council of Norway, KOMMERSFORSK
- The Regional Health Authority of Western Norway
- The Norwegian Parkinson's Disease Association
- Haukeland University Hospital

The NADbrain study: a pharmacokinetic study of NAD-replenishment in human blood and brain

Disease: Parkinson's disease
Type of study: Interventional trial

Coordinating investigator: Christian Dölle
Study director: Charalampos Tzoulis

Background: To further develop the potential of NAD-replenishment therapy (NRT) as a neuroprotective therapy, we need to determine the optimal dosing regimen, including dose size and frequency. The NADbrain study will determine the optimal dosing regimen by performing a parallel assessment of NRT pharmacokinetics in the blood and brain of healthy human subjects and subjects with Parkinson's disease (PD).

The primary objective of the NADbrain study is to determine the change over 20 days in the blood NAD-metabolome and cerebral NAD levels, following the administration of oral NAD replenishment therapy (NRT) with the following NAD precursors: NR 600 mg x 2 daily, NMN 600 mg x 2 daily.

Design: The NADbrain study will perform a parallel assessment of NRT pharmacokinetics in the blood and brain of healthy human subjects and subjects with Parkinson's disease (PD). A total of 10 healthy individuals (5 men and 5 women) and 10 individuals with PD (5 men and 5 women) will undergo repeated blood sampling and 31P-MRS brain scans for two 20-days periods, each of which will start with 8 days of daily intake of NR 600 mg x 2, or NMN 600 mg x 2. The two 20-days periods will be 14 days apart to allow for washout of the previous compound. Blood will be analysed for NR and NAD-metabolites using HPLC-MS. By this approach, we will measure the simultaneous change in NAD-metabolism over time in blood and brain and establish blood and brain pharmacokinetics for NRT in humans. Based on these results, we will determine the optimal dosing frequency of NRT in healthy individuals and individuals with PD.

Primary endpoint: The change of cerebral NAD levels (measured by 31P-MRS) and of blood NAD-metabolites (measured by HPLC-MS), over time (20 days), after the administration of oral NRT with the following NAD precursors: NR 600 mg x 2 daily, NMN 600 mg x 2 daily.

Status: The study was completed in 2023 and the data is currently analysed.

Participating centre

- Haukeland University Hospital, Bergen

Funding

- The Norwegian Parkinson's disease association
- The Research Council of Norway, Neuro-SysMed
- The Research Council of Norway, KOMMERSFORSK
- The Regional Health Authority of Western Norway
- Haukeland University Hospital

The NOPARK study: a phase III randomised controlled trial of nicotinamide riboside in early Parkinson's disease

Disease: Parkinson's disease
Type of study: Interventional trial

Coordinating investigator: Brage Brakedal
Study director: Charalampos Tzoulis

Background: Parkinson's disease (PD) is a major cause of death and disability and has a devastating global socioeconomic impact. Available treatments are purely symptomatic and there is an urgent need for disease-modifying therapies. Previous research by Neuro-SysMed and others suggests that nicotinamide adenine dinucleotide (NAD) replenishment therapy may be neuroprotective in PD and delay neurodegeneration and clinical disease progression. Encouraged by these findings, we are conducting NOPARK, a phase II double-blinded randomised clinical trial of oral NR in early PD.

The primary objective of the NOPARK study is to determine whether a high dose of oral NR delays disease progression in PD measured by the change in total MDS-UPDRS.

Design: NOPARK is a phase III double-blinded randomised clinical trial of oral NR, 1000 mg per day, in early PD. NOPARK will recruit a total of 400 patients with early-stage PD (within two years from diagnosis) from 10 centres across Norway. Study duration will be one year.

Primary endpoint: The between-group (NR vs. placebo) difference of the change in the total MDS-UPDRS score between baseline and end of study (week 52).

Status: The study is ongoing and has included 385/400 participants. It is estimated to be completed in March 2025.

Participating centres

- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- Vestre Viken Hospital, Drammen
- University Hospital of North Norway, Tromsø
- Førde Hospital, Førde
- Dr. Karen Herlofson, Arendal
- Haugesund Hospital, Haugesund
- Molde Hospital, Molde

Funding

- KLINBEFORSK
- The Regional Health Authority of Western Norway
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- Participating hospitals

The NOPARK extension study: an open label trial of long-term treatment with nicotinamide riboside (NR) in Parkinson's disease

Disease: Parkinson's disease
Type of study: Interventional trial

Coordinating investigator: Brage Brakedal
Study director: Charalampos Tzoulis

Background: We are conducting a phase-II, double-blinded randomised clinical trial of oral nicotinamide riboside (NR) in early Parkinson's disease (PD) (see the NOPARK study). To evaluate the long-term safety of NR in PD, and to offer participants the opportunity to benefit from potential neuroprotective effects, we are conducting an open label extension study offering to enrol all participants who completed the NOPARK trial.

The primary objective of the NOPARK extension study is to assess the safety profile of long-term treatment with oral NR.

Design: The NOPARK extension study is a phase II open label clinical trial of oral NR, 1200 mg per day, in PD. The NOPARK extension study is recruiting participants who have completed the NOPARK study, from 10 centres across Norway.

Primary endpoint: The frequency of reported adverse events (AE) among all participants in the NOPARK open label extension.

Status: The study is ongoing and has included 250/400 participants. It is estimated to be completed in March 2025. The NOPARK extension study will be completed when the NOPARK study has been concluded and analysed.

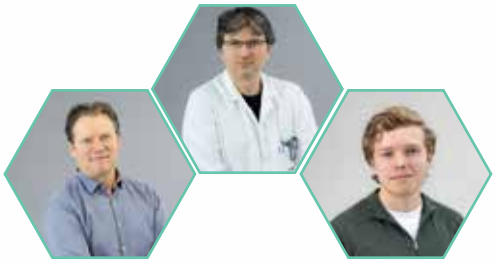
Participating centres

- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- Vestre Viken Hospital, Drammen
- University Hospital of North Norway, Tromsø
- Førde Hospital, Førde
- Dr. Karen Herlofson, Arendal
- Haugesund Hospital, Haugesund
- Molde Hospital, Molde

Funding

- KLINBEFORSK
- The Regional Health Authority of Western Norway
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- Participating hospitals

The NADAPT study: A phase II randomised controlled trial of NAD replenishment therapy for atypical parkinsonism



Disease: Parkinson's disease
Type of study: Interventional trial

Coordinating investigators: Geir Olve Skeie & Gard S. Johanson
Study director: Charalampos Tzoulis

Background: Atypical parkinsonian syndromes (APS), including progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal syndrome (CBS), are major and entirely unaddressed health challenges. There are currently no treatments able to improve function or delay disease progression in APS, and patients succumb to rapidly increasing disability, with an estimated overall survival of 3-10 years from diagnosis. Despite their devastating health impact, there is currently no clinical treatment research on PSP, MSA, or CBS in Norway, and very few initiatives globally.

Groundbreaking research from the Tzoulis group has nominated the NAD-precursor nicotinamide riboside (NR) as a potential disease-modifying therapy for neurodegenerative parkinsonisms. Motivated by this discovery, we will perform the NADAPT study: a phase-II, double-blind randomised trial of NR in PSP, MSA and CBS. Given the dismal prognosis and complete lack of treatment options for individuals with APS, this trial is both timely and necessary.

The primary objective of the NADAPT study is to determine whether treatment with NR, 3000 mg daily, can delay disease progression in PSP, MSA, and/or CBS.

Design: NADAPT is a phase II double-blind randomised clinical trial of oral NR in APS. Eligible patients will be recruited into three parallel cohorts, including PSP (n=130), MSA (n=165) and CBS (n=30-50). In each cohort, participants will be randomised 1:1 on NR 3000 mg per day or placebo and followed for 78 weeks. Participants will be recruited from Norway, the UK, and France.

Primary endpoint: the between-group (NR vs. placebo) difference in the change from baseline to end of study in disease-specific clinical severity scores (PSPRS, UMSARS, etc.).

Status: The study was initiated in December 2023.

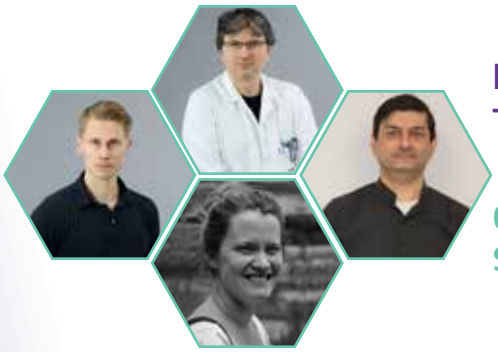
Participating centres

- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- Vestre Viken Hospital, Drammen
- University Hospital of North Norway, Tromsø
- Førde Hospital, Førde
- Dr. Karen Herlofson, Arendal
- Haugesund Hospital, Haugesund
- Molde Hospital, Molde
- UCL Queen Square Institute of Neurology, UK
- Pitie Salpetriere hospital, Paris, France

Funding

- The Norwegian Parkinson's Disease Association
- KLINBEFORSK
- Helse Vest
- DAM-Foundation
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- Participating hospitals

The STRAT-PARK study: a prospective multimodal cohort study to stratify Parkinson's disease and other parkinsonisms



Disease: Parkinson's disease
Type of study: Observational trial

Coordinating investigators: Simon Kverneng & Kjersti Stige
Study directors: Charalampos Tzoulis & Mandar Jog

Background: Neurodegenerative parkinsonisms (NDPs) affect more than 10 million people worldwide today and an estimated 20 million by 2040. NDPs are divided into the phenotypically defined syndromes of Parkinson´s disease (PD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal syndrome (CBS). To date, all trials of putative neuroprotective agents for NDP have been invariably unsuccessful, and evidence suggests that this may largely be due to substantial molecular heterogeneity underlying each of these disorders. The vast clinicopathological diversity observed within each NDP entity (i.e., PD, PSP, MSA, CBD) has led to the hypothesis that each of these may not be a single pathogenic entity, but rather multiple disorders that are driven by different molecular processes and may, therefore, respond differently to therapies targeting specific biological pathways. Under this assumption, clinical trials of potential neuroprotective compounds should not be addressing each NDP syndrome as a single entity, but rather target specific subgroups of patients with a homogeneous pathophysiology. However, efforts to identify molecular disease subtypes have not been successful.

The STRAT-PARK initiative is a multi-centre longitudinal cohort study aiming to stratify NDPs according to underlying biological mechanisms, so that tailored treatments can be developed and applied.

The primary objective of the STRAT-PARK initiative is to stratify and/or reclassify neurodegenerative parkinsonisms (NDP), according to underlying molecular disease mechanisms, and develop clinically applicable biomarkers enabling: (i) the classification of patients for participation in targeted clinical trials and (ii) monitoring of treatment efficacy in targeted clinical trials.

Design: STRAT-PARK is a prospective, longitudinal observational cohort study. A total of 2000 individuals with PD, DLB, PSP, MSA, CBS, and healthy controls will be included from HUS, St. Olavs Hospital in Trondheim, and the Center of Excellence for Parkinson's disease at the Lawson Institute for Research, London, Ontario, Canada. Participants will be followed longitudinally with systematic clinical assessment, neuroimaging, collection of biological material, and postmortem brain collection.

Status: STRAT-PARK is ongoing and a total of 350 participants have been recruited at the end of 2023. This is a critical milestone as we are now able to implement the first analyses in the dataset. The first research papers form the START-PARK cohort were submitted in 2023.

Participating centres

- Haukeland University Hospital, Bergen
- St. Olav's University Hospital, Trondheim
- London Movement Disorders Center, and Center of Excellence for Parkinson's disease, the Lawson Institute for Research, London, Ontario, Canada

Funding

- Michael J Fox Foundation
- Gerda Meyer Nyquist Guldbrandson og Gerdt Meyer Nyquist legat
- Helse Midt
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- Participating hospitals

The NO-ALS study: a phase-II, multicentre, double-blinded randomised clinical trial of oral NR and pterostilbene in early ALS

Disease: ALS
Type of study: Interventional trial

Coordinating investigators: Tale L. Bjerknes & Ole-Bjørn Tysnes
Study directors: Ole-Bjørn Tysnes & Charalampos Tzoulis

Background: There are currently no neuroprotective treatments for ALS with a significant impact on disease progression. Previous research by the PD Node and others has nominated NAD-replenishment therapy as a promising neuroprotective strategy against neurodegeneration. Moreover, a recently published small trial using a combination of the NAD-precursor nicotinamide riboside (NR) and sirtuin booster pterostilbene, showed encouraging findings in ALS. To test the potential of this strategy as a neuroprotective therapy for ALS, we are running the NO-ALS trial.

The primary objective of the NO-ALS study is to determine whether a high dose of oral NR/pterostilbene delays disease progression in ALS measured by the revised ALS-FRS (ALS functioning rating scale).

Design: NO-ALS is a multicentre, phase II randomised double-blinded clinical trial, comparing combined oral NR and pterostilbene to placebo in early ALS. A total of 180 patients will be nation-wide recruited to study arm 1.

Primary endpoint: Between-group difference in the change in total ALS-FRS score between baseline and end of study.

Status: Patients have been included since October 2020. By the end of 2023, a total of 277 patients have been included, 143 in study arm 1 which requires 180 included patients. The study is expected to close inclusion by the end of 2024. Four new NO-ALS centres have joined since 2022 (Bodø, Lillehammer, Molde and Kristiansand).

Participating centres

- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- Drammen Hospital, Vestre Viken
- St. Olav's University Hospital, Trondheim
- Stavanger University Hospital, Stavanger
- University Hospital of North Norway, Tromsø
- Førde Central Hospital, Førde
- Haugesund Hospital, Haugesund
- Nordland Hospital Trust, Bodø
- Innlandet Hospital Trust, Lillehammer
- Molde Hospital
- Sørlandet Hospital Trust, Kristiansand

Funding

- The Regional Health Authority of Western Norway
- KLINBEFORSK
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals

The NO-ALS extension study: an open label study of long-term therapy with NR and pterostilbene in ALS

Disease: ALS
Type of study: Interventional trial

Coordinating investigators: Tale L. Bjerknes & Ole-Bjørn Tysnes
Study director: Ole-Bjørn Tysnes

Background: Patients who have fulfilled the NO-ALS study will after the one-year randomisation period be invited to participate in the open label NO-ALS extension trial where all patients will receive active treatment. This is mainly a safety protocol to study long term safety of the treatment, but efficacy parameters will also be followed (ALSFRS-R and Vital capacity).

The primary objective of the NO-ALS extension study is to determine the long-term safety of treatment with oral NR and pterostilbene in ALS.

Design: NO-ALS extension is a multi-centre, phase II, open label clinical trial of NR/pterostilbene, in ALS. The study will continue until the NO-ALS trial is concluded.

Primary endpoint: The frequency of reported adverse events (AE) among all participants in the NO-ALS open label extension.

Status: By end of 2023, more than 100 patients are followed in the extension study.

Participating centres

- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- Drammen Hospital, Vestre Viken
- St. Olav's University Hospital, Trondheim
- Stavanger University Hospital, Stavanger
- University Hospital of North Norway, Tromsø
- Førde Central Hospital, Førde
- Haugesund Hospital, Haugesund
- Innlandet Hospital Trust, Lillehammer
- Nordland Hospital Trust, Bodø
- Namsos Hospital
- Molde Hospital
- Telemark Hospital Trust, Skien
- Østfold Hospital Trust, Kalnes
- Vestfold Hospital Trust, Tønsberg
- Sørlandet Hospital Trust, Kristiansand

Funding

- The Regional Health Authority of Western Norway
- KLINBEFORSK
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals

The STRAT-ALS study: an initiative to stratify amyotrophic lateral sclerosis

Disease: ALS
Type of study: Observational trial

Coordinating investigators: Tale L. Bjerknes & Ole-Bjørn Tysnes
Study directors: Ole-Bjørn Tysnes & Charalampos Tzoulis

Background: Patients with ALS have highly variable clinical phenotypes. Symptoms most commonly start in the extremities, although ~25% of cases exhibit predominantly bulbar symptoms at disease onset, including dysphagia and dysarthria. Extraocular and sphincter muscles are generally spared until late in the disease course. Survival is highly variable, as respiratory failure and death occurs on average 2-3 years after diagnosis, but 5-10% of patients survive 10 years post-diagnosis. Overall, it has not been possible to distinguish familial and sporadic ALS based on clinical phenotypes.

To address the probable heterogeneity of mitochondrial function in ALS, Neuro-SysMed aims to conduct STRAT-ALS, a longitudinal cohort study to stratify ALS according to underlying biological mechanisms, so that tailored treatments can be developed and applied. Initially, the focus will be mitochondrial markers, based on well-established techniques and preliminary results from studies on Parkinson's disease. The study will probably start in 2024.

Primary objective: To stratify ALS according to underlying molecular disease mechanisms and develop clinically applicable biomarkers enabling: (i) the classification of patients for participation in targeted clinical trials and (ii) monitoring of treatment efficacy in targeted clinical trials.

Design: STRAT-ALS is a prospective, longitudinal observational cohort study. Participants will be followed longitudinally with systematic clinical assessment, neuroimaging, collection of biological material, and postmortem brain collection.

Status: STRAT-ALS protocols were finalised in 2022 and the study is expected to start in 2024. Only patients from Haukeland University Hospital will participate.

Participating centre

- Haukeland University Hospital, Bergen

Funding

- The Regional Health Authority of Western Norway (Helse Vest) postdoc for Tale L. Bjerknes
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Donations from Nils Arne Morka

The ALS LTMV study: effects of long-term ventilation support on the quality of life of ALS patients and their families

Disease: ALS
Type of study: Interventional trial

Coordinating investigators: Tale L. Bjerknes & Ole-Bjørn Tysnes
Study director: Ole-Bjørn Tysnes

Background: The physical and psychological suffering of individuals with ALS is immense. Moreover, the lack of neuroprotective treatment and high level of disability means that the direct and indirect costs per patient are substantial and higher than for any other neurological illness. The economic burden of ALS in the USA is estimated to be 279-472 million dollars per year. For a patient depending on tracheostomy invasive ventilation (TIV) in Norway, it is estimated that the cost of care would be more than 5 million NOK annually. The use of TIV varies substantially between countries. In England it is rarely used, while in Japan, 29,3% of patients receive this treatment. In Europe and USA, the use varies from 5-10%. In Norway, 6,7% of male patients and 3,7% of female patients received TIV between 2002 and 2007. Data from the National Registry for Long-Term Mechanical Ventilation (LTMV) showed that in 2017, there were 32 ALS patients treated with TIV and 81 using non-invasive ventilation (NIV). In the period 2015-2020, 256 ALS patients started LTMV. Survival of ALS patients receiving TIV varies from 8 to 89 months, probably reflecting the different countries' medical practices, organisation of care, cultural differences, and economic considerations.

Primary objective: In the present study, the aim is to increase the knowledge on how life-sustaining ventilator support with NIV or TIV affects the quality of life (QoL) in ALS patients, life partners and children, in Norway. The results from the study may provide crucial information for clinicians and patients on one of the most difficult ethical issues of ALS treatment. We anticipate that this information will facilitate a shared decision-making process, weighing benefits and disadvantages in a wider perspective.

Design: The ALS LTMV study is an observational clinical trial, where the quality of life will be assessed in ALS patients receiving NIV or TIV.

Primary endpoint: The HRQOL, global QoL and disease specific QoL in ALS patients before and after the introduction of life sustaining LTMV.

Status: During 2022, funding was secured, and new research nurses were added to the team, as well as participating hospitals. The study has started in 2023. Currently Haukeland University Hospital, and Oslo University Hospital, Ullevål are including patients.

Participating centres

- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- St. Olav's University Hospital, Trondheim
- Stavanger University Hospital, Stavanger
- University Hospital of North Norway, Tromsø
- Vestfold Hospital Trust, Tønsberg
- Innlandet Hospital, Lillehammer
- Nordland Hospital Trust, Bodø
- Sørlandet Hospital Trust Kristiansand

Funding

- KLINBEFORSK
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Participating hospitals

N-DOSE AD: A dose optimisation trial of nicotinamide riboside in Alzheimer's disease

Disease: Dementia
Type of study: Interventional trial

Coordinating investigator: Kristoffer Haugarvoll
Study directors: Kristoffer Haugarvoll & Charalampos Tzoulis

Background: Alzheimer's disease (AD) is the most common progressive neurodegenerative dementia and predominantly affects older women. The prevalence of AD in Norway in 2020 was estimated to be 8.4% in individuals aged 70 years or older the prevalence was 9,3% in women and 7.3% in men, respectively, with no disease-modifying treatment available.

It is paramount to target novel biological mechanisms therapeutically. Increasing evidence supports that boosting cellular levels of nicotinamide adenine dinucleotide (NAD) confers neuroprotective effects in both healthy aging and neurodegeneration. NAD is an essential cofactor for a number of metabolic reactions. Boosting NAD levels could potentially help ameliorate several major processes implicated in the pathogenesis of Alzheimer disease, including mitochondrial respiratory dysfunction, neuroinflammation, epigenomic dysregulation and increased neuronal DNA damage. NAD can be replenished via supplementation of nicotinamide riboside (NR), a vitamin B3 molecule and biosynthetic precursor of NAD.

The primary objective of the N-DOSE AD study is to determine the Optimal Biological Dose (OBD) for NR, defined as the dose required to achieve maximal cerebral NAD increase (measured by 31P-MRS or CSF metabolomics), or maximal alteration in cerebral metabolism patterns (measured by FDG-PET), or maximal proportion of MRS-responders, in the absence of unacceptable toxicity.

Design: N-DOSE AD is a randomised double-blinded placebo-controlled trial (RCT) to assess the optimal biological dose for nicotinamide riboside (NR) in Alzheimer's dementia. Individuals with probable mild or moderate AD (n=80) will be randomised to receive placebo (n=20), 1000 mg of NR (n=20) or increasing doses (1000 mg, 2000 mg, 3000 mg) of NR (n=40) over 12 weeks. The selected dose range is within the safety limits for healthy humans.

Primary endpoint: The between-visit change in the following parameters: 1) Cerebral NAD levels (measured by 31P-MRS). 2) Proportion of MRS responders 3) CSF NAD and related metabolite levels (measured by HPLC-MS metabolomics, or the NADmed method) 4) Brain metabolic expression (measured by FDG-PET).

The between-visit difference in the placebo group will be assessed to determine the specificity of the findings to the NR-therapy. The between-visit difference in the 1000 mg NR group will be assessed to identify any time effects and differentiate those from dose-effects. Status: The study was initiated in 2022. The first 33 participants were included in 2023.

Participating centres

- Haraldsplass Deaconess Hospital, Bergen
- Haukeland University Hospital, Bergen

Funding

- The Research Council of Norway, Neuro-SysMed
- The Regional Health Authority of Western Norway
- Haraldsplass Deaconess Hospital
- Haukeland University Hospital
- The University of Bergen

The STRAT-COG study: a prospective cohort study to stratify dementia

Disease: Dementia
Type of study: Interventional trial

Coordinating investigator: Ragnhild Eide Skogseth
Study director: Kristoffer Haugarvoll

Background: Dementia, including Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB), is the most common group of neurodegenerative disorders. Dementia is a heterogeneous group of disorders, where a mixture of several types of pathologies is often present in individual patients.

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.

STRAT-COG is a study to better understand mixt pathologies in dementia and to identify sub-groups of disease that reflect underlying biology. The group proposes to 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. The study also includes a brain donation program.

Primary objective: To establish a cohort with multidimensional data that can be orderly integrated into the complex clinical and biological spectrum of dementia, and to 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.
Design: Cohort study with biannual follow-up.

Status: The study was initiated in 2022. The first 100 participants (individuals suffering from dementia and control individuals) have been included. A brain bank has been established.

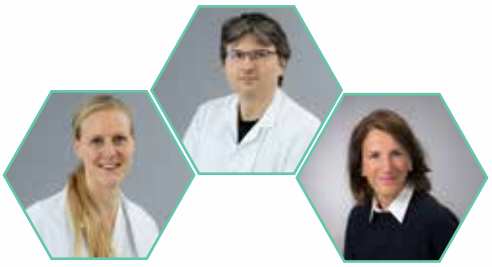
Participating centres

- Haraldsplass Deaconess Hospital, Bergen
- Haukeland University Hospital, Bergen

Funding

- The Research Council of Norway, Neuro-SysMed
- The Regional Health Authority of Western Norway
- Haraldsplass Deaconess Hospital
- Haukeland University Hospital
- University of Bergen

The NADage study: a phase II randomised controlled trial of nicotinamide riboside in aging-related frailty



Disease: Alzheimer's disease
Type of study: Interventional trial

Coordinating investigator: Katarina Lundervold
Study directors: Charalampos Tzoulis & Bettina Husebø

Background: There are currently no treatments that can prevent pathological brain aging and cognitive decline in the elderly. Achieving this requires neuroprotective interventions during prodromal stages of the disease, i.e., while it is still possible to avert irreversible neurodegeneration and prevent clinical progression to dementia. We propose that this can be achieved by augmenting brain nicotinamide adenine dinucleotide (NAD)-metabolism in the non-demented, elderly, frail population.

Frailty is defined as a geriatric syndrome of multi-system physiological deterioration, which is closely associated with pathological brain aging and a significantly increased risk of dementia, including mild cognitive impairment (MCI), Alzheimer's disease (AD) and vascular dementia. Frailty may therefore be considered a precursor state to cognitive disorders, offering a therapeutic window for disease prevention. The ideal preventive strategy during this window would involve agents that not only enhance general neuronal resilience but also bolster resistance to disease-specific stressors, while being safe and suitable for long-term use in individuals at risk of cognitive disorders. We propose that this can be achieved through NAD-replenishment therapy, employing oral precursors such as nicotinamide riboside (NR). To test this hypothesis, we are conducting NADage, a phase II double-blinded randomised clinical trial of oral NR in ageing-related frailty.

The primary objective of the NADage study is to determine whether treatment with NR, 2000 mg daily, can increase intrinsic capacity in a community-dwelling older population living with frailty, as measured by the change from baseline to week 52 in the 6-minute walk test (6MWT). Secondary objectives include assessment of cognitive function and overall quality of life.

Design: NADage, a phase II double-blinded randomised clinical trial of oral NR, 2000 mg per day, in older individuals with mild to moderate frailty. NADage will recruit a total of 100 participants from all over Norway. Study duration will be one year.

Primary endpoint: The between-group difference in the change in gait speed from baseline to week 52 as assessed by the 6-minute walk test (and concurrent sensor-based gait speed assessment) in a community dwelling frail older population.

Status: The study protocol is completed, and necessary approvals obtained. Recruitment will start in 2024.

Participating centre

- Haukeland University Hospital, Bergen

Funding

- The Rieber Foundation
- The University of Bergen
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital

The ActiveAgeing study – the Helgetun branch

Disease: Across all four diseases
Type of study: Observational trial

Coordinating investigator: Elise Førsund
Study director: Bettina Husebø

Background: The world population is rapidly ageing due to increased life expectancy and declining birthrates. Consequently, older adults are now expected to live at home for longer, even in countries like Norway which has a long tradition of institutionalised care. However, ageing at home may lead to social isolation and a more sedentary lifestyle, which is associated with declining health and greater need for care. One strategy to meet this challenge is to develop alternative living solutions, in between ageing at home and a nursing home, which aim to support good health and well-being by promoting active ageing.

The primary objective is to explore active ageing in a community-based living environment for older adults.

Design: This branch of the ActiveAgeing project primarily uses a qualitative research approach, consisting of interview data from 15 residents (11 female, 4 male, ages 62-84) of a community-based living environment for older adults called Helgetun, situated in Bergen, Norway. Additionally, the project is collecting sensor data from wearable devices (Empatica E4, FitBit Sense, Oura Ring) to investigate adaption and implementation of smart technology for older adults. Sensor data is collected over two sessions, each for 2 weeks continuously for each participant.

Status: The study was initiated in the spring of 2021 and all data was collected in 2021/2022. The first manuscript is in the publication phase, and we are currently working on the analysis for a second manuscript.

Participating centre

- Helgetun Living-Lab

Funding

- The University of Bergen
- The GC Rieber Foundation

The ActiveAgeing study – the DIGI.PARK branch

Disease: Parkinson's disease
Type of study: Observational trial

Coordinating investigators: Haakon Reithe & Monica Patrascu
Study directors: Bettina Husebø & Charalampos Tzulis

Background: Current tools for assessing clinical phenotype and severity in Parkinson's disease (PD) are based on observation while the patient performs a series of tasks. Most established is the Unifying PD Rating Scale (UPDRS), which is considered gold standard for assessing the efficacy of clinical trials testing symptomatic and neuroprotective agents. Meanwhile, these tools are limited by lack of objectiveness, low sensitivity and reproducibility, and vast variation depending on the time of the examination, time of last received dose of dopaminergic treatment, etc. One approach to circumvent these limitations and establish more objective measures of severity is that of digital phenotyping via the use of wearable sensors.

The primary objective of the DIGI.PARK study is to explore the use of wearables for symptom tracking in home-dwelling people with Parkinson's disease.

Design: This branch of the ActiveAgeing project is an observational study comprised of two phases. During the first phase, data is collected from people with Parkinson's disease (n=15) and older adults (n=15) residing at Helgetun, Bergen, Norway. A 2-week data collection is conducted in the participants' home, employing clinical assessment tools (cognitive assessment, parkinsonian symptomology, sleep disturbances), two smart watches (Fitbit and EmpaticaE4) and a smart ring (Oura).

The first phase data analysis involves a cross-correlation analysis between the three devices and the quality of the data, including comparisons with self-reported diary logs. The second phase of the study is based on the results of the first phase, as the data collection procedure is refined according to first-phase data analysis. The second phase will involve data collection from persons with Parkinson's disease and their spouses, to compare the crossover effects of the disease. Both phases will include the design of specific Parkison's disease digital biomarkers for symptom tracking.

Status: The first phase study was initiated in the spring of 2021 and all data was collected in 2021/2022. The comparative cross-correlation analysis of the three wearable devices is finalised, a digital biomarker for tremor quantification and a digital biomarker for physical activity response are designed, with publications in progress.

Participating centre

- Helgetun Living-Lab

Funding

- The University of Bergen
- The GC Rieber Foundation
- The Research Council of Norway, Neuro-SysMed
- The Regional Health Authority of Western Norway

The DIPH.DEM study

Disease: Dementia
Type of study: Observational trial

Coordinating investigator: Lydia D. Boyle
Study directors: Monica Patrascu & Bettina Husebø

Background: Almost 90% of people with dementia develop behavioural and psychological symptoms (BPSD). Recent research shows that data acquired from mapping the physical, mental, and social activities of a person can serve as a marker for some clinical conditions, including BPSD. The application of digital phenotyping for non-motor symptoms in people with dementia is still mostly unexplored, therefore there is value in investigating whether digital phenotyping can enhance the objectivity of measuring activity changes during the last period of life.

The primary objective of the study is to use sensing-based digital phenotyping combined with validated assessment tools to describe the activity trajectory and associated processes that occur during long-term stay in the nursing home.

Design: DIPH.DEM, a 1-year cross-sectional observational study (n=25), will recruit participants living at the Bergen Red Cross Nursing Home if they are >64 years with possible cognitive impairment (>0 on the Clinical Dementia Rating scale) or a likely diagnosis of dementia (based on medical record review), and no delirium (<4 on 4 A's Test for Delirium). Sensing technology used in the study will include a tri-axial Garmin smartwatch (activity, heart rate) and a wireless, radar technology Somnofy (respiration, light, sound, air quality, movement, sleep) unit mounted bedside. Data collection will occur at baseline for 7 days and include sensor observation and traditional proxy-rated questionnaires. Measurements will be repeated every six months for up to 1 year, with continuous measurement between 8-12 weeks after a significant event causing a change in health status. Analyses of the data will be used to develop a model based on activity through agitation, apathy, sleep disturbances and activities of daily living.

Primary endpoint: Change in activities of daily living (ADL) assessed over the data collection period and estimation of activity changes and selected behavioural disturbances resulting from the combined digital phenotype modelling.

Status: The study was initiated in May 2023, has now received ethical approval (REK), and began with active recruiting efforts at Bergen Red Cross Nursing Home in January 2024.

Participating centres

- Bergen Red Cross Nursing Home
- Haraldsplass Deaconess Hospital (Neuro-SysMed)

Funding

- The Regional Health Authority of Western Norway
- The Norwegian Research Council (Neuro-SysMed)

The DARK.DEM study

Disease: Dementia
Type of study: Randomized controlled trial

Coordinating investigator: Line Iden Berge
Collaborators: Elisabeth Flo-Groeneboom & Tone E. G. Henriksen

Background: Behavioural and psychological symptoms of dementia (BPSD) such as agitation, psychosis and depression are prevalent, often treatment resistant and associated with reduced cognition, level of functioning, quality of life and mortality. The "gold standard" for assessment is retrospective proxy rating with psychometric scales, yet the low test-retest reliability challenges evaluations over time. This barrier can be overcome by "digital phenotyping" that is, characterisation of human behaviour by moment-by-moment monitoring with personal digital devices. Moreover, in dementia, circadian rhythms become less robust, which potentiates BPSD. As such, chronotheraphy, i.e., interventions targeting the circadian rhythm, is promising. Intrinsically photosensitive retinal ganglion cells (ipRGC) monitor the perception of day and night and are maximally sensitive to light with short wavelength. This discovery paved the way for the virtual darkness therapy, that is, solely exposure to light deprived of blue wavelengths in the evening and night.

The primary objective: To develop and evaluate digital phenotyping and virtual darkness therapy to enhance BPSD management in specialised dementia care and facilitate implementation in municipal dementia care.

Design: WP1-2 will be conducted at NKS Olaviken Gerontopsychiatric Hospital, WP3 in Bergen municipality. WP1) DIG.DEM: In a sample of 8-10 patients, neuropsychiatric symptoms will be assessed with CMAI, NPI-12 and CSDD over 24 hours and these data will be correlated with data from Empatica embrace wristband on movement, heart rate variability, skin temperature and oxygen saturation, Next, we will apply signal processing on raw data and develop own digital biomarkers for agitation, depression and sleep disturbances. WP2) DARK.DEM RCT: Inclusion criteria: dementia related agitation (CMAI ≥45), all etiologies and stages, age ≥55. Exclusion criteria: use of beta-blockers or melatonin, clinically significant pain (MOBID-2≥3), total blindness. A total of 72 patients will be randomised to treatment as usual or 14 days with add on treatment with blue light depleted environment from 18-08, provided with circadian lightning in secluded units. Primary outcome is 14-day change in CMAI, secondary outcomes include change in NPI-12, CSDD, QoL, ADL, use of psychotropic drugs and restraints, length of hospital stay. WP3) DECIDE. DEM: Focus group interviews with staff on feasibility, barriers and enablers. Transcribed interviews will be interpreted using the hermeneutical approach.

Primary endpoint: Change in agitation assessed with CMAI from baseline to day 14.

Status: The study was initiated in august 2023, we have recruited two PhD candidates and one post-doc. We have applied for REK approval, are developing a statistical analysis plan, and will register the trial in clinicaltrials.gov. Inclusion of participants will start august 2024.

Participating centres

- NKS Olaviken Gerontopsychiatric Hospital and the Bergen municipality.

Funding

- The Research Council of Norway
- University of Bergen

The 5-D study: Decoding Death and Dying in people with Dementia by Digital thanotyping

Disease: Dementia
Type of study: Observational trial

Coordinating investigator: Monica Patrascu
Study director: Bettina Husebø

Background: How can we recognise that a person with dementia is at the end of life? When we are dying, our physical, mental, and social abilities are gradually declining. No reliable method of predicting perceived dying currently exists although the technology is available (sensors, algorithms).

The aim of Decoding Death and Dying in Dementia by Digital thanotyping (5-D) is to provide methods and tools to diagnose and describe dying to an unprecedented level of accuracy and robustness, within a timespan larger than is possible now, focusing on the case of dying people with dementia as one of the most vulnerable and difficult to study groups. 5-D combines clinical assessment tools with wearable sensing technology to monitor a) pain and distressing symptoms, b) behavioural and psychological symptoms in dementia (BPSD), c) oral changes, and to decode "the point of no return" as the beginning of perceived dying.

To obtain this outcome in nursing home patients with dementia, we will test the main hypothesis: from monitoring the evolution of thanotype components over time and their interdependencies, the prediction of the "point of no return" is possible.

The objectives of 5-D are:

1. Collect data using sensors and validated assessment scales.
2. Develop estimation methods for BPSD from sensor measurements.
3. Develop digital tools to capture the expression of pain.
4. Determine the relationship between breathing and oral symptoms.
5. Develop models for symptom interdependencies at the end of life and the "point of no return".
6. Perform human-in-the-loop validation of developed tools, models, and algorithms.

The ground-breaking interdisciplinary novelty of 5-D endeavours to enhance our understanding of end-of-life underlying pain and symptoms in people with dementia. Advancing our theoretical knowledge to uncover how, when, and why perceived dying can be identified, opens the doors for transferable research across several scientific fields.

Status: The study received funding in 2023 and starts 01.01.2024.

Participating centres

- Several nursing homes in the municipalities of Bergen, Voss, and Alver

Funding

- ERC Consolidator Grant (2024-2028)
- The University of Bergen

Illustration: Colourbox.com

MINI BIOGRAPHIES OF PHD CANDIDATES AND POSTDOCS

An ambitious scientific team, comprised of researchers with differing backgrounds, is the driving force behind Neuro-SysMed's activity. An important mission of Neuro-SysMed is to provide a strong support system for our up-and-coming researchers and to recruit talents from all over the world. We here show mini biographies of current PhD candidates and postdocs affiliated to Neuro-SysMed, in alphabetical order.

SHAMUNDEESWARI ANANDAN (postdoc)
MS in biotechnology, PhD, is currently pursuing her postdoc project under Professor Myhr, as part of the Clinical Neurology and Biomarker Research Group. Her project aims at establishing unique brain-derived blood based exosomal biomarkers for personalised anti-CD20 therapy, first of its kind, deciphering the immune status between central nervous system and circulating blood in relapsing MS patients. Hence, the overall goal is to optimise treatment outcomes and reduce the frequency of adverse effects. Anandan has a tenacious quench for exploring new arenas and is also the academic responsibility and scientific coordinator at Neuro-SysMed Research School (NEUROSYSM910) and the Bergen Multiple Sclerosis Research Group.

BIRGITTE BERENTSEN (postdoc)
PhD in neuroscience and currently a postdoc at Neuro-SysMed. She is also the head of the Bergen BrainGut Research Group, University of Bergen, and manager of the National Center for Functional Gastrointestinal Disorders, Haukeland University Hospital. She currently supervises three PhD students, two medical students and three master students. Her main research interests are disturbances of the gut-brain axis and gut-first Parkinson's disease. Through clinical data and histological and molecular analyses of the intestinal wall, Berentsen investigates prodromal, pre-clinical and clinical PD pathology of the gut.

HAAKON BERVEN (PhD candidate)
MD from the University of Southern Denmark and MS in bioinformatics and computational biology from Newcastle University. He is currently a PhD candidate in the Tzoulis group at Neuro-SysMed. He has recently conducted the NR-SAFE trial, investigating the safety of high dose Nicotinamide Riboside (NR) treatment in Parkinson's disease and is currently conducting the N-DOSE trial, investigating the biological response to increasing doses of NR in Parkinson's disease.

TALE LITLERE BJERKNES (postdoc)
MD from the Norwegian University of Science and Technology, and a PhD from the Kavli Institute for Systems Neuroscience where she worked on a project focusing on the development of spatial representation and memory. She is currently a resident at the Department of Neurology, Haukeland University Hospital and a postdoc in the Tzoulis group, Neuro-SysMed. Her research project aims to elucidate the role of mitochondrial dysfunction in amyotrophic lateral sclerosis (ALS), by stratifying ALS patients based on changes in the mitochondrial respiratory chain in neurons and associated alterations in mitochondrial DNA. She also investigates various aspects of quality of life in ALS patients, their partners and children, including the impact of life-prolonging treatment with long term mechanical ventilation.

LYDIA BOYLE (PhD candidate)
M.Phil in global health studies from the University of Bergen and Doctor of Physical Therapy (DPT) from the University of Texas Medical Branch. Lydia is currently a PhD candidate at the University of Bergen, Center for Elderly and Nursing Home Medicine (SEFAS). Her project, funded by Helse Vest and in partnership with Neuro-SysMed, will investigate phenotyping using sensing technology for persons with dementia at the end of life (DIPH.DEM).

BRAGE BRAKEDAL (postdoc)
MD working at the Department of Neurology at Haukeland University Hospital and was a PhD candidate at Neuro-SysMed in the Tzoulis group and had his doctoral defence in April 2023. His PhD project concerned applying the Norwegian prescription database to study epidemiology and potential disease-modifying drugs in Parkinson´s disease. Currently, he is a postdoc in the Tzoulis group.

KARINE EID (PhD candidate)
MD from the Norwegian University of Science and Technology. Eid was a PhD candidate in Neuro-SysMed and BERG Research Groups in Department of Neurology until February 2024. Eid defended her thesis "Multiple adversity: Childhood abuse, adult abuse, and perinatal depression in women with multiple sclerosis. A register-based cohort study" on February 23rd. Eid will start working as a postdoc in Neuro-SysMed from June 2024, with a research project on MS and migraine.

CAROLINE BENEDICTE NITTER ENGEN (postdoc)
MD (2013) and PhD from UiB (2020). She currently works as a postdoctoral fellow at Neuro-SysMed (50%), in the POND research group headed by Jan Reinert Karlsen. She is also pursuing a clinical specialisation in psychiatry, working (50%) at the Division for Mental Health Care at Helse Bergen. Her academic work and interests include the concept of suffering and philosophical, ethical, and societal aspects of (bio)medicine and (bio)technology. She is interested in the mechanisms and processes involved in the production of medically informed visions of the future (such as precision medicine) and is in that regard particularly concerned with questions related to epistemology, normativity, responsibility, uncertainty and ambiguity in medical knowledge and practice culture. In her postdoctoral project, she draws on these perspectives in relation to emerging medical practices in the management of severe progressive neurological conditions.

ELISE FØRSUND (PhD candidate)
Molecular biologist and MS on the correlation between aging cells and Parkinson's disease. Currently, she is a PhD candidate in the ActiveAgeing project, led by Bettina Husebø. Her PhD project focuses on healthy elderly people and how their living environment affects ageing, primarily concerning residents of the senior housing project "Helgetun" in Bergen.

GLORIA GAMIZ (postdoc)
PhD from University of Granada in 2022 where she specialised in exploring the principles determining protein stability, folding kinetics and structure. Currently, she is a postdoc in the Martinez lab where her research is focused on studying the molecular homeostasis of tyrosine hydroxylase. This work aims to develop novel therapies to address conditions associated with dysregulation of dopamine synthesis.

LASSE GIIL (postdoc)
MD with a PhD in immune biomarkers in Alzheimer's disease in 2019. He is currently studying metabolic biomarkers in relation to the risk of incident dementia and in the study of delirium. Currently, he is working as a physician at Haukeland University Hospital, Department of Cardiology, as an assistant professor at the University of Bergen and as a postdoctoral researcher at Neuro-SysMed, location Haraldsplass Deaconess Hospital.

JOHANNES JERNQVIST GAARE (postdoc)
MD and PhD from the University of Bergen. His PhD work focused on the genetics of Parkinson's disease, specifically how multiple mutations across biological pathways can affect the risk of developing Parkinson's disease. He is currently working as a postdoc in the Tzoulis group, primarily studying the role of DNA methylation in Parkinson disease.

IDA VIKTORIA HERDLEVÆR (postdoc)
MSc in medical cell biology and a PhD from the University of Bergen (2021) in paraneoplastic cerebellar degeneration. Currently, she will do her postdoc on multiple sclerosis in the MS research group aiming at establishing blood-based biomarkers for disease activity and personalised therapies in multiple sclerosis.

AHMAD INTAKHAR (PhD candidate)
MSc in microbiology, medical science, and systems biology, and currently a PhD candidate in the MS Node. His research focuses on novel molecular biomarker candidates in multiple sclerosis pathology, more specifically neuroprotection and myelin repair.

KUNWAR JUNG (postdoc)
PPhD from Martinez's lab at the UiB on posttranslational modification and protein-protein interaction involved in the function and regulation of aromatic amino acid hydroxylases with implications in dopamine-related neurological disorders. Jung is currently a postdoc funded by the KG Jebsen Centre for Parkinson's Disease (DECODE-PD). He has expertise in various cellular and molecular biology techniques, confocal imaging, and target-based and phenotypic drug screening. His work focuses on screening for small-molecule compounds (drug repurposing) with therapeutic potential to enhance mitochondrial complex I targeting mitochondrial dysfunction in PD.

AKASH KAPALI (PhD candidate)
MSc in international health from the University of Bergen. Currently, he is a PhD candidate in the DRONE (Drug Repurposing fOr Neurological disEases) Research Group led by Trond Riise, where his works focuses on the role of established and novel risk factors for multiple sclerosis using Norwegian health registries.

TROND-ANDRÉ KRÅKENES (PhD candidate)
MSc in nanoscience from the University of Bergen. He is since 2023 a PhD candidate in the Martinez group. His PhD project is focused on three presynaptic proteins: α-synuclein, TH and VMAT2. The project aims to better understand the role of these proteins in the regulation of dopamine homeostasis and in Parkinson's disease.

SIMON ULVENES KVERNENG (PhD candidate)
MD from the University of Bergen and currently a PhD candidate in the Tzoulis group. His research is focused on stratification of Parkinson's disease, with emphasis on finding biomarkers of mitochondrial dysfunction in peripheral tissues. He coordinates the STRAT-PARK study at Haukeland University Hospital.

INGRID ANNE LIE (PhD candidate)
MD from the Norwegian University of Science and Technology (NTNU), and a PhD candidate in the Neuro-SysMed MS Node until her doctoral defence in February 2023. Her PhD research focused on biomarkers of axonal damage and neurodegeneration in people with MS, with special interest in imaging markers of diffuse grey matter damage.

PEDER LILLEBOSTAD (PhD candidate)
MSc in biomedicine from the University of Bergen, with a background in fMRI and brain connectivity. Currently a PhD candidate in Neuro-SysMed, specialising on imaging-based biomarkers of PD. Working on substantia nigra segmentation in STRAT-PARK using deep neural networks and multiparametric MRI, with plans to expand to the complete set of basal ganglia. Other interests include applied graph theory and reproducible science.

KATARINA LUNDERVOLD (PhD candidate)
MD specialising in neurology at the Haukeland University Hospital and currently a PhD candidate in the Tzoulis group at Neuro-SysMed. Her PhD research focuses on the brain-gut axis to improve our understanding of preclinical and clinical gastrointestinal biomarkers to make advancement towards developing a neuroprotective therapy in Parkinson disease. Furthermore, she is exploring NAD replenishment therapy in Parkinson's disease and in an elderly frail community-dwelling population.

BRICE SYLVAIN DANIEL MARTY (postdoc)
MS in electrical engineering, modelling and systems from Université Toulouse III, France, and PhD in neuroscience from the Université Libre de Bruxelles, Belgium. After a postdoctoral and a lecturer position at the school of Psychology at Bond University, Gold Coast, Australia, he is currently a postdoctoral fellow at the Centre for Elderly and Nursing Home Medicine (SEFAS) at University of Bergen. He's working on the development of digital biomarkers for symptom tracking in real-world everyday life for persons with dementia and Parkinson's disease. As part of Neuro-SysMed, he is also working on the use of functional Near infrared spectroscopy as diagnostic tool for Parkinson's disease, and he designed a course in algorithm and coding for health researchers without computer sciences background.

ASIEH ABOLPOUR MOFRAD (postdoc)
PhD in Informatics Psychology (Jan. 2021) from OsloMet University and another PhD in informatics (Nov. 2021) from the University of Bergen. She is currently a postdoc at the Department of Global Public Health and Primary Care, UiB, and a member of the DRONE project (Drug Repurposing for NEurological diseases). She utilises state-of-the-art machine learning techniques to analyse Norwegian health registry data, aiming to find possible drug candidates for treatments of Parkinson's disease.

HILDE NORBORG (PhD candidate)
MD from the University of Bergen (2017) and is currently a PhD candidate in the MS Node, focusing on disease modifying therapies in multiple sclerosis.

NELSON OSUAGWU (PhD candidate)
MSc in biomedicine and in biotechnology from the University of Bergen and Inland Norway University of Applied Sciences, respectively. Currently, he is a PhD candidate in the Tzoulis group, where his project is focused on developing an in vitro protein translation inhibition cell model for Parkinson's disease.

MONICA PATRASCU (postdoc)
PhD in Systems Engineering and a MSc in Intelligent Systems from University Politehnica of Bucharest, Romania. They are the coordinator of the Complex Systems Laboratory (xLab) at University Politehnica of Bucharest, working with complex and intelligent systems, a postdoctoral fellow at the Centre for Elderly and Nursing Home Medicine (SEFAS) at the University of Bergen, Norway, working with modeling complex biosystems and, as part of Neuro-SysMed, developing digital biomarkers for symptom tracking in real-world everyday life for older adults, persons with dementia including the end of life, and Parkinson's disease.

HAAKON REITHE (PhD candidate)
MSc in behavioural neuroscience from the University of Bergen and currently a PhD candidate at the Center for Elderly and Nursing Home Medicine (SEFAS) and Neuro-SysMed. His PhD project is a part of the DIGI. PARK project and focuses on the use of wearable sensor devices and other digital tools for the detection and monitoring of symptoms associated with PD, exploring the development of digital biomarkers for research and clinical purposes.

ANNA RUBIOLO (PhD candidate)
MSc in Neuroscience from the University of Trieste and Helsinki. Currently, she is a PhD candidate in the Tzoulis group, affiliated with the KG Jebsen Center for Parkinson's Disease. Her research is focused on confirming the existence of subtypes of idiopathic Parkinson's disease based on mitochondrial dysfunction, specifically related to respiratory complex I deficiency.

BRIT ELLEN RØD (PhD candidate)
MD from the University of Bergen and has been working as a resident in neurology at the Department of Neurology, Haukeland University Hospital. She is currently a PhD candidate in the MS Node, focusing on therapy with anti-CD20 monoclonal antibodies in patients with multiple sclerosis.

LIV MARIE RØNHOVDE (PhD candidate)
MSc in Clinical Psychology (Cand. Psychol.) at St.Olavs Hospital and The Norwegian University of Science and Technology. She is currently a PhD candidate associated to the MS Node. Her PhD research is focused on cognitive behavioural therapy for insomnia in multiple sclerosis, with Bø as co-supervisor.

STINE SCHIKORA-RUSTAD (PhD candidate)
MD and neurologist at the Department of Neurology, Sørlandet Hospital, Kristiansand, Norway. She is currently a PhD candidate associated to the MS Node. Her PhD research is focused on haematopoietic stem cell transplantation in multiple sclerosis patients, with Torkildsen as co-supervisor.

TROND TRÆTTENBERG SERKLAND (PhD candidate)
MD, senior consultant in clinical pharmacology and currently a PhD candidate associated to the MS Node. The objective of his project is to clarify whether clinical pharmacological tools can contribute with useful decision support in establishment of personalised treatment of multiple sclerosis with monoclonal antibodies against CD20 positive B-cells.

RAGNHILD SKOGSETH (postdoc)
Geriatrician, associate professor at UiB and currently a postdoctoral fellow at Neuro-SysMed. She is leading the clinical dementia studies at Haraldsplass Deaconess Hospital. Her main research interests are dementia with Lewy bodies, frailty, biomarkers and neuropathology.

ELLEN SKORVE (PhD candidate)
MD from the University of Bergen (2012) and has been working as a resident in neurology at the Department of Neurology, Haukeland University Hospital. She is currently a PhD candidate in the MS Node, focusing on assessment of cognitive function in newly diagnosed multiple sclerosis patients.

MAGNE HAUGLAND SOLHEIM (PhD candidate)
MSc in statistics and chief engineer in the Core Facility for Biostatistics and Data Analysis at UiB. Currently, he is a part time PhD candidate in the DRONE project, where he uses health registries to study amyotrophic lateral sclerosis.

KJERSTI STIGE (PhD candidate)
MD from the University of Tromsø. Currently, she is a PhD-student at the Norwegian University of Science and Technology (NTNU) and works as a neurology resident at St. Olav's University Hospital. She has a particular interest in movement disorders and currently focuses on the Neuro-SysMed STRAT-PARK study.

MAGNUS SVENSEN (PhD candidate)
MSc in analytical chemistry from the University of Bergen (2022) and currently a PhD candidate in Tzoulis' group. His project focuses on the usage of phosphorus-based magnetic resonance spectroscopy (31P-MRS) to find potential biomarkers for diagnosis, stratification and treatment response in Parkinson's, Alzheimer's and ALS.

KRISTIN EIDSHEIM SØNNESYN (PhD candidate)
MD from the University of Bergen (2015). Resident in geriatrics at the Department of Medicine at Haraldsplass Deaconess Hospital and PhD candidate in Professor Haugarvoll and Associate Professor Skogseth's group at Neuro-SysMed. Her PhD project focuses on the prodromal phase of dementia with Lewy bodies.

TAI, MARY DAYNE SIA (PhD candidate)
MSc in biomedical science from the University of Bergen. She is currently a PhD student at the Martinez group, working on a project that focuses on protein homeostasis as a therapeutic target for dopamine deficiency.

TITLESTAD, IRIT (PhD candidate)
MSc in clinical diabetes nursing from the Western Norway University of Applied Sciences, and currently a PhD candidate in the Neuro-SysMed Dementia Node. Her PhD project focuses on blood and cerebrospinal fluid (CSF) biomarkers that can identify patients with increased risk for delirium. In addition, the project aims to validate the diagnosis of delirium in a large biobank study on community-dwelling older adults.

TORGAUTEN, HILDE MARIE (PhD candidate)
MD from the University of Oslo (2012) and has been working as a resident in neurology at the Department of Neurology, Haukeland University Hospital. She is currently a PhD candidate in the MS Node, focusing on rituximab therapy in multiple sclerosis patients.

TUOMINEN, JULIA AXIINA (PhD candidate)
MSc in behavioural neuroscience from the University of Bergen, and currently a PhD candidate in the DRONE project at the Section for Epidemiology and Medical Statistics. She investigates associations between the use of prescription medications and Parkinson's disease, with the aim of identifying drugs that may alter the disease process by preventing or delaying the onset and progression of the disease.

WILLUMSEN, JOHANNES (PhD candidate)
MD and consultant neurologist at the Department of Neurology, Møre and Romsdal Hospital Trust, Molde, Norway. He is currently a PhD candidate associated to the MS Node. His PhD research is focused on epidemiology and life expectancy in multiple sclerosis patients, with Myhr as co-supervisor.

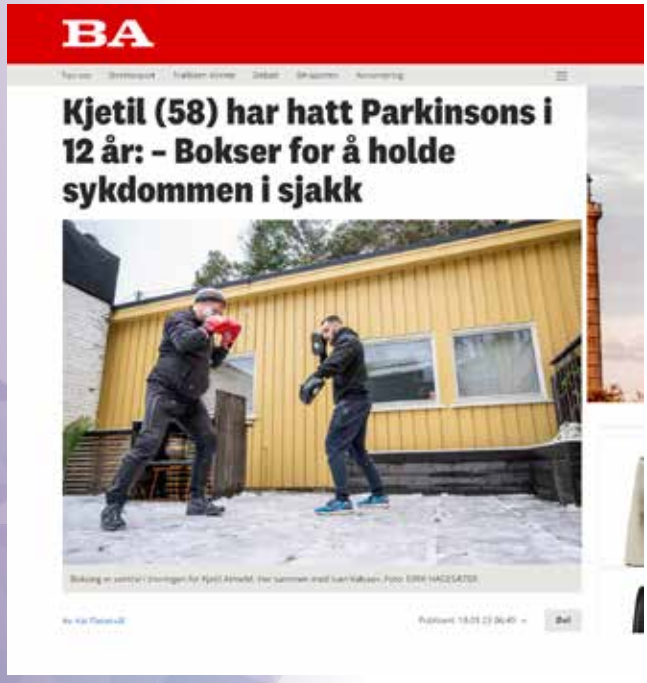
KRISTINE YTREHUS-LYNUM (PhD candidate)
MSc in Clinical Psychology (Cand. Psychol.) at St.Olavs Hospital and The Norwegian University of Science and Technology. She is currently a PhD candidate associated to the MS Node. Her PhD research is focused on cognitive behavioural therapy for insomnia in multiple sclerosis, with Bø as co-supervisor.

NEURO-SYSMED IN THE NEWS

News stories featuring Neuro-Sysmed in 2023 in the media.

January 2, 2023, VG Pluss: "Professor: De ukjente faktorene som kan beskytte mot MS". Interview with Professor Lars Bø, about factors that might prevent MS.

January 10, 2023, Bergensavisen Pluss: "Kjetil (58) har hatt Parkinsons i 12 år: - Bokser for å holde sykdommen i sjakk". Patient case on Parkinson's. Interview with Professor Tzoulis.



January 12, 2023, Dagbladet: "- RØYKING KAN ØKE MS-RISIKO MED 50 PROSENT". Patient case highlighting risk factors for MS, particularly smoking, and interview with Professor Lars Bø.

January 18, 2023, Forskning.no: "MS-pasienter som har kjøpt stamcellebehandling i utlandet skal nå kartlegges". Also in Forskersonen Jan. 18. Concerning the RAM-MS and SAFE-MS studies.

January 19, 2023, Bergensavisen Pluss: "Demente Kjell ble innlagt på kommunens sengepost: Funnet alene på Danmarks plass av forbipasserende". Patient case, on missing follow-up for Alzheimer patients in municipal care. Interview with Professor Husebø on the special needs of this patient group.

January 20, 2023, Tidsskrift for Den norske legeforening: "Nye sentre skal gi flere kliniske studier i Norge". A commentary piece from several authors, among them Professor Myhr, on six NorTrials centres sentre for treatment research at the university hospitals, among them neurological, and the aim to increase the amount of clinical studies.

January 24, 2023, Dagbladet: "- ØKER DEMENSRISIKO MED 165 PROSENT". (Paper version, no link available.) Also in Allers March 3. Story on a Swedish trial showing risk factors for dementia. Interview with Professor Husebø with advice on preventing the disease.

January 29, 2023, TV2: "ALS-pasient satte rekord med tankekraft". American patient case with an ALS patient communication through an innovative brain implant. Interview with Professor Tysnes.

January 30, 2023, Dagens Medisin: "Kritisk til OUS' håndtering av Ekspertpanel-henvisninger". On the inclusion of Professor Tysnes as expert in the National Expert Panel for the Specialist Health Services to also cover the ALS field.

January 30, 2023, På Høyden: "Vil integrere kunst og kultur i medisin". Also in Ballade Feb. 1. Interview with Professor Geir Olve Skeie who is researching the effects of music on Parkinson patients.

January 30, 2023, Tidsskrift for Den norske legeforening: "- Det må satses på hjemmetjenestene". Interview with Professor Husebø on geriatric care of the future, and the ActiveAgeing project for dementia patients.

February 10, 2023, NRK: "Tror vitaminkapsel kan bremse aldring". Interview with Professor Tzoulis on the NAD trials. Also in Aldring og Helse March 20.

February 11, 2023, Dagbladet Pluss: "Victorias (24) dødsdom: Ingen vei tilbake". Also in KK March 5. Patient case on ALS, interview with Professor Tysnes. Follow-up story in Dagbladet March 25, incl. mention of the NO-ALS study.

February 17, 2023, Fædrelandsvennen – Login: "Eivor trodde hun bare var sliten. Så oppdaget legene hva som var galt." Also in Stavanger Aftenblad, ITromsø and Bergens Tidende Feb. 17. Patient case on MS, interview with Professor Myhr.

February 20, 2023, Dagbladet Pluss: "Hyller ny MS-medisin: - Svært effektiv". On the approval of the MS drug Kesimpta (ofatumumab) in Norway, interview with Professor Torkildsen.

March 3, 2023, Se og Hør EXTRA: "GRÅT DA HAN FIKK BESKJEDEN". Patient case on MS, interview with Professor Myhr.

March 30, 2023, NRK Vestland: "Stilte feil diagnose - Solfrid har ikke Parkinsons sykdom likevel". Update story in NRK May 26. Patient case on misdiagnosis of Parkinson's, and the need for better diagnosing tools, interview with Professor Tzoulis.

April 17, 2023, Bergens Tidende: "På den siste jobbreisa merka Magnus at noko var gale. No blir hjernen brukt til forsking." Patient case on Alzheimer's and participant in the N-DOSE AD study, and interview with Drs. Skogseth and Haugarvoll.

May 3, 2023, TV2: "Håper dette kan hjelpe mot de dødeligste hjernegåtene". Interview with Frank Riemer on his work at Neuro-SysMed, and how AI can improve diagnosis.

VEILEDER: Frank Riemer forteller at han har studenter som både prøver å forbedre skanning-bildene, og sammenligner algoritmer fra gammel og ny maskinlæring. Foto: Penelope Alida Larsen / TV 2

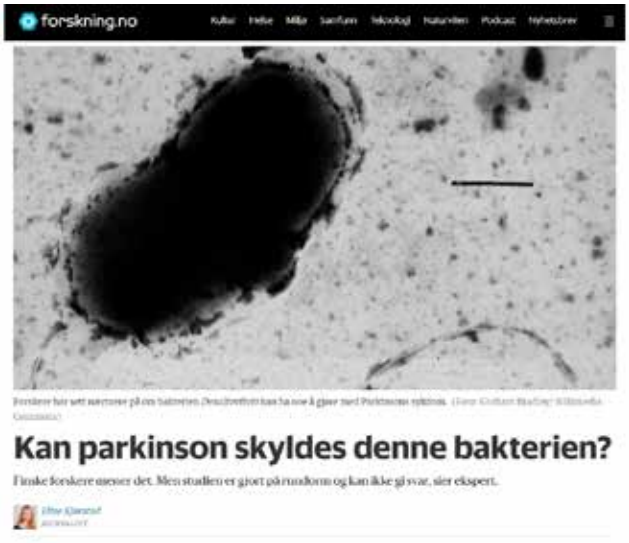
May 4, 2023, Tidsskrift for Den norske legeforening: "Behandling av motoriske symptomer ved Parkinsons sykdom". Article by several authors, among them Professor Tysnes, proposing methods for medical treatment of motor symptoms of Parkinson's disease.

May 8, 2023, På Høyden: "ERC til Valen og Husebø". Also in UiB News May 5. On the ERC consolidator grant to Professor Husebø for dementia project.

May 9, 2023, Psykologisk.no: "Norsk forsker studerer hvordan sensorteknologi kan forutsi døden". Also in UiB News May 5. Professor Husebø receiving ERC funding for a project investigating how assistive technology can be used to recognise symptoms among people with dementia who are near the end of life.

May 15, 2023, Legemiddelindustriforeningen: "Økning i industristudier innen hjernehelse". On the effect of the NorTrials centres, leading to an increased interest from the industry in brain health studies, interview with Professor Myhr.

May 16, 2023, Forskning.no: "Kan parkinson skyldes denne bakterien?". Also in ABC Nyheter May 21. Concerning investigations on theoretical association between the Desulfovibrio bacteria and Parkinson's disease, interview with Professor Tzoulis.



May 25, 2023, UiB News: "Årets Falch-forelesning: Alberto Ascherio".

NYHET

Årets Falch-forelesning: Alberto Ascherio

Flere hundre overværte Harvardprofessorens forelesning med tittelen: "The Epstein-Barr virus as the leading cause multiple sclerosis and the possible viral etiology of other neurodegenerative diseases".

June 16, 2023, Dagens Medisin: "Mener flere MS-pasienter bør få tilbud om stamcellebehandling i Norge". On the limited stem cell treatment option in Norway for MS, interview with Professor Torkildsen.

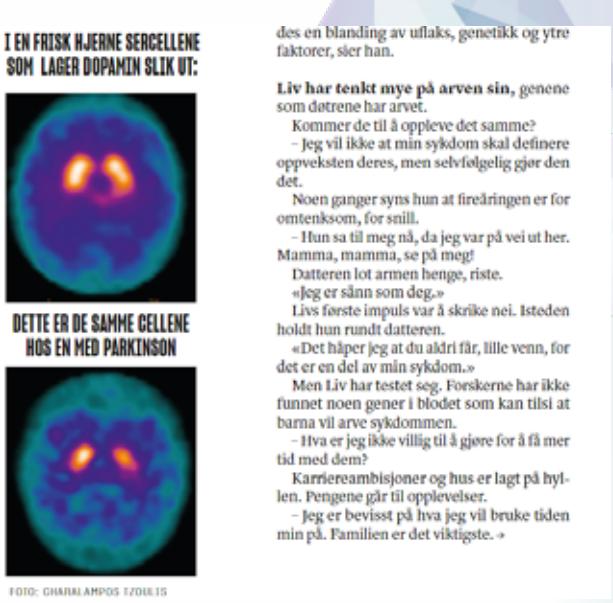
Dagens Medisin

Mener flere MS-pasienter bør få tilbud om stamcellebehandling i Norge

500-600 norske MS-pasienter har reist utenlands for å få stamcellebehandling. Flere bør få slik behandling i Norge mener fagfolk, MS-forbundet – og Frp som fredag fremmer forslag om dette i Stortinget.

June 16, 2023, Placera.se: "Chromadex: ChromaDex, a Global Authority on Nicotinamide Adenine Dinucleotide (NAD+), Celebrates the 10th Anniversary of its ChromaDex External Research Program (CERP)" On the ChromaDex External Research Program (CERP) and their Niagen® ingredient (patented nicotinamide riboside or NR), referral to Neuro-SysMed publication and the NADPARK study, interview with Professor Tzoulis.

August 12, 2023, VG Pluss: "Liv Pilbeam (37) har Parkinson: - Jeg må legges inn". Patient case on Parkinson's, interview with professor Tzoulis.



I EN FRISK HJERNE SERCELLENE SOM LAGER DOPAMIN SLIK UT:

DETTE ER DE SAMME CELLENE HOS EN MED PARKINSON

FOTO: GHARIAMPOS TZOULIS

des en blanding av uflaks, genetikk og ytre faktorer, sier han.

Liv har tenkt mye på arven sin, genene som døtrene har arvet.

Kommer de til å oppleve det samme?

– Jeg vil ikke at min sykdom skal definere oppveksten deres, men selvfølgelig gjør den det.

Noen ganger syns hun at fireåringen er for omtenksom, for snill.

– Hun sa til meg nå, da jeg var på vei ut her. Mamma, mamma, se på meg!

Datteren lot armen henge, riste.

«Jeg er sånn som deg.»

Livs første impuls var å skrike nei. Isteden holdt hun rundt datteren.

«Det håper jeg at du aldri får, lille venn, for det er en del av min sykdom.»

Men Liv har testet seg. Forskerne har ikke funnet noen gener i blodet som kan tilsi at barna vil arve sykdommen.

– Hva er jeg ikke villig til å gjøre for å få mer tid med dem?

Karriereambisjoner og hus er lagt på hylla. Pengene går til opplevelser.

– Jeg er bevisst på hva jeg vil bruke tiden min på. Familien er det viktigste. →

August 23, 2023, Dagens Medisin: "MS-medisiner inkludert på WHO-liste: - Et stort fremskritt for internasjonalt MS-arbeid". On the inclusion of MS drugs on the WHO list of medicine that all countries should have available for their citizens. Interview with Professor Myhr, who has contributed with input related to getting rituximab on the list.

August 30, 2023, NRK Trøndelag: "På ett år gikk Sonja

Dagens Medisin

MS-medisiner inkludert på WHO-liste: – Et stort fremskritt for internasjonalt MS-arbeid

Verdens helseorganisasjon (WHO) har ført opp tre medikamenter på sin liste over medisiner alle land må ha tilgjengelig for sine innbyggere.

Berg fra å planlegge ektemannens begravelse til å feire gullbryllup". Patient case on Parkinson's, interview with Professor Tzoulis.

September 20, 2023, Dagbladet: "Ny studie: MS kobles til sykdom". On Neuro-SysMed research indicating an association of the Epstein Barr virus with MS, and

hope of a possible cure. Interview with Professors Torkildsen and Myhr. Based on the UiB News story Sept. 21, 2023: "Bergensforskere leder EU-prosjekt om MS og kyssesykevirus". Also in På Høyden Sept. 21, Nynorsk Pressekontor Sept. 22, Nationen Sept. 25, and MedWatch Sept. 27. Separate interview in Dagens Medisin Sept. 22, 2023: "Leder internasjonalt forskningsprosjekt: - Vi er nærmere en løsning på MS-gåten enn noen gang"


HELSE

Oppsiktsvekkende MS-nyhet fra norske

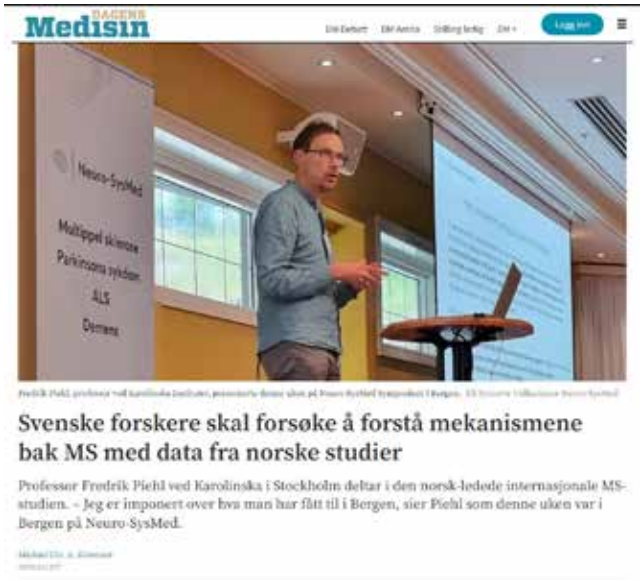
– Vi tror nå at det kan være mulig å kurere sykdommen, og hindre at den bryter ut i det hele tatt, sier en av de norske forskerne som skal lede en stor, internasjonal MS-studie.

TROR VI SNART KAN KURERE MS

September 22, 2023, Strandbuen Login: "Anti-aldringsforsker: - Jeg spiser én om morgenen og én om kvelden". Also in Avisa Nordland, Rana Blad and Nidaros Sept. 24, and in Østlands-Posten Sept. 25, Oppland Arbeiderblad Sept. 30, Fredrikstad Blad and Tidens Krav Pluss Oct. 28. On supplements that can slow down aging and prevent Alzheimer's, among them NAD+. Comment from Professor Tzoulis.

September 26, 2023, Dagens Medisin: "Studie har undersøkt om det er mulig å predikere depresjon hos MS-pasienter". Story from the Neuro-SysMed Annual Meeting 2023, interview with Researcher Frank Riemer. September 28, 2023, Tidens Krav: "- Sykdommen har gått i dvale, og jeg vil ikke vekke den". Patient case on MS and stem cell treatment abroad, interview with Professor Torkildsen on the RAM-MS study.

September 29, 2023, Dagens Medisin: "Svenske forskere skal forsøke å forstå mekanismene bak MS med data fra norske studier". Story from the Neuro-SysMed Annual Meeting 2023, interview with Professor Fredrik Piehl.


Medisin

Svenske forskere skal forsøke å forstå mekanismene bak MS med data fra norske studier

Professor Fredrik Piehl ved Karolinska i Stockholm deltar i den norsk-ledede internasjonale MS-studien. – Jeg er imponert over hva man har fått til i Bergen, sier Piehl som denne uken var i Bergen på Neuro-SysMed.

October 5, 2023, Dagens Medisin: "- Nærmere en løsning på MS-gåten enn noen gang". On the granting of 80 mill NOK from Horizon Europe to the Neuro-SysMed TAF1 project, interview with Professors Torkildsen and Myhr.


VIAGRA RESEPTFRI 50 mg sildenafil

25

DAGENS Medisin

80 millioner EU-kroner til stort MS-prosjekt

October 5, 2023, Dagens Medisin: "Undersøker om

medisiner for andre diagnoser kan ha effekt hos parkinsonpasienter". Story from the Neuro-SysMed Annual Meeting 2023, interview with PhD student Julia Tuominen.


Dagens Medisin

Undersøker om medisiner for andre diagnoser kan ha effekt hos parkinsonpasienter

Forskere i Bergen undersøker om noen medisiner som er på markedet for andre diagnoser, kan bremse sykdomsutviklingen og dødeligheten hos parkinsonpasienter.

October 9, 2023, Dagens Medisin: "Koblet MoBa-data mot MS-registeret for å få svar om D-vitamin". Story from the Neuro-SysMed Annual Meeting 2023, interview with PhD student Akash Kapali.


Dagens Medisin

Koblet MoBa-data mot MS-registeret for å få svar om D-vitamin

Er det sollys eller D-vitamin i seg selv som beskytter mot MS? Norsk studie basert på data fra MoBa-undersøkelsen støtter opp om det siste.

October 9, 2023, Aftenposten – Login: "Norge har flere mennesker med MS enn andre land. Kan kyssesyken være en del av årsaken?". Also in Bergens Tidende Oct. 14. Patient case on MS, interview with Professors Torkildsen and Myhr.

October 12, 2023, Dagens Medisin: "Studie støtter at B-cellebehandling er effektiv på grunn av endring i immunresponsen mot EBV. On B-cell therapy in MS, interview with Brit Ellen Rød.


Dagens Medisin

Studie støtter at B-cellebehandling er effektiv på grunn av endring i immunresponsen mot EBV

October 13, 2023, HealthTalk: "MS-pasienter byttet fra medisin inn i venen til under huden: - Spesielt attraktive data". Substituting anti-CD20-therapy with ofatumumab for MS patients, interview with Professor Torkildsen.


Health Talk

ECTRIMS 2023:

MS-pasienter byttet fra medisin inn i venen til under huden: – Spesielt attraktive data

– Det som studien viser er spesielt attraktivt med ofatumumab (Kesimpta) er at den nesten ikke påvirker immunoglobulin (Ig)-nivåene, sier UiB-professor og Haukeland-overlege.

October 13, 2023, LMI: "North of the ordinary - norsk aften i Milano". Article from a NorTrials and Innovation Norway meeting in Milano in connection with the ECTRIMS conference, featuring Professors Torkildsen and Myhr. Also in Dagens Medisin Oct. 16: "Kliniske studier i Norge: - NorTrials skal fungere som "én vei inn" og være nasjonalt kontaktpunkt".


LMI

North of the ordinary – norsk aften i Milano

October 13, 2023, Dagens Medisin: "Studie viser økende sykefravær allerede ti år før MS-diagnose: - Et veldig viktig budskap". On possible onset of MS up to 10 years before diagnosis, interview with Professor Torkildsen.

October 17, 2023, Dagens Medisin: "Norske sykehus med i industristudie på ny MS-medisin: - Ved full klaff er effekten lik stamcellebehandling". On the GLOBEAM study on MS where Neuro-SysMed will participate. Interview with Professors Torkildsen and Myhr.


Dagens Medisin

Norske sykehus med i industristudie på ny MS-medisin: – Ved full klaff er effekten lik stamcellebehandling

Legemiddelselskapet Roche har startet en fase 1-medikamentstudie på en helt ny form for B-cellebehandling. Norge skal, som et av få land i Europa, delta i industristudien.

October 17, 2023, Dagens Medisin: "Seks norske forskere: Dette trekker de frem som høydepunkter fra årets ECTRIMS-kongress". Six Norwegian attending researchers interviewed on the highlights of the ECTRIMS conference on MS in Milan, among them Professor Torkildsen.

November 8, 2023, Dagsavisen: "Frp foreslår at flere skal få omdiskutert MS-behandling". Political debate about availability of stem cell therapy for MS in Norway, mention of the RAM-MS study.

November 11, 2023, NRK Rogaland: "Én sykdom - to helt forskjellige skjebner". To patient case stories on MS, interview with Professor Torkildsen on the RAM-MS study.


Én sykdom – to helt forskjellige skjebner

November 13, 2023, VG: "Tror vitaminpille kan bremse aldring". On the possibility for NAD+ as inhibitor for Parkinson's, interview with Professor Tzoulis.

November 17, 2023, Hordaland Folkeblad: "– Demens er helsevesenets klimakrise". On Neuro-SysMed's N-DOSE study, determining the optimal dose and effect for nicotinamide riboside in Alzheimer's, interview with research nurse Kristine Skeie and Dr. Haugarvoll.


NYHENDE

– Demens er helsevesenets klimakrise

November 20, 2023, Helse Sør-Øst: "Tildeling av 196 millioner kroner til nasjonale kliniske behandlingsstudier". ON the RCN's KLINBEFORSK program funding to 12 clinical studies, among them Professor Tzoulis and the NADAPT study.

November 30, 2023, Placera: "Chromadex A Milestone Phase I Randomized, Double-Blind Clinical Trial Demonstrates High-Dose Niagen®, Patented Nicotinamide Riboside (NR), Supplementation Induces a Potent NAD+ Response and Is Associated With Mild Improvement in Parkinson's Disease (PD)". On the results of Niagen® in a Neuro-SysMed publication in Nature Communications, from the NR-SAFE study, interview with Professor Tzoulis.

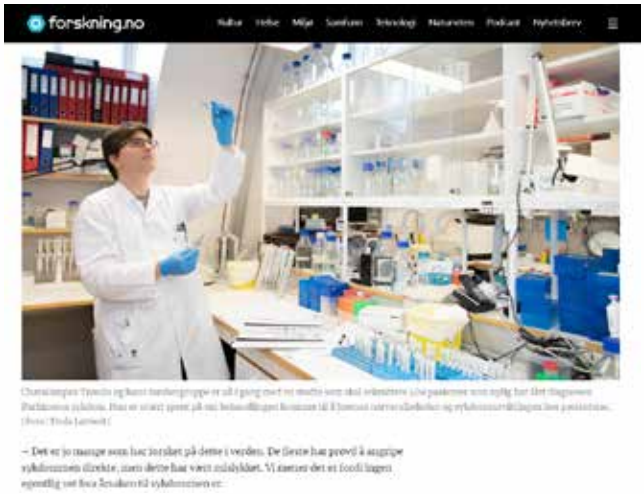
December 2, 2023, Adresseavisen: "Reisen til Russland ble redningen". Patient case on stem cell treatment for MS, interview with Professor Bø on the RAM-MS study.

December 5, 2023, Adresseavisen Pluss: "Må vente flere år på forsinket studie: - Vår opplevelse er at systemet er viktigere enn pasientene". About the RAM-

MS study and its delay because of the pandemic, interview with Professor Bø.


Må vente flere år på forsinket studie: – Vår opplevelse er at systemet er viktigere enn pasientene

December 5, 2023, Forskning.no: "Frans Olaf fikk hjernesykdommen som øker raskest i verden". Patient case on Parkinson's and participation in the NOPARK study, interview with Professor Tzoulis. Also in ABC Nyheter Dec. 10.


forskning.no

December 6, 2023, Forskning.no: "Knøttsmå biter av plast kan gi Parkinsons, ifølge studie på celler og mus - Gjenspeiler ikke mennesker, sier forsker". Professor Tzoulis commenting on a study indicating that microplastic can lead to Parkinson's in mice.

December 6, 2023, Dagbladet: "Medisiner kobles til parkinsons-risiko". On the registry-based drug screening project of the Neuro-SysMed Drug Discovery Node, with results associating various medications as increasing or decreasing risk for Parkinson's. Interview with Researcher Julia Romanowska and Professor Riise.


Dagbladet

Medisiner kobles til Parkinsons-risiko

December 12, 2023, Bergens Tidende – Login: "Stadig flere får Parkinson i Norge. Urolig nattesøvn fra rundt 40-årsalderen kan være tegn på alvorlig sykdom". Patient case on Parkinson's and focus on sleep disorders as a possible early symptom. Interview with Professor Tzoulis. Also in Aftenposten Dec. 11, Stavanger Aftenblad Dec. 12., Fædrelandsvennen Dec. 13 and Adresseavisen Dec. 16.


Aftenposten

Stadig flere får Parkinson i Norge. Urolig nattesøvn fra rundt 40-årsalderen kan være tegn på alvorlig sykdom.

PUBLICATION LIST 2023

Relevant publications from the Neuro-SysMed researchers in 2023.

1. Comparative Effectiveness of Autologous Hematopoietic Stem Cell Transplant vs Fingolimod, Natalizumab, and Ocrelizumab in Highly Active Relapsing-Remitting Multiple Sclerosis. **Kalincik et al, incl. Torkildsen Ø, Bo L, Lehmann AK.** *JAMA Neurol.* 2023 Jul 1;80(7):702-713. doi: 10.1001/jamaneurol.2023.1184. PMID: 3743740

2. Characteristics of the Ontario Neurodegenerative Disease Research Initiative cohort. **Sunderland KM et al, incl. Jog M.** *Alzheimers Dement.* 2023 Jan;19(1):226-243. doi: 10.1002/alz.12632. Epub 2022 Mar 30. PMID: 36318754

3. Mitochondrial haplogroups and cognitive progression in Parkinson's disease. **Liu G et al. incl. Tysnes OB,** *Brain*. 2023 Jan 5;146(1):42-49. doi: 10.1093/brain/awac327. PMID: 36343661 Free PMC article.

4. New centres to carry out more clinical trials in Norway. **Skoie IM, Skogås JG, Langø T, Myhr KM, Myhre PL, Goll R, Fretland SØ, Helland Å.***Tidsskr Nor Laegeforen.* 2023 Jan 20;143(2). doi: 10.4045/tidsskr.22.0722. Print 2023 Jan 31. PMID: 36718905 English, Norwegian. No abstract available.

5. Cognitive and Motor Decline in Dementia with Lewy Bodies and Parkinson's Disease Dementia. **Gonzalez MC el al incl. Tysnes OB.** *Mov Disord Clin Pract*. 2023 May 5;10(6):980-986. doi: 10.1002/mdc3.13752. eCollection 2023 Jun. PMID: 37332651

6. Inflammatory Biomarkers in Newly Diagnosed Patients With Parkinson Disease and Related Neurodegenerative Disorders. **Pedersen CC, Ushakova A, Skogseth RE, Alves G, Tysnes OB, Aarsland D, Lange J, Maple-Grødem J.** *Neurol Neuroimmunol Neuroinflamm*. 2023 May 31;10(4):e200132. doi: 10.1212/NXI.0000000000200132. Print 2023 Jul. PMID: 37258413 Free PMC article.

7. NR-SAFE: a randomized, double-blind safety trial of high dose nicotinamide riboside in Parkinson's disease. **Berven H, Kverneng S, Sheard E, Søgnen M, Af Geijerstam SA, Haugarvoll K, Skeie GO, Dölle C, Tzoulis C.** *Nat Commun*. 2023 Nov 28;14(1):7793. doi: 10.1038/s41467-023-43514-6. PMID: 38016950 Free PMC article. Clinical Trial.

8. Seed Amplification Assay as a Diagnostic Tool in Newly-Diagnosed Parkinson's Disease. **Oftedal L, Maple-Grødem J, Tysnes OB, Alves G, Lange J.** *J Parkinsons Dis*. 2023;13(5):841-844. doi: 10.3233/JPD-230065. PMID: 37393438 Free PMC article.

9. Ocrelizumab and ofatumumab, but not rituximab, trigger complement induction in vitro. **Førde JL, Herfindal L, Myhr KM, Torkildsen Ø, Mollnes TE, Skrede S.** *Int Immunopharmacol*. 2023 Nov;124(Pt B):111021. doi: 10.1016/j.intimp.2023.111021. Epub 2023 Oct 9. PMID: 37816262

10. Potassium channels in behavioral brain disorders. Molecular mechanisms and therapeutic potential: A narrative review. **Alam KA, Svalastoga P, Martinez A, Glennon JC, Haavik J.** *Neurosci Biobehav Rev.* 2023 Sep;152:105301. doi: 10.1016/j.neubiorev.2023.105301. Epub 2023 Jul 4. PMID: 37414376 Review.

11. Identification of diagnostic and prognostic biomarkers of PD using a multiplex proteomics approach. **Maple-Grødem J, Ushakova A, Pedersen KF, Tysnes OB, Alves G, Lange J.** *Neurobiol Dis*. 2023 Oct 1;186:106281. doi: 10.1016/j.nbd.2023.106281. Epub 2023 Sep 4. PMID: 37673381

12. Advancing nutrition science to meet evolving global health needs. **Neufeld LM, Ho E, Obeid R, Tzoulis C, Green M, Huber LG, Stout M, Griffiths JC.** *Eur J Nutr.* 2023 Dec;62(Suppl 1):1-16. doi: 10.1007/s00394-023-03276-9. Epub 2023 Nov 28. PMID: 38015211 Free PMC article.

13. Altered transcriptome-proteome coupling indicates aberrant proteostasis in Parkinson's disease. **Dick F, Tysnes OB, Alves GW, Nido GS, Tzoulis C.** *iScience*. 2023 Jan 4;26(2):105925. doi: 10.1016/j.isci.2023.105925. eCollection 2023 Feb 17. PMID: 36711240 Free PMC article.

14. Humoral response to Epstein-Barr virus in patients with multiple sclerosis treated with B cell depletion therapy. **Rød BE, Wergeland S, Bjørnevik K, Holmøy T, Ulvestad E, Njølstad G, Myhr KM, Torkildsen Ø.** *Mult Scler Relat Disord*. 2023 Nov;79:105037. doi: 10.1016/j.msard.2023.105037. Epub 2023 Sep 30. PMID: 37804765 Clinical Trial.

15. Beta2-adrenoreceptor agonists and long-term risk of Parkinson's disease. **Tuominen JA, Bjørnevik K, Romanowska J, Solheim MH, Grydeland TB, Cortese M, Scherzer CR, Riise T, Igland J.** *Parkinsonism Relat Disord*. 2023 May;110:105389. doi: 10.1016/j.parkreldis.2023.105389. Epub 2023 Mar 31. PMID: 37027994

16. Discontinuation of dimethyl fumarate in multiple sclerosis - a nationwide study. **Roar M, Nielsen ARH, Berg JM, Sirakov G, Stilund M, Schäfer J, Ratzer R, Frederiksen J, Asgari N, Ashna SN, Jensen HB, Kant M, Theódorsdóttir Á, Illes Z, Sellebjerg F, Magyari M, Schlosser LM, Nordborg H, Wergeland S, Sejbaek T.** *Mult Scler Relat Disord*. 2023 Dec;80:105127. doi: 10.1016/j.msard.2023.105127. Epub 2023 Nov 5. PMID: 37956521

17. Predictors of hospitalization due to infection in rituximab-treated MS patients. **Karlowicz JR, Klakegg M, Aarseth JH, Bø L, Myhr KM, Torgauten HM, Torkildsen Ø, Wergeland S.** *Mult Scler Relat Disord*. 2023 Mar;71:104556. doi: 10.1016/j.msard.2023.104556. Epub 2023 Feb 11. PMID: 36842313

18. Nicotinamide riboside supplementation is not associated with altered methylation homeostasis in Parkinson's disease. **Gaare JJ, Dölle C, Brakedal B, Brügger K, Haugarvoll K, Nido GS, Tzoulis C.** *iScience*. 2023 Feb 27;26(3):106278. doi: 10.1016/j.isci.2023.106278. eCollection 2023 Mar 17. PMID: 36936793 Free PMC article.

19. Treatment of motor symptoms in Parkinson's disease. **Dietrichs E, Alves G, Benjaminsen E, Johansen KK, Tysnes OB.** *Tidsskr Nor Laegeforen*. 2023 May 4;143(7). doi: 10.4045/tidsskr.22.0804. Print 2023 May 9. PMID: 37158528 English, Norwegian.

20. Neuropsychiatric Symptom Burden across Neurodegenerative Disorders and its Association with Function. **Kapustin D et al, incl. Jog M.** *Can J Psychiatry*. 2023 May;68(5):347-358. doi: 10.1177/07067437221147443. Epub 2023 Jan 13. PMID: 36637224 Free PMC article.

21. Classification and staging of Parkinson's disease using video-based eye tracking. **Brien DC, Riek HC, Yep R, Huang J, Coe B, Areshenkoff C, Grimes D, Jog M, Lang A, Marras C, Masellis M, McLaughlin P, Peltsch A, Roberts A, Tan B, Beaton D, Lou W, Swartz R; ONDRI Investigators; Munoz DP.** *Parkinsonism Relat Disord*. 2023 May;110:105316. doi: 10.1016/j.parkreldis.2023.105316. Epub 2023 Feb 8. PMID: 36822878

22. Microstructural changes precede depression in patients with relapsing-remitting Multiple Sclerosis. **Riemer F, Skorve E, Pasternak O, Zaccagna F, Lundervold AJ, Torkildsen Ø, Myhr KM, Grüner R.** *Commun Med (Lond)*. 2023 Jun 22;3(1):90. doi: 10.1038/s43856-023-00319-4. PMID: 37349545 Free PMC article.

23. White matter hyperintensities and smaller cortical thickness are associated with neuropsychiatric symptoms in neurodegenerative and cerebrovascular diseases. **Ozzoude M et al, incl. Jog M.** *Alzheimers Res Ther*. 2023 Jun 20;15(1):114. doi: 10.1186/s13195-023-01257-y. PMID: 37340319 Free PMC article.

24. Childbirth delivery mode and the risk of multiple sclerosis: a prospective population-based study. **Kapali A, Daltveit AK, Myhr KM, Bjornevik K, Baldin E, Pugliatti M, Riise T, Cortese M.** *J Neurol Neurosurg Psychiatry*. 2023 Dec 14;95(1):8-13. doi: 10.1136/jnnp-2023-331241. PMID: 37479464

25. An Association of Chitinase-3 Like-Protein-1 With Neuronal Deterioration in Multiple Sclerosis. **Ahmad I, Wergeland S, Oveland E, Bø L.** *ASN Neuro*. 2023 Jan-Dec;15:17590914231198980. doi: 10.1177/17590914231198980. PMID: 38062768 Free PMC article.

26. Brief international cognitive assessment for MS (BICAMS) and global brain volumes in early stages of MS - A longitudinal correlation study. **Skorve E, Lundervold AJ, Torkildsen Ø, Riemer F, Grüner R, Myhr KM.** *Mult Scler Relat Disord*. 2023 Jan;69:104398. doi: 10.1016/j.msard.2022.104398. Epub 2022 Nov 5. PMID: 36462469

27. The ANeED study - ambroxol in new and early dementia with Lewy bodies (DLB): protocol for a phase IIa multicentre, randomised, double-blinded and placebo-controlled trial. **Chwiszczuk LJ, Breitve MH, Kirsebom BB, Selnes P, Fløvig JC, Knapskog AB, Skogseth RE, Hubbers J, Holst-Larsen E, Rongve A.** *Front Aging Neurosci*. 2023 May 26;15:1163184. doi: 10.3389/fnagi.2023.1163184. eCollection 2023. PMID: 37304077 Free PMC article.

28. Cancer related mortality in multiple sclerosis. A population based cohort study. **Grytten N, Myhr KM, Celius EG, Benjaminsen E, Midgard R, Vatne A, Aarseth JH, Mannseth J, Torkildsen Ø.** *Mult Scler Relat Disord*. 2023 Jan;69:104417. doi: 10.1016/j.msard.2022.104417. Epub 2022 Nov 17. PMID: 36423459

29. Physical Activity in Multiple Sclerosis: Meeting the Guidelines at the Time of the COVID-19 Pandemic. **Pedullà L, Santoyo-Medina C, Novotna K, Moumdjian L, Smedal T, Arntzen EC, van der Linden ML, Learmonth Y, Kalron A, Güngör F, Nedeljkovic U, Kos D, Jonsdottir J, Coote S, Tacchino A.** *J Neurol Phys Ther*. 2023 Apr 1;47(2):112-121. doi: 10.1097/NPT.0000000000000430. Epub 2023 Jan 31. PMID: 36753458

30. Editorial: New cerebrospinal fluid research to uncover mechanisms driving neurological and psychiatric diseases, volume II. **Skripuletz T, Torkildsen Ø.** *Front Neurol*. 2023 Dec 12;14:1346377. doi: 10.3389/fneur.2023.1346377. eCollection 2023. PMID: 38148983 Free PMC article. No abstract available.

31. Interferon β1a treatment does not influence serum Epstein-Barr virus antibodies in patients with multiple sclerosis. **Lie IA, Rød BE, Kvistad SS, Holmøy T, Myhr KM, Torkildsen Ø, Wergeland S.** *Mult Scler Relat Disord.* 2023 Feb;70:104530. doi: 10.1016/j.msard.2023.104530. Epub 2023 Jan 21. PMID: 36701908

32. Robot-assisted investigation of sensorimotor control in Parkinson's disease. **Tamilselvam YK, Jog M, Patel RV.** *Sci Rep.* 2023 Mar 23;13(1):4751. doi: 10.1038/s41598-023-31299-z. PMID: 36959273 Free PMC article.

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PERSONNEL LIST 2023

People affiliated to Neuro-SysMed in 2023.

Name	Node	Position
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Intakhar Ahmad	MS node	PhD candidate
Shamnundeswaari Anandan	MS node	Postdoc
Martine Baug	MS node	Med. student
Lars Bø	MS node	Professor
Karine Eid	MS node	PhD candidate
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Sonia Gavasso	MS node	Researcher
Randi Haugstad	MS node	Study nurse
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Ida Herdlevær	MS node	Postdoc
Akash Kapali	MS node	PhD candidate
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Christopher Elnan Kvistad	MS node	Researcher
Ingrid Anne Lid	MS node	PhD candidate
Hilde Norborg	MS node	PhD candidate
Håkon Olsen	MS node	Master student
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Gala Prado	PD node	Clinical research fellow, Lawson
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Mari Klauset Holtom	ALS node	Study nurse
Tina Rekand	ALS node	Researcher
Marit Rensaa	ALS node	Study nurse
Carolin Sparchholz	ALS node	PhD candidate
Tina Taule	ALS node	Researcher
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Kristina Skeie	Dementia node	Study nurse
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Monica Patrascu	Care node	Postdoc
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Yamila Torres Cleuren	Administration	Research advisor
Marianne Flatebø	Administration	Trial coordinator
Renate Gruner	Imaging - MMIV	Professor
Liesbeth Kroondijk	Lab/research support	Research technician
Vegar Løland	Administration	Economy controller (HUH)
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Gry Hilde Nilsen	Lab/research support	Research technician
Frank Riemer	Imaging - MMIV	Researcher
Omnia Shadad	Lab/research support	Research technician
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