Neuro-SysMed

Centres for Clinical Treatment Research

ANNUAL REPORT 2022

A centre for clinical treatment research
on neurological diseases

CONTENT

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Directors' Comments

2022 has been a highly successful and productive year for Neuro-SysMed. The results of our first completed clinical trial, NADPARK, were published early this year and are generating major international attention. The study, which was conducted by the Parkinson's disease (PD) Node under the leadership of Professor Tzoulis, showed that 30 days of treatment with oral nicotinamide riboside (NR) increased nicotinamide adenine dinucleotide (NAD) levels in the brain, and altered cerebral metabolism, associated with clinical improvement in individuals with early-stage PD. These encouraging findings have nominated NAD-replenishment as a potential neuroprotective strategy for PD, and have set the foundations for multiple ongoing trials with NAD precursors at our Centre. This includes the phase II NO-PARK study, which has already included more than half of its target population of 400 participants.

Another important milestone of the Centre was completion of the recruitment phase of the OVERLORD-MS study, which compares the efficacy of rituximab and ocrelizumab in newly diagnosed, treatment naïve patients with multiple sclerosis (MS). Torkildsen and colleagues at 12 hospitals in Norway and Sweden included 214 patients within the pre-planned two-year inclusion period. The patients will be followed for two and a half years, meaning that results are expected to be published in 2025.

Our flagship ALS study, the NO-ALS trial, has included more than half its target population of 180 patients, across 13 hospitals in Norway. Moreover, our first trial in dementia has started: the N-DOSE-AD study is a phase II randomized blinded dose optimization trial, aiming to determine the optimal biological dose of NR in Alzheimer's disease. Altogether, Neuro-SysMed is currently approaching inclusion of approximately 1200 patients across 20 interventional trials and 10 observational trials, including more than 20 hospitals in Norway, Sweden, Denmark, and the Netherlands. While these numbers also include participation in approximately 15 trials sponsored by the pharmaceutical industry, the vast majority of participants (> 80%) are enrolled in investigator-driven trials.

The recently published scientific paper on the role of the Epstein-Barr virus (EBV) in MS, by Bjørnevik and Cortese et al., who are both alumni of the MS-group, was also greatly celebrated at Neuro-SysMed in 2022. The Harvard-based group showed that previous EBV infection, in a complex interplay with other risk factors, is probably required for the future development of MS. This finding has led to intense research on the importance of EBV for the development of the disease, as well as a potential treatment target for prevention and disease modulation. Neuro-SysMed are currently leading several initiatives on this topic, with exciting perspectives of new treatment targets in MS.

Establishing the national NorTrials platform, of which the Brain Health Centre is closely associated with Neuro-SysMed, was yet another important milestone during 2022. NorTrials is based on a partnership between the regional health authorities and the organisations for the pharmaceutical and medical device industries, and aims to attract multi-centre international industry sponsored trials to Norway, thereby rendering new treatments early available for Norwegian patients. We have high expectations that this initiative will increase the number of clinical trials in Norway. Still, to maximize the accessibility of clinical trials to Norwegian patients and healthcare professionals, we need to establish better information-platforms. This will be critical for achieving future recruitment goals for academia- and industry-sponsored studies alike. To meet this challenge, Neuro-SysMed and partners will further develop our own information platform, MedHjelper: https://medhjelper.com/.

Securing external funding is crucial for both ongoing and new developments at the centre. We are therefore happy that several researchers at Neuro-SysMed successfully obtained new external funding during 2022, covering all our diseases and strengthening our research portfolio. We have also recruited several talented young researchers during the past year and have continued to develop and widen our Research School activities, further supporting our early career researchers.

Looking back at 2022, we cannot help but feel content and inspired by what has been achieved by our Centre. At the same time, we look ahead in excitement and optimism, ready to meet the challenges of improving healthcare for brain diseases.

Kjell-Morten Myhr
Neuro-SysMed Director

Charalampos Tzoulis
Neuro-SysMed Co-Director

Vision and Goals

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

The overarching aim of Neuro-SysMed is to develop new and/or improved treatments and treatment strategies for our patients. The Centre facilitates early access to such new therapies for patients across Norway through participation in national and international randomized clinical trials.

"Our ultimate goal is to lower the burden of disease"

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

More specifically, Neuro-SysMed continues to work towards:

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

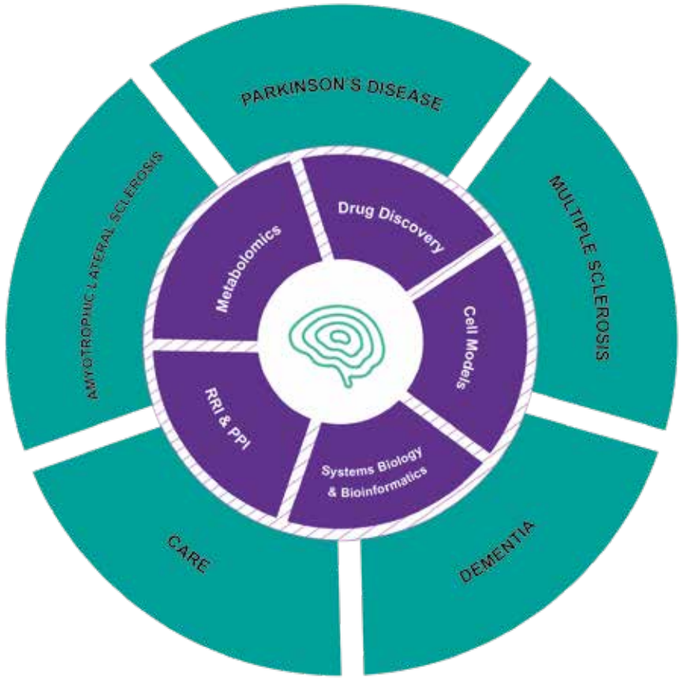
Research Plan and Strategy

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

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

In terms of systems medicine, our Parkinson's disease (PD) team is setting up the path for others to follow, with the ParkOme project having mapped molecular profiles from tissue samples of more than 1,300 brains of deceased patients with PD and other neurodegenerative diseases – the largest brain omics database for PD in the world. From this study, a new subtype of PD has been identified, expected to be published during 2023. Work to develop clinical biomarkers is ongoing in all four diseases. Several cell models have been developed and are being used to screen and discover new treatments. We are also well underway with our in-silico drug screening, based on the national Norwegian registries.

To better visualize the activities going across the numerous research groups involved in Neuro-SysMed, we have organized these into 10 research nodes as described from page 32.



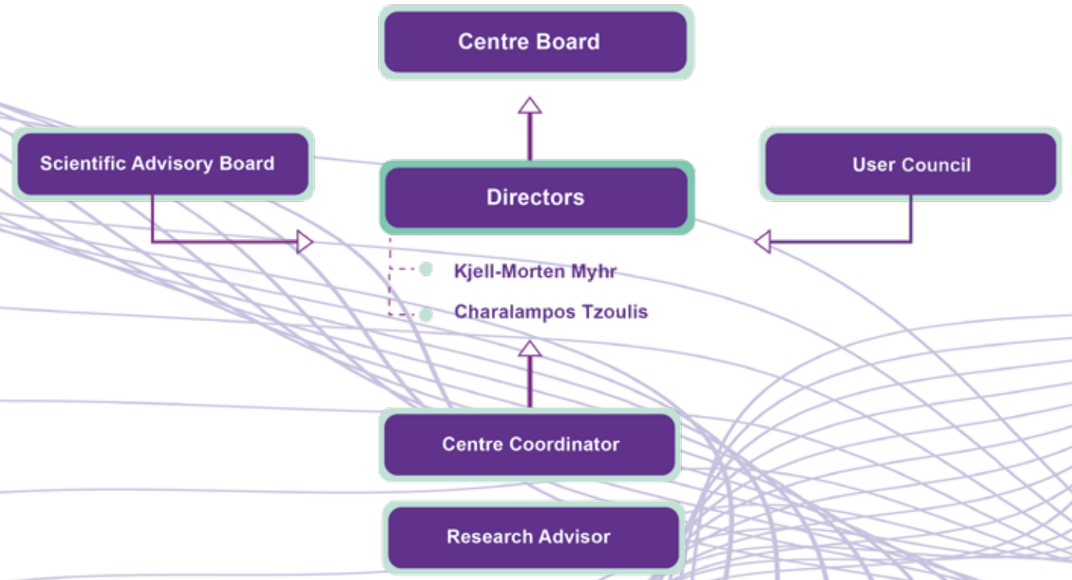
Organization of the Centre

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

Organizational structure

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

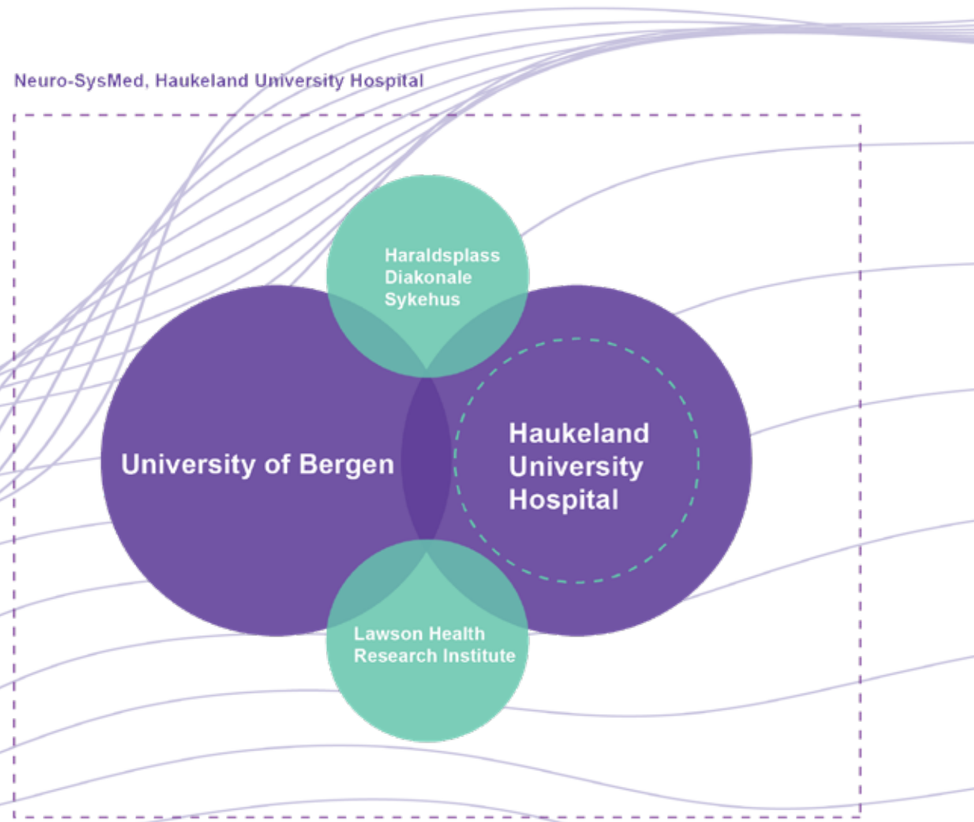
The **Centre Board** includes members from the host and partner institutions. The board is chaired by Professor Per Bakke, Dean of the Medical Faculty, UiB, and the other board members are Eivind Hansen, Chief Executive Officer (CEO) of HUH, Torhild Næss Vedeler, Director of the Neurology Clinic, HUH,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



Cooperation between partners

Most of the work is physically located at the Haukeland medical campus (HUH, UiB, HDS). The Neuro-SysMed researchers work across departments and institutions using their resources and facilities. The Neuro-SysMed laboratory, administration, most offices, and most of the clinical work are located at the Neurology Clinic, HUH. In addition, resources such as imaging, bio-banking, stem cell facilities, core facilities at The Medical Faculty, including animal facilities, and biostatisticians, among others, are available for Neuro-SysMed at all three institutions in Bergen. This close co-localization allows for close interactions between the research groups to work towards shared projects and goals. Each research group has weekly meetings and often invite members from other groups to take part in scientific discussions, often pertaining to the different research nodes. After the challenging COVID pandemic waves, we were able to start our seminar series in 2022 as well as a small symposium in clinical trials design, providing crucial meeting points for scientific discussions and cooperation for all Centre members, students and interested collaborators.

The Lawson Health Research Institute is involved in the research related to Parkinson's disease and cooperates with the other partners in that field. Regular digital meetings have been carried out with the teams at Lawson, and since mid-2022, physical research visits have been resumed.



Core Centre Personnel and Facilities

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

The Neuro-SysMed laboratory

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

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

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

The ***computational unit*** comprises five expert *bioinformaticians*, including a *Data Manager* who performs a complete range of big data analyses – from raw-data pre-processing to sophisticated supervised and unsupervised analytical approaches. Most of the data storage and computational work takes place on the innovative cloud-based data-cluster of Neuro-SysMed, developed in collaboration with the Helse Vest IT Department and Microsoft Azure.

Clinical Trials Unit

> "At the heart of Neuro-SysMed are the clinical trials. In 2022, the Centre had 26 investigator-initiated trials in addition to 14 industry sponsored trials"

To administer this substantial number of trials, we have two *trial coordinators* as part of our core team, in addition to our ten *research nurses*. Practical planning of the clinical trials (including protocols, ethics approvals, site recruitment, monitoring, etc.), patient recruitment and execution, data monitoring and analysis are coordinated by our clinical trials unit together with the PI of each study. We have a dedicated ***medicine room***, administered by our trial coordinators for the storage, packaging, and labelling of trial medications. The unit plans trials initiated by Neuro-SysMed PIs in collaboration with external investigators or the industry, enabling patient participation in national and international multi-centre trials. The Research and Development Department at Haukeland University Hospital assists in coordinating and negotiating industry-sponsored clinical studies.

The role of the trial coordinators

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

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

The importance of Neuro-SysMed research nurses

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

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

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

Neuro-SysMed administration

In addition to the personnel actively involved with the lab, data, and clinical trials coordination and management, Neuro-SysMed has a dedicated *Centre Coordinator, Research Advisor, Communications Officer*, and a *Research School Coordinator*. The administration is further supported the by administrative teams from the host and partner institutions.

Research Advice & Project Development

During 2022, Neuro-SysMed has experienced a very high level of research activity in the Centre, and this has benefitted not only the research output, but also the successful development of new projects, resulting in excellent external funding recruitment throughout the year.

Responsible for this support function: Senior Advisor Yamila Torres Cleuren

After two years of interrupted activity due to the pandemic, this year has allowed the groups to catch up on planned activities. The Centre has been building connections and consortia during this time, and we are now starting to see the results in the shape of increased collaborations (both national and international) and increased funding to our projects. Our highly interdisciplinary set-up allows us to design projects across the research groups, taking advantage of the different expertise available.

"An asset for our Centre is the work across the diseases; findings from one disease are being translated into the others (e.g., from PD to ALS, dementia, and MS), and we have developed new laboratory and clinical trial projects thanks to the interactions between the research groups"

In addition, big efforts have gone towards European grants, which we see as long-term aims of the research at the Centre, as well as towards increasing the visibility of the Centre. This is crucial for the success of our clinical trials, and to ensure that our projects go beyond national borders, increasing not only our national but our international collaborations.

In 2022, we have continued to receive external funding from our Regional Health Authorities (Helse Vest) in PhD projects, postdocs, short-term projects, a clinical career grant and open project support for our clinical and translational projects; from KLINBEFORSK, we have secured funding for another national ALS trial focusing on the effects of long-term ventilation support on the quality of life for ALS patients and their families; and funding from private donors and foundations, providing invaluable support for our projects especially in the start-up phase. In addition, we have secured 5 MNOK in funding from the Norwegian Research Council for the first commercialization project to come from Neuro-SysMed, on the use of NAD boosting to treat Parkinson's disease.

Professor Tzoulis and Senior Researcher Irene Flønes secured international funding from the Michael J. Fox Foundation's "Biomarkers to Support Therapeutic Trials Program," to a project aiming to identify a novel subtype of Parkinson's disease driven by mitochondrial dysfunction, and to develop clinically applicable biomarkers enabling patient selection for targeted therapeutic trials. Getting this funding is a great boost for our teams and a sign of Neuro-SysMed research reaching the international stage.

Support for early career researchers

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

– Yamila Torres Cleuren,

Senior Advisor.

A highlight in 2022 was the Helse Vest Clinical Career Grant to one of postdoctoral fellows, Christopher Kvistad, showing the calibre of our young researchers and the exciting research that they do. Christopher was awarded with a 4-year clinical career fellowship for the project "Harnessing the full neuroregenerative potential of mesenchymal stem cells (NEURO-MSC)". He will use this career grant to set up his node research node and build his own independent research.

User Council

Neuro-SysMed established a User Council ultimo 2019, serving as an advisory body with representatives from all the relevant patient organizations, with two representatives per disease group.

The importance of the user voice in research

User participation and user involvement in research and innovation processes is about letting those who know the needs be part of shaping the agenda. There is an explicit expectation that research projects should take advantage of the experience and knowledge built by those who live with or near the patient – those who can closely observe how the disease progresses and what the day-to-day life is like for those living with the diagnosis. User involvement is an approach for making certain that this competence and this perspective has a natural place and voice in the research projects. The user perspective can be useful both 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 diagnosis. When funding research and innovation projects, the government expects user experience and knowledge to be taken into account to a larger degree. 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 User Council was elected for two years of service in October 2021. Neuro-SysMed is perceived to still be in a start-up phase. There have already been some replacements in the User Council due to internal changes in the user organizations.

Meetings in 2022

In 2022, there were two meetings. The April meeting was a one-day meeting, while the autumn meeting was held over two days as a workshop. The participants were very pleased with this meeting format, allowing them time to get to know each other and the researchers, as well as more time to discuss the issues at hand.

Members of the User Council

- **Lise Johnsen, Norwegian MS Society (Chair)**
- **Trine Lise Corneliussen, Norwegian Parkinson Association (Vice-Chair)**
- **Gudrun Østhassel, Norwegian MS Society**
- **Ragnhild Stenshjemmet Støkket, Norwegian Parkinson Association**
- **Mirjeta Emini, National Association for Public Health**
- **Kristin Reimers Kardel, National Association for Public Health**
- **Marit Stensen, ALS Norway**
- **Gry Lien, ALS "Alltid Litt Sterkere"**
- **Ditte Staldgaard, National Association for Public Health (deputy)**
- **Mona Bahus, ALS Norway (deputy)**
- **Therese Asbjørnsen, ALS "Alltid Litt Sterkere" (deputy)**
- **Magne Wang Fredriksen, Norwegian MS Society (deputy)**

What do we seek to achieve?

According to our mandate, the User Council works to:

- Be a link between users and the Centre
- Contribute with knowledge and experience from a user perspective to the research
- Represent the User Council at various events
- Work for political attention to the work of the Centre and increased funding of research related to neurodegenerative diseases in general
- Contribute towards good principles for user involvement

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

- Identify current topics or challenges
- Contribute to improved research design
- Contribute to better recruitment of patients and their participation while there
- Contribute to the dissemination of research results
- Give feedback on language, how to present the message, and on dissemination channels
- Bring in new perspectives in the analysis of results

Courses for researchers and user representatives during the fall of 2022

"User participation in medical research" is a three-day course arranged by the Centre, with Tone Skår and Nina Louise Jebsen as responsible. The course aims to facilitate user involvement in medical research and consists of lectures, group assignments and discussions. The course took place in 2022 in November, well attended by both researchers and user representatives. Several of the User Council members participated.

Status of the cooperation 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, and all agree that our organizations should be involved in the development of the Centre. Even so, our processes are still in a phase where we are trying to find the best framework for our cooperation and establish ways of user contributions.

– Lise Johnsen, User Council Chair

Lise Johnsen, User Council Chair and member of the Norwegian MS Society, Heidi Anita Andreassen, living with ALS, and Gry Lien, member of the User Council and board member of the ALS Association Alltid Litt Sterkere, providing their perspectives at the Neuro-SysMed/CCBIO User participation course in 2022. Photo by Nina G. Torkildsen.

Finances and Gender Balance

As it did in 2020-2021, the COVID-19 pandemic affected the Centre's activities in early 2022, but we were soon able to increase our activity levels as planned. This is also reflected in the amount of funding used throughout the year and our success in recruiting new researchers and personnel for our projects.

Neuro-SysMed funding

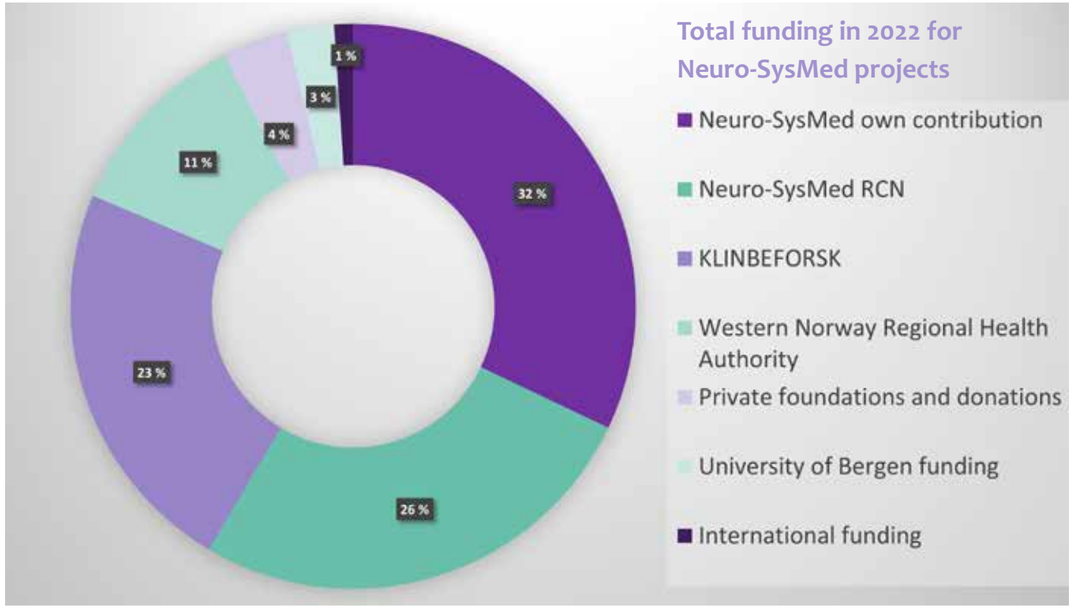
Neuro-SysMed was awarded 160 MNOK in funding from the Norwegian Research Council (RCN), which was matched with 160 MNOK in own contribution from the consortium (Haukeland University Hospital, University of Bergen, Haraldsplass Deaconess Hospital, and the Lawson Health Research Institute in London, Ontario), for the eight-year duration of the Centre (2019-2027).

Funding in 2022

In 2022, Neuro-SysMed core funding resulted in 54.3 MNOK, of which 24.5 MNOK were from the Norwegian Research Council and 29.7 MNOK were own contribution from the consortium. The Centre currently has 23 investigator-initiated clinical trials, running or in preparation, in addition to the translational research projects, which requires large resources in terms of personnel, infrastructure and running costs. Altogether, we have so far successfully obtained over 300 MNOK in additional external funding for these activities since the project start in autumn 2019.

Funds used in 2022

In 2022, a total of 92.5 MNOK were spent on Neuro-SysMed projects, of which 42% were from additional external funding (Figure 1 – total spending in 2022 in Neuro-SysMed projects). The KLINBEFORSK program, funded by the regional health trusts, is the largest external funding contributor, followed by the Western Norway Regional Health Authority and various private sponsors. In addition, we have several University of Bergen funded PhD positions and innovation projects (UiB Idé), and international funding.



Gender distribution

Of 159 people in Neuro-SysMed in 2022, 96 are females and 63 are male. Of our PhD candidates and postdoctoral researchers, 29 are female and 26 are male. Of our MSc and medical students, 13 are female and 8 are male. We find that there is gender balance in the clinicians working at the Centre, while all nurses are women, as are most technicians and administrative staff.

Steps taken towards gender balance

While there is a majority of female employees (~60%), they are in minority in leadership positions – a common challenge in academia. Therefore, we have made efforts on career-building workshops and individual advise, including support for the larger fellowship and research project grant applications. This work is being led by our research advisor, with support from the Centre's research node leaders. The advice is tailored to the biomedical and clinical researchers, as they meet very differing career challenges. While this initiative benefits everyone, we address the special challenges that women face in their academic career advancements. These efforts are reflected in an increase of publications with female senior/last authorship, increased successful research funding, and an increase of supervisory roles of the female researchers.

Innovation

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

We have integrated innovative approaches to our clinical trials and translational research. This is reflected in the activities we have been organizing for our students (a four ECTS PhD course in health innovation in collaboration with CCBIO, started in 2021) and a Symposium on Clinical Trials Design, aimed at encouraging new methodological and design approaches to overcome the obstacles hampering therapeutic breakthroughs in neurological diseases.

Our Research Advisor, together with the innovation advisors in our host and partner institutions, works closely with our PIs and researchers in mapping out their activities and plans to identify potential new projects and ideas. Part of our strategic planning is to support their project development with research applications, commercialization, and Intellectual Property strategy discussions (together with our technology transfer office, VIS), or support to develop proof-of-concept ideas.

Two examples of innovative projects coming from our researchers would be our **DIGI.PARK research project** in which sensor and tracking technologies are used in order to better understand Parkinson's disease, bringing together mathematicians, clinicians, patients, and other experts; and **the "Communicating Cognitive Decline" (CCD)** project where Amy van der Hooven's tactile and visual toolkit was set to be tested to better communicate and assess cognitive decline. This was a combined effort with researchers from the design discipline, clinicians, patients, and RRI experts. These two examples are representative of Neuro-SysMed's approach to work with projects across disciplines and to involve users directly in the development of new tools.

Neuro-SysMed has strong collaborations with industry. Two such examples would be the projects with **Otivio** and **Project Ipsilon**. The Norwegian company Otivio has developed a medical device that increases blood circulation in the lower extremities, called "FlowOx". Based on anecdotal reports of pain and spasticity relief in MS by using the device, the Centre has performed a pilot study aiming at validation of these reports. Positive results from the pilot are currently further extended into a larger placebo-controlled phase 2 trial. The Dutch-Japanese technology company Project Ipsilon has developed a tablet-based software application that aims to measure several indicators of neurological damage, including increased response time and loss of accuracy. The centre will license this application in the STRAT-PARK study to evaluate whether it is suitable to detect early cognitive decline in this patient population. If successful, this will be a valuable tool to evaluate outcome measures in clinical trials for several of the Centre's disease programs and may even be useful in rehabilitation therapy. The Centre has continued the process of establishing a state-of-the-art online storage and analysis solution in cooperation with **Helse Vest IT**, **Capgemini** and **Microsoft**. This resource is now available to all the research groups at the Centre and is administered by a dedicated Data Manager.

Visual and tactile communication tool kit designed by Amy van den Hooven, designer and creator of the Open Pain Lab. The tool kit can be used by patients, caregivers, medical professionals and researchers to better explain and understand illness experiences of different diseases within Neuro-SysMed.

From the Neuro-SysMed Centre Board



Text by Per Bakke (Dean, Faculty of Medicine, University of Bergen), Kjerstin Fyllingen (CEO of Haraldsplass Deaconess Hospital) and Eivind Hansen (CEO of Haukeland University Hospital)

A shared responsibility

As a Centre for Clinical Treatment Research (FKB), Neuro-SysMed is part of the authorities' commitment to clinical trials as an integral part of the treatment that is offered to Norwegian patients. Such studies can contribute to novel treatment of conditions with no therapeutic options, or to improving and supplementing existing treatment options.

In addition to the establishment of the FKB program, the national program KLINBEFORSK for clinical treatment research in the specialist health services is also a part of the authorities' initiative. This program supports national clinical trials of high quality with predictable funding.

The national action plan for clinical trials aims for 5% of chronic disease patients in the specialist health services to participate in clinical treatment studies. Large national researcher-initiated studies will be an important prerequisite for us to achieve this objective. This also requires that arrangements are made for good recruitment to such studies, primarily of participating patients, but equally important also for qualified study personnel including doctors and nurses. Our hospitals and educational institutions must therefore facilitate this, find the time and ensure good and effective support systems and career paths for doctors, nurses and others who want to work with clinical trials. Funding schemes, regulations, approval schemes and IT systems that support systematic building of knowledge integrated as a natural part of patient care, must also be established, and developed.

This creates a unique interaction arena for the universities, colleges and hospitals in both education and research, for the benefit of the patients. Clinical trials should be implemented as part of both basic and specialist education in the health services. This would also provide a unique opportunity to link the basic research environments to the clinical environments for the development of translational projects on ground-breaking innovations.

High recruitment rates for clinical trials also requires knowledge and easily available information on current studies. Patients and relatives must be able to easily search for information on relevant studies for the disease in question. At the same time, healthcare personnel must, in a busy everyday life, be able to easily look up corresponding information to find relevant studies for their patient.

In some cases, this will require a cultural change in the health services – creating the idea that all patients might benefit from participation in a clinical study.

The hospitals and their clinical departments have the responsibility to offer their patients participation in clinical trials. To achieve this, it is important to build infrastructures that support participation, both through investments in the study nurse services as well as making it possible for doctors to participate in current studies. The hospitals have a shared national responsibility for achieving the 5% target, and every hospital must therefore facilitate and stimulate the initiation of their own studies with an invitation for national participation. However, equally important is joining initiatives and accepting invitations from other hospitals.

Text by Caroline Engen, Postdoc at Neuro-SysMed, SVT, UiB

On knowing the patient

"The good physician treats the disease; the great physician treats the patient who has the disease"

- Sir William Osler (1849-1919)

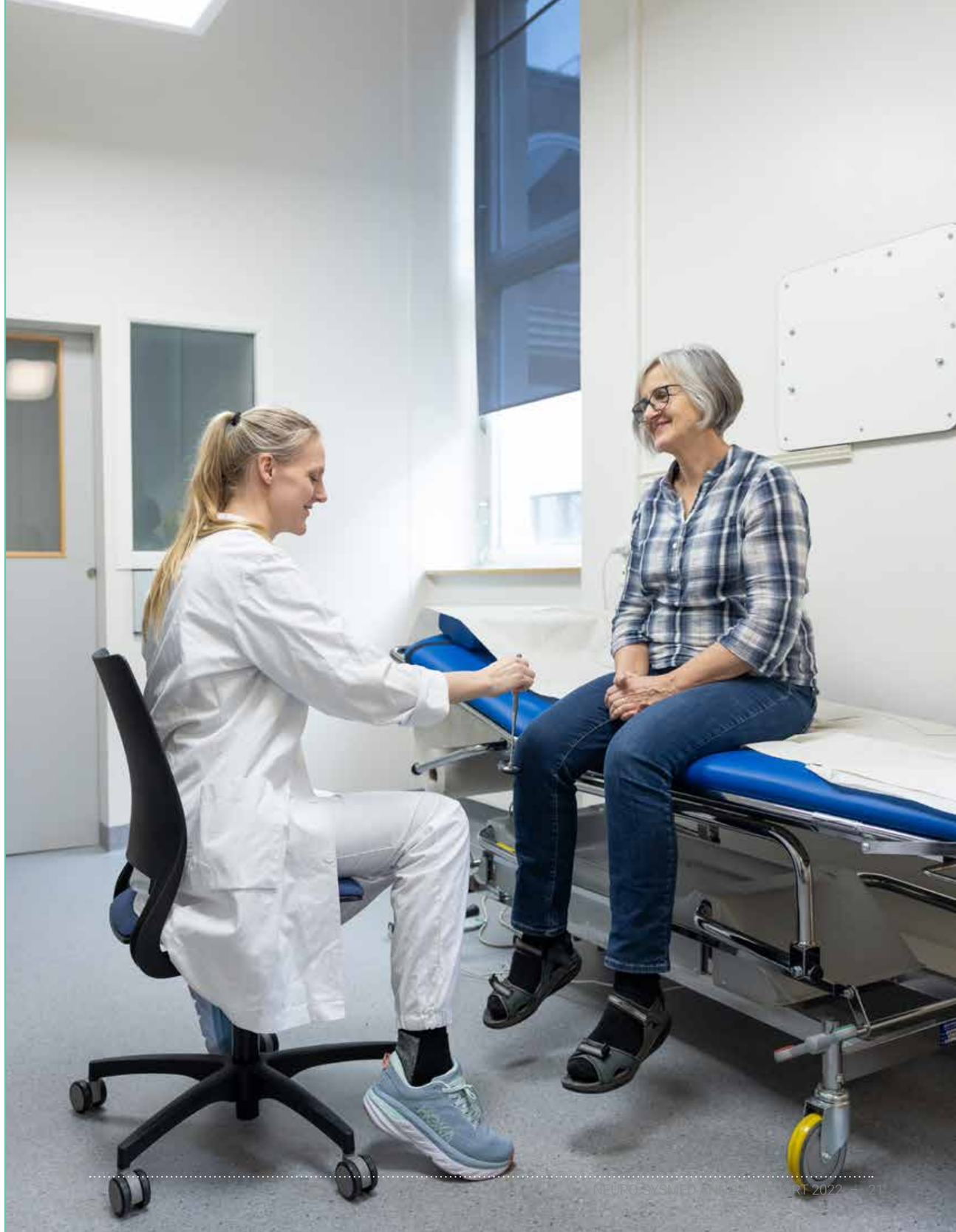
Patient-centredness is the very essence and ethos of medicine. How patient-centredness is understood, and how it is practiced, relates to ways of knowing in medicine. Emerging medical practices and imaginaries of medical futures are increasingly reliant on objectifying and externalising technologies. The patient is known through biometrics and datapoints, arguably at the expense of the human element.

Advances in medical science has rendered the human body progressively visible, available, and manageable. The understanding of persons, however, of consciousness, morals, meaning and suffering, the very substance that makes humans human, is made ever more insubstantial by the epistemologies and methodologies of the natural sciences. Within the mechanical, predictable, and controllable worldview of scientific medicine, the traditional art of medicine is considered redundant. Patients and what ails them are seen and approached as mere puzzles to be solved and physicians are reduced to mere technicians. Medical scientists concerned with the brain study causation, not reasons, they study behaviour, not agency or intentionality, and gradually the traditional object of medicine, the person, falls out of view. This tension, between patients as bodies and persons, is the paradox of modern medicine.

Imaginaries of more precise and technologically informed medical practices, like precision medicine, are gradually taking up more space in the public vocabulary, in policy, in research programs and in the health service. Central in these developments is the goal of reforming medicine's place and space in life, from a reactive practice to a proactive practice, able to predict, intervene preventively and thus avert health loss. These ambitions and visions are closely related to emerging disruptive technologies, that enable molecular basal and functional profiling, technologies and methods that intervene in the molecular, technologies that enable the manipulation of cell identity, cellular destiny, and function, as well as technologies that are used in, on and outside the body for profiling and intervention, such as nanotechnology, sensor technology and functional imaging technologies. Central is the convergence between biotechnology and information and communication technologies. It is artificial intelligence, and machine learning that largely make biotechnology and thus precision medicine possible. It is in continuous interaction with these technologies that human life is imagined living in a future where precision medicine has been fully realized. Precision medicine thus includes, involves, and invokes technology which set the very boundary conditions and fabric of bodies and life in rapid motion.

Scientific medical knowledge and medical practice reshape not only bodies but also persons, their meaning structures, and social and cultural conditions. Anticipating and shaping this new landscape of bodies, of persons and medical practices the natural sciences are of little use. Other conceptual tools are needed to reflect upon emerging normative terrain and the re-distribution of roles, power-structures, and the place and space for persons, the ones to be born, the healthy, the ones at risk, the ones living with a manifest health loss and the ones who are dying. Through the disruption of the ontology of the body, questions related to the nature and qualities of the human and the humane are brought to the forefront, highlighting the need for epistemic humility and a curiosity towards plural ways of knowing in medicine.

"The nature of disease and suffering and the goals of precision medicine" (NEUROSYSM940) is a PhD course organized by the POND research group that will take place in April 2023. The course aims to foster discussions on these topics among participants.



Text by Kjetil Bjørnevik, Assistant Professor, Harvard University
(Neuro-SysMed associated researcher)

Research stays abroad: benefits for building a career in academia

Promoting international mobility is a high priority for academic institutions, as it provides researchers at all levels with opportunities to build research skills and expand their network at top academic institutions around the world. Building an international network is becoming increasingly important for a career in academia, as it is critical for accessing certain funding mechanisms, such as European Commission funding, and it can increase the visibility of research, thus broadening its impact. However, international mobility among academics in Norway remains relatively low, which likely reflects some of the barriers and challenges that exist in international mobility.

> "International experience can make students more competitive when applying for future postdoctoral fellowships or faculty positions"

Research on international mobility has found numerous benefits for stay abroad. These include opportunities to obtain innovative skills and knowledge, achieve higher levels of scientific production, and career advancement. For early-stage academics, such as PhD students, a stay abroad offers exposure and learning opportunities at top academic institutions they may not have access to otherwise because of the highly competitive admission process. Moreover, the international experience can make these students more competitive when applying for future postdoctoral fellowships or faculty positions, which are increasingly difficult to obtain.

For researchers at mid to late-career stages, obtaining a regular research position at a leading institution abroad can be challenging because of the large pool of applications from all over the world. However, most institutions welcome visiting researchers for extended periods, which can provide unique opportunities for building skills and networks. Even short-term stays, such as a few months, have shown long-term benefits in research studies. This strongly suggests that academics at all stages of their career should be encouraged to go abroad at some point in their career.

The complexity of planning, concerns about funding, and issues related to personal or family circumstances may explain some of the hesitance to pursue research stays abroad. While most researchers at Norwegian institutions are eligible for visas for most of the countries where the institutions most relevant for research stays are located, the visa application process can take a long time, and the institutions they would like to visit may have specific requirements, such as language tests that can take some time to prepare for. Therefore, plans for stays may need to start years before the travel, which can make it challenging to fit them into a 3-year PhD or postdoctoral fellowship program, unless the plans are made in the beginning or even before the program starts. Additionally, a stay abroad, especially in the US, can be very costly and challenging to afford on regular grants. Finally, many institutions prefer longer research stays, such as one year, which may be difficult to combine with personal and family responsibilities.

In conclusion, research stays abroad provide unique opportunities and can play a major role in career building in academia. Thus, academic institutions should continue to promote international mobility and work to reduce the barriers and challenges academics face when they plan and undertake their stays abroad.

Research School in Translational Neuroscience

Since the launch of the Neuro-SysMed Research School in Translational Neuroscience in March 2021, a broad range of PhD- courses has been established. PIs and researchers from different fields are responsible for the courses, promoting high quality education to students, aiming at building a strong foundation for their research.

The Research School aims at providing PhD candidates with relevant courses to fulfil mandatory credit points for the PhD training program at the University of Bergen. Another important objective is to provide an ambitious and inspiring environment to motivate future research among junior scientists as well as the established seniors, and to help them in developing their scientific network. 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 established 7 courses providing PhD students with a total of 19 ECTS:

- **NEUROSYSM910 – Neuro-SysMed Junior Scientist Symposium (start 2023)**
- **NEUROSYSM920 – Neuro-SysMed Seminars and Symposium (started 2022, running continuously)**
- **NEUROSYSM930 – Applied bioinformatics and data analysis in medical research (started 2022)**
- **NEUROSYSM940 – The nature of disease and suffering and the goals of precision medicine (start 2023)**
- **CCBIONEUR910 – Patient and public involvement in medical and health research (started 2021, last held in 2022)**
- **CCBIONEUR911 – Clinical trials (started 2021, next course in 2023)**
- **CCBIONEUR912 – Health innovation (started 2021, next course in 2024)**

In 2022, we hosted the course **CCBIONEUR910** in collaboration with the Centre for Cancer Biomarkers (CCBIO), and we launched the two new PhD level courses **NEUROSYSM920** and **NEUROSYSM930**.

CCBIONEUR910 – Patient and Public Involvement in Medical and Health Research

CCBIONEUR910 is a 2 ECTS course aiming at the development of networks across professionals, mainly researchers, and users of health services, and facilitate communication and sharing of experience from multiple perspectives. The course also intends to stimulate increased participation in clinical trials by users of the health services, by presenting methods for how to implement user involvement into practice. The main objectives of the course are to develop the participants' capacity to assess and convey the value of patient and public involvement in general, and to promote productive user involvement in different research projects.

The course spans over three days, addressing challenges from both researcher- and user representative perspectives. Group sessions include both pre-organized case discussions as well as project presentations from the research school participants. The researchers are challenged to present highlights from the group sessions for plenary discussions and comments. The course was last held in November/ December 2022.

Panel debate at the CCBINEUR910 course in 2022. Photo by Tone Skår.

NEUROSYSM930 Applied bioinformatics and data analysis in medical research

This course focuses on practical aspects and methodological considerations necessary when dealing with human derived data, such as data sensitivity, limited sample sizes, sample misclassification, choice of appropriate statistical models, and covariates, and tissue heterogeneity. This 3 ECTS course is highly beneficial for participants with a research interest in bioinformatics, biology, medicine, or clinical research in general. It is open for researchers, postdocs, PhD students, master students, students enrolled in the Medical Student Research Program and others interested in the topic. The course was launched in November 2022.

New Research School courses in 2023

During 2022, two new courses were approved by the Medical Faculty for starting in 2023: NEUROSYSM910 – the Junior Scientist Symposium, aiming at developing research leadership for young scientists (January 2023), and NEUROSYSM940 – The nature of disease and suffering and the goals of precision medicine (April 2023).

"It is a great privilege as coordinator of The Neuro-SysMed Research School in Translational Neuroscience to provide a stimulating scientific environment devoted to excellence in teaching and research for young researchers, to let their thoughts and ideas flourish"

– Nina Grytten Torkildsen, coordinator of the Neuro-SysMed Research School.


From NEUROSYSM930.


From NEUROSYSM930, organized by Kim Brügger, Fiona Dick, Gonzalo Nido and Lilah Toker.

Organizers and coordinators of the CCBINEUR910 course in 2022. Nina Jebsen, Rasmus Humlevik, Tone Skår, Hilde Norborg, Nina G. Torkildsen and Kjell-Morten Myhr.

Completed doctorate degrees

Researcher education at all levels is central for Neuro-SysMed. In 2022, we had the opportunity to celebrate five completed PhD degrees.

Multiple Sclerosis Node

Espen Benjaminsen April 25, 2022 successfully defended his PhD thesis “Multiple sclerosis in Northern Norway, epidemiology and comorbidity” at the Arctic University of Norway. Supervisors were Professor Karl Bjørnar Alstadhaug and Professor Kjell-Morten Myhr.

Alok Bahn December 9, 2022 successfully defended his PhD thesis “Neurofilament Light-Chain as a biomarker in multiple sclerosis: A ten year follow-up study” at the University of Bergen. Supervisors were Professor Elisabeth Farbu, Professor Guido Alves and Professor Kjell-Morten Myhr.

Parkinson’s Disease Node

Brage Brakedal April 28, 2022 successfully defended his PhD thesis “Applying the Norwegian prescription database to study epidemiology and potential disease-modifying drugs in Parkinson´s disease” at the University of Bergen. Supervisors were Dr. Kristoffer Haugarvoll, Professor Charalampos Tzoulis and Professor Ole-Bjørn Tysnes.

Cell Models Node

Sepideh Mostafavi February 2, 2022 successfully defended her PhD thesis “Using induced pluripotent stem cells for modeling POLG mitochondrial disease” at the University of Bergen. Supervisors were Professor Laurence A. Bindoff and Professor Christian A. Vedeler.

Care Node

Torstein Frugård Habiger June 17, 2022 successfully defended his PhD thesis “The relationship between psychosis symptoms and pain in nursing home residents” at the University of Bergen. Supervisors were Professor Bettina S. Husebo, Professor Wilco P. Achterberg and Professor Elisabeth Flo-Groeneboom.

Alok Bahn receiving his PhD degree. Photo by Thor Brødreskift, UiB Flickr.

Neuro-SysMed Seminars

The overarching aim of the Neuro-SysMed Seminars is to share knowledge between the research groups and the different research disciplines working at Neuro-SysMed.

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 research environments at all partner institutions.

Participation in the seminar series provides 3 ECTS for PhD candidates and is part of the Neuro-SysMed PhD School of Translational Neuroscience under the subject code NEUROSYSM920, covering both the Neuro-SysMed Seminars and the Annual Symposium. Six seminars covering different topics were organized during 2022:

MAY 24

Øivind Torkildsen, Neuro-SysMed PI, Professor at the Department for Clinical Medicine, University of Bergen, and Senior Consultant at the Department of Neurology, Haukeland University Hospital, Bergen.
Title of the talk: *The role of Ebstein-Barr Virus in MS*

JUNE 22

Charalampos Tzoulis, Co-Director of the Neuro-SysMed, Professor of Neurology at the Department for Clinical Medicine, University of Bergen, and Senior Consultant at the Department of Neurology, Haukeland University Hospital, Bergen.
Title of the talk: *NAD replenishment therapy in Parkinson's disease: A New Hope?*

SEPT 14

Kristin Nielsen Varhaug, MD, PhD, Researcher at Neuro-SysMed, and Senior Consultant at the Department of Neurology, Haukeland University Hospital, Bergen
Title of the talk: *The role of mitochondrial function and dysfunction in Multiple Sclerosis*

OCT 11

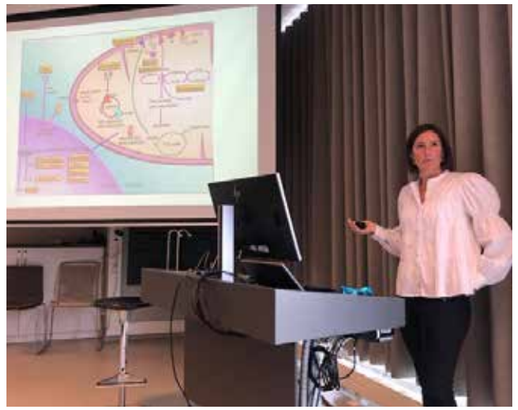
Paula Perez Pardo, Assistant Professor, Department of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands.
Title of the talk: *Gut microbes in Parkinson's disease: opportunities for microbial-based therapies*

NOV 16

Jan Reinert Karlsen, Associate Professor and Neuro-SysMed PI, and coordinator for Major Issues in Research and Society and leader of Research Group Theory of Science at the Centre for the Study of the Sciences and the Humanities, University of Bergen.
Title of the talk: *Sufferings in ageing persons. Is reflection relevant for precision medicine?*

DEC 14

Bettina Husebø, Neuro-SysMed PI, Professor at the Department of Global Public Health and Primary Care, University of Bergen, and Head of the Centre for Elderly and Nursing Home Medicine.
Title of the talk: *Paradigm Change in Elderly Care: Can Artificial Intelligence Support Us to Understand Dementia?*



Special Topic Symposium: Clinical Trials Design

In November 2022, we had the pleasure of having a special topic symposium on Clinical Trials Design. The objective of this symposium was to present and discuss the current challenges and opportunities in clinical trials in neurodegeneration and neuroinflammation.

For this symposium, our clinical trial staff was invited to join, learn from, and discuss with experts in their fields. With a total of 50 attendants, it was a great success and a learning experience for all involved.

Day 1 opened with a presentation from Neuro-SysMed Co-Directors Kjell-Morten Myhr and Charalampos Tzoulis on a general introduction into the challenges of clinical trials design in Neuro-SysMed diseases. This was followed by a talk by guest speaker Professor Roshan Das Nair (University of Nottingham, UK, and Sintef, Norway) on decentralized clinical trials and complex intervention trials, giving a great overview of his experience and providing inspiration for how to do such trials in Norway with new technologies. Neuro-SysMed PIs Øivind Torkildsen, Ole-Bjørn Tysnes and Kristoffer Haugarvoll did some short sessions on the challenges faced in outcome measures design for MS, ALS and dementia. While each disease faces unique challenges, they share common issues in the way they are measured, with novel outcomes being needed.

After the break, guest speaker Dr. Kjetil Bjørnevik (Harvard University, USA) presented digitally on emulated clinical trials, a very new and emerging field of research that can complement trials. Lastly, Biogen speakers Katja Stahl and Helle Seem presented the regulatory requirements and practical examples from real world experiences in Biogen clinical trials, providing great inspiration and practical considerations for those promising trials advancing through to phase III.

Day 2 started with a talk from Professor Tim Friede (University of Gottingen, Germany) on a novel adaptive design strategy that increases the efficiency of clinical trials. His expertise on statistics provided great topics for discussion and novel design ideas for Neuro-SysMed studies. Dr. Austin Smith (regulatory expert from Link Medical) followed up by discussing the regulatory requirements for preclinical and clinical (combined) development of new treatment options, providing updated information and knowledge on current practices and what to expect from the regulatory process. Our Centre Co-Director Professor Charalampos Tzoulis then presented the challenge of designing trials for neurodegenerative diseases, focusing on the problems of time and space.

After a short break, our second digital speaker, Dr. Suvankar Pal (University of Edinburgh, Scotland, UK), presented their motor neuron disease systematic multi-arm adaptive randomized trial. Their results were very encouraging and provide a strong foundation for future studies with similar design. Lastly, Professors Myhr and Tzoulis summarized the discussions of an inspiring and successful symposium, which had been very productive and educational on the latest advances on designing clinical trials.

RESEARCH NODES

In previous years, we have reported the work by each principal investigator and their respective research groups separately. During the development of the Neuro-SysMed activities, we have seen a need to improve this presentation focusing on research areas across research groups in the Centre. In addition, during 2022 we had some changes to our principal investigator team: with Professor Laurence Bindoff having retired in 2021, Senior Researcher Xiao Liang has taken over responsibility of the cell models; Professor Inge Jonassen is the head of the Department of Informatics, and therefore has also taken a step back as principal investigator and will instead continue his work as a Neuro-SysMed collaborator; Professor Christian Vedeler is head of the Department of Clinical Medicine and therefore his work on biomarkers has been integrated in the multiple sclerosis node.

Picture from the PI seminar in November 2022, with some of the Neuro-SysMed PIs, the Research School leader and the research advisor: Charalampos Tzoulis, Kjell-Morten Myhr, Kristoffer Haugarvoll, Nina Grytten Torkildsen, Inge Jonassen, Aurora Martinez, Ole-Bjørn Tysnes, Yamila Torres Cleuren, Bettina Husebø and Jan Reinert Karlsen.

We have now organized Neuro-SysMed into the following 10 nodes:

- **Multiple Sclerosis (MS) Node**, led by **Professor Kjell-Morten Myhr**, coordinating clinical studies in MS
- **Parkinson's Disease (PD) Node**, led by **Professor Charalampos Tzoulis**, coordinating clinical studies in PD
- **Amyotrophic Lateral Sclerosis (ALS) Node**, led by **Professor Ole-Bjørn Tysnes**, coordinating clinical studies in ALS
- **Dementia Node**, led by **Dr. Kristoffer Haugarvoll**, coordinating clinical studies in dementia
- **Care Node**, led by **Professor Bettina Husebø**, coordinating clinical studies in care and palliation
- **Drug Discovery Node**, led by **Professors Aurora Martinez and Trond Riise**, coordinating drug discovery activities for novel and repurposed compounds
- **Cell Models Node**, led by **Dr. Xiao Liang and Dr Christian Dölle**, coordinating development and characterization of cell models for the purpose of drug discovery
- **Metabolomics Node**, led by **Professor Mathias Ziegler**, coordinating studies of metabolism, including metabolomics analyses for biomarker discovery
- **Systems Biology & Bioinformatics Node**, led by **Professor Charalampos Tzoulis**, 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**, is coordinating RRI/PPI and philosophy of neurodegeneration

The Multiple Sclerosis (MS) Node

Biomarkers and tailored therapies for patients with multiple sclerosis

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

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

Key node partner: Christian Vedeler
Professor Christian Vedeler is head of the Department of Clinical Medicine, UiB, and senior consultant at the Department of Neurology, Haukeland University Hospital, Bergen. He is also the head of the Neuroimmunology Biomarker Research Group and is widely acknowledged in the fields of biomarker research. He is leading the biomarker studies focusing on multiple sclerosis – with the potential for translation into the other diseases as well.

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

Node activities

The MS Node has a broad experience focusing on risk factors and treatment of the disease. Ongoing research projects are aiming at defining at the importance of potential risk factors as well as optimizing treatments strategies at different stages of the disease. The MS Node is also targeting novel treatment strategies for possible prevention of the disease. Overall, it aims at developing tailored treatment strategies for patients with MS. Major challenges are how to improve treatment strategies for already available disease-modifying therapies, and how to define new disease pathways that can be targeted by novel therapies. The latter is especially needed for the progressive disease courses in MS. The MS Node is currently running eight investigator and seven 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 patient with breakthrough disease activity.
- **The OVERLORD-MS study** is a non-inferiority study evaluating and comparing the efficacy and safety of rituximab (500 mg) and ocrelizumab (600 mg) in newly diagnosed relapsing remitting MS patients. This study will also evaluate the switch from ocrelizumab to rituximab therapy at the end of the study. The study completed inclusion in November 2022 (n=214), and the patients will be followed for two and a half years.

- **The COVID-19 vaccine response study** evaluates the impact of various disease-modifying therapies on the vaccination response in MS patients.
- **The SMART-MS study** is a placebo-controlled, cross-over pilot study (n=18) evaluating regenerative effects from mesenchymal autologous stem cells in progressive MS.
- **The FlowOx-MS study** is a pilot trial (n=10) to explore whether a pulsating negative pressure therapy device can improve spasticity and pain in lower extremities of patients with MS. This is now the basis for a Scandinavian placebo-controlled phase-II trial evaluating spasticity and pain reduction in 60 MS patients.
- **REDUCE-MS** is a controlled trial investigating extended dosing intervals on rituximab therapy. About 200 patients who have been stable on standard dosing intervals of 500 mg intravenous every six months will be randomized for further standard dosing intervals or extended dosing intervals of 12 months. Patients will be evaluated for efficacy and safety outcomes – as well as for potential biomarkers that can guide for further dosing intervals.
- **NORSEMAN-MS** is a placebo-controlled add of nicotinamide riboside (NR) to standard care in progressive multiple sclerosis. Patients (n=300) will receive oral NR 500 mg x 2 or placebo for two years, followed by a six-month observation period for confirmed evaluation of disability progression scores. The primary endpoint is the proportion of patients with confirmed disability progression in the Expanded Disability Status Score (EDSS), the Nine-Hole-Peg test (9-HPT) or Timed 25 Foot Walking (T25FW).
- **TAF-MS** is a placebo-controlled add on proof-of-concept study of Tenofovir Alafenamide fumarate (TAF) to standard natalizumab infusion therapy. Stable natalizumab treated RRMS patients (n=24) will receive placebo, 25 mg or 75 mg of TAF for six months. The primary endpoint is the proportion of patients with reduced Epstein-Barr virus shedding in saliva. Secondary endpoints are efficacy and safety of the TAF therapy. The study will start mid-2023.

The MS Node serves also as the national coordinator for three industry-sponsored multicentre randomized clinical trials in both relapsing-remitting and

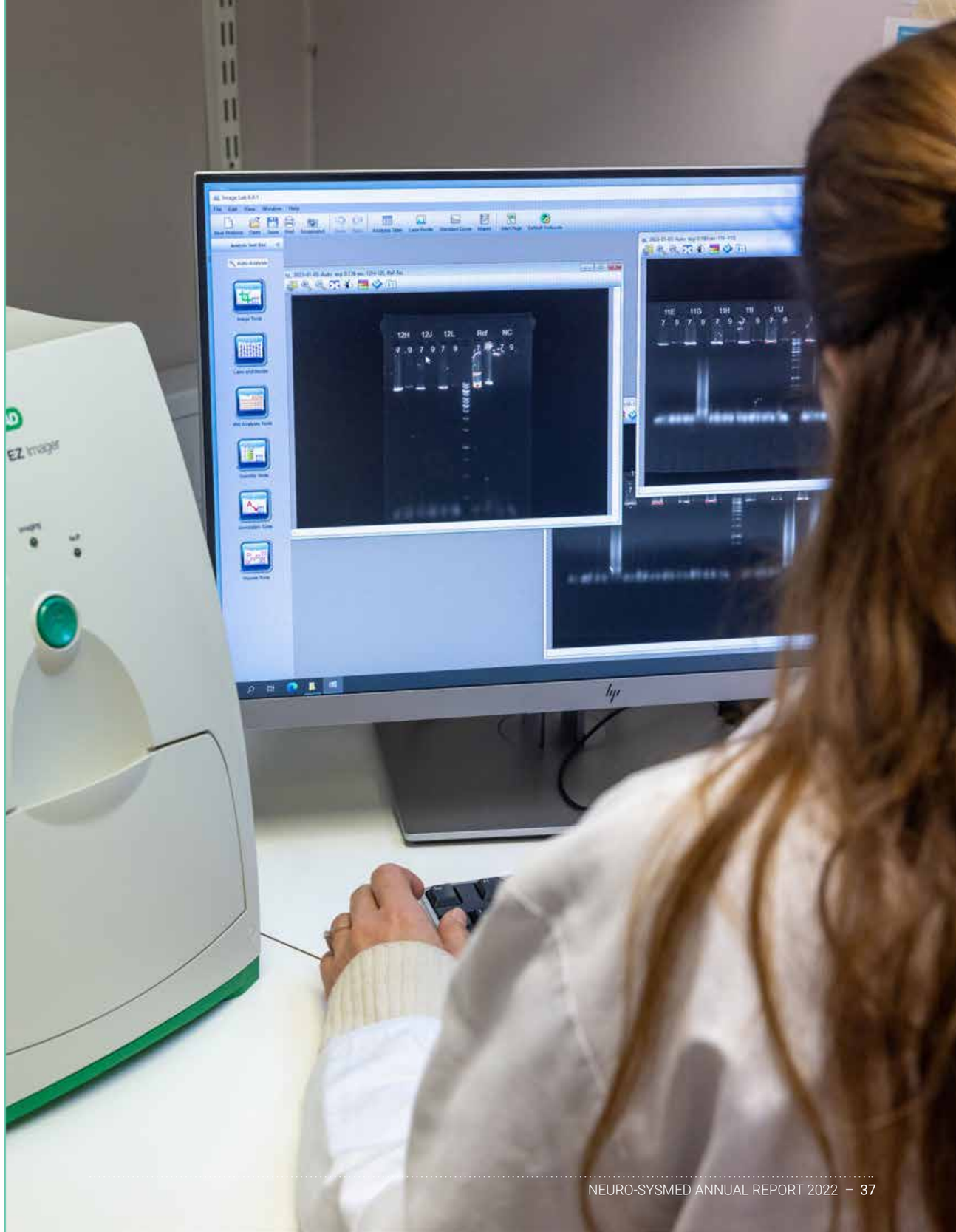
progressive disease. In addition, they are the national coordinator in the two extension studies and another two safety studies sponsored by the industry.

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

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

Selected publications from 2022:

1. **Nygaard GO, Torgauten H, Skattebøl L, Høgestøl EA, Sowa P, Myhr KM, Torkildsen Ø, Celius EG**. Risk of fingolimod rebound after switching to cladribine or rituximab in multiple sclerosis. *Mult Scler Relat Disord.* 2022 Jun;62:103812. doi: 10.1016/j.msard.2022.103812. Epub 2022 Apr 17. PMID: 35462167.
2. **Rød BE, Torkildsen Ø, Myhr KM, Bø L, Wergeland S**. Safety of breast feeding during rituximab treatment in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2022 Jul 25;94(1):38-41. doi: 10.1136/jnnp-2022-329545. Online ahead of print. PMID: 35879056.
3. **Lie IA, Wesnes K, Kvistad SS, Brouwer I, Wergeland S, Holmøy T, Midgard R, Bru A, Edland A, Eikeland R, Gosal S, Harbo HF, Kleveland G, Sørenes YS, Øksendal N, Barkhof F, Vrenken H, Myhr KM, Bø L, Torkildsen Ø**. The Effect of Smoking on Long-term Gray Matter Atrophy and Clinical Disability in Patients with Relapsing-Remitting Multiple Sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2022 Jun 23;9(5):e200008. doi: 10.1212/NXI.0000000000200008. Print 2022 Sep. PMID: 35738901.
4. **König M, Torgauten HM, Tran TT, Holmøy T, Vaage JT, Lund-Johansen F, Nygaard GO**. Immunogenicity and Safety of a Third SARS-CoV-2 Vaccine Dose in Patients With Multiple Sclerosis and Weak Immune Response After COVID-19 Vaccination. *JAMA Neurol*. 2022 Mar 1;79(3):307-309. doi: 10.1001/jamaneurol.2021.5109. PMID: 35072702.
5. **Kvistad SAS, Burman J, Lehmann AK, Tolf A, Zjukovskaja C, Melve GK, Bø L, Torkildsen Ø**. Impact of previous disease-modifying treatment on safety and efficacy in patients with MS treated with AHSCT. *J Neurol Neurosurg Psychiatry*. 2022 Aug;93(8):844-848. doi: 10.1136/jnnp-2022-328797. Epub 2022 May 4. PMID: 35508373.
6. **Lie IA, Kaçar S, Wesnes K, Brouwer I, Kvistad SS, Wergeland S, Holmøy T, Midgard R, Bru A, Edland A, Eikeland R, Gosal S, Harbo HF, Kleveland G, Sørenes YS, Øksendal N, Varhaug KN, Vedeler CA, Barkhof F, Teunissen CE, Bø L, Torkildsen Ø, Myhr KM, Vrenken H**. Serum neurofilament as a predictor of 10-year grey matter atrophy and clinical disability in multiple sclerosis: a longitudinal study. *J Neurol Neurosurg Psychiatry*. 2022 Jun 1;93(8):849-57. doi: 10.1136/jnnp-2021-328568. Online ahead of print. PMID: 35649699.
7. **Skorve E, Lundervold AJ, Torkildsen Ø, Riemer F, Grüner R, Myhr KM**. Brief international cognitive assessment for MS (BICAMS) and global brain volumes in early stages of MS - A longitudinal correlation study. *Mult Scler Relat Disord*. 2023 Jan;69:104398. doi: 10.1016/j.msard.2022.104398. Epub 2022 Nov 5. PMID: 36462469.
8. **Karlowicz JR, Klakegg M, Aarseth JH, Bø L, Myhr KM, Torgauten HM, Torkildsen Ø, Wergeland S**. Predictors of hospitalization due to infection in rituximab-treated MS patients. *Mult Scler Relat Disord*. 2023 Feb 11;71:104556. doi: 10.1016/j.msard.2023.104556. Online ahead of print. PMID: 36842313.
9. **Kvistad CE, Kråkenes T, Gjerde C, Mustafa K, Rekand T, Bø L**. Safety and Clinical Efficacy of Mesenchymal Stem Cell Treatment in Traumatic Spinal Cord Injury, Multiple Sclerosis and Ischemic Stroke - A Systematic Review and Meta-Analysis. *Front Neurol*. 2022 May 30;13:891514. doi: 10.3389/fneur.2022.891514. eCollection 2022. PMID: 35711260.



The Parkinson's Disease (PD) Node

Biomarkers and tailored therapies for Parkinson's disease

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

Node leader: Charalampos Tzoulis
Charalampos Tzoulis, MD, PhD is a professor of neurology and neurogenetics at the University of Bergen and Haukeland University Hospital. Professor Tzoulis is an expert on movement disorders and neurodegeneration, including dementia and parkinsonism. His research focuses on exploring the role of mitochondrial dysfunction in Parkinson's disease (PD), with the aim to improve patient diagnosis and develop neuroprotective therapies. Currently, he is the head of the Neuromics Research Group, director of the K.G Jebsen Centre for Translational Research in Parkinson's disease, and co-director of the Neuro-SysMed Centre, where he has the overarching responsibility for neurodegeneration research.

Key node partner: Mandar S. Jog
Professor Mandar S. Jog, MD, FRCPC, is widely acknowledged as a leader in research and innovation in the fields of movement disorders and neurodegeneration, and is director of the London Movement Disorders Centre, Ontario, Canada. He is the co-PI of the STRAT-PARK initiative, and head of the study arm in Canada.

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

Node activities

Basic and translational research at the PD Node has nominated mitochondrial function and NAD-metabolism as promising therapeutic targets primarily for PD and, by extension, other neurodegenerative and neuroinflammatory disorders, including Alzheimer's disease, ALS, and multiple sclerosis. 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 individualized medicine in PD, by running an international initiative aiming to stratify PD according to underlying molecular mechanisms and develop biomarkers for patient selection for tailored therapies. Finally, the PD Node runs world-class translational research aiming to identify novel therapeutic targets and candidate therapies for PD and emerging subtypes thereof.

During 2022, the PD Node made key advances in their clinical research projects, which include six clinical trials, and one prospective cohort study:

- **The NADPARK study** is a phase I randomized, double blinded trial, aiming to assess the tolerability, cerebral bioavailability, and molecular effects of NAD-replenishment therapy with nicotinamide riboside (NR) in PD. The trial was completed with highly encouraging results, nominating NR as a potential neuroprotective agent for PD and other neurodegenerative disorders. The study was published in the prestigious journal Cell Metabolism (PMID: 35235774).

- **The NR-SAFE study** is a phase I randomized, double blinded trial, with the primary objective to assess the safety and tolerability of high dose NR therapy (3,000mg daily) in PD. The study was completed, and the results establish the safety profile of high dose NR therapy, allowing dose optimization studies to be conducted (see N-DOSE).
- **The N-DOSE study** is a phase II randomized, double blinded dose-optimization 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 was initiated and is actively recruiting with 10/80 patients enrolled.
- **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 initiated and is actively recruiting.
- **The NO-PARK study** is a phase-II randomized, 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. NO-PARK is actively recruiting with 260/400 participants enrolled.
- **The NO-PARK 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 PD. The study is actively recruiting with 150/400 participants enrolled.
- **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. The STRAT-PARK study represents a vast clinical endeavour, co-led by Charalampos Tzoulis in Norway and Mandar Jog in Canada. A total of 2,000 patients and controls will be recruited from three clinical centres: Haukeland University Hospital (HUH) in Bergen, St. Olavs University Hospital in Trondheim and the London Movement Disorders Centre (LMDC), Ontario, Canada. The study is actively recruiting with 230 participants enrolled. Notably, the STRAT-PARK initiative was awarded funding from the Michael J Fox Foundation in 2022.

Selected publications from 2022:

1. **Fernández-Vizarra E, López-Calcerrada S, Sierra-Magro A, Pérez-Pérez R, Formosa LE, Hock DH, Illescas M, Peñas A, Brischigliaro M, Ding S, Fearnley IM, Tzoulis C, Pitceathly RDS, Arenas J, Martín MA, Stroud DA, Zeviani M, Ryan MT, Ugalde C.** Two independent respiratory chains adapt OXPHOS performance to glycolytic switch. *Cell Metab*. 2022 Nov 1;34(11):1792-1808.e6. doi: 10.1016/j.cmet.2022.09.005. Epub 2022 Oct 4. PMID: 36198313.

2. **Flønes IH, Nyland H, Sandnes DA, Alves GW, Tysnes OB, Tzoulis C.** Early Forms of α-Synuclein Pathology Are Associated with Neuronal Complex I Deficiency in the Substantia Nigra of Individuals with Parkinson's Disease. *Biomolecules*. 2022 May 25;12(6):747. doi: 10.3390/biom12060747.PMID: 35740871.

3. **Flønes IH, Tzoulis C.** Mitochondrial Respiratory Chain Dysfunction-A Hallmark Pathology of Idiopathic Parkinson's Disease? *Front Cell Dev Biol*. 2022 Apr 1;10:874596. doi: 10.3389/fcell.2022.874596. eCollection 2022.PMID: 35433702.

4. **Brakedal B, Toker L, Haugarvoll K, Tzoulis C.** A nationwide study of the incidence, prevalence and mortality of Parkinson's disease in the Norwegian population. *NPJ Parkinsons Dis*. 2022 Mar 2;8(1):19. doi: 10.1038/s41531-022-00280-4.PMID: 35236852.

5. **Brakedal B, Dölle C, Riemer F, Ma Y, Nido GS, Skeie GO, Craven AR, Schwarzlmüller T, Brekke N, Diab J, Sverkeli L, Skjeie V, Varhaug K, Tysnes OB, Peng S, Haugarvoll K, Ziegler M, Grüner R, Eidelberg D, Tzoulis C.** The NADPARK study: A randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. *Cell Metab*. 2022 Mar 1;34(3):396-407.e6. doi: 10.1016/j.cmet.2022.02.001. PMID: 35235774.

6. **Szwedo AA, Dalen I, Pedersen KF, Camacho M, Bäckström D, Forsgren L, Tzoulis C, Winder-Rhodes S, Hudson G, Liu G, Scherzer CR, Lawson RA, Yarnall AJ, Williams-Gray CH, Macleod AD, Counsell CE, Tysnes OB, Alves G, Maple-Grødem J; Parkinson's Incidence Cohorts Collaboration.** GBA and APOE Impact Cognitive Decline in Parkinson's Disease: A 10-Year Population-Based Study. *Mov Disord*. 2022 May;37(5):1016-1027. doi: 10.1002/mds.28932. Epub 2022 Feb 2.PMID: 35106798

The Dementia Node

Biomarkers and tailored therapies for dementia

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

Node leader: Kristoffer Haugarvoll

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

Key node partner: Bettina Husebø

Bettina Husebø, MD, PhD is a professor at the Medical Faculty, UiB, where she also is the head of the Centre for Elderly and Nursing Home Medicine (SEFAS). Since 2019, she is also the head of Innovation at her department, the Department of Global Public Health and Primary Care (IGS). Her research focus is on care with a special focus on dementia, palliative medicine and care, pain assessment, impact of pain on behavioural disturbances in patients with dementia, psychometrics and algesimetry. She is also the leader for Neuro-SysMed's Care Node.

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 2022, 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 randomized, double blinded dose-optimization trial of NR in AD. The primary objective is to determine the optimal biological dose of NR for AD, so that larger trials focusing on efficacy can be designed. The study was initiated and is actively recruiting with 10/80 patients enrolled.
- **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. This will enable us to elucidate how the mixture of different molecular pathologies affects prognosis, and to stratify individual patients suffering from dementia based on underlying biological processes. The STRAT-COG study includes a brain donation program. The study is actively recruiting with 40 participants enrolled.

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

Selected publications from 2022:

1. **Solvang SH, Hodge A, Watne LO, Cabral-Marques O, Nordrehaug JE, Giles GG, Dugué PA, Nygård O, Ueland PM, McCann A, Idland AV, Midttun Ø, Ulvik A, Halaas NB, Tell GS, Giil LM.** Kynurenine Pathway Metabolites in the Blood and Cerebrospinal Fluid Are Associated with Human Aging. *Oxid Med Cell Longev*. 2022 Oct 21;2022:5019752. doi: 10.1155/2022/5019752. eCollection 2022. PMID: 36312896.
2. **Watne LO, Pollmann CT, Neerland BE, Quist-Paulsen E, Halaas NB, Idland AV, Hassel B, Henjum K, Knapskog AB, Frihagen F, Raeder J, Godø A, Ueland PM, McCann A, Figved W, Selbæk G, Zetterberg H, Fang EF, Myrstad M, Giil LM.** Cerebrospinal fluid quinolinic acid is strongly associated with delirium and mortality in hip-fracture patients. *J Clin Invest*. 2023 Jan 17;133(2):e163472. doi: 10.1172/JCI163472. PMID: 36409557.
3. **Borda MG, Jaramillo-Jimenez A, Giil LM, Tovar-Rios DA, Soennesyn H, Aarsland D.** Body mass index trajectories and associations with cognitive decline in people with Lewy body dementia and Alzheimer's disease. *Health Sci Rep*. 2022 May 2;5(3):e590. doi: 10.1002/hsr2.590. eCollection 2022 May. PMID: 35509416.
4. **Boyle LD, Husebo BS, Vislapuu M.** Promotors and barriers to the implementation and adoption of assistive technology and telecare for people with dementia and their caregivers: a systematic review of the literature. *BMC Health Serv Res*. 2022 Dec 23;22(1):1573. doi: 10.1186/s12913-022-08968-2. PMID: 36550456.
5. **Ito E, Nouchi R, Dinet J, Cheng CH, Husebø BS. The Effect of Music-Based Intervention on General Cognitive and Executive Functions, and Episodic Memory in People with Mild Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of Recent Randomized Controlled Trials. Healthcare (Basel). 2022 Aug 3;10(8):1462. doi: 10.3390/healthcare10081462. PMID: 36011119. Review.**
6. **Husebo BS, Vislapuu M, Cyndecka MA, Mustafa M, Patrascu M.** Understanding Pain and Agitation Through System Analysis Algorithms in People With Dementia. A Novel Explorative Approach by the DIGI.PAIN Study. *Front Pain Res (Lausanne)*. 2022 Mar 17;3:847578. doi: 10.3389/fpain.2022.847578. eCollection 2022. PMID: 35369536
7. **Book chapter by Haugarvoll:** Genetics of Tremors | Tremors | *Oxford Academic* (oup.com)

The ALS Node

Clinical studies and stratification of ALS

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

Node leader: Ole-Bjørn Tysnes
Ole-Bjørn Tysnes is a consultant neurologist at the Department of Neurology at Haukeland University Hospital, and professor of neurology at the University of Bergen. He has for many years focused on research in ALS and Parkinson's disease and is PI of the ongoing ALS studies at Neuro-SysMed.

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 recently published, small study suggested that the combination of NR and pterostilbene (a sirtuin activator), may have added benefit in patients with ALS (PMID: 30668199). Encouraged by this evidence, the ALS Node conducts clinical trials to determine whether combination therapy of NR and pterostilbene may inhibit neurodegeneration and increase survival and quality of life in patients with ALS. Another area the ALS Node is particularly active on, is evaluating the effect of life-prolonging interventions, such as mechanical ventilation, on the quality of life of patients and their informal caregivers. Finally, the ALS Node conducts research aiming to improve the diagnosis and tailored treatment opportunities for patients.

During 2022, the ALS node made substantial advances in their clinical research projects, which include three clinical trials, and one prospective cohort study:

1. **The NO-ALS study** is a phase-II randomized, 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. NO-ALS is actively recruiting.
2. **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.
3. **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.
4. **STRAT-ALS**: The ALS Node is carrying out a stratification study in ALS (STRAT-ALS), recording detailed clinical data and collecting biological materials inclusive autopsies from ALS patients and controls. Through this work, the group aims to stratify ALS patients by clinical, genetic and biological characteristics for improved tailoring of treatment trials and future therapies.

Selected publications from 2022:

1. **Johanson GAS, Tysnes OB, Bjerknes TL,** Use of Off-Label Drugs and Nutrition Supplements among Patients with Amyotrophic Lateral Sclerosis in Norway, *Neurology Research International*, vol. 2022, Article ID 1789946, 6 pages, 2022. https://doi.org/10.1155/2022/1789946

2. **Olsen CG, Busk ØL, Aanjesen TN, Alstadhaug KB, Bjørnå IK, Braathen GJ, Breivik KL, Demic N, Flemmen HØ, Hallerstig E, HogenEsch I, Holla ØL, Jøntvedt AB, Kampman MT, Kleveland G, Kvernmo HB, Ljøstad U, Maniaol A, Morsund ÅH, Nakken O, Novy C, Rekand T, Schlüter K, Schüler S, Tveten K, Tysnes OB, Holmøy T, Høyer H. Genetic** Epidemiology of Amyotrophic Lateral Sclerosis in Norway: A 2-Year Population-Based Study. *Neuroepidemiology.* 2022;56(4):271-282. doi: 10.1159/000525091. Epub 2022 May 16. PMID: 35576897.

3. **Taule T, Morland AS, Aßmus J, Tysnes OB, Rekand T.** Translation, cultural adaptation, and validation of a screening test for cognitive and behavioural changes in amyotrophic lateral sclerosis. *Disabil Rehabil.* 2022 Nov;44(23):7069-7077. doi: 10.1080/09638288.2021.1980621. Epub 2021 Nov 2. PMID: 34726988.

The Care Node

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

Node leader: Bettina Husebø
Bettina Husebø, MD, PhD is a professor at the Medical Faculty, UiB, where she also is the head of the Centre for Elderly and Nursing Home Medicine (SEFAS). Since 2019, she is also the head of Innovation at her department, the Department of Global Public Health and Primary Care (IGS). Her research focus is on care with a special focus on dementia, palliative medicine and care, pain assessment, impact of pain on behavioural disturbances in patients with dementia, psychometrics and algesimetry. She is also the leader for Neuro-SysMed's Care Node.

Node activities

The Care Node has highlighted the necessity for a paradigm change in elderly care and argues for digital phenotyping and utilization of wearable devices to allow for real-time monitoring of function and quality of life, thereby optimizing individualized intervention.

Current studies

- **The ActiveAgeing study**. Husebø leads the ActiveAgeing project which started in February 2021, with PhD Candidate Haakon Reithe (psychologist) and Postdoctoral Researcher Juan Carlos Torrado Vidal (computer scientist), whereas PhD Candidate Elise Førsund (microbiologist) and Researcher Monica Pătrașcu (systems engineer) joined in August 2021. The project goal is to investigate digital phenotyping in older adults with and without PD by wearable devices to improve our understanding of the ageing process and PD. For this purpose, two smartwatches (Fitbit Sense and Empatica E4) and a smart ring (Oura Ring) are utilized in the project. These instruments can measure movements, heart rates, and electrodermal activities, which yield information about activity, sleep, and stress, among other. The project duration is four years, and it consists of two sub-projects: DIGI.PARK and ACT.LIVE.
- **The DIGI.PARK study** aims to study digital phenotyping to better understand sub-types and symptoms in people with PD. The study will ascertain whether this technology can help identify, track, and predict symptom associations of PD. It will also investigate new outcome measures for clinical trials in PD. Partners or spouses of people with PD will also be included to explore the impact of the disease in a patient-caregiver dyad. The data retrieved from the devices will be analysed using artificial intelligence and digital signal processing techniques, to facilitate clinical assessment and decision-making. In particular, the team will focus on a subgroup of artificial intelligence methods called explainable artificial intelligence.
- **ACT.LIVE** is a study in collaboration with the GC Rieber Foundation, the University of Bergen, and the Helgetun Living Lab. Helgetun is an innovative living environment for seniors located in Bergen, aimed to support social, mental, and physical activities of older adults. The Helgetun residents are encouraged to self-organize and to participate in their favourite activities. For instance, they volunteer in the Eplekarten kindergarten, do gardening, work with the animals in the farm, and are supporting each other whenever needed. The project aims to quantify and understand the effect on this living environment on their ageing process, and to what extent it fosters an active lifestyle. For this purpose, the subjects' daily life will be monitored with wearable devices, and qualitative interviews will be conducted to explore technology acceptance, the social living context, and their experiences with their own ageing process. These data will be compared to collected data from people who wish to live at Helgetun and are allocated to a Helgetun waiting list. ACT.LIVE will integrate data sources in a mixed-method approach.

After obtaining ethical approval from NSD, the Helgetun participants were recruited, and the first digital data collection is completed. Regular data acquisitions are planned for comparison. In the next step, people with PD from the STRAT.PARK study are enrolled in the study and followed over a cumulative 2-year period.

Photo: Silje K. Robinson

Selected publications from 2022:

1. **Torrado JC, Husebo BS, Allore HG, Erdal A, Fæø SE, Reithe H, Førsund E, Tzoulis C, Patrascu M.** Digital phenotyping by wearable-driven artificial intelligence in older adults and people with Parkinson's disease: Protocol of the mixed method, cyclic ActiveAgeing study. *PLoS One.* 2022 Oct 14;17(10):e0275747. doi: 10.1371/journal.pone.0275747. eCollection 2022. PMID: 36240173.
2. **Gedde MH, Husebo BS, Mannseth J, Naik M, Selbaek G, Vislapuu M, Berge LI.** The impact of medication reviews by general practitioners on psychotropic drug use and behavioral and psychological symptoms in home-dwelling people with dementia: results from the multicomponent cluster randomized controlled LIVE@Home.Path trial. *BMC Med.* 2022 May 26;20(1):186. doi: 10.1186/s12916-022-02382-5. PMID: 35614509. Clinical Trial.
3. **Vislapuu M, Berge LI, Angeles RC, Kjerstad E, Mannseth J, Achterberg WP, Husebo BS.** Factors associated with formal and informal resource utilization in nursing home patients with and without dementia: cross-sectional analyses from the COSMOS trial. *BMC Health Serv Res.* 2022 Nov 2;22(1):1306. doi: 10.1186/s12913-022-08675-y. PMID: 36324159 Free PMC article. Clinical Trial.
4. **Berge LI, Gedde MH, Torrado Vidal JC, Husebo B, Hynninen KM, Knardal SE, Madsø KG.** The acceptability, adoption, and feasibility of a music application developed using participatory design for home-dwelling persons with dementia and their caregivers. The "Alight" app in the LIVE@Home.Path trial. *Front Psychiatry*. 2022 Aug 18;13:949393. doi: 10.3389/fpsyt.2022.949393. PMID: 36061298; PMCID: PMC9433972.
5. **Sallnow, L., Smith, R., Ahmedzai, S., Bhadelia, A., Chamberlain, C., Cong, Y., . . . Wyatt, K. (2022).** Report of the Lancet Commission on the Value of Death: Bringing death back into life. *The Lancet (British Edition)*, 399(10327), 837.

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 leader of the Biorecognition Research Unit. She investigates the molecular mechanisms underlying neurometabolic and neurological disorders applying multidisciplinary and translational approaches. The research group has expertise in compound screening and early-stage drug discovery and aims to develop preventive and corrective therapies for Parkinson's disease. She also has expertise in phenylketonuria and genetic parkinsonisms.

Trond Riise has a background in mathematics/statistics and works as a professor in epidemiology at the University of Bergen. He leads the DRONE group – Drug RepurpOsing for NEurological diseases. Riise's research has been related to epidemiological studies of neurological diseases including Parkinson's disease and multiple sclerosis. The focus has been to identify environmental factors that, by their own or in combinations, significantly change the disease risk.

The group of Professor Martinez has expertise and skills in biophysics, structural biology, drug design, cellular biology and animal models of disease. In Neuro-SysMed, the research focuses on target identification and *in vitro* and *in cellulo* drug screening, among other using cell models developed by the Cell Models Node. The Martinez Lab is a specialized screening site at the NOR-Openscreen and EU-Openscreen networks.

The DRONE group, led by Professor Riise, 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.

Node activities

The activities of the Drug Discovery Node in 2022 comprised:

- **Tyrosine hydroxylase as a treatment target in PD**. In collaboration with the lab of JM Valpuesta (CNB-CSIC, Madrid), the Drug Discovery Node has recently solved the cryo-EM structure of full-length human tyrosine hydroxylase (TH) with and without dopamine, that acts as a feedback inhibitor and regulator of TH enzymatic activity (Bueno-Carrasco et al., 2022). These structures reveal novel details on possible interface regions for protein regulatory interactions that control TH and dopamine levels and represent targets for discovery of dopaminergic therapies in Parkinson's disease (PD).
- **VMAT2 as a treatment target in PD**. This project studies interactions of TH with the vesicular monoamine transporter 2 (VMAT2) and α-synuclein, all of them important targets in PD. In a recent project, Neuro-SysMed researcher Svein Isungset Støve has screened for compounds modulating VMAT2, has obtained effective inhibitors that have a potential for treatment of Tardive Dyskinesia (Støve et al., 2022) and continues the search for activators and stabilizers that can increase dopamine sequestration (in preparation). The identification of activators or stabilizers of VMAT2 is especially interesting, as high cytoplasmic levels of DA are associated with cytotoxicity, and stimulation of VMAT2 in early stages of PD is a therapeutic approach of increasing interest.
- **Modulators of proteostasis**. The Drug Discovery Node has developed novel screening assays which have been successfully applied to identify modulators of proteostasis and protein stability, of application in neurodegeneration (Støve et al., 2022 and Martin-Malpartida et al., 2022).
- **Mitochondrial function**. The Drug Discovery Node continues the optimization of screens and assays targeting neuronal respiratory complex I deficiency and impaired mitochondrial DNA homeostasis, in collaboration with Professor Charalampos Tzoulis.
- **Registry-based drug screening**. Riise's group is conducting a comprehensive registry-based drug-screening project which involves screening of all prescriptions given to all Norwegians since 2004. These prescriptions (about 800 mill) are linked to the incidence of Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). The overall objective of the project is to evaluate whether existing drugs (molecules) can be repurposed as effective treatment of PD, ALS and MS. A full screen of drugs associated with PD-risk has been completed, and in collaboration with Clemens Scherzer, director of The Neurogenomics Lab at Harvard University, we are currently validating 72 promising drugs using neurons from patient stem cells carrying the SNCA triplication linked to autosomal dominant PD.

Selected publications from 2022:

1. **Støve SI, Skjevik ÅA, Teigen K, Martinez A.** Inhibition of VMAT2 by β2-adrenergic agonists, antagonists, and the atypical antipsychotic ziprasidone. *Commun Biol.* 2022 Nov 23;5(1):1283. doi: 10.1038/s42003-022-04121-1. PMID: 36418492; PMCID: PMC9684503.
2. **Martin-Malpartida P, Hausvik E, Underhaug J, Torner C, Martinez A, Macias MJ.** HTSDSF Explorer, A Novel Tool to Analyze High-throughput DSF Screenings. *J Mol Biol*. 2022 Jun 15;434(11):167372. doi: 10.1016/j.jmb.2021.167372. Epub 2021 Nov 19. PMID: 35662461.
3. **Bueno-Carrasco MT, Cuéllar J, Flydal MI, Santiago C, Kråkenes TA, Kleppe R, López-Blanco JR, Marcilla M, Teigen K, Alvira S, Chacón P, Martinez A, Valpuesta JM.** Structural mechanism for tyrosine hydroxylase inhibition by dopamine and reactivation by Ser40 phosphorylation. *Nat Commun.* 2022 Jan 10;13(1):74. doi: 10.1038/s41467-021-27657-y. PMID: 35013193; PMCID: PMC8748767.

The Cell Models Node

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

Node leaders: Kristina Xiao Liang & Christian Dölle

Dr. Kristina Xiao Liang is a senior researcher and team leader in the Mitochondrial Stem Cell Research group. She is a dentist by training and obtained her PhD in 2013 from UiB. She is an expert in induced pluripotent stem cell (iPSC) derived models of neurological disease, including 2D and 3D culture modes.

Dr. Christian Dölle is the Head of Molecular Biology at the Neuromics research group at Neuro-SysMed. A biochemist by training, he obtained his PhD in molecular biology/biochemistry in 2008. He is an expert in mitochondrial biology and NAD metabolism, and has extensive experience in establishing and studying neuronal cell models.

Together, they have established a repertoire of different models focused on mitochondrial impairment, abnormal protein aggregation, and other pathways shown to be affected in patients with the disease groups of Neuro-SysMed.

Node activities

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

Several models have been established, including multiple cell models of mitochondrial dysfunction, ribosomal inhibition, α-synuclein aggregation, human iPSC-derived neuronal and astrocytic 2D cultures with different aspects of mitochondrial impairment (respiratory complex I deficient and aberrant mtDNA homeostasis), and human iPSC-derived 3D brain organoids with similar phenotypes. The Cell Models Node will continue to implement mechanistic analyses of these models (including multi-omics characterization) and initiate high-throughput drug screening in collaboration with the Drug Discovery Node.

Selected publications from 2022:

1. **Chen A, Kristiansen CK, Høyland LE, Ziegler M, Wang J, Sullivan GJ, Li X, Bindoff LA, Liang KX.** POLG mutations lead to abnormal mitochondrial remodeling during neural differentiation of human pluripotent stem cells via SIRT3/AMPK pathway inhibition. *Cell Cycle.* 2022 Jun;21(11):1178-1193. Doi: 10.1080/15384101.2022.2044136. Epub 2022 Mar 17. PMID: 35298342; PMCID: PMC9103491.

2. **Kristiansen CK, Chen A, Høyland LE, Ziegler M, Sullivan GJ, Bindoff LA, Liang KX.** Comparing the mitochondrial signatures in ESCs and iPSCs and their neural derivations. *Cell Cycle*. 2022 Oct;21(20):2206-2221. Doi: 10.1080/15384101.2022.2092185. Epub 2022 Jul 10. PMID: 35815665; PMCID: PMC9518993.

The Metabolomics Node

The Metabolomics node conducts cutting-edge research to elucidate disease-specific alterations in metabolism, with the potential to be translated into novel therapeutic targets and biomarkers for diagnosis and evaluation of treatment response. In addition, the node coordinates the metabolomics analyses conducted as part of the clinical trials within Neuro-SysMed and develops and implements the technologies to assess the NAD metabolome.

Node leader: Mathias Ziegler

Professor Ziegler is a world leading expert on mitochondrial biology and NAD-metabolism and leads the Molecular Bioenergetics and Signaling Group at the Department of Biomedicine, University of Bergen (UiB). Currently, he is also involved in two EU networks and core PI in the recently established KG Jebsen Center for Parkinson's Disease. Moreover, he coordinates three projects funded by the Research Council of Norway. In his experimental research, Ziegler has made key contributions to the discovery of fundamental biological processes in cellular bioenergetics and signalling related to human health. Over the past years, his group has developed advanced technologies to study the biology of NAD and other vital cofactors. These techniques are instrumental to establish bioenergetics and NAD status in patient samples from Neuro-SysMed's clinical studies.

Key node partner: Ines Heiland

Professor Heiland is an expert in theoretical biochemistry and mathematical modelling. She is a professor for molecular biology and bioinformatics at the University of Tromsø, and an adjunct professor at the Department of Clinical Medicine, UiB, for her involvement in Neuro-SysMed research activities. She is furthermore chair of the International Study Group in Systems Biology (ISGSB) and head of the board of the Norwegian Research School for Bioinformatics, Biostatistics and Systems Biology. Her research group is building mathematical models of biochemical processes to predict biomarkers, treatment response and disease outcome for different diseases. In addition, they are developing data analysis pipelines and machine learning approaches for mass spectroscopy data analysis of metabolic signatures and fluxes and protein modifications dynamics.

Node activities

Perturbations of mitochondrial function and energy metabolism play an important role in neurodegenerative processes. Decreased oxidative phosphorylation can lead to ATP deficiency, accumulation of reactive oxygen species and aberrant metabolism of NAD+, one of the most critical molecules for bioenergetic conversions and signalling in human cells. Conversely, modulation of cellular bioenergetics, via NAD-replenishment and other routes, is a promising novel therapeutic strategy to counteract neurodegeneration, which Neuro-SysMed is heavily invested in (see the clinical nodes).

Metabolic changes play a central pathogenic role in all four neurological diseases targeted by Neuro-SysMed. Moreover, changes in metabolism are often detectable in clinically available tissues (e.g., CSF or blood due to systemic effects or leakage), which makes them suitable for biomarker development, and their study is likely to yield therapeutic targets amenable to existing drugs. Despite this clear potential, the metabolome of individuals with PD, dementia, ALS and MS remains largely unexplored.

Developing the infrastructure for NAD metabolomics has been a large undertaking and in autumn of 2022, the Metabolomics Node made an agreement with the Department of Biology, UiB, securing stable access to LC-MS equipment and technical support. This will allow the node to continue supporting the clinical trials.

In addition, they are very happy to have been able to recruit a new researcher, Dr. Suraj Sharma, who is working closely with Professors Ziegler and Heiland. His research revolves around harnessing multi-omics data of patients with PD, dementia, ALS and MS, to: 1) identify metabolic biomarkers for diagnosis, prognosis, therapeutic response, and patient stratification and 2) to develop modelling approaches to identify novel therapeutic targets.

To do this, they are using both publicly available datasets (e.g., UK Biobank, PPMI) and metabolomic, proteomic, transcriptomic, epigenomic and genomic data generated from ongoing cohort and clinical intervention studies at Neuro-SysMed, to develop mathematical modelling approaches to predict metabolic alterations for different disease subtypes and individual patients. These models shall enable prediction of treatment responses as well as potentially enable early patient stratification and provide mechanistical insights into the development of disease. New data analysis pipelines especially for metabolomics analyses are being developed to be used for the analysis of currently acquired data, future clinical studies and the development of future diagnostics.

Selected publications from 2022:

Sharma S, Hsieh YC, Dietze J, Bockwoldt M, Strømland Ø, Ziegler M, Heiland I. Early Evolutionary Selection of NAD Biosynthesis Pathway in Bacteria. *Metabolites.* 2022 Jun 21;12(7):569. Doi: 10.3390/metabo12070569. PMID: 35888693; PMCID: PMC9316036.

The Systems Biology & Bioinformatics (SBB) Node

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

Node leader: Charalampos Tzoulis

Charalampos Tzoulis, MD, PhD is a professor of neurology and neurogenetics at the University of Bergen and Haukeland University Hospital. Professor Tzoulis is an expert on movement disorders and neurodegeneration, including dementia and parkinsonism. His research focuses on exploring the role of mitochondrial dysfunction in Parkinson's disease (PD), with the aim to improve patient diagnosis and develop neuroprotective therapies. Currently, he is the head of the Neuromics Research Group, director of the K.G Jebsen Centre for Translational Research in Parkinson's disease, and co-director of the Neuro-SysMed Centre, where he has the overarching responsibility for neurodegeneration research.

Node activities

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

During 2022, the Systems Biology & Bioinformatics (SBB) Node made substantial advances:

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

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

Several key milestones were reached in 2022. The transcriptome and coding genome sequence of more than 1,300 brain samples were mapped using high-depth RNA-sequencing. This is currently the largest transcriptomic repository of neurodegenerative parkinsonism's in the world, and comprises individuals with PD, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, dementia with Lewy bodies, Alzheimer's disease, and healthy controls. In addition, the proteome of ~500 of the same samples was mapped, and single-nucleus RNA-sequencing was performed on 50 individuals. The data is currently being analysed and integrated and several publications are planned submitted in 2023. Preliminary analyses have already revealed novel insight into the role of methylation in the mitochondrial genome, and the transcriptome-proteome coupling in the PD brain (in press in 2022). Furthermore, using the Norwegian prescription registry, the team has revealed novel and dynamic aspects of PD epidemiology in the entire Norwegian population.

Selected publications from 2022:

1. **Guitton R, Nido GS, Tzoulis C.** No evidence of extensive non-CpG methylation in mtDNA. *Nucleic Acids Res*. 2022 Sep 9;50(16):9190-9194. doi: 10.1093/nar/gkac701. PMID: 35979955 .

2. **Flønes IH, Nyland H, Sandnes DA, Alves GW, Tysnes OB, Tzoulis C.** Early Forms of α-Synuclein Pathology Are Associated with Neuronal Complex I Deficiency in the Substantia Nigra of Individuals with Parkinson's Disease. *Biomolecules*. 2022 May 25;12(6):747. doi: 10.3390/biom12060747.PMID: 35740871.

3. **Guitton R, Dölle C, Alves G, Ole-Bjørn T, Nido GS, Tzoulis C.** Ultra-deep whole genome bisulfite sequencing reveals a single methylation hotspot in human brain mitochondrial DNA. *Epigenetics*. 2022 Aug;17(8):906-921. doi: 10.1080/15592294.2022.2045754. Epub 2022 Mar 7.PMID: 35253628.

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, PhD, Cand. Philol., 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, MD, PhD, is a postdoc (50%) and specialist in training (psychiatry) (50%). Her research spans development of personalized molecular therapy for acute myeloid leukaemia, RRI of precision medicine and philosophy of suffering.

Node activities

The RRI/PPI Node is responsible for three projects:

1. A research project entitled "Philosophy of precision medicine in severe chronic neurological diseases (POS-PM)."
2. An innovation project entitled "Communicating cognitive decline: Language games with tactile and visual objects (CCD)." The project was a proof of concept to test Amy van den Hooven's visual and tactile tool kit, created during her Master's in Design.
3. 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.

During 2022, Engen and Karlsen have been working on a co-authored monograph (working title: *Precision and Suffering*). The book will contain the development of a novel model of suffering and its application in RRI engagements with precision medicine. They are in contact with a publisher. The year 2022 also saw the successful securing of funds from *UiB idé* for an innovation project (CCD) and its start-up during the autumn. Ultimo 2022, the node finalised a course description to be delivered during the spring of 2023.

The node is also conducting **extensive dissemination activities**, including:

- Engen C. (participant by invitation), "Lidelse i psykiatri - mellom dialog og tvang" Dialogisk Cafè, Bergen Public Library, February 15, 2022
- Engen C. (participant by invitation), "Bioteknologidagen Bergen 2022 – Persontilpasset medisin: revolusjon eller håp til en høy pris?", Bioteknologirådet, Litteraturhuset i Bergen, February 24, 2022. https://www.youtube.com/watch?v=kf3p26p3B0Q&t=3766s
- Engen C. and Karlsen J. (participants by invitation), "Kan medisinen svekke menneskets evne til å bære lidelse?" Filosofisk poliklinikk, Litteraturhuset i Bergen, March 2, 2022. https://www.youtube.com/watch?v=1QLXp_Dsfus

Selected publications from 2022:

1. **Engen, C. (2022). The Dynamics of the Labelling Game: An Essay On FLT3 Mutated Acute Myeloid Leukaemia FLT3 Mutated Acute Myeloid Leukaemia. Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern. A. Bremer and R. Strand. Cham, Springer International Publishing: 121-132.**
2. **Engen, C. (2022). Introduction to the Imaginary of Precision Oncology. Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern. A. Bremer and R. Strand. Cham, Springer International Publishing: 17-28.**
3. **Strand, R. and C. Engen (2022). Filled with Desire, Perceive Molecules. Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern. A. Bremer and R. Strand. Cham, Springer International Publishing: 251-267.**
4. **Engen C. (2022) Legen, medisinen og fremtiden. Michael; 19: 247–52.**

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 randomized, double-blind setup. *Observational trials* involve following and characterizing 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 23 ongoing or planned studies:

- MS — The RAM-MS study: a randomized 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 SMART-MS study: Study of Mesenchymal Autologous stem cells as Regenerative Treatment for Multiple Sclerosis
- MS — The NORSEMAN Study: Nicotinamide Riboside Supplementation in Progressive Multiple Sclerosis: A Randomised Controlled Trial
- MS — COVID-19 vaccination response in multiple sclerosis patients receiving various disease-modifying therapies
- MS — The REDUCE-MS study: Rituximab Extended Dose interval in mUltiple sCIErosis
- MS — The FlowOX-MS study-2: Efficacy of intermittent negative pressure by FlowOX on spasticity in multiple sclerosis
- MS — The TAF-MS study: Tenofovir alafenamide fumarate (TAF) and Epstein-Barr virus infection in multiple sclerosis – a proof of concept study
- PD — The NADPARK study: a phase I double-blinded randomized pilot trial of NAD-supplementation in drug naïve Parkinson's disease
- PD — The NOPARK study: a phase II randomized controlled trial of nicotinamide riboside in early Parkinson's disease
- PD — The NOPARK extension study: an open label trial of long-term treatment with nicotinamide riboside (NR) in Parkinson's disease
- PD — The 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 NO-PSP study: a phase II randomized controlled trial of NAD-replenishment therapy in Progressive Supranuclear Palsy
- PD — The STRAT-PARK study: a prospective multimodal cohort study to stratify Parkinson's disease and other parkinsonisms
- PD — The DIGI.PARK study: a trial of active wearable sensing technology as disease progression markers and treatment outcome measures in Parkinson's disease (PD)
- 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
- ALS — The NO-ALS study: a phase-II, multi-centre, double-blinded randomized clinical trial of oral NR and pterostilbene in early ALS
- ALS — The NO-ALS extension study: an open label study of long-term therapy with NR and pterostilbene in ALS
- ALS — The STRAT-ALS study: an initiative to stratify amyotrophic lateral sclerosis
- ALS — The ALS LTMV study: effects of long-term ventilation support on the quality of life of ALS patients and their families

CLINICAL STUDIES IN THE MULTIPLE SCLEROSIS (MS) FIELD

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

Coordinating investigator: Øivind Torkildsen /
Study director: Lars Bø

Disease: Multiple Sclerosis
Type of study: Interventional trial

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

This is a multidisciplinary, international treatment trial, involving the Department of Haematology (Dr. Anne Kristine Lehmann), the Department of Transfusion Medicine and Immunology (Professor Einar Kristoffersen) and the Department of Neurology (Professor Øivind Torkildsen) in close collaboration with coordinating centres in all Norwegian health regions.

The objectives are to investigate 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 randomized controlled trial comparing the efficacy and safety of HSCT (n=50) compared to standard high-efficacy therapies (n=50) in highly active multiple sclerosis with breakthrough disease activity.

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

Status: Until now, 75 patients have been enrolled in the study, and enrolment will continue until the target of 100 patients is reached. Patients from all health regions in Norway are screened and randomized at the University Hospital of North Norway (Tromsø), St. Olav's Hospital (Trondheim), Akershus University Hospital (Lørenskog), and Haukeland University Hospital (Bergen). Norwegian patients randomized 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.

The international study sites are located in Copenhagen (DK), Amsterdam (NL), Uppsala and Gothenburg (S).

SUPPORT:

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
- VU University Medical Centre, Amsterdam

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

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

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

Disease: Multiple Sclerosis
Type of study: Interventional trial

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

Rituximab has been used for the treatment of rheumatological diseases and haematological cancers since 1998, and due to patency expiration, costs only a fraction of ocrelizumab. If rituximab proves similar effects as ocrelizumab, it may therefore reduce the annual cost for MS-therapy by several hundred million NOK in Norway alone and give MS-patients access to highly effective treatment at an earlier timepoint. In this study, the MS Node therefore aims to compare the efficacy and safety of rituximab to ocrelizumab for treatment of newly diagnosed treatment naïve patients with relapsing-remitting MS.

The objective of this a randomized double-blinded non-inferiority study is to evaluate whether rituximab has comparably efficacy and safety as ocrelizumab in the treatment of newly diagnosed patients with multiple sclerosis.

Design: This is a randomized, double-blinded, controlled non-inferiority trial comparing the efficacy and safety of rituximab (n=125) to ocrelizumab (n=83) in newly diagnosed relapsing-remitting MS patients.

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

Status: The first patient was recruited at Haukeland University Hospital in early November 2020 and the study was fully included in 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.

SUPPORT:

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

Sweden
- Karolinska Institutet, 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 SMART-MS study: Study of Mesenchymal Autologous stem cells as Regenerative Treatment for Multiple Sclerosis

Coordinating investigator: Christopher Kvistad /
Study director: Lars Bø

Disease: Multiple Sclerosis
Type of study: Interventional trial

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 neuroregenerative 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 randomized 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 currently 13 patients have been enrolled in the study.

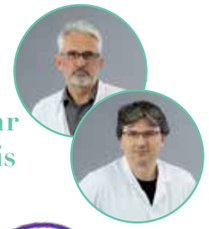
SUPPORT:

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

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



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

Disease: Multiple Sclerosis
Type of study: Interventional trial

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 disease course in progressive multiple sclerosis (PMS). 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 PMS.

Design: This is a randomized double-blinded study where 300 patients with progressive MS receive oral 500 mg oral nicotinamide riboside (NR) (n=150) or placebo (n=150) 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 protocol is approved by the Regional Committees for Medical and Health Research Ethics, Western Norway, and clarified by the Norwegian Medicines Agency. Nicotinamide riboside (NR) and placebo capsules will be supplied free of cost by Elysium Health, New York, USA. Estimated study start is Q2 2023.

SUPPORT:

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

Other study centres in Norway are to be decided.

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)

COVID-19 vaccination response in multiple sclerosis patients receiving various disease-modifying therapies

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

Disease: Multiple Sclerosis
Type of study: Observational trial

Background: Previous studies have concluded 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 immunosuppressive effects and may therefore influence the immune response to various vaccines. Although limited data are available, our MS group has previously shown that interferon-beta therapies do not influence the vaccination response, while glatiramer acetate, natalizumab, fingolimod, and especially mitoxanthrone, may influence the efficacy of vaccination. 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 current challenge of COVID-19 vaccination, the MS group aimed to perform a study on efficacy and safety of COVID-19 vaccines in MS-patients.

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

Design: This is a prospective observational trial evaluating vaccination responses of COVID-19 vaccines in MS-patients receiving different disease-modifying therapies.

Primary endpoint: Humoral vaccine response to 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.
Coordinating investigator for the MS-arm of the study is Øivind Torkildsen, and the project will be included in the thesis of PhD Candidate Dr. Hilde Marie Torgauten.

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

Results so far have shown that rituximab and fingolimod reduce the humoral vaccination response to COVID-19 vaccines, and that booster vaccines improve this vaccine response.1,2 Further studies on cellular immune responses will be conducted.

References
1. **König M et al.** Immunogenicity and Safety of a Third SARS-CoV-2 Vaccine Dose in Patients With Multiple Sclerosis and Weak Immune Response After COVID-19 Vaccination. *JAMA Neurol* 2022;79:307-309.
2. **König M et al.** Humoral immunity to SARS-CoV-2 mRNA vaccination in multiple sclerosis: the relevance of time since last rituximab infusion and first experience from sporadic revaccinations. *J Neurol Neurosurg Psychiatry* 2021:jnnp-2021-327612.

SUPPORT:

Participating Centres
- Haukeland University Hospital, Bergen
- Oslo University Hospital, Oslo
- Sørlandet Hospital Trust, Kristiansand

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

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

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

Disease: Multiple Sclerosis
Type of study: Interventional trial

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 is a single starting dose of 1000 mg infusion, followed by 500 mg infusions every six months for an undefined time. The therapy seems safe, and limited side effects are reported, where neutropenia, lymphopenia, hypogammaglobulinemia and infections are the most frequent adverse events. Real world experience indicate that B-cells may be depleted for a longer period of time, even for at least 12 months, and longer dosing intervals than 6 months (e.g., due to intercurrent illness or pregnancy planning) seems safe. Based on these observations, the MS research group aims to investigate whether an extended dosing interval from 6 to 12 months is safe in relapsing-remitting MS.

The group aims to enrol clinical stable patients who have received a standard dose of rituximab in six months intervals for at least two years. The patients will be randomized for further therapy with the same dose (500 mg) at either 6 months or 12 months intervals, and followed by frequent monitoring, by clinical, MRI and blood biomarker measurements, such as serum neurofilament, B-cell counts, rituximab serum concentration and anti-drug antibodies.

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

Design: This is a randomized controlled open label trial comparing the efficacy and safety of standard interval dosing (SID – of six months; n=100) to extended interval dosing (EID – of twelve months; n=100) of rituximab in relapsing-remitting MS patients.

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

Status: This study has been postponed, mainly due to the COVID-19 pandemic. The study protocol will be finalized and prepared for submission to the Regional Committees for Medical and Health Research Ethics Western Norway, and the Norwegian Medicines Agency during Q2-2023. Estimated study start is Q3 2023.

SUPPORT:

Participating Centres
Norway
- Haukeland University Hospital, Bergen

Other study centres in Norway are to be decided.

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 FlowOX-MS study-2: Efficacy of intermittent negative pressure by FlowOX on spasticity in multiple sclerosis

Coordinating investigator &Study director:
Kjell-Morten Myhr

Disease: Multiple Sclerosis
Type of study: Interventional trial

Background: The treatment of pain and spasticity in multiple sclerosis (MS) is often challenging due to suboptimal effects, and reasonable goals are often to alleviate and not eliminate the symptoms. This may lead to despairing patients, often trying alternative treatment strategies. In this context, several MS-patients have tried a new treatment method shown to reduce lower extremity pain by improved blood circulation in the lower extremities. A pressure chamber (FlowOx) sealed around the patient's legs just below the knee, applies a negative pressure and atmospheric pressure cycles. The treatment is currently approved and used for selected patients with arterial insufficiency caused by intermittent claudication or diabetes-related leg ulcers. A recent pilot study showed significant relief of pain and spasticity with consequent improvement in functional levels in 10 MS patients.

The objective is to evaluate the clinical effects of treatment with – 40 mm Hg intermittent negative pressure applied by FlowOx2.0 on spasticity caused by multiple sclerosis (MS).

Design: This is a randomized double-blinded study where 60 patients with spasticity due to MS will receive 40 Hg intermittent negative pressure applied by FlowOx2.0 (n=30 active treatment) or 10 Hg intermittent negative pressure applied by FlowOx2.0 (n=30 placebo treatment) for four weeks, followed by an open label extension period of a total of 6 months.

The primary endpoint is the change in self-reported spasticity using Numeric Rating Scale (NRS) after 4 weeks.

Status: The Ethical Committees and the National Medicines Agencies in Sweden and Denmark have approved the protocol. The approval is pending in Norway. Patients are currently enrolled in Sweden. Estimated study start in Denmark and Norway is Q2 2023.

SUPPORT:

Participating Centres
- Haukeland University Hospital, Bergen
- NeuroCentrum, Stockholm, Sweden
- Department of Neurology, Motala Hospital, Motala, Sweden
- Department of Clinical Medicine - The Department of Neurology, Aarhus University Hospital, Denmark

Funding
- Haukeland University Hospital
- The University of Bergen
- Otivio AS, Oslo

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

Coordinating investigator &Study director:
Øivind Torkildsen

Disease: Multiple Sclerosis
Type of study: Interventional trial

Background: Novel insights from the MS research group indicate that infection with the Epstein-Barr Virus (EBV) is the leading cause of MS. As EBV infection is persistent for life, the virus could act 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 tested in MS patients. This trial could lead to a new paradigm in MS therapy, as it will test a drug that may target the underlying cause of the disease.

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

Design: This is a randomized double-blinded, placebo-controlled trial comparing the efficacy and safety of two doses of Tenofovir alafenamide fumarate (TAF) (n= 16) to placebo (n=8) on EBV viral infection as add on therapy in stable RRMS patients receiving natalizumab therapy.

The primary endpoint is safety and tolerability of the drug and change in EBV shedding in saliva after 6 months of treatment.

Status: Funding is established for the trial, from a research grant from the Norwegian MS Society and the Helse Vest Regional Health Authorities, and the protocol for the trial is finalized for submission to the ethical committee. A pilot testing of methods to evaluate EBV shedding in saliva has been conducted, with positive results. The protocol will be submitted for evaluation by regulatory authorities by Q1 2023 and estimated start of patient recruitment is Q3 2023.

SUPPORT:

Participating Centres
Norway
- Haukeland University Hospital, Bergen
- Stavanger University Hospital, Stavanger
- Førde Hospital, Førde
- Haugesund Hospital, Haugesund

Sweden
- Karolinska Institute, Stockholm

USA
- Harvard University, Boston

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

CLINICAL STUDIES IN THE PARKINSON'S DISEASE (PD) FIELD

The NADPARK study: a phase I double-blinded randomized pilot trial of NAD-supplementation in drug naïve Parkinson's disease

Coordinating investigator: Brage Brakedal /
Study director: Charalampos Tzoulis

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

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.

The primary objective of the NADPARK study is to assess safety and tolerability, cerebral bioavailability, neurometabolic impact, clinical and molecular effects of NR therapy in PD.

Design: NADPARK is a phase I randomized, double-blinded trial. A total of 30 individuals with newly diagnosed, drug-naïve PD were randomized to NR 1000mg/day or placebo for 30 days. Measures include safety, scale-based clinical assessment, brain NAD-levels by ^{31}phosphorous magnetic resonance spectroscopy (31P-MRS), cerebral metabolic pattern by 8fluoro-deoxyglucose positron emission tomography (FDG-PET), NAD-metabolome in blood, muscle and cerebrospinal fluid (CSF), and transcriptomics in blood and CSF.

Primary endpoint: The between-group difference in the neurometabolic response, comparing baseline and end of study.

Status: The study was published in 2022. NR treatment was well tolerated and led to a significant but variable increase in cerebral NAD levels, measured by ^{31}phosphorous magnetic resonance spectroscopy (31P-MRS), and related metabolites in the cerebrospinal fluid (CSF). Moreover, NR recipients showing increased brain NAD levels exhibited altered cerebral metabolism, measured by ^{18}fluoro-deoxyglucose positron emission tomography (FDG-PET), and this was associated with a mild but statistically significant clinical improvement. Furthermore, NR augmented the NAD metabolome and induced transcriptional upregulation of processes related to mitochondrial, lysosomal, and proteasomal function in blood cells and/or skeletal muscle. Furthermore, NR decreased the levels of inflammatory cytokines in serum and cerebrospinal fluid. These findings nominate NR as a potential neuroprotective therapy for PD, warranting further investigation in larger trials.

SUPPORT:

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 NOPARK study: a phase II randomized controlled trial of nicotinamide riboside in early Parkinson's disease

Coordinating investigator: Brage Brakedal /
Study director: Charalampos Tzoulis

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

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

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

Status: The study is ongoing and has included 260/400 participants. It is estimated to be completed in December 2024.

SUPPORT:

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

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

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

Coordinating investigator: Brage Brakedal /
Study director: Charalampos Tzoulis

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

Background: We are conducting a phase-II, double-blinded randomized clinical trial of oral nicotinamide riboside (NR) in early Parkinson's disease (PD) (see 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 enroll 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 recruits participants who have completed the NOPARK study, from 10 centres across Norway.

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

Status: The study is ongoing and has included 100/400 participants. It is estimated to be completed in March 2025. The NOPARK extension study will be completed when the NOPARK study has been concluded and analyzed.

SUPPORT:

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

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

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

Coordinating investigator: Haakon Berven /
Study director: Charalampos Tzoulis

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

Background: While previous findings from the Parkinson's Disease (PD) Node nominate NR as therapy for PD, the observed effects were heterogeneous across the study population, raising the question of individualized dose-dependent responses. The optimal NR dose for neurological intervention is unknown, and doses over 2,000 mg daily have not been tested in humans. To be able to conduct a dose-optimization 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 3,000mg oral NR in PD.

The primary objective of the NR-SAFE study is to determine the safety of oral NR 3000mg 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 randomized double-blinded placebo-controlled trial to assess the safety and tolerability of NR at a dose of 3000mg per day. Twenty individuals with PD will receive NR 3,000 mg or placebo (1:1 randomization) 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 in 2022 and the results submitted for publication. 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).

SUPPORT:

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

Coordinating investigator: Haakon Berven /
Study director: Charalampos Tzoulis

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

Background: While previous findings from the Parkinson's Disease (PD) Node nominate NR as therapy for PD, the observed effects were heterogeneous across the study population, raising the question of individualized dose-dependent responses. Thus, the optimal NR dose for neurological intervention is unknown. N-DOSE is a dose-optimization trial of NR in PD, which will address this important knowledge gap.

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

Design: N-DOSE is a randomized 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 randomized 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 3000mg at one-month intervals. Measures will include clinical, neuroimaging (31P-MRS, FDG-PET), molecular, and biochemical endpoints. Study duration will be three months.

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

Status: The study was initiated in 2022.

SUPPORT:

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

Coordinating investigator: Christian Dölle /
Study director: Charalampos Tzoulis

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

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

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

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

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

Status: The study was initiated in 2022.

SUPPORT:

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 NO-PSP study: a phase II randomized controlled trial of NAD-replenishment therapy in Progressive Supranuclear Palsy

Coordinating investigator: Geir Olve Skeie /
Study director: Charalampos Tzoulis

Disease: Progressive Supranuclear Palsy (PSP)
Type of study: Interventional trial

Background: PSP is one of the most common forms of neurodegenerative parkinsonism, after Parkinson's disease (PD), and an important cause of disability and death on a global scale. Currently, there are no neuroprotective therapies able to delay or arrest disease progression in PSP. Moreover, unlike PD, symptomatic dopaminergic therapy is usually ineffective. Patients become quickly care-dependent, due to rapidly increasing motor and cognitive disability, with an estimated overall survival of 3-8 years from diagnosis.

Previous research by the PD Node has nominated the NAD-precursor nicotinamide riboside (NR), as a potential neuroprotective and symptomatic therapy for neurodegenerative parkinsonisms. Encouraged by these findings, we will perform the NO-PSP study: a phase-II, double-blinded randomized trial of NR in PSP.

The primary objective of the NO-PSP study is to determine whether treatment with NR, 3000 mg daily, can delay disease progression in PSP, as measured by the change from baseline to week 52 in the PSPRS total score.

Design: NO-PSP is a phase II double-blind randomized clinical trial of oral NR,3000 mg per day, in PSP. The study will recruit a total of 200 participants with PSP from all of Norway, France, Canada, and the UK. Study duration will be one year.

Primary endpoint: the between-group (NR vs. placebo) difference in the change from baseline in the total PSPRS at 52 weeks.

Status: The study protocol was established, approvals applied for, and partial funding was acquired in 2022. Recruitment is estimated to start in June 2023.

SUPPORT:

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

Funding
- The Norwegian Parkinson's Disease Association
- 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

Coordinating investigator: Simon Kverneng /
Study directors: Charalampos Tzoulis & Mandar Jog

Disease: Parkinson's disease & other neurodegenerative parkinsonisms
Type of study: Observational trial

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 suggest 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-center longitudinal cohort study aiming to stratify NDPs according to underlying biological mechanisms, so that tailored treatments can be developed and applied.

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

Design: STRAT-PARK is a prospective, longitudinal observational cohort study. A total of 2,000 individuals with PD, DLB, PSP, MSA, CBS, and healthy controls will be included from HUS, St. Olavs Hospital in Trondheim, and the Center of Excellence for Parkinson's disease at the Lawson Institute for Research, London, Ontario, Canada. Participants will be followed longitudinally with systematic clinical assessment, neuroimaging, collection of biological material, and postmortem brain collection.

Status: STRAT-PARK is ongoing and a total of 250 participants have been recruited at the end of 2022. This is a critical milestone as we are now able to implement the first analyses in the dataset. Moreover, a steady-recruitment rate has been reached at ~150 new participants per year. Notably, external funding was obtained on a subproject of STRAT-PARK from the ***Michael J Fox Foundation,*** to start Feb 2023.

SUPPORT:

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

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

The DIGI.PARK study: a trial of active wearable sensing technology as disease progression markers and treatment outcome measures in Parkinson's disease (PD)

Coordinating investigator: Bettina Husebø /
Study directors: Bettina Husebø & Charalampos Tzoulis

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

Background: The ability to perform accurate and reproducible clinical evaluation of individuals with PD is currently hindered by two major limitations: 1) Clinical assessment is largely based on subjective assessment by the treating neurologist – either empirically, or by means of systematic clinical scales, such as the Unified Parkinson's Disease Rating Scale (UPDRS). The subjective nature of these assessments introduces high variability in clinical assessment, which in turn biases clinical observational and treatment studies. 2) The patients' extent and severity of clinical dysfunction varies considerably over a 24h period, partly due to the effects of dopaminergic treatment. Thus, the state of the patient witnessed during a clinical session is not necessarily representative of the individual's condition. The DIGI.PARK study addresses these limitations by researching the use of wearable sensing devices to monitor essential motor (e.g., tremor, balance, bradykinesia) and non-motor (e.g., sleep, apathy) features of PD, continuously over time with higher temporal resolution.

Objectives: DIGI.PARK aims to design digital phenotyping algorithms and associated digital biomarkers to recognize symptoms in persons with PD. The study will ascertain whether this technology can help identify, track, and predict symptom associations of PD. It will also investigate new outcome measures (digital biomarkers) for clinical trials that address PD.

Design: Patients with PD and neurologically healthy controls are fitted with wearable sensing devices of two types: smartwatches (Fitbit Sense and Empatica E4) and a smart ring (Oura Ring). These instruments can measure movement (3-axes acceleration), heart rate, and electrodermal activity, which can yield information such as activity, sleep, and stress. The clinical assessment scales are UPDRS, the Montreal Cognitive Assessment (MoCA), the Geriatric Depression Scale (GDS), the Geriatric Anxiety Inventory (GAI), the Apathy Evaluation Scale (AES), and the REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ). Self-reported diaries of activities and medication times are logged. The data retrieved from the devices will be analysed using artificial intelligence and digital signal processing techniques, beginning with a comparative analysis, followed by a before/after longitudinal analysis of medication effect, and finally design of digital biomarkers with clinical significance.

Primary endpoint: Validated digital biomarkers to track PD symptoms over time with sufficient sensitivity to medication (confidence >95%).

Status: The first part of the data collection was finalized in December 2022 with N=15 participants with PD and N=15 controls. A method article was published in October 2022 (DOI: doi.org/10.1371/journal.pone.0275747).

SUPPORT:

Participating Centre
- Haukeland University Hospital, Bergen

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

CLINICAL STUDIES IN THE DEMENTIA FIELD

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

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

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

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

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

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

Design: N-DOSE AD is a randomized 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 randomized 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 1000mg NR group will be assessed to identify any time effects and differentiate those from dose-effects.

Status: The study was initiated in 2022. The first 2 participants were included in December 2022.

SUPPORT:

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

Coordinating investigator: Ragnhild Eide Skogseth /
Study director: Kristoffer Haugarvoll

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

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

The central hypothesis in this project is that converging molecular pathways exist across subtypes of dementia, but also that there are underlying subtypes that may not be fully reflected in the current classification system of dementia.

STRAT-COG is a study to better understand mixt pathologies in dementia and to identify sub-groups of disease that reflect underlying biology. The group proposes to identify biological overlap and disease subtypes, based on a transdisciplinary approach integrating cognitive testing, clinical investigations, neuroimaging and molecular biomarkers. Thus, this approach will enable us to reclassify and stratify dementia according to underlying biological patterns. The study also includes a brain donation program.

Primary objective: To establish a cohort with multidimensional data that can be orderly integrated into the complex clinical and biological spectrum of dementia, and to stratify it into subclasses with homogeneous biology and prognosis. This knowledge will then be used to develop diagnostic and prognostic biomarkers and identify novel therapeutic targets.

Design: Cohort study with biannual follow-up.

Status: The study was initiated in 2022. The first 50 participants (individuals suffering from dementia and control individuals) have been included. A brain bank has been established.

SUPPORT:

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

CLINICAL STUDIES IN THE AMYOTROPHIC LATERAL SCLEROSIS (ALS) FIELD

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

Coordinating investigator: Ole-Bjørn Tysnes /
Study Directors: Ole-Bjørn Tysnes &
Charalampos Tzoulis

Disease: ALS
Type of study: Interventional trial

Background: There are currently no neuroprotective treatments for ALS with a significant impact on disease progression. Previous research by the PD Node and others has nominated NAD-replenishment therapy as a promising neuroprotective strategy against neurodegeneration. Moreover, a recently published small trial using a combination of the NAD-precursor nicotinamide riboside (NR) and sirtuin booster pterostilbene, showed encouraging findings in ALS. To test the potential of this strategy as a neuroprotective therapy for ALS, the Tysnes and Tzoulis groups 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 multi-centre, phase II randomized 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 the study arm 1.

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

Status: Patients have been included since October 2020. By the end of 2022, a total of 201 patients have been included, 95 in the study arm 1 which require 180 included patients. The study is expected to close by the end of 2024. Four new NO-ALS centres have joined in 2022 (Bodø, Lillehammer, Molde and Kristiansand).

SUPPORT:

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

Coordinating investigator & Study director: Ole-Bjørn Tysnes

Disease: ALS
Type of study: Interventional trial

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

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

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

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

Status: By end of 2022, 106 patients have been recruited to the study.

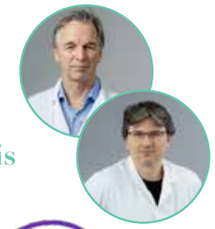
SUPPORT:

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

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

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

Coordinating investigator: Tale Bjerknes /
Study Directors: Ole-Bjørn Tysnes &
Charalampos Tzoulis



Disease: ALS
Type of study: Observational trial

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

To address the probable heterogeneity of mitochondrial function in ALS, Neuro-SysMed aims to conduct STRAT-ALS, a longitudinal cohort study to stratify ALS according to underlying biological mechanisms, so that tailored treatments can be developed and applied. Initially, the focus will be mitochondrial markers, based on well-established techniques and preliminary results from studies on Parkinson's disease. The study will start in 2023.

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

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

Status: STRAT-ALS protocols were finalized in 2022 and the study is expected to start in 2023.

SUPPORT:

Funding
- Helse Vest postdoc for Tale L. Bjerknes
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- The University of Bergen
- Donations from Nils Arne Morka

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

Coordinating investigator: Tale Bjerknes /
Study Director: Ole-Bjørn Tysnes

Disease: ALS
Type of study: Observational trial

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, organization of care, cultural differences, and economic considerations.

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

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

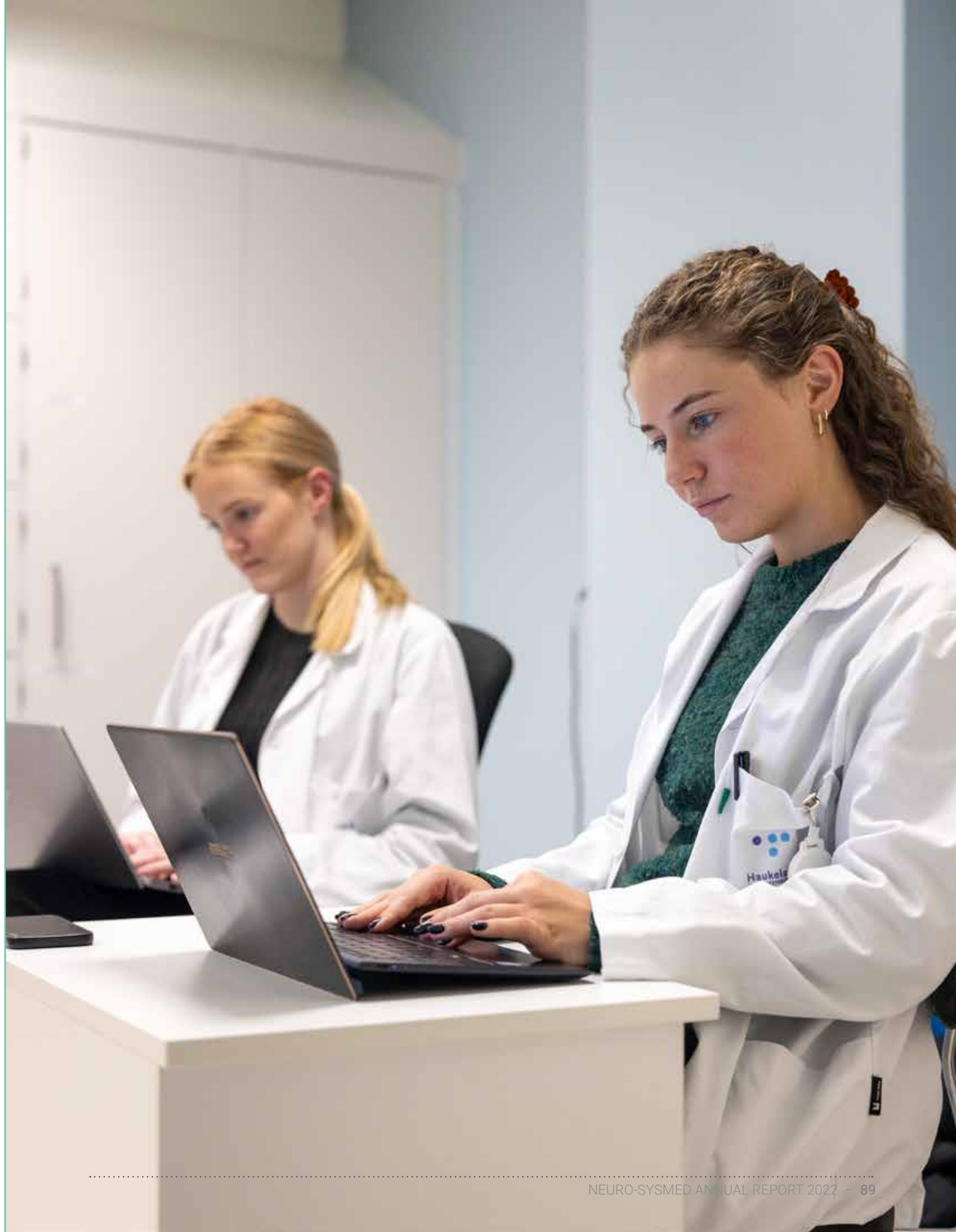
Primary endpoint: The HRQOL, global QoL and disease-specific QoL in ALS patients before and after the introduction of life sustaining LTMV.

Status: During 2022, funding was secured, and new research nurses were added to the team, as well as participating hospitals. The study is planned to start Q1 of 2023.

SUPPORT:

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

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



Mini Biographies of PhD candidates and postdocs

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

ANANDHAN, SHAMUNDEESWARI (postdoc)
MSc in biotechnology and a PhD from the University of Bergen focused on single cell mass cytometry by time of flight (CyTOF), with prospective exploration of novel biomarkers in ovarian cancer. Currently, she is pursuing her postdoc on multiple sclerosis in the MS Node. Her project aims at establishing blood-based biomarkers for personalized anti-CD20 therapy in multiple sclerosis.

AUR, DORIAN (clinical research fellow)
PhD from the University of Bucharest in automatic systems and postdoctoral fellowships in computational neuroscience from Western Ontario University, Barrow Neurological Institute and Stanford University. He works in the Jog group where his project focuses on integrating multimodal brain imaging techniques with novel computational techniques and non-invasive stimulation.

BENJAMINSEN, ESPEN (PhD candidate)
MD and consultant neurologist at the Department of Neurology, Nordland Hospital Trust, Bodø, Norway. He has been working as a PhD candidate associated to the MS Node, until his doctoral defence in April 2022. His PhD research focused on epidemiology and comorbidity in multiple sclerosis patients, with Myhr as co-supervisor.

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

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

BHAN, ALOK (PhD candidate)
MD from Trondheim (2009), and currently a consultant neurologist at the Department of Neurology, Stavanger University Hospital, Stavanger. He has been working as a PhD candidate associated to the MS Node, until his doctoral defence in December 2022. His PhD research focused on neurofilament light-hain as a biomarker in multiple sclerosis, with Myhr as co-supervisor.

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

BOYLE, LYDIA (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. During her masters, she investigated promotors and barriers to implementation of technology for persons with dementia. She has 12 years of clinical experience as a licensed physical therapist. Lydia is currently a PhD candidate at the Center for Elderly and Nursing Home Medicine (SEFAS) and Neuro-SysMed, with a project that aims to phenotype for changes in activity at the end-of-life in persons with chronic cognitive impairment using sensing technologies (DIPH.DEM).

BRAKEDAL, BRAGE (postdoc)
MD working at the Department of Neurology at Haukeland University Hospital and was a PhD candidate at Neuro-SysMed in the Tzoulis group and had his doctoral defence in April 2022. His PhD project concerned applying the Norwegian prescription database to study epidemiology and potential disease-modifying drugs in Parkinson´s disease. Currently, he is a postdoc in the Tzoulis group.

DICK, FIONA (postdoc)
MSc in bioinformatics from the Free University of Berlin. She did her PhD in the Tzoulis group studying gene expression in the Parkinson's disease brain. Her expertise is in the analysis of transcriptomic and proteomic data derived from human brain tissue. Currently, she is a postdoc in the same group, focusing on the identification of disease initiation and progression markers from longitudinal RNASeq data.

EID, KARINE (PhD candidate)
MD from the Norwegian University of Science and Technology, and currently a PhD candidate at Neuro-SysMed and the BERG Research Group. Eid has an epidemiological research project with focus on multiple sclerosis and mental health in pregnancy, and early life trauma in multiple sclerosis. The project uses data from the Norwegian Mother, Father and Child Cohort study, the MS Registry, and the Medical Birth Registry.

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

FLØNES, IRENE (postdoc)
MD from the University of Bergen with an expertise in pathology and immunohistochemistry. She did her PhD in the Tzoulis group, studying mitochondrial mechanisms in neurodegeneration. Her work currently focuses on the role of the mitochondrial respiratory chain in neurodegenerative disease.

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

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

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

HABIGER, TORSTEIN FRUGÅRD (PhD candidate)
MD from the University of Bergen in 2019, and a PhD candidate at the Centre for Elderly Care and Nursing Home Medicine (SEFAS) with Bettina Husebø (Dementia Node/Care Node) as main supervisor, until his doctoral defense in June 2022. His PhD work focused on the relationship between psychosis symptoms and pain in nursing home residents. He has since been working as a resident at Haugesund Hospital.

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

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

JUNG, KUNWAR (postdoc)
PhD from the University of Bergen in 2021 where he studied posttranslational modification and protein-protein interaction of enzymes from the aromatic amino acid hydroxylase family, especially tyrosine hydroxylase and phenylalanine hydroxylase. Currently, he is a postdoc in the Martinez lab, funded by the KG Jebsen Centre for Parkinson's Disease (DECODE-PD). His postdoc research aims to elucidate the physiological and pathological mechanisms by mitochondrial dysfunction and dopamine dysregulation contributing to neurodegeneration and to build cell-based assays for screening to validate targeted therapies, notably towards dysregulation of dopamine synthesis and Complex I deficiency.

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

KRISTIANSEN, CECILIE (PhD candidate)
MSc in biomedicine from the University of Bergen and currently a PhD candidate working together with Dr. Kristina Xiao Liang on modelling mitochondrial disease using stem cells. Her work is focused on the use of patient-specific iPSC-derived neural stem cells to establish a platform for application in compound screening, with the aim of identifying drug that mitigate mitochondrial dysfunction.

KRÅKENES, TROND-ANDRÉ (PhD candidate)
MSc in nanoscience from the University of Bergen. He is since 2022 a PhD candidate in the Martinez group. His PhD project is focused on three presynaptic proteins: α-synuclein, TH and VMAT2. The project aims to better understand the role of these proteins in the regulation of dopamine homeostasis and in Parkinson's disease.

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

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

LILLEBOSTAD, PEDER (PhD candidate)
MSc in biomedicine from the university of Bergen, with specialization in MRI analysis. He is currently a PhD candidate at MMIV, where he is involved with the STRAT-PARK study in the search for imaging-based correlates to PD symptomatology, through the application of machine learning and other computational methods.

KVISTAD, CHRISTOPHER ELNAN (postdoc)
MD from the University of Leipzig, 2007, PhD within stroke treatment from 2015 and a specialist in neurology from 2018. Until 2023, he is a postdoc in neuroregeneration with mesenchymal stem cells and coordinating investigator in the SMART-MS study. He received a clinical career grant starting in 2023 and will work within the field of stem cell-based neuroregeneration.

LUNDERVOLD, KATARINA (PhD candidate)
MD specializing in neurology at the Haukeland University Hospital and currently a PhD candidate in the Tzoulis group at Neuro-SysMed. Her PhD research focuses on the brain-gut axis to improve our understanding of preclinical and clinical gastrointestinal biomarkers to make advancement towards developing a neuroprotective therapy in Parkinson disease.

MOSTAFAVI, SEPIDEH (PhD candidate)
MS in molecular biology and in microbiology, both from the University of Bergen. She has since 2014 been working with stem cell projects, and was until her doctoral defense in February 2022 a PhD candidate at Neuro-SysMed with Professor Laurence A. Bindoff and Professor Christian A. Vedeler as supervisors. Her PhD project focused on using induced pluripotent stem cells for modeling POLG mitochondrial disease. She currently focuses on performing single nuclei gene expression isolated from PD brains using 10x genomics technology at the Neuromics lab.

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

NORBORG, HILDE (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.

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

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

RØD, BRIT ELLEN (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.

SERKLAND, TROND TRÆTTENBERG (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 personalized treatment of multiple sclerosis with monoclonal antibodies against CD20 positive B-cells.

SHARMA, SOUMYA (clinical research fellow)
DM in neurology from G.B Pant hospital, New Delhi, India. She is currently working as a clinical fellow under the supervision of Dr. Mandar Jog at the London Movement Disorders Centre, Canada and is spearheading the research project STRAT-PARK at the Canadian Centre. Her main focus of research is understanding the role of micro-vasculature in the pathophysiology of Parkinson's disease using novel imaging methods.

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

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

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

STIGE, KJERSTI (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.

SUNDARESAN, JANANI (PhD candidate)
MSc in molecular biology, and currently a PhD candidate in the group of Professor Tzoulis. Her PhD project focuses on changes of histone acetylation in Parkinson's disease, and their role in the pathophysiology of the disease.

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

TAMILSELVAN, YOKESH (PhD candidate)
MSc in electrical and computer engineering at Clemson University and currently a PhD candidate in the CSTAR and London Movement Disorders Group at the University of Western Ontario. His PhD project is focused on developing robotic and deep learning techniques to enhance the assessment, diagnosis, and treatment procedures for Parkinson's disease.

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

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

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

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

“Looking back at 2022, we cannot help but feel content and inspired by what has been achieved by our Centre. At the same time, we look ahead in excitement and optimism, ready to meet the challenges of improving healthcare for brain diseases.”

– Neuro-SysMed directors

Neuro-SysMed in the News

News stories featuring Neuro-Sysmed in 2022 in the media.

January 24, 2022, Dagens Medisin, "Får tilgang på ny MS-medisin i stamcellestudie." Interview with Øivind Torkildsen about the RAM-MS study.

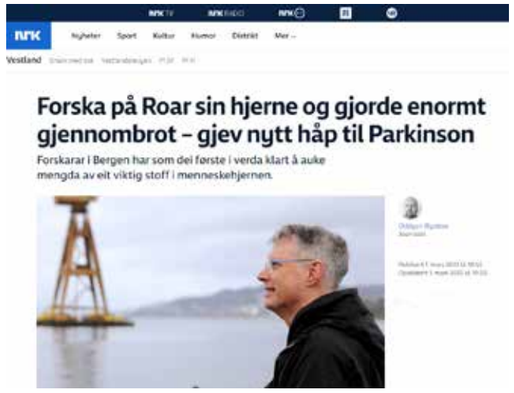
January 27, 2022, Dagens Medisin, "Det største gjennombruddet innen MS på tyve år." Interview with Kjell-Morten Myhr og Øivind Torkildsen for expert statements on the Cortese and Bjørnevik study on the Epstein-Barr virus as possible cause of MS.

January 29, 2022, VG, "Fra dødsdom til håp," patient case on ALS, interview with Ole-Bjørn Tysnes.

January 31, 2022, Harstad Tidende, "Personer med demens fikk mer alvorlig angst og depresjon under pandemien." Also similar articles the same period in Nordnorsk debatt, Aftenposten and Bergens Tidende, all concerning the September 2021 publication "The consequences of COVID-19 lockdown for formal and informal resource utilization among home-dwelling people with dementia: results from the prospective PAN.DEM study" co-authored by Bettina Husebø.

February 25, 2022, Dagens Medisin, "Svarer om stamcellebehandling for MS-pasienter," about the RAM-MS study and comments from the Minister of Health and Care services.

March 1, 2022, NRK Vestland, "Forska på Roar sin hjerne og gjorde enormt gjennombrot – gjev nytt håp til Parkinson," patient case on Parkinson's and about the NO-PARK study, interview with Charalampos Tzoulis. Also similar articles in the same period in Bergensavisen, NTB, ABC Nyheter, Handikapnytt, Forskerforum, Vårt Land and Avanza.



March 7, 2022, Dagens Medisin, "Stort kutt for Nasjonal kompetansetjeneste for MS," on a national reorganization leading to cuts in the Norwegian Multiple Sclerosis Competence Centre, interview with Lars Bø. Also similar articles in the same period at Helse Bergen, Bergens Tidende and Fædrelandsvennen.

March 10, 2022, Bergens Tidende, "Parkinson-senter etableres i Bergen," on the desicion and funding to establish a Parkinson Research Centre in Bergen. Interview with Charalampos Tzoulis. Similar articles the following days in NTB, Aldring og Helse, NRK Vestland, Dagens Medisin, Bergensavisen and Norges Parkinsonforbund.

March 15, 2022, På Høyden, "Tverrfaglig forskning skal flytte forskningsfronten," on funding from the Research Council of Norway to Mathias Ziegler's HubMOL project.

March 18, 2022, LMI, "Dette er de 6 NorTrials-sentrene," on the coming new NorTrials centres, among them the centre "Hjernehelse og nevrologiske sykdommer" (brain health and neurological diseases) to be led by Kjell Morten Myhr.

April 5, 2022, Dagens Medisin, "Leger peker på utfordringer med MS-medisin," on the MS drug fingolimod, interview with Lars Bø.

April 14, 2022, Businesswire, "Chromadex Corp: ChromaDex External Research Program (CERPâ") Celebrates Over 250 Research Agreements With 235+ Researchers Around the World," on the company's collaboration partners, among them Neuro-SysMed researchers working with NR (Niagen).

April 28, 2022, Dagens Medisin, "Bettina Husebø fikk Demensforskningsprisen 2022," on the awarding of the national Dementia Research Award to Bettina Husebø. Similar articles in NTB, MSN, Avisa Møre, Nynorsk Pressekontor, Psykologisk.no, På Høyden, Bergensavisen, Haugesund Avis, Bergens Tidende and Kongehuset.

April 27, 2022, Dagbladet, "Studie: Dette kan utløse MS," about possible triggers of MS, interview with Lars Bø.

May 6, 2022, Klikk.no, "Charlotte er i slutten av 20-årene når hun begynner å føle seg rar. Hun er totalt uforberedt på diagnosen som venter henne," patient case on MS, interview with Lars Bø.

May 11, 2022, Dagbladet, "MS-studie med nytt funn," on MS patients after stem cell therapy, interview with Øivind Torkildsen.


Dagbladet

MS-studie med nytt funn

En ny norsk studie har sett på hvordan det går med MS-pasienter etter stamcellebehandling. - Interessant og viktig, mener lege.

OVERLEGE: Øivind Torkildsen er overlege ved Haukeland universitetssykehus. Foto: Privat.

Nora Charlotte Lindtner

May 14, 2022, Dagbladet, "Vivians budskap før hun dør," patient case on ALS, interview with Ole-Bjørn Tysnes.

May 20, 2022, Forskning.no, "Norske MS-pasienter fortviler. Hvorfor får de ikke stamcellebehandling?" about Norwegian MS patients going abroad to get stem cell therapy paid by themselves. Interview with Lars Bø. Same article in ABC Nyheter.


forskning.no

Norske MS-pasienter fortviler. Hvorfor får de ikke stamcellebehandling?

Den norske MS-studien som skal sammenligne stamcelleterapi med bremsemedisiner er forsinket. Årsens drar hundrevis av pasienter til utlandet for å stoppe sykdommen med stamcelleterapi.

May 23, 2022, Sykepleien, "NorTrials skal få flere kliniske studier til Norge," on the NorTrials collaboration between Norwegian hospitals and industry. Kjell-Morten Myhr is leader of the focus area brain health and neurological diseases.


Sykepleien Forskning Fagutvikling Nyheter Debatt Stillinger

NYHETER | PUBLISERT 23.05.2022

NorTrials skal få flere kliniske studier til Norge

Norske sykehus skal sammen med industrien samarbeide for at flere pasienter får tilgang til nye behandlingsmetoder.

May 27, 2022, Dagens Medisin, "100 millioner kroner til klinisk forskning," on funding from the national KLINBEFORSK program to among other Ole-Bjørn Tysnes.

June 26, 2022, Tidens Krav, "Parkinsons får flere deler i hjernen til å dø og det er ikke noe å gjøre for å bremse det: - En svært ubehagelig opplevelse," on Parkinson's and effects, interview with Charalampos Tzoulis. Same article also in Halden Arbeiderblad, Telemarksavisa, Romerikes Blad, Akershus Amtstidende, Østlandets Blad and Oppland Arbeiderblad.

July 4, 2022, Dagens Medisin, "Revidert retningslinje for MS-behandling på høring," on an ongoing revision of national guidelines on MS treatment. Interview with Kjell-Morten Myhr.


Dagens Medisin

Revidert retningslinje for MS-behandling på høring

Nytt i nasjonal retningslinje for MS-behandling er blant annet anbefaling om tidlig diagnostikk og høyeffektiv behandling. Selve dokumentet er også forsøkt kortet ned og lettere å lese.

June 29, 2022, På Høyden, "Høg kvalitet på innovasjonsidear," on UiB Idé funding to innovative research projects, among them Jan Reinert Karlsen and his project Communicating cognitive decline: Language games with tactile and visual objects.

July 4, 2022, Bergens Tidende, "Sollaug (76) dekte heimen med gule post it-lappar: - Eg trudde ikkje eg hadde demens," patient case on dementia, wanting to donate her brain to Neuro-SysMed research.


Bergens Tidende

Sollaug (76) dekte heimen med gule post it-lappar: – Eg trudde ikkje eg hadde demens

No skal forskarar studere hjernen hennar. Håpet er å finne ut kvifor nokre får demens, og korleis ein kan behandle sjukdomen betre.

July 18, 2022, Dagens Medisin, "Stor svensk MS-studie: Færre attakker med rituksimab," on a Swedish study on rituksimab, interview with Øivind Torkildsen. Similar article in Dagbladet.

August 21, 2022, Oppland Arbeiderblad, "Sivanja (44) blir aldri helt frisk - men har det bra der hun er i dag," patient case on MS, Lars Bø referred to in fact box.

August 22, 2022, Dagbladet, "Ny studie: - Mareritt kan tyde på alvorlig sykdom," interview with Charalampos Tzoulis.

September 7, 2022, Dagbladet, "ALS: Glenns siste reise," patient case on ALS, interview with Ole-Bjørn Tysnes.


Dagbladet

ALS:

Glenns siste reise

Trebarnsfaren Glenn Råna kommer til å dø i løpet av noen år. Denne uka begynner han en reise gjennom Europa for å oppfylle guttedrømmene.

LIVSGLAD: Glenn Råna ser fram mot de neste ukene. Foto: Kristian Ridder-Nielsen Dagbladet

Sondre Andreas Wedøe Nodland

September 13, 2022, Dagens Medisin, "Norske forskere med ny kunnskap om Parkinson," on an Oslo study on Parkinson's, interview with Charalampos Tzoulis.

September 15, 2022, Dagens Medisin, "Revidert retningslinje for MS-behandling publisert," on the publication of the revised national guidelines on MS treatment, a work led by Kjell-Morten Myhr. Also an article at Helsedirektoratet.

September 29, 2022, Norges Parkinsonforbund, "Millioner til eget forskningssenter for parkinson," on a new centre for Parkinson's research, to be led by Charalampos Tzoulis. Similar article in NTB and Dagens Medisin.


Norges Parkinsonforbund

Millioner til eget forskningssenter for parkinson

October 7, 2022, Dagens Medisin, "Fagmiljøet enig om å være lojal til anbudsvinner," on changing from MS drug Fampyra to the cheaper Fampridine Accord, interview with Lars Bø.

October 11, 2022, Dagbladet, "Studie gir håp om MS-gjennombrudd," patient case on MS, interview with Kjell-Morten Myhr.

October 27, 2022, Dagens Medisin, "Studie: - Lav risiko for infeksjonsrelaterte innleggelser med rituksimab," on a Neuro-SysMed study on rituksimab presented at ECTRIMS 2022, Amsterdam.


Dagens Medisin

Studie: – Lav risiko for infeksjonsrelaterte innleggelser med rituksimab

Seks prosent av pasientene som fikk behandling med legemidler ble lagt inn på grunn av infeksjoner innen fem år, viser en studie utført ved Haukeland universitetssjukehus.

October 28, 2022, Dagens Medisin, "MS-studie: Legemiddel like effektivt som stamcelle-behandling," on a Neuro-SysMed study suggesting that stem cell treatment is better than fingolimod, but comparable to okrelizumab and natalizumab in MS attacks.

October 28, 2022, Dagens Medisin, "Studie: Høyere attakkrate med rituksimab enn okrelizumab," Øivind Torkildsen commenting on okrelizymab versus rituksimab, and referring to the RAM-MS og Overlord studies for further investigating.


Dagens Medisin

Studie: Høyere attakkrate med rituksimab enn okrelizumab

Den årlige attakkraten var høyere blant MS-pasientene som fikk rituksimab enn pasientene som fikk okrelizumab.

Julie Kalveland

November 8, 2022, Dagens Medisin, "Pasientforening vurderer søksmål mot staten," on the MS Association's possible lawsuit against the government for having to go abroad for stem cell therapy. Referral to the RAM-MS study.

November 11, 2022, Dagens Medisin, "Ole-Bjørn Tysnes blir nytt medlem i Ekspertpanelet," on Ole-Bjørn Tysnes' appointment as member of the Expert Panel, as an ALS expert.


Dagens Medisin

Ole-Bjørn Tysnes blir nytt medlem i Ekspertpanelet

Nevrolog Ole-Bjørn Tysnes skal gi råd om behandling av pasienter med amyotrofisk lateralskleorose (ALS).

Julie Kalveland

November 11, 2022, Dagens Medisin, "Ny ALS-medisin til vurdering," Ole-Bjørn Tysnes asked to comment on new ALS drug, Relyvri/Albrioza, recently approved by the FDA and considered in Norway. Similar article at Forskning.no, Dagbladet and ABC Nyheter.

November 18, 2022, Helse Vest, "Glade forskingsprisvinnarar," on the awarding of the Helse Vest 2022 awards, among then the prestigeous Research Award to Kjell Morten Myhr. Similar aricles at Helse Stavanger, Helse Bergen, Stavanger Aftenblad, Dagens Medisin and uib.no.


Glade forskingsprisvinnarar

– Helse Vest har som mål at forsking og innovasjon skal vere av høg kvalitet, og til nytte for pasientane våre. Det bidreg årets vinnarar til, i aller høgste grad, sa Agnes Landstad, styreleiar i Helse Vest, på årets forskingskonferanse. Tre prisar blei delte ut på tre ulike område, til vinnarane frå Helse Bergen og Helse Stavanger.

Publisert 18.11.2022 / Sist oppdatert 23.11.2022

Frå venstre: Styreleiar Agnes Landstad, Thomas Lechner, Anna Marie Moe Øvsteba, Kjell-Morten Myhr, Olga Therese Oussdal, Conrad Bjørshol, Gro Anita Fonnes Flaten og Bjørn Egil Vikse. Foto: Silje Katrine Robinson

November 22, 2022, Ringerikes Blad, "Superkjendisene hjelper ALS-syke Remi (26) med å oppfylle sin store drøm: - Betyr alt for meg," patient case on ALS, interview with Ole-Bjørn Tysnes.

November 29, 2022, Dagens Medisin, "Norske forskere med funn om delirium", on research results from among other Lasse Melvær Giil and the association between quinolic acid and delirium, and also closely connected with brain cell damage. The story was also on national TV, NRK and radio, Bergensavisen and Psykologisk.no.


Dagens Medisin

Verdens største på spinalvæsker ved delirium

Leiv Otto Watne Foto: Ahus

Lasse Melvær Giil Foto: Privat

November 28, 2022, Dagens Medisin, "Internasjonale forskere foreslår ny definisjon av sykdommen MS," Kjell-Morten Myhr asked to comment on an international suggestion to characterize MS based on underlying biology rather than how it appears clinically.


Dagens Medisin

Internasjonale forskere foreslår ny definisjon av sykdommen MS

– Jeg ble veldig entusiastisk da jeg så denne artikkelen. Det er bra at dette tas opp og systematiseres, sier overlege Øro Owren Nygaard.

Julie Kalveland

December 6, 2022, Dagens Medisin, "Nesten 90 prosent av MS-pasientene får høyeffektiv medisin først," Kjell-Morten Myhr and Øivind Torkildsen interviewed about the OVERLORD study.

December 9, 2022, Sykepleien, "Dette må til for at sykehjem skal ta i bruk ny forskning," Bettina Husebø asked to comment on a study with a score sheet for anxiety in dementia patients. Same article at Forskning.no.


forskning.no

Ny studie: Dette må til for at sykehjem skal ta i bruk ny forskning

Å få en kunnskap inn i sykepleiernes hverdag, er mye mer kompliset enn tidligere antatt, ifølge en ny norsk studie ved Høgskolen på Vestlandet.

December 9, 2022, UiB News, "Michael J. Fox Foundation funding to Professor Tzoulis," on funding from the Michael J. Fox Foundation for a project aiming to identify a novel subtype of Parkinson's disease driven by mitochondrial dysfunction, and to develop clinically applicable biomarkers enabling patient selection for targeted therapeutic trials.


UNIVERSITY OF BERGEN

Michael J. Fox Foundation funding to Professor Tzoulis

Professor Charalampos Tzoulis receives $300,000 (3MNOK) from the prestigious Michael J. Fox Foundation.

December 23, 2022, Dagens Medisin, "Gleder seg over nye resultater om multippel sklerose," interview with Kjell-Morten Myhr, asked to summarize neurological research in 2022.

December 23, 2022, Forskning.no, "2022 var året da forskerne fant sterke bevis for hva som kan gi MS," on the Bjørnevik and Cortese study associating the Epstein Barr virus with MS.


forskning.no

2022 var året da forskerne fant sterke bevis for hva som kan gi MS

Epstein Barr-virus er en viktig årsak til multippel sklerose. Science regner funnet som et av årets viktigste vitenskaps-gjennombrudd. På sikt kan en vaksine utrydde den alvorlige nevrologiske sykdommen MS, tror forskere.

Publication list 2022

Relevant publications from the Neuro-SysMed researchers in 2022.

1. **Jensen SM, Müller KI, Mellgren SI, Bindoff LA, Rasmussen M, Ørstavik K, Jonsrud C, Tveten K, Nilssen Ø, Van Ghelue M, Arntzen KA.** Epidemiology and natural history in 101 subjects with FKRP-related limb-girdle muscular dystrophy R9. The Norwegian LGMDR9 cohort study (2020). *Neuromuscul Disord*. 2023 Feb;33(2):119-132. doi: 10.1016/j.nmd.2022.11.005. Epub 2022 Nov 25. PMID: 36522254.

2. **Oftedal L, Maple-Grødem J, Dalen I, Tysnes OB, Pedersen KF, Alves G, Lange J**. Association of CSF Glucocerebrosidase Activity With the Risk of Incident Dementia in Patients With Parkinson Disease. *Neurology*. 2023 Jan 24;100(4):e388-e395. doi: 10.1212/WNL.0000000000201418. Epub 2022 Oct 17. PMID: 36253102.

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

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

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

6. **Lobbezoo F, Verhoeff MC, Aarab G, Husebø BS, van der Torre W, Volgenant CMC**. The contribution of palliative oral health care to dying with dignity. *J Am Dent Assoc*. 2023 Jan;154(1):3-5. doi: 10.1016/j.adaj.2022.08.015. Epub 2022 Oct 15. PMID: 36253165.

7. **Helvik AS, Bergh S, Kabukcuoğlu K, Šaltytė Benth J, Lichtwarck B, Husebø B, Tevik K.** Prevalence and persistent prescription of analgesic drugs in persons admitted with dementia to a nursing home - A longitudinal study. *PLoS One*. 2022 Dec 30;17(12):e0279909. doi: 10.1371/journal.pone.0279909. eCollection 2022. PMID: 36584218.

8. **Boyle LD, Husebo BS, Vislapuu M**. Promotors and barriers to the implementation and adoption of assistive technology and telecare for people with dementia and their caregivers: a systematic review of the literature. *BMC Health Serv Res*. 2022 Dec 23;22(1):1573. doi: 10.1186/s12913-022-08968-2. PMID: 36550456.

9. **Bjerknes TL, Steihaug OM, Haugen M, Hjelland IE, Vedeler CA**. Case report: Pain in anti-DPPX encephalitis. *Front Neurol*. 2022 Dec 14;13:1091688. doi: 10.3389/fneur.2022.1091688. eCollection 2022. PMID: 36588910.

10. **Kropotov A, Kulikova V, Solovjeva L, Yakimov A, Nerinovski K, Svetlova M, Sudnitsyna J, Plusnina A, Antipova M, Khodorkovskiy M, Migaud ME, Gambaryan S, Ziegler M, Nikiforov A**. Purine nucleoside phosphorylase controls nicotinamide riboside metabolism in mammalian cells. *J Biol Chem*. 2022 Dec;298(12):102615. doi: 10.1016/j.jbc.2022.102615. Epub 2022 Oct 18. PMID: 36265580.

11. **Lüscher B et al. (incl. Ziegler M)**. ADP-ribosyltransferases, an update on function and nomenclature. *FEBS J*. 2022 Dec;289(23):7399-7410. doi: 10.1111/febs.16142. Epub 2021 Sep 13. PMID: 34323016.

12. **Støve SI, Skjevik ÅA, Teigen K, Martinez A**. Inhibition of VMAT2 by β2-adrenergic agonists, antagonists, and the atypical antipsychotic ziprasidone. *Commun Biol*. 2022 Nov 23;5(1):1283. doi: 10.1038/s42003-022-04121-1. PMID: 36418492.

13. **Vislapuu M, Berge LI, Angeles RC, Kjerstad E, Mannseth J, Achterberg WP, Husebo BS.** Factors associated with formal and informal resource utilization in nursing home patients with and without dementia: cross-sectional analyses from the COSMOS trial. *BMC Health Serv Res*. 2022 Nov 2;22(1):1306. doi: 10.1186/s12913-022-08675-y. PMID: 36324159.

14. **Fernández-Vizarra E, López-Calcerrada S, Sierra-Magro A, Pérez-Pérez R, Formosa LE, Hock DH, Illescas M, Peñas A, Brischigliaro M, Ding S, Fearnley IM, Tzoulis C, Pitceathly RDS, Arenas J, Martín MA, Stroud DA, Zeviani M, Ryan MT, Ugalde C**. Two independent respiratory chains adapt OXPHOS performance to glycolytic switch. *Cell Metab*. 2022 Nov 1;34(11):1792-1808.e6. doi: 10.1016/j.cmet.2022.09.005. Epub 2022 Oct 4. PMID: 36198313.

15. **Eid K, Torkildsen Ø, Aarseth J, Celius EG, Cortese M, Holmøy T, Kapali A, Myhr KM, Torkildsen CF, Wergeland S, Gilhus NE, Bjørk MH**. Abuse and revictimization in adulthood in multiple sclerosis: a cross-sectional study during pregnancy. *J Neurol*. 2022 Nov;269(11):5901-5909. doi: 10.1007/s00415-022-11249-x. Epub 2022 Jul 3. PMID: 35780399.

16. **Taule T, Morland AS, Aßmus J, Tysnes OB, Rekand T.** Translation, cultural adaptation, and validation of a screening test for cognitive and behavioural changes in amyotrophic lateral sclerosis. *Disabil Rehabil*. 2022 Nov;44(23):7069-7077. doi: 10.1080/09638288.2021.1980621. Epub 2021 Nov 2. PMID: 34726988.

17. **Torkildsen Ø, Rød BE, Bø L, Wergeland S, Holmøy T, Myhr KM.** Breastfeeding and treatment for multiple sclerosis. *Tidsskr Nor Laegeforen*. 2022 Oct 24;142(15). doi: 10.4045/tidsskr.22.0529. Print 2022 Oct 25. PMID: 36286559.

18. **Torrado JC, Husebo BS, Allore HG, Erdal A, Fæø SE, Reithe H, Førsund E, Tzoulis C, Patrascu M.** Digital phenotyping by wearable-driven artificial intelligence in older adults and people with Parkinson's disease: Protocol of the mixed method, cyclic ActiveAgeing study. *PLoS One*. 2022 Oct 14;17(10):e0275747. doi: 10.1371/journal.pone.0275747. eCollection 2022. PMID: 36240173.

19. **Nakken O, Holmøy T, Stigum H, Myhr KM, Dahl J, Heldal E, Meyer HE**. Strong tuberculin response after BCG vaccination is associated with low multiple sclerosis risk: a population-based cohort study. *Int J Epidemiol*. 2022 Oct 13;51(5):1637-1644. doi: 10.1093/ije/dyac039. PMID: 35278068.

20. **Kristiansen CK, Chen A, Høyland LE, Ziegler M, Sullivan GJ, Bindoff LA, Liang KX**. Comparing the mitochondrial signatures in ESCs and iPSCs and their neural derivations. *Cell Cycle*. 2022 Oct;21(20):2206-2221. doi: 10.1080/15384101.2022.2092185. Epub 2022 Jul 10. PMID: 35815665.

21. **Solvang SH, Hodge A, Watne LO, Cabral-Marques O, Nordrehaug JE, Giles GG, Dugué PA, Nygård O, Ueland PM, McCann A, Idland AV, Midttun Ø, Ulvik A, Halaas NB, Tell GS, Giil LM**. Kynurenine Pathway Metabolites in the Blood and Cerebrospinal Fluid Are Associated with Human Aging. *Oxid Med Cell Longev*. 2022 Oct 21;2022:5019752. doi: 10.1155/2022/5019752. eCollection 2022.PMID: 36312896.

22. **Mayala S, Herdlevær I, Haugsøen JB, Anandan S, Blaser N, Gavasso S, Brun M**. GUBS: Graph-Based Unsupervised Brain Segmentation in MRI Images. *J Imaging*. 2022 Sep 27;8(10):262. doi: 10.3390/jimaging8100262. PMID: 36286356

23. **Willumsen JS, Grytten N, Aarseth J, Myklebust TÅ, Myhr KM, Midgard R.** Mortality and cause of death in multiple sclerosis in western Norway 1950-2021: a registry-based linkage study. *J Neurol Neurosurg Psychiatry*. 2022 Sep 12;93(11):1154-61. doi: 10.1136/jnnp-2022-329169. Online ahead of print. PMID: 36096665.

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25. **Lie IA, Wesnes K, Kvistad SS, Brouwer I, Wergeland S, Holmøy T, Midgard R, Bru A, Edland A, Eikeland R, Gosal S, Harbo HF, Kleveland G, Sørenes YS, Øksendal N, Barkhof F, Vrenken H, Myhr KM, Bø L, Torkildsen Ø.** The Effect of Smoking on Long-term Gray Matter Atrophy and Clinical Disability in Patients with Relapsing-Remitting Multiple Sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2022 Jun 23;9(5):e200008. doi: 10.1212/NXI.0000000000200008. Print 2022 Sep. PMID: 35738901.

26. **Helvik AS, Bergh S, Šaltytė Benth J, Selbaek G, Husebo BS, Tevik K**. Pain in nursing home residents with dementia and its association to quality of life. *Aging Ment Health*. 2022 Sep;26(9):1787-1797. doi: 10.1080/13607863.2021.1947968. Epub 2021 Jul 11. PMID: 34251936.

27. **Berge LI, Gedde MH, Torrado Vidal JC, Husebo B, Hynninen KM, Knardal SE, Madsø KG**. The acceptability, adoption, and feasibility of a music application developed using participatory design for home-dwelling persons with dementia and their caregivers. The "Alight" app in the LIVE@Home. Path trial. *Front Psychiatry*. 2022 Aug 18;13:949393. doi: 10.3389/fpsyt.2022.949393. eCollection 2022. PMID: 36061298.

28. **Samotus O, Mahdi Y, Jog M**. Real-World Longitudinal Experience of Botulinum Toxin Therapy for Parkinson and Essential Tremor. *Toxins (Basel)*. 2022 Aug 17;14(8):557. doi: 10.3390/toxins14080557. PMID: 36006219.

29. **Ito E, Nouchi R, Dinet J, Cheng CH, Husebø BS**. The Effect of Music-Based Intervention on General Cognitive and Executive Functions, and Episodic Memory in People with Mild Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of Recent Randomized Controlled Trials. *Healthcare (Basel)*. 2022 Aug 3;10(8):1462. doi: 10.3390/healthcare10081462. PMID: 36011119.

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31. **Hallin EI, Trætteberg Serkland T, Myhr KM, Grytten Torkildsen Ø, Skrede S**. Ocrelizumab quantitation by liquid chromatography-tandem mass spectrometry. *J Mass Spectrom Adv Clin Lab*. 2022 Jul 22;25:53-60. doi: 10.1016/j.jmsacl.2022.07.004. eCollection 2022 Aug. PMID: 35910410.

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33. **Kvistad SAS, Burman J, Lehmann AK, Tolf A, Zjukovskaja C, Melve GK, Bø L, Torkildsen Ø.** Impact of previous disease-modifying treatment on safety and efficacy in patients with MS treated with AHSCT. *J Neurol Neurosurg Psychiatry*. 2022 Aug;93(8):844-848. doi: 10.1136/jnnp-2022-328797. Epub 2022 May 4. PMID: 35508373.

34. **Guitton R, Dölle C, Alves G, Ole-Bjørn T, Nido GS, Tzoulis C**. Ultra-deep whole genome bisulfite sequencing reveals a single methylation hotspot in human brain mitochondrial DNA. *Epigenetics*. 2022 Aug;17(8):906-921. doi: 10.1080/15592294.2022.2045754. Epub 2022 Mar 7. PMID: 35253628.

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38. **Varhaug KN, Hikmat O, Bindoff LA**. [Mitochondrial disease caused by the m.3243A>G mutation]. *Tidsskr Nor Laegeforen*. 2022 Jun 27;142(10). doi: 10.4045/tidsskr.21.0729. Print 2022 Jun 28. PMID: 35763848 Review. Norwegian.

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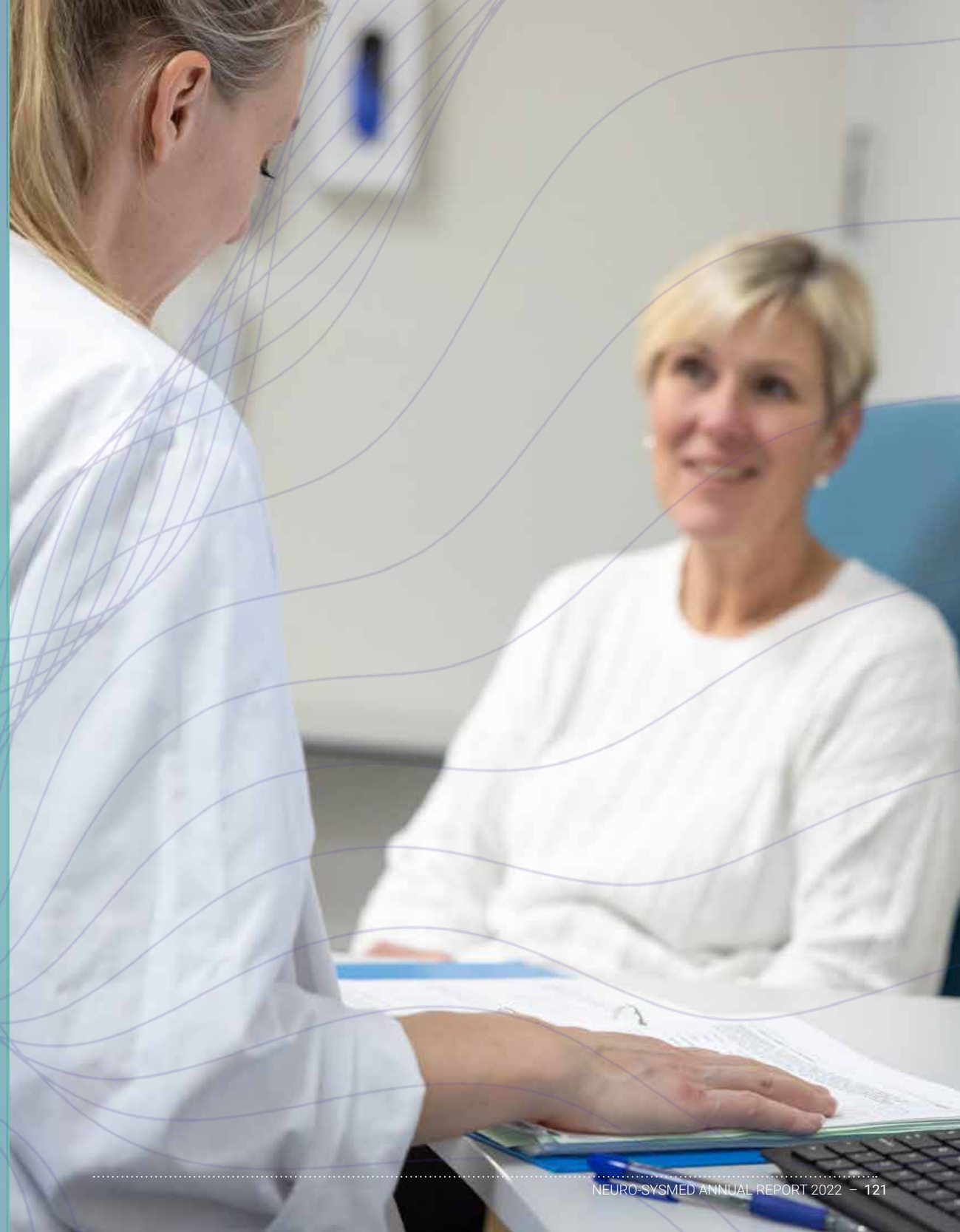

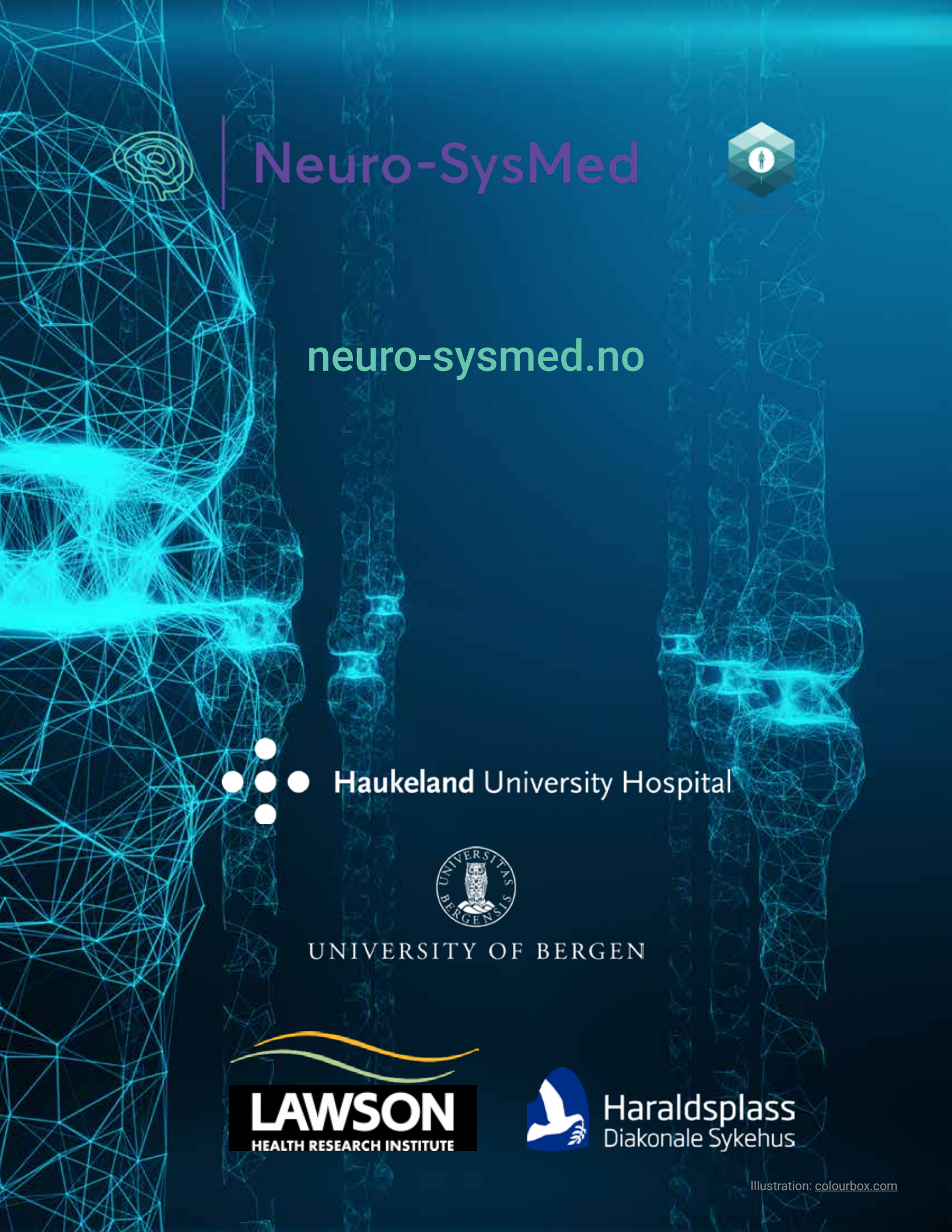

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