Centre for
Clinical Treatment
Research

Neuro-SysMed

2024

ANNUAL REPORT

CONTENT

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DIRECTORS' COMMENTS

2024 has been an exciting and productive year for Neuro-SysMed across our four disease groups.

This was a year with particularly strong focus on expanding our international collaborations. We have held the "kick-off meeting" for our new Horizon Europe MS-project, "EBV-MS", aiming to develop preventive interventions for MS, with partners from five countries in Europe and the USA. Together with our partners from three European countries, we initiated our Era4health EU-funded project "NADage", aiming to explore treatment and preventive measures for age-related frailty and associated dementia risk. Furthermore, with our upcoming SLEIPNIR and HYDRA multi-arm trial platforms, we have entered an ambitious and exciting Global Coalition for Platform Trials in Parkinson's diseases (PD), as one of five members across Europe, USA, and Australia.

On the trial front, great progress has been made. The first anti-EBV trial against MS started in January and was almost fully enrolled by the end of the year, while our NOPARK and OVERLORD trials, both large pivotal studies in PD and MS, respectively, were fully enrolled and will conclude in 2025. We are expecting these first results from large-scale trials at our Centre with great hope and anticipation! In addition, our Phase II ALS and Alzheimer's disease trials, NO-ALS and N-DOSE AD, respectively, were nearly fully enrolled in 2024.

Our translational research has made important advances, including the discovery of a mitochondrial subtype of PD, immune cell treatment response biomarker profiles in MS, genetic findings in ALS, and intriguing results from single-cell omics analyses using our state-of-the-art infrastructure.

Our Centre is constantly attracting the attention of national and international mainstream media, as well as the interest of major political figures in Norway. In 2024, this included a visit by former prime minister and leader of the party "Høyre" Erna Solberg, and the chair of the Norwegian Brain Council. Discussion topics included opportunities for the continuation of our Centre beyond 2027 and for a National Brain Health strategy. Neuro-SysMed's directors also participated in debates at the Arendalsuka to discuss the National Action Plan for Clinical Studies, as well as the future of MS therapy, with participation from the state secretary from the Ministry of Health and Care Services and the Research Council of Norway.

Last but not least, 2024 was a good year for funding. We secured important new research grants (approaching 80 MNOK in 2024) across all disease groups from multiple sources, including Helse Vest (the Regional Health Authority of Western Norway), the DAM Foundation, the EU, and our patient associations. Additionally, the PD and Care Nodes advanced to the second round in the application process for a Centre of Excellence in Innovation (SFI), which will be funded by the Research Council of Norway. This means that two of the three applications from UiB that advanced were from Neuro-SysMed.

We therefore enter 2025 with great momentum and all indications suggesting that we are heading into another stimulating year with exciting and excellent research!

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 therapies and improved treatment strategies. The Centre facilitates early access to these new therapies for patients across Norway through participation in national and international randomised clinical trials. Our ultimate goal is to reduce the burden of disease.

The Centre has established a comprehensive, novel support framework to address the unmet treatment needs of Norwegian patients with these four diseases. By doing so, we enable patients from all over Norway to access cutting-edge treatment trials, and we develop precision medicine. Specifically, Neuro-SysMed continues to work towards:

- discovering novel therapeutic compounds through both *in silico* and *in vitro* screening and assessing them in novel disease models
- conducting clinical trials and bringing cutting-edge research to patients
- developing biomarkers for disease detection, patient stratification, treatment response, and precision medicine
- enhancing patient care by improving daily function and quality of life
- introducing systems medicine into Norwegian neurology

RESEARCH PLAN AND STRATEGY

Neuro-SysMed's clinical trials are central to its mission, with samples and data from the trials informing the Centre's translational research activities. Research spans across different groups and expertise, involving large interdisciplinary efforts to achieve its goals.

Neuro-SysMed organises and conducts randomised clinical trials to evaluate the efficacy and safety of therapies, using novel or established drugs with new indications that may delay or halt disease progression, reduce symptoms, or optimise care for affected individuals. While each study has its own scientific questions and efficacy endpoints, all projects contribute data, such as clinical scores, DNA and RNA data, blood and cerebrospinal fluid analyses, tissue sample analyses, and brain images. The collected information can then be used to define biomarkers that enable early and precise diagnosis, stratify patients within each disease, define treatment response, and achieve accurate prognosis and tailored treatment options for individual patients.

In terms of systems medicine, our PD Node is leading the way. The ParkOme project has mapped molecular profiles from tissue samples from more than 1,300 brains of deceased patients with PD and other neurodegenerative diseases, creating 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 specifically for screening and discovering new treatments. Additionally, we are making significant progress in *in silico* drug screening, utilizing national Norwegian registries to enhance our efforts in identifying effective therapies.

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 (HDH) in Bergen, Norway. Neuro-SysMed is funded by the Research Council of Norway (RCN) and the host and partner institutions.

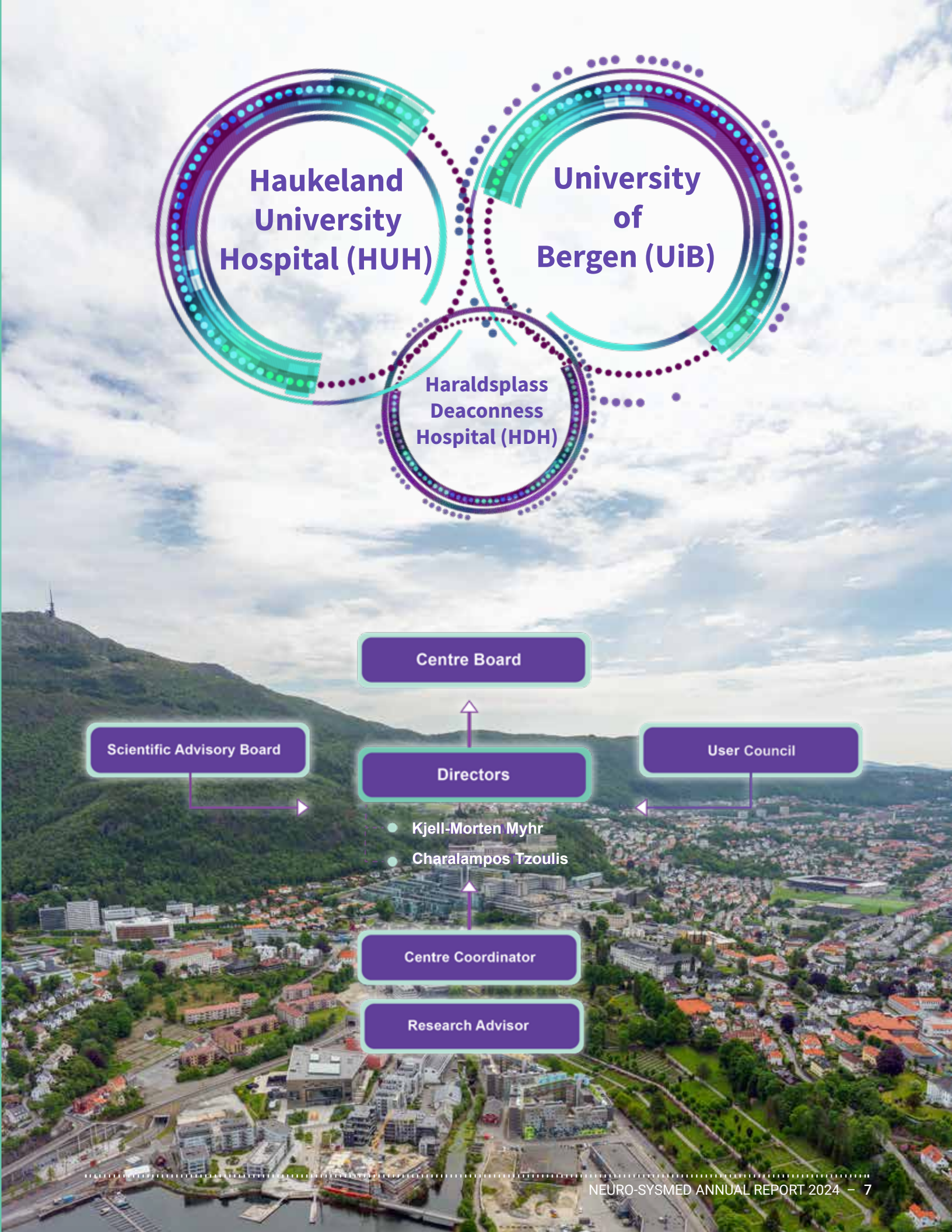
Organisational structure

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 (MED), 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 HDH, 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, and Lemia Boussaada, 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, advise 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 Campus (HUH, UiB, HDH). 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 2024, we have continued organising our monthly seminar series and a larger symposium organised in the autumn term with all Neuro-SysMed members and invited international speakers. These activities provide crucial meeting points for scientific discussions and cooperation for all Centre members, students, and interested collaborators.


Haukeland University Hospital (HUH)
University of Bergen (UiB)
Haraldsplass Deaconness Hospital (HDH)
Centre Board
Scientific Advisory Board
User Council
Directors
Kjell-Morten Myhr
Charalampos Tzoulis
Centre Coordinator
Research Advisor

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.

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, Hanne-Linda Nakkestad, in charge of the day-to-day management of the facilities, in addition to technicians assisting with sample processing from the clinical trials as well as with 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.
- 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.
- Seed-amplification assay (SAA) equipment.
- Ultra-freezer facility hosting a human brain and tissue bank.
- Nanoparticle tracking analyses (NTA) for Extracellular vesicles (EVs) characterisation (NanoSight)

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. This is being led by Gonzalo Sanchez Nido and Dimitrios Kleftogiannis.

Clinical Trials Unit

At the heart of Neuro-SysMed are the clinical trials. In 2024, the Centre had 37 investigator-initiated clinical trials in addition to several industry-sponsored trials. To administer this substantial number of trials, we have a full-time clinical coordinator, Ingunn Anundskås, as part of our core team, in addition to

our twelve research nurses and part-time coordinators from HUH's R&D department. Practical planning of the clinical trials (including protocols, ethics approvals, site recruitment, monitoring, etc.), patient recruitment and execution, and 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 medication coordinator 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.

Neuro-SysMed administration

During 2024, we recruited Mona Machrouh to assist with the coordination of the Centre, while Yamila Torres Cleuren has continued to have the overarching management responsibility of the Centre, taking care of both pre- and post-award phases of our external funding and leading our research and innovation strategy. In addition to the personnel actively involved with the laboratory, 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 2024, Neuro-SysMed has maintained a high level of research activity at the Centre. This ongoing dedication has not only enhanced the research output but also facilitated the successful development of new projects, leading to excellent external funding recruitment throughout the year.

Responsible for this function: Senior Advisor Yamila Torres Cleuren

The Centre has been buzzing with activity as we continue to forge powerful scientific collaborations and consortia. We're thrilled to see the fruits of our labour with a continued partnership both nationally and internationally, reflected in significant funding for our projects. Our dynamic, interdisciplinary approach allows us to craft innovative projects across research groups, leveraging the diverse expertise available.

One of our greatest strengths is our cross-disease research. Breakthroughs in one area, such as PD, are being translated into advancements for ALS, dementia, and MS. This synergy has sparked the creation of new laboratory and clinical trial projects, thanks to the interactions between our research teams.

We have continued to make strides in securing European grants, which are pivotal for the long-term success of our research. Increasing the Centre's visibility has been a key focus, ensuring our projects transcend national borders and enhance both our national and international collaborations.

A good example of our success this year is the new European project "NADage", which we are leading and will start in 2025. This project received funding from the ERA4HEALTH program "Nutribrain". This funding is a great boost and a testament to Neuro-SysMed's growing international reputation.

In 2024, we continued to attract funding from various sources. Our Regional Health Authorities (Helse Vest) supported us with two PhD projects, one postdoc, a clinical fellowship grant, 3 open project support grants for our clinical and translational projects, and one strategic research grant of 20 MNOK. KLINBEFORSK funded our first national dementia trial with 25 MNOK, while the Norwegian Research

Council provided commercialisation funding to two new projects. Additionally, the UiB, private donors, patient organisations, and foundations have provided crucial support, especially for projects in their start-up phase.

– Yamila Torres Cleuren,
Senior Advisor

"Our success in securing this funding from Helse Vest (the Western Norway Regional Health Authorities) reflects the urgent need for improved patient stratification and personalised treatment approaches in MS. This project exemplifies the strength of interdisciplinary collaboration within our Centre, bringing together expertise from clinical neurology, immunology, and bioinformatics. Careful planning, the selection of well-defined cohorts, and the use of high-quality datasets from ongoing clinical trials allow us to generate new knowledge while ensuring the validation of our data-driven discoveries. The enthusiasm of our collaborators, the dedicated support from the leadership of Neuro-SysMed, and the invaluable guidance of our research advisor were key factors in making this application successful."

Dimitrios Kleftogiannis obtained his first open project support from the Western Norway Regional Health Authorities in 2024, starting in 2025 with the project "Assisting personalised treatment decisions in multiple sclerosis using data-driven immunological signatures."

"HYDRA is a part of our Norwegian multi-arm, multi-stage initiative, with the ultimate goal of identifying treatments that can halt disease progression in those affected with PD. The awarding of funding needed to establish the HYDRA platform would not have been possible had it not been for Professor Tzoulis and the DECODE-PD research group, the Neuro-SysMed and its research advisor, and our colleagues in Neurology departments throughout Norway, who are essential to this work."

Irene Hana Flønes obtained her first large funding grant in 2024 with 20 MNOK from the Western Norway Regional Health Authorities' strategic funding scheme to establish "HYDRA – an adaptive design, multi-arm, multi-stage platform trial for PD."

THE SCIENTIFIC ADVISORY BOARD

Neuro-SysMed is advised by a Scientific Advisory Board (SAB), consisting of Professors Kailash Bhatia, Raymond Koopmans, and Xavier Montalban.

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 PD.

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 Centre 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 MS and has been a PI in more than 150 clinical trials.

Neuro-SysMed's principal investigators for MS and dementia met with their relevant SAB members during the 2024 Annual Symposium to discuss their projects, planned activities, and how they work with the rest of the Centre. This led to fruitful discussions and insightful feedback on the individual projects. In general, the SAB members were very impressed with the high volume of investigator-initiated trials and their quality. Follow-up discussions have continued for the Centre's MS research where new cutting-edge methods are being applied for new trials together with the EBV-MS consortium. The SAB members also contributed with scientific talks at the Neuro-SysMed Annual Symposium.


Neuro-SysMed
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THE USER COUNCIL

Neuro-SysMed's User Council was established in the early phase of the Centre (2019) and 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 are about including those who know the needs in 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, or the patients themselves who have first-hand experience in living with the diagnosis. User involvement is an approach for systematically ensuring that this competence and perspective have 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 diseases.

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 from across the country to participation in clinical trials
- design of user-friendly information from Neuro-SysMed
- communication of research results
- bringing attention to the Centre's work
- informing about the role and importance of a user representative

Further, the User Council works to increase awareness of the opportunities for patients and caregivers to participate in clinical trials. Many patients, and health professionals, are still not aware of this as a treatment option.

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 to include our organisations in the work of the centre. Nevertheless, there are still challenges related to user participation in the projects. Continuous efforts are needed to establish effective and practical frameworks for collaboration between researchers and users.

Activities in 2024

- Several members of the User Council attended the course Patient and Public Involvement in Medical and Health Research, a collaboration between Neuro-SysMed, REMEDY, NorHEAD, MATRIX, NorCRIN, and FORMI, and supported by the Dam Foundation through the Norwegian National Association for Public Health. The course is designed to facilitate user involvement in medical and health research and consists of lectures, group work, and discussions. The course was held in April and is intended for researchers as well as user representatives, facilitating interaction and collaboration.
- We were involved in planning Neuro-SysMed's participation at the public event Arendalsuka 2024.
- We have been actively working with the need to establish a funding mechanism for user involvement in research projects before the projects have received financing.

- We have been working to establish a seamless structure for involving user representatives in research projects through the use of the User Involvement Checklist in Research, currently to be found on Neuro-SysMed's web pages.

Meetings in 2024

In 2024, there were two User Council meetings. The spring meeting in April was a half-day meeting, while the autumn meeting was a full-day meeting. The participants appreciated having a full day as that allowed more time to discuss current issues as well as to get comprehensive updates on ongoing projects for all four disease groups.

– Lise Johnsen, User Council Chair

Members of the User Council in 2024

- **Lise Johnsen**, Norwegian MS Society (Chair)
- **Jan Anders Istad**, Norwegian MS Society
- **Ragnhild Stenshjemmet Støkket**, Norwegian Parkinson's Association (until July 2024)
- **Lemia Boussaada**, Norwegian Parkinson's Association (from July 2024)
- **Kjell Grorud**, Norwegian Parkinson's Association
- **Kristin Reimers Kardel**, Norwegian National Association for Public Health
- **Ditte Staldgaard**, Norwegian National Association for Public Health
- Marit Stensen, ALS Norway Foundation
- **Lise Stousland**, ALS Association – Always a Little Stronger
- **Mirjeta Emini**, Norwegian National Association for Public Health (deputy)
- **Mona Bahus**, ALS Norway Foundation (deputy)
- **Therese Asbjørnsen**, ALS Association – Always a Little Stronger (deputy)
- **Magne Wang Fredriksen**, Norwegian MS Society (deputy)

The user council was elected for two years in April 2024.

NEURO-SYSMED IN NUMBERS

The level of activity during 2024 were similar to the previous year (2023), with new projects starting and others approaching their last year of activity. We are increasing our international funding and spent a total of 105 million NOK on Neuro-SysMed-related projects during 2024.

Neuro-SysMed funding

The core activities of Neuro-SysMed are funded through the Research Council of Norway's (RCN) Centre for Clinical Treatment Research scheme. In 2024, this amounted to 25.4 MNOK as own contribution from the consortium institutions and 21.8 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.

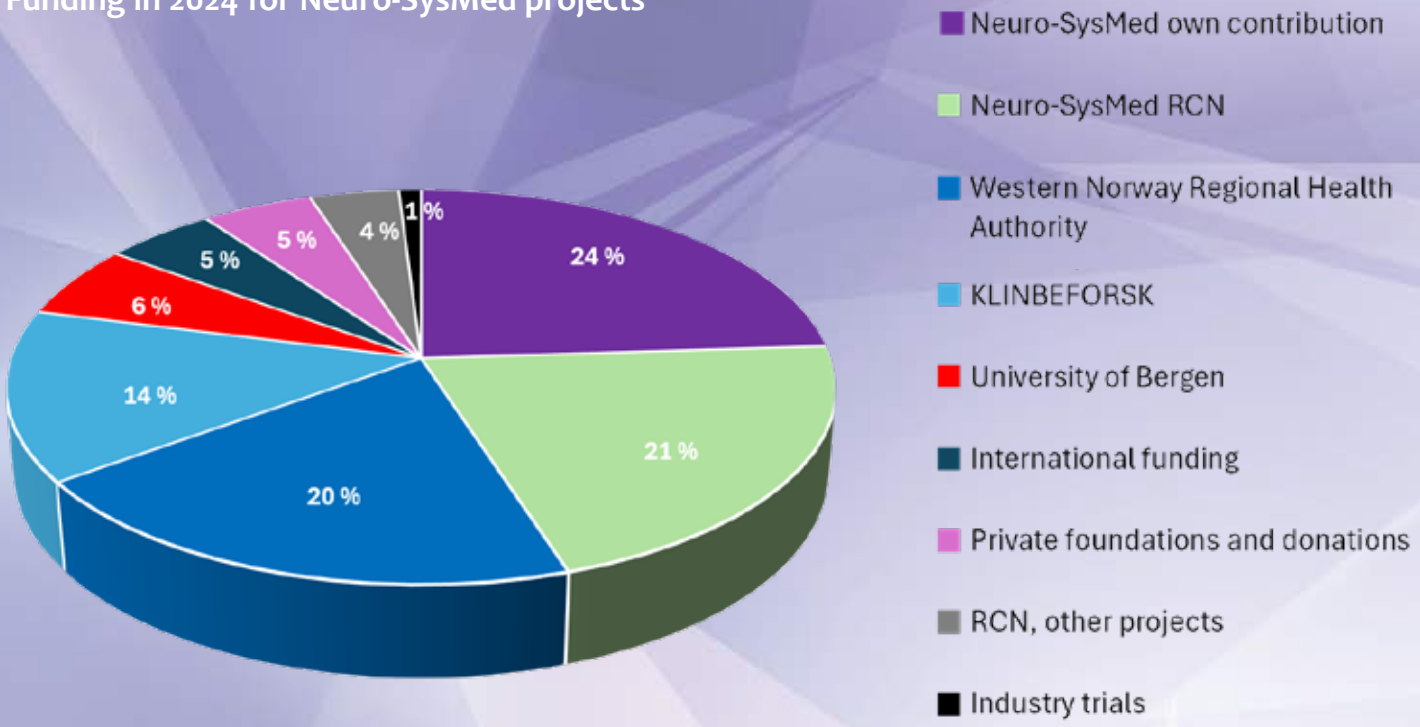
The Western Norway Regional Health Authority was the biggest funding source for 2024 with 20 MNOK spent, followed by the KLINBEFORSK program with 14.2 MNOK. In addition, we have several UiB funded PhD positions, RCN funded innovation projects, EU and US-funded projects, other RCN funded research and commercialisation projects, private foundations and donations (including patient organisations), and income from industry trials. Excitingly, the share of international project funding has been consistently increasing each year.

Neuro-SysMed in numbers

Our teams boast a wide range of expertise, encompassing master-level and medical research students, PhD candidates, postdoctoral fellows, senior researchers, clinicians, research technicians, research nurses, clinical trial coordinators, and administrative staff.

While approximately 60% of our staff is female, there is a notable overrepresentation of men in leadership roles. To address this, we have been proactively recruiting and training women for senior positions. This initiative has led to a continuous rise in publications with female senior authorship, increased successful research funding, and more women in supervisory roles. We remain committed to supporting their careers.

Funding in 2024 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 into our clinical trials and translational research. This is evident in the activities we organise for our students and the discussions during our Annual Symposium. A major goal of these discussions is to encourage new methodological and design approaches to overcome obstacles hampering therapeutic breakthroughs in neurological diseases.

Our Research Advisor, along with innovation advisors from our host and partner institutions, collaborates closely with our PIs and researchers to map out their activities and plans, identifying potential new projects and ideas. As part of our strategic planning, we support project development through research applications, commercialisation, and intellectual property strategy discussions (in collaboration with our technology transfer office VIS), as well as developing proof-of-concept ideas. In 2024, three innovation projects received funding: two from the Norwegian Research Council and one from Digital Life Norway, all focusing on developing new therapies for neurological diseases. This broadening of our portfolio reflects our commitment to innovation.

Our Horizon Europe project, including a clinical trial aiming at defining new therapies that influence the chronic Epstein-Barr virus (EBV) infection, has led to several innovation initiatives, facilitated by VIS – as MS therapy as well as therapy for EBV infection in general.

Inspired by the Norwegian government's push to increase health exports and strengthen the health industry, we expanded our industry collaborations in 2024. These collaborations involve biomarker research, implementing new laboratory-based assays, and developing new health technologies for diagnostics and monitoring.

With our largest trials concluding in 2025, significant effort has gone into designing new trials and trial platforms for the next cycle of studies. One such trial is HYDRA, a multi-arm, multi-stage (MAMS) trial designed to study multiple treatments simultaneously for PD. This trial was developed in close collaboration with all Norwegian hospitals participating in PD trials, with input from statistical experts and similar platform trials in the UK and France. This led to the establishment of the MAMS in the PD consortium, which had its first official meeting in London in 2024.

A key aspect of our academic-initiated trials is industry collaboration. Over the first five years of our Centre, we have established many new collaborations and continue to test new treatments, providing a state-of-the-art testing arena for promising therapies in neurological diseases.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NEURO-SYSMED VIEWPOINT

Text by Kjell-Morten Myhr and Øivind Torkildsen

The World's Best Treatment for Norwegian Patients with Multiple Sclerosis (MS) – A 30 Years of Development

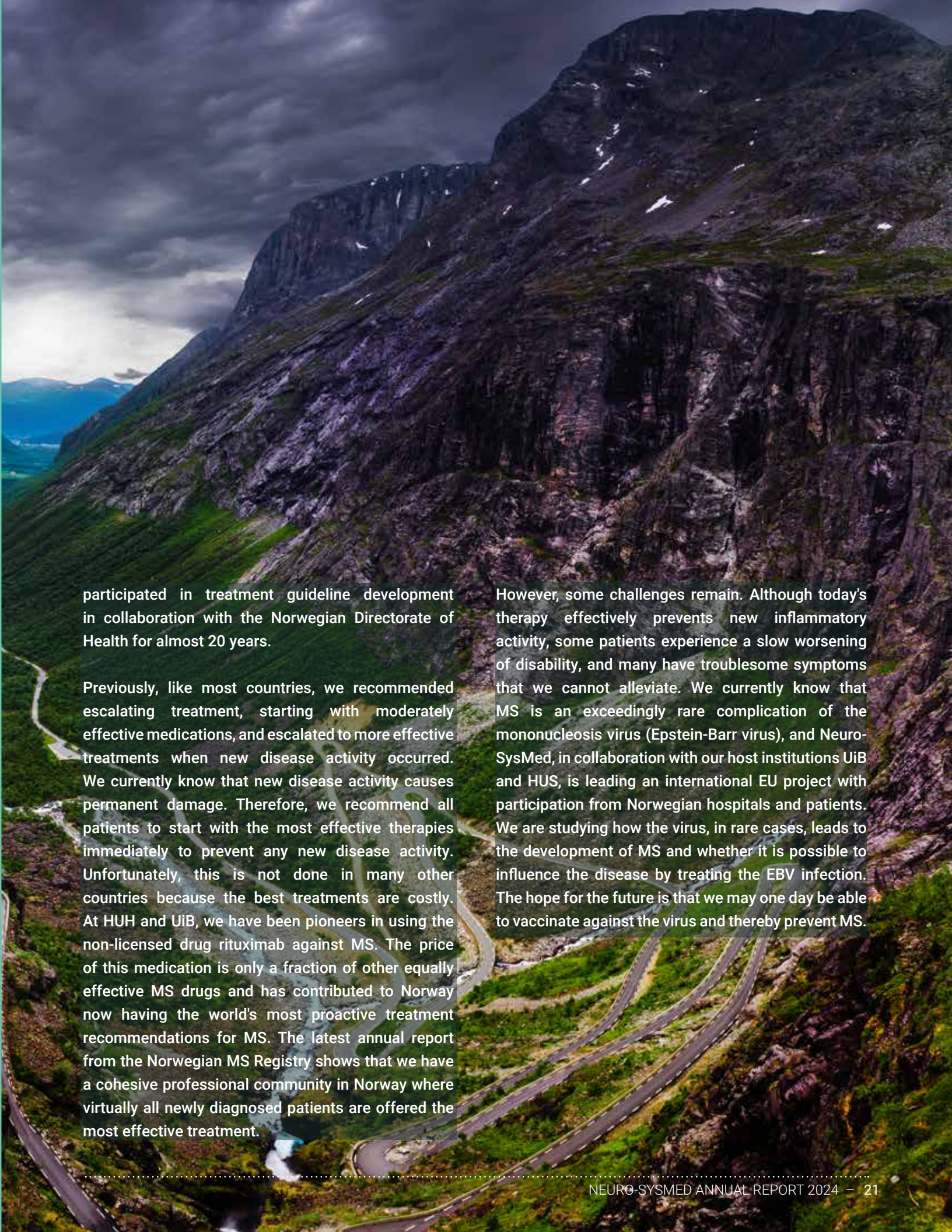
Norway has the world's most proactive treatment strategy for MS. Unlike many other countries, Norwegian patients receive the most effective MS therapy right from the onset of the disease, significantly reducing the likelihood of new relapses.

MS is a debilitating autoimmune disease that affects the brain and spinal cord, damaging the myelin sheath of nerve fibres, leading to subsequent nerve cell damage. This damage disrupts nerve impulse conduction and can cause a range of symptoms, including vision problems, sensory disturbances, coordination issues, and motor function impairments.

For those who have worked in neurology for some time, the transformation in MS treatment is nothing short of revolutionary. Not long ago, MS was one of the most severe diagnoses a patient could receive, often leading to rapid disability and even early death. The first breakthrough came in 1993 with a research report on a treatment that could slow disease progression, followed by the approval of the first MS medication in the USA two years later (1995). Thus, 2025 marks the 30th anniversary of the beginning of this pivotal moment in MS therapy.

The University of Bergen (UiB) and Haukeland University Hospital (HUH) have played crucial roles in this journey. From the outset, they have collaborated with all neurological departments in Norway and have participated in over 50 clinical trials involving more than 1200 Norwegian patients. The studies have been initiated by Norwegian researchers in close collaboration with patients and the MS Society in Norway, by the pharmaceutical industry through international multi-centre studies, or as collaborative projects between researchers, industry, and patient associations. This collaboration has been crucial for the development of MS treatment options, both to slow the disease progression and to alleviate troublesome symptoms.

Simultaneously, clinical neurology researchers and clinicians have in close partnership with the MS Society maintained a fruitful dialogue with health authorities to make new treatments available for Norwegian patients on an early stage. Norwegian neurologists, nurses, and the MS Society have also



participated in treatment guideline development in collaboration with the Norwegian Directorate of Health for almost 20 years.

Previously, like most countries, we recommended escalating treatment, starting with moderately effective medications, and escalated to more effective treatments when new disease activity occurred. We currently know that new disease activity causes permanent damage. Therefore, we recommend all patients to start with the most effective therapies immediately to prevent any new disease activity. Unfortunately, this is not done in many other countries because the best treatments are costly. At HUH and UiB, we have been pioneers in using the non-licensed drug rituximab against MS. The price of this medication is only a fraction of other equally effective MS drugs and has contributed to Norway now having the world's most proactive treatment recommendations for MS. The latest annual report from the Norwegian MS Registry shows that we have a cohesive professional community in Norway where virtually all newly diagnosed patients are offered the most effective treatment.

However, some challenges remain. Although today's therapy effectively prevents new inflammatory activity, some patients experience a slow worsening of disability, and many have troublesome symptoms that we cannot alleviate. We currently know that MS is an exceedingly rare complication of the mononucleosis virus (Epstein-Barr virus), and Neuro-SysMed, in collaboration with our host institutions UiB and HUS, is leading an international EU project with participation from Norwegian hospitals and patients. We are studying how the virus, in rare cases, leads to the development of MS and whether it is possible to influence the disease by treating the EBV infection. The hope for the future is that we may one day be able to vaccinate against the virus and thereby prevent MS.

NEURO-SYSMED VIEWPOINT

Text by Johannes Gaare & Charalampos Tzoulis

Isolated REM Sleep Behavior Disorder – A Unique Opportunity for Prevention in Parkinson's Disease

Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD) is a condition in which individuals physically act out their dreams due to a loss of normal muscle paralysis during REM sleep. While this may sound like a harmless sleep issue, RBD is, in fact, one of the most powerful early warning signs of serious neurodegenerative disease.

In particular, isolated RBD (iRBD) - meaning RBD in the absence of diagnosed neurological disease or other known triggers, is now recognized as the prodromal stage of α-synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). More than 75% of people with PD, and nearly 90% of those with DLB or MSA, report having had RBD symptoms for years prior to their diagnosis. On average, iRBD precedes clinical diagnosis by 10–15 years.

Long-term studies show that individuals with iRBD convert to a diagnosed α-synucleinopathy at a rate of about 6% per year, with over 90% converting within 15 years. This gives us a unique opportunity for early intervention and treatment of neurodegeneration in its nascent stages.

iRBD affects ~1% in the population >50 years, translating to ~14,000 individuals in Norway. Because of the long window before diagnosis, high predictive value, and relatively mild symptoms early on, people with iRBD are now considered ideal candidates for neuroprotective clinical trials - that is, studies aimed at delaying or preventing the onset of PD and related diseases.

There are several advantages in testing neuroprotective therapies on patients with iRBD, rather than manifest PD, DLB, or MSA:

1. ***A long prodromal time window*** offering the opportunity for early intervention, while there is still time to prevent irreversible degeneration.
2. ***High predictive power:*** the vast majority (>90%) of individuals with iRBD will develop an α-synucleinopathy.
3. ***Substantial potential for disease modification***: when started at RBD onset, a treatment that slows disease progression by ~30% could delay the onset of PD, DLB, or MSA by 3–5 years and provide 6–10 total extra years without severe disability.
4. ***Less treatment interference:*** absence of symptomatic dopaminergic therapy interfering with the effects of the trials.

While some may raise ethical concerns about informing people of their risk, the global medical

consensus now strongly supports transparency. iRBD is not merely a risk factor; it is already a sign of ongoing neurodegeneration. Informing patients empowers them to make choices about preventive care and participate in trials that could benefit themselves and others. Moreover, trial participation offers concrete benefits:

1. **Awareness and empowerment to participate in preventive trials:** iRBD is not a risk factor, but a prodromal stage of PD, DLB, or MSA. Thus, a person with iRBD is already suffering from ongoing neurodegeneration. For those reasons, the current consensus in the global medical community is that patients with iRBD should always be informed of their risks to enable informed decision-making regarding participation in neuroprotective trials.
2. **Access to specialized care:** Research studies provide regular follow-up with a clinical neurologist, a service not typically available to individuals with iRBD. Most individuals with iRBD remain undiagnosed until pronounced neurodegenerative symptoms manifest, commonly leading to a delayed diagnosis of α-synucleinopathy and delayed initiation of supportive/symptomatic management. Early identification and regular monitoring will help address dysfunction associated with prodromal symptoms and leads to an early diagnosis of PD, DLB, or MSA, enabling early initiation of supportive treatment.
3. **Management of symptoms:** individuals with prodromal α-synucleinopathy may experience a variety of symptoms including anxiety, depression, constipation, mild cognitive impairment, autonomic dysfunction, and gradually increasing signs of parkinsonism. Furthermore, iRBD can cause considerable somatic and psychological distress, with violent dream enactments leading to potential injuries for the patients or their partners. The substantial impact on the quality of life for both the patient and their partners underscores the need for early and effective management. As such, RBD trials not only contribute to the scientific understanding of α-synucleinopathies but also directly benefit participants by enhancing their quality of life and health outcomes.

By identifying and monitoring individuals with iRBD, we can both advance scientific understanding of α-synucleinopathies and improve health outcomes for patients and their families. For all these reasons, we believe that iRBD trials are not only ethically justified – they are essential to the future of neurodegenerative disease research and care.

NEURO-SYSMED VIEWPOINT

Text by Charalampos Tzoulis

Will we ever achieve disease modification for Parkinson's disease?

Parkinson's disease (PD) affects over 10 million people globally and is now regarded as the fastest growing cause of neurological disability worldwide. Yet, more than two centuries since Dr. James Parkinson's seminal 1817 essay "*An Essay on the Shaking Palsy*", we still lack a disease-modifying therapy, that is, a therapy that can slow, halt, or prevent the progression of the disease.

By the end of 2024, at least 70 clinical trials of potential disease-modifying therapies (DMTs) had been conducted in PD. Despite promising preclinical data, every trial failed to deliver clinical benefit. These trials targeted mechanisms such as mitochondrial dysfunction, lysosomal failure, inflammation, and α-synuclein aggregation – all of them pathways strongly implicated in PD pathogenesis. So why has it been so difficult to achieve a breakthrough?

In my view, the challenge lies in what I call the four therapeutic obstacles of PD:

1. **Choice of target.** While several biological processes are implicated in PD – including mitochondrial dysfunction, α-synuclein aggregation, impaired proteostasis, and neuroinflammation – the underlying sequence of events and causal relationship these may have with the disease are unclear. In other words, it is unknown whether these processes are drivers of the disease, consequences, or epiphenomena. Without clarity, choosing the right therapeutic target remains a major challenge.
2. **Target engagement.** A fundamental challenge is that investigational compounds advance to efficacy trials without adequate evidence of target engagement (i.e., interaction of the treatment with its intended biological target/pathway) in the patient brain. Without this evidence, the therapeutic potential of a compound remains speculative, rendering costly and time-consuming trials futile. Considering the rapid increase in drug trials for PD, there is an urgent need for a de-risking strategy ensuring only therapies with robust target engagement proceed to later trial stages.
3. **Heterogeneity.** While referred to as a single entity, PD is not a single disease but a clinical syndrome encompassing diverse phenotypes and underlying biology. Individuals vary widely in age of onset, symptom profile, rate of progression, and pathology. This heterogeneity suggests the existence of biologically distinct subtypes of PD, each of which may respond differently to therapy. Precision medicine approaches, including stratifying patients into subtypes and assigning them to specific experimental treatment regimens, are essential but currently underdeveloped.
4. **Late intervention.** All trials of potential disease modifying therapies are currently conducted on patients on a post-diagnosis stage. PD has a long prodromal phase preceding diagnosis by up to

decades. At the time of diagnosis, clinical motor and non-motor symptoms are usually well-established and affected individuals have already lost more than 60% of their dopaminergic neuron population in the *substantia nigra pars compacta*. Moreover, it is possible that, at the time of diagnosis, runaway pathological processes, such as α-synuclein misfolding and prion-like cell-to-cell transmission, are already at play, making attempts at neuroprotection futile, or at least more difficult to achieve. Thus, late intervention is an important obstacle hindering therapeutic breakthroughs for PD. Consequently, there is a growing realization that targeting the disease before the time of diagnosis, i.e., in its prodromal phase, would be the critical point at which to intervene. To achieve a significant disease modifying effect against these diseases, we need to shift our efforts from treatment to prevention. This can be achieved by initiating an intervention in the prodromal phase of the disease, while there is still time to prevent irreversible neuronal loss and before the neurodegenerative process has progressed beyond the point of no return.

While our failure to make an impact on PD is disappointing – even demotivating at times – important progress is being made worldwide. At our Centre, we are leading research efforts that directly aim to address all four obstacles. Our mechanistic studies in molecular biology and bioinformatics are uncovering novel therapeutic targets. At the same time, our trials with nicotinamide adenine dinucleotide (NAD) augmentation adopt a broad-spectrum approach, aiming to enhance neuronal resilience by targeting multiple pathogenic pathways simultaneously. In terms of heterogeneity, we have discovered a subtype of PD characterized by sever and widespread mitochondrial complex I deficiency and are now attempting to establish clinically applicable biomarkers enabling patient selection in the clinic. Our pioneering ***SLEIPNIR*** platform is designed to test multiple compounds for target engagement in parallel, advancing only the most promising candidates to ***HYDRA***, our phase III multi-arm, multi-stage (MAMS) efficacy trial platform. Last but not least, we are preparing to launch the world's first preventive trials in PD, recruiting individuals in the prodromal phase – identified via REM sleep behavior disorder (RBD).

These are just a few of the many initiatives around the world working toward the same goal. Thus, while the field has faced disappointments, the momentum has never been stronger – and the hope for disease modification in PD has never been greater.

RESEARCH SCHOOL IN TRANSLATIONAL NEUROSCIENCE

The Neuro-SysMed Research School in Translational Neuroscience has established a broad range of PhD courses. All research nodes from our various fields are responsible for organising these courses, promoting high-quality education for PhD candidates and other students, and aiming to build a strong foundation for their research.

The Research School aims at providing PhD candidates with relevant courses to fulfil mandatory credit points (ECTS) 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, second 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 2025).
- CCBIONEUR911, Clinical Trials, 2 ECTS (started 2021, next course in 2026).
- CCBIONEUR912, Health Innovation, 4 ECTS (started 2021, next course in 2026).

2024 course activities

In 2024, we hosted the established courses NEUROSYSM910, NEUROSYSM920, NEUROSYSM930, and NEUROSYSM940, and in collaboration with CCBIO, we organised CCBIONEUR910 and CCBIONEUR911.

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 research as well as giving feedback to other young researchers. The course is organised continuously, twice every semester. See the separate chapter on the Junior Scientist Symposium.

NEUROSYSM920, Neuro-SysMed Seminars and Symposium

This 3 ECTS course is organised with monthly seminars and an annual compulsory 2-day international Neuro-SysMed Symposium in the autumn at Solstrand Hotel. The objective is to provide knowledge on research of the Neuro-SysMed focus fields of MS, PD, 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 2024 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, 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 third time in November 2024.

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' research projects, this course aims 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 arranged for the second time in November 2024.

CCBIONEUR910, Patient and Public Involvement in Medical and Health Research

The main objective of this 2 ECTS course is to develop the participants' capacity to assess and convey the value of patient and public involvement in general, as well as promoting productive user involvement in their research projects. The purpose of participation is to gain knowledge of the researcher's responsibility for patient and public involvement to be integrated into the entire process in a clinical research project - from planning to project implementation and publication. The course is a collaboration between Neuro-SysMed, CCBIO, REMEDY, NorHEAD, MATRIX, NorCRIN and FORMI, and the project is supported by the Dam Foundation through the Norwegian Health Association. The course took in 2024 place during 3 days in April and combined plenary discussions and group sessions involving user representatives and patient organisations, with presentations from national and international lecturers. The course was arranged for the third time in 2024.

CCBIONEUR911, Clinical Trials

This 2 ECTS course qualifies for a Good Clinical Practice (GCP) certificate upon completion of the program and covers several aspects of clinical trials – from design planning to execution – with learning examples from cancer research and neurological research alike. The participant gains knowledge about how and why clinical trials are performed according to good clinical practice and regulatory protocols for clinical trials. The course participants will be able to critically assess the feasibility and challenges when running clinical trials and be able to prepare their research staff in the conduction of clinical trials. The course took place for the second time in January 2024.

NEURO-SYSMED SEMINARS

Neuro-SysMed Seminars

The overarching aim of the Neuro-SysMed Seminars is to share knowledge between the research nodes and the different research disciplines within Neuro-SysMed, as well as providing professional updates 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 2024, including additional special seminars.

JAN 10

Tale Bjerknes (MD, PhD), Postdoctoral Fellow at HUH, and Professor Ole-Bjørn Tysnes (MD, PhD), Principal Investigator (PI) for the ALS node at HUH and the UiB.
Title of the talk: *ALS – update on genetics, biomarkers and clinical studies at Neuro-SysMed*

FEB 14

Professor Bettina Husebø (MD, PhD), PI for the Care Node at the UiB, PhD Candidate Elise Førsund, and Postdoctoral Fellows Monica Patrascu and Brice Marty, Care Node.
Title of the talk: *Can digital phenotyping replace the care for my granny?*

MAR 13

Caroline Engen (MD, PhD), Postdoctoral Fellow and Co-PI for the Responsible Research and Innovation (RRI) Node at the UiB.
Title of the talk: *Restructuring Neurology: Responsible Research and Innovation (RRI)*

APR 24

Associate Professor Kristoffer Haugarvoll (MD, PhD), PI for the Dementia Node at HUH and the UiB.
Title of the talk: *Disease mechanism in Alzheimer`s disease*

MAY 15

Svein Isungset Støve (MSc, PhD), Researcher in the Drug Discovery Node at the UiB.
Title of the talk: *Screening for activity modulators of targets relevant for Parkinson's disease and hyperkinetic movement disorders*

SEP 11

Dimitrios Kleftogiannis (MSc, PhD), Senior Bioinformatician and Co-Leader of the Bioinformatics Node at the UiB and HUH.
Title of the talk: *Leveraging million single-cell data for clinical trials and precision medicine in neurological diseases*

OCT 23

Julia Romanowska (MSc, PhD), Researcher in the Drug Discovery Node at the UiB.
Title of the talk: *DRONE perspective on how drug consumption is associated with neurodegenerative diseases*

NOV 27

Professor Kjell-Morten Myhr (MD, PhD), Director of Neuro-SysMed and PI of the MS Node, and Professor Øivind Torkildsen (MD, PhD) in the MS Node, the UiB and HUH.
Title of the talk: *Epstein-Barr virus infection: a treatable cause of multiple sclerosis?*

DEC 11

Professor Charalampos Tzoulis (MD, PhD), Co-Director of Neuro-SysMed and PI for the PD Node at the UiB and HUH.
Title of the talk: *Tackling the rising challenge of α-synucleinopathies: Is there light at the end of the tunnel?*

MAY 23

SPECIAL EVENT, Honorary Doctorate Lecture: Professor Robert Ascherio, Harvard T.H. Chan School of Public Health and Harvard Medical School.
Title of the talk: *EBV causes MS: does it also drive MS pathology?*

THE NEURO-SYSMED ANNUAL SYMPOSIUM

Neuro-SysMed hosted its 2nd Annual Symposium on September 30 and October 1, 2024, at the historic Solstrand Hotel outside of Bergen. Altogether, 125 participants from the Neuro-SysMed research fields, in a very international mix, enjoyed scientific talks, discussions, posters and ad hoc meetings.

Besides being the Neuro-SysMed event of the year, the Annual Symposium is part of the course NEUROSYSM920 – Neuro-SysMed seminars and symposium, at the Neuro-SysMed Research School for Translational Neuroscience.

The Neuro-SysMed Directors Kjell-Morten Myhr and Charalampos Tzoulis opened the program of the symposium with a talk on current challenges in clinical trials in MS and neurodegeneration, touching upon today's status on therapies, particular challenges and areas of research, including Neuro-SysMed's current projects and a discussion on the design of future clinical trials.

In a session on dementia and sustainability in care, **Raymond Koopmans** (Radboud University Medical Centre, the Netherlands) gave a talk on severe or extreme behaviour in dementia, which clearly constitute a major challenge for the multidisciplinary teams that try to care for these patients. This was followed by a joint talk by **Ipsit Vahia** (McLean Hospital, Harvard University, USA) and **Catharyn Gildesgame** (Mass General Brigham Behavioral and Mental Health, USA) on developing academia–industry partnerships for a new wave of aging care where we incorporate technology into the clinic as well as in senior centres and in research. **Heather Allore** (Yale School of Medicine, USA) explained pragmatic clinical trials and how they differ from traditional explanatory clinical trials. The session was completed with talks from two of Neuro-SysMed's researchers, **Kristoffer Haugarvoll** sharing his experience from user involvement in dementia research, and **Ragnhild Eide Skogseth** with an overview of STRAT-COG, a prospective cohort study to stratify dementia. A session in neurodegeneration explored various current research projects that aim for disease modification, including **Olivier Rascol** (Toulouse University Hospital, France) and **Ambra Stefani** (Medical University of Innsbruck, Austria).

The word of this year's symposium turned out to be *α-synucleinopathies*, brought up in many of the talks, including a discussion on Controversy in Prevention of Neurodegeneration between **Charalampos Tzoulis**, Neuro-SysMed's PD Node, and **Caroline Engen**, Neuro-SysMed's RRI/PPI Node, moderated by **Ambra Stefani.** The discussion stirred much engagement in the

audience, including socio-economic concerns and the question of how much the patient can benefit from knowing.

The MS session featured MS expert **Xavier Montalban** (Vall d'Hebron University Hospital, Barcelona, Spain), who showed the timeline of the McDonald diagnostic criteria, a set of guidelines to help neurologists diagnose whether someone has MS or another disease. The McDonald criteria were recently (2024) revised, and Montalban explained the revisions and what this means for treatment strategies and choice of clinical trial design. Clinical trial design in MS was also the focus for **Gavin Giovannoni** (Queen Mary University of London, UK), who discussed the mode of action of potential antiviral therapy against the Epstein-Barr virus (EBV), including preventive vaccines, and what this will mean for the design of future clinical trials. **Kjetil Bjørnevik** (Harvard T. H. Chan School of Public Health, USA) explained target trial emulation, an emerging methodological approach that can improve the use of observational data by avoiding fundamental errors that can result in erroneous causal conclusions. **Tomas Kalincik** (Royal Melbourne Hospital & University of Melbourne, Australia) focused on observational data in his talk, discussing several methodological aspects of contemporary research of treatment effectiveness in observational data in neurology, with a focus on MS. This session was completed by the Neuro-SysMed researchers **Brit Ellen Rød** and **Øivind Torkildsen**, who presented recent Neuro-SysMed work.

The last session focused on biomarkers and imaging, where **Natalia Drosu** (Massachusetts General Hospital, USA) explained how her team uses celiac disease as a model for understanding MS, as this is the only autoimmune condition with an HLA class II association where the underlying mechanism has been explained. **Arianna Ciullini** (Carlo Besta Neurological Institute, Italy) explained work on the identification of early and peripheral biomarkers for α-synucleinopathies by seed amplification assay (SAA). **Laura Airas** (Turku University, Finland) showed her group's work with PET-imaging as a tool for treatment response assessments addressing mechanisms contributing to neurodegeneration in progressive MS. PET-imaging was also a topic for **Andrea Varrone** (Karolinska Institutet, Sweden), who discussed its use for PD.

The program also included a successful poster session where 22 high-quality posters were discussed and evaluated. Congratulations to **Elisabeth Claire Evjenth** for Best Poster by the evaluation committee and **Anna Rubiolo** for Best Poster by audience voting!

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

SCIENTIFIC PROGRAM

Day 1: Monday September 30, 2024

Neuro-SysMed Annual Symposium

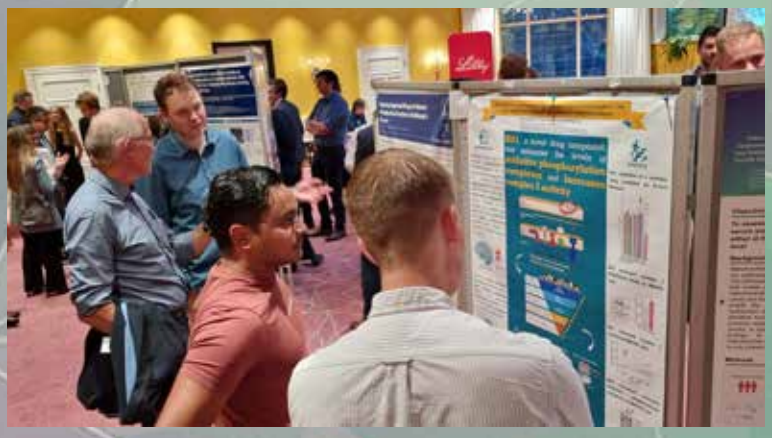
08:00-09:20	Registration and coffee
09:20-10:00	Kjell-Morten Myhr & Charalampos Tzoulis: Current Challenges in Clinical Trials in MS and Neurodegeneration

SESSION 1: DEMENTIA AND SUSTAINABILITY IN CARE, chair: Kristoffer Haugarvoll

10:00-10:20	Raymond Koopmans: Very severe or extreme behaviors in dementia: a challenge for multidisciplinary teams
10:20-11:10	Ipsit Vahia & Catharyn Gildesgame: Developing academia-industry partnerships for a new wave of aging care
11:10-11:35	Heather Allore: Pragmatic Clinical Trials for Older Adults
11:35-11:47	Kristoffer Haugarvoll: Experience from user involvement in dementia research
11:47-12:00	Ragnhild Skogseth: The STRAT-COG study – working towards prediction of cognitive decline in individual patients
12:00-13:00	Lunch break

SESSION 2: NEURODEGENERATION: THE HUNT FOR DISEASE MODIFICATION, chair: Raymond Koopmans

13:00-13:30	Olivier Rascol: The LIXIPARK trial: lessons for the future
13:30-14:00	Ambra Stefani: Isolated REM sleep behavior disorder as target for neuroprotective interventions: Advantages and drawbacks
14:00-14:15	Johannes J. Gaare: α-synucleinopathies: Shifting the focus from the clinical to the prodromal phase
14:15-14:30	Irene Fløtnes: SLEIPNIR – a Clinical Trial Accelerator and Derisking Platform for Parkinson's Disease
14:30-14:45	Frank Riemer: Using MRI to evaluate microglia activation in neurodegeneration and inflammation
14:45-15:10	Coffee break
15:10-16:10	Controversy in prevention of Neurodegeneration Discussion between Charalampos Tzoulis and Caroline Engen. Moderator: Ambra Stefani
16:10-18:00	Break and Check-in
18:00-19:30	**POSTER SESSION & Aperitif, same room as the talks, chairs: Ragnhild Skogseth and Christian Dölle**
19:30	Dinner



Day 2: Tuesday October 1, 2024

Neuro-SysMed
Annual Symposium

SESSION 3: CURRENT CHALLENGES IN MS CLINICAL TRIALS, chair: Kjell-Morten Myhr

09:00-09:30	Xavier Montalban: Revised Diagnostic Criteria in MS – and Their Influence on Treatment Strategies and Clinical Trial Design
09:30-10:00	Gavin Giovannoni: Clinical trial design and outcome measures for the evaluation of potential EBV antiviral therapies in multiple sclerosis
10:00-10:30	Kjetil Bjørnevik: Opportunities and advantages of using emulated target trials
10:30-10:50	Coffee break
10:50-11:20	Tomas Kalincik: Evidence from observational data to guide treatment of multiple sclerosis
11:20-11:35	Brit Ellen Rød: Comparative Effectiveness of Cladribine and Rituximab in Patients with RRMS
11:35-12:00	Øivind Torkildsen: Discussion: Challenges in study design and outcome measures for MS in an era of high-efficacy therapy
12:00-13:00	Lunch break

SESSION 4: BIOMARKERS & IMAGING OUTCOMES IN CLINICAL TRIALS, chair: Charalampos Tzoulis

13:00-13:30	Natalia Drosu: EBV-specific T cells as biomarkers for antiviral dosing studies
13:30-14:00	Laura Airas: PET-imaging as a tool for treatment response assessments addressing mechanisms contributing to neurodegeneration in progressive MS
14:00-14:20	Arianna Ciullini: Identification of early and peripheral biomarkers for alpha-synucleinopathies by seed amplification assay
14:20-14:50	Andrea Varrone: PET Imaging Biomarkers for Parkinson´s disease
14:50-15:05	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 to give feedback to their peers.

A main ambition is also to strengthen the scientific networks and to encourage candidates to establish relations to other scientists. The symposia are organised 4 times annually, twice every semester. Each symposium is normally organised with a keynote lecture, followed by 4 PhD candidates/postdoctoral researchers who present their work. Subsequently, there are final discussions. The presentations are of own research with special attention to presentation techniques and quality.

The symposia are chaired by coordinators recruited from postdocs and PhD candidates within Neuro-SysMed. Attendance provides 3 ECTS if the candidate has participated in minimum 4 symposia, written and submitted 4 scientific reports of scientific presentations at the symposia, and presented own research at one of the symposia.

We are happy to see that the participants engage in scientific discussions and take advantage of peer reviews and comments. This will strengthen the scientific quality of their work and boost their scientific thinking.

MARCH 22, 2024

Auditorium 4, BB building
Academic responsible: Shamundeeswari Anandan
Chair: Irene Flønes

09.00-09.10	Welcome and Introduction
09.10-10.10	Keynote lecture by **Andreas Hillestad Schei**, psychologist at the UiB occupational health service: "Ups and downs of the PhD"
10.10-10.30	*Coffee break*
10.30-10.55	**Anna Stylianou Lerpold**: "Elucidating the molecular effects of NAD-replenishment therapy in Parkinson's disease"
10.55-11.20	**Enny Stulien Lauen**: "Identifying mitochondrial dysfunction in skeletal muscle in patients with Alzheimer's disease"
11.20-12.00	*Lunch*
12.00-12.25	**Shridar Amogh Patil**: "Systematic meta-analysis of genome-wide transcriptomics of Parkinson's disease brain"
12.25-12.50	**Tina Emilie Johnsen**: "Gray Matter Microstructure and Genetic Risk in Adolescents with Anxiety"
12.50-13.00	Concluding remarks

MAY 31, 2024

Auditorium 4, BB-Building
Academic responsible: Shamundeeswari Anandan
Chairs: Sepideh Mostafavi and Eirik Solheim

09.00-09.10	Welcome and introduction
09.10-10.10	**Irene Flønes**: "Complex I deficiency stratifies idiopathic Parkinson's disease"
10.10-10.30	*Coffee break*
10.30-10.55	**Monica Patrascu**: "A dynamic systems approach to digital phenotyping in dementia and PD"
10.55-11.20	**Synne Geithus**: "Unbiased molecular stratification of PD"
11.20-12.00	*Lunch*
12.00-12.25	**Karina Maciak**: "Deciphering MS pathophysiology. The role of blood patelets and circulating exosomes"
12.25-12.50	**Simon Kverneng**: "GDF-15 as a potential stratification biomarker for mitochondrial dysfunction in idiopathic PD"
12.50-13.00	Concluding remarks

OCTOBER 18, 2024

Room 3B109F, BB-Building
Academic responsible: Shamundeeswari Anandan
Chair: Håkon Olsen

09.00-09.10	Welcome and introduction
09.10-10.10	**Oliver Vanderpoorten**: "NANOSPACER: Nano-fluidic sizing of extracellular vesicles (EVs) and biomacromolecules in solution"
10.10-10.30	*Coffee break*
10.30-10.55	**Vladan Milosevic**: "The use of imaging mass cytometry for in-depth profiling of the tumour microenvironment"
10.55-11.20	**Brit Ellen Rød**: "Comparative effectiveness of rituximab vs cladribine in patients with relapsing-remitting MS"
11.20-12.00	*Lunch*
12.00-12.25	**Amy van den Hooven**: "Clinic of the Future: Designing Dialogues for Care"
12.25-12.50	**Emma Rigg**: "Influence of miR-146a-5p in brain metastatic development"
12.50-13.00	Concluding remarks

NOVEMBER 29, 2024

Auditorium 4, BB-Building
Academic responsible: Shamundeeswari Anandan
Chair: Ida Herdlevær

09.00-09.10	Welcome and introduction
09.10-10.10	Keynote session by **Yamila Nicole Torres Cleuren**, Senior Scientific Advisor, Neuro-SysMed: "How to make it in science."
10.10-10.30	*Coffee break*
10.30-10.55	**Max Korbmacher**: "PROMising: Patient Recorded Outcome Measures predict multiple sclerosis trajectories better than brain, blood and genotyping"
10.55-11.20	**Julia Saltyte Benth**: "Parkinson's disease in women and men. Sex differences in cognitive symptoms, mild cognitive impairment, and dementia"
11.20-12.00	*Lunch*
12.00-12.25	**Jonas Bull Haugsøen**: "Immune Reconstitution after Hematopoietic Stem Cell Transplantation in Multiple Sclerosis"
12.25-12.50	**Kjell Inge Erikstad**: "Improving Diagnostics in Paraneoplastic Neurological Syndromes: Optimization of a Cell-Based Assay for SOX1 Antibody Detection"
12.50-13.00	Concluding remarks

COMPLETED DOCTORAL DEGREES

Researcher education at all levels is central for Neuro-SysMed. In 2024, we had the opportunity to celebrate five completed PhD degrees.

In the MS Node

Intakhar Ahmad January 16, 2024, successfully defended his PhD thesis "Novel biomarkers in multiple sclerosis pathology with a focus on neuroprotection and myelin repair" at the University of Bergen. Main supervisor was Professor Lars Bø, and co-supervisors were Associate Professor Stig Wergeland and Senior Researcher Eystein Oveland.

Karine Eid February 23, 2024, successfully defended her PhD thesis "Multiple adversity: Childhood abuse, adult abuse, and perinatal depression in women with multiple sclerosis" at the University of Bergen. Main supervisor was Professor Marte-Helene Bjørk, and co-supervisors were Professor Øivind Torkildsen and Professor Emeritus Nils Erik Gilhus.

Ellen Danielsen Skorve April 19, 2024, successfully defended her PhD thesis "Cognitive assessment in the early stages of multiple sclerosis" at the University of Bergen. Main supervisor was Professor Kjell-Morten Myhr, and co-supervisors were Professor Øivind Torkildsen and Professor Astri J. Lundervold.

In the PD Node

Nelson Osuagwu June 5, 2024, successfully defended his PhD thesis "Molecular mechanisms of mitochondrial dysfunction in neurodegenerative diseases" at the University of Bergen. Main supervisor was Charalampos Tzoulis, and co-supervisor was Christian Dölle.

In the Care Node

Maarja Vislapuu April 19, 2024, successfully defended her PhD thesis "Informal and formal resource utilisation in the care for people with dementia" at the University of Bergen. Main supervisor was Professor Bettina S. Husebø, and co-supervisors were Professor Egil Kjerstad and Associate Professor Line Iden Berge.


2D18

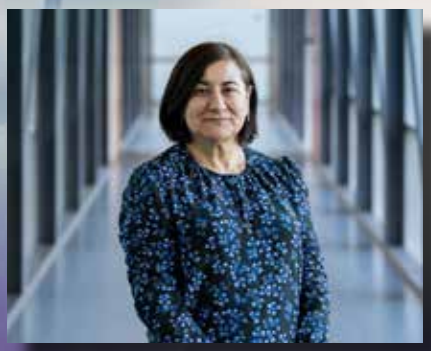
RESEARCH NODES

Neuro-SysMed's research activities are organized in Reseach Nodes based on disease focus or supporting research fields, with cross-node communication and collaboration.







Neuro-SysMed is organised in 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 Associate Professors **Kristoffer Haugarvoll and Ragnhild Eide Skogseth**, 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
- **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 MS

The Multiple Sclerosis (MS) Node conducts cutting-edge translational and clinical research with the aim of facilitating early diagnosis and treatment, and enhancing the quality of life for individuals with MS.

Node leader: Kjell-Morten Myhr

Kjell-Morten Myhr is a senior consultant and professor of neurology. Since 2001, he has 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). He is currently the director of Neuro-SysMed.

The MS Node has longstanding and internationally recognized research expertise ranging from basic immunopathological characterisation and preclinical animal studies to epidemiology, clinical course, imaging, clinical trials, health economics, and patient-reported outcome measures.

Research Focus

The MS Node is addressing major challenges in MS therapy, aiming to optimise the treatment of relapsing-remitting MS with early high-efficacy therapies and stem cell therapy for patients experiencing breakthrough disease activity. Additionally, we are focusing on treating the neurodegenerative component in progressive MS, as well as the symptomatic management of pain and spasticity. Most recently, we are exploring novel antiviral treatment targets for the treatment and prevention and of the disease.

Node Activities

The MS Node has extensive experience in various aspects of diagnosing and treating MS. Ongoing research projects aim to define the importance of potential risk factors and biomarkers for prognosis and treatment response with the goal of optimizing treatment strategies at different disease stages. Overall, the goal is to develop tailored treatment strategies for MS patients. Major challenges include enhancing the use of existing disease-modifying therapies and defining new disease pathways that can be targeted by novel treatments, which is especially crucial for addressing the neurodegenerative component in progressive MS. Additionally, we are developing new treatment strategies for potential disease prevention. Currently, the MS Node is conducting twelve investigator-initiated and six 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-remitting MS patients.
- **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 intervals of rituximab therapy. Patients that have been stable on standard 6-month dosing intervals of rituximab for 36 months (during the OVERLORD-MS study) will extend the dosing interval to 12 months for a 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, evaluates the clinical efficacy of vaccination.

- **The SMART-MS study** is a placebo-controlled, crossover pilot study evaluating regenerative effects from mesenchymal autologous stem cells in patients with 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 cladribine study** is a prospective registry-based observational study comparing the efficacy of these therapies among de novo patients and those who 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 evaluating the safety and efficacy of tenofovir alafenamide fumarate (TAF) 25 mg or placebo to standard natalizumab infusion therapy for six months of therapy.
- **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 patients with multiple sclerosis.
- **The 3TR – Taxonomy, Treatment, Target and Remission – study** is an international EU-funded observational study to define treatment response biomarkers for different immune mediated diseases.

Industry-sponsored clinical trials:

- An Extension Study of the Roche P-trials to Investigate Safety and Effectiveness of Ocrelizumab in Participants with Multiple Sclerosis (MS). Sponsor: Roche.
- A Rollover Study to Evaluate the Long-Term Safety and Efficacy of Ocrelizumab in Patients with Multiple Sclerosis (OLERO). Sponsor: Roche.
- A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants with Multiple Sclerosis. Sponsor: Sanofi.
- Primary Progressive Multiple Sclerosis (PPMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168) (PERSEUS). Sponsor: Sanofi.
- Non-relapsing Secondary Progressive Multiple Sclerosis (NRSPMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168) (HERCULES). Sponsor: Sanofi.
- LEMTRADA-PASS Study: A prospective, multicentre, observational, post-authorisation safety study to evaluate the long-term safety profile of LEMTRADA® (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis. Sponsor: Sanofi.

Biomarker Studies

The MS Node is currently involved in immune phenotyping cells from patients included in ongoing clinical trials to identify biomarkers for treatment response. Our goal is to define disease remission to tailor dosing, treatment duration, and patient selection for different therapies.

Additionally, we are studying the potential of extracellular vesicles as biomarkers for disease activity and response to B-cell depletion therapy in relapsing-remitting MS.

We also conduct preclinical cell culture and animal studies to evaluate possible disease pathways of progressive MS and the regenerative potential of stem cell therapy, as well as the role of microglia in these disease processes.

Treatment responses are further assessed using neurofilament biomarkers in both cerebrospinal fluid and serum. In collaboration with the Mohn Medical Imaging and Visualization Centre at Haukeland University Hospital, we evaluate treatment responses using magnetic resonance imaging (MRI).

MS-registry studies

The MS-registry part of the MS Node is conducting long-term safety studies of MS-therapies and analysing real-world data on treatment compliance and factors influencing discontinuation rates for ongoing therapies. They are also evaluating benefit from early high-efficacy treatment compared to an escalation treatment strategy.

Selected publications from 2024:

- **Eid K, Torkildsen Ø, Aarseth J, Cortese M, Holmøy T, Myhr KM, Riise T, Wergeland S, Gilhus NE, Bjørk MH.** Migraine in the multiple sclerosis prodrome: a prospective nationwide cohort study in pregnant women. *J Headache Pain* 2024;25(1):225. doi: 10.1186/s10194-024-01941-w. PMID: 39710642
- **Torgauten HM, Onyango TB, Ljostveit S, Hallin EI, Serkland TT, Skrede S, Langeland N, Cox RJ, Wergeland S, Myhr KM, Torkildsen Ø.** Hospitalisations and humoral COVID-19 vaccine response in vaccinated rituximab-treated multiple sclerosis patients. *Mult Scler Relat Disord* 2024;89:105770. doi: 10.1016/j.msard.2024.105770. PMID: 39029342
- **Lereim RR, Nytrova P, Guldbrandsen A, Havrdova EK, Myhr KM, Barsnes H, Berven FS.** Natalizumab promotes anti-inflammatory and repair effects in multiple sclerosis. *PLoS One* 2024;19(3):e0300914. doi: 10.1371/journal.pone.0300914. eCollection 2024. PMID: 38527011
- **Gottschlich KN, Zolic-Karlsson Z, Aas E, Kvistad SAS, Bø L, Torkildsen Ø, Lehmann AK.** Healthcare utilization and costs associated with autologous haematopoietic stem cell transplantation in Norwegian patients with relapsing remitting multiple sclerosis. *Mult Scler Relat Disord* 2024;84:105507. doi: 10.1016/j.msard.2024.105507. PMID: 38412758
- **Torkildsen Ø, Myhr KM, Brugger-Synnes P, Bjørnevik K.** Antiviral therapy with tenofovir in MS. *Mult Scler Relat Disord* 2024;83:105436. doi: 10.1016/j.msard.2024.105436. PMID: 38217968
- **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* 2024;271(4):1610-1617. doi: 10.1007/s00415-023-12047-9. 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 Parkinson's Disease (PD) and other neurodegenerative 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 Co-Director of the Neuro-SysMed, and Director of the DECODE-PD, KG Jebsen Centre for Translational Research in Parkinson's disease. An internationally recognised expert in movement disorders and neurodegeneration, Prof. Tzoulis has made significant scientific contributions, particularly in understanding mitochondrial dysfunction and NAD metabolism in PD.

The PD Node is globally acknowledged for implementing full-cycle translation – from the laboratory to the bedside and back – and for being a world leader in NAD-replenishment therapy for neurodegeneration. The Node's work 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. Notably, in 2024, they published groundbreaking results identifying for the first time a subtype of PD characterised by severe and widespread mitochondrial dysfunction. To enable tailored treatment, they run world-class translational research aiming to identify novel therapeutic targets and candidate therapies for PD and emerging subtypes thereof.

Furthermore, the PD Node leads and is currently establishing a multiarm multistage (MAMS) platform trial for PD – one of five initiatives in the world – as well as the first ever globally trial accelerator and derisking platform designed to assess target penetration and engagement of promising treatments for PD.

During 2024, the PD Node made key advances in their clinical research projects, which include nine clinical trials, and two prospective cohort studies:

- **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 study will be completed in 2025.
- **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 study was completed in 2024 and the results submitted for publication.
- **The NOPARK 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 study will be completed in 2025.

- **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 study will be completed in 2025.
- **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).
- **SLEIPNIR** is the world's first clinical trial accelerator and derisking platform for PD. A multiarm platform designed to assess whether promising disease-modifying therapies engage their intended targets in the human brain, to decide whether they should enter efficacy testing. The platform was developed in 2024 and will start in 2025.
- **HYDRA** aims to revolutionise PD trials through an adaptive, multi-arm, multi-stage (MAMS) platform efficacy trial. This innovative approach simultaneously evaluates multiple potential disease-modifying treatments against a single placebo, with the flexibility to discontinue ineffective treatments and reallocate participants to more promising interventions.
- **NADream** is a randomised double-blind trial to explore the effects of NAD-augmentation therapy on human sleep physiology.
- **NOR-RBD** is a longitudinal cohort and clinical trial platform for prodromal α-synucleinopathies, identified by REM-sleep behaviour disorder (RBD).
- **NADage** is a phase II randomised, double blinded trial of NAD-augmentation with NR in aging-related frailty.
- **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.

Industry-sponsored clinical trial:

- **The REASON study**, led by Biogen: A Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of BIIB094 in Adults With Parkinson's Disease.

Selected publications from 2024:

- **Nido GS, Castelli M, Mostafavi S, Rubiolo A, Shadad O, Alves G, Tysnes OB, Dölle C, Tzoulis C.** Single-nucleus transcriptomics reveals disease- and pathology-specific signatures in α-synucleinopathies. *Brain*. 2024 Nov 15:awae355. doi: 10.1093/brain/awae355. Online ahead of print. PMID: 39546628.
- **Dick F, Johanson GAS, Tysnes OB, Alves G, Dölle C, Tzoulis C.** Brain Proteome Profiling Reveals Common and Divergent Signatures in Parkinson's Disease, Multiple System Atrophy, and Progressive Supranuclear Palsy. *Mol Neurobiol.* Epub 2024 Aug 21. doi: 10.1007/s12035-024-04422-y. PMID: 39164482.
- **Flønes IH, Toker L, Sandnes DA, Castelli M, Mostafavi S, Lura N, Shadad O, Fernandez-Vizarra E, Painous C, Pérez-Soriano A, Compta Y, Molina-Porcel L, Alves G, Tysnes OB, Dölle C, Nido GS, Tzoulis C.** Mitochondrial complex I deficiency stratifies idiopathic Parkinson's disease. *Nat Commun.* 2024 Apr 29;15(1):3631. doi: 10.1038/s41467-024-47867-4. PMID: 38684731.
- **Stige KE, Kverneng SU, Sharma S, Skeie GO, Sheard E, Søgnen M, Geijerstam SA, Vetås T, Wahlvåg AG, Berven H, Buch S, Reese D, Babiker D, Mahdi Y, Wade T, Miranda GP, Ganguly J, Tamilselvam YK, Chai JR, Bansal S, Aur D, Soltani S, Adams S, Dölle C, Dick F, Berntsen EM, Grüner R, Brekke N, Riemer F, Goa PE, Haugarvoll K, Haacke EM, Jog M, Tzoulis C.** The STRAT-PARK cohort: A personalized initiative to stratify Parkinson's disease. *Prog Neurobiol*. 2024 May;236:102603. doi: 10.1016/j.pneurobio.2024.102603. PMID: 38604582.
- **Hong Y, Zhang Z, Yangzom T, Chen A, Lundberg BC, Fang EF, Siller R, Sullivan GJ, Zeman J, Tzoulis C, Bindoff LA, Liang KX.** The NAD+ Precursor Nicotinamide Riboside Rescues Mitochondrial Defects and Neuronal Loss in iPSC derived Cortical Organoid of Alpers' Disease. *Int J Biol Sci.* 2024 Jan 25;20(4):1194-1217. doi: 10.7150/ijbs.91624. eCollection 2024. PMID: 38385069.

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 PD and is PI of the ongoing ALS studies at Neuro-SysMed.

The ALS node conducts clinical, genetic 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. At the end of 2024, 335 patients are included in the NO-ALS trial.

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. We have initiated the ALS-LTMV study to evaluate the effect of life prolonging therapies on the quality of life in patients, spouse and children.

Finally, the ALS Node conducts research aiming to improve the diagnosis and tailored treatment opportunities for patients and we are planning research for ALS clusters in Norway.

During 2024, 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 conducting a stratification study in ALS (STRAT-ALS), recording detailed clinical data and collecting biological materials including autopsies from ALS patients and controls.
- **The CARDINALS study:** International industry multi-centre study on an anti-inflammatory drug on progression of ALS. Finished in December 2024. Negative study.

Selected publications from 2024:

- **Olsen CG et al.** Amyotrophic lateral sclerosis caused by the C9orf72 expansion in Norway - prevalence, ancestry, clinical characteristics and sociodemographic status. *Amyotroph Lateral Scler Frontotemporal Degener*. 2024 Sep 24:1-9
- **Novy C et al.** Repeat expansions in AR, ATXN1, ATXN2 and HTT in Norwegian patients diagnosed with amyotrophic lateral sclerosis. *Brain Commun*. 2024 Mar 14;6(2):fcae087. doi: 10.1093/braincomms/fcae087. eCollection 2024. PMID: 38585669.
- **Van Damme P et al.** European Academy of Neurology (EAN) guideline on the management of amyotrophic lateral sclerosis in collaboration with European Reference Network for Neuromuscular Diseases (ERN EURO-NMD). *Eur J Neurol*. 2024 Jun;31(6):e16264.
- **4. Taule T, Tysnes OB, Aßmus J, Rekand T.** A prospective study for using cognitive decline as a predictor for survival and use of feeding/respiratory support for patients with motor neuron disease in Norway. *Ann Palliat Med*. 2024 Jan;13(1):86-92.

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 leaders: Kristoffer Haugarvoll and Ragnhild Eide Skogseth

***Kristoffer Haugarvoll**, MD, PhD is principal investigator (PI) in the Bergen Dementia Research Group, Associate Professor at the University of Bergen 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.*

***Ragnhild Eide Skogseth**, MD PhD, is an associate professor at the University of Bergen and a consultant geriatrician and principal investigator (PI) for dementia studies at Haraldsplass Deaconess Hospital. Dr Skogseth's clinical expertise includes neurodegeneration, dementia and biomarkers. Her main research focus is dementia and neurodegeneration in particular dementia related to Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), and novel biomarkers to better diagnose these diseases.*

Additional key node partner is Bettina Husebø (see next page).

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 2024, 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. By the end of 2024, 70 out of 80 planned trial participants have been randomised in the trial.
- **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 also 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).

Industry-sponsored clinical trial:

- **PROGRESS-AD**: the global Phase 2 clinical trial by GSK and Alector of AL101/GSK4527226 in patients with early Alzheimer's disease (AD).

Selected publications from 2024:

- **Titlestad I, Haugarvoll K, Solvang SH, Norekvål TM, Skogseth RE, Andreassen OA, Årsland D, Neerland BE, Nordrehaug JE, Tell GS, Giil LM.** Delirium is frequently underdiagnosed among older hospitalised patients despite available information in hospital medical records. *Age Ageing*. 2024 Feb 1;53(2):afae006. doi: 10.1093/ageing/afae006.
- **Titlestad I, Watne LO, Caplan GA, McCann A, Ueland PM, Neerland BE, Myrstad M, Halaas NB, Pollmann CT, Henjum K, Ranhoff AH, Solberg LB, Figved W, Cunningham C, Giil LM.** Impaired glucose utilization in the brain of patients with delirium following hip fracture. *Brain*. 2024 Jan 4;147(1):215-223. doi: 10.1093/brain/awad296.

THE CARE NODE

The Care Node focuses on older adults and people with complex conditions including neurological diseases such as dementia and PD. They aim to contribute to better health and end-of-life care for older adults living at home or in institutions, by promoting research-based knowledge about age-related diseases, care services, and the living situation for all people involved. The Centre for Elderly and Nursing Home Medicine (SEFAS) constitutes Neuro-SysMed's Care Node.

Node leader: Bettina Husebø

Bettina Husebø, MD, PhD is a professor and the head of the Centre for Elderly and Nursing Home Medicine (SEFAS), which in 2024 expanded from 12 to 22 staff members, still counting as the centre is expanding its activities. Professor Husebø is a specialist in anaesthesiology, intensive care, palliative care, and nursing home medicine. Her clinical research has been focused on method development and randomised controlled intervention trials, including nursing home patients and home-dwelling people with dementia, highlighting the assessment and treatment of pain, neuropsychiatric and behavioural disturbances, medication reviews, and end-of-life care. Her recent work involves a transdisciplinary approach on technology, smart living, and artificial intelligence in healthy older adults and people with complex conditions, such as dementia and PD. She is also key node partner in the Neuro-SysMed Dementia Node.

Node activities

The Care Node works to discover, validate, and translate novel approaches to improve our understanding of good ageing and to support our society in developing high-quality treatment and care. They strive to facilitate healthy and independent ageing for older adults, and to support informal (relatives) and formal (healthcare professionals) caregivers. Their work investigates innovative methods of symptom assessment, non-pharmacological interventions, service provision and living environments. This includes innovative use of sensing technology that encompasses active and passive sensors integrated in the person's environment, and digital phenotyping, that is, the determination of a person's characteristics by its digital data, such as data from smartwatches, smart rings and wall mounted sensors. The 2024 activities of the Node were greatly expanded as the CC.AGE and 5-D projects recruited additional expertise who started their work alongside of already well-established projects, and by being granted the new EI ROBOT project.

Current studies

- **CC.AGE**: The Trond Mohn Research Foundation and the University of Bergen generously provided financial support in 2023 to SEFAS to establish the Centre for Complex Conditions and Ageing (CC.AGE). Here, they investigate the use of novel technology and high-quality care to improve the lives of older persons with complex conditions living at home. CC.AGE began in 2024.
- **The 5-D project, Decoding Death and Dying in people with Dementia by Digital thanotyping (5-D)** is a unique project supported by the European Research Council (ERC), investigating how sensing technology can be used to recognise symptoms among people with dementia at the end of life. By collecting data from nursing home residents, the project will develop methods and tools that can provide a more precise understanding of pain and symptoms at the end of life. 5-D includes the complementary sub-studies DIPH.DEM, mapping the changes in activity of people with dementia at the end of life, and ORAL.DEM, evaluating the oral health status of people with dementia at the end of life and identifying the best measures to enhance oral care.
- **DARK.DEM** is a randomised controlled trial to test whether virtual darkness can alleviate agitation in people with dementia. It is funded by the Research Council of Norway (RCN) and the University of Bergen (UiB) and aims to enhance diagnostics and treatment of behavioural and psychological symptoms of dementia in specialised and municipal dementia care.

- **EI ROBOT, Emotion-Intelligent Robot System for People with Impaired Cognition**, is a new project in collaboration with Vitalthings (NO), Mentech (NL), and SARA B.V. (NL), with funding from the European Union program Eureka Eurostars, the Norwegian Research Council and the Netherlands Enterprise Agency. Here, the aim is to develop an emotion-intelligent robot system to enhance the well-being of persons with dementia or other intellectual disabilities residing in long-term care institutions through personalised interactions while supporting care professionals.
- **The ActiveAgeing study consists of two branches – the DIGI.PARK branch and the Helgetun branch**. The Helgetun branch is exploring how living in an innovative, community-based environment can affect the lives of older adults, using a qualitative approach. Helgetun is an innovative ad unique residential project that aims to foster active ageing with facilities to increase physical, mental and social activities. The goal of the project is that the residents manage to live at home longer, with better physical and mental health. DIGI.PARK is an observational study based on quantitative research, exploring the use of wearable sensor devices for symptom tracking in home-dwelling people with PD.

Selected publications from 2024:

- **Førsund E, Torrado Vidal JC, Fæø SE, Reithe H, Patrascu M, Husebo BS.** Exploring active ageing in a community-based living environment: an ethnographic study in the Western Norway context. *Front Public Health*. 2024 Apr 30;12:1380922. doi: 10.3389/fpubh.2024.1380922. eCollection 2024. PMID: 38745999.
- **Vislapuu M, Patrascu M, Allore H, Husebo BS, Kjerstad E, Gedde MH, Berge LI.** Feedback System Analysis of a Multicomponent Intervention on Dyads of Home-Dwelling Persons with Dementia and Their Caregivers: Results from the LIVE@Home.Path Trial. *Innov Aging*. 2024 Feb 23;8(3):igae020. doi: 10.1093/geroni/igae020. eCollection 2024. PMID: 38550899.
- **Patrascu M., Berge L.I., Vislapuu M., Husebo B.S.** Circadian Rhythm Stability Analysis from Actigraphy Data in Persons with Dementia. *European Control Conference, ECC 2024, Stockholm, Sweden, IEEE,* ISBN 978-3-9071-4410-7, doi 10.23919/ECC64448.2024.10591189.

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 proficiency in biophysics, structural biology, drug design, cellular biology, and animal disease models. The methodological expertise contributed to Neuro-SysMed includes target identification and compound screening utilising both biophysical and cellular screens. It includes mechanistic validation of optimal hits and comprehensive knowledge of the progression from early-stage drug discovery to the identification of best leads for proof-of-concept in patients, aiming to develop preventive and corrective therapies for PD and other parkinsonian disorders.*

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 PD 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 2024 comprised:

• **Mitochondrial function**. In collaboration with Charalampos Tzoulis, the Drug Discovery Node has conducted a cell-based screening campaign to identify already approved drugs that can counteract the neuronal respiratory complex I (CI) deficiency observed in a subgroup of PD. One of the identified hit compounds by Postdoc Kunwar Jung-Kc is an FDA-approved drug with the potential to enhance mitochondrial function, and that has shown promising results in enhancing mitochondrial CI protein levels and promoting mitochondrial biogenesis. Further studies are being conducted to identify the mechanisms by which the drug interacts with the cellular components to modulate mitochondrial function, with the goal of elucidating potential therapeutic effects in PD. The project has recently received additional funding from the Norwegian Parkinson's Disease Research Foundation to advance the drug discovery efforts, and to validate, characterise and prepare hit compounds from the drug screening to inclusion in clinical trials.

• **Tyrosine hydroxylase (TH) as a treatment target in PD and parkinsonisms.** In a recent collaboration with the labs of Angeles García-Cazorla (Hospital Sant Joan de Déu, Barcelona) and Antonella Consiglio (Bellvitge University Hospital-IDIBELL, Barcelona), we have discovered that supplementation with the TH cofactor tetrahydrobiopterin (BH4) increases TH+ cells and DA, and improves motor outcomes in a THD mouse model, highlight the therapeutic potential of BH4 for specific TH variants and in parkinsonisms (Jung-Kc et al., 2024). Recently, the Node has also identified DNAJC12 as the molecular HSP40 cochaperone that maintains TH stability and decreases its propensity to aggregate. The solved structure of the complex by Cryo-EM (Tai et al., 2024) is facilitating the discovery of stabiliser drugs of TH and the TH:DNAJC12 complex.

• **VMAT2 as a therapeutic target in PD.** This project studies the vesicular monoamine transporter 2 (VMAT2) which is responsible for packaging monoamines such as DA 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 regulating DA signalling is not yet known. The VMAT2 project is led by Neuro-SysMed researcher Svein Isungset Støve, who has screened for compounds that modulate VMAT2 activity using both biophysical and cellular assays and has identified potent inhibitors of VMAT2 that have a potential for the treatment of Tardive Dyskinesia, as well as modulators of VMAT2 protein expression that can increase VMAT2 levels and subsequently DA sequestration. The identification of activators or stabilisers of VMAT2 is 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 PD, ALS, and 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 Professor 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.).

Trond Riise's 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.

In 2025, the methods used for PD will be expanded to MS as a part of the Horizon-funded EBV-MS project. Persons with severe EBV-infections will be identified through diagnostic codes for mononucleosis in registry-data. We will use prescription-data for the time-period after the EBV infection to identify molecules associated with the risk of developing MS and with the time to MS-diagnosis. This can be helpful in understanding the mechanisms for disease development and be used to identify possible new treatments.

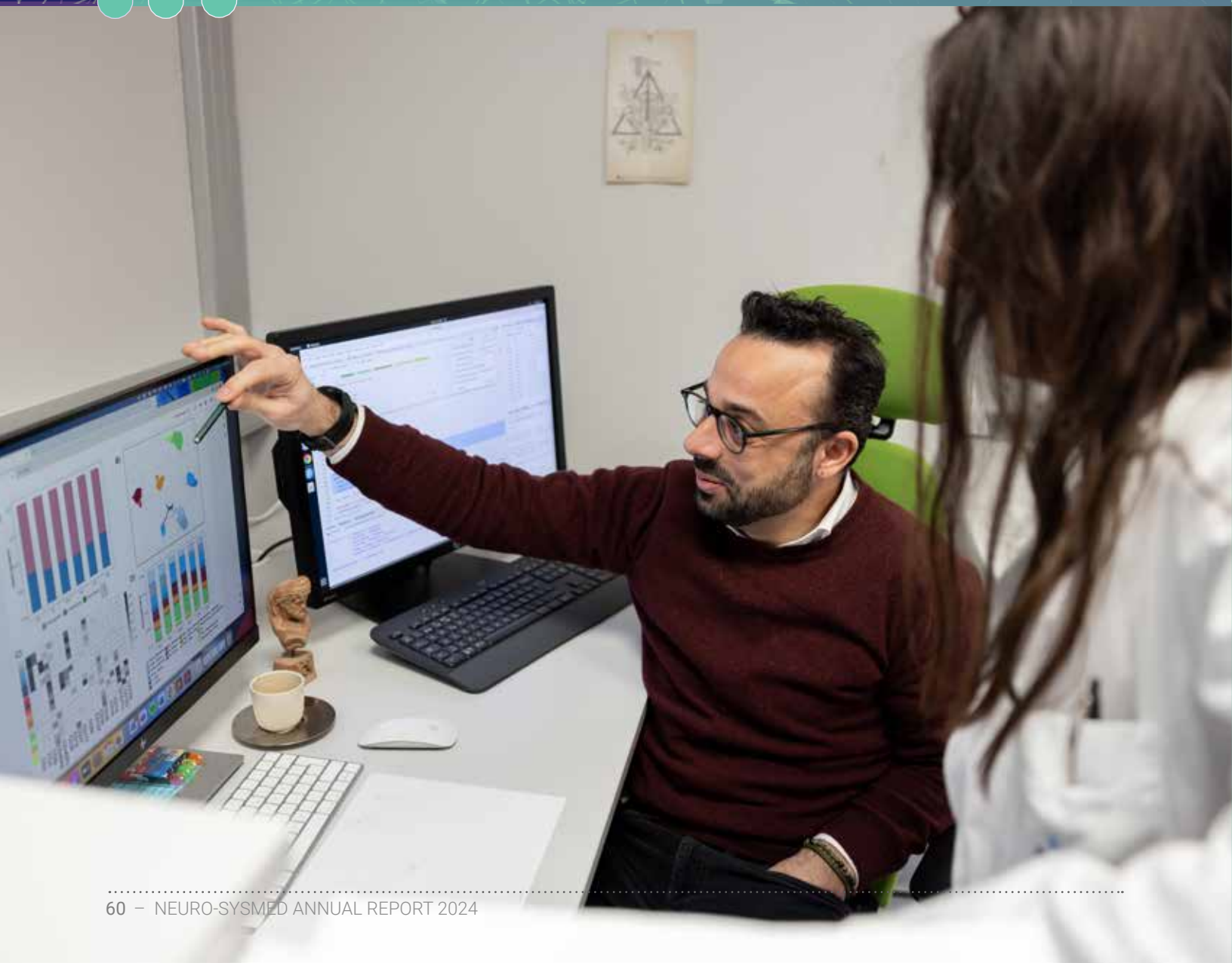
Trond Riise will retire in 2025, and the new leader of the DRONE group will be Associate Professor Jannicke Igland. She is a statistician with long experience from registry-based epidemiology, including pharmacoepidemiology. She has been part of the DRONE-group from the start and is main supervisor and co-supervisor for two of the PhD students and three master students in the group.

Selected publications from 2024:

- **Wang X, Marmouzi I, Finnie PSB, Bucher ML, Yan Y, Williams EQ, Støve SI, Lipina TV, Ramsey AJ, Miller GW, Salahpour A.** Tricyclic and tetracyclic antidepressants upregulate VMAT2 activity and rescue disease-causing VMAT2 variants. *Neuropsychopharmacology*. 49(11):1783-1791. doi: 10.1038/s41386-024-01914-2.
- **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*. 47(3):494-508. doi: 10.1002/jimd.12702.
- **Thöny B, Ng J, Kurian MA, Mills P, Martinez A.** Mouse models for inherited monoamine neurotransmitter disorders. *J Inherit Metab Dis*. 47(3):533-550. doi: 10.1002/jimd.12710.
- **Tai MDS, Gamiz-Arco G, Martinez A.** Dopamine synthesis and transport: current and novel therapeutics for parkinsonisms. *Biochem Soc Trans*. 52(3):1275-1291. doi: 10.1002/jimd.12710.
- **Ruisch IH, Widomska J, De Witte W, Mota NR, Fanelli G, Van Gils V, Jansen WJ, Vos SJB, Fóthi A, Barta C, Berkel S, Alam KA, Martinez A, Haavik J, et al.** Molecular landscape of the overlap between Alzheimer's disease and somatic insulin-related diseases. *Alzheimers Res Ther*. 16(1):239. doi: 10.1186/s13195-024-01609-2.
- **Tai MDS, Ochoa L, Flydal M, Velasco-Carnero L, Muntaner J, Santiago C, Gamiz-Arco G, Moro F, Jung-Kc K, Gil-Cantero D, Marcilla M, Kallio J, Muga A, Valpuesta JM, Cuellar J, Martinez A.** Structural recognition and stabilization of tyrosine hydroxylase by the J-domain protein DNAJC12. *Nat Commun*. In Press.


analysis type
not stratified
women only
men only
ATC group
HR

THE SYSTEMS BIOLOGY AND BIOINFORMATICS (SBB) NODE



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 S. Nido and Dimitrios Kleftogiannis

Dr. Gonzalo S. Nido *is a senior researcher in computational biology 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 PD 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.*

The concept of systems medicine in neurology is the backbone of the Centre. 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. Leveraging the wealth of data collected through our clinical and translational activities, and utilizing supervised and unsupervised data-analysis models, including artificial intelligence (AI), the Systems Biology & Bioinformatics (SBB) Node is developing specific and sensitive biomarker systems. These systems aim to enable and refine early and precise diagnosis, stratification, and prediction of treatment response.

2024 Advances:

• **The ParkOme Initiative:** Integrates multiomics and clinicopathological data to understand Parkinson's disease (PD) and discover biomarkers and treatment targets. This involves mapping data layers (genome, epigenome, transcriptome, etc.) and using high-throughput single-cell analyses, pathology-guided single-cell transcriptomics, and Xenium spatial transcriptomics.

• **Multiple Sclerosis Single-Cell Omics:** Combines single-cell omics with clinicopathological data to understand MS mechanisms. Advanced machine learning methods characterise immune landscapes in MS patients undergoing therapies like rituximab and aHSCT. High-dimensional cytometry and 10X Genomics platform are used to establish patient-centric treatment foundations.

Key Milestones in 2024:

• **Single-Nucleus RNA Sequencing:** Applied to nearly 300,000 nuclei from individuals with PD and other conditions, identifying novel cell-specific gene expression changes.

• **PD Stratification:** Identified two PD subtypes based on neuronal respiratory complex I deficiency, with distinct molecular and clinical profiles.

• **Transcriptome Mapping:** Mapped the full transcriptome of over 1300 brains from neurodegenerative disease patients, with publications and a public database expected in 2025.

• **MS Single-Cell Analysis:** Collected and analysed over 200 million single cells from MS patients, providing insights into immune system reconstitution.

• **Funding and Platforms:** Secured funding for investigating peripheral blood immunological signatures in MS and established a multimodal omics analysis platform. Additional funding was obtained for single-cell transcriptomics in PSP, CBD, and DLB, and for a high-resolution spatial transcriptomics platform.

The SBB Node's data, analyses, and computational software have led to several publications in high-impact journals and presentations at major international conferences, garnering significant interest and recognition.

Selected publications from 2024:

- **Nido GS, Castelli M et al.** Single-nucleus transcriptomics reveals disease-and pathology-specific signatures in α-synucleinopathies. *Brain* (2024). DOI: 10.1093/brain/awae355
- **Fløtnes IH, Toker L, et al.** Mitochondrial complex I deficiency stratifies idiopathic Parkinson's disease. *Nature Communications* (2024). DOI: 10.1038/s41467-024-47867-4
- **Kleftogiannnis D, Gavasso S et al.** Automated cell type annotation and exploration of single-cell signaling dynamics using mass cytometry. *Iscience* (2024). DOI: 10.1016/j.isci.2024.110261
- **Sharma S et al.** GEMCAT-a new algorithm for gene expression-based prediction of metabolic alterations. *NAR Genom Bioinform*. 2025 Jan 31;7(1):lqaf003.

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 postdoctoral fellow (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.*

The RRI/PPI Node is responsible for four projects/ activities:

- A research project entitled "Philosophy of precision medicine in severe chronic neurological diseases (POS-PM)."
- 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 the autumn of 2023, NeuroDialogues plans to continue its sessions in the spring and autumn of 2025, providing a platform for critical engagement with these issues emerging from Neuro-SysMed.
- Standard of procedure (SOP) for RRI/PPI in clinical trials.

During 2024, Engen and Karlsen continued to work on their co-authored monograph (working title: Precision and Suffering). The book will contain the development of a novel model of suffering to be applied in RRI engagements with precision medicine. The NeuroDialogues initiative was temporally discontinued due to low attendance rates, but its main idea, i.e. that of creating an interdisciplinary space in which scientific staff can engage with RRI/PPI issues in neurology, was continued in the form of a SOP (standard operating procedure). The idea is to create a procedure for addressing ethical, epistemological, and societal issues in project design and implementation. The SOP is under development and testing.

Selected dissemination activities from 2024:

- Engen, C. "Designerbabyer - Science fiction eller virkelighet?" Panel discussion at Bergen Offentlige Bibliotek, 12 March 2024.
- Engen, C. "Restructuring Neurology: Responsible Research and Innovation (RRI)" Presentation at Neuro-Sys-Med seminar series, Armauer Hansen Hus, 13 March 2024.
- Engen, C. "I møte med det uforutsigbare: Usikkerhet i medisin og helsefag." Dialogue meeting at Filosofisk Poliklinikk, Alrek Helseklynge, 10 April 2024.
- Engen, C. "Hva skal medisinen med refleksjon og klokskap, når vi har kunstig intelligens?" Full-day seminar at Filosofisk Poliklinikk, Alrek Helseklynge, 3 May 2024.
- Engen, C. "Futures of Cancer Research and Cancer Care." Panel discussion at Solstrand (CCBIO-VBP Research Meeting), 29 August 2024.
- Engen, C. "Controversy in Prevention of Neurodegeneration." Discussion with Charalampos Tzoulis, moderated by Ambra Stefani, at Solstrand (Neuro-SysMed), 30 September 2024.
- Engen, C. "Kulturell iatrogenese" Dialogue meeting at Filosofisk Poliklinikk, 21 October 2024.
- Engen, C. "Håp og helse" Dialogue meeting at Filosofisk Poliklinikk, 11 December 2024.
- Karlsen, JR. "The nature and limits of autonomy" invited lecture at Etikksalongen, Haukeland University Hospital, 7 November.
- Karlsen, JR. "The easy death in complex societies" invited lecture and panel discussion at the seminar "End of life – is it our own choice?" at Haraldsplass Deaconess University College, 12 December.
- Karlsen, JR. "What is Edification?" keynote lecture at the conference "From selfie to interplay – edification in education" at The University of Agder, 4-5 December.

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 34 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 COVID-19 Vaccine Response Study
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
MS	The Rituximab Versus Cladribine Study
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 Activity in People with Multiple Sclerosis
MS	The NorseMS Study: A Digital Therapeutic to Improve Insomnia in Multiple Sclerosis – A Randomised Controlled Trial
MS	The 3TR Study – Taxonomi, Treatment, Target and Remisson
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	SLEIPNIR: a Clinical Trial Accelerator and Derisking Platform for Parkinson's Disease
PD	The NADAPT Study: A Phase II Randomised Controlled Trial of NAD Replenishment Therapy for Atypical Parkinsonism
PD	HYDRA: An Adaptive Multiarm Multistage Clinical Trial for Parkinson's Disease
PD	NAD-RBD: A Randomised Double-blind Trial of NAD Replenishment Therapy to Prevent α-Synucleinopathies
PD	NADream: A Randomised Double-blind Trial to Explore the Effects of NAD Augmentation Therapy on Sleep Physiology
PD	The NADage Study: A Randomised Double-blind Trial of NAD Replenishment Therapy on Aging
PD	NOR-RBD: A Longitudinal Cohort and Clinical Trial Platform for Prodromal α-Synucleinopathies
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, Multicentre, 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 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
CAR	CC.AGE: Complex Conditions and Ageing
CAR	Decoding Death and Dying in People with Dementia by Digital Thanotyping (5-D)
CAR	Digital Phenotyping for Changes in Activity at the End of Life in People with Dementia (DIPH.DEM)
CAR	Oral Care at the End of Life in People with Dementia (ORAL.DEM)
CAR	The ActiveAgeing Study – the Helgetun Branch
CAR	The ActiveAgeing Study – the DIGI.PARK Branch
CAR	Virtual Darkness and Digital Phenotyping in Specialised and Municipal Dementia Care (DARK.DEM)

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. The trial is coordinated by HUH in close collaboration with centres in all Norwegian health regions, plus 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 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 December 2024, 96 patients have been included in the study, and enrolment will continue until the target of 100 patients is reached. In Norway, patients from all health regions are screened at the University Hospital of North Norway (Tromsø), St. Olav's Hospital (Trondheim), Akershus University Hospital (Lørenskog), and Haukeland University Hospital (HUH, 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

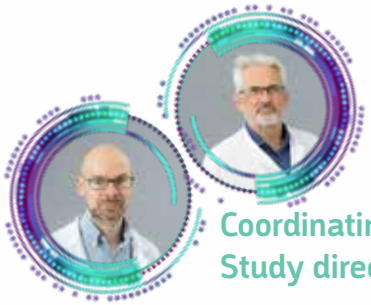
Denmark
- Copenhagen University Hospital, Rigshospitalet

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
- The 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) indicates 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, it costs only a fraction of ocrelizumab. If rituximab proves to have similar effects as ocrelizumab, it may therefore reduce the annual cost for MS-therapy by several hundred million NOK in Norway alone and give MS-patients access to highly effective treatment at an earlier 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 to 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. The study will finalize during 2025.

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 Trust, Bodø
- Namsos Hospital Trust, Namsos
- Molde Hospital Trust, Molde
- Sørlandet Hospital Trust, Kristiansand
- Telemark Hospital Trust, Skien
- Vestre Viken Hospital Trust, 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 observational 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 who continue with 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

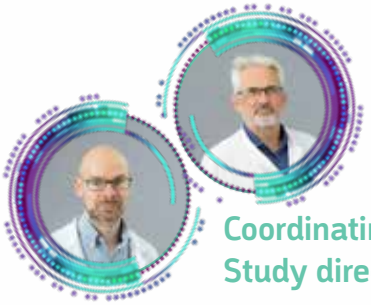
Norway
- Haukeland University Hospital, Bergen
- Oslo University Hospital, Oslo
- Akershus University Hospital, Lørenskog
- Stavanger University Hospital, Stavanger
- University Hospital of North Norway, Tromsø
- Nordland Hospital Trust, Bodø
- Namsos Hospital Trust, Namsos
- Molde Hospital Trust, Molde
- Sørlandet Hospital Trust, Kristiansand
- Telemark Hospital Trust, Skien
- Vestre Viken Hospital Trust, 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 the efficacy and safety of extending the dosing interval from 6 to 12 months in RRMS.

All patients finishing the OVERLORD-MS study who 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

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 Trust, Bodø
- Namsos Hospital Trust, Namsos
- Molde Hospital Trust, Molde
- Sørlandet Hospital Trust, Kristiansand
- Telemark Hospital Trust, Skien
- Vestre Viken Hospital Trust, Drammen

Sweden
- Karolinska Institute, Stockholm

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 COVID-19 Vaccine Response Study

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 but focusing on rituximab treatment.

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 from the patients treated at Haukeland University Hospital show that rituximab treated patients have reduced humoral response to COVID-19 vaccination, but there were not an increased frequency or severity of COVID infections among the patients (https://pubmed.ncbi.nlm.nih.gov/39029342/). This indicate that rituximab treated patients have normal clinical effects from vaccination. Similar results have been shown in a large Norwegian MS-Registry based cohort as well (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

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

Disease: Multiple sclerosis
Type of study: Interventional trial

Coordinating investigator: Christopher Elnan Kvistad
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, who have experienced worsening of disability during the last two years, 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 2024, about 40 patients are included. A total of 18 hospitals have expressed their interest in participation.

Participating centres

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

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 Rituximab Versus Cladribine Study

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: Results from the study show that rituximab is superior compared to cladribine as evaluated by MRI and clinical disease activity. Brit Ellen Rød presented the data the European Committee for Treatment and Research in MS (ECTRIMS) in Copenhagen, September 2024, and received the first price for the best young investigator. The article describing the results are in the review process in The Multiple Sclerosis Journal.

Participating centres

- Haukeland University Hospital, Bergen
- Oslo University Hospital, Oslo

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: Patient recruitment has been performed and analyses of the EBV shedding in saliva underway.

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 Activity in People with Multiple Sclerosis

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 safety and efficacy of tenofovir alafenamide (TAF) on Epstein-Barr virus infection in patients with relapsing-remitting MS (RRMS).

Design: This is a randomised double-blinded, placebo-controlled trial comparing the safety and efficacy 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: Inclusion of patients started early 2024, and by December 2024, 41/50 patients have been 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
- 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
- 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 evaluate 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 Norwegian University of Science and Technology, Trondheim
- The Central Regional Health Authority of Norway
- Haukeland University Hospital, Bergen
- The University of Bergen
- The Foundation DAM

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

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 aim to include at least 280 patients, and by early December 2024, we have included 272 patients. 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 evaluated 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 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 cerebral NAD levels measured by 31P-MRS).

Status: The study is fully enrolled and will be concluded in May 2025.

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 blood and brain pharmacokinetics of NAD replenishment therapy (NRT) using Nicotinamide Riboside (NR) or Nicotinamide Mononucleotide (NMN).

Design: The NAD-brain study will perform a parallel assessment of NAD replenishment therapy (NRT) pharmacokinetics in the blood and brain of healthy human subjects. A total of 6 healthy individuals (3 men and 3 women) will undergo repeated blood sampling and 31P-MRS brain scans during two 20-day periods, each of which will start with 8 days of daily intake of Nicotinamide Riboside (NR) 600mg x 2, or Nicotinamide Mononucleotide (NMN) 600mg x 2. The two 20-day periods will be 14 days apart to allow for washout of the previous compound.

Moreover, a total of 6 healthy individuals (3 men and 3 women) and 6 individuals with PD (3 men and 3 women) will receive NR 1200 mg daily (600 mg x 2) for 4 weeks, with a total measurement/assessment period of 7 weeks, and undergo repeated blood sampling and 31P-MRS brain scans once per week during this time.

Blood will be analysed for NAD-metabolites. The simultaneous change in NAD-metabolism over time in blood and brain will be assessed and blood and brain pharmacokinetics for NRT in humans will be established.

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

Status: The study was completed in 2024, and the results submitted for publication.

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 fully enrolled and will be concluded in June 2025.

Participating centres

- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- Vestre Viken Hospital, Drammen
- Østfold Hospital, Kalnes
- Nordland Hospital, Bodø
- University Hospital of North Norway, Tromsø
- Førde Hospital, Førde
- Dr. Karen Herlofson, Arendal
- Sørlandet Hospital 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 fully enrolled and will be concluded in June 2025.

Participating centres

- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- Vestre Viken Hospital, Drammen
- Østfold Hospital, Kalnes
- Nordland Hospital, Bodø
- University Hospital of North Norway, Tromsø
- Førde Hospital, Førde
- Dr. Karen Herlofson, Arendal
- Sørlandet Hospital 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 in ongoing and has 30 participants enrolled.

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

SLEIPNIR: a Clinical Trial Accelerator and Derisking Platform for Parkinson's Disease

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

Coordinating investigators: Irene Flønes
Study director: Charalampos Tzoulis

Background: There are currently no disease-modifying therapies (DMTs) capable of halting the progression of Parkinson's disease (PD), with over 70 negative trials. A fundamental challenge is that investigational compounds advance to efficacy trials without adequate evidence of target engagement (i.e., interaction of the treatment with its intended biological target/pathway) in the patient brain. Without this evidence, the therapeutic potential of a compound remains speculative, rendering costly and time-consuming trials futile. To address this pressing need, we have established SLEIPNIR, a platform trial designed to assess target engagement of tentative DMTs in PD.

SLEIPNIR will test 3-4 candidate DMTs per operational cycle (1.5 years). The chosen compounds are supported by robust preclinical data establishing safety and neuroprotective effects in relevant models and have undergone phase I clinical safety testing. This strategic intervention is poised to significantly accelerate the path to breakthrough treatments for PD.

The primary objective is to evaluate whether the tested compounds engage their intended biological targets in the patient brain.

Primary endpoint: The between-group (active treatment vs. placebo) difference in appropriate measures of target penetration and/or engagement.

Status: The protocol was established in 2024. Recruitment is planned to start in Q3 2025 (depending on funding).

Participating centre

- Haukeland University Hospital, Bergen

Funding

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

HYDRA: An Adaptive Multiarm Multistage Clinical Trial for Parkinson's Disease

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

Coordinating investigators: Geir Olve Skeie & Irene Flønes
Study director: Charalampos Tzoulis

Background: There are no disease-modifying therapies (DMTs) for PD and current trial designs are highly inefficient. The HYDRA initiative aims to revolutionise PD trials through an adaptive, multi-arm, multi-stage (MAMS) platform trial. This innovative approach simultaneously evaluates multiple DMTs against a single placebo, with the flexibility to discontinue ineffective treatments and reallocate participants to more promising arms. HYDRA will include 800 participants from 12 centres across Norway and test the efficacy of three potential DMTs in delaying the progression of PD, assessed by the total MDS-UPDRS score. Secondary outcomes include cognitive function, daily life activities, quality of life, and caregiver impact. Exploratory objectives involve digital and molecular biomarkers, long-term treatment effects, and personalised medicine strategies.

HYDRA's adaptive design ensures rigorous drug selection and employs a decentralised approach to minimise participant discomfort and enhance national recruitment. This platform will provide conclusive evidence on DMT efficacy within a 5-year period, potentially leading to regulatory approval and transforming PD treatment paradigms. The HYDRA initiative promises to enhance trial efficiency, accelerate therapeutic breakthroughs, reduce trial costs and duration, and improve the quality of life for individuals with PD. The study will recruit patients from across all four health regions of Norway. Additional patients will be recruited by our international partners, as necessary.

The primary objective: The HYDRA initiative aims to accelerate breakthroughs in the field of PD therapeutics by testing multiple potential disease-modifying therapies (DMTs) in parallel, with significantly less participants, shorter trial time, and substantially lower costs, compared to testing these treatments individually.

The primary objective is to evaluate whether the tested compounds can delay the progression of PD.

Primary endpoint: The between-group (NR vs. placebo) difference of the change in motor severity, measured by MDS-UPDRS part III, between baseline and end of study (week 52).

Status: The study has received funding, and the protocol is being established. Recruitment is planned to start in Q1 2026.

Participating centres

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

Funding

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

NAD-RBD: A Randomised Double-blind Trial of NAD Replenishment Therapy to Prevent α-Synucleinopathies

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

Coordinating investigator: Johannes Jernqvist Gaare
Study director: Charalampos Tzoulis

Background: NAD-RBD introduces a groundbreaking approach to combat α-synucleinopathies, relentlessly progressive neurodegenerative disorders, comprising Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). While these conditions currently lack disease-modifying therapies, our research has nominated NAD replenishment as a promising intervention. Key to this strategy is targeting the prodromal phase of α-synucleinopathies, marked by isolated REM sleep Behaviour Disorder (iRBD).

NAD-RBD, a Phase III multi-centre, randomised, double-blind, placebo-controlled study, will evaluate the efficacy of NAD-replenishment therapy in halting the progression of motor and cognitive dysfunction in individuals with iRBD. We plan to enrol 400 participants across 11 centres in Norway and treat them for 24–58 months, with time to motor or cognitive progression milestone or phenoconversion as primary outcome. The adaptive treatment duration will optimise the therapeutic window per individual. The study emphasises personalised medicine, developing biomarkers for disease stratification and prediction of treatment response. The partly decentralised design will minimise patient discomfort and lower operational costs. This pioneering initiative shifts focus from treating to preventing neurodegenerative diseases, potentially easing the burden on patients, caregivers, and healthcare systems while significantly enhancing life quality for millions at risk of α-synucleinopathies.

The primary objective of the project is to assess the clinical efficacy of NR in delaying the progression of motor dysfunction, cognitive dysfunction, or phenoconversion in individuals with iRBD.

Status: The protocol has been established. Recruitment is planned for Q4 2025.

Participating centres

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

Funding

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

NADream: A Randomised Double-blind Trial to Explore the Effects of NAD Augmentation Therapy on Sleep Physiology

Disease: Healthy individuals
Type of study: Interventional trial

Coordinating investigator: Katarina Lundervold
Study director: Charalampos Tzoulis

Background: Sleep disorders, including insomnia, REM sleep behaviour disorder (RBD), and other parasomnias, are strongly associated with pathological brain aging and neurodegenerative disorders, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and Alzheimer's disease. Our earlier trials in PD, the **NADPARK** and **NR-SAFE** studies (PMID: 35235774, 38016950), have indicated that NAD-augmentation therapy with oral NR may have beneficial effects on human sleep physiology and improve sleep quality in people with neurodegenerative disorders. This is also supported by studies in rodents. However, the effects of NAD-augmentation therapy on human sleep physiology have not been formally studied.

NADream is a randomised, double-blind, placebo-controlled, Phase I study, which will explore the effects of NAD-augmentation therapy on human sleep. A total of 20 (10 men and 10 women) healthy volunteers will be recruited and randomised on NR 2000 mg per day or placebo for 4 weeks. In addition, each participant will undergo two cycles of sleep deprivation at baseline and the end of the trial. Measurements will include polysomnography to quantitatively assess relevant electrophysiological properties of the brain, such as sleep pressure, as well as a multitude of clinical and biochemical assessments. Based on the results of the **NADdream** trial, we will design and implement appropriate measures of treatment effects on sleep in our NAD-trials in neurodegenerative and neuroinflammatory diseases. Moreover, we will identify whether oral NR treatment has potential in ameliorating sleep quality in health and disease.

Objectives: The trial is exploratory. The main objective is to assess the effects of NR on the quality of sleep (polysomnography- and questionnaire-based endpoints) and on the recovery rate from sleep deprivation (i.e., quantification of sleep pressure and clinical rating).

Status: The study is funded, and protocol has been established during 2024. Recruitment will start in Q2 2025.

Participating centres

- Haukeland University Hospital, Bergen

Funding

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

The NADage Study: A Randomised Double-blind Trial of NAD Replenishment Therapy on Aging

Disease: Age-related frailty and associated cognitive dysfunction
Type of study: Interventional trial

Coordinating investigator: Katarina Lundervold
Study director: Charalampos Tzoulis

Background: Frailty is a major source of morbidity and disability, as well as a prodromal state for cognitive impairment and dementia. Thus, frailty allows us to intervene in pre-dementia states before neurodegeneration has reached a point of no return. Preclinical and clinical evidence supports that NAD-replenishment therapy with NR targets molecular processes that play key role in frailty and neurodegeneration (i.e., mitochondrial function, proteostasis, and neuroinflammation). We will, therefore, test whether NR treatment can ameliorate frailty and associated cognitive, motor, and other forms of dysfunction.

In the NADage trial, 100 trial participants will be recruited and randomly assigned (1:1) to either NR 2,000 mg (1,000 mg x 2) daily (n=50), or placebo (n=50) for a 52-week period. During the study period, participants will be assessed at five in-clinic visits (week 0, 12, 26, 40, 52) with clinical, neuroimaging, and laboratory measures, in addition to long-term monitoring using wearables.

Primary objective is to assess the efficacy of NR in improving motor function in elderly, community-dwelling, frail individuals.

Status: Funding is secured, and screening started in Q4 2024 and will initiate recruitment in Q1 2025.

Participating centre

- Haukeland University Hospital, Bergen

Funding

- Horizon – ERA4HEALTH
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- The DAM Foundation
- The GC Rieber Foundation

NOR-RBD: A Longitudinal Cohort and Clinical Trial Platform for Prodromal α-Synucleinopathies

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

Coordinating investigator: Johannes Jernqvist Gaare
Study director: Charalampos Tzoulis

Background: α-synucleinopathies are an important group of relentlessly progressive, debilitating, and incurable neurodegenerative disorders, comprising Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Before the diseases become clinically manifest, they are preceded by a long prodromal phase that can last up to 20 years. Current treatments make no impact on disease progression, and trials of potential disease-modifying therapies have so far been unsuccessful. There is a need to shift our efforts from treatment to prevention by initiating interventions in the prodromal phase of the disease.

REM-sleep behaviour disorder (RBD) is a parasomnia, characterised by loss of muscle atonia during REM-sleep, resulting in dream enactment. Isolated RBD (iRBD, i.e. RBD without other overt neurodegenerative manifestations) is associated with an exceedingly high risk of future development of an α-synucleinopathy and is considered to be the most specific marker of being in the prodromal stage of an α-synucleinopathy. After 15 years, > 90% of individuals with iRBD will have developed PD, DLB or MSA.

The NOR-RBD platform is an initiative with three main goals: 1) establish a longitudinal cohort of individuals with iRBD to facilitate the development of predictive biomarkers for risk stratification; 2) establish a structured health care program for individuals in the prodromal stages of α-synucleinopathies; 3) initiate neuroprotective clinical trials in iRBD patients.

The overarching objective of the project is to establish the NOR-RBD platform for longitudinal follow up for patients with prodromal α-synucleinopathy (as defined by the presence of iRBD) and initiate neuroprotective clinical trials.

Status: The study received funding to start, and the protocol has been established. Recruitment will start in Q2 2025.

Participating centres

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

Funding

- The Regional Health Authority of Western Norway
- 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.

Status: STRAT-PARK is ongoing and a total of ~350 participants have been recruited at the end of 2024. The study protocol and characteristics of the population were published in 2024. Analyses of the collected material and data are ongoing and four original papers were submitted in 2024 and are accepted or under review/revision.

Participating centres

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

Funding

- Michael J Fox Foundation
- Gerda Meyer Nyquist Guldbrandson and Gerdt Meyer Nyquist legat
- Helse Midt-Norge
- 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 evaluate 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. The study is expected to close inclusion during 2025.

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: Patients are regularly being included in the extension study until the NO-ALS study ends.

Participating centre

- 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 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: The study is currently recruiting patients at Haukeland University Hospital, Oslo University Hospital, Akershus University Hospital, University Hospital of Northern Norway, Tromsø and St. Olav University Hospital. Sørlandet Hospital Trust Kristiansand and Stavanger University Hospital will start recruiting during the first half of 2025.

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
- 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 investigators: Ragnhild Eide Skogseth & Kristoffer Haugarvoll
Study director: Kristoffer Haugarvoll

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 several 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. 69 out of a total of 80 study participants have been included by the end of 2024.

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 investigators: Ragnhild Eide Skogseth & Kristoffer Haugarvoll
Study directors: Ragnhild Eide Skogseth & 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. By end of 2024, 166 individuals living with dementia and 47 control individuals have been included. A brain bank has been established as part of the study.

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

CC.AGE: Complex Conditions and Ageing

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

Coordinating investigators: Monica Patrascu, Line Berge, Zoya Sabir, Jutta Dierkes
Study director: Bettina Husebø

Background: Providing care and support for the steadily growing population of older adults with chronic complex conditions (CCC) is one of the key challenges of our society. Most older adults do not want to be institutionalised – research has consistently shown that they wish to live independently at home for as long as possible. At the same time, in the coming years, the healthcare system will register a lack of professional health care workers to match future demands, which calls for a paradigm change. The Trond Mohn Research Foundation and the University of Bergen generously provided financial support to SEFAS to establish the Centre for Complex Conditions and Ageing (CC.AGE).

The primary aim of CC.AGE is to improve the living situation for older adults with chronic complex conditions to live safely and independently at home with a good quality of life. At the same time, CC.AGE aims to support their relatives and municipal healthcare professionals. To achieve this, we aim to:

- design, implement, and assess the efficacy of a research-based digital plug-and-play platform with a range of technologies integrated into a mobile tool for use at home.
- identify traditional care areas which can be safely replaced by digital support.
- determine specifications for integrating existing technologies and for developing new products that will be able to sustain 'plug-and-play' integration.
- perform cost-benefit analyses.
- contribute to the design and testing of a social living environment.

Design: CC.AGE employs major transdisciplinary collaboration between medicine, nutrition, systems science, artificial intelligence, software engineering, economy, and ethics that builds on existing evidence, user-involvement, and methodological expertise. The approach of CC.AGE is highly multidisciplinary, encompassing 7 work packages (WPs). The central activity will be a 12-month randomised controlled trial (RCT) to explore the effect and cost-effectiveness of a multicomponent intervention in home-dwelling people with complex conditions.

Status: CC.AGE began its work on February 1st, 2024, and held its opening ceremony in the University Aula on October 1st, 2024. The project's vast reach and multidisciplinarity were highlighted through several insightful contributions from our national and international colleagues and collaborators. All activities in the work packages are directed toward the establishment of the RCT, estimated to begin in 2026.

Funding

- The Trond Mohn Research Foundation
- The University of Bergen

Decoding Death and Dying in People with Dementia by Digital Thanotyping (5-D)

Disease: Dementia
Type of study: Observational trial

Coordinating investigator: Monica Patrascu
Study director: Bettina Husebø

Background: People with dementia at the end of life are one of the most vulnerable and difficult groups to study, as they have difficulties in expressing themselves. The incidence of dementia is expected to triple by 2050 in Europe. Studies show that people with dementia in nursing homes often experience behavioural and psychological symptoms (agitation, depression, anxiety, apathy, psychosis, sleep and appetite disturbances), as well as pain. Under-treatment and over-treatment may aggravate these symptoms, reducing quality of life. Moreover, in the process of dying, our physical, mental and social capacities gradually decrease, making proper treatment challenging. A greater understanding of the end of life for people with dementia is of the utmost importance to improve their care. Additionally, almost 40% of people with dementia die unexpectedly. If we can recognise when the person is in the final phase, we can alert the family and make the end as comfortable and soothing as possible for both the individual and their loved ones.

Primary objective: The 5-D project 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 people with dementia as one of the most vulnerable and difficult groups to study.

The results of the 5-D project can provide crucial and transferable information, with the goal of optimizing individualised treatment for dementia residents. A better understanding of how, why and when people with dementia have reached the last phase of life will provide knowledge that can also be transferred to other scientific fields or diseases. This might improve the quality of life, including the end of life, and provide better and personalised palliative care to those who cannot express their symptoms or pain.

Design: 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) changes in oral status, and d) to decode "the point of no return" as the beginning of perceived dying. The sensors are designed to avoid noticeable discomfort or distress. Garmin Venu detects pulse and movement, and Somnofy detects sleep patterns, movement, and air quality. We are running the complementary DIPH. DEM and ORAL.DEM sub-studies to inform the 5-D project.

Status: Ethical approvals are obtained, and PhD candidates, postdocs and researchers have been and are being recruited. Ten nursing homes in the municipalities of Bergen, Alver and Voss have joined the project. Information meetings have been conducted in all, and educational sessions have started in six nursing homes. Recruitment of more nursing homes is ongoing. Data collection has already started in the first four nursing homes. 78 participants were included by December 2024.

Participating centres

So far, ten nursing homes in the municipalities of Bergen, Voss and Alver. This number increases continuously.

Funding

- The European Research Council (ERC)
- The University of Bergen
- The Regional Health Authorities (Helse Vest)

Digital Phenotyping for Changes in Activity at the End of Life in People with Dementia (DIPH.DEM)

Disease: Dementia
Type of study: Observational trial

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

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 in nursing home patients with dementia.

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. DIPH.DEM functions as a pilot to the larger 5-D project.

Design: DIPH.DEM is a 1-year cross-sectional observational study (n=25), recruiting 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 4A's Test for Delirium). Sensing technology used in the study includes a triaxial Garmin smartwatch (activity, heart rate) and a wireless, radar technology Somnofy (respiration, light, sound, air quality, movement, sleep) unit mounted bedside. Data collection occurs at baseline for 7 days and include sensor observation and traditional proxy-rated questionnaires. Measurements are 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 received ethical approval (REK), and began with active recruiting efforts at Bergen Red Cross Nursing Home in January 2024. The first article is under review, the second article in progress, and we are preparing for the second round of data collection in winter 2024/2025.

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)

Oral Care at the End of Life in People with Dementia (ORAL.DEM)

Disease: Dementia
Type of study: Observational trial

Coordinating investigator: Monica Patrascu
Study director: Bettina Husebø

Background: Caring for individuals with advanced dementia presents unique challenges, particularly in recognizing when they are approaching the end of life. The Lancet Commission for "The value of death" has highlighted the importance of this phase, stressing the need for timely identification to enable effective end-of-life planning and care. Despite the significance of this stage, oral health is often overlooked in dementia health care.

People with dementia frequently struggle with basic oral hygiene due to memory loss and impaired motor skills. This leads to different dental issues such as poor oral hygiene and unhealthy dietary behaviour resulting in many oral problems including caries and periodontal lesions. These challenges contribute to malnutrition, discomfort, and a decline in overall health. Incorporating oral health into palliative care helps researchers identify effective ways to improve patient outcomes and better understand the overall needs of people with dementia.

ORAL.DEM and is a collaboration between Haraldsplass Deaconess Hospital (HDH), SEFAS, and the Department of Clinical Dentistry, UiB. The results of the study will be informing the larger 5-D project.

Primary objective: ORAL.DEM aims to develop a state-of the art method to assess oral health symptoms in people with dementia during the last period of life. We will create an advanced method for evaluating the oral health status, detect possible microbial profile changes and assess any imbalance in molecules involved in the inflammatory and resolution molecules that might occur.

Design: ORAL.DEM will recruit 150 nursing home patients with dementia (≥ 65 years). Every 6 months, clinical assessments will be conducted to evaluate oral mucosa, gingival tissue, saliva levels, and record any lesions such as caries and gingivitis. Caries assessment will follow WHO guidelines. Unstimulated saliva samples will be collected at baseline and every six months to measure salivary pH and buffer capacity, while plaque samples will be analysed using the Human Oral Microbial Identification Microarray (HOMIM). Gingival crevicular fluid (GCF) will also be collected for future analysis, ensuring a comprehensive assessment of oral health in this vulnerable population. In the longer run, we expect that this comprehensive approach not only enhances the quality of life for vulnerable individuals but also reduces healthcare burdens caused by untreated oral health issues, ultimately benefiting society.

Status: Data collection started in November 2024, with 10 nursing homes lined up for participation and the potential to include more if needed. Prior to data collection, the interobserver reliability has been conducted in collaboration with the Department of Odontology, UiB, to ensure consistency and accuracy in data collection. ORAL.DEM, as part of the 5-D project, has been approved by the National Ethics Committee (NEM nr 2023/166).

Participating centres

- 10 nursing homes in the Bergen area

Funding

- The Regional Health Authority of Western Norway

The ActiveAgeing Study – the Helgetun Branch

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

Coordinating investigator: Elise Førsund
Collaborators: Bettina Husebø

Background: Chronic complex conditions including age-related neurological diseases pose one of the greatest challenges facing science and society. Demographic studies show that patient numbers will continue to grow, and older adults with complex conditions are increasingly constituting major challenges to healthcare provision in the 21st century. Care today is very costly, and loneliness is a threat. Self-management and independence should exist alongside social activities and healthcare services. The Care Node wish to explore and use novel technology and smart buildings to innovate care and treatment for the elderly through sustainable business models and look at how we can implement new scientific knowledge into action more effectively and efficiently. One such pilot project is Helgetun, built and financed by the GC Rieber Foundations. Helgetun is a senior community-based living environment located in a rural area of Bergen. It aims to promote active ageing by facilitating mental, social, and physical participation. It consists of 31 rental apartments and several shared facilities. At Helgetun, residents can join a variety of activities and gatherings, as well as volunteer at the nearby farm and kindergarten.

The primary objective is to evaluate how this way of living can reduce loneliness and potentially delay the development of complex chronic conditions, allowing people to live longer independently at home. Based on observations, interviews, and sensor data from wearable devices, we are investigating how living at Helgetun affects the lives of the residents.

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) from Helgetun. 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 article was published in Frontiers in April 2024. A second article is currently under review, and we are working on the analysis for a third manuscript.

Participating centre

- Helgetun Living-Lab

Funding

- The GC Rieber Foundation
- The University of Bergen
- The Research Council of Norway

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 Tzoulis

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 DIGItal phenotyping in people with PARKinson's disease (DIGI.PARK) study is to explore the use of wearables for symptom tracking in home-dwelling people with PD.

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 PD (n=14) 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 Sense and Empatica E4) and a smart ring (Oura).

The first phase of data analysis involves a cross-evaluation between the three devices and their output, 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 PD 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. The first manuscript is under review; the second and third manuscript are 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

Virtual Darkness and Digital Phenotyping in Specialised and Municipal Dementia Care (DARK.DEM)

Disease: Dementia
Type of study: Randomized controlled trial

Coordinating investigator: Line Iden Berge
Collaboratos: 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, chronotherapy, 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, and we have recruited two PhD candidates, one postdoc and a research nurse. The 9th of September 2024 we had a kick-off with the staff at the hospital. We are currently recruiting participants, the procedures including the virtual darkness therapy is perceived well by both the staff and the patients. We aim to include 72 patients by the end of 2026.

Participating centre

- NKS Olaviken Gerontopsychiatric Hospital, Bergen

Funding

- The Norwegian Research Council
- The University of Bergen

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 (2024) PhD candidates and postdocs affiliated to Neuro-SysMed's nodes, in alphabetical order.

LISA AASLESTAD (PhD candidate)

MSc in 2024 at the UiB/SEFAS with the thesis "Bridging Gaps: Wearable sensing-driven assessment of REM sleep behavior disorder in PD. Results from the DIGI. PARK study." She is currently a PhD candidate at SEFAS/Neuro-SysMed's Care Node, working with the Centre for Complex Conditions and Ageing (CC.AGE). In this project, she will concentrate on developing a digital solution aimed at enhancing sleep health, with the goal of improving activity levels and the overall quality of life among older adults.

SHAMUNDEESWARI ANANDAN (postdoc)

MSc in biotechnology and PhD in molecular biology (cancer). She is currently pursuing her postdoc project in the MS Node. 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 she holds the academic responsibility for the Junior scientist Symposia (NEUROSYSM910) at the Neuro-SysMed Research School.

BIRGITTE BERENTSEN (postdoc)

PhD in neuroscience and currently a postdoc at Neuro-SysMed in the PD Node. She is also the head of the Bergen BrainGut Research Group, University of Bergen, and head of section for digital treatment in IBS (Mage-tarmskolen), Department of Internal Medicine, 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 PD. Through clinical data and histological and molecular analyses of the intestinal wall, Berentsen investigates prodromal, preclinical 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 PD Node at Neuro-SysMed. He has recently conducted the NR-SAFE trial, investigating the safety of high dose Nicotinamide Riboside (NR) treatment in PD and is currently conducting the N-DOSE trial, investigating the biological response to increasing doses of NR in PD.

TALE LITLERE BJERKNES (PhD candidate)

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 ALS Node at 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, Centre for Elderly and Nursing Home Medicine (SEFAS)/Neuro-SysMed's Care Node. 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 did his PhD at Neuro-SysMed in the PD Node. He completed 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 PD Node in the NO-PARK study.

VALENTINA CASADEI (postdoc)

Engineer and PhD who received her master's degree in biomedical engineering from the Università Politecnica delle Marche (Italy), and her doctorate from the University of Liverpool, specializing in biomedical signal processing and measurement uncertainty quantification. She is currently a postdoc at SEFAS/ Neuro-SysMed's Care Node, working on identification and extraction of biomarkers for behaviours and psychological symptoms of dementia (BPSD) in the DARK.DEM study.

KARINE EID (postdoc)

MD from the Norwegian University of Science and Technology. She completed her PhD in the Neuro-SysMed MS Node and BERG-HEAD Research Group using the MoBa Cohort, the MS registry, and the Norwegian Patient Registry to study history of childhood abuse, adult abuse, and perinatal depression in women with MS. Currently, she is a postdoc on a project that will study migraine in the prodromal phase of MS.

CAROLINE BENEDICTE NITTER ENGEN (postdoc)

MD (2013) and PhD from UiB (2020). She is currently a postdoctoral fellow at Neuro-SysMed (50%) in and co-node leader of the RRI/PPI Node, in collaboration with Jan Reinert Karlsen. In parallel, she is pursuing a clinical specialization in psychiatry, working (50%) at the Division for Mental Health Care at Helse Bergen. Her academic work explores the concept of suffering and the philosophical, ethical, and societal dimensions of (bio)medicine and (bio)technology. She is particularly interested in the mechanisms shaping medically informed visions of the future, such as precision medicine, and how these intersect with epistemology, normativity, responsibility, uncertainty, and ambiguity in medical knowledge and practice cultures.

ELISE FØRSUND (PhD candidate)

Molecular biologist and MS on the correlation between aging cells and PD. Elise is currently working on her PhD on the "ActiveAgeing" project, Helgetun branch, at SEFAS/Neuro-SysMed's Care Node. Her PhD is qualitative and focuses on new living environments for older adults and the implementation of smart technology for this age group. She has a background as a civil engineer and molecular biologist, where she in her master's looked at the correlation between the lipid composition of aging neurons and the development of Parkinsons disease.

GLORIA GAMIZ (postdoc)

PhD from the 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 in the Drug Discovery Node, 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.

SYNNE GEITHUS (PhD candidate)

MSc in molecular medicine from NTNU, Trondheim. She is currently a PhD candidate in the PD Node, affiliated with the K.G. Jebsen Centre for Parkinson's disease with Gonzalo Sanchez Nido as the main supervisor. Her thesis focuses on the bioinformatical approach to stratify PD using transcriptomics data.

LASSE GIIL (postdoc)

MD with a PhD in immune biomarkers in Alzheimer's disease in 2019. He is studying metabolic biomarkers in relation to the risk of incident dementia and in the study of delirium. Clinically, he is working as a physician at Haukeland University Hospital, Department of Cardiology, as a professor at the University of Bergen and as a postdoctoral researcher at Neuro-SysMed in the Dementia Node.

JOHANNES JERNQVIST GAARE (postdoc)

MD and PhD from the University of Bergen and in 2024 a postdoc at Neuro-SysMed in the PD Node. His PhD work focused on the genetics of PD, specifically how multiple mutations across biological pathways can affect the risk of developing PD. His postdoc work focused on the role of DNA methylation in Parkinson disease. He is currently leading the clinical trials on REM sleep behaviour disorder, focusing on prodromal neurodegeneration.

ANNE THERESE HATLE (PhD candidate)

Occupational therapist with a master's degree in evidence-based practice in health sciences. Since 2022, Anne Therese has been a lecturer in the occupational therapy bachelor's program at Western Norway University of Applied Sciences. In April 2024, she started as a doctoral candidate at SEFAS/Neuro-SysMed's Care Node. Her research is focusing on Decoding Death and Dying in people with Dementia by Digital thanotyping (5-D), a groundbreaking study financed by the European Research Council (ERC Consolidator Grant) to precisely investigate the end of life in nursing home patients with dementia utilizing digital technology.

IDA VIKTORIA HERDLEVÆR (postdoc)

PhD in neuroimmunology from the University of Bergen (2021) where she specialized in paraneoplastic cerebellar degeneration. Currently, she is a postdoc in Neuro-SysMed's MS Node, and the Biomarker and Neuroimmunology Research group, led by Kjell-Morten Myhr and Christian Vedeler, respectively. Her project focuses on identifying prognostic biomarkers, with the aim of being able to offer patient-tailored treatment with a greater degree of predictability and a reduced risk of complications.

EIRIN HILLESTAD (PhD candidate)

Eirin holds an MPhil in Media Studies from the University of Bergen and has completed continuing education in counselling at VID Specialized University. She is currently a PhD candidate at SEFAS/Neuro-SysMed's Care Node, researching volunteer support for older home-dwelling people living with dementia. Her project involves interviewing volunteers, volunteer coordinators, individuals with dementia, and their relatives, as well as conducting participant observations. Eirin works at the Dignity Centre as a Specialist and Research Developer.

KAMILLA HAUGLAND-PRUITT (postdoc)

Kamilla has a PhD in neuroscience from the Arctic University of Norway (UiT), in which she focused on growth hormone modulation of hippocampal activity concerning aging and dementia. At SEFAS/Neuro-SysMed's Care Node, she works as a postdoctoral researcher on the 5-D project, investigating decoding death and dying in people with dementia. Kamilla takes part in data collection, analyses, and supervision of PhD students. As a neuroscientist, Kamilla is particularly interested in the link between brain activity and digital phenotypes, and how to improve the quality of life for elderly with cognitive deficits.

GARD AASMUND SKULSTAD JOHANSON (PhD candidate)

MD from the University of Bergen in 2022, and currently a PhD candidate in the PD Node. His focus is atypical parkinsonisms and especially progressive supranuclear palsy (PSP), where he focuses on elucidating the role of mitochondrial dysfunction in the pathogenesis of PSP. He is also coordinating the NADAPT multicentre clinical trial, studying NAD-replenishment therapy in atypical parkinsonism.

JUSTIN HAUGLAND-PRUITT (PhD candidate)

M.Phil in Global Health from the UiB. During his masters, he explored the experiences and perceptions of medical overuse among migrant health professionals in Norway. Justin is currently a PhD candidate at SEFAS/Neuro-SysMed's Care Node on the CC.AGE project and working closely with BCEPS. He will be studying the ethical and regulatory challenges surrounding assistive technologies, algorithms, and AI in research involving older adults with dementia.

AHMAD INTAKHAR (PhD candidate)

MSc in microbiology, medical science, and systems biology, and until January 2024 a PhD candidate in the MS Node. His research focused on novel molecular biomarker candidates in multiple sclerosis pathology, more specifically neuroprotection and myelin repair.

KUNWAR JUNG (postdoc)

PhD 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) and included in the PD Node. 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, and the Drug Discovery Node, 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/ Drug Discovery Node. 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 PD.

SIMON ULVENES KVERNENG (PhD candidate)

MD from the University of Bergen and currently a PhD candidate in the PD Node. His research is focused on stratification of PD, with emphasis on finding biomarkers of mitochondrial dysfunction in peripheral tissues. He coordinates the STRAT-PARK study at Haukeland University Hospital.

PEDER LILLEBOSTAD (PhD candidate)

MSc in biomedicine from the University of Bergen, specializing in fMRI and brain connectivity. Currently a PhD candidate at Neuro-SysMed in the PD Node, working on imaging biomarkers, especially image segmentation in neuromelanin MRI.

KATARINA LUNDERVOLD (PhD candidate)

MD specializing in neurology at the Haukeland University Hospital and currently a PhD candidate in the PD Node at Neuro-SysMed. Her PhD research focuses on the brain-gut axis in neurodegenerative disorders and NAD replenishment therapy in PD, frailty and sleep.

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 SEFAS/Neuro-SysMed's Care Node. He is working on the development of digital biomarkers for symptom tracking in real-world everyday life for persons with dementia and PD. He is working on the use of functional near infrared spectroscopy as diagnostic tool for PD, 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 was a postdoc of the DRONE project until March 2024, where she utilised state-of-the-art machine learning techniques to analyse Norwegian health registry data, aiming to find possible drug candidates for treatments of PD. She moved on to the Machine Learning Group in the Informatics Department, UiB, and is still working with the DRONE project in the Drug Discovery Node through supervision of 3 master students.

KJERSTI NEDRESKÅR (PhD candidate)

Kjersti holds a bachelor's degree in cell and molecular biology from the NTNU and a Cand.Psychol. from the University of Oslo. She has seven years of experience as a clinical psychologist and is currently doing her PhD at SEFAS/Neuro-SysMed's Care Node on the DARK.DEM project. Her doctoral work is qualitative and focuses on the implementation of new methods for diagnosis and treatment of behavioral and psychological symptoms of dementia in specialized and municipal dementia care.

HILDE NORDBORG (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. Until June 2024, he was a PhD candidate in the PD Node, where his project is focused on developing an *in vitro* protein translation inhibition cell model for PD.

MONICA PATRASCU (postdoc)

PhD in Systems Engineering and an MSc in Intelligent Systems from the University Politehnica of Bucharest, Romania, with a general research focus on complex psycho-social and biosystems, artificial intelligence, mobile robotics, and symptom tracking for neurological diseases. At SEFAS/Neuro-SysMed's Care Node, Monica is the main technology designer, focusing on developing digital biomarkers for symptom tracking in real-world everyday life for older adults, persons with dementia including the end of life, and PD.

HAAKON REITHE (PhD candidate)

Haakon has a background in psychology and neuroscience where he developed a keen interest in the measurement of human physiology and cognition. He is currently a PhD candidate in the ActiveAgeing study of the Care Node, working on the DIGI.PARK branch. There, he is mainly focusing on cross-evaluating devices for Parkinson's research and clinical use and testing a SEFAS-developed algorithm which quantifies the energy of tremors in ranges 3 to 12 Hz, including testing and validating the algorithm by comparing TI pre and post medication.

ANNA RUBIOLO (PhD candidate)

MSc in Neuroscience from the University of Trieste and Helsinki. Currently, she is a PhD candidate in the PD Node, and affiliated with the KG Jebsen Center for Parkinson's Disease. Her research is focused on confirming the existence of subtypes of idiopathic PD 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.

ZOYA SABIR (postdoc)

MS and PhD in Clinical Nutrition from the University of Bergen. In her PhD project, she investigated associations of dietary patterns and protein intake with muscle mass and strength in community-dwelling older adults. She is currently a postdoctoral fellow at SEFAS/ Neuro-SysMed's Care Node, working on the CC.AGE project. Her work within CC.AGE will mainly focus on food environments, hydration, and nutritional status in older adults with chronic complex conditions. This will include an evaluation of digital methods for assessment of dietary intake and hydration status, with the goal of protecting older adults from nutritional deficiencies and dehydration.

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.

SUNNIVA VIBE SKAGEN (PhD candidate)

MS in psychology from 2023 with a specialization in behavioral neuroscience. Her thesis, titled "An Exploration of the Effects of tDCS on the Supplementary Motor Complex and its Impact on Inhibitory Control: Implications for Tourette's Syndrome," investigated the effects of transcranial direct current stimulation (tDCS) on inhibitory control. Currently, Sunniva is currently working as a PhD candidate at SEFAS/Neuro-SysMed's Care Node, specifically with the DARK.DEM study, which investigates the potential therapeutic benefits of darkness therapy for reducing agitation in individuals with dementia.

RAGNHILD EIDE SKOGSETH (postdoc)

MD, PhD, associate professor at the University of Bergen and a consultant geriatrician and principal investigator (PI) for dementia studies at Haraldsplass Deaconess Hospital. She is also currently a postdoctoral fellow at Neuro-SysMed in the Dementia Node. Dr Skogseth's clinical expertise includes neurodegeneration, dementia and biomarkers. Her main research focus is dementia and neurodegeneration in particular dementia related to Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), and novel biomarkers to better diagnose these diseases.

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 was until February 2024 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/the Drug Discovery Node, 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 in the PD Node.

MAGNUS SVENSEN (PhD candidate)

MSc in analytical chemistry from the University of Bergen (2022) and currently a PhD candidate in the PD Node. 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.

IRIT TITLESTAD (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.

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 the Dementia Node at Neuro-SysMed. Her PhD project focuses on the prodromal phase of dementia with Lewy bodies.

HILDE MARIE TORGAUTEN (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 and vaccination in MS patients.

MARY DAYNE SIA TAI (PhD candidate)

MSc in biomedical science from the University of Bergen. She is currently a PhD student at the Martinez group/ the Drug Discovery Node at Neuro-SysMed, working on a project that focuses on protein homeostasis as a therapeutic target for dopamine deficiency.

JULIA AXIINA TUOMINEN (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/Drug Discovery Node at Neuro-SysMed. 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.

JOHANNES WILLUMSEN (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 2024 in the media. Date (most recent first), media, title and name of mentioned or interviewed person from the Neuro-SysMed nodes.

Dec. 17, 2024, Vogue: *Are Anti-Aging NAD+ Infusions Too Good to Be True?* Charalampos Tzoulis.

Dec. 12, 2024, Studvest: *Studenter og eldre skal bo side om side. - Som en italiensk landsby*. Bettina S. Husebø.

Dec. 9, 2024, Bergens Tidende: *Vil ha toppjobben igjen. Disse vil hun ha med seg*. Kjell-Morten Myhr.

Dec. 9, 2024, Khrono: *UiB-rektor stiller til valg med helt nytt rektorat.* Kjell-Morten Myhr.

Nov 28, 2024, Dagbladet: *Advarer: Øker demensrisikoen med 90 prosent*. Bettina S. Husebø.

Nov. 25, 2024, NRK: *Denne pulsklokka skal avsløra kva tid døden begynner: – Når er «point of no return»?* Bettina S. Husebø and Kamilla Haugland-Pruitt. As webnews article and news video at Dagsrevyen.

Nov. 13, 2024, På Høyden: *Fem UiB-miljøer søker SFI-status*. Charalampos Tzoulis, and Bettina S. Husebø.

Oct. 28, 2024, Aftenposten: *Dødshjelpdebatt på faglige premisser.* Opinion piece signed by 52 doctors and other health professionals, including Bettina S. Husebø.

Oct. 23, 2024, KK: *Medisin mot MS godkjent: - Veldig effektivt.* Øivind Torkildsen.

Oct. 19, 2024, Dagbladet: *Helt frisk - så kommer sjokket*. Ole-Bjørn Tysnes, ALS patient case.

Oct. 7, 2024, LMI: *Forskningsdagene 2024: Folkeopplysning om kliniske studier*. Kjell-Morten Myhr.


LMI

Forskningsdagene 2024:
Folkeopplysning om kliniske studier

Oct. 3, 2024, Health Talk: *Dette er de viktigste fremskrittene innen forskning på multippel sklerose (MS)*. Øivind Torkildsen.

Sep. 30, 2024, NTB Info: *Åpner nytt senter for sammensatte sykdommer og aldring*. Bettina Husebø.

Sep. 28, 2024, Fredriksstad Blad: *Fredrikstad MS-forening*. Kjell-Morten Myhr.

Sep. 27, 2024, NRK Innlandet: *Brukte 20 millioner kroner på et senter fagmiljøet ikke vil ha*. Ole-Bjørn Tysnes.

Sep. 20, 2024, Dagens Medisin: *Fikk «Young investigator award» for sitt bidrag på MS-kongress: – Veldig artig*. Brit Ellen Rød.

Sep. 19, 2024, Dagens Medisin: *MS-legemidler: - En vellykket norsk strategi*. Øivind Torkildsen.


Medisin

MS-legemidler: – En vellykket norsk strategi

– Vi ser en effekt som er mye større enn det som er vist tidligere, sier professor og overlege Øivind Torkildsen. Onsdag presenterte han baseline data fra OVERLORD-MS-studien på årets ECTRIMS kongress.

Sep. 19, 2024, Health Talk: *Nye fireårs-resultater på MS-medisin: - Dette er gode data*. Øivind Torkildsen.

Sep. 15, 2024, Bergensavisen: *Lokal seniorlandsby vekker oppsikt*. Bettina Husebø. Also in Fanaposten, Sep. 13, 2024. - *Her er det mye å hente inspirasjon fra. Den lokale seniorlandsbyen vekker oppsikt*.

Sep. 3, Helse Bergen News: *Haukeland stiller sterkt på Forskingsdagane 2024*. Neuro-SysMed.

Aug. 19, 2024, Health Talk: *MS-forskerne åpner for fremtidig kur - men det blir langt frem i tid*. Kjell-Morten Myhr og Øivind Torkildsen.


Health Talk Nyhetsbrev Podcast Annonsere

MS-forskerne åpner for fremtidig kur - men det blir langt frem i tid

Norske MS-eksperter trekker frem Norge som et foregangsland innen behandling av multippel sklerose (MS). Nå håper de at norsk forskning kan bidra til de neste fremskrittene innen behandling av sykdommen.

Jul. 30, 2024, Gudbrandsdølen Dagningen: *- Spennende å være med på utviklingen. Lovende framskritt i MS-behandling*. Lars Bø.


FRA ARKIVET

Lovende framskritt i MS-behandling: – Spennende å være med på utviklingen

Lars er med på å knekke MS-gåten

Lars Bø har forsket på MS siden 1998 og leder nå flere lovende forskningsprosjekter, inkludert en stor studie på stamcelletransplantasjon.

Jul. 4, 2024, LabioTech: *Parkinson's disease: biotech's pursuit for more therapies*. Charalampos Tzoulis.

Jul. 7, 2024, Fosna-Folket: - *Jeg lurte meg selv. Ingen skulle vite om den alvorlige sykdommen*. Lars Bø.

Jun. 17, 2024, Bergens Tidende: *Her kommer eldreboliger med plass til studenter. – Vi vil avlaste det offentlige*. Bettina Husebø.

Jun. 14, 2024, Helse Bergen News: *Gler seg over høg aktivitet ved Neuro-SysMed*. Kjell-Morten Myhr, Charalampos Tzoulis.

Jun. 7, 2024, UiB News: *Brukermedvirkning i kreftforskning er fremdeles under utvikling*. Neuro-SysMed course.

Jun. 7, 2024, Bergens Tidende: *Syv triks for å få et (nesten) evig liv*. Bettina Husebø.

Jun. 7, 2024, UiB News: *En viktig møteplass for brukere og forskere i medisinsk og helsefaglig forskning*. Neuro-SysMed course.

May 30, 2024, ImProntalaQuila.com: *Sclerosi multipla, ogni anno solo in Italia colpisce 3.600 persone*. Kjell-Morten Myhr. Same in 17 other Italian media.

May 29, 2024, ClicMedicina: *Congresso FISM 2024. Salute del cervello e prevenzione della sclerosi multipla. Nuovi criteri per diagnosi e trattamenti*. Kjell-Morten Myhr. Same in In Terris - News Online May 30, 2024, and in StraNotizie.it May 29, 2024.

May 28, 2024, Pledge Times: *Multiple Sclerosis Week, the Fism Congress on prevention and early diagnosis in Rome.* Kjell-Morten Myhr. Same article in 13 Italian media.

May 7, 2024, VG: *For Thea Marlene (23) endte kyssesyken i kronisk utmattelse*. Kjell-Morten Myhr, patient case.

Apr. 24, 2024, KK: *Gir nytt håp til MS-syke*. Øivind Torkildsen.

Apr. 23, 2024, NRK Vestland: *Trur på gjennombrot i Parkinsons-forsking*. Charalampos Tzoulis.

Apr. 17, 2024, UiB News: *Stor interesse for Fakultetets dag 2024*. Neuro-SysMed.

Apr. 12, 2024, UiB News: *Prisvinnere på Fakultetets dag 2024.* Kjell-Morten Myhr and the MS group, and Aurora Martinez.

Apr. 10, 2024, NRK: *Parkinsondagen*. Charalampos Tzoulis.

Apr. 10, 2024, UiB News: *Mottar 400 000 for kurs i brukermedvirkning i forskning*. Support for Neuro-SysMed course.

Apr. 5, 2024, Vi over 60: *MS kobles til virussykdom*. Øivind Torkildsen, Kjell-Morten Myhr.

Apr. 5, 2024, UiB News: *Ny æresdoktor håper å lage en vaksine mot MS.* Neuro-SysMed, Trond Riise.

Apr. 1, 2024, Dagens Medisin: *Natalizumab kan brukes som brobehandling*. Lars Bø.

Mar. 21, 2024, Shifter: *Sliter med å skape business av helseforskning*. Neuro-SysMed mentioned as worldleading research environment.

Mar. 15, 2024, JIMD Podcasts: *BH4 in tyrosine hydroxylase deficiency.* Kunwar Jung-KC.

Mar. 10, 2024, ABC Nyheter: *Hva er NMN-tilskudd, og virker det?* Charalampos Tzoulis.

Mar. 10, 2024, Østlands-Posten: *De lærde strides, og i midten står Erlend (48) med en alvorlig sykdom og et avslag fra kommunen*. Parkinson patient case, Charalampos Tzoulis.

Mar. 10, 2024, TV2: *Siri (73) vil bidra til å løse demensgåten*. Dementia patient case and Neuro-SysMed trial. Ragnhild Eide Skogseth and Kristoffer Haugarvoll.

Mar. 1, 2024, Vi over 60: *Medisiner kobles til Parkinson.* DRONE project, Trond Riise and Julia Romanowska. Also in Swedish newspapers in January, such as in Expressen.

Feb. 24, 2024, NRK Trøndelag: *Dette tror norske eksperter vil bli lyspunkt og gjennombrudd innen demensforskning i 2024*. Kristoffer Haugarvoll.

Feb. 20, 2024, Dagens Medisin: *Data fra «komplett negativ studie» brukt i 40 publikasjoner og seks doktorgrader.* Kjell-Morten Myhr, Øivind Torkildsen and Randi Haugstad.


Medisin

Data fra «komplett negativ studie» brukt i 40 publikasjoner og seks doktorgrader

Haukeland universitetssjukehus ble nylig stemplet som dårligst i Norge på publisering av resultater fra kliniske studier. Men bildet er ikke helsvart i Bergen.

Jan. 31, 2024, Khrono: *Disse skal dele ut milliarder til forskning.* Bettina Husebø appointed in the Health Portfolio Board for the Research Council of Norway.


Khrono

De skal dele ut milliarder til forskning. Her møtes de for første gang

Professor Terje Lohndal synes det er fryktinngytende å tenke på hvor mye forskningspenger han skal være med på å fordele.

Norges Parkinsonforbund, 2024: *Atypisk parkinsonisme og NAD: Nå kan du delta i behandlingsstudie*. Charalampos Tzoulis.


Norges Parkinsonforbund

Forside / Aktuelt / Atypisk parkinsonisme og NAD: Nå kan du delta i behandlingsstudie

Atypisk parkinsonisme og NAD: Nå kan du delta i behandlingsstudie

I 2024 starter professor Charalampos Haris Tzoulis og hans kollegaer ved Neuro-SysMed en ny behandlingsstudie for mennesker med atypisk parkinsonisme. Se opptak av nettmøte med mer informasjon.

EU-Openscreen Newsroom, 2024: EU-Openscreen (EU-OS) highlighted the success story on the impactful collaboration between Maria Macias and her team from IRB_Barcelona and the EU-Openscreen partner site, at the University of Bergen, Norway, with Aurora Martinez and Kunwar Jung K C, and the Chemistry Partner Site from Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany, with Marc Nazaré.

Axonet No. 2, 2024, page 20–21: *Arendalsuka, Debatt om fremtidens muligheter for MS-behandling* and *Debatt om kliniske studier*. Kjell-Morten Myhr.

PUBLICATION LIST 2024

Relevant publications from the Neuro-SysMed researchers in 2024.

1. Migraine in the multiple sclerosis prodrome: a prospective nationwide cohort study in pregnant women. **Eid K, Torkildsen Ø, Aarseth J, Cortese M, Holmøy T, Myhr KM, Riise T, Wergeland S, Gilhus NE, Bjørk MH.** *J Headache Pain*. 2024 Dec 23;25(1):225. doi: 10.1186/s10194-024-01941-w. PMID: 39710642.

2. Subcellular NAD+ pools are interconnected and buffered by mitochondrial NAD. **Høyland LE, VanLinden MR, Niere M, Strømland Ø, Sharma S, Dietze J, Tolås I, Lucena E, Bifulco E, Sverkeli LJ, Cimadamore-Werthein C, Ashrafi H, Haukanes KF, van der Hoeven B, Dölle C, Davidsen C, Pettersen IKN, Tronstad KJ, Mjøs SA, Hayat F, Makarov MV, Migaud ME, Heiland I, Ziegler M**. *Nat Metab*. 2024 Dec;6(12):2319-2337. doi: 10.1038/s42255-024-01174-w. Epub 2024 Dec 13. PMID: 39702414.

3. Effect of alemtuzumab on fatigue, quality of life, and patient/caregiver-reported outcomes in relapsing-remitting multiple sclerosis-A real-world evidence study. **Frederiksen JL, Massacesi L, Nielsen HH, Rini A, Baldi E, Mirabella M, Antonella FFM, Lus G, Paolicelli D, Kant M, Salemi G, Aguglia U, Comi C, De Riz M, Barcella V, Flemmen HØ, Protti A, Farbu E, van Exel J, Torkildsen Ø.** *Mult Scler Relat Disord*. 2025 Jan;93:106214. doi: 10.1016/j.msard.2024.106214. Epub 2024 Dec 3.PMID: 39642455.

4. Single-nucleus transcriptomics reveals disease- and pathology-specific signatures in α-synucleinopathies. **Nido GS, Castelli M, Mostafavi S, Rubiolo A, Shadad O, Alves G, Tysnes OB, Dölle C, Tzoulis C**. *Brain*. 2024 Nov 15:awae355. doi: 10.1093/brain/awae355. Online ahead of print. PMID: 39546628.

5. Risk factors and evolution of weight loss in Parkinson's disease: A 9-year population-based study. **Kristiansen I, Hiorth YH, Ushakova A, Tysnes OB, Alves G**. *Parkinsonism Relat Disord*. 2024 Dec;129:107181. doi: 10.1016/j.parkreldis.2024.107181. Epub 2024 Oct 22. PMID: 39486154.

6. Safety and efficacy of evobrutinib in relapsing multiple sclerosis (evolutionRMS1 and evolutionRMS2): two multicentre, randomised, double-blind, active-controlled, phase 3 trials. **Montalban X, Vermersch P, Arnold DL, Bar-Or A, Cree BAC, Cross AH, Kubala Havrdova E, Kappos L, Stuve O, Wiendl H, Wolinsky JS, Dahlke F, Le Bolay C, Shen Loo L, Gopalakrishnan S, Hyvert Y, Javor A, Guehring H, Tenenbaum N, Tomic D; evolutionRMS investigators (Torkildsen).** *Lancet Neurol*. 2024 Nov;23(11):1119-1132. doi: 10.1016/S1474-4422(24)00328-4. Epub 2024 Sep 19.PMID: 39307151 Clinical Trial.

7. Molecular landscape of the overlap between Alzheimer's disease and somatic insulin-related diseases. **Ruisch IH, Widomska J, De Witte W, Mota NR, Fanelli G, Van Gils V, Jansen WJ, Vos SJB, Fóthi A, Barta C, Berkel S, Alam KA, Martinez A, Haavik J, O'Leary A, Slattery D, Sullivan M, Glennon J, Buitelaar JK, Bralten J, Franke B, Poelmans G**. *Alzheimers Res Ther*. 2024 Oct 28;16(1):239. doi: 10.1186/s13195-024-01609-2. PMID: 39465382.

8. Harmonized Data Quality Indicators Maintain Data Quality in Long-Term Safety Studies Using Multiple Sclerosis Registries/Data Sources: Experience from the CLARION Study. **Hillert J, Butzkueven H, Magyari M, Wergeland S, Moore N, Soilu-Hänninen M, Ziemssen T, Kuhle J, Pontieri L, Forsberg L, Aarseth JH, Zhu C, Sicignano N, Mushnikov V, Bezemer I, Sabidó M.** *Clin Epidemiol*. 2024 Oct 17;16:717-732. doi: 10.2147/CLEP.S480525. eCollection 2024. PMID: 39435029.

9. The Therapeutic Potential of Exosomes from Mesenchymal Stem Cells in Multiple Sclerosis. **Kråkenes T, Sandvik CE, Ytterdal M, Gavasso S, Evjenth EC, Bø L, Kvistad CE**. Int J Mol Sci. 2024 Sep 24;25(19):10292. doi: 10.3390/ijms251910292. PMID: 39408622. Review.

10. The recurrence of disease activity after ocrelizumab discontinuation in multiple sclerosis. **Coerver E, Schoof L, Hogenboom L, Wessels M, van Ruyven P, van Samkar A, Mostert J, van Kempen Z, van Oosten BW, Wokke BH, Tallantyre E, Myhr KM, Torkildsen O, Killestein J, Smets I, Strijbis E.** *Mult Scler Relat Disord.* 2024 Nov;91:105900. doi: 10.1016/j.msard.2024.105900. Epub 2024 Sep 28. PMID: 39369631.

11. Amyotrophic lateral sclerosis caused by the C9orf72 expansion in Norway - prevalence, ancestry, clinical characteristics and sociodemographic status. **Olsen CG, Malmberg VN, Fahlström M, Alstadhaug KB, Bjørnå IK, Braathen GJ, Bråthen G, Demic N, Hallerstig E, Hogenesch I, Horn MA, Kampman MT, Kleveland G, Ljøstad U, Maniaol A, Morsund ÅH, Nakken O, Schlüter K, Schuler S, Seim E, Flemmen HØ, Tysnes OB, Holmøy T, Høyer H**. *Amyotroph Lateral Scler Frontotemporal Degener.* 2025 Feb; 26(1-2):132-140. doi: 10.1080/21678421.2024.2405118.Epub 2024 Sep 24. PMID: 39316038.

12. TPPU_DSF: A Web Application to Calculate Thermodynamic Parameters Using DSF Data. **Martin-Malpartida P, Torner C, Martinez A, Macias MJ**. *J Mol Biol*. 2024 Sep 1;436(17):168519. doi: 10.1016/j.jmb.2024.168519. Epub 2024 Mar 6. PMID: 39237200

13. Brain Proteome Profiling Reveals Common and Divergent Signatures in Parkinson's Disease, Multiple System Atrophy, and Progressive Supranuclear Palsy. **Dick F, Johanson GAS, Tysnes OB, Alves G, Dölle C, Tzoulis C**. *Mol Neurobiol.* 2025 Mar;62(3):2801-2816. doi: 10.1007/s12035-024-04422-y. Epub 2024 Aug 21. PMID: 39164482.

14. Serum neurofilament light at diagnosis: a prognostic indicator for accelerated disease progression in Parkinson's Disease. **Pedersen CC, Ushakova A, Alves G, Tysnes OB, Blennow K, Zetterberg H, Maple-Grødem J, Lange J.** *NPJ Parkinsons Dis*. 2024 Aug 21;10(1):162. doi: 10.1038/s41531-024-00768-1. PMID: 3916426.

15. Orthostatic Hypotension and Risk of Mild Cognitive Impairment and Dementia in Parkinson's Disease. **Hiorth YH, Schulz J, Pedersen KF, Tysnes OB, Alves G.** *Mov Disord Clin Pract*. 2024 Nov;11(11):1365-1372. doi: 10.1002/mdc3.14179. Epub 2024 Aug 6. PMID: 39108067.

16. Hospitalisations and humoral COVID-19 vaccine response in vaccinated rituximab-treated multiple sclerosis patients. T**orgauten HM, Onyango TB, Ljostveit S, Hallin EI, Serkland TT, Skrede S, Langeland N, Cox RJ, Wergeland S, Myhr KM, Torkildsen Ø.** *Mult Scler Relat Disord*. 2024 Sep;89:105770. doi: 10.1016/j.msard.2024.105770. Epub 2024 Jul 15. PMID: 39029342.

17. Automated cell type annotation and exploration of single-cell signaling dynamics using mass cytometry. **Kleftogiannis D, Gavasso S, Tislevoll BS, van der Meer N, Motzfeldt IKF, Hellesøy M, Gullaksen SE, Griessinger E, Fagerholt O, Lenartova A, Fløisand Y, Schuringa JJ, Gjertsen BT, Jonassen I.** *iScience*. 2024 Jun 12;27(7):110261. doi: 10.1016/j.isci.2024.110261. eCollection 2024 Jul 19. PMID: 39021803.

18. Significance of utilizing in silico structural analysis and phenotypic data to characterize phenylalanine hydroxylase variants: A PAH landscape. **Himmelreich N, Ramón-Maiques S, Navarrete R, Castejon-Fernandez N, Garbade SF, Martinez A, Desviat LR, Pérez B, Blau N**. *Mol Genet Metab.* 2024 Jul;142(3):108514. doi: 10.1016/j.ymgme.2024.108514. Epub 2024 Jun 13. PMID: 38905920.

19. Activation of Neurotoxic Astrocytes Due to Mitochondrial Dysfunction Triggered by POLG Mutation. **Liang KX, Chen A, Kianian A, Kristiansen CK, Yangzom T, Furriol J, Høyland LE, Ziegler M, Kråkenes T, Tzoulis C, Fang EF, Sullivan GJ, Bindoff LA.** *Int J Biol Sci.* 2024 May 11;20(8):2860-2880. doi: 10.7150/ijbs.93445. eCollection 2024. PMID: 38904024.

20. Dopamine synthesis and transport: current and novel therapeutics for parkinsonisms. **Tai MDS, Gamiz-Arco G, Martinez A.** *Biochem Soc Trans*. 2024 Jun 26;52(3):1275-1291. doi: 10.1042/BST20231061. PMID: 38813865. Review.

21. Neural regeneration in the human central nervous system-from understanding the underlying mechanisms to developing treatments. Where do we stand today? **Kvistad CE, Kråkenes T, Gavasso S, Bø L.** *Front Neurol*. 2024 May 9;15:1398089. doi: 10.3389/fneur.2024.1398089. eCollection 2024. PMID: 38803647. Review.

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PERSONNEL LIST 2024

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Jan Aarseth	MS Node	Researcher, MS Registry
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Karine Eid	MS Node	PhD Candidate
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Sonia Gavasso	MS Node	Researcher
Andrea Habbestad	MS Node	PhD Candidate
Randi Haugstad	MS Node	Study Nurse
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Ida Herdlevær	MS Node	Postdoc
Max Korbmacher	MS Node	Researcher
Torbjørn Kråkenes	MS Node	Researcher
Christopher Elnan Kvistad	MS Node	Researcher
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Brit Ellen Rød	MS Node	PhD Candidate
Liv Marie Rønhovde	MS Node	PhD Candidate
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Ellen Skorve	MS Node	PhD Candidate
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Amy van den Hooven	MS Node	PhD Candidate
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Christian Dölle	PD Node	Researcher
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Liv Toril Møen	Dementia Node	Clinician
Amr Ahmed Mahmoud Ahmed Omara	Dementia Node	Clinician
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Kristina Skeie	Dementia Node	Study Nurse
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Kamilla Pruitt Haugland	Care Node	Postdoc
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Tanja Lukkari	Care Node	Research Nurse
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Anders Engeland	Drug Discovery Node, *in silico*	Professor
Jannicke Igland	Drug Discovery Node, *in silico*	Associate Professor
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Ines Heiland	Metabolomics	Professor
Suraj Sharma	Metabolomics	Researcher
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Caroline Engen	RRI/PPI Node co-leader	Postdoc

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Yamila Torres Cleuren	Research management	Head of Research and Innovation
Elisabeth Evjenth	Lab/research support	Technician and Medication Coordinator
Marianne Flatebø	Administration	Trial Coordinator
Liesbeth Kroondijk	Lab/research support	Research Technician
Mona Machrouh	Administration	Centre and Project Coordinator
Yana Mikhaleva	Lab/research support	Research Technician
Sepideh Mostafavi	Lab/research support	Researcher
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Cecilie Totland	Lab/research support	Researcher
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