Neuro-SysMed

fkb Centres for Clinical Treatment Research

# ANNUAL REPORT 2021

A centre for clinical treatment research
on neurological diseases

# Contents




Illustration cover and this page: www.colourbox.com.
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ART DIRECTION/LAYOUT: Inhouse UiB by Eli Synnøve Vidhammer.




# Director's Comments

2021 has been a highly active and productive year for Neuro-SysMed. Although still heavily encumbered by the COVID-19 pandemic, the Centre succeeded in recruiting patients into eight academic clinical trials, all of which have been conceived and initiated at Neuro-SysMed. In addition, patients were recruited in two industry-sponsored trials. In total, we are now approaching 500 patients enrolled in clinical studies initiated by our Centre. The vast majority of Norwegian Departments of Neurology (14/17) are currently participating in our studies, or plan to do so, together with five international centres in Sweden, Denmark and The Netherlands. Moreover, Neuro-SysMed has initiated research projects along with partners in the USA and Canada. Another major highlight of 2021 was the completion of the NADPARK phase I trial in Parkinson's disease, the results of which were recently published in the prestigious journal Cell Metabolism.

During 2021, The Ministry of Health and Care Services launched a "National Action Plan for Clinical Trials". The overarching aim is to double the number of clinical trials and to include at least 5 % of patients with chronic diseases followed in the Specialist Health Services in Norway. There are currently approximately 25 000 people with MS, PD and ALS in Norway and it is estimated that ~80 % of these are being actively followed up at hospitals. Thus, our activity at Neuro-SysMed alone covers nearly 50% of the goals laid down by the Ministry of Health and Care Services. At the same time, our research activity in dementia is rapidly increasing, with several clinical trial initiatives ready to be launched during 2022.

Our experiences from two years of active recruitment of hospitals, study centres and patients into clinical trials demonstrate a need for education of personnel and allocation of resources at the hospitals to meet the challenges of participation in clinical treatment research. There is clearly a need for integrating clinical trial treatment research into every day clinical practice, underpinning the ambition of offering all patients the possibility for participation. The Research School at Neuro-SysMed aims to meet the educational need by teaching and inspiring health care personnel, researchers, and patients for participation in clinical trial research. During 2021, we organized open teaching courses covering the topics of clinical trials, user participation, and health innovation. Further courses are in development to support education for participation in clinical treatment research.

To further enhance clinical treatment research in Norway, Neuro-SysMed aims to also increase the recruitment of Norwegian patients into multicentre international pharmaceutical company sponsored studies. Accordingly, Neuro-SysMed has regular contacts with the Norwegian Association of the Pharmaceutical Industry. The centre also supports the NorTrial coordination initiative to increase numbers of studies available for Norwegian hospitals and patients, and suggests a NorTrial centre focusing on Brain Health.

Kjell-Morten Myhr
Director of Neuro-SysMed

# Research Areas and Goals

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

**Vision and goals**
The overarching aim of Neuro-SysMed is to develop new or improved treatment strategies for patients with multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and dementia. The Centre facilitates early access to such new therapies for patients across Norway through participation in national and international randomized clinical trials.

**Research plan and strategy**
Neuro-SysMed is organizing and conducting randomized clinical treatment trials to evaluate the efficacy and safety of therapies, novel or established drugs with new indications, that may delay or even arrest disease progression, ameliorate symptoms or optimize care for affected individuals. 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 will be integrated, in order to define biomarkers that enable early and precise diagnosis, subgrouping of patients within each disease, accurate prognosis and tailored treatment choices for individual patients.

Thus, Neuro-SysMed aims to develop early and improved treatment strategies for patients with severe diseases of the central nervous system.

Randomized clinical trials are the backbone of the Centre activities. These trials cannot be conducted at a sufficient scale with the Centre funding alone. Consequently, the Centre staff are continuously working to secure additional external funding for the trials and ongoing research activities.

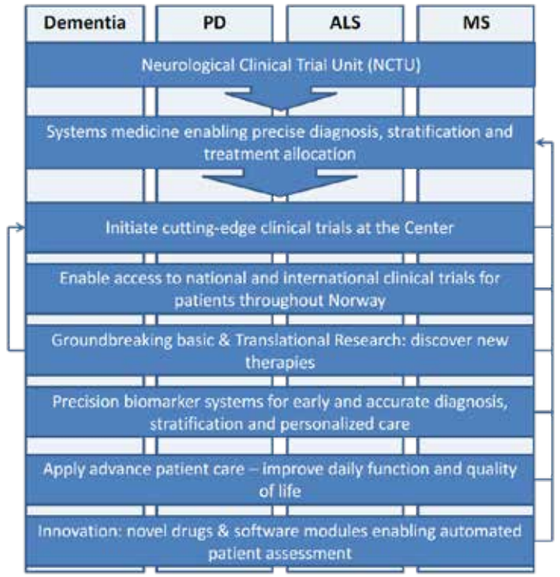



*Figure: Research plan*

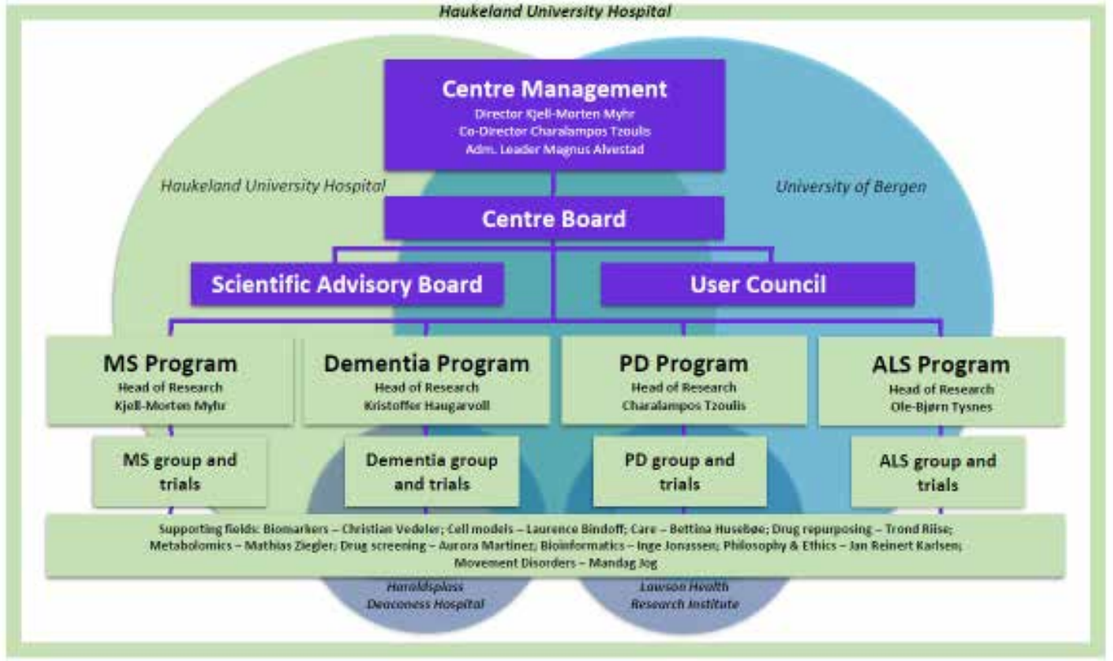


# Organization

**The project owner and host institution of the Centre is Haukeland University Hospital (HUH), but the work of the Centre, both financially and in terms of research activity, is split equally between HUH and the University of Bergen (UiB). The Centre is hosted by the Neurology Clinic at HUH, while the corresponding host at the UiB is the Department of Clinical Medicine at the Faculty of Medicine (MED). Additional partners are Haraldsplass Deaconess Hospital (HDS) in Bergen and Lawson Health Research Institute (Lawson) in Ontario, Canada.**

**Organizational structure**
The Centre is led by Professor Kjell-Morten Myhr (Centre Director and Head of the Multiple Sclerosis Program), Professor Charalampos Tzoulis (Centre Co- Director and Head of the Neurodegeneration Program), and Magnus Alvestad, Head of Administration. The board of the Centre includes members from the host and partner institutions. The board is chaired by Professor Per Bakke, Dean of Medicine, 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, Anita Sæløen Hop, Chair of the User Committee at 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 is also supported by a Scientific Advisory Board and a User Council (see next page).

**Cooperation between partners**
The work is integrated at Haukeland University Hospital and the University of Bergen. Many researchers have positions at both institutions, and even those that only have a position at one institution, have access to resources at the other. Similarly, researchers at other faculties than MED at UiB are also closely integrated in the Centre's research activity. Haraldsplass Deaconess Hospital is focusing on dementia research, in close cooperation with the other institutions, i.e., PhD candidates at the UiB who will perform all their research at Haraldsplass. The Lawson Health Research Institute is most closely involved in the research related to Parkinson's disease and cooperates with the other partners in that area.



# Scientific Advisory Board

**The mandate of the Scientific Advisory Board (SAB) is to provide the Centre management with scientific and strategic advice related to the research and study activity. The international SAB members are all highly renowned scientists within Neuro-SysMed's focus areas.**

Due to the COVID-19 pandemic, the scientific advisory board did not have physical meetings during 2021. However, relevant discussions with individual members related to disease specific topics have taken place. Physical disease-specific meetings are scheduled for the spring of 2022 and a joint seminar will be organized during the fall of 2022.

**Members:**

**Professor Kailash Bhatia, Queen Square Institute, UCLH, London, UK – neurodegeneration**

Kailash Bhatia is a Professor of Clinical Neurology, and a Fellow of the Royal College of Physicians as well as the American Academy of Neurology. He has over 500 publications, including almost 400 peer-reviewed papers. He published "Marsden's book of Movement disorders", a comprehensive piece of work which has been highly acclaimed. He is the current Chair of the Movement Disorders subcommittee of the European Neurological Society (ENS) and serves on various committees of the International Movement Disorders Society.

**Professor Albert Ludolph, University Hospital of Ulm, Germany – ALS**

Professor Albert Ludolph is the Chairman of the Department of Neurology at the University Hospital and Medical Faculty of Ulm. He is also acting Director of the Academic Neuroscience Centre of the University of Ulm. He has established and leads the ALS-Centre at the University Hospital of Ulm and directs a multidisciplinary team for ALS care, clinical and experimental research.

**Professor Xavier Montalban, Vall d'Hebron University Hospital, Barcelona, Spain – multiple sclerosis**

Professor Xavier Montalban is the Chair of the Department of Neurology-Neuroimmunology and Director of the Multiple Sclerosis Centre of Catalonia at Vall d'Hebron University Hospital in Barcelona, as well as the Chief of the Neuroimmunology Research Group at Vall d'Hebron Research Institute. From July 2017 to May 2020, he has been Professor of Medicine, the Director of the Division of Neurology at the University of Toronto and Director of the MS Centre at St Michael's Hospital. He has authored over 500 original and revision publications in international peer-reviewed journals as well as several book chapters.

**Professor Raymond Koopmans, Radboud University, Netherlands – dementia**

Professor Raymond Koopmans studies the course of dementia in nursing home patients, including a number of publications on medication use and polypharmacy. He leads the "Elderly care medicine" research group at the Radboud University Medical Centre.

**Simon Denegri OBE, The Academy of Medical Sciences, UK – user involvement**

Simon Denegri is the Executive Director of the UK Academy of Medical Sciences. Prior to joining the Academy, he was the NIHR National Director for Patients, Carers and the Public and, before that, Chief Executive at the Association of Medical Research Charities (AMRC).


Simon Denegri accepted an invitation to the SAB in 2021 and has already contributed with valuable guidance concerning the patient and public involvement (PPI) activities at the Centre, most recently at the CCBIONEUR910 course on Patient and Public Involvement in Medical and Health 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.

**User participation is important!**
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. 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 that live 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.

**Status of the cooperation with Neuro-SysMed**
The cooperation with the researchers and the administrative group is well-functioning. Our experience is that all parties are trying to achieve 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 structure for our cooperation between researchers and users.

**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 to the research
- Represent the User Council at various events
- Work for political attention for 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 users participating as user representatives in research projects. We see that users can for example:

- Identify topics or challenges
- Contribute to improvements in research design
- Contribute to better recruitment of patients
- Disseminate research results
- Give feedback on language, how to present the message, and good channels
- Bring in new perspectives in the analysis of results

**Courses for researchers and user representatives during the fall of 2021**
"User participation in medical research" is a three-day course arranged by the Centre for the first time this fall. Tone Skår and Nina Louise Jebsen created this course in the Neuro-SysMed research school to train participants for user involvement in research, and it consisted of lectures, group assignments and discussions. Both researchers and user representatives were active participants.

**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"

The User Council was elected for two years of service in October 2019. There have already been some replacements in the User Council due to internal changes in the organization. At the fall meeting, it was decided that the current group of members would continue for another two years with the same Chair and Vice-Chair.

**Meetings in 2021**
In 2021, there were two meetings. The April meeting was a digital meeting due to COVID-19. In October, many of us attended in person, while some participated digitally.

*Lise Johnsen, User Council Chair*

# Finances and Gender Balance

**As it did in 2020, the COVID-19 pandemic affected the Centre's activities during 2021 to some degree. However, thanks to our hard-working researchers successfully adapting their activities, the total activity approached the planned level.**

## Core funding in 2021

In 2021, the centre received 22.3 million Norwegian kroner (MNOK) in funding from the Research Council of Norway (RCN). Haukeland University Hospital (HUH) contributed with 10.8 MNOK, the University of Bergen (UiB) with 7.3 MNOK, Lawson with 1.3 MNOK and Haraldsplass Deaconess Hospital (HDH) with 0.7 MNOK, resulting in total core Neuro-SysMed funding of 42.5 MNOK (Figure 1) including in-kind contributions, up from 28.1 MNOK in 2020.


*Figure 1: Core funding sources in 2021*

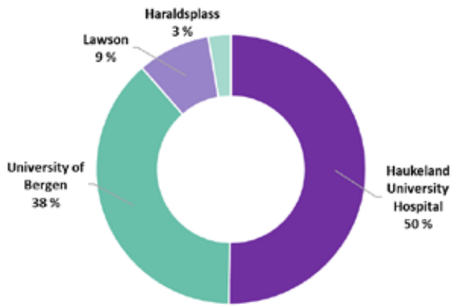



*Figure 2: Core Neuro-SysMed funds spending in 2021*

## Spending in 2021

HUH spent about 21.3 MNOK of core centre funds in 2021. UiB spent 16.3 MNOK; Lawson spent 3.7 MNOK, with activity being higher than expected because of good recruitment to the STRAT-PARK Parkinson's disease cohort trial. HDH spent about 1.1 MNOK on dementia research. Total expenses were 42.5 MNOK (Figure 2).

## Additional External Funding

The Centre currently has 17 investigator-initiated trials, running or in preparation, as well as some smaller research projects. Altogether, we have successfully obtained over 200 MNOK of additional external funding for these activities. Additionally, we have secured in-kind contributions from participating hospitals for most of these trials (not shown in graph). The KLINBEFORSK program, funded by the regional health trusts, is the largest contributor, followed by the Western Norway Regional Health Authority and various private sponsors (Figure 3).

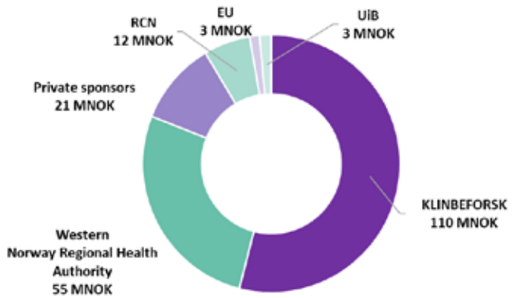



*Figure 3: External funding obtained by the centre research groups since the opening in October 2019*



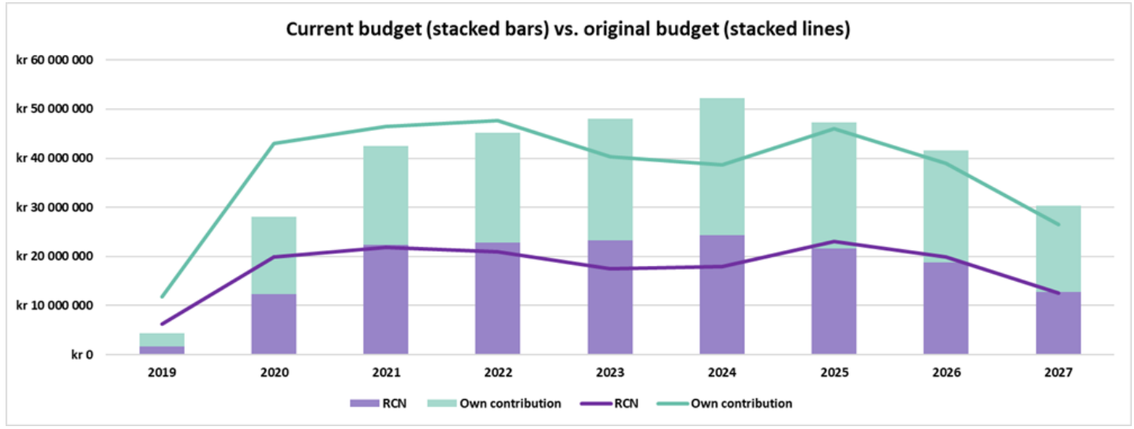



*Figure 4: Current budget vs. original budget. Centre activities were heavily impacted by COVID-19 and therefore slower progress was made in 2019 and 2020, until almost reaching the expected levels during 2021.*

## Budget

In the original Centre budget from 2019, plans were made for a rapid increase of Centre activities to an annual budget level at about 40 million NOK (lines in the graph). This was later adjusted to a less progressive start, mainly due to COVID-19 challenges. Re-budgeting was performed during 2020 and in the fall of 2021 (bars in the graph). Thus, the Centre's activities were significantly lower than initially planned for during 2020, but with a spending of 42.5 MNOK in 2021, we almost approached the planned level of 46.5 MNOK. Some trials have delayed recruitment of patients, resulting in planned peak activity during 2023-2025 (Figure 4).

## Gender distribution

Of 134 people in the Neuro-SysMed groups, 54 are male and 80 are female. Of 64 candidates in PhD or Postdoc fellowship positions, 30 are male and 34 are female. Only 2 out of 13 principal investigators are female, but the Centre has an active strategy to educate and recruit female researchers for future PI responsibilities. In the larger group of 21 key researchers (including the principal investigators), there are six women. Looking at all clinicians working at the Centre, there is a gender balance (10 male and 9 female), and in the next generations of clinicians in general and neurologists in particular, women are clearly in the majority. The Centre's nine study nurses are all women.


# The Neuro-SysMed Laboratory

**Head: Charalampos Tzoulis**
**Manager: Hanne Linda Nakkestad**

The Neuro-SysMed laboratory provides critical infrastructure required to support the clinical and translational research taking place at the Centre. The offices and laboratory benches of the Neuro-SysMed laboratory currently host 40 people, including laboratory engineers and researchers at all levels, from postgraduate students to senior scientists. The Neuro-SysMed laboratory comprises state-of-the-art wet-lab and computational facilities.

The wet-lab facilities include the following functional units: i) General purpose molecular biology laboratory; ii) Tissue processing and morphology/microscopy laboratory; iii) Cell-culture facilities including induced pluripotent stem cell work; iv) Biomarker facility including a Simoa Quanterix digital biomarker detection platform; v) Genomics facility including a dedicated 10X Chromium platform for high-throughput parallel single-cell analyses; vi) Ultrafreezer facility hosting a human brain and tissue bank.

The computational unit comprises five expert bioinformaticians, including a Data Manager, who perform a complete range of big data analyses - from raw-data preprocessing 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.


Photos by Hanne Linda Nakkestad and Magnus Alvestad



# Research Advice & Project Development

**With the increased research activity at Neuro-SysMed, we have been able to start developing new project ideas and to work on attracting additional funding during 2021. A major priority at this stage is to ensure that we can keep a high level of activity at Neuro-SysMed, both in the lab and in the clinical trials.**

We are designing projects across the research groups, taking advantage of the different expertise available. Further, 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), and we have developed new lab and clinical trial projects thanks to the interactions between the research groups.

In addition, big efforts are going towards European grants, which we see as a long-term goal of the research at the center, and towards increasing the visibility of the center. This is crucial for the success of our clinical trials, and to ensure our projects go beyond national borders, increasing not only our national but our international collaborations.

We have had big success in securing funding in 2021 for new or ongoing clinical trials (e.g. RAM-MS, NO-PARK, N-DOSE), several PhD and Postdoc positions funded by UiB and the Regional Health Authorities, and additional project funding via the Regional Health Authorities and private donations. Moreover, our co-Director Professor Tzoulis has received funding for a new K.G. Jebsen Centre for translational research on Parkinson's disease. Results from this activity will lead to new clinical trials. This in turn will allow for increased activity at Neuro-SysMed. Altogether, the external funding will cover fundamental projects during the next few years, ensuring continuation of a broad and cutting-edge research activity.

We are continuing our efforts towards supporting the careers of early-stage researchers, through workshops and seminars, funding to support their research and positions, and advice to develop their own projects and attract external funding. We are now starting to see these programs give results, with several of our younger researchers attracting funding, (co-)supervising students, and gaining independence. We will continue with these programs, and further develop them to adapt to their new roles and needs.

*– Yamila Torres Cleuren, Senior Advisor.*

Photo by Helse Bergen.

# Systems Medicine

**The concept of systems medicine in neurology is the backbone of the Centre. Through collecting a wealth of data from the Centre's ongoing clinical studies, a clinical pipeline is gradually constructed to: 1) screen, recruit and systematically assess patients, 2) assign patients to appropriate experimental treatment protocols that most closely match their disease profile, and 3) precisely monitor treatment effects and outcomes. This will enable patients, and their caregivers, to receive tailored/personalised treatment as well as the opportunity of participating in cutting-edge clinical research.**

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

Using supervised and unsupervised data-analysis models, including artificial intelligence (AI), the Centre will develop specific and sensitive biomarker systems to enable and refine early and precise diagnosis, stratification, and prediction of treatment response. The concept is schematically represented in the figure.

Patients from all of Norway enter our individual clinical trials via the Neuro-logical Clinical Trial Unit (NCTU). The Neuro-SysMed pipeline systematically characterizes patients using routine and experimental examinations. Based on the initial assessment, patients are nominated for standard or experimental intervention (trial of therapy or care-based study). These are implemented either locally at the Centre, the patient's local or regional hospital, or abroad as appropriate. Screening packages are performed at inclusion, during follow-up and after the study period. Trial outcomes are registered and fed into the Neuro-SysMed database. Supervised and unsupervised data analysis algorithms are trained and validated against the database to generate future biomarkers for patient stratification, treatment selection and monitoring. The Systems Medicine Unit is highly integrated with the one-stop-shop NCTU. Together, these tasks support the clinical trials and biomarker discovery.

Early in the process of planning the Centre, it became clear that the IT tools to realize the Centre's vision within systems medicine were not available. To meet this essential need, an innovation project was initiated by Neuro-SysMed in collaboration with the regional IT department, Microsoft, and CAP Gemini, to establish a platform for storage and high throughput data analysis in the Azure cloud. This platform, which is now established and running, hosts the wealth of data generated by Neuro-SysMed, as well as the tools and pipelines required for basic and advanced computational analyses and high-dimensional integration of data.

During 2021, the Neuro-SysMed Digital Cluster (NSM-Cluster) transitioned from alpha- to beta-version and then to fully operational state. The NSM-Cluster is developed and maintained by a dedicated team comprising a Data Manager (Melanie Liedtke) and a Systems Bioinformatician (Kim Brügger) who are working tirelessly with the regional IT Department and Microsoft to further augment and adapt the infrastructure to the needs of the ongoing research at the Centre. Neuro-SysMed plans to publish the detailed setup of the infrastructure, along with the methodological approach and pipeline structure, via open access and encourages others to apply similar solutions in the management of other complex disease data. This work has already attracted substantial attention from other research groups and the Research Council of Norway.

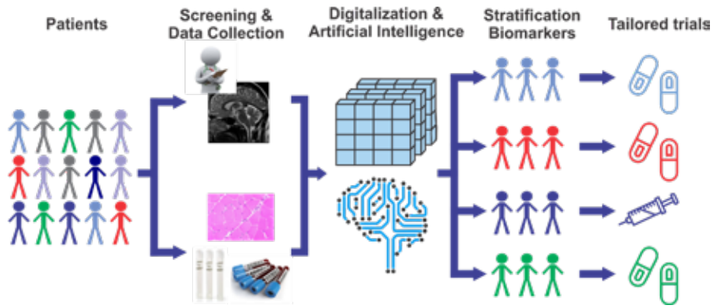



*Figure: Neuro-SysMed pipeline*



# Innovation

**Realizing the impact from research in Neuro-SysMed requires innovation, but innovation should also influence how we do research. In 2021, the Centre launched the MED.hjelper web portal, as well as continuing work in two projects with industry partners. Additionally, Neuro-SysMed organized a four ECTS PhD course in health innovation in collaboration with CCBIO. The Centre has also continued the process of establishing a state-of-the-art online storage and analysis solution in cooperation with Helse Vest IKT, Capgemini and Microsoft. This resource is now available to all the research groups in the Centre. See the previous page for details.**

## MED.hjelper

In collaboration with the Technology Transfer Office of Western Norway (VIS), Neuro-SysMed has implemented MED.hjelper, an online solution that makes it easier for patients and their supporters to identify and participate in appropriate clinical trials. This is useful for Neuro-SysMed as a tool to improve information and patient recruitment in our own trials, but it also supports any trial in any medical field. Tone Skår at VIS has been the driving force behind this project.


## Otivio

The Norwegian innovation company Otivio has developed a medical device that increases blood circulation in the lower extremities, called "FlowOx". A pressure chamber is sealed around the patient's legs just below the knee, where it applies pulsed negative pressure cycles. The treatment is currently approved for selected patients with arterial insufficiency that causes intermittent claudication or diabetes-related leg ulcers. Several MS patients have reported significant relief of pain and spasticity with consequent improvement in functional level. The centre has performed a pilot study aiming at validation of these anecdotal reports. Based on the results of the pilot, Neuro-SysMed is now planning both a small extension and a larger phase 2 study.

## Project Ipsilon

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 be useful in rehabilitation therapy.

COMMENTARY

# Collaboration to meet future challenges

**By Eivind Hansen and Per Bakke**

Neuro-SysMed is now in its third year as the first Research centre for clinical treatment research funded by the Research Council of Norway. Neuro-SysMed is important to the Faculty of Medicine and Haukeland University Hospital for several reasons.

First, the clinicians and scientists involved in the Centre are producing high quality research and novel data that will benefit the patients with neurodegenerative diseases. Results from the Neuro-SysMed studies have the potential to reassess the way we look at these diseases and the potential to improve their prognosis.
Second, Neuro-SysMed is important as a role model for collaboration between the Hospital and the Faculty on clinical studies. The research activity in the Centre is dependent on a close collaboration between the two institutions that contribute with the necessary and complimentary infrastructure and expertise needed to succeed. The Faculty of Medicine and Haukeland University Hospital will jointly prioritize and facilitate the further development of this important research.

The Ministry of Health and Care Services in Norway recently launched a national action plan for clinical studies. The plan includes the aim of doubling the numbers of clinical studies in the specialist healthcare service, combined with the ambition that 5% of patients with chronic illness followed at hospitals will participate in such studies. This will be an important and major challenge for the hospitals in the years to come.

In order to achieve this ambitious goal, enhanced cooperation between the universities and hospitals in Norway is required. Neuro-SysMed will be in the forefront to achieve this goal for the Centre's diseases but may also be an example of how this challenge can be solved for other disciplines. The Centre will also contribute through the development of research infrastructure that can be used by other centres and other disciplines that meet similar challenges.

Finally, Neuro-SysMed is important to facilitate recruitment of young doctors into research and academic positions. Recent years have seen a decline in full time professors with a medical background. Successful centres like Neuro-SysMed may work to change this trend. That would benefit both the Hospital and the Faculty, and above all the patients.

Neuro-SysMed thus represents nicely how centres like this create added value for research beyond their own subject area, also for host and partner institutions that further develop collaboration to solve common tasks and challenges.

We look forward to the further development of the Centre performing important research for the benefit of our patients.

*Eivind Hansen*
*CEO of Haukeland University Hospital*

*Per Bakke*
*Dean, Faculty of Medicine, University of Bergen*



Haukeland University Hospital, UiB Medical Faculty and Haraldsplass Deaconess Hospital.Photo by Helse Bergen, Jonny Engelsvoll

# Treatment guidelines supporting equality of early high effective therapy for people with MS in Norway

**By Kjell-Morten Myhr and Lise Johnsen**

The Norwegian Multiple Sclerosis Registry and Biobank (MS-Registry) is a National medical quality register aiming at registering all persons with MS in order to ensure the best available and equal treatment across Norway. The latest annual report (2020) showed that about 80% of all MS patients are included in the MS-Registry, and that 90% of newly diagnosed patients were included. Furthermore, the report shows that about 70% newly diagnosed patients received their diagnosis within two years after their first symptom, and that 60% received disease-modifying therapy within one month after the diagnosis. Of the patients with relapsing-remitting MS, as many as 70% started with high-efficacy therapy. Seen over time, this is a very encouraging development, but the numbers could have been even better.

At the same time, the report shows a large unwanted variation across the hospitals in Norway. The reasons for this are probably many, but an important factor is an outdated national guideline for treatment of multiple sclerosis, focusing on escalation treatment strategy. This includes starting with less effective therapies, followed by escalation to high-efficacy therapies, only in the event of therapy failure. The current available treatment options, combined with increasing evidence for better outcome from early start-up with high-efficacy therapies, calls for a change in treatment guidelines.

Another factor that may lead to variation across the hospitals is that, due to the high cost, early initiation of high-efficacy therapies for the majority of patients requires extensive use of off-label treatment with rituximab. The Norwegian health authorities, through the “Beslutningsforum”, have approved this therapy, but unfortunately, not all departments make full use of this opportunity.

The Norwegian MS Society and Norwegian MS experts have jointly expressed concern related to this challenge and have therefore systematically worked for harmonization of a more offensive treatment strategy. The prerequisite for the use of rituximab is the systematic registration of treatment in the Norwegian MS-Registry, as well as the implementation of a randomized treatment trial for comparison of off-label cost-effective rituximab with the approved next generation drug, ocrelizumab at a significantly higher cost. Neuro-SysMed is currently conducting this study (The OVERLORD-MS study) funded by the Regional Health Authorities (KLINBEFORSK), the Research Council of Norway, and participating hospitals. At best, results from this study can be available in early 2025. Therefore, Norwegian MS experts and the Norwegian MS Society are now participating in a revision of the Norwegian MS-therapy guidelines, in parallel with ongoing studies and MS-Registry documentation. Results from the OVERLORD-MS study, and from another rituximab trial in Norway (NOR-MS), combined with the MS-Registry data are, however, of great importance for evaluation of long-term safety and efficacy of this therapy.

The Norwegian Directorate of Health is responsible for this guideline revision that are focusing on the importance of early diagnosis and early start with high-efficacy therapy. At the same time, the guideline will also focus on the importance of user involvement and tailored therapy for the individual patient.

The guideline-group works well together, aiming at a clear goal of a revised treatment guideline supporting equality of early high-efficacy therapy for people with MS across Norway. We are therefore very optimistic and hope that this will be a “game changer” for future MS care in Norway.

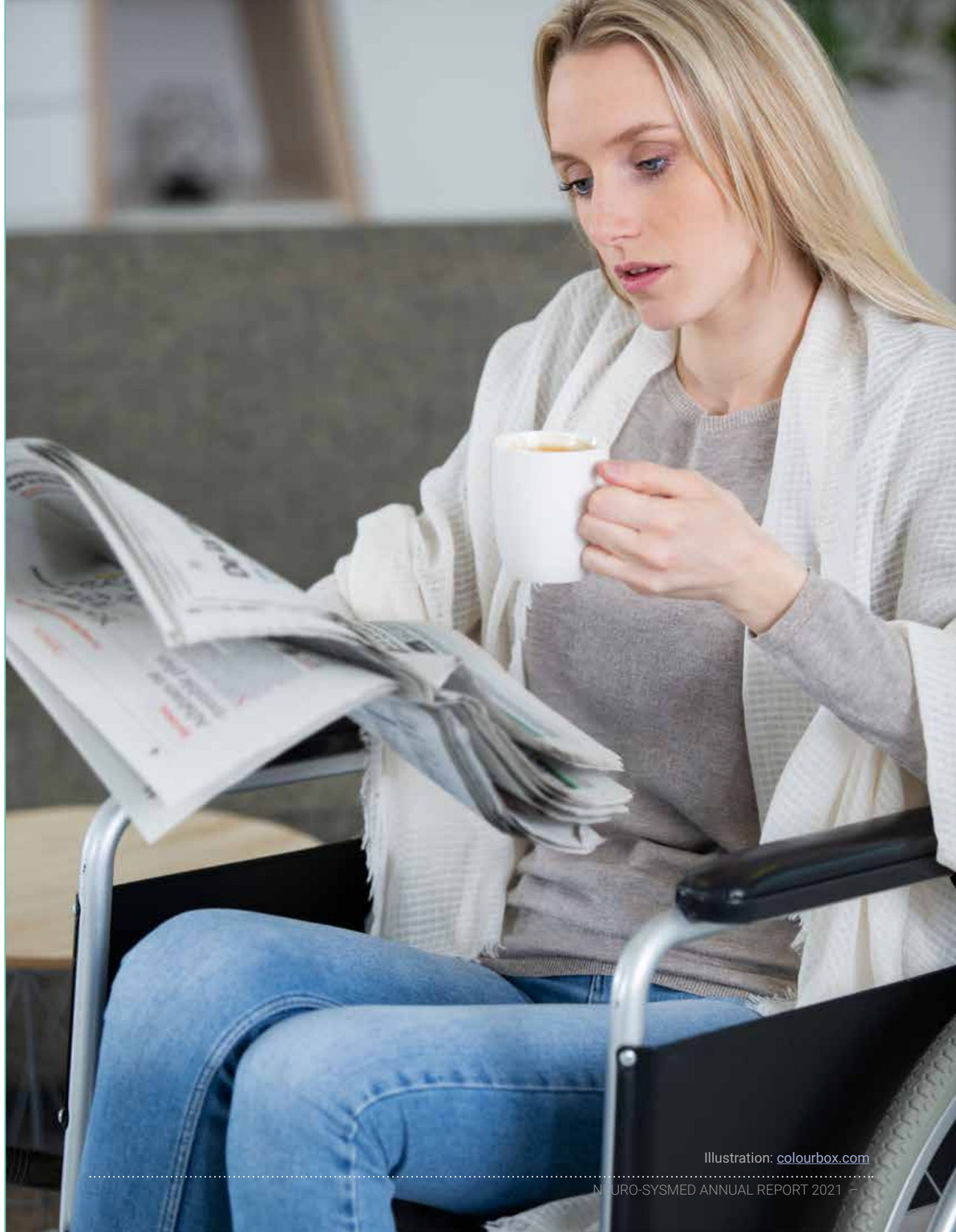


Illustration: colourbox.com

# The conundrum and growing challenge of Parkinson's disease

**By Charalampos Tzoulis**

While references to parkinsonian symptoms can be found since ancient records, the first systematic medical description of the PD syndrome was published by British physician James Parkinson in 1817, in his "Essay on the Shaking Palsy"[1]. Today, PD affects 1-2% of the population above the age of 65 years, and is a major cause of death and disability, with a rapidly growing global socioeconomic impact[2,3]. As of 2020 there is an estimated 10 million people living with PD worldwide, a number which is expected to double by the year 2040. Current treatments for PD can provide partial symptomatic relief, mainly for motor symptoms, but make no substantial impact on disease progression[4–6]. As a result, patients confront a future of progressive disability, placement at nursing homes which society finds increasingly difficult to finance, and premature death. Particularly alarming is the fact that, despite several candidate neuroprotective therapies showing encouraging preclinical results, these have failed to show disease-modifying effects in clinical trials[4,7]. Thus, there is an urgent need to increase global efforts in PD research. Moreover, our failure to make a significant impact, suggests that a paradigm shift is needed in the way the clinical and scientific community are approaching the problem.

Two major obstacles are preventing mechanistic and therapeutic breakthroughs in PD:

First, we lack understanding of the mechanisms underlying the initiation and progression of the disease. Without this knowledge, we are not able to develop therapies specifically targeting the processes driving neuronal dysfunction and death (i.e., neuroprotective therapies).

Second, patients with PD exhibit a wildly variable constellation of symptoms. This phenotypical diversity has led to the hypothesis that PD may not be a single pathogenic entity, but rather a group of disorders that are driven by different molecular processes and may, therefore, respond differently to therapies targeting specific biological pathways.[3,8] If this is indeed the case, such heterogeneity would dilute the biological signal in observational and interventional studies, thereby preventing mechanistic and therapeutic breakthroughs alike. Thus, successful stratification of iPD and identification of any biological disease subtypes is a key research priority.

The PD research program at Neuro-SysMed aims to revolutionize the treatment of PD by addressing both of these critical limitations. The STRAT-PARK study recruits individuals with PD with the aim to stratify them using a bottom-up approach, where distinctive molecular features rather than clinical profiles are used to classify patients. Results from our analyses indicate that we may have already identified a distinct disease subtype driven by a specific molecular mechanism. If confirmed by our ongoing work, this discovery will have the potential to revolutionize the field of PD, radically changing the way the disease is currently approached by scientists and clinicians – moving away from a single entity, of obscure and presumably complex etiology, and into molecularly defined disease subtypes, driven by specific pathogenic processes.

While the search for specific mechanisms driving PD in each patient is ongoing, and before we possess the ability to classify our patients for tailored trials, we are testing a different approach for treatment of unstratified PD populations. Rather than targeting specific single mechanisms believed to contribute to the disease, we are attempting to shield neurons against multiple disease-related stresses, by optimizing their metabolic state. To this end, we are supplementing the brain with the essential molecule NAD – a versatile and vital coenzyme involved in a myriad of biological processes from DNA-repair and gene expression regulation to energy metabolism and signaling[8]. The NADPARK study, our completed phase I trial of NAD-replenishment in PD, was recently published with highly encouraging results (see own section)[9]. The larger, phase-II study NOPARK is currently ongoing and several more studies are about to start in 2022. At the same time, inspired by the research and findings of our group, NAD-replenishment has become a major theme at Neuro-SysMed with ongoing and/or planned studies across all four of our diseases.

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# Breakthrough research in neurodegeneration requires a brain bank

**By Kristoffer Haugarvoll and Charalampos Tzoulis**

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson disease or ALS, are characterized by progressive loss of neurons in the central nervous system (brain and spinal cord), resulting in a multitude of progressive and debilitating neurological symptoms, such as impairment of movement, neuropsychiatric dysfunction, and dementia. Since age is the most important risk factor for neurodegenerative diseases, they have an ever-increasing health and socioeconomic impact as the median age of the population constantly rises. More than 100.000 individuals were suffering from dementia in Norway in 2020, and this number is expected to more than double by 2050.

No cell or animal models accurately reflect the complex mechanisms underlying neurodegenerative diseases in humans. Therefore, studying human brain tissue donated by individuals who suffered from neurodegenerative diseases and neurologically healthy persons (i.e., controls) is absolutely essential for gaining insight into the mechanisms driving the initiation and progression of neurodegeneration. Improved insight into the underlying molecular mechanisms in neurodegeneration is, in turn, crucial in order to develop neuroprotective treatments able to delay or arrest disease progression. The research potential and advantages of having access to human brain tissue are even greater today, since recent technological breakthroughs have made it possible to study human brain tissue at unprecedented scale and resolution, e.g. at the molecular- and microscopic level.

Furthermore, pathological examination of the brain after death is currently the only way to confirm the diagnosis of neurodegenerative diseases. Thus, a national infrastructure enabling brain examination and storage for diagnostic and research purposes is an essential asset in the combat against neurodegeneration. Such an infrastructure is commonly referred to as a brain bank and its main function is to collect, store and characterize brain tissue form a large number of donor with brain diseases, as well as healthy controls.

Norway currently lacks a national brain bank infrastructure. This unmet need represents an important weakness in our current diagnostic system and holds back research efforts to elucidate and treat neurodegenerative disorders.

During the last 10 years, the Tzoulis and Haugarvoll groups have initiated a major endeavor to build a Norwegian Brain Bank. Through their combined efforts, and in collaboration with excellent clinical cohorts, such as the ParkWest study, led by another Neuro-SysMed PI, Professor Tysnes, they have collected more than 200 brains, currently housed at the ultrafreezer section of the Neuro-SysMed Centre.

While a good start, these efforts remain at an infantile stage, far from being able to support national (and international) research in neurodegeneration. Our ambition is to take this initiative to the next level and establish a national brain bank infrastructure, serving clinicians and researchers in all of Norway and internationally. Moreover, such a brain bank will achieve excellent synergy with the extensive health registries, population-based health studies and clinical cohort studies already existing in Norway, propelling Norwegian neurological research to international excellence.

To achieve these goals, we are preparing an application to the Infrastructure Program of the Research Council of Norway.

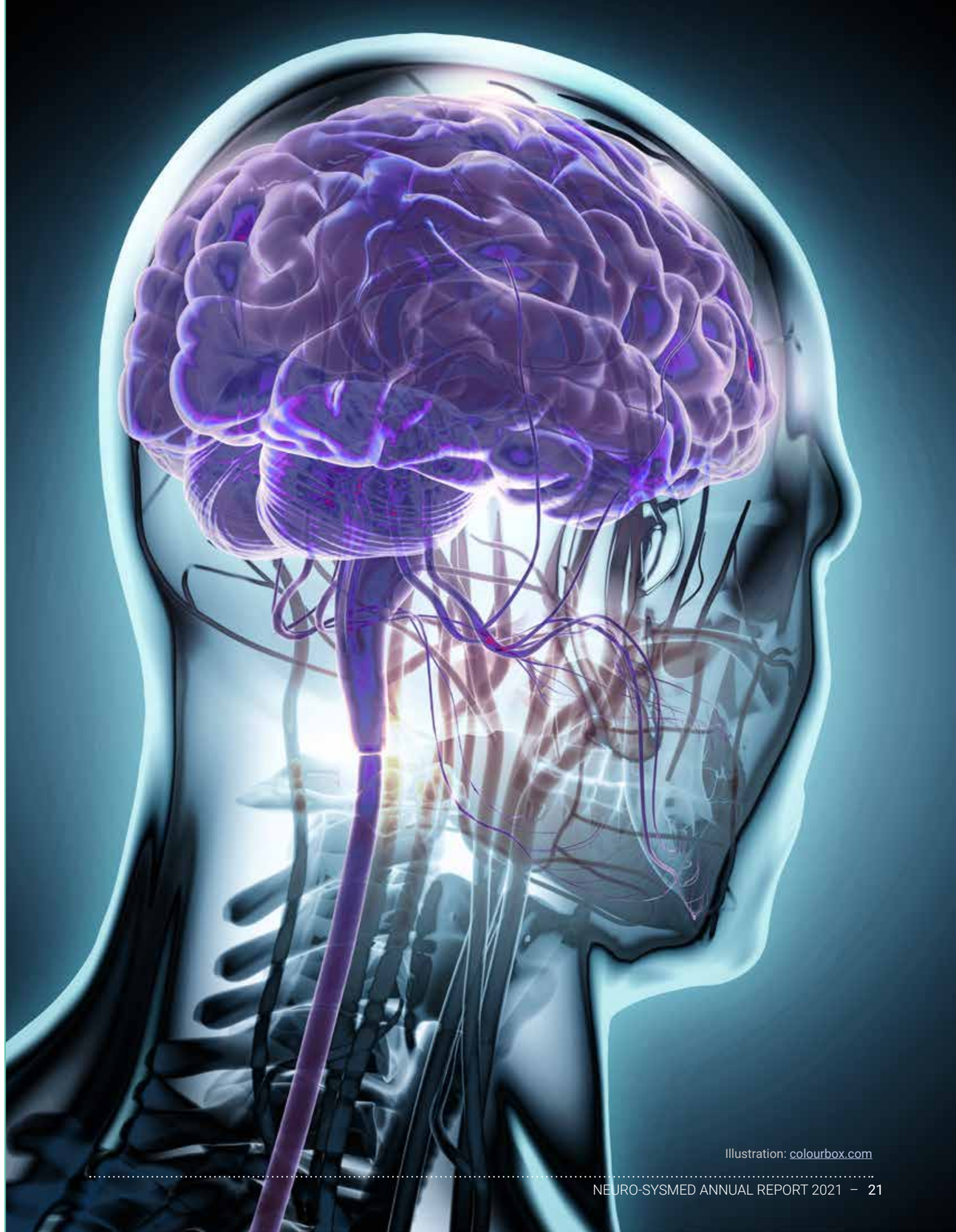


Illustration: colourbox.com

Illustration: colourbox.com





# Living with amyotrophic lateral sclerosis (ALS)

**By Ole-Bjørn Tysnes**

Being diagnosed with ALS is a terrifying and devastating experience. One's entire life is turned upside-down. Mean age of onset is 60 years, and it is not unusual to be diagnosed in the forties or fifties. While the reaction to being diagnosed with this incurable and fatal illness varies considerably between individuals, most plunge into a severe grief reaction, including a feeling of helplessness and impeding doom.

In the aftermath of the initial shock, patients eventually reach the stage of acceptance and realize that important decisions have to be taken. *Shall we move to another house/flat? We will need a place where I can live with increasing disability. How will this be accepted for my spouse who may live for many years after I am gone? How long will it take?* The neurologist cannot be precise. On average survival time is 3 years from diagnosis, but 20% may live more than 10 years. *Is it possible to organize our home so that I can keep living here? Would my spouse prefer to keep on living here after I am gone, or is that not an option? How will symptoms develop? Will I be able to communicate by speech or will I soon have to write down everything or even worse, will I need computer-based aides to talk to my family. How will I die? Will I suffocate?*

Information is essential when following ALS patients and their families. It is an art of balance to inform carefully but correctly. The neurologist must try to see into the future. Usually, the next 3 months can be planned for. A need to change accommodation must be discussed early. Most other decisions can wait except if the patient want to push the information. Aids, communication, swallowing problems with loss of weight, drooling, reduced respiration and end-of-life issues, can be discussed and handled when the time is there.

Most ALS patients report acceptable quality of life after the trauma that follows the diagnosis. They discover life in a new way. They are not able to do all the things they did before, but life is not as cruel as they envisaged the first days after the diagnosis. They become able to laugh again. They discover that they have not lost the interests they had before being diagnosed. Sports, politics, news and culture are still interesting and engaging. Rights of patients with chronic diseases becomes important. The need to collaborate with professionals in your home is a challenge. Patients become surprised they can feel quality in their life with such a disease. They can tell me "I would never have thought I could say that I feel OK in such a condition".

Although patients are able to live with quality in their lives after an ALS diagnosis, there is an urgent need for treatment that may stop or delay development of symptoms. We have now included more than 140 patients in the NO-ALS trial. This is the first Norwegian drug trial in ALS. It represents a hope for a better future for ALS patients. Hopefully we will organize the NO-ALS trial so well that big pharma industry will look to Norway when they in the future have exiting drugs to study in ALS.

Nothing will be better for the ALS patients than a realistic hope for a future treatment.

# Research School in Translational Neuroscience

**The Neuro-SysMed Research School in Translational Neuroscience was launched in March 2021, and the first courses was organized during the autumn term the same year. The vision is to provide sustainable networks of researchers and support, in order to encourage young researchers to expand their promising career beyond an accomplished PhD thesis or a postdoctoral fellowship.**

Research School leader: Nina Grytten Torkildsen in collaboration with the Neuro-SysMed Director and Co-Director.

The Research School aims at providing PhD candidates with relevant courses to fulfil obligatory credit points for the PhD training program at the University of Bergen. Another important objective for the Research School is to educate health care personnel and researchers in clinical trial performance and provide an inspiring and ambitious environment facilitating future research among junior scientists as well as the established seniors.

Three initial PhD level courses was launched in collaboration with the Centre for Cancer Biomarkers CCBIO in the autumn of 2021.

## CCBIONEUR910 – Patient and Public Involvement in Medical and Health Research

CCBIONEUR910 is a two ECTS course aiming at creating a platform for competence development and networking across professionals, including researchers, health care personnel and user representatives, to facilitate communication and sharing of experience from multiple perspectives. The course also aims to stimulate for increased user participation in research and implement methods for user involvement throughout research projects. The overall objective of the course is to develop the participants' capacity to assess and convey the value of patient and public involvement in general, as well as promoting productive user involvement in participants' research projects.

The course spans over three days and encompasses a broad spectrum of national and international lectures from researcher and user organizations, professionalized users and health care personnel employees assigned to specific user representation tasks. Challenges are addressed from both researcher- and user representative perspectives, and specific advice as well as professional and personal opinions are shared. The course promotes an atmosphere of reflected open-mindedness, and an overall pragmatic attitude to find common denominators and move forward in the heterogeneous meadow of user representation in medical research.

CCBIONEUR910 took place at the brand new Eitri Medical Incubator, UiB. Photo: Tone Skår

Nina Jebsen (CCBIO), Kjell-Morten Myhr (Neuro-SysMed) and Tone Skår (Neuro-SysMed and VIS) are academic responsible for the course. Hilde Norborg (Neuro-SysMed) and Pål Tore Bentsen (CCBIO) are course coordinators.

## CCBIONEUR911 – Clinical Trials in Cancer and Neurological Research

CCBIONEUR911 includes modules based on the ICH Good Clinical Practice (GCP). It covers topics from design planning to execution, such as general principles of clinical trials, ethics and the patient perspectives, GCP overview, operations and practicalities, formalities and regulations, translational research protocols, making clinical trials part of normal clinical operations, success factors and clinical trials in the future. Learning examples from cancer research and neurological research are embedded in the sessions. This course provides two ECTS in addition to qualifying for the GCP certificate.

The course spans over two days and include a broad spectrum of national lectures by researchers, health care personnel, and representatives from user organizations, pharmaceutical industry as well as regulatory bodies.

Line Bjørge (CCBIO) and Øivind Grytten Torkildsen (Neuro-SysMed) are academically responsible for this course. Benedicte Sjo Tislevoll (CCBIO) and Hilde Norborg (Neuro-SysMed) are course coordinators.

The CCBIONEUR911 team

## CCBIONEUR912 – Health Innovation Course

CCBIONEUR912 is the first PhD course at UiB on health innovation and is a unique opportunity for researchers at the beginning of their research careers, giving insights on how to bring research to society. The course provides perspectives on an alternative, entrepreneurial career path, and inspiring the attendees with examples of people who have walked this path before them. The overall aim of this course is to encourage and enable PhD students and young researchers to identify and evaluate the innovation potential in their own research projects and provide them with the knowledge needed to be able to do this. The course provides inspiration and practical knowledge on alternative ways to realize the innovation potential from research projects.

This four ECTS course benefits greatly from inspirational presentations from affiliates of both CCBIO and Neuro-SysMed, sharing their professional expertise and experience. Altogether, the various presentations displayed a wide variety of "problems" and "solutions" and various routes to exploitation of research-driven innovations. The course thus includes a broad spectrum of national and international lectures by researchers, research advisors, and representatives from technology transfer offices and entrepreneurs in start-up companies. An absolute highlight on this course was the inspirational talk in the keynote lecture by Professor Robert Langer, founder of numerous companies, amongst them Moderna.

Bob Langer on a live streaming from MIT

Agnete Engelsen (CCBIO) and Magnus Alvestad (Neuro-SysMed) are academic responsible for this course. Ning Lu (CCBIO) and Hilde Norborg (Neuro-SysMed) are course coordinators.

## Coming new courses

The Neuro-SysMed Research School in Translational Neuroscience are planning establishment of research courses and activities by 2022 in the following subjects:

- Suffering by POND Philosophy of Neuro-degeneration with PI Jan Reinert Karlsen and Postdoc Caroline Benedicte Nitter Engen
- Bioinformatics for Clinical Studies / Applications with Lilya Toker, Gonzalo S. Nido, Kim Brugger and Fiona Dick
- Seminars and Annual Symposium
- Junior Scientist Symposium

# Neuro-SysMed recruitment and research education

**Neuro-SysMed has a strong focus on educating researchers in the field of clinical treatment research, and this is integrated into all activities at the Centre.**

The Centre provides research training in a broad spectrum of topics, including the pathogenesis and basic understanding of fundamental disease processes, epidemiological research, big-data analyses, statistic and bioinformatics, as well as design and implementation of clinical trials. In addition, Neuro-SysMed provides training of health care personnel, including nurses, physicians, laboratory technicians and study coordinators. Recruitment and training of PhD students and Postdoctoral fellows are central to our research and educational activities.

Neuro-SysMed aims to recruit at least one PhD candidate and/or postdoctoral fellow for each of our clinical trials, and other projects. The Centre organizes weekly meetings and seminars within the research groups, as well as regular joint meetings across research groups and disciplines. At these meetings, the PhD students and Postdoctoral fellows present their projects, including results and strategies for further scientific and career development, and receive critical feedback from all attendees.

**The Neuro-SysMed Research School in Translational Neuroscience** (see previous pages) is an overarching structure of the research training. The school organizes seminars, symposiums and specific courses that award the attendees ECTS credits needed for the research educational programs.

Photo by Tone Skår

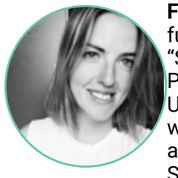


# Completed Academic Degrees

**Researcher education at all levels is central for Neuro-SysMed. Six PhD candidates with Neuro-SysMed funding successfully defended their theses during 2021. Their work were initiated prior to the start of the Centre, but the topics were within the core activity of the Centre.**

## Parkinsons disease:

**Johannes Jernqvist Gaare** March 5, 2021 successfully defended his PhD thesis "Exploring the genetic contribution to idiopathic Parkinson disease" at the University of Bergen. Main supervisor was Professor Charalampos Tzoulis, and co-supervisors were PhD Kristoffer Haugarvoll and Professor Ole-Bjørn Tysnes. Press release is available at uib.no/nye-doktorgrader.



**Fiona Dick** October 1, 2021 successfully defended her PhD thesis "Studies of gene expression in the Parkinson's disease brain" at the University of Bergen. Main supervisor was Professor Charalampos Tzoulis, and co-supervisor was Dr. Gonzalo S. Nido. Press release is available at uib.no/nye-doktorgrader.

## Multiple Sclerosis:

**Silje Agnethe Stokke Kvistad** April 15, 2021 successfully defended her PhD thesis "Multiple sclerosis - the impact of environmental- and lifestyle factors" at the University of Bergen. Main supervisor was Professor Øivind Torkildsen, and co-supervisor was Professor Kjell-Morten Myhr. Press release is available at uib-no/nye-doktorgrader.

**Ragnhild Reehorst Lereim** June 23, 2021 successfully defended her PhD thesis "Using mass spectrometry-based proteomics to improve the understanding of multiple sclerosis treatments" at the University of Bergen. Main supervisor was Dr. Harald Barsnes, and co-supervisors were Professor Frode S. Berven, Dr. Astrid Guldbrandsen and Dr. Eystein Oveland. Press release is available at uib-no/nye-doktorgrader.

## Central nervous system biomarkers:

**Kristin Wesnes** June 6, 2021 successfully defended her PhD thesis "The impact of lifestyle factors on disease risk and long-term disability progression in multiple sclerosis" at the University of Bergen. Main supervisor was Professor Kjell-Morten Myhr, and co-supervisors were Professor Trond Riise and Associate Professor Kjetil Bjørnevik. Press release is available at uib-no/nye-doktorgrader.

**Kristin Nielsen Varhaug** November 26, 2021 successfully defended her PhD thesis "Mitochondrial biomarkers and biomarkers of mitochondrial disease" at the University of Bergen. Main supervisor was Professor Laurence A. Bindoff, and co-supervisor was Professor Christian A. Vedeler. Press release is available at uib-no/nye-doktorgrader.

# PRINCIPAL INVESTIGATORS AND RESEARCH GROUPS

**The Centre includes 13 principal investigators with separate research groups. Some groups are focusing on one of the specific diseases of the Centre, while others work across the diseases. Some groups have all their activity within the Centre, and thus comprises the core activity of Neuro-SysMed, while others contribute with defined and important projects into the Centre. Several groups have projects spanning for the whole lifetime of the Centre, while others have most of their planned activities later in the lifetime of the Centre – dependent on activities and deliveries of other groups. For each group, the group members that are involved in Neuro-SysMed projects are listed, as well as some recent key publications from the group.**

# The Multiple Sclerosis Research Group

## Biomarkers and tailored therapies for patients with multiple sclerosis

## PI: 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 first KG Jebsen Centre for Medical Research (in MS), and is currently the Director of the Norwegian Centre for Clinical Treatment Research in Neurology, Neuro-SysMed.**

The Multiple Sclerosis (MS) Research Group aims at developing tailored treatment strategies for patients with MS. Major challenges are how to improve treatment strategies for already available disease-modifying therapies,[1] 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.

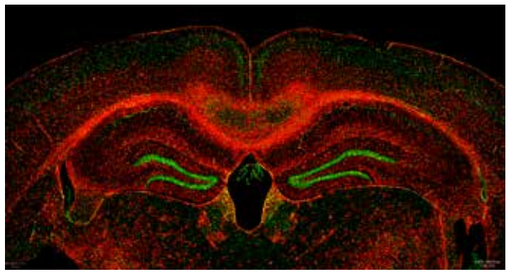
The MS-group is currently recruiting patients into five investigator initiated clinical trials:

- **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** evaluates and compares the efficacy and safety of rituximab and ocrelizumab in newly diagnosed relapsing-remitting MS patients.
- **The COVID-19 vaccine response study** evaluates the impact of various disease-modifying therapies on the vaccination response in MS patients.[2,3]
- **The SMART-MS study** evaluates regenerative effects from mesenchymal autologous stem cells in progressive MS.
- **The FlowOx-MS study** is a pilot trial to explore if pulsating negative pressure therapy device can improve spasticity and pain in lower extremities of patients with MS.

Further, the MS Research group serves as the national coordinator for three industry-sponsored multicentre randomized clinical trials in both relapsing-remitting and progressive disease, and recruiting site for another. We are also national coordinator in the extension phase of additional six industry sponsored multicentre clinical trials.[4]

In collaboration with the Neuroimmunology & Biomarker Group at the Centre, the MS group 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.[5-7] We also perform preclinical animal studies to evaluate possible disease pathways of progressive MS, and regenerative potentials of stem cell therapy. In addition, we evaluate treatment responses by neurofilament in both spinal fluid and serum.[8-11] In collaboration with the Mohn Medical Imaging and Visualization Centre at the Hospital, we evaluate treatment responses by magnetic resonance imaging (MRI).

The MS group also include projects aiming at identifying modifiable risk factors for the disease that may influence disease progression, or even risk of side effects from therapies.[12-14] This includes studies of comorbidity, with especially focus on cancer, as well as registry projects analysing real world data on treatment compliance and factors influencing discontinuation rates for ongoing therapies.[14-20]



*Mouse brain from cuprozone trial dyed with GFAP (red: astrocytes) and DAPI (green: cell cores). Kråkenes/Kvistad.*



## GROUP MEMBERS

**PIs and Senior Researchers**
Kjell-Morten Myhr, MD, PhD, Group Leader
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Kjersti Furuseth, RN

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Lars Martin R. Skår, Medical Student

**PhD Alumni**
Agnes E. Nystad, MD, PhD

**Core personnel supporting all research groups.*

## SELECTED KEY PUBLICATIONS


1. Holmøy T *et al*. Disease-modifying therapy for multiple sclerosis. Tidsskr Nor Laegeforen 2021;141.
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.
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# The Neuromics Research Group

## Biomarkers and tailored therapies for Parkinson's disease

## PI: Charalampos Tzoulis

**Charalampos Tzoulis is a Professor of Neurology and Neurogenetics at the University of Bergen and Haukeland University Hospital. As a clinical neurologist, Professor Tzoulis is an expert on movement disorders and neuro-degeneration, 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, an interdisciplinary research group comprising 35 members and integrating clinical, molecular and computational neuroscientists, with the common goal of deciphering and treating Parkinson's disease. Tzoulis is also Director of the K.G Jebsen Center for Translational Research in Parkinson's disease, and co-Director of Neuro-SysMed, where he leads the research on PD and other neurodegenerative disorders.**

During 2021, Professor Tzoulis' group made key-advances in their research projects:

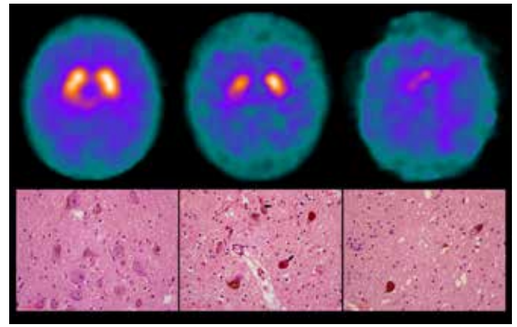
1. **The NADPARK study**[1] was completed and the results published. NADPARK is a phase I randomized, double-blinded trial, aiming to assess the tolerability, cerebral bioavailability and molecular effects of NR therapy in PD. A total of 30 individuals with newly diagnosed, drug-naïve PD were randomized to NR 500 mg x2/day or placebo for 30 days. The study showed encouraging results, which were published in the prestigious journal Cell Metabolism[1].

2. **The NO-PARK study** study is a phase-II randomized, double-blind clinical trial trial, designed to test the potential of NR as a neuroprotective therapy delaying neurodegeneration and clinical disease progression in PD. NO-PARK has initiated in more centers across Norway and now includes seven hospitals. In addition, at least four more hospitals are expected to initiate patient recruitment during 2022. 120 participants are included as of the end of 2021. When completed, this study will provide a definite answer to whether NR-therapy can delay the progression of PD.

3. **The NR-SAFE study** is a phase I, randomized, double-blind safety trial. It is plausible that the beneficial effects of NR in PD, observed in the NADPARK study, are dose-dependent and more prominent at higher doses. NR doses of up to 2000 mg per day have been tested in healthy humans with no signs of toxicity. However, the safety and tolerability of even higher doses is untested. NR-SAFE will assess the safety and tolerability of an oral dose of 3000 mg NR daily. During 2021, the study protocol was designed, and funding and all necessary regulatory approvals were obtained. The study will start in March 2022.

4. **The STRAT-PARK initiative** is a longitudinal population-based cohort study aiming to identify biological subtypes of PD. The heterogeneity of PD is a major obstacle preventing the development of patient-tailored therapies. Here, the aim is to stratify PD by identifying and characterizing subgroups of patients with distinct clinical and/or molecular characteristics. Moreover, the group aims to develop biomarkers enabling patient stratification in clinical practice. The STRAT-PARK study represents a vast clinical endeavour where a total of 1,500-2,000 patients and controls will be recruited from three clinical centres. As of the end of 2021, 100 participants have been included in the STRAT-PARK study.

5. **The ParkOme initiative** aims to elucidate mechanisms driving disease initiating and progression in PD, and to apply this knowledge to identify novel biomarkers and therapies. The group is mapping the molecular landscape of PD in key-regions of a large number (n > 1000) of fresh-frozen post-mortem brain samples. In each bulk-tissue sample, they are constructing a multilayer molecular map combining the genome, DNA-methylation, selected histone modifications, chromatin accessibility, transcriptome and proteome. This data is being integrated with clinical, environmental and epidemiological information. Analyses of the ParkOme data have already generated novel insights into the genetics and gene-expression profile of PD.



DAT-scans and histological sections of a healthy individual (left) and persons with parkinsonism.



## GROUP MEMBERS

**Senior Researchers**
Charalampos Tzoulis, MD, PhD, Group Leader
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Lilah Toker, PhD
Gonzalo S Nido, PhD
Geir Olve Skeie, PhD

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Brage Brakedal, MD, PhD
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Fiona Dick, PhD

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**Technicians**
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Dagny Ann Sandnes, MSc*
Gry Hilde Nilsen, MSc*
Martina Galatea Castelli, PhD*
Yana Mikhaleva
Omnia Shadad*
Sepideh Mostafavi
Kim Brugger*

**Core personnel of Neuro-SysMed*

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1. Brakedal B, Dölle C, Riemer F, Ma Y, Nido GS, Skeie GO, et al. The NADPARK study: A randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. Cell Metabolism. 2022;34:396-407.e6.
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# The Bergen Dementia Research Group

## PI: Kristoffer Haugarvoll

**The Bergen Dementia Research Group is located at Haraldsplass Deaconess Hospital and Haukeland University Hospital. The research group has a particular focus on neurodegenerative dementias, such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). Including their overlapping pathologies, also known as mixed pathologies. The group aims at identifying novel biomarkers for dementia and stratifying dementias according to underlying molecular patterns. Importantly, we aim to develop novel treatments for dementias.**

Kristoffer Haugarvoll, MD, PhD is Principal Investigator (PI) in the Bergen Dementia Research Group and 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.

The group aims at identifying novel biomarkers for dementia and stratifying dementias according to underlying molecular patterns. They are now starting a new cohort study – STRAT-COG. This study aims to establish a comprehensive biomarker panel for dementia by combining existing biomarkers for Alzheimer's disease pathology with biomarkers for neuronal loss and α-synuclein pathology. This will enable the group 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.

By conducting clinical trials, the Bergen Dementia Research Group group will contribute to developing novel treatments for neurodegenerative dementias, with a special focus on strategies that could boost brain metabolism.

The Bergen Dementia Research Group is a partner in the ANeED study: Ambroxol in New and Early DLB, A Phase IIa Multicentre Randomized Controlled Double Blind Clinical Trial (PI: Arvid Rongve).

The Bergen Dementia Research Group is recruiting individuals with mild cognitive impairment to the ongoing Dementia Disease Initiation (DDI) study (PI: Tormod Fladby).



### GROUP MEMBERS

Kristoffer Haugarvoll, MD, PhD, Group Leader
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Lasse Giil, MD, PhD, Postdoc
Kristin Eidsheim Sønnesyn, MD

Irit Titlestad, PhD Candidate
Kristina Skeie, Research Nurse
Lone Birkeland Johansen, Research Nurse

### SELECTED KEY PUBLICATIONS


1. Brakedal B, Tzoulis C, Tysnes OB, Haugarvoll K. NSAID use is not associated with Parkinson's disease incidence: A Norwegian Prescription Database study. LoS One. 2021 Sep 7;16(9):e0256602. doi: 10.1371/journal.pone.0256602. PMID: 34492069
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Photo: Ingrid Færøyvik/Haraldsplass Deaconess Hospital

# Clinical Treatment for ALS

## PI: Ole-Bjørn Tysnes

**Ole-Bjørn Tysnes is a Consultant Neurologist in 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.**

Basic and clinical research on Parkinson's disease, led by the Tzoulis group at Neuro-SysMed, have nominated NAD-replenishment therapy with nicotinamide riboside (NR) as a potential neuroprotective intervention against neurodegeneration. Interestingly, these findings suggest that NR-mediated neuroprotection targets and ameliorates multiple stress-processes associated with neurodegeneration and may, therefore, be applicable across neurodegenerative diseases. Moreover, one recently published, small-scale study suggested that the combination of NR and pterosstilben (a sirtuin activator), may delay disease progression in ALS (PMID: 30668199).

Based on this evidence, the group hypothesized that oral administration of combination therapy with NR and pterostilbene will inhibit neurodegeneration and increase survival and quality of life in patients with ALS. To test the hypothesis, we are now running a phase-II, multi-centre, double-blinded randomized clinical trial of oral NR and pterostilbene in early ALS (NO-ALS study). Based on power estimations, a total of 180 patients are needed in study arm 1. Patients are recruited throughout Norway. The study has also has a study Arm 2 for patients not fulfilling inclusion criteria of arm 1. The study was started in October 2020. By end of 2021, 129 patients were included in the study, 49 of these are in study Arm 1. All study centres are active, including patients across of Norway.

In addition to the NO-ALS study, the ALS study group in Neuro-SysMed 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. The ALS group has recently performed a questionnaire study to record the use of off-label therapies, as well as supplement use of vitamins and other compounds. The results from this study will be published in 2022.

The NO-ALS project has the potential to discover a therapy, modulating disease activity and progression in ALS, thus vastly improving patient care and prognosis. The study has received support from Helse Vest and KLINBEFORSK.

Read more in the Trials section.



### GROUP MEMBERS

Ole-Bjørn Tysnes, PhD, MD, Professor, Head of the Study
Marit Renså, Study Nurse
Tiina Rekand, PhD, Professor
Tale Litlere Bjerknes, Study Physician, PhD
Tina Taule, PhD, Researcher
Romain Guitton, PhD, MD
Synnøve Bartz-Johannesen, Study Nurse

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Illustration: iStockphoto.com

# The ActiveAgeing Group

## PI: Bettina Husebø

**The ActiveAgeing project started in February 2021, with PI Bettina Husebøe, 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.**

The ageing population is increasing worldwide at a fast rate. However, the resources for care cannot grow at the same rate. In Norway today, 1 in 7 employees work in healthcare, and with estimated demographic development, the numbers will increase to 1 in 3 in 2050. Moreover, neurological diseases such as dementia and Parkinson's Disease (PD) are increasing among older adults, which significantly raises the caregiving demand. Thus, the Centre for Elderly and Nursing Home Medicine (SEFAS), University of Bergen, (UiB), identified the necessity for a paradigm change in elderly care and argue for digital phenotyping and utilization of wearable devices.

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 others. The project duration is four years, and it consists of two sub-projects: DIGI.PARK and ACT.LIVE.

**DIGI.PARK** is a study in collaboration with Neuro-SysMed, the Research Council of Norway, and UiB. DIGI.PARK 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 that address PD. Partners or spouses of people with PD will also be included to explore the impact of the disease in a patient-caregiver dyad (Fig 1). 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 GC Rieber Foundation, UiB, 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 favorite 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 Fig 1). ACT.LIVE will integrate data sources in a mixed-method approach.

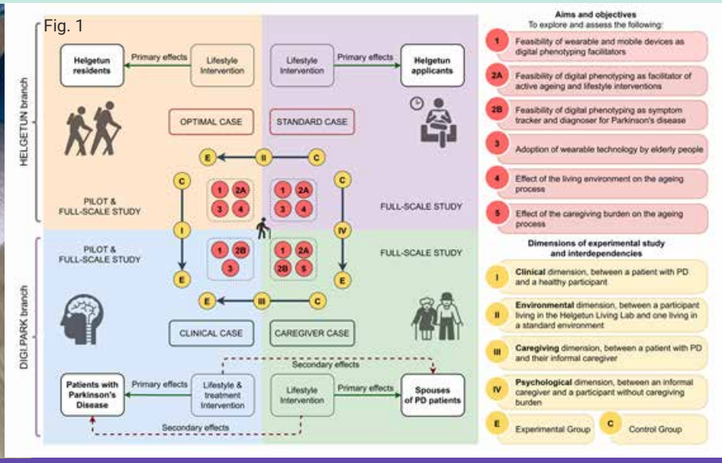
After obtaining ethical approval from NSD, the Helgetun participants were recruited, and the first digital data collection is completed. Regular data acquisitions are planned for comparison. In the next step, people with PD from the STRAT.PARK study are enrolled in the study and followed over a cumulative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



## GROUP MEMBERS

Bettina S. Husebø, MD, PhD, Professor, PI, Centre Leader at SEFAS, UiB
Ane Erdal, PhD, Researcher
Monica Patrascu, PhD, Researcher
Juan Carlos Torrado Vidal, PhD, Postdoc
Haakon Reithe, PhD Candidate
Elise Førsund, PhD Candidate
Rune Samdal, Co-Researcher (user representative)

Fig. 1

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- Husebo BS, Kerns RD, Han L, et al. Pain, Complex Chronic Conditions and Potential Inappropriate Medication in People with Dementia. Lessons Learnt for Pain Treatment Plans Utilizing Data from the Veteran Health Administration. Brain Sci 2021;11(1):86.
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- Gedde MH, Husebo BS, Mannseth J, et al. Less Is More: The Impact of Deprescribing Psychotropic Drugs on Behavioral and Psychological Symptoms and Daily Functioning in Nursing Home Patients. Results From the Cluster-Randomized Controlled COSMOS Trial. Am J Geriatr Psychiatry 2021; 29(3): 304-315.
- Wagatsuma S, Yamaguchi T, Berge LI, et al. How, Why and Where it Hurts—Breaking Down Pain Syndrome Among Nursing Home Patients with Dementia: A Cross-Sectional Analysis of the COSMOS Trial. Pain Manage Nurs 2021.

# The Biorecognition Unit

## PI: Aurora Martinez

**Aurora Martinez is a Professor at the Department of Biomedicine, UiB, and leader of the research Unit Biorecognition. 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.**

The Biorecognition Unit has expertise and skills in biophysics, structural biology, drug design, cellular biology and animal models of disease, investigating how structure determines molecular recognition, stability and function in selected biomolecular networks. The main research focus is on inborn errors of metabolism and neurotransmitter dysfunction, notably parkinsonisms, and the group applies compound screening and early-stage drug discovery in the development of mechanistic therapies. The group is a specialized screening site at the NOR-Openscreen and EU-Openscreen networks. Their main activities in Neuro-SysMed concern the molecular-level understanding of the organization and regulation of relevant presynaptic dopaminergic proteins, and collaboration with partners on drug discovery, aiming at the recovery of mitochondrial function and dopamine regulation. The activities in 2021 were supported by grants from RCN and Helse-Vest RHF.

In 2021, the group obtained important results on the regulation of phenylalanine- and tyrosine hydroxylase (PAH and TH) and their dysfunctional pathways to disease. They characterized a valuable mouse model with the mutation Pah-R261Q, leading to a paradigm shift in the understanding of PKU pathology from a loss-of-PAH function disorder to include a gain-of-function due to toxic protein misfolding and aggregation (Aubi et al. 2021). This study provides novel targets and mechanisms in proteostasis dysregulation, which is predominant in neurodegenerative disorders. Moreover, several group members (photo), in collaboration with the lab of JM Valpuesta (CNB-CSIC, Madrid), have recently solved the cryo-EM structure of full-length human TH with and without dopamine, acting as a feedback inhibitor and regulator of TH (Bueno-Carrasco et al. 2022; fig. 1). These structures are a long-awaited achievement that reveals possible interface regions for protein-protein regulatory interactions that control TH and dopamine levels and represent targets for discovery of dopaminergic therapies in Parkinson's disease (PD).

A continuation of the project includes interactions of TH with the vesicular monoamine transporter 2 (VMAT2) and α-synuclein, also important targets in PD. In a recent project, Neuro-SysMed researcher Svein Isungset Støve has screened for compounds modulating VMAT2, has obtained effective inhibitors (Støve et al., in revision) and continues the search for activators (In preparation). Identification of activators 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. The group has developed novel screening assays which have been successfully applied to identify modulators of proteostasis and protein stability, of application in cancer (Dublang et al., 2021), but also in neurodegeneration (Walløen et al., 2021 and in preparation).

The group also continues the optimization of screens and assays of the neuronal respiratory complex I deficiency and impaired mitochondrial DNA homeostasis, in collaboration with Profs. Charalampos Tzoulis and Laurence A. Bindoff.



### GROUP MEMBERS

Aurora Martinez, PhD, Professor, Group Leader
Knut Teigen, PhD, Professor
Ming Ying, Senior Engineer
Svein I. Støve, PhD, Postdoc, UiB
Marte I. Flydal, PhD, Researcher, HUS
Karina S. Prestegård, Industrial PhD, RCN/Pluvia
Mary Dayne Sia Tai, MS, PhD Candidate, UiB
Kunwar Jung KC, PhD Candidate, UiB (PhD as of Sept. 21)
Trond-André Kråkenes, Master Student (MS as of Oct. 21)
Fredrik Gullaksen Johannessen, PhD Candidate

The group includes 13 members in total. The 10 above participate in projects related to Neuro-SysMed.

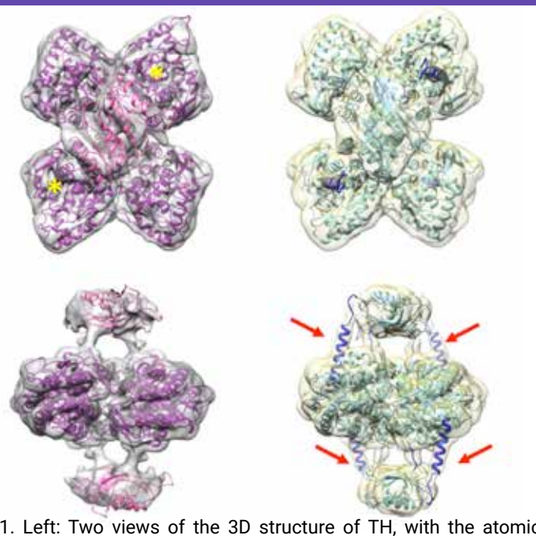

Fig. 1. Left: Two views of the 3D structure of TH, with the atomic model generated inside, where the yellow stars point to two of the active centers of TH. Right: The same two views of the 3D structure in the presence of dopamine, which regulate TH by inhibiting activity via the introduction of a helical part of the protein (marked with red arrows) in the active center.

Fig. 2. From the left: Rune Kleppe, Trond-André Kråkenes, Marte Innselset Flydal, Knut Teigen and Aurora Martinez. Photo: Svein Isungset Støve.

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# The Mitochondrial Medicine and Neurogenetics Research Group (MMN)

## PI: Laurence Bindoff

**The MMN group studies primary mitochondrial diseases, such as those caused by mutations in POLG and mitochondrial DNA, as well as mitochondrial dysfunction in other diseases, e.g. Parkinson's and other neurodegenerative disorders.**

Whilst the link between primary mitochondrial defects and disease is clear, multiple lines of evidence link mitochondrial dysfunction with neurodegeneration. Thus, either mitochondrial dysfunction is a "common" final pathway for neuronal death (i.e. in all forms of neurodegeneration) or mitochondrial "promiscuity", i.e. their involvement in almost every cellular process, means that any changes are secondary and mitochondria are either not involved in the disease process or only partly so.

Using induced pluripotent stem cells (iPSC), the group has generated dopaminergic neurones, motor neurones, glial cells such as astrocytes and oligodendrocytes, and mesenchymal cells such as cardiomyocytes. The MMN group's main role in Neuro-SysMed is to provide expertise in generating stem cell models in appropriate cell lineages (e.g. neuronal or glial) that can provide insight into the mechanisms of neurodegeneration. In 2021, this work was extended into the area of complex structures called organoids and have successfully generated cortical organoids ("brains in dish") from patients with mitochondrial disease and controls.

Building on the group's earlier studies, they have published their methods for assessing mitochondrial function in individual cells and shown that both nicotinamide riboside (a vitamin B3 precursor) and N-acetylcysteine amide (a free radical scavenger) both ameliorate mitochondrial dysfunction driven by POLG mutations. They have also submitted work showing that astrocytes from POLG are toxic for neurones confirming that these cells are not simply bystanders in the disease process, but actually participate. Astrocyte involvement in neurodegeneration is an exciting and novel area and these ground breaking findings suggest that mitochondrial dysfunction may be a common stimulus driving astrocyte conversion from normal to the toxic A1 type that damage and potentially kills neurones.

In addition to the work with neural lineages, the MMN group completed work showing how mitochondria are remodelled during cardiomyocyte differentiation.

The group's clinical work in 2021 included collaborative work on two mitochondrial diseases, BCS1L and DHX30, as well as continuing the studies of POLG related disease. Together with colleagues from Padua, Italy, Gothenburg, Sweden and Cambridge, UK, the MMN group showed that a mouse model of POLG disease manifested a limited phenotype and instability of the polymerase gamma holoenzyme due to catalytic subunit depletion.

The search for biomarkers has continued and this will be extended into other mitochondrial factors, including free mtDNA in serum in collaboration with Professor Valerio Carelli, Bologna, Italy. Kristin N. Varhaug successfully defended her thesis entitled "Mitochondrial biomarkers and biomarkers of mitochondrial disease", November 2021.

There have been several major changes in personnel during 2021. Professor Bindoff is retired as of 01.11.2021, but continues his active participation as Emeritus Professor. The models and drug screening work relating to PD conducted by Prof. Bindoff's group are being carried forward under the group of Prof. Tzoulis. Dr. Yu Hong left the group for family reasons and returned to China, and Anbin Chen completed his PhD work and has submitted his thesis for evaluation in China. Three new Master Students joined the group.



## GROUP MEMBERS

**PIs and senior researchers**
Laurence Bindoff, Emeritus Professor, Group Leader
Kristina Xiao Liang, PhD, Senior Researcher

**PhD Candidates**
Sepideh Mostafavi, MS (defended 03.02.2022)
Cecilie Kristensen, MS
Anbin Chen, MS, (submitted December 2021)
Kristin Nielsen Varhaug, MD, (successfully defended 26.11.21, continued as a Postdoc)

**Master Students**
Sharika Marjan
Tsering Yangzom
Bjørn Christian Lundberg

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1. Björkman K *et al*. Phenotypic spectrum and clinical course of single large-scale mitochondrial DNA deletion disease in the paediatric population: a multicentre study. J Med Genet. 2021.
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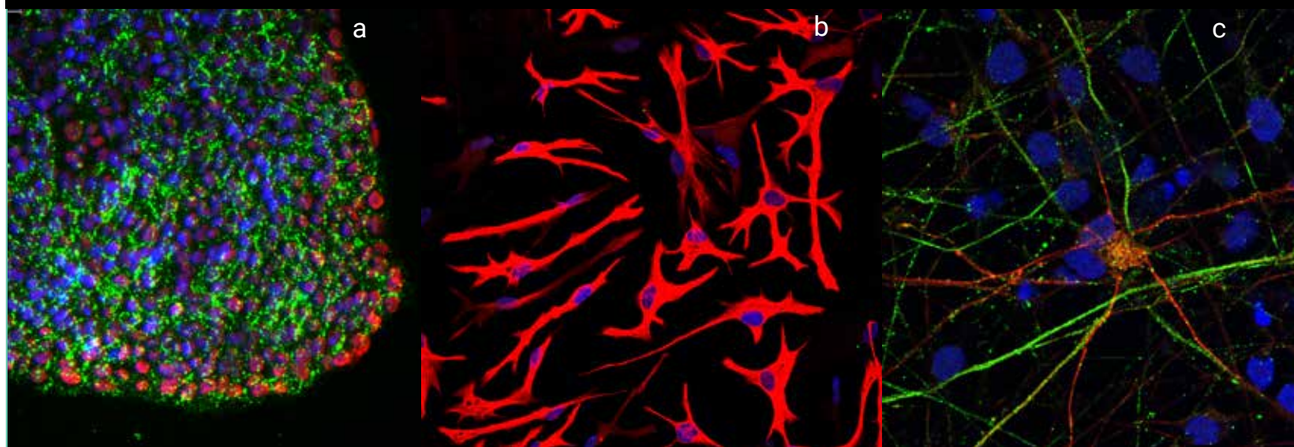
a. Induced pluripotent cells (iPSC) stained with SSEA4(red) and Sox2(green): b. iPSC-derived astrocytes stained with glial fibrillary acidic (GFAP)(red) double cortin (Dcx)(green); iPSC-derived dopaminergic neurons stained for tyrosine hydroxylase (green) and GFAP(red).



# Molecular Bioenergetics and Signaling Group

## PI: 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 UiB Department of Biomedicine. Metabolic alterations are hallmarks of many diseases. Perturbations of energy metabolism are particularly critical in neurodegenerative processes, owing to the impairment of mitochondrial functions often caused by altered mitochondrial DNA homeostasis.**

Metabolic alterations are hallmarks of many diseases. Perturbations of energy metabolism are particularly critical in neurodegenerative processes owing to the impairment of mitochondrial functions often caused by altered mitochondrial DNA homeostasis. Decreased oxidative phosphorylation leads to ATP deficiency, accumulation of reactive oxygen species and depletion of neuronal NAD+, one of the most critical molecules for bioenergetic conversions and signalling in human cells. Modulation of mitochondrial bioenergetics may be an effective therapeutic strategy to counteract neurodegeneration and drugs boosting mitochondrial biogenesis and function have indeed been associated with decreased incidence of Parkinson's disease and dementia in various independent studies.

Based on these findings, the Ziegler and Tzoulis groups propose that therapies promoting mitochondrial function via replenishing the NAD+ pool can shield neurons against the neurodegenerative processes and delay disease progression. This hypothesis has, indeed, become a major theme in the clinical trials running at the Center - across all four diseases. Nicotinamide riboside (NR) is a well-established precursor which effectively elevates NAD+ synthesis and is non-toxic in animals and humans. It is fully approved for human use, has good oral bioavailability, crosses the blood-brain barrier and has been shown to extend lifespan in yeast and to have strong neuroprotective effects in animals. Therefore, NR should be an excellent candidate for correcting NAD+ deficiency and rectifying the metabolic impairment in neurodegeneration.

Using various cell systems and state-of-the-art metabolomics approaches, the group is studying the impact of NAD+ deficiency on major cellular bioenergetics and signalling systems. Previously, they have established cellular NAD+ turnover rates in human cell lines and identified metabolic adjustments evoked by chronic NAD+ deficiency. Mimicking age-dependent decline of NAD levels using genetic engineering to introduce NAD consuming enzyme activities into various subcellular compartments, they found that the mitochondrial NAD pool appears to be particularly sensitive to alterations. They also developed a highly sensitive and fast LC-MS-based method to measure the key bioenergetic nucleotides (ATP, ADP, NAD+, NADH, NADP+, NADPH) in biological samples (see figure).

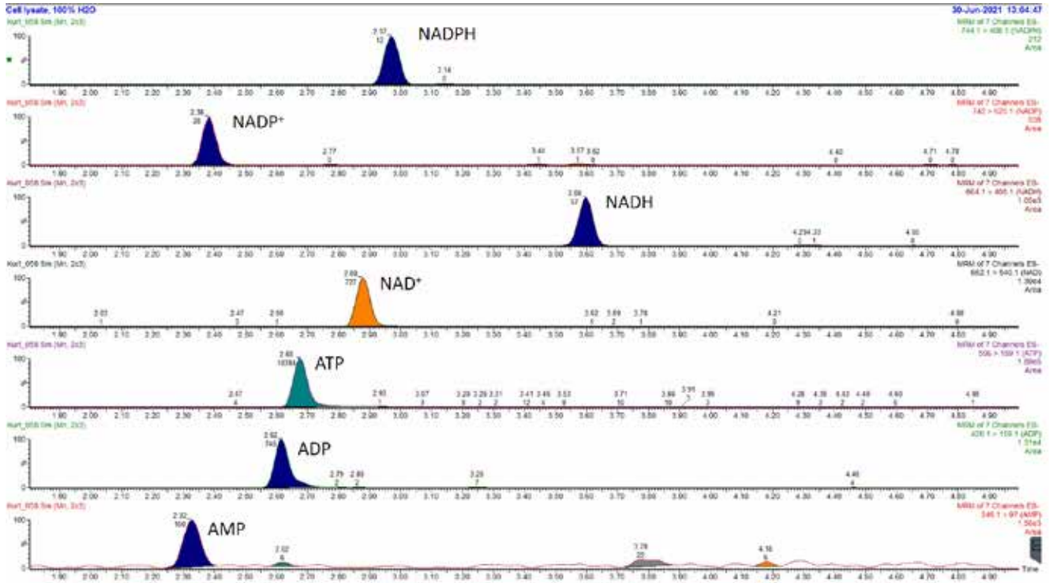
Moreover, the group established a method to determine downstream metabolites of NAD supplementation such as N-methyl2-pyridone (Me-2-PY). The resolution and sensitivity of the method enabled the reliable measurement of this NR degradation product in the cerebrospinal fluid (CSF) of the participants in the NAD-PARK study. Patients receiving NR supplementation had a significant increase in Me-2-PY in CSF supporting the availability of nutritional NR to the brain.

The group is now extending the scope of NAD-derived analytes to deepen the clinical and mechanistic understanding of NR supplementation.



## GROUP MEMBERS

Mathias Ziegler, MD, PhD, Professor, Group Leader
Lena Elise Høyland, MSc, PhD Candidate
Lars J. Sverkeli, MSc, PhD Candidate
Eugenio Ferrario, MSc, PhD Candidate
Joseph Diab, PhD, Postdoc
Marc Niere, PhD, Senior Engineer

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# The Neuroimmunology and Biomarker Group

## PI: Christian Vedeler

**Christian Vedeler is a professor of neurology and neuroimmunology at the University of Bergen and senior consultant at Haukeland University Hospital. He is the director of the Neuro-Immunology Laboratory and has for many years developed and established clinically relevant biomarkers for diagnosis and treatment of neurological diseases. Professor Vedeler is an international expert in immune mediated paraneoplastic neurological diseases and his expertise include neuro-immunology, biomarker establishment, autoimmunity and neurodegeneration.**

The Neuroimmunology and Biomarker Group is developing quality-controlled diagnostic and biomarker assays based on state-of-the-art technologies. They use mass and flow cytometry for deep immune phenotyping to study the immune response in blood and CSF and the composition of cell products to evaluate treatment safety and response. They develop functional and quantitative assays for antibody-based therapy such as receptor occupancy for mass cytometry to monitor drug efficacy in patients. The group further develops and establishes CSF and serum biomarker assays such as for neurofilament (NFL) and intrathecal immunoglobulins. Based on quanterix technology, they measure NFL-light chain in serum samples from patients to monitor treatment response and disease progression in neurological diseases. They also do basic research on stem cell research, as well as characterizing new potential biomarkers for neurodegeneration such as cerebellar degeneration related proteins. In collaboration with the Department of Medical Biochemistry and Pharmacology, they have established a very sensitive capillary gel electrophoresis method that substantially increased sensitivity and specificity of oligoclonal immuno-globulins in CSF of patients with MS and other neuroinflammatory diseases. The group contributes with standard operating procedures for laboratory manuals in clinical trials and optimizing standard protocols for preparing and biobanking of patient samples.

The group focuses on translational single cell omics research from the clinical trials in two stem cell intervention trials, inspired by the potentially large benefits of the two stem cell clinical trials organized by the MS-group at Neuro-SysMed. The RAM-MS study seeks to reconstitute the immune system of RRMS patients with a distinct inflammatory component by hematopoietic stem cell transplantation (HSCT). The SMART-MS study seeks to induce the endogenous regenerative potential in the central nervous system (CNS) of MS patients with a distinct neuro-degenerative disease course, PPMS and SPMS, with mesenchymal stem cells (MSC).

Mouse models with stem cells have been established through the cuprizone model (demyelinating model; Figure 1) and the EAE model (experimental autoimmune encephalomyelitis). The models include four groups: 1) healthy mice (control), 2) diseased mice with placebo injection (saline), 3) diseased mice with BM-MSC injection (bone marrow-derived mescenchymal stem cells) and 4) diseased mice with SHED-MSC injection (stem cells from human exfoliated deciduous teeth). Through these experiments we can measure if the MSC injection causes regeneration in the CNS.

The group further studies the brain microenvironment in post-mortem tissues. They use state of the art imaging mass cytometry to characterize the brain microenvironment at unpresented resolution. They are particularly interested in immunologically competent cells in brain, such as microglia and astrocytes, and study the cell interactions to investigate disease mechanisms and new treatment targets (Figure 2 and 3). In addition, the group is working on a set of important proteins, called cerebellar degeneration proteins (CDR1, CDR2, CDR2L), which they have localized to important cell organelles that are essential for neuronal functions, being nuclear speckles, Golgi apparatus and mitochondrial transport. The proteins will be further characterized in knock-out cells. Since the proteins are involved in neuronal death, they will be tested as potential biomarkers for neurodegenerative diseases.



### GROUP MEMBERS

Christian Vedeler, MD, PhD, Professor, Group Leader
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Torbjørn Kråkenes, Researcher, PhD
Christopher Kvistad, MD, PhD
Shamundeeswari Anandan, Researcher, PhD
Kristin Varhaug, MD, PhD
Eirik Solheim, PhD Candidate
Jonas Haugsøen, Stud. Med.
Kjell Inge Erikstad, Stud. Med.

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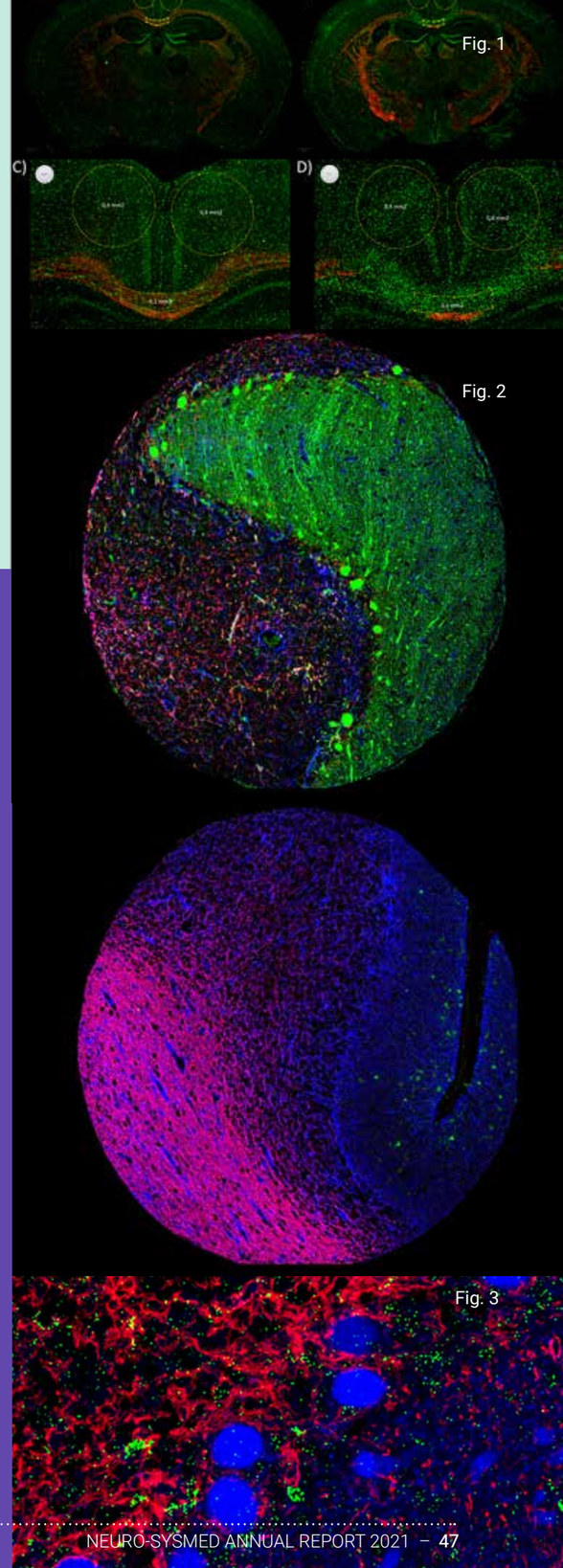


Fig. 1

Fig. 2



Fig. 3

# Motion Biomechanics and Biomarkers in Parkinson's Disease

## PI: Mandar S. Jog

**Professor Mandar S. Jog, MD, FRCPC, is an internationally renowned expert in movement disorders, including dystonia, tremor, ataxia and Parkinson's disease, and runs a state-of-the- art centre dedicated to the diagnosis and treatment of patients with these common and debilitating disorders. He is also widely acknowledged as a leader in research and innovation in the fields of movement disorders and neurodegeneration.**

Professor Jog's early research advanced the understanding of how neuronal networks function in animal models. He then transferred these findings to the clinic and translated them into novel therapeutic approaches as well as smart technologies to objectify clinical assessment and treatment of patients. His seminal scientific work has made outstanding contributions to improving the care and quality of life of patients with movement disorders.

Together with Professor Tzoulis, Professor Jog has a key role in the design and implementation of the STRAT-PARK study. In addition, he is also participating in a clinical trial for treatment of tremor with Botulinum toxin.

Professor Jog and his team have contributed significantly to the study of movement disorders over the years. Innovations developed in their laboratory, such as TremorTek, a measurement system for injection of Botulinum toxin for tremor and Spinal cord stimulation for gait failure in Parkinson's disease, have had significant impact on patient management. Furthermore, various new technologies such as whole-body Kinematics for objective motion capture in movement disorders and robotics to assess the biomechanics of the upper limb are being developed in Jog's laboratory.

In 2021, one of the research focuses has been therapeutic application of a novel trans cranial electrical stimulation technique in various movement disorders such as Parkinson's disease, Huntington's disease and dystonia with promising preliminary results. Advances in imaging methods have prompted collaborations with world renowned imaging experts with very productive results. A unique and innovative method of imaging in Parkinson's disease has been explored and the results are awaited. Dr. Jog has considerable experience studying animal models of Parkinson's disease. Currently, under his supervision, effects of intra-cerebral Botulinum toxin is being investigated in hemi-parkinsonian rat models.

Ongoing projects include:

- STRAT-PARK: A prospective multimodal cohort study to stratify Parkinson's disease
- Role of Nigral microvasculature in the pathophysiology of Parkinson's disease: A neuroimaging study
- Non-invasive brain stimulation in Huntington's disease
- A trial of trans cranial pulsed current stimulation in (tPCS) on Parkinson's disease OFF state
- Non-invasive brain stimulation in cervical dystonia
- Upper Limb Perception of Force in Parkinson's Disease
- Long-term effects of the administration of botulinum toxin BoNT-A in a preclinical model of Parkinson's disease
- Robot assisted investigation of sensorimotor integration in Parkinson's Disease (PD)



## GROUP MEMBERS

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Saurabh Bansal, MD, DM, Postdoc
JiaRen Chai, MD, Postdoc
Heather Russell, RN, Clinical Nurse
Olivia Samotus, MSc, PhD Candidate
Yokesh Tamilselvam, MSc, PhD Candidate
Dorian Aur, PhD, Research Analyst
Yekta Mahdi, B.HSc, Research Assistant

Photos by the Jog group.

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# The DRONE group – Drug Repurposing for Neurological diseases

## PI: Trond Riise

**The project aims to develop new and effective treatments for the neurological diseases Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). Principal Investigator Trond Riise has a background in mathematics/statistics and works as a professor in epidemiology at the University of Bergen, Norway.**

**Trond 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.**

Dr. Riise has an extensive collaboration with researchers at Harvard University, where he previously was a visiting professor. He is also currently a core investigator of the Center for Parkinson Precision Neurology at Brigham and Women's Hospital and Harvard University. Riise has also been a visiting professor at the Universities of Ferrara and Bologna, Italy. Riise's international collaborators are key researchers in this NeuroSysMed project.

Dr. Riise is Head of Research of a comprehensive 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.

The group is introducing an initial screening phase in humans that will form the basis for new hypotheses that in a second phase will be tested and validated in mechanistic experiments using human iPSC-derived neurons and animal models. This approach might be referred to as "inverse translational research" and represents a novel use of Norwegian health registries.

Read more in the Trials section.



## GROUP MEMBERS

Trond Riise, PhD, Professor, Group Leader
Anne Kjersti Daltveit, PhD, Professor
Anders Engeland, PhD, Professor
Jannicke Igland, PhD, Associate Professor
Julia Romanowska, PhD, Bioinformatician
Magne Solheim, Statistician, PhD Candidate (ALS)
Akash Kapali, PhD Candidate (MS)
Julia Axiina Tuominen, PhD Candidate (PD)
Kjetil Bjørnevik, MD, PhD, Supervisor, Harvard School of Public Health
Marianna Cortese, MD, PhD, Supervisor, Harvard School of Public Health
Asieh Abolpour Mofrad, Postdoc, Artificial Intelligence
Kari Juul, technical staff

### NATIONAL COLLABORATORS

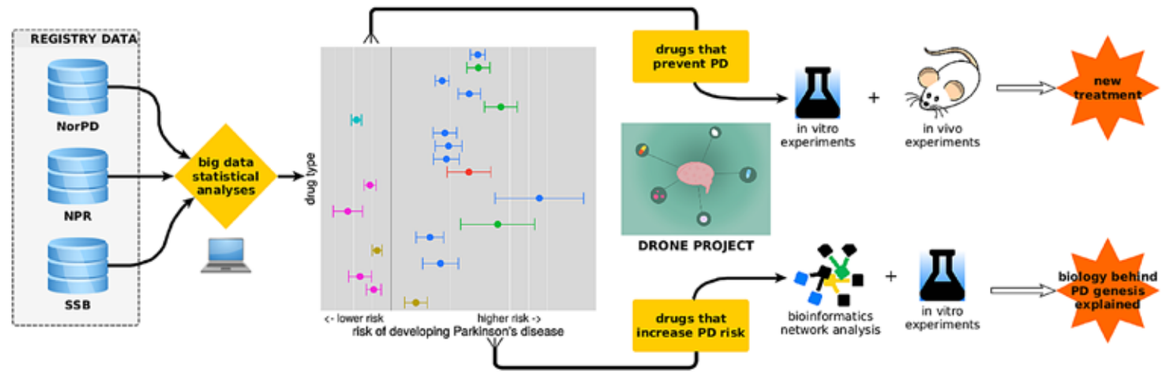
Kari Furu, PhD, Senior Researcher, Norwegian Prescription Database, Norwegian Institute of Public Health.
Trygve Holmøy, MD, Professor, Institute of Clinical Medicine, University of Oslo

### INTERNATIONAL COLLABORATORS

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

## SELECTED KEY PUBLICATIONS


1. Antonazzo IC, Poluzzi E, Forcesi E, Riise T, Bjørnevik K, Baldin E, Muratori L, De Ponti F, Raschi E. Liver injury with drugs used for multiple sclerosis: A contemporary analysis of the FDA Adverse Event Reporting System. Multiple Sclerosis 2019;25:1633-40.
2. Olsen AL, Riise T, Scherzer C. Promise for Parkinson's: Discovering new benefits from old drugs with big data. Editorial. JAMA Neurology 2018;75(8):917-20.
3. Cortese M, Riise T, Engeland A, Ascherio A, Bjørnevik K. Urate and the risk of Parkinson's disease in men and women. Parkinsonism and Related Disorders 2018;52:76-82.
4. Mittal S, Bjørnevik K, Im DS, Flierl A, Dong X, Locascio JJ, Abo KM, Long E, Jin M, Xu B, Xiang YK, Rochet JC, Engeland A, Rizzu P, Heutink P, Bartels T, Selkoe DJ, Caldarone BJ , Glicksman MA, Khurana V, Schüle B, Park DS, Riise T, Scherzer CR. β2-Adrenoreceptor is a Regulator of the α-Synuclein Gene Driving Risk of Parkinson's Disease. Science 2017;357:891-8.

# The Bioinformatics Research Group

## PI: Inge Jonassen

**Inge Jonassen has broad expertise within bioinformatics with a focus on development and application of informatics methods for the analysis of molecular biology data. His research interests include methods for the automatic discovery of patterns, data analysis, algorithms and machine learning applied on molecular biology data, and he is Head of the Department of Informatics and Director of the Computational Biology Unit, CBU, a leading hub of bioinformatics research spanning both the basic and applied fields.**

In context of Neuro-SysMed, the Jonassen group is working with Tzoulis and colleagues on development and application of methods to analyze omics data for PD patients and controls. The work has benefited from earlier work in the Jonassen group developing novel methods for gene expression deconvolution resulting in the method Deblender, developed in collaboration with the Akslen and Wik groups at the Centre for Cancer Biomarkers (CCBIO), UiB, published in BMC Bioinformatics in 2018. In a later publication in collaboration with Tzoulis and colleagues, the group showed the importance of taking tissue composition into account in analysis of gene expression data, showing that previous expression signatures developed for Parkinson's disease to a large extent were driven by alterations in cell composition (published in Acta Neuro Comm in 2020).

Further work involve co-analysis of proteomics and transcriptomics level data from the same patients – work that is on-going and not yet published. Jonassen is planning recruitment of a post-doctoral researcher to work between Jonassen/CBU and the Tzoulis group on applying methods for multi-omics analysis on data from PD patients and controls, and an internal proposal for work in this direction has been authored by Jonassen and Kjell Petersen at CBU.

Through his engagement in the pan-European bioinformatics infrastructure ELIXIR and as Head of ELIXIR Norway, Jonassen has also worked to establish infrastructure for controlled sharing of molecular level and clinical data supporting medical biomedical research findings. As one of the first in Europe, ELIXIR Norway is ready to operate a node of the federated European Genome-phenome Archive – enabling controlled sharing of data that due to consent or other legal constraints cannot be deposited in international repositories. Through ELIXIR Norway, the Jonassen group has also worked to provide solutions for analyzing human molecular level data as well as phenotypic data in secure environments and to establish better support for data management and FAIR data sharing for Norwegian life science research projects.



### GROUP MEMBERS

Inge Jonassen, Professor, PhD, Head of the Department of Informatics
Kjell Petersen, Researcher, PhD, Head of the Service Group at the Computational Biology Unit, UiB

### SELECTED KEY PUBLICATIONS

1. Lavrichenko, Ksenia; Helgeland, Øyvind; Njølstad, Pål R; Jonassen, Inge; Johansson, Stefan. SeeCiTe: a method to assess CNV calls from SNP arrays using trio data. Bioinformatics 37, 13, 1876-1883, 2021, Oxford University Press.

2. Zhang, Xiaokang; Jonassen, Inge; Goksøyr, Anders. Machine Learning Approaches for Biomarker Discovery Using Gene Expression Data. Exon Publications, 53-64, 2021.

3. Lavrichenko, Ksenia; Johansson, Stefan; Jonassen, Inge. Comprehensive characterization of copy number variation (CNV) called from array, long-and short-read data. BMC genomics, 22, 1, 1-15, 2021, BioMed Central.

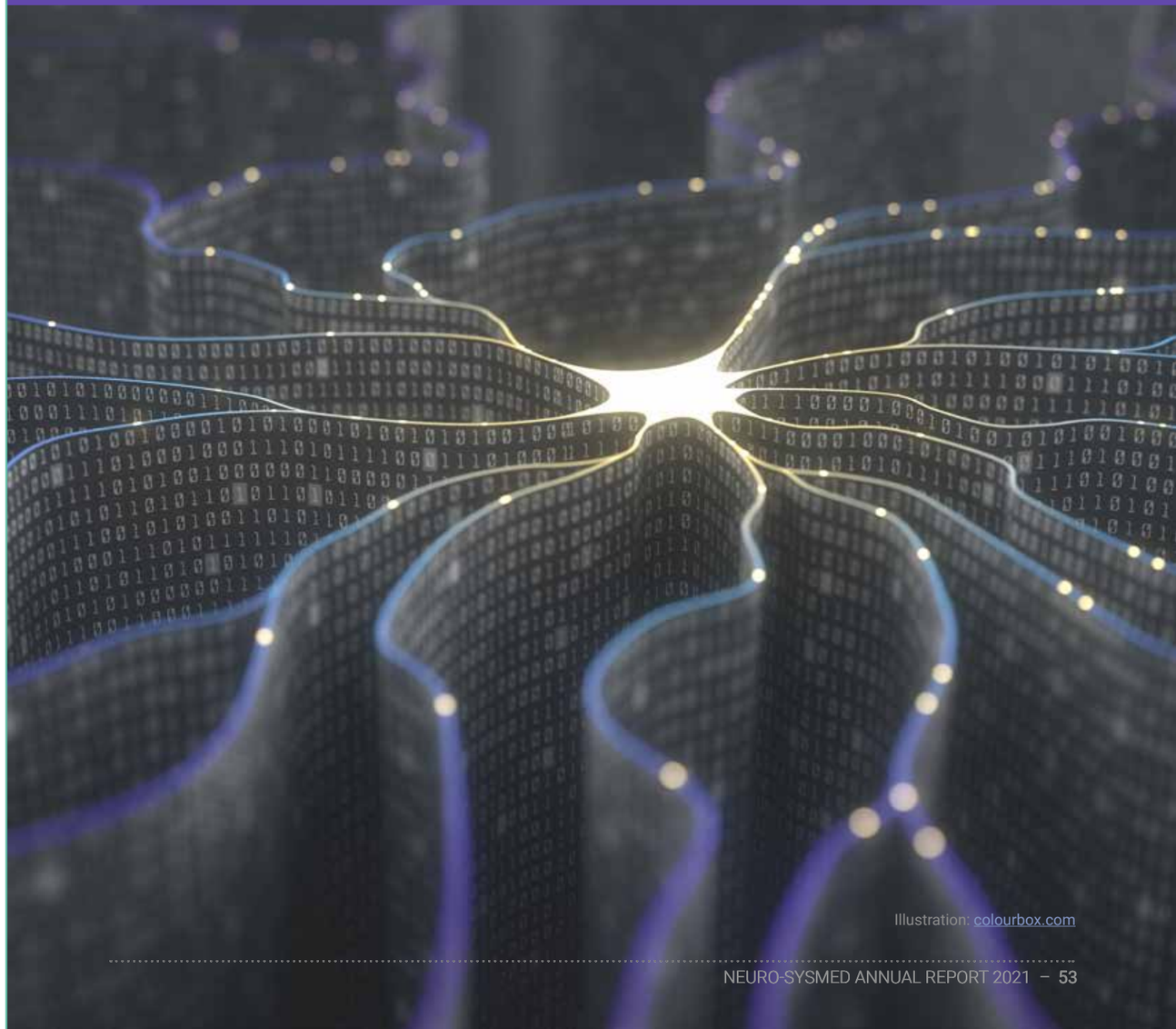


Illustration: colourbox.com

# The Philosophy of Neurodegeneration Group

## PI: Jan Reinert Karlsen

**Jan Reinert Karlsen is Associate Professor at the Centre for the Study of the Sciences and the Humanities (SVT), an inter-disciplinary and inter-faculty research unit at the University of Bergen. Karlsen has been instrumental in developing and delivering the prizewinning interdisciplinary course-portfolio 'Major Questions in Research and Society'. His research interests revolve around (1) the philosophical clarification of the concept of suffering and the critical and reflexive meta-study of the knowledge of suffering as well as disciplines that study suffering, (2) knowledge cultures and interdisciplinary teaching and learning, and (3) the philosophy of post-genomic science and precision medicine.**

The research focus of The Philosophy of Neurodegeneration Group has been on mapping and critically assessing conceptions of suffering in different academic and non-academic thought traditions. The group has been studying the medical discourse on suffering emerging in the 1980s in particular, as well as more long-standing discourses within sociology, anthropology, philosophy, and psychology. Drawing on the manifold of discipline-based conceptualizations, they have begun building an integrative model for synthesizing different dimensions of suffering. The model will be used in their work to open up precision medicine in severe chronic neurological diseases for critical and constructive deliberations about responsible precision medicine (i.e., RRI). Karlsen believes there is a strong need to complement the disease-centric gaze of precision medicine with more holistic approaches, placing disease burdens in a broader dynamic of the lived life of patients' and caregivers' experiences, including their carrying capacities in face of loss of self, function, and meaning. The group's aim is to use this model to design reflexive studies involving people living with severe chronic neurological diseases and their caregivers.

During the Spring of 2021, the group successfully recruited a postdoc to the project entitled, "Philosophy of precision medicine in severe chronic neurological diseases." Caroline Engen, MD, PhD, commenced working with the project in September 2021. Caroline will be affiliated with Neuro-SysMed in a 50% position over six years while also working on her clinical specialty in psychiatry.

The group also started collaborating with Amy Van Den Hooven, a Bergen based award winning Canadian designer, who will be collaborating in developing communication tools for caregivers and people living with severe chronic neurological diseases. The collaboration led to the articulation of a prospective PhD project in discursive design: "Insight into dementia: Developing communication tools through discursive design" (funding pending). The construction of this project enabled the group to form concrete partnerships with members of the User Council at Neuro-SysMed

The pandemics has effectively stopped plans to organize semi-regular events at Neuro-SysMed. However, it has also given ample time to plan such events. The aim is to re-boot this activity in 2022, engaging staff in reflection and discussion on important RRI-topics in precision medicine.

Important activities in 2021 include engagements in the public dialogue, such as Engen's lecture "Knowledge is power – on sales success and the (un)critical eye of research?" at Filosofisk poliklinikk, Litteraturhuset in Bergen, February 2021. The group has also contributed to research school activities with the lecture "Ethics - Knowledge and care in the midst of shifting paradigms" as part of the course CCBIONeur911: Clinical Trials in Cancer and Neurological Diseases in September 2021, and with the lecture/workshop "Thoughts and reflections on cancer and "The Good Life" in the course CCBIO903: Cancer Research - Ethical, Economic and Social Aspects in September 2021. In the beginning of of the same month, Karlsen was invited by Klinisk etikkomité at Haukeland University Hospital to deliver a lecture entitled "The autonomous human: Autonomy as problem and response to value based questions in medical science and practice" at a workshop. He also contributed with a lecture "Knowledge about domains / knowledge about knowledge: Complementary aspects of sustainability as thought and action" at the workshop Embedding sustainability in academic cultures and activities at the Sustainable Development Goals (SDG) conference in Bergen, in the Day Zero program, February 2021. These public and academic engagements showcase the importance of ethical reflection, RRI and sustainability when addressing dilemmas and complex challenges arising in the science-society interface.

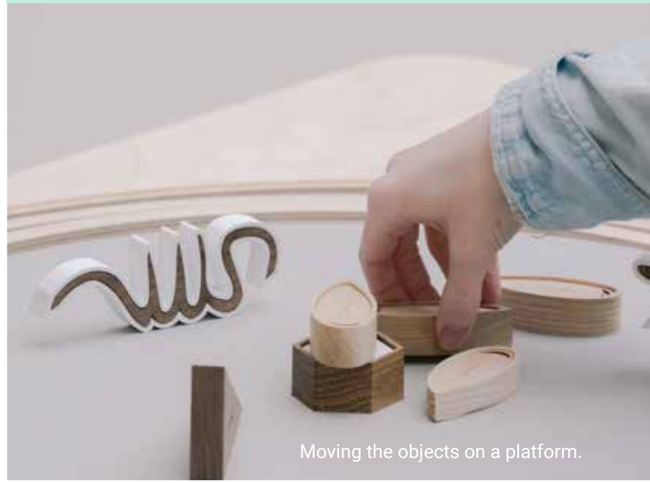


## GROUP MEMBERS

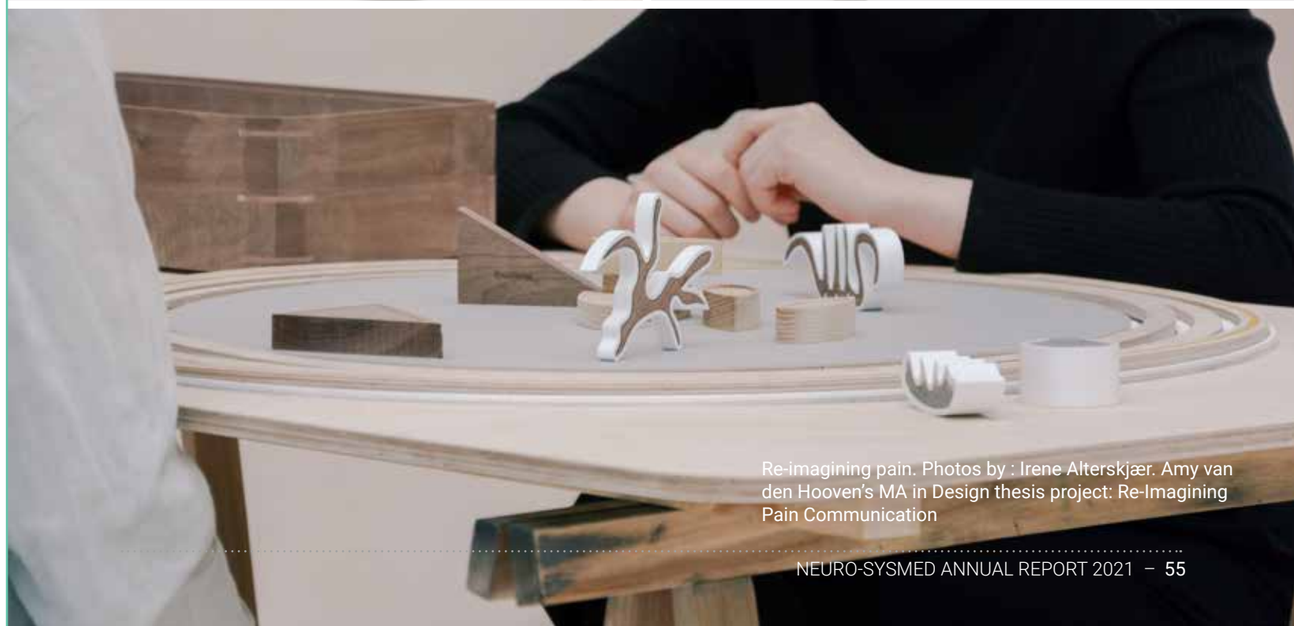
Jan Reinert Karlsen, Cand. Philol., PhD, Associate Professor, Group Leader
Caroline Benedicte Nitter Engen, MD, PhD, Postdoc
Amy Van Den Hooven, MA in design, designer, The Open Pain Lab, CEO and founder

**Affiliated group members:**
Berge Osnes, Cand. Psychol., PhD, Associate Professor
Håvard Øritsland Eggestøl, PhD, Senior Advisor, The Norwegian Biotechnology Advisory Board
Roger Strand, Dr. Scient., Professor, Group Leader of the ELSA-team at the Centre for Cancer Biomarkers (CCBIO)

Placing a pain object.



Moving the objects on a platform.



Re-imagining pain. Photos by : Irene Alterskjær. Amy van den Hooven's MA in Design thesis project: Re-Imagining Pain Communication

# TRIALS AND RESEARCH

**Randomized clinical trials are the backbone of Neuro-SysMed activities. While each study has its own scientific questions and efficacy endpoints, all projects running under the Centre contribute with data to a common Neuro-SysMed database. Other studies aiming at characterizing diseases are also contributing to the Neuro-SysMed database. Using this database, the vast amount of information collected at the Centre will be integrated in order to define biomarkers that enable early and precise diagnosis, subgrouping of patients within each disease, accurate prognosis and tailored treatment choices.**

**Planned or ongoing clinical trials, as well as some other research projects, are described for each disease. Most of the projects are dependent on extensive collaborations with other hospitals and other research groups, acknowledged as key external collaborators under each disease and/or project.**

# Multiple Sclerosis Background and Studies

**Multiple sclerosis (MS) is a progressive demyelinating, inflammatory, and neurodegenerative immune mediated disease, characterized by multiple lesions with demyelination and axonal loss in the brain and spinal cord. The disease is caused by a complex interplay between genetic and environmental factors. Numerous normal gene-variants (polymorphisms) seem to influence the risk of MS. Some of the most important environmental risk factors include Epstein-Barr virus infections, low levels of Vitamin D, smoking and overweight. Some of these risk factors may also influence further disease course and treatment responses.**

Head of Research, Kjell-Morten Myhr

Most patients with MS (85-90%) experience repeated episodes of symptoms from the CNS, called relapsing-remitting MS (RRMS). These episodes are followed by partial or fully remissions (recovery). Nevertheless, if not effectively treated, accumulating disability will usually appear along the disease course, and a substantial proportion will convert to a secondary progressive course (SPMS) with gradual worsening. Fewer patients (10-15%) experience a gradual worsening (without recovery) from the beginning of the disease, called primary progressive MS (PPMS).

No cure for MS is available, but acute episodes (relapses) are shortened by courses of high dose methylprednisolone. Increasing numbers of disease-modifying therapies reduce the relapse-frequency and disability progression, most effectively in the early inflammatory phase of the disease. With the development of more effective therapies, the aim of treatment has changed dramatically during the last decades, from simply reducing relapse rates and slowing of disability progression to preventing all evidence of new disease activity.

Early initiation of highly effective therapy is probably the best way to avoid permanent disability in relapsing-remitting MS. Careful risk stratification among the increasing numbers of treatment options minimizes the risk of serious side effects associated to the highly effective drugs. The aim should therefore be that most patients receive the most effective therapy option from onset of the disease. **The OVERLORD-MS study** aims at evaluating such a strategy, at a sustainable cost for society.

Treatment failure during ongoing therapy is another challenge. **The RAM-MS study** evaluates autologous hematopoietic stem cell transplantation (HSCT) compared to standard highly effective therapies as a treatment strategy for patients with ongoing disease activity during disease-modifying therapies.

How to treat progressive disease is yet another major challenge in MS. The MS research group at Neuro-SysMed therefore aims to explore treatment strategies for progressive MS (PMS) in two studies. **SMART-MS** is a pilot study that evaluates whether treatment with autologous bone marrow derived mesenchymal stem cells is feasible, safe and can promote neural repair in PMS. Another study aims to evaluate whether an increase in neuronal NAD levels can improve mitochondrial function, rescue neuronal function, and reduce cell death seen in PMS.

Tailored symptomatic therapy and rehabilitation to reduce potential disabling symptoms to improve overall functioning are yet another topic for research. The group therefore performs a pilot study to explore a new **treatment strategy for spasticity and pain in MS**.

The COVID-19 pandemic illustrates the importance for vaccination. The group is therefore performing a **vaccine response study** to evaluate the efficacy of the COVID-19 vaccine in MS patients receiving various immunotherapies.

Enabling Norwegian patients to participate in the development of novel therapies provided by international pharmaceutical companies is another objective of Neuro-SysMed. The MS-group is therefore participating in several international multicentre randomized clinical treatment trials, including two trials of Burton's tyrosine kinases inhibitors in PMS.

Thus, the overall aim of MS-research in Neuro-SysMed is to improve MS care by optimizing available therapies, developing new treatment strategies, and make new therapies available for Norwegian patients in an early stage, preferably through participation in randomized clinical trials.

*For collaborative studies on biomarker detection and disease mechanisms – see description by The Neuroimmunology & Biomarker Group.*



## National and international collaborators in MS

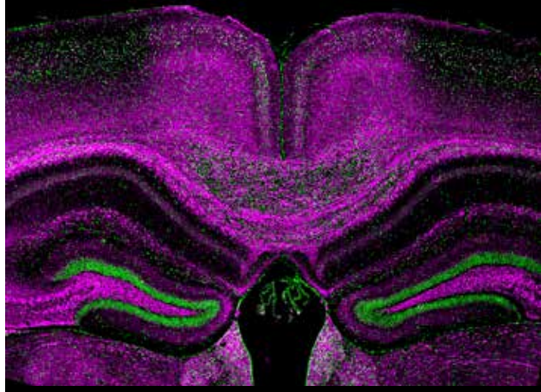
Years of successful, MS-research has been dependent on extensive local, national and international collaboration. Our network is important for further research in Neuro-SysMed, and some of our key collaborators are listed below:

**International collaborators**

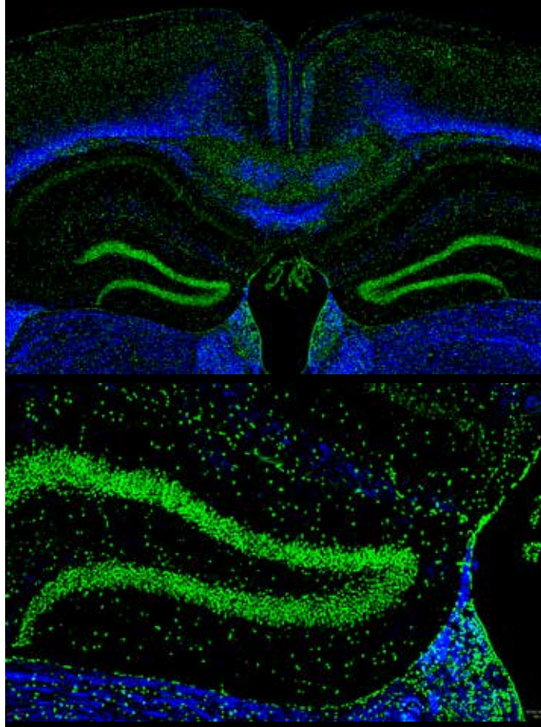
- Professor Fredrik Piehl, Karolinska Institutet, Stockholm, Sweden
- Professor Anders Svenningsson, Karolinska Institutet, Stockholm, Sweden
- Dr. Katharina Fink, Karolinska Institutet, Stockholm, Sweden
- Professor Jan Lycke, Sahlgrenska University Hospital, Sweden
- Associate Professor Joachim Burman,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

**Norwegian collaborators**

- Dr. Linn H. Steffensen, University Hospital of North Norway, Tromsø
- Associate Professor Margitta Kampman, University Hospital of North Norway, Tromsø
- Dr. Kjersti Aakvik, University Hospital of North Norway, Tromsø
- Professor Karl Bjørnar Alstadhaug, Nordland Hospital Trust, Bodø
- Dr. Petter Wilhelm Bockmann, Nordland Hospital Trust, Bodø
- Dr. Per Lopen, Namsos Hospital Trust, Namsos
- Dr. Stephan Schuler, Namsos Trust Hospital, Namsos
- Dr. Kathrine Lian, St. Olavs University Hospital, Trondheim
- Dr. Åse Hagen Morsund, Molde Hospital Trust, Molde
- Dr. Johannes Willumsen, Molde Hospital Trust, Molde
- Dr. Kristin Lif Breivik, Førde Hospital Trust, Førde
- Dr. Ineke HogenEsch, Haugesund Hospital Trust, Haugesund
- Dr. Alok Bhan, Stavanger University Hospital, Stavanger
- Dr. Alla Nikolajevo Serada Bru, Stavanger University Hospital, Stavanger
- Professor Elisabeth Farbu, Stavanger University Hospital, Stavanger
- Dr. Åslaug Rudjord Lorentzen, Sørlandet Hospital Trust, Kristiansand
- Dr. Ingvild Jullun Leiknes, Sørlandet Hospital Trust, Kristiansand
- Dr. Heidi Øyen Flemmen, Telemark Hospital Trust, Skien,
- Dr. Cecilia Smith Simonsen Vestre Viken Hospital Trust, Drammen,
- Dr. Gro Owren Nygård, Oslo University Hospital, Oslo
- Dr. Marton König, Oslo University Hospital, Oslo
- Dr. Einar Høgestøl, Oslo University Hospital, Oslo
- Professor Hanne F Harbo, Oslo University Hospital, Oslo
- Professor Mona Beyer, Oslo University Hospital, Oslo
- Professor Trygve Holmøy, Akershus University Hospital, Lørenskog
- Dr. Rune A Høglund R, Akershus University Hospital, Lørenskog
- Associate Professor Andreas Lossius, Akershus University Hospital, Lørenskog



Neurofilament staining (magenta) and cell nuclei (green; DAPI) in a cuprizone mouse brain. Next photo: zoomed in. Kråkenes/Kvistad.



Myelin staining (blue; PLP1) and cell nuclei (green; DAPI) in a cuprizone mouse brain. Next photo: zoomed in. Kråkenes/Kvistad.

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

## PI: Lars Bø

**A randomized clinical trial for comparing autologous hematopoietic stem cell transplantation (HSCT) versus alemtuzumab, cladribin or ocrelizumab in MS; the RAM-MS study.**

HSCT is a promising therapy in MS, but limited data from randomized clinical trials (RCTs) are 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), 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 whether HSCT is a safe and effective therapy in highly active multiple sclerosis compared to standard high-efficacy therapies, and to establish sufficient evidence to support routine use of HSCT in MS.

**The primary endpoint** of the study is the 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.

Until now, 67 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 Hospital, Trondheim
- University Hospital of North Norway, Tromsø

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

*Denmark*
- Copenhagen University Hospital, Rigshospitalet, Copenhagen

*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





# Trial: Early B-cell depletion therapy in MS

## PI: Øivind Torkildsen

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

B cell depletion therapies (rituximab, ocrelizumab, ofatumumab) are proven highly effective in MS. A Norwegian HTA indicate similar treatment effects from rituximab and ocrelizumab – but clearly, state that more data, preferably from a RCT is needed.

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

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

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

The first patient was included at Haukeland University Hospital early November 2020 and currently about 117 patients have been enrolled in the study at seven hospitals. Altogether, 13 hospitals in Norway and Sweden plan to participate.

**SUPPORT:**

**Participating Centres**
*Norway*
- Haukeland University Hospital, Bergen
- Oslo University Hospital, Oslo
- Akershus University Hospital, Lørenskog
- Stavanger University Hospital, Stavanger
- St Olav's Hospital, Trondheim
- University Hospital of North Norway, Tromsø
- Nordland Hospital Trust, Bodø
- Namsos Hospital, Namsos
- Molde Hospital, Molde
- Sørlandet Hospital Trust, Kristiansand
- Telemark Hospital Trust, Skien
- Vestre Viken Hospital Trust, Drammen

*Sweden*
- Karolinska Institutet, Stockholm

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

# Trial: Mesenchymal Autologous stem cells in progressive MS

## PI: Lars Bø

**Study of Mesenchymal Autologous stem cells as Regenerative Treatment for Multiple Sclerosis; the SMART-MS study.**

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

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).

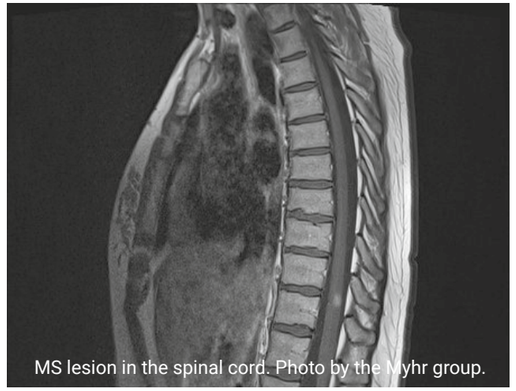
The first patient was included at Haukeland University Hospital in August 2021 and currently five patients have been enrolled in the study.

**SUPPORT:**

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

*Germany*
- University Hospital in Ulm

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



MS lesion in the spinal cord. Photo by the Myhr group.





# Trial: The COVID-19 vaccination response in MS patients

## PI: Øivind Torkildsen

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

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 reduce the immune response to various vaccines. Although limited data are available, our MS-research group has previously shown that interferon-beta therapies do not influence the vaccination response, whereas glatiramer acetate, natalizumab, fingolimod, and especially mitoxanthrone may reduce 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-research group aimed to perform a study on efficacy and safety of COVID-19 vaccines in MS-patients.

**The objectives** are 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.

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.

PI 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.

Patients have been recruited for participation at Haukeland University Hospital, Oslo University Hospital, 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
- University of Bergen
- The Norwegian MS Registry

# Trial: Spasticity therapy in MS

## PI: Kjell-Morten Myhr

**A pilot study to evaluate a novel treatment strategy for spasms in multiple sclerosis; the FlowOX-MS study.**

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, called "FlowOx". A pressure chamber 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. Several MS patients, who reported significant relief of pain and spasticity with consequent improvement in functional level, approached the producer (Otivio, Oslo) and the Norwegian MS Society to explore the possibility for systematic evaluation of this possible new therapy for spasticity.

The MS Research Group at Neuro-SysMed reviewed patient reports, that all described pain and especially spasticity relief during and after the use of FlowOx. The mechanism of action is unclear, but could possibly be linked to massive activation of arteriovenous reflex in the lower extremities that may modulate signal transmission at the spinal cord level with a consequently effect on spasticity and pain. Based on these few, but consistent reports of pain and spasticity relief from the use of FlowOx, the MS group aimed to perform an explorative pilot study of 10 patients to evaluate safety and efficacy of pulsating negative pressure therapy. This user-initiated treatment trial include MS patients for six months of open label therapy with FlowOx.

**The objective** is to evaluate whether patients' reported spasticity is reduced after one months of pulsating negative pressure therapy (FlowOx). Several secondary and tertiary endpoints are included.

**The primary endpoint** of the study is to evaluate change in self-reported spasticity using the numerical rating scale (NRS) over the last 24 hours after daily 1-hour self-treatment with FlowOx from baseline to week four.

In case of a positive result, the group will consider to design a placebo-controlled trial to further explore a positive effect of FlowOx on pain and spasticity in MS.

A study protocol has been approved by the Regional Committees for Medical and Health Research Ethics Western Norway, and the Norwegian Medicines Agency. Ten patients were included in May-June 2021 for six months of therapy.

Overall, preliminary analyses suggest that the self-reported efficacy of the intervention is in favour of FlowOx therapy. However, due to dropouts during summer holidays, five more patients will be recruited, during Q2 2022, and changes in symptoms and function will also be evaluated by neurophysiological measurements. The Ethical Committee has approved this extension, and recruitment is ongoing.

**SUPPORT:**

**Participating Centre (single centre pilot)**
- Haukeland University Hospital, Bergen

**Funding**
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- University of Bergen
- Otivio AS, Oslo





# Research: Genetic susceptibility in MS

## PI: Stig Wergeland

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

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

The objectives are to identify possible novel genetic risks of MS and possible biomarkers for diagnosis and disease progression, and further exploit the obtained insight of disease mechanisms to identify novel therapeutic targets.

DNA samples from about 2500 MS patients in the Norwegian MS Registry and about 3000 controls, mainly from the HUSK-study (https://husk-en.w.uib.no/) will be analysed by whole exome sequencing and data will be available for analyses from Q3 2022. The group will then analyse the data for possible novel genetic risks of MS or possible biomarkers for diagnosis and disease progression, and further exploit the obtained insight of disease mechanisms to identify possible novel therapeutic targets.

The project has unexpectedly been further postponed due to practical issues related to transportation of samples to the group's collaborator (Regeneron) in the USA – related to COVID-19 pandemic restrictions. The Regional Committee for Medical and Health Research Ethics Western Norway has approved the study, and contract for collaboration with HUSK and the exome sequencing providers (Regeneron) is finalized. All formal approvals are thus available, and the data will be available for further analyses in Q3/Q4 2022.

**SUPPORT:**

**Participating Centres**
- The Norwegian MS Registry
- Haukeland University Hospital, Bergen
- University of Bergen

**Funding**
- The Norwegian MS Registry
- The Research Council of Norway, Neuro-SysMed
- Haukeland University Hospital
- University of Bergen
- Regeneron

# Trial: Nicotinamide Riboside in progressive MS

## PI: Kjell-Morten Myhr and Charalampos Tzoulis

**A randomized, double-blinded, phase-I/II clinical trial of nicotinamide riboside (NR) in progressive MS.**

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 bioenergetic conversion and signalling in human cells.

Detailed information related to mitochondrial dysfunction and nicotinamide riboside (NR) supplementation is given in section: “Therapies targeting mitochondrial dysfunction”.

**The objective** is to study whether oral supplementation with nicotinamide riboside (NR) as add-on to standard care, reduces disability progression in PMS, and thus is a novel therapy for this devastating MS disease course.

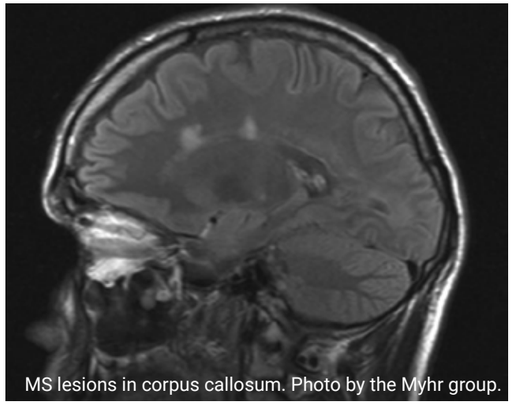
The Regional Health Authority of Western Norway has secured study funding, and ChromaDex (Irvine, California) will provide nicotinamide riboside (NR) and placebo capsules.

The study has unfortunately been further postponed, mainly due to the COVID-19 pandemic, but 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 Q2-2022 and estimated study start is Q4 2022.

**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
- University of Bergen
- Participating hospitals
- ChromaDex (Irvine, California)



MS lesions in corpus callosum. Photo by the Myhr group.





# Trial: Rituximab dose-extension study in relapsing-remitting MS

## PI: Øivind Torkildsen

**Rituximab Extended Dose interval in mUltiple sClErosis; the REDUCE-MS study.**

B-cell depletion therapy is highly effective in relapsing-remitting MS. Rituximab seems to have comparable efficacy and safety profile as 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, but 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 (i.e. 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 one year. 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 plasma 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 changed.

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

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 Q2-2022 and estimated study start is Q4 2022.

**SUPPORT:**

**Participating Centres**
- Haukeland University Hospital, Bergen
- Other 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
- University of Bergen
- The DAM foundation
- Participating hospitals

# Collaboration with pharmaceutical industry – multicentre international randomized clinical trials

**The Multiple Sclerosis Research Group participates in several industry sponsored clinical trials. Some of them were ongoing at the time when Neuro-SysMed was established (1-6), and four new studies have been added (7-10).**

1. Tysabri observation Trial in RRMS, Phase IV, 2007. Long-term safety and efficacy observational study of natalizumab (Biogen) (KM Myhr national coordinator)

2. Ocrelizumab vs Interferon beta-1a sc. trice weekly in RRMS, the OPERA trial Phase III trial, 2011. Open label extension (Roche) (KM Myhr national coordinator)

3. A prospective, multicenter, observational, post-authorization safety study (PASS) to evaluate the long-term safety profile of LEMTRADA® (alemtuzumab) treatment in patients with recurrent multiple sclerosis PASS - OBS13434 (REK-Nord 2014/1892) (Sanofi) (L Bø PI at Haukeland University Hospital)

4. A Nordic observational trial to evaluate the efficacy of Lemtrada© (Alemtuzumab) on fatigue, quality of life and partient reported outcome measures in patients with relapsing-remitting MS. REK-Sør-Øst 2016/661 (Sanofi) (Ø Torkildsen national coordinator)

5. Ocrelizumab (open label) in RRMS – safety and efficacy extension study, the CASTING and later LIBERTO study Phase IV, 2018 (Roche) (KM Myhr national coordinator)

6. Oral Cladribine or placebo in Early MS (CIS) – long term follow-up, the CLASSIC MS study Phase-IV, 2019 (NCT03961204) (Merck) (KM Myhr national coordinator)

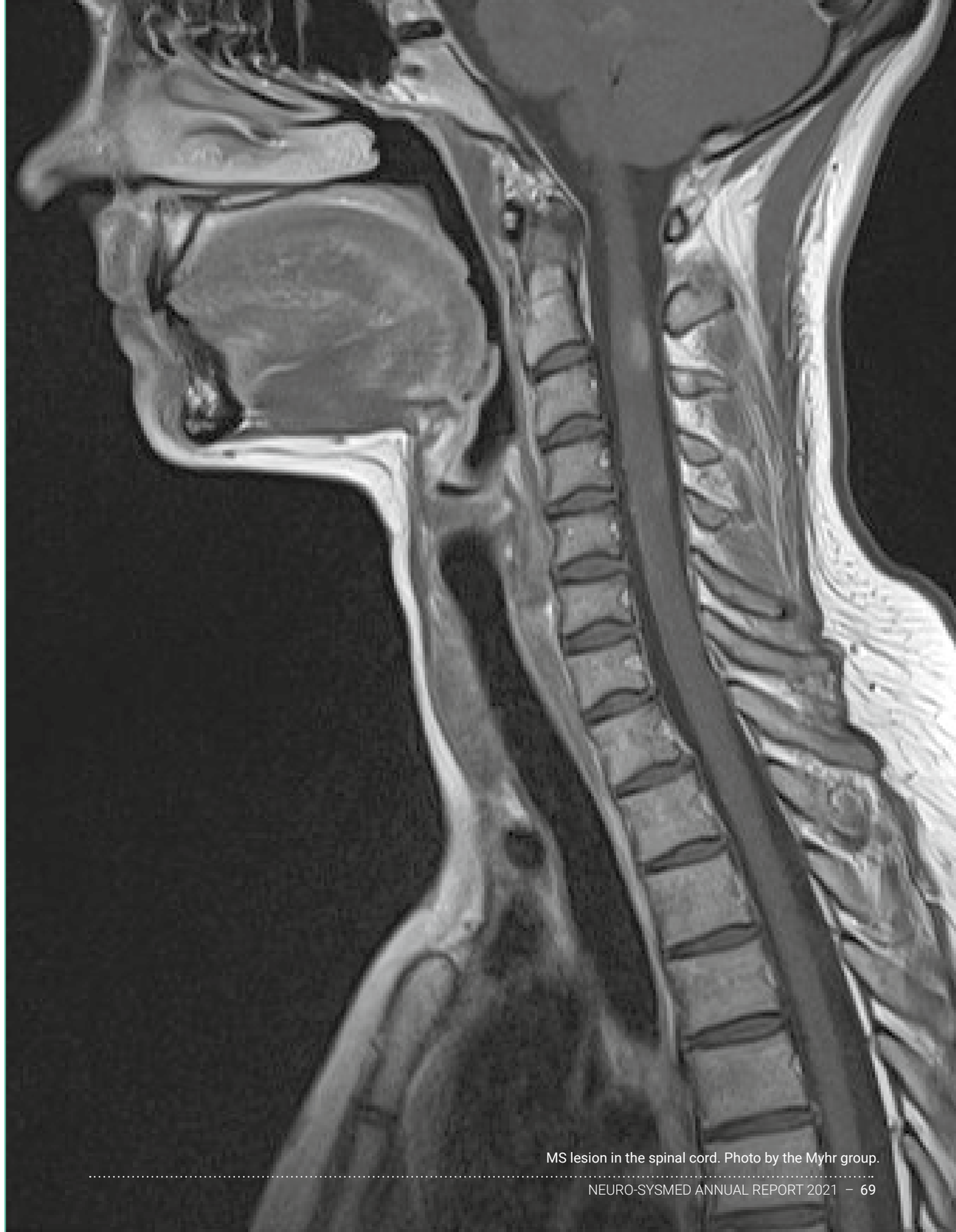
7. Primary Progressive Multiple Sclerosis (PPMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (2020) (SAR442168) (PERSEUS) (Sanofi) (Ø Torkildsen national coordinator)

8. Non-relapsing Secondary Progressive Multiple Sclerosis (NRSPMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (2020) (SAR442168) (HERCULES) (Sanofi) (Ø Torkildsen national coordinator)

9. Study of Evobrutinib in Participants with Relapsing Multiple Sclerosis (RMS) (2020) (evolutionRMS2) (Merck) (Ø Torkildsen national coordinator)

10. An Open-label Study Evaluating Ofatumumab Treatment Effectiveness and PROs in subjects With RMS Transitioning From Dimethyl Fumarate or Fingolimod to Ofatumumab (ARTIOS) (2020) (Novartis) - (KM Myhr PI at Haukeland University Hospital)





MS lesion in the spinal cord. Photo by the Myhr group.

# Parkinsons's Disease

**Parkinson's disease (PD) is a major cause of death and disability and has a devastating global socioeconomic impact. It affects 1-2% of the population above the age of 65 and its prevalence increases as the population ages. In Europe alone, PD affects ~1.2 million people and has an estimated cost of €14 billion/year.**

Head of Research, Charalampos Tzoulis

Available treatments are purely symptomatic, and trials of potential neuroprotective agents have been unsuccessful, despite encouraging preclinical results. In the absence of neuroprotective therapies, patients confront a future of progressive disability, early institutionalization, and premature death. With the number of patients expected to double by 2040, the need for understanding and treating PD is one of greatest challenges facing science and society today, and a top priority for healthcare and biomedical research.

**Ongoing PD research at Neuro-SysMed**

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

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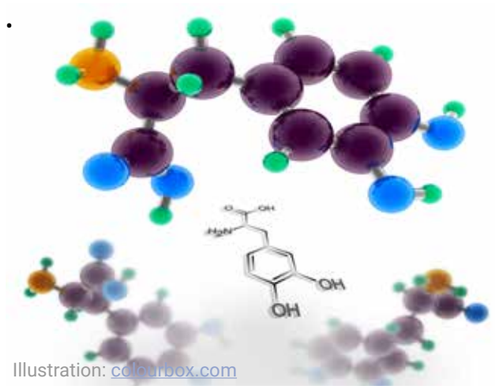



Illustration: colourbox.com

**National and international collaborators in PD research**

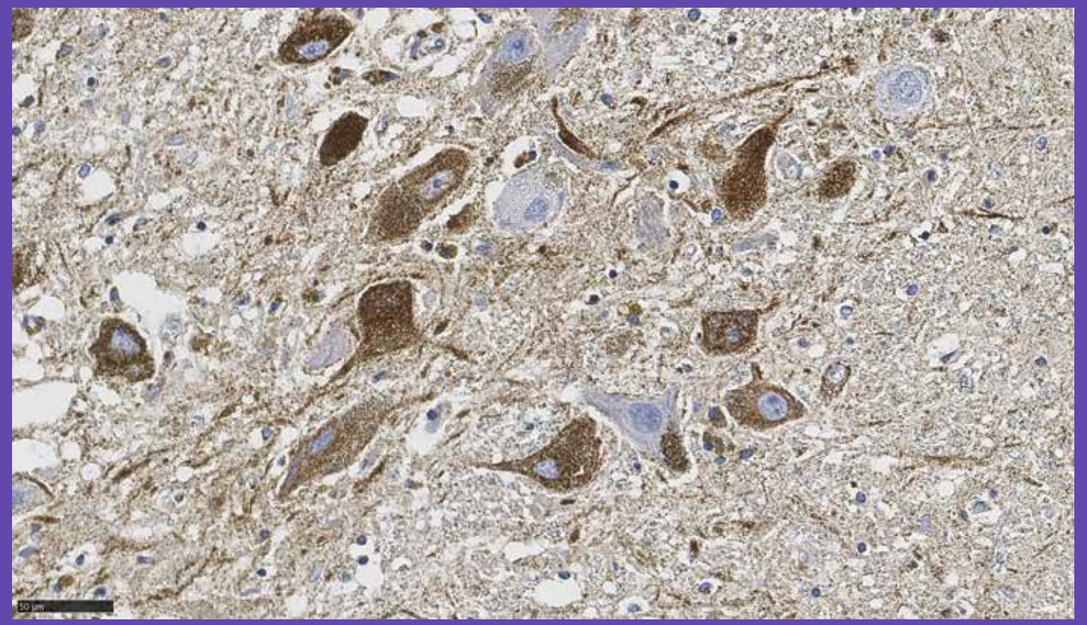
We are privileged to have an extensive network of national and international collaborators contributing to our PD research. A few of these are listed below:

**International:**

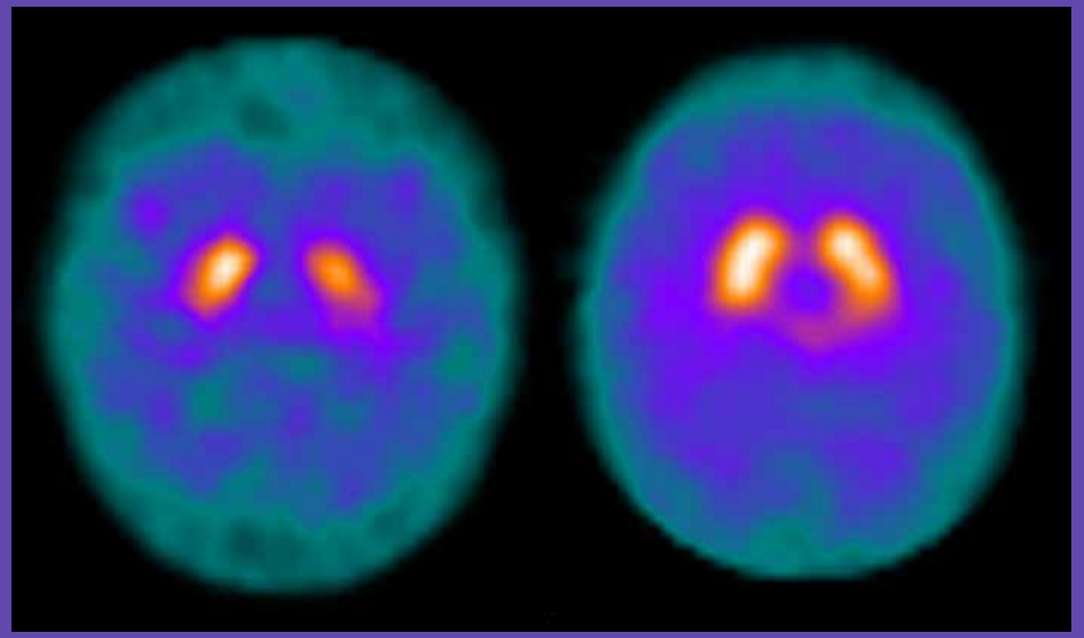
**P**rofessor David Eidelberg, Center for Neurosciences, Institute of Molecular Medicine, The Feinstein Institutes for Medical Research, Manhasset, NY, USA; Professor Kailash Bathia, Sobell Department of Movement Neuroscience at the Institute of Neurology, UCL, Queen Square, London, UK; Professor Nikolaos P. Daskalakis, McLean Hospital/Harvard Medical School, Massachusetts, USA; Dr. Lara Kular, Karolinska Institute, Stockholm, and Professor Leonidas Stefanis, University of Athens, Greece.

**National:**

Professor Mathias Toft, Oslo University Hospital; Dr. Lasse Pihlstrøm, Oslo University Hospital; Professor Christofer Lundqvist, Akershus University Hospital (AHUS), Oslo; Dr. Krisztina Johansen, Akershus University Hospital (AHUS), Oslo; Dr. Kari Anne Bjørnarå, Vestre Viken Hospital, Drammen; Dr. Anna Kaja Rognerud, Vestre Viken Hospital (DH), Drammen; Professor Jan Aasly, St. Olavs University Hospital (St. Olavs), Trondheim; Professor Hallvard Lilleng, University Hospital of North Norway (UNN), Tromsø; Dr. Karen Herlofson private practice and Arendal Hospital (AH), Arendal; Dr. Stig Hegrestad, Førde Central Hospital (FCH), Førde; Dr. Aliaksei Labusau, Førde Central Hospital (FCH), Førde; Dr. Ineke Hogenesch, Haugesund Hospital; Dr. Axel Simonsen, Nordland Hospital, and Dr. Eldbjørg Hustad, Molde Hospital.



Mitochondrial complex I immunohistochemistry in the dopaminergic substantia nigra of a person with PD. Unstained neurons (bluish) are deficient for complex I. Photo: Tzoulis/Fløne s



Dopamine transporter imaging (DAT-scan) showing nigrostriatal denervation in a person with PD (left), compared to a healthy person (right).

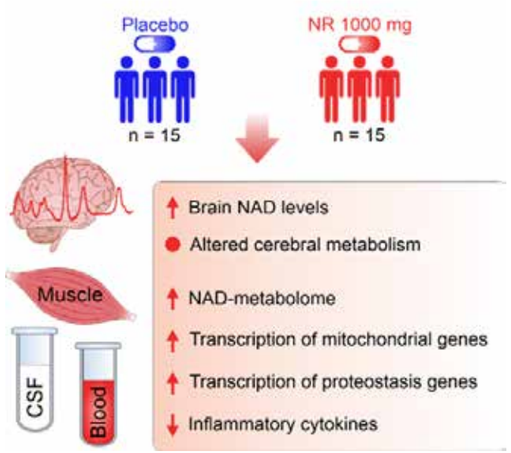
# Trial: NAD-PARK

## PI: Charalampos Tzoulis

**A randomized, double-blinded, phase-I clinical trial of nicotinamide riboside (NR) in PD.**

**Background:** A rapidly growing body of evidence suggests that mitochondrial dysfunction plays a key-role in the pathogenesis of PD. The Tzoulis group has shown that impaired neuronal mtDNA homeostasis and anatomically widespread neuronal respiratory complex I deficiency occur in the PD brain. These defects are predicted to compromise neuronal metabolism, including ATP deficiency and depletion of NAD+. Decreased NAD+ levels would, in turn, further impair neuronal function and survival, due to exacerbated bioenergetic dysfunction, impaired DNA repair, altered signaling, and dysregulation of gene expression due to aberrant histone acetylation. The Tzoulis group has indeed recently shown that genome-wide histone hyperacetylation occurs in the PD brain, possibly due to decreased activity of the NAD-dependent deacetylase enzymes known as sirtuins.

Thus, augmenting cerebral NAD metabolism could ameliorate several processes implicated in the pathogenesis of PD. NAD can be replenished via supplementation of its biosynthetic precursor nicotinamide riboside (NR), which has been shown to be well-tolerated in humans. The goal of the phase-I NADPARK trial was to determine whether NR is safe, augments cerebral NAD levels, and affects cerebral metabolism in patients with PD.




**Objectives:** to determine tolerability and cerebral bioavailability of NAD supplementation therapy with NR in PD.

**Design:** A total of 30 individuals with newly diagnosed, drug naïve PD were randomized to NR 500 mg x2/day or placebo for 30 days. Participants were followed with clinical examination, blood tests, muscle biopsy cerebrospinal fluid sampling, and structural and functional neuroimaging, including in vivo measurement of cerebral NAD-levels by phosphorus magnetic resonance spectroscopy (31P-MRS) of the brain.

**Primary endpoint:** brain penetration and target engagement, as measured by cerebral NAD-levels (31P-MRS) and glucose utilization (FDG-PET).

**Status: T**he NAD-PARK trial is completed and showed encouraging results, which were published in the prestigious journal Cell Metabolism [2].

In summary, the NADPARK study showed that intake of NR 1000mg daily was well tolerated and led to a significant, but variable, increase in cerebral NAD levels (measured by 31phosphorous magnetic resonance spectroscopy, 31P-MRS) and related metabolites in the cerebrospinal fluid (CSF). NR recipients showing increased brain NAD levels exhibited altered cerebral metabolism, measured by 18fluoro-deoxyglucose positron emission tomography (FDG-PET), and this was associated with mild clinical improvement. 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 Centres**
- Haukeland University Hospital, Bergen

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





# Trial: NO-PARK

## PI: Charalampos Tzoulis

**A randomized, double-blinded, phase-II clinical trial of nicotinamide riboside (NR) in PD.**

**Background:** Translational research by us and others nominates NAD supplementation as a potential neuroprotective therapy for PD. The central hypothesis of NO-PARK is that oral administration of the NAD precursor NR can boost neuronal NAD levels and ameliorate mitochondrial dysfunction in PD. This, in turn, will rectify neuronal metabolism and inhibit neurodegeneration, resulting in amelioration of clinical symptoms and delayed PD progression. See details under the NAD-PARK trial.

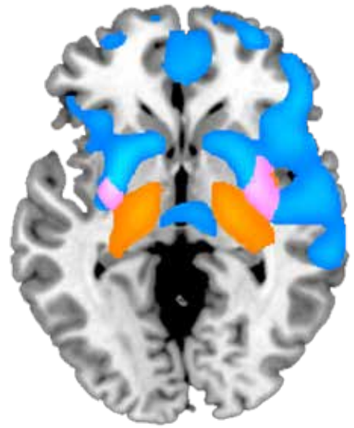
**Objectives:** To determine whether NR-therapy is neuroprotective in PD, and able to delay disease progression.

**Design:** NO-PARK is a multi-centre, phase II randomized double-blinded clinical trial, comparing NR to placebo in individuals with early-stage PD. Individuals with PD (n = 400) are being recruited starting 01/10/2020 from centres across all four health regions of Norway. *The following sites are actively recruiting*: 1) Haukeland University Hospital (HUS, leading site), Bergen; 2) Akershus University Hospital (AHUS), Akershus, Oslo; 3) Ullevål University Hospital (UUH), Oslo; 4) Rikshospitalet (RH), Oslo; 5) Drammen Hospital (DH), Drammen; 6) Dr Karen Herlofson Practice and Arendal Hospital (AH), Arendal; 7) Førde Central Hospital (FCH), Førde. *In addition, these partners are expected to initiate patient recruitment during 2022:* St Olavs University Hospital in Trondheim, Haugesund Hospital, Nordland Hospital in Bodø, Molde Hospital, and Tromsø University Hospital.

After the initial assessment, participants are randomly assigned to either NR 500 mg x 2/day, or placebo and followed with regular clinical examination, brain imaging and blood tests for a total period of one year.

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

**Status:** The NO-PARK trial is ongoing and has as of the end of 2021 included 120 participants.



**SUPPORT:**

**Participating Centres/Partners:**
- Haukeland University Hospital, Bergen
- Akershus University Hospital, Oslo
- Ullevål University Hospital, Oslo
- Rikshospitalet, Oslo
- Vestre Viken Hospital, Drammen
- St. Olavs University Hospital, Trondheim
- Dr Karen Herlofson and Arendal Hospital Arendal
- Førde Central Hospital, Førde

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

# Trial: NR-SAFE

## PI: Charalampos Tzoulis

**A phase I, randomized, double-blinded, safety trial of high-dose nicotinamide riboside (NR) in PD.**

**Background:** It is plausible that the beneficial effects of NR in PD, observed in the NADPARK study, are dose-dependent and more prominent at higher doses. NR doses of up to 2000mg per day have been tested in healthy humans with no signs of toxicity. However, the safety and tolerability of even higher doses is untested.

**Primary Objective** is to determine the safety of oral NR dose of 3000mg daily for a period of 4 weeks in individuals with Parkinson's disease (PD). Safety is defined as:

1. The absence of moderate or severe, acute or subacute adverse effects associated with an oral NR dose of 3000mg daily.
2. No significant change in clinical laboratory values associated with an oral NR dose of 3000mg daily.
3. No significant change in vital parameters associated with an oral NR dose of 3000mg daily.

**Secondary objectives** include to assess the following in relation to an oral NR dose of 3000mg daily:

1. Tolerability defined as self-reported mild adverse effects by subjects.
2. Changes in the NAD metabolome and related metabolites

**Design:** A phase I, randomized, double-blind trial. A total of 20 patients with PD will be recruited and randomized (1:1) to either NR 1500mg x 2 daily or placebo. Patients will be followed for 4 weeks with the following measures:

1. Clinical assessment (clinical examination, vital signs, ECG) at baseline and every week
2. Safety blood parameters at baseline, days 3, 5, 7, and then every week
3. Screening for adverse events at baseline, days 3, 7, and then every week
4. Blood and urine for metabolomics collected at baseline and day 28

**Primary outcome** is the between group (NR vs. placebo) difference in

1. Reported moderate/severe acute and subacute adverse effects at the end of study
2. Safety laboratory values
3. Vital parameters

**Secondary outcomes:**

1. Self-reported mild adverse effects after 4 weeks of follow up.
2. NAD metabolome in whole blood/PBMC measured by mass spectrometry.

**Status:** The NR-SAFE trial has secured funding and obtained all required regulatory approvals during 2021. Recruitment will start in March 2022.

**SUPPORT:**

**Participating Centres**

- Haukeland University Hospital, Bergen

**Funding**

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





# Trial:DIGI.PARK

## PI: Bettina Husebøe and Charalampos Tzoulis

**A trial of active sensor-technology as disease progression markers and treatment outcome measures in PD.**

**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 treatment-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 will attempt to address these limitations by harnessing the potential of active sensor technologies – such as rings and bracelets – which can monitor essential motor (e.g., tremor, balance, bradykinesia) and non-motor (e.g., sleep, apathy) features of PD, continuously over time. DIGI-PARK is performed as a collaboration with the Centre PIs Professor Bettina Husebø and Professor Charalampos Tzoulis.

**Objectives:** DIGI.PARK 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 that address PD.

**Design:** Patients with PD and neurologically healthy controls, recruited among the patient partners or spouses, will be fitted with sensor technologies such as smartwatches (Fitbit Sense and Empatica E4) and a smart ring (Oura Ring). These instruments can measure movements, heart rates, and electrodermal activities, which yield information about activity, sleep, and stress, among others. 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.

**Status**: The DIGI.PARK study has secured funding and obtained all required regulatory approvals during 2021. Recruitment will start in January 2022.

**SUPPORT:**

**Participating centres/partners**

- Haukeland University Hospital, Bergen

**Funding:**

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

# Research: Cohort study STRAT-PARK

## PIs: Charalampos Tzoulis and Mandar Jog

**A population-based cohort study from three centres across Norway and Canada.**

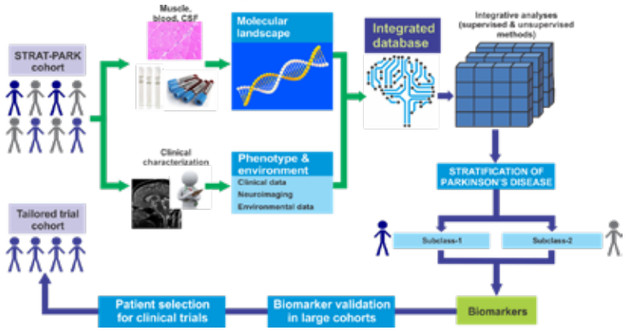
**Background:** A major bottleneck hindering breakthroughs in PD research is the disorder's vast biological heterogeneity. Although PD is commonly referred to as a single entity, evidence suggests that it is, in fact, an umbrella term, comprising a spectrum of disorders with overlapping clinical symptoms,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

**Objectives:** To stratify PD based on underlying molecular pathogenesis and develop biomarkers enabling patient stratification in clinical practice.

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

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

**Status**: Participant recruitment is ongoing in Haukeland University Hospital (HUS), Bergen, St. Olav's University Hospital, Trondheim, and The London Movement Disorders Centre (LMDC), Ontario, Canada. As of the end of 2021, 100 participants have been included in the STRAT-PARK study.




**SUPPORT:**

**Participating Centres/Partners:**
- Haukeland University Hospital, Bergen
- St Olav's University Hospital, Trondheim
- The London Movement Disorders Centre (LMDC), Ontario, Canada

**Funding:**
- K.G Jebsen Foundation
- The Trond Mohn Foundation
- The Regional Health Authority of Western Norway
- Haukeland University Hospital
- University of Bergen
- The Research Council of Norway, Neuro-SysMed





# Research: The ParkOme – a multidimensional molecular atlas of PD

## PI: Charalampos Tzoulis

**Developing comprehensive molecular database and network to understand Parkinson's disease.**

**Background:** Progress in the PD field is impeded by lack of mechanistic understanding and biological heterogeneity. Much of what we know regarding the involvement of these processes in the pathophysiology of PD comes either from the study of monogenic diseases, whose relevance for idiopathic PD is highly uncertain, or from cell and animal models that do not accurately reflect human disease. Thus, the most accurate source of information for iPD remains the study of patients. The ParkOme initiative involves an innovative, transdisciplinary approach employing multidimensional integration of biological systems (genome, epigenome, transcriptome, proteome) with high quality clinical and environmental data, in order to unravel the molecular pathogenesis of PD.

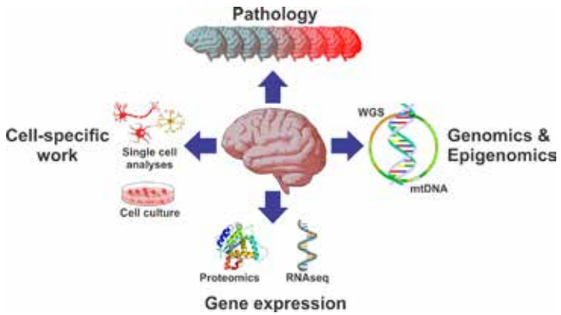
**Objectives:** The ParkOme initiative aims to advance the insight into the pathogenesis of PD, by generating a multi-omic atlas of the PD brain, muscle, blood, and gut, at the tissue and single-cell level.

**Design:** Genomic, epigenomic, transcriptomic and proteomic data are currently being generated in key-regions of fresh-frozen post-mortem brain (n > 1,000), as well as *in vivo* blood samples, muscle, and gastrointestinal biopsies. In each bulk-tissue sample, the group is constructing a multilayer molecular map combining the genome, DNA-methylation, selected histone modifications, chromatin accessibility, transcriptome, and proteome. To mitigate the confounder of cellular heterogeneity, they are conducting additional studies in single cells using a dual strategy: 1) High-throughput single-cell analyses, using our 10X Genomics platform. 2) Pathology-guided single-cell transcriptomics to elucidate the selective neuronal vulnerability to PD-associated pathology such as α-synuclein aggregation, mitochondrial or lysosomal dysfunction.

The group is interrogating the ParkOme using a combination of powerful supervised and unsupervised computational analyses (including artificial intelligence). Molecular signatures defining PD and its subclasses will be identified and translated into 1) Disease models recapitulating subclasses of human disease. These will be developed and characterized in the group's cell model workflow (section 2.4), 2) Precision biomarkers for patient stratification in clinical practice and 3) Therapeutic targets tailored to the molecular profile of patients.

Biomarkers and therapies emerging from this work will trigger clinical studies at the Neuro-SysMed Centre. The ParkOme data analyses are being carried out by the Bioinformatics Unit of the Tzoulis group in collaboration with the Helse Vest IKT Department and Microsoft Azure.

**Status:** In 2021, the group completed RNA sequencing of an unprecedented 800 brain samples of individuals with PD, other parkinsonisms and healthy controls. This data has been analysed with multiple novel and intriguing findings and several publications are underway. The first experiments of single-cell transcriptomics, using the dedicated 10X-Chromium platform, have been completed and data from 50 brains from patients with PD, MSA and healthy controls are currently being analysed.




**Funding:**
- The Regional Health Authority of Western Norway
- The Research Council of Norway, Neuro-SysMed
- The Research Council of Norway, FRIPRO
- The Trond Mohn Foundation
- Haukeland University Hospital
- The University of Bergen
- K.G Jebsen Foundation

# Dementia Studies

**Neurodegenerative dementias such as Alzheimer's disease and Dementia with Lewy Bodies are characterized by progressive neuronal cell loss in the brain that results in cognitive impairment, i.e. symptoms such as memory loss and difficulties with thinking, problem-solving or language. These symptoms are often mild in the beginning, but for someone suffering from dementia they have become severe enough to affect daily life. Age is the most important risk factor for neurodegenerative dementias and more people will suffer from dementia as the mean age in the population increases. Better diagnosis and treatment for dementias is urgently needed.**

Head of Research, Kristoffer Haugarvoll

More than 101,000 individuals (or 1.88% of the population) were estimated to suffer from dementia in Norway in 2020, see demenskartet.no. This number is expected to more than double by 2050. Alzheimer's disease is the most common form of neurodegenerative dementia. Dementia with Lewy Bodies is another common form of dementia that is closely related to Parkinson's disease.

Neurodegenerative dementias are characterized by deposition of abnormal proteins in the brain. The pathological hallmarks of Alzheimer's disease are extracellular accumulation of amloid β (Aβ) peptide in the brain ("senile plaque") and by intraneuronal accumulation of hyperphosphorylated tau protein in neurofibrillary tangles. This is accompanied by synaptic and neuronal losses. The histopathological hallmark of dementia with Lewy bodies (DLB) and Parkinson's disease (PD) is the loss of dopaminergic neurons in the substantia nigra associated with intraneuronal α-synuclein protein inclusions called Lewy pathology (Lewy bodies and Lewy neurites). However, in most cases a mixture of pathologies can be identified in the very same brain. This is indicating that our current diagnostic scheme, where the diagnosis is based on clinical syndromes, is too simplistic and fails to reflect the complexity that is occurring in the brain.

Our understanding of the molecular pathogenesis of dementia is limited. The molecular mechanisms that lead to dementia need to be elucidated in order to identify novel therapeutic targets that can prevent disease progression. The contribution of several molecular etiologies simultaneously has to be considered when deciphering the molecular etiology of dementia, as most brains exhibit more than one type of pathology. This has been clearly shown in Brain Bank studies where only a minority of individuals with a pathological diagnosis of Alzheimer's disease had pure Alzheimer Disease.

There is an urgent need for comprehensive biomarkers for dementia diagnosis, disease overlap, and disease progression. Biomarkers would be of particularly high value in dementia as neurodegeneration is already advanced at the time of clinical diagnosis. Furthermore, biomarkers are necessary to provide surrogate endpoints to evaluate the clinical efficacy of new neuroprotective therapies. Hence, biomarkers are pivotal to identify patients with prodromal dementia that may be ideal candidates for neuroprotective therapies. Neuropathological verification remains the gold standard for diagnosis of dementia and is key to validate the relation between ante-mortem biomarkers from peripheral tissue and final pathology in the brain.

Dementia research at Neuro-SysMed aims to better diagnose and classify dementia by applying biomarkers. In STRAT-COG study we aim at identifying predictors for prognosis and to identify subgroups of dementia patients that may benefit from personalized treatments in the future. We also aim at initiating novel treatment studies in dementia. We are participating in the ongoing Ambroxol in New and Early DLB, A Phase IIa Multicentre Randomized Controlled Double Blind Clinical Trial (ANeED), led by Arvid Rongve.

**National and international collaborators**

- Professor Dag Årsland, King's College London, UK and Stavanger University Hospital, Norway
- Associate Professor Arvid Rongve, Department of Research and Innovation, Haugesund Hospital, Helse Fonna, Haugesund and Department of Clinical Medicine (K1), University of Bergen, Norway.

Illustration: colourbox.com

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

## PI: Kristoffer Haugarvoll

**STRAT-COG Biomarkers for Improved Diagnosis and Treatment in Dementia.**

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 STRAT-COG cohort study aims at identifying molecular processes that are relevant across sub-groups of dementia and processes that can help stratify dementia into sub-groups that reflect underlying biology. The central hypothesis in this project is that converging molecular pathways exist across subtypes of dementia, but also that there are underlying subtypes that may not be fully reflected in the current classification system of dementia.

We propose 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.

**Our overarching objective** is to establish a cohort with multidimensional data that can be integrated in order to the complex clinical and biological spectrum of dementia and stratify it into subclasses with homogeneous biology and prognosis. This knowledge will then be used to develop diagnostic and prognostic biomarkers and identify novel therapeutic targets.

**Secondary objectives** include:
1) Establish and characterize the STRAT-COG cohort, a dementia cohort focusing on AD and DLB;

2) Elucidate genome-wide epigenetic and transcriptomic signatures associated with dementia;

3) Establish an objective molecular classification system for dementia;

4) Develop precision biomarkers for accurate molecular diagnosis and patient stratification in clinical practice.

**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



Cognitive testing. Photo: Ingrid Færøyvik/Haraldsplass Deaconess Hospital

# Clinical Treatment for ALS

**ALS is a fatal neurodegenerative disorder of unknown etiology for which there is no effective treatment. Progressive denervation of neuromuscular synapses in the peripheral nervous system (PNS) and degeneration of upper and lower motor neurons in the nervous system (CNS) result in muscle weakness, atrophy, paralysis and ultimately death for many patients within 2-3 years from the onset of symptoms.**

Head of Research, Ole-Bjørn Tysnes

Initial presentation of ALS varies between affected individuals, but typical symptoms are associated to spinal-onset disease (muscle weakness of the limbs), or bulbar-onset disease (difficulty with speech and swallowing).

ALS is the most common illness in the class of motor neuron disease (MND). In Norway, the disease has an estimated prevalence of 7.5-8 per 100.000. Age of onset is typically between 55 and 65 years of age, making ALS the most frequent neurodegenerative disorder in mid-life. Earlier symptom onset are more often seen in familial cases. The last decades, insights from clinical, imaging and neuropathological data have shifted the focus from looking upon ALS as a neuromuscular, to a neurodegenerative disease. The central nervous system is extensively involved, exemplified by the strong association of ALS with frontotemporal dementia (FTD). FTD, a frequent cause of dementia with onset younger than 65 years of age, involve in particular the frontal and temporal cortices. It is now recognized that the two conditions exist on a spectrum where 5-10% of ALS patients will develop frontotemporal dementia and as many as 50% show some deficits on detailed neuropsychological tests. Similarly, up to 15% of patients with FTD eventually fulfill the diagnostic criteria for ALS, and about 50% have some motor involvement. A shared genetic risk factor for both disease groups is the hexanucleotide repeat expansion in the C9orf72 gene. This is the most common underlying genetic cause of both ALS and FTD, accounting for 40 % of familial ALS cases and 25 % of familial FTD cases.

Sporadic ALS (sALS) accounts for 90% of cases and has no clear etiology, while familial ALS (fALS) accounts for 10% of cases and contains an underlying genetic component. However, while these two forms differ in causation, they appear pathologically and clinically indistinguishable.

There is no known cure for ALS. There are two approved medications to treat ALS, riluzole (a glutamate blocker) and edaravone (a free radical scavenger), but with limited efficacy. Riluzole, approved in 1995, is administered orally twice daily and delays time to tracheostomy or death in patients with ALS by 2-3 months (Miller et al. 2012). Edaravone, approved in the US in 2017, is administered in courses intravenously, and shows some efficacy in only a small subset of patients with ALS.

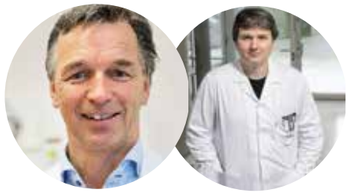
Currently, research at Neuro-SysMed includes three trials:

- The NO-ALS study: A phase-II, multi-center, double-blinded randomized clinical trial of oral NR and pterostilbene in early ALS.
- An open label extension trial for patients who have fulfilled the NO-ALS protocol.
- The STRAT-ALS cohort trial: Mitochondrial biomarkers to stratify amyotrophic lateral sclerosis.

**National collaborators:**
Tromsø: Birgitta Kampmann, MD, PhD, Associate Professor
St. Olavs, Trondheim: Helene Ballo Kvernmo, MD
Førde: Elin Seim, MD
Stavanger: Katrin Schlüter, MD
Drammen: Ingrid Bjørnå, MD
OUS, Oslo: Angelina Maniaol, PD, PhD
Ahus, Oslo: Trygve Holmøy, PhD, MD, Professor
Ahus, Oslo: Ola Nakken, MD, PhD
Ahus, Oslo: Hilde Nilsen, PhD, Professor
Ahus, Oslo: Evandro Fei Fang, PhD, Researcher

Illustration: colourbox.com

# The double-blinded randomized NO-ALS trial



## PIs: Ole-Bjørn Tysnes and Charalampos Tzoulis

**A phase-II, multi-center, double-blinded randomized clinical trial of oral NR and pterostilbene in early ALS; the NO-ALS study.**

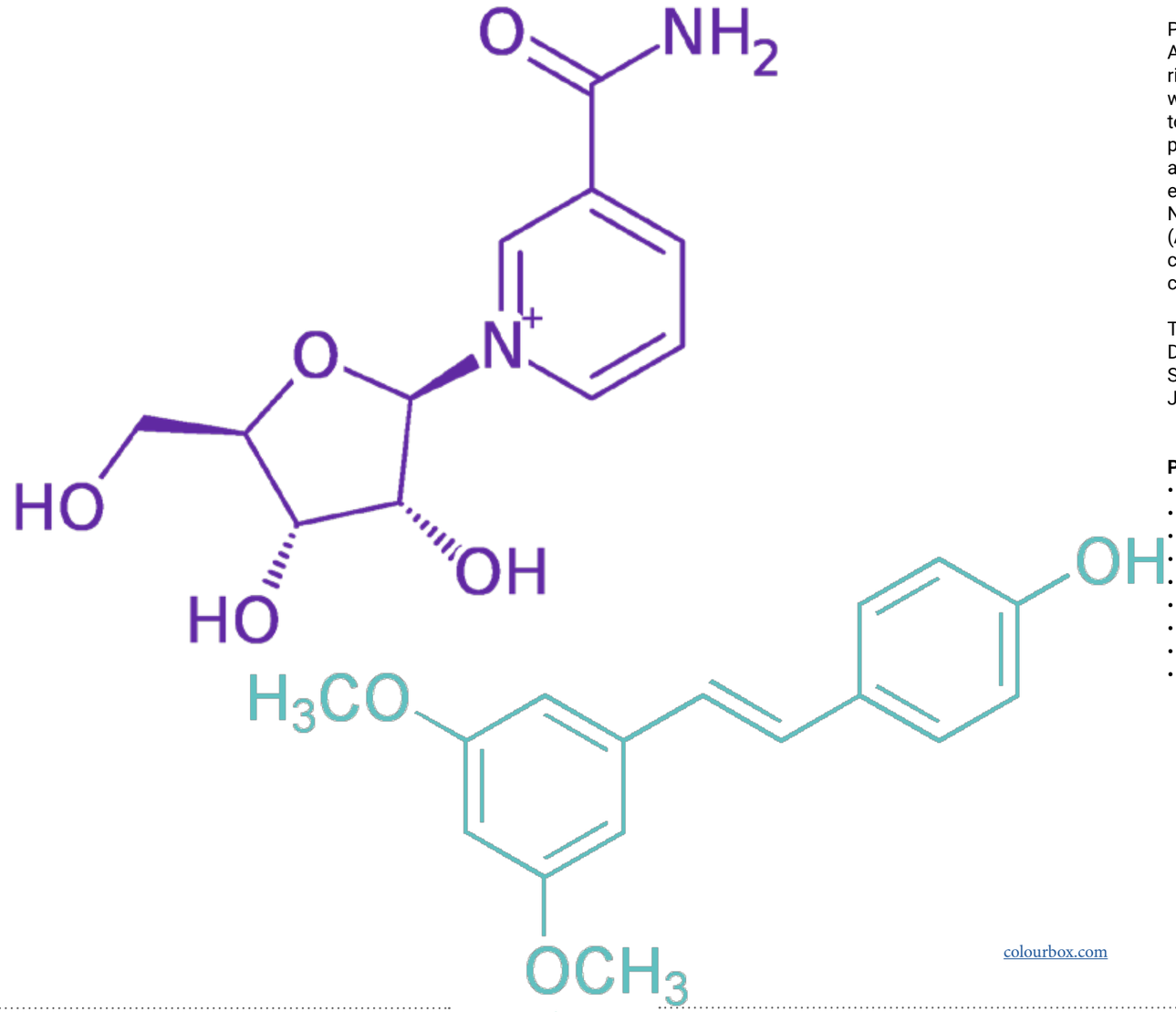
To test the potential of NR (nicotinamide riboside) as a neuroprotective therapy for ALS, the Tysnes and Tzoulis groups are running the NO-ALS trial, a multi-centre, phase II randomized double-blinded clinical trial, comparing combined oral NR and pterostilbene to placebo in early ALS. A total of 180 patients will be nation-wide recruited to the study Arm 1.

This novel project has the potential to discover a disease modifying therapy in ALS, thus vastly improving patient care and prognosis.

Patients have been included since October 2020. By end of 2021, a total of 129 patients have been included, 49 in the study arm 1 which require 180 included patients The study is expected to close by the end of 2023.

**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 Hospital, Førde
- Haugesund Hospital, Haugesund

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




colourbox.com





# Open label clinical trial: The NO-ALS extension trial

## PI: Ole-Bjørn Tysnes

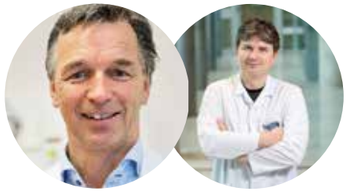
**An open label extension trial for patients who have fulfilled the NO-ALS protocol.**

Patients who have fulfilled the double-blinded NO-ALS protocol comparing high doses of Nicotinamide riboside (NR) and Pterostilbene (Pt) versus placebo will after the one-year randomization period be invited to the open label NO-ALS extension trial where all patient will receive active treatment. This is most of all a safety protocol to study eventual long term side effects of long-term treatment with high doses of NR/Pt, but effect parameters will also be followed (ALSFRS-R and Vital capacity). The intension is to continue this treatment until the NO-ALS trial is concluded.

The study is conducted by professor Ole-Bjørn Tysnes, Dr. Tale Litleré Bjerknes and professor Tiina Rekand. Study nurses are Marit Renså and Synnøve Bartz-Johannessen.

**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 Hospital, Førde
- Haugesund Hospital, Haugesund

# A cohort trial: The STRAT-ALS trial



## PIs: Ole-Bjørn Tysnes and Charalampos Tzoulis

### Postdoc: Tale Litlere Bjerknes

**STRAT-ALS: Mitochondrial biomarkers to stratify amyotrophic lateral sclerosis.**

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.

Mitochondria are the main generators of cellular ATP through the process of oxidative phosphorylation, which takes place at the mitochondrial respiratory chain. Neurons depend on a particularly high energy turnover to survive and function. Notably, while the brain only makes ~2% of the body mass, it accounts for ~20% of the body's total oxygen and glucose utilization. Moreover, mitochondria have important roles in calcium homeostasis, regulation of cellular proliferation and apoptosis, certain heme and steroid synthesis reactions, as well as being the main site for reactive oxygen species (ROS) production. Mitochondrial DNA has a higher mutation rate than the nuclear DNA, and motor neurons might also be especially vulnerable to these changes given that these cells are especially energy demanding and live and function throughout the entire lifetime of a person.

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 2022.

**Funding:**

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

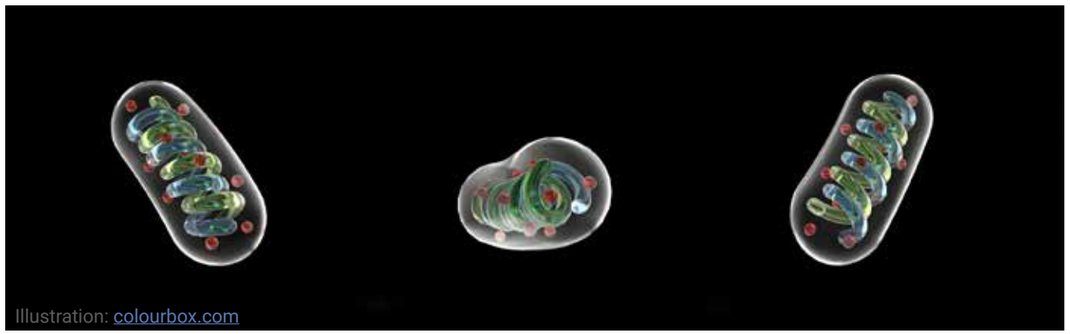


Illustration: colourbox.com





# Joint fields research for PD, MS and ALS: Drug-screening project

## PI: Trond Riise

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

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

The commonly used model when developing new medical treatment is the so-called translational research approach where findings in basic science experiments are transferred to clinical medicine by combining resources, expertise, and techniques within various fields in a highly interdisciplinary manner. A limitation to this approach is that it is dependent on existing hypotheses and knowledge on disease mechanisms for the first phase in basic sciences experiments. Furthermore, findings in animal models may not be directly relevant for human disease, and studies comparing the representativeness of animal models for human disease show overall poor results. The Riise group is addressing these limitations by introducing an initial screening phase in humans that will form the basis for new hypotheses that in a second phase will be tested and validated in mechanistic experiments using human iPSC-derived neurons and animal models. This approach might be referred to as "inverse translational research" and represents a novel use of Norwegian health registries.

The group is currently evaluating whether use of any of the 1600 drugs used in Norway are associated with a decreased – or – increased risk of developing PD, ALS or MS. An initial screening has identified 31 specific drugs that are reducing the risk of developing PD after controlling for multiple testing (False Discovery Rate). These drugs plus an additional 40 drugs showing a markedly reduced risk on PD, - but not surviving the FDA-criteria due to low exposure in the general population - were entered in a second phase where the dose-response effect of these drugs and the variation of effect according to number of years prior onset to PD were estimated. A subset of these drugs showing a sufficiently dose-response effect are now being evaluated according to expansion studies where the effect of drugs targeting the same receptors or proteins are estimated. A final list of drugs created this spring (2022) will be entered into experimental studies at a molecular level, where an ultimate validation will be performed.

Any of the drugs that will be validated in all phases of this study are likely to represent reliable and plausible biological mechanisms relevant for the disease. As these drugs have a known safety profile, the results from this study could form a direct basis for phase-II clinical studies in humans. This could lead to novel treatment that may benefit those affected by diseases in considerable shorter time than in a more traditional drug development approach.

**Funding:**

- Research Council of Norway, Neuro-SysMed
- University of Bergen
- Michael J. Fox foundation
- Participating Centers
- Research Council of Norway, FRIPRO

# Neuro-SysMed in the News

**News stories featuring Neuro-Sysmed in 2021 in the media.**

**December 26, 2021, Dagbladet**, "Det er håpløst. Jeg er så redd", patient case on MS, interview with Lars Bø.

**December 4, 2021, KK**, "Agnes skulle til linsekontroll - ble sendt til sykehuset", patient case on MS, interview with Lars Bø


kk

Synsforstyrrelser:

Agnes skulle til linsekontroll – ble sendt til sykehuset

– Har du hørt om MS, spurte nevrologen. Det hadde ikke Agnes (22).

STØTTE: Agnes finner støtte hos moren Linni, som først fikk sjokk da Agnes fikk MS-diagnosen. FOTO: Andreas Hagerud

**December 3, 2021, Lommelegen,** "Heidi fikk ALS: - Jeg fikk følelsen av at jeg burde skynde meg å leve", patient case and info on ALS, interview with Ole-Bjørn Tysnes.

**December 2, 2021, Medical Faculty, UiB News**, "35 millioner til Parkinsonforskning", article on new funding to PD research and PI Tzoulis.


35 millioner til Parkinsonforskning

**October 16, 2021, Stavanger Aftenblad**, "Da demensen tok ordene fra Atle, sluttet mange å snakke til ham. – Det gjorde meg så vondt, sier hans kone", patient case on dementia, interview with Tzoulis.


Stavanger Aftenblad

Da demensen tok ordene fra Atle, sluttet mange å snakke til ham. – Det gjorde meg så vondt, sier hans kone.

– Jeg opplevde at folk krysset veien for å unngå oss. Da bestemte jeg meg for å ta affære, sier Anne Berge Pedersen.

**November 30, 2021, Department of Clinical Medicine, UiB News**, "Bringing the patient perspective into research", article on the new Neuro-SysMed/CCBIO course in Patient and Public Involvement in Medical and Health Research.

**November 29, 2021, Dagbladet**, "Kims budskap før han dør", patient case on ALS, referring to Neuro-SysMed research.

**November 27, 2021, Trønder Avisa**, "Martha Grønning (35) fra Skogn ble symptomfri etter MS-behandling i Mexico", patient case on MS, referral to the RAM-MS stydy and Lars Bø.

**November 17, 2021, Dagens Medisin**, "Håper på omlegging av Nye metoder", on political decisions on availability of MS treatment, interview with Lars Bø.

**November 12, 2021, Akershus Universitetssykehus**, "Ny studie viser sammenheng mellom overvekt og MS", on a study showing a correlation between overweight and MS, co-authors are Øivind Torkildsen and Nina Grytten.



**October 22, 2021, Dagens Medisin,** "– Godt nok, er ikke godt nok", on a debate at the Post ECTRIMS-meeting on MS treatment of the future, with Lars Bø as one of the panelists.

**October 20, 2021, Dagens Medisin,** "Flere MS-pasienter inn i studier", on the RAM-MS and the OVERLORD studies, interview with Torkildsen.

**October 16, 2021, vi.no,** "– Jeg kan ikke bare sitte inne og kjenne på alt som er vondt", patient case on MS, referring to Neuro-SysMed research.


vi.no

– Jeg kan ikke bare sitte inne og kjenne på alt som er vondt

Lisbeth fikk MS-diagnose som 41-åring. Nå lever hun en dag av gangen - men passer på å nyte livet mest mulig her og nå.

LEVER MED MS: – Jeg vil oppmuntre dem som er der med sorgen over det de har mistet, jeg vet det går over. Det blir bedre, sier Lisbeth, som ble syk i 2011. Foto: Irene Jacobsen

Irene Jacobsen

**October 16, 2021, Bergens Tidende Magasinet**, "Kjærlighet når demensen rammer", patient case on dementia, interview with Tzoulis.

**October 15, 2021, Dagens Medisin,** "Fant alvorlige konsekvenser av medikamentbytte", practice changing research on drug switch from fingolimod to either kladribin or rituksimab, Myhr as co-author.


Medisin

Fant alvorlige konsekvenser av medikamentbytte

Flere norske forskere presenterer praksisendrende resultater i poster på ECTRIMS om medikamentbytte fra fingolimod (Gilenya). – Funnene gjør at man ikke bør skifte disse pasientene til kladribin (Mavenclad) sier overlege Gro Owren Nygaard på OUS.

Lasse Moe

**October 15, 2021, Dagbladet**, "Professor: Dette kan utløse MS", Lars Bø comments on a new MS study.


Dagbladet

Professor: Dette kan utløse MS

En ny, svensk studie har funnet sammenheng mellom tidligere sykdom og utviklingen av den nevrologiske sykdommen MS. – Viktig for oss, sier MS-syk.

VIKTIG: Trine Laurendz Hassel mener ny forskning rundt årsak til MS kan føre til at flere oppdager sykdommen tidligere. Foto: Kristin Svorte

Karoline Skeide, Kristin Svorte (foto)

**October 14, 2021, Dagens Medisin,** "Ikke farlig med stamcellebehandling etter langvirkende behandling", on a study showing that stem cell treatment is safe after treatment with rituksimab, interview with Torkildsen.

**October 13, 2021, Dagens Medisin**, "Norsk rekorddeltakelse på MS-kongress", on record participation from Norway on the virtual MS convention ECTRIMS, interview with Myhr.


Medisin

Norsk rekorddeltakelse på MS-kongress

Onsdag starter den virtuelle MS-kongressen ECTRIMS – med hele 17 norske forskningsbidrag.

Lasse Moe

**October 2, 2021, Ringerikes Blad and September 27, Hadeland**, "Remi (25) fra Hønefoss ble uhelbredelig syk med ALS: – Det var et grusomt sjokk", patient case on ALS, interview with Ole-Bjørn Tysnes.

**September 19, 2021, Dagbladet**, "Resultat Oslo Maraton Dødssyke Glenns elleville bragd: - Helt sinnssykt", patient case on ALS patient in Oslo Marathon, referral to ALS info from Ole-Bjørn Tysnes.

**September 17, 2021, Dagbladet**, "Glenn skal dø: - Jeg nekter", patient case on ALS patient climbing mountains, referral to ALS info from Ole-Bjørn Tysnes.

**September 14, 2021, Dagens Medisin**, "Starter ny studie på stamcelle-transplantasjon for MS-pasienter", on startup of an MS trial on mesenchymal stem cells.


**September 10, 2021, Allers,** "En utfordring i Norge", article on MS research in Norway, referring to Neuro-SysMed research trials.

**September 5, 2021, Dagbladet,** "Glenn (44) trosser dødssykdommen: - Jakter lyspunkter", patient case on ALS patient, referral to ALS info from Ole-Bjørn Tysnes.

**August 26, 2021, Dagens Medisin**, "Reviderer retningslinjer for MS-behandling", on a national update on the guidelines for MS therapy, interview with Myhr.


**August 6, 2021, SEFAS, UiB News**, "Measuring the advantages of an active life", article on the project "ActiveAgeing".

**July 18, 2021, Romsdals Budstikke**, "Agnes (22) skulle bare til optikeren - få dager senere fikk hun alvorlig diagnose", patient case on MS, interview with Torkildsen.

**July 12, 2021, Dagens Medisin,** "Jubler over storsatsing på kreft, revmatisme og hodepine", article on new centres for clinical treatment research, referring to Neuro-SysMed as the first centre established.

**July 2, 2021, Dagens Medisin**, "Fikk pandemi-nei – men flere sykehus har likevel gitt behandlingen", on a political no to the MS drug tysabri, interview with Lars Bø.

**June 28, 2021, Tønsberg Blad,** "Vi må forske mer på hjernehelse", commentary from a politician on research on ALS, referring to the NO-ALS study at Neuro-SysMed. Same article in Østlandsposten, Sandefjords Blad, and Gjengangeren.

**June 21, 2021, Tidsskriftet for Den Norske Legeforening,** "Fødselsdepresjon er vanligere hos kvinner med multippel sklerose", on a study showing that birth depression is more common in women with MS, with co-authors Torkildsen and Wergeland. Also in Dagens Medisin.


**June 4, 2021, Dagbladet**, "MS-pasienter skuffet over utvikling", on reactions to a political no to a new MS drug, comments from Lars Bø.

**June 2, 2021, Dagens Medisin**, "– Persontilpasset behandling er fine ord, men brukes bare i taler", on a political no to the MS drug ofatumumab, interview with Torkildsen.

**May 28, 2021, Dagens Medisin,** "Stortinget ba om tiltak for at flere skal få stamcellebehandling", on political meetings for stem cel treatment for MS, interview with Torkildsen.



**May 25, 2021, Melanor,** "MED.hjelper - ny nettside for kliniske studier", on the new MED.hjelper website.

**May 23, 2021, Fjordenes Tidende**, "Torbjørn er hjerneforsker og prøver å løse en stor medisinsk gåte", profile interview with Torbjørn Kråkenes.


**May 21, 2021, Dagens Medisin**, "Nytt nettsted skal hjelpe fagfolk og pasienter å finne kliniske studier", on the new tool Med.hjelper, interview with Myhr.

**May 18, 2021, Nidaros**, "Innstiller på at «right to try» ikke bør vedtas: – Ille at de ikke ønsker å gi oss muligheten", on a political recommendation on not to pass the Right To Try act. Neuro-SysMed referred to for its ALS research.

**May 18, 2021, Nidaros**, "Opplever plutselig bedring: – Jeg klarer å bevege på kroppsdeler jeg ikke har klart på ti måneder", patient case on ALS, improvement when participating in the NO-ALS study.


**May 10, 2021, Tidsskriftet for Den Norske Legeforening,** "Behandling som begrenser multippel sklerose", chronicle on MS reducing treatment with Myhr and Bø as co-authors.

**May 4, 2021, Dagbladet,** "Cathrine (43) ble kvitt plagene", successful patient case after treatment with rituksimab for MS, interview with Torkildsen.

**April 1, 2021, NRK**, "Mystisk hjernesykdom forbløffer leger i Canada", on a new brain disease discovered in Canada, interview with Tzoulis.

**March 12, 2021, LMI**, "Som å vinne i lotto", on a seminar held about clinical trials, lecture by Neuro-SysMed nurse Randi Haugstad. Incl. MED.hjelper video link.


**March 8, 2021, CCBIO, UiB News**, "Research school collaboration between centers of excellence", on the new collaboration between CCBIO and Neuro-SysMed.

**March 2, 2021, Dagens Medisin**, "Det ble ingen ny løsning for barn med multippel sklerose: – Ikke greit, sier MS-lege", on a political no to the MS drug fingolimod to children, interview with Lars Bø.

**February 27, 2021, NRS P3,** "Marte Julie (28) forsøker å løse et av verdens største mysterier", profile article on a young brain researcher, referral to Tzoulis.

**February 25, 2021, Dagens Medisin,** "En kamp ingen kan vinne alene", chronicle on the need for a global and national effort to stop dementia, referring to Neuro-SysMed as a shining example of a national research environment.

**February 24, 2021, Dagens Medisin**, "Ny versjon av gammel MS-medisin kan føre til gjeninnføring", on a new assessment of the MS drug natalizumab, interview with Lars Bø.


**February 19, 2021, NRK Sami Radio**, "Ung MS-pasient måtte til Moskva for å få behandling", patient case on stem cell treatment, interview with Torkildsen.

**February 18, 2021, Nofima/NTB**, "MS – ny forskning baner vei for en ny kurs", on a research collaboration between Neuro-SysMed and Nofima on MS, interview with Vedeler and Myhr.


**February 17, 2021, Varden**, "I Sverige er behandlingen gratis, i Norge må Verena ty til loppemarked og Spleis", patient case on MS, and stem cell treatment not commonly available in Norway, interview with Lars Bø. Also in Agderposten.

**February 5, 2021, KK**, "- Jeg sa til Kenneth at han kunne forlate meg", patient case on MS, and stem cell treatment not commonly available in Norway, interview with Lars Bø. Also in Lofotposten.

**January 31, 2021, iFinnmark**, " - Der og da tenkte jeg det aller verste", patient case on MS, and stem cell treatment not commonly available in Norway, interview with Øivind Torkildsen. Also in Trønder Avisa.


**January 28, 2021, Dagens Medisin**, "– Det største gjennombruddet innen MS på tyve år", on the Bjornevik study on Epstein-Barr as cause of MS, interview with Torkildsen and Myhr.

**January 25, 2021, NRK**, "Når Siri døyr, vil ho donera hjernen til ny bank", on a brain bank in Bergen, interview with Tzoulis.

**January 24, 2021, Dagens Medisin**, "Får tilgang på ny MS-medisin i stamcellestudie", on the RAM-MS study, interview with Torkildsen.

**January 18, 2021, Se og Hør,** "Jeg vil ha livet mitt tilbake", patient case on MS, comment from Torkildsen.

**January 5, 2021, NRK**, "Norske forskarar vil revolusjonere MS-behandlinga med billegare medisin", on the Overlord study, interview with Torkildsen.


**January 2, 2021, Drammens Tidende**, "MS-spesialist: - Vi trenger fortsatt mer dokumentasjon", on the need for more documentation for stem cell treatment in MS, interview with Lars Bø.



# Social media examples in 2021

# Publication list 2021

Relevant publications from the Neuro-SysMed PIs in 2021.


1. **Greenlee JE, Carlson NG, Abbatemarco JR, Herdlevær I, Clardy SL, Vedeler CA.** Paraneoplastic and Other Autoimmune Encephalitides: Anti-neuronal Antibodies, T Lymphocytes, and Questions of Pathogenesis. Front Neurol. 2022 Jan 17;12:744653. doi: 10.3389/fneur.2021.744653. PMID: 35111121; PMCID: PMC8801577.

2. **Rana N, Suliman S, Mohamed-Ahmed S, Gavasso S, Gjertsen BT, Mustafa K.** Systemic and local innate immune responses to surgical co-transplantation of mesenchymal stromal cells and biphasic calcium phosphate for bone regeneration. Acta Biomater. 2022 Mar 15;141:440-453. doi: 10.1016/j.actbio.2021.12.027. Epub 2021 Dec 28. PMID: 34968726.

3. **Raspotnig M, Kråkenes T, Herdlevær I, Haugen M, Vedeler C.** Expression of cerebellar degeneration-related proteins CDR2 and CDR2L in human and rat brain tissue. J Neuroimmunol. 2022 Jan 15;362:577766. doi: 10.1016/j.jneuroim.2021.577766. Epub 2021 Nov 11. PMID: 34823119.

4. **Liang KX, Chen A, Kristiansen CK, Bindoff LA.** Flow Cytometric Analysis of Multiple Mitochondrial Parameters in Human Induced Pluripotent Stem Cells and Their Neural and Glial Derivatives. J Vis Exp. 2021 Nov 8;(177). doi: 10.3791/63116. PMID: 34806709.

5. **Mostafavi S, Balafkan N, Pettersen IKN, Nido GS, Siller R, Tzoulis C, Sullivan GJ, Bindoff LA.** Distinct Mitochondrial Remodeling During Mesoderm Differentiation in a Human-Based Stem Cell Model. Front Cell Dev Biol. 2021 Oct 14;9:744777. doi: 10.3389/fcell.2021.744777. PMID: 34722525; PMCID: PMC8553110.

6. **Høglund RAA, Meyer HE, Stigum H, Torkildsen Ø, Grytten N, Holmøy T, Nakken O.** Association of Body Mass Index in Adolescence and Young Adulthood and Long-term Risk of Multiple Sclerosis: A Population-Based Study. Neurology. 2021 Dec 7;97(23):e2253-e2261. doi: 10.1212/WNL.0000000000012957. Epub 2021 Oct 25. PMID: 34697245.

7. **König M, Lorentzen ÅR, Torgauten HM, Tran TT, Schikora-Rustad S, Vaage EB, Mygland Å, Wergeland S, Aarseth J, Aaberge IAS, Torkildsen Ø, Holmøy T, Berge T, Myhr KM, Harbo HF, Andersen JT, Munthe LA, Søraas A, Celius EG, Vaage JT, Lund-Johansen F, Nygaard GO.** 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 Oct 20:jnnp-2021-327612. doi: 10.1136/jnnp-2021-327612. Epub ahead of print. PMID: 34670844.

8. **Chen A, Kristiansen CK, Hong Y, Kianian A, Fang EF, Sullivan GJ, Wang J, Li X, Bindoff LA, Liang KX.** Nicotinamide Riboside and Metformin Ameliorate Mitophagy Defect in Induced Pluripotent Stem Cell-Derived Astrocytes With POLG Mutations. Front Cell Dev Biol. 2021 Sep 24;9:737304. doi: 10.3389/fcell.2021.737304. PMID: 34631714; PMCID: PMC8497894.

9. **Pakdaman Y, Denker E, Austad E, Norton WHJ, Rolfsnes HO, Bindoff LA, Tzoulis C, Aukrust I, Knappskog PM, Johansson S, Ellingsen S.** Chip Protein U-Box Domain Truncation Affects Purkinje Neuron Morphology and Leads to Behavioral Changes in Zebrafish. Front Mol Neurosci. 2021 Sep 24;14:723912. doi: 10.3389/fnmol.2021.723912. PMID: 34630034; PMCID: PMC8497888.

10. **Silva-Pinheiro P, Pardo-Hernández C, Reyes A, Tilokani L, Mishra A, Cerutti R, Li S, Rozsivalova DH, Valenzuela S, Dogan SA, Peter B, Fernández-Silva P, Trifunovic A, Prudent J, Minczuk M, Bindoff L, Macao B, Zeviani M, Falkenberg M, Viscomi C.** Correction to 'DNA polymerase gamma mutations that impair holoenzyme stability cause catalytic subunit depletion'. Nucleic Acids Res. 2021 Oct 11;49(18):10803. doi: 10.1093/nar/gkab837. Erratum for: Nucleic Acids Res. 2021 May 21;49(9):5230-5248. PMID: 34520541; PMCID: PMC8501975.

11. **van Pijkeren A, Dietze J, Brotons AS, Egger AS, Lijster T, Barcaru A, Hotze M, Kobler P, Dekker FJ, Horvatovich P, Melgert BN, Ziegler M, Thedieck K, Heiland I, Bischoff R, Kwiatkowski M.** Combined Metabolic and Chemical (CoMetChem) Labeling Using Stable Isotopes-a Strategy to Reveal Site-Specific Histone Acetylation and Deacetylation Rates by LC-MS. Anal Chem. 2021 Sep 28;93(38):12872-12880. doi: 10.1021/acs.analchem.1c01359. Epub 2021 Sep 14. PMID: 34519498; PMCID: PMC8482368.

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13. **Brakedal B, Tzoulis C, Tysnes OB, Haugarvoll K.** NSAID use is not associated with Parkinson's disease incidence: A Norwegian Prescription Database study. PLoS One. 2021 Sep 7;16(9):e0256602. doi: 10.1371/journal.pone.0256602. PMID: 34492069; PMCID: PMC8423296.

14. **Bringeland GH, Blaser N, Myhr KM, Vedeler CA, Gavasso S.** Wearing-off symptoms during standard and extended natalizumab dosing intervals: Experiences from the COVID-19 pandemic. J Neurol Sci. 2021 Oct 15;429:117622. doi: 10.1016/j.jns.2021.117622. Epub 2021 Aug 22. PMID: 34474301; PMCID: PMC8445695.

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16. **Brunetti D, Catania A, Viscomi C, Deleidi M, Bindoff LA, Ghezzi D, Zeviani M.** Role of PITRM1 in Mitochondrial Dysfunction and Neurodegeneration. Biomedicines. 2021 Jul 17;9(7):833. doi: 10.3390/biomedicines9070833. PMID: 34356897; PMCID: PMC8301332.

17. **Norborg H, Riise T, Myhr KM, Grytten N, Wergeland S.** Real-world discontinuation rate of teriflunomide and dimethyl fumarate in multiple sclerosis. Mult Scler J Exp Transl Clin. 2021 Jun 14;7(2):20552173211022027. doi: 10.1177/20552173211022027. PMID: 34188949; PMCID: PMC8209840.

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19. **Pakdaman Y, Berland S, Bustad HJ, Erdal S, Thompson BA, James PA, Power KN, Ellingsen S, Krooni M, Berge LI, Sexton A, Bindoff LA, Knappskog PM, Johansson S, Aukrust I.** Genetic Dominant Variants in STUB1, Segregating in Families with SCA48, Display In Vitro Functional Impairments Indistinctive from Recessive Variants Associated with SCAR16. Int J Mol Sci. 2021 May 30;22(11):5870. doi: 10.3390/ijms22115870. PMID: 34070858; PMCID: PMC8199271.

20. **Silva-Pinheiro P, Pardo-Hernández C, Reyes A, Tilokani L, Mishra A, Cerutti R, Li S, Rozsivalova DH, Valenzuela S, Dogan SA, Peter B, Fernández-Silva P, Trifunovic A, Prudent J, Minczuk M, Bindoff L, Macao B, Zeviani M, Falkenberg M, Viscomi C.** DNA polymerase gamma mutations that impair holoenzyme stability cause catalytic subunit depletion. Nucleic Acids Res. 2021 May 21;49(9):5230-5248. doi: 10.1093/nar/gkab282. Erratum in: Nucleic Acids Res. 2021 Oct 11;49(18):10803. PMID: 33956154; PMCID: PMC8136776.

21. **Toker L, Tran GT, Sundaresan J, Tysnes OB, Alves G, Haugarvoll K, Nido GS, Dölle C, Tzoulis C.** Genome-wide histone acetylation analysis reveals altered transcriptional regulation in the Parkinson's disease brain. Mol Neurodegener. 2021 May 5;16(1):31. doi: 10.1186/s13024-021-00450-7. PMID: 33947435; PMCID: PMC8097820.

22. **Eid K, Torkildsen ØF, Aarseth J, Flemmen HØ, Holmøy T, Lorentzen ÅR, Myhr KM, Riise T, Simonsen C, Torkildsen CF, Wergeland S, Willumsen JS, Øksendal N, Gilhus NE, Bjørk MH.** Perinatal Depression and Anxiety in Women With Multiple Sclerosis: A Population-Based Cohort Study. Neurology. 2021 Jun 8;96(23):e2789-e2800. doi: 10.1212/WNL.0000000000012062. Epub 2021 Apr 21. PMID: 33883236; PMCID: PMC8205461.

23. **Hytönen MK, Sarviaho R, Jackson CB, Syrjä P, Jokinen T, Matiasek K, Rosati M, Dallabona C, Baruffini E, Quintero I, Arumilli M, Monteuuis G, Donner J, Anttila M, Suomalainen A, Bindoff LA, Lohi H.** In-frame deletion in canine PITRM1 is associated with a severe early-onset epilepsy, mitochondrial dysfunction and neurodegeneration. Hum Genet. 2021 Nov;140(11):1593-1609. doi: 10.1007/s00439-021-02279-y. Epub 2021 Apr 9. PMID: 33835239; PMCID: PMC8519929.

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29. **Herdlevær I, Haugen M, Mazengia K, Totland C, Vedeler C.** Paraneoplastic Cerebellar Degeneration: The Importance of Including CDR2L as a Diagnostic Marker. Neurol Neuroimmunol Neuroinflamm. 2021 Feb 2;8(2):e963. doi: 10.1212/NXI.0000000000000963. PMID: 33531379; PMCID: PMC8057066.

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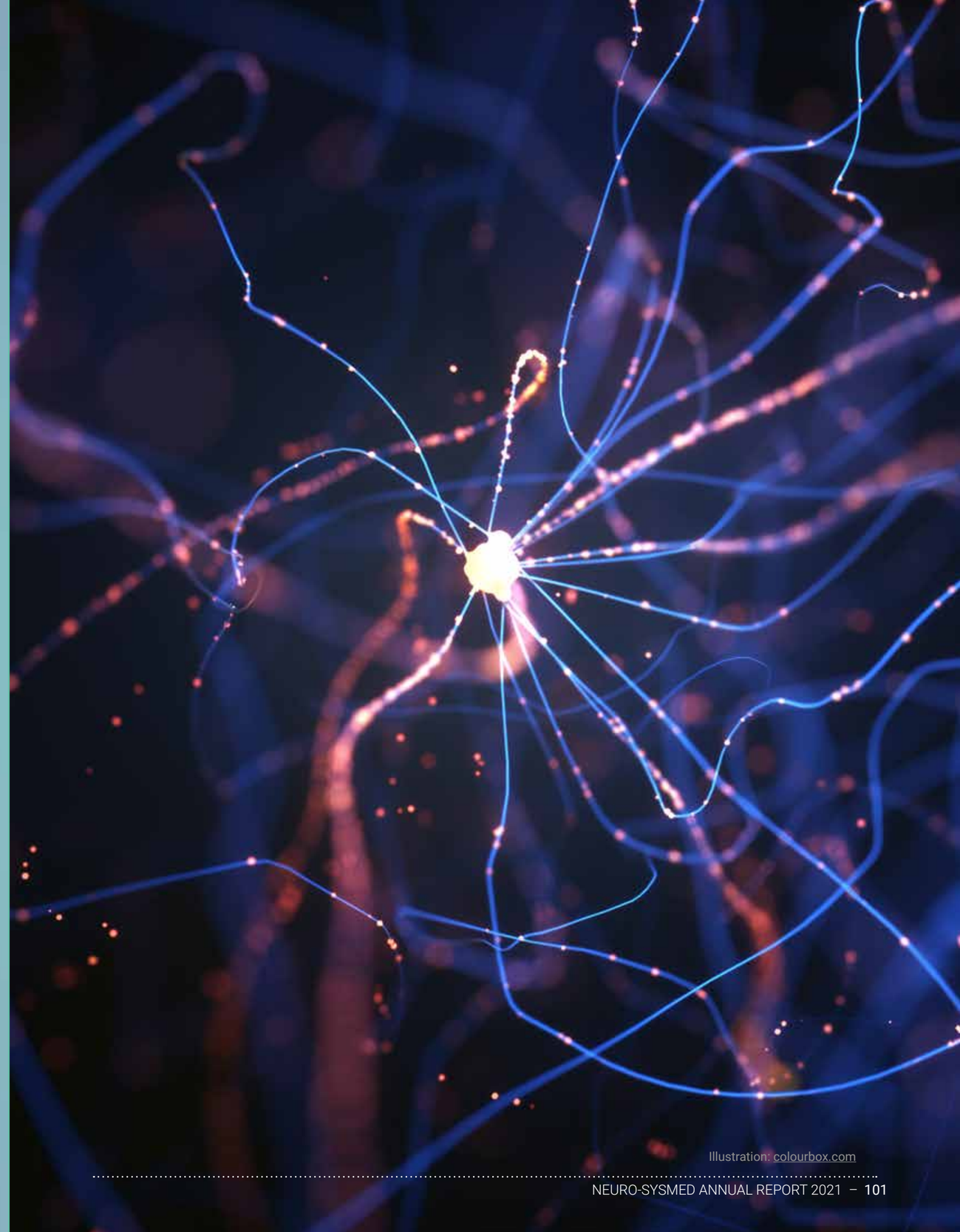

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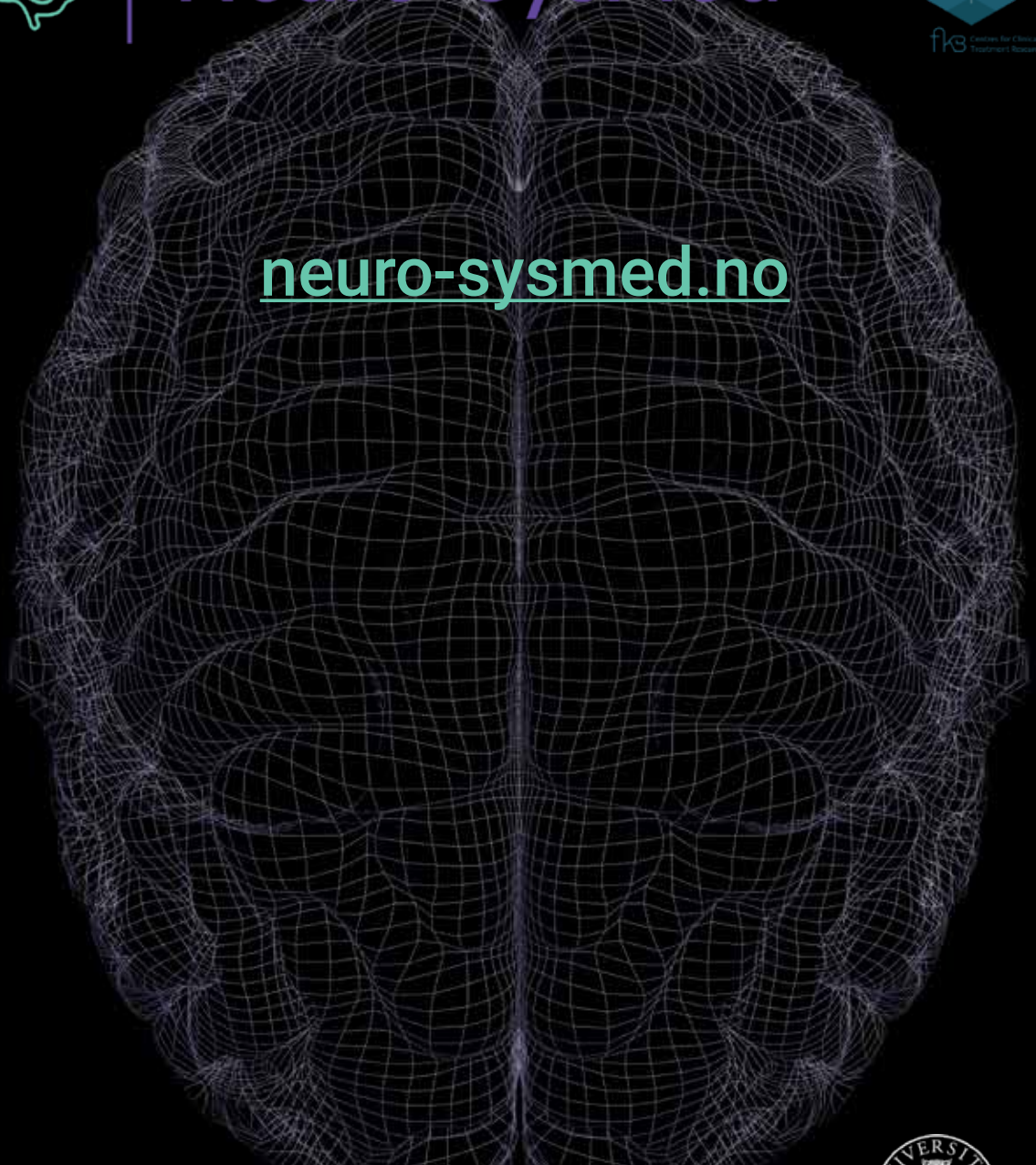

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