Neuro-SysMed

Centres for Clinical Treatment Research

ANNUAL REPORT 2020

A centre for clinical treatment research on neurological diseases

Contents

Painting "Tale" by Junie Lindblom (junielindblom.no), 1 in a series of 3 gifted to Neuro-SysMed by a patient, Ellen Tove Lindblom.

EDITORS: Kjell-Morten Myhr, Charalampos Tzoulis, Magnus Alvestad, Eli Synnøve Vidhammer.
ART DIRECTION/LAYOUT: Inhouse UiB by Eli Synnøve Vidhammer.

Director's Comments

The year of 2020 has been challenging, both for research, teaching and patient care. The COVID-19 pandemic has influenced all activities at Neuro-SysMed. Patient recruitment for clinical trials was temporary closed for several months due to hospital decisions to restrict patient consultations to critical health care only. Multiple sclerosis (MS) clinical trials were temporarily stopped due to the potential increased risk of infections during MS-immunotherapy. Norwegian Medicines Agency and the Ethics Committees prioritized application related to COVID-19 studies for several months, and thus postponed all kinds of Neuro-SysMed applications. In addition, reduced research laboratory activity and limitations in everyday interaction between physicians, researchers and research technicians has been a major challenge for all Neuro-SysMed projects. Reduced travelling to both national and international conferences and meetings have further decreased the important informal interaction with researchers to develop new ideas and collaborations for further research.

However, in spite of these challenges, Neuro-SysMed has achieved major steps forward to meet our commitments as the first Norwegian Centre of Clinical Treatment Research. We are recruiting patients into four clinical trials in multiple sclerosis (MS). In Parkinson's disease (PD), one trial was completed and two more clinical studies are ongoing. One clinical trial is recruiting in amytrophic lateral sclerosis (ALS), in addition to a questionnaire survey. We are also about to initiate a study in dementia and participate in a clinical trial for the treatment of Lewy body dementia at Haraldsplass Deaconess Hospital in close collaboration with Helse Fonna. Through all these trials, we are currently collaborating with more than 15 hospitals and thus provide the possibility for patient participation across Norway.

We further continue our commitments to ongoing multicentre international randomized clinical trials (RCT) in MS, organized by pharmaceutical companies. This activity is expanded by four new RCTs in MS and several more are planned for PD. In collaboration with the R&D unit at Haukeland University Hospital, we have established a clinical trial unit (CTU), and we are developing a One-Stop-Shop for clinical trials. In collaboration with the regional IT Department and Microsoft, the centre has established a system for cloud storage and analyses of sensitive data. Most recently, we have also announced the Neuro-SysMed Research School for teaching and education of researchers, health care personnel and users in all aspects of clinical treatment trial research.

Clinical treatment research is challenging and often very time-consuming. However, organizing clinical trials together with user representatives, researchers, and health care personnel across Norway is a great experience. They provide hope for new or better therapies to our patients, and are therefore an important driving force of the centre. We are all looking forward for new achievements that can make a difference for our patients.

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, blood and cerebrospinal fluid analyses, and brain images, to a common Neuro-SysMed database. Using this database, the vast amount of information collected at the centre wil 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 (i.e. personalized medicine). Thus, Neuro-SysMed aims to develop early and improved treatment strategies for patients with serious diseases of the central nervous system.

Randomized clinical trials are the backbone of the centre activities, and cannot be 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.

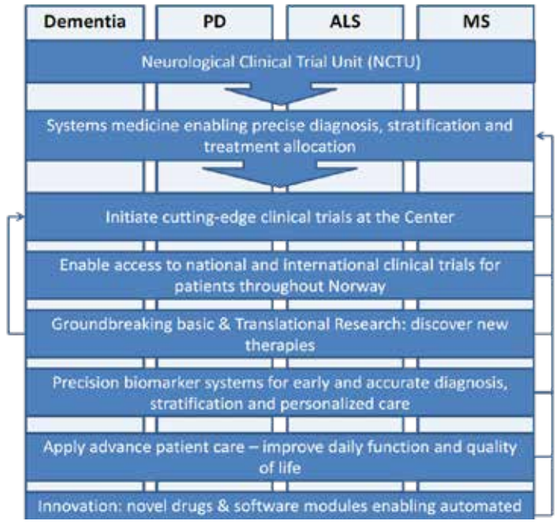


Figure: Research plan

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 (HDH) in Bergen and Lawson Health Research Institute (Lawson) in Ontario, Canada.

Organizational structure
The centre is led by Professor Kjell-Morten Myhr (Centre Director and head for the multiple sclerosis program), Professor Charalampos Tzoulis (Vice Centre Director and head for the neurodegeneration program), and Magnus Alvestad, head of administration.

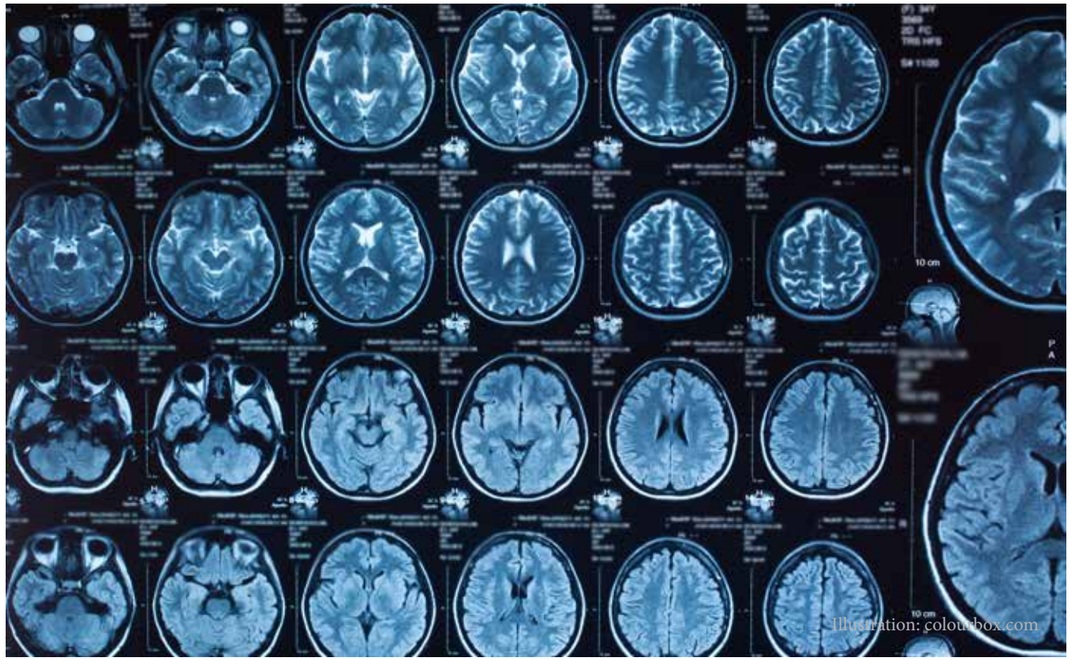
The board of the centre has organized their first meeting, and include members from the host and partner institutions. The board is chaired by Professor Per Bakke, Dean of Medicine, UiB, and the other board members are Eivind Hansen, Director of HUH, Torhild Næss Vedeler, Director of the Neurology Clinic, HUH, Helge Ræder, Vice Dean for Innovation, MED, UiB, and Kjerstin Fyllingen, Director of the HDH, 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 in 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. several PhD candidates at the UiB will perform all of their research at Haraldsplass.

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



Scientific Advisory Board

The mandate of the Scientific Advisory Board (SAB) is to provide the centre management with advice on scientific matters and strategic direction. 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 meet during 2020. However, relevant discussions with individual members related to disease specific topics have taken place.

Members:

- Professor Kailash Bathia, Queen Square Institute, UCLH, London, UK – neurodegeneration
- Professor Albert Ludolph, University Hospital of Ulm, Germany – ALS
- Professor Xavier Montalban, Vall d'Hebron University Hospital, Barcelona, Spain – multiple sclerosis
- Professor Raymond Koopmans, Radboud University, Netherlands – dementia

User Council

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

The User Council had two meetings in 2020; an on-site meeting in Bergen January 22, and an online meeting September 28.

All organizations have the opportunity to provide input on issues they would like to bring up for discussion in the User Council. Neuro-SysMed researchers and administration members also participate in the meetings, providing updates to the User Council on new and ongoing research projects.

Members in 2020:

- Lise Johnsen (Chair) – Norwegian MS Society
- Trine Lise Corneliussen (vice-Chair) – Norwegian Parkinson's Association
- Gudrun Østhassel – Norwegian MS Society
- Ragnhild S. Støkket – Norwegian Parkinson's Association
- Gry C. Aarnes – Norwegian Health Association
- Kristin Reimsers Kardel – Norwegian Health Association
- Lise Stousland Flesjå – ALS Norge
- Gry Lien – Alltid Litt Sterkere
- Mona Bahus (deputy) – ALS Norge
- Ivar Talmoen (deputy) – Alltid Litt Sterkere
- Mona Enstad (deputy) – Norwegian MS Society

"The collaboration is still in its early days but has got off to a good start, with positive and constructive discussions. We look forward to the further development of the centre, and to contribute even more to the progress as user representatives."

– Lise Johnsen, Chair.

Illustration: colourbox.com

Finances and Gender Balance

Neuro-SysMed opened in October 2019, and had been running for almost half a year when the COVID-19 pandemic closed down the University of Bergen and reduced the health care services across Norway to a minimum. Short-term plans were adapted for work that could be continued, especially for analysis and planning, while several clinical trials were delayed. During the fall, some activities were almost normalized. Overall, the centre approaches about 65% of the planned activity according to the original budget. No activity has been terminated, and the delays will be caught up during the first coming years.

Overall funding in 2020

In 2020, the centre received 12.3 MNOK in funding from the Research Council of Norway. Haukeland University Hospital (HUH) and the partners contributed 15.8 MNOK, resulting in total centre funding of 28.1 MNOK (figure 1).

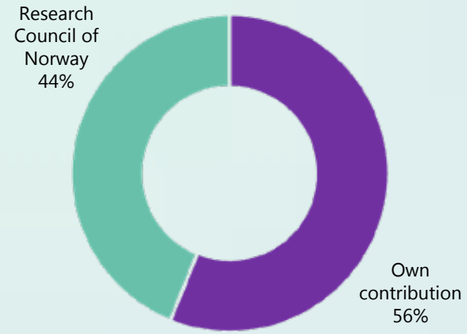


Figure 1: Funding sources in 2020

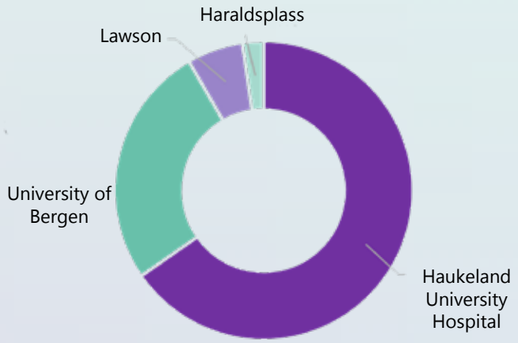


Figure 2: Spending in 2020

Spending in 2020

HUH spent about 18.3 MNOK in 2020. The University of Bergen (UiB) spent almost 7.4 MNOK. Lawson spent 1.7 million NOK, and Haraldsplass Deaconess Hospital spent about 0.7 MNOK. Total expenses were 28.1 MNOK. Over the lifetime of the centre, the total spending at HUH and the UiB will be approximately the same amount, about 150 MNOK each. Thus, the own contribution from HUH and UiB will be balanced in the coming years (figure 2).

Additional External Funding

The centre currently has 13 trials, running or in preparation, that have altogether secured over 130 million NOK of additional external funding for completing these studies. Additionally, in-kind contributions have been secured from participating hospitals for most of these trials. 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).

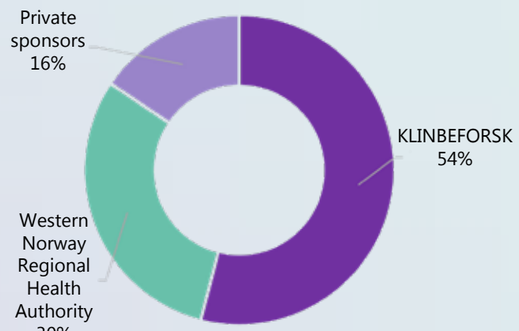


Figure 3: External funding

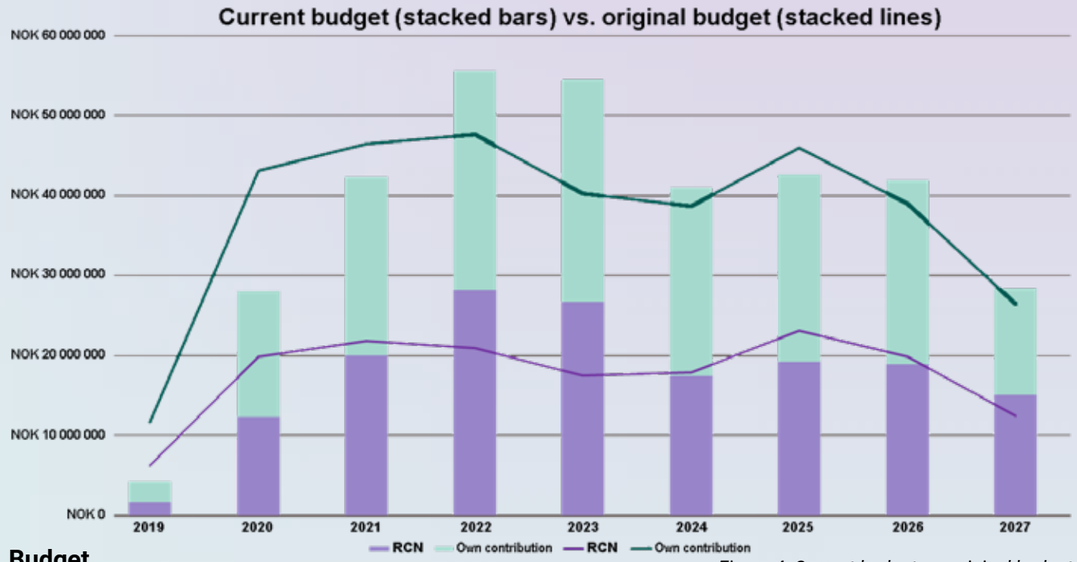


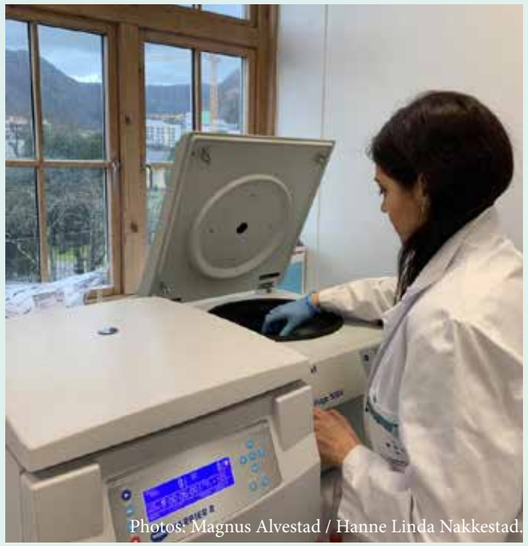
Figure 4: Current budget vs. original budget

Budget

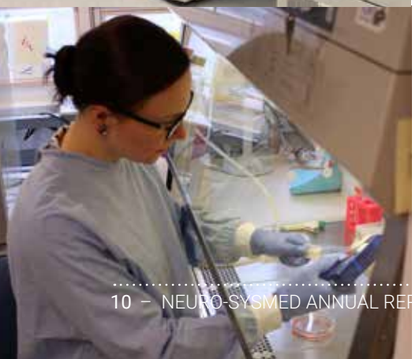
In the original centre budget from 2019, plans were made for a rapid increase of centre activities, to an annual budget level at about 40 million NOK (lines in the graph). This was later adjusted to a less progressive start, and mainly due to COVID-19 challenges, re-budgeting was performed during 2020 (bars in the graph). Thus, centre activities were lower than expected during the spring and summer 2020 but approached again originally research plans at the end of the year. Some activities, especially related to clinical trials, have clearly been postponed, resulting in planned peak activity during 2022 and 2023 (figure 4).

Gender

Out of 129 people in the Neuro-SysMed groups, 57 are men and 72 are women. Out of 64 candidates in PhD or Postdoc fellowship positions, 30 are men and 34 are women. Only 2 out of 13 principal investigators are women, but the centre has an active strategy to train and prepare female researchers for future PI responsibilities.



Photos: Magnus Alvestad / Hanne Linda Nakkestad.



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 persons, including laboratory engineers and researchers at all levels, from pregraduate 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 regional ICT Department and Microsoft Azure (see details in the Systems Medicine section, page 12).

Research Advisor Support

Yamila Torres Cleuren joined Neuro-SysMed in the fall of 2020 as a research advisor in a 50% position. She is working with all Neuro-SysMed PIs on their research plans and goals, sketching out research paths and interactions between the groups. In addition, she is providing an application writing training program for young researchers.

Neuro-SysMed's activity has steadily been increasing since the startup. There is a high level of activity in the centre working on expanding existing projects, and a key part of the research advisors' support is in developing these project ideas to realize their full potential.

Another key focus is supporting the younger researchers. In 2020, Neuro-SysMed organized three workshops focusing on grant application writing skills. The first focused on Helse Vest applications for PhD and postdoc positions, and the remainder two aimed at early career researchers (postdocs and above) who are getting ready to apply for their own funding. With a total of 14 participants representing junior researchers from all Neuro-SysMed groups, there were great discussions in the group and a lot of great input. These sessions covered a range of topics, from how to build a CV and how to find relevant calls, to more practical aspects such as how to write an application. This group of junior researchers will continue to receive support through career development advice, assistance in application writing, and meetings to discuss their individual needs.

"Now that Neuro-SysMed's activity is ramping up, we can start to see some results and the untapped potential of new projects."

– Yamila Torres Cleuren, Senior Advisor.

Photos: Magnus Alvestad / Hanne Linda Nakkestad / Ziegler group.

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 gradially contructed 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 will enter via the Neurological Clinical Trial Unit (NCTU). The Neuro-SysMed pipeline will systematically characterize 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 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 will host the wealth of data generated by Neuro-SysMed as well as the tools required for basic and advanced computational analyses and high-dimensional integration of data.

During 2020, Neuro-SysMed's data platform was established and is now in the alpha-version. The Neuro-SysMed team has been empowered with a dedicated Data Manager (Melanie Liedtke) and a Systems Bioinformatician (Kim Brügger) who are working tirelessly with the regional IT Department and Microsoft to fully implement this solution. Estimated transition to the beta-version is by April 2021, and the platform is estimated to be fully operational for the entire centre by June 2021. The centre plans to publish its methodological approach, via open access, and encourages others to apply similar solutions in the management of other complex diseases. This work has already attracted substantial attention from other research groups and the Research Council of Norway.

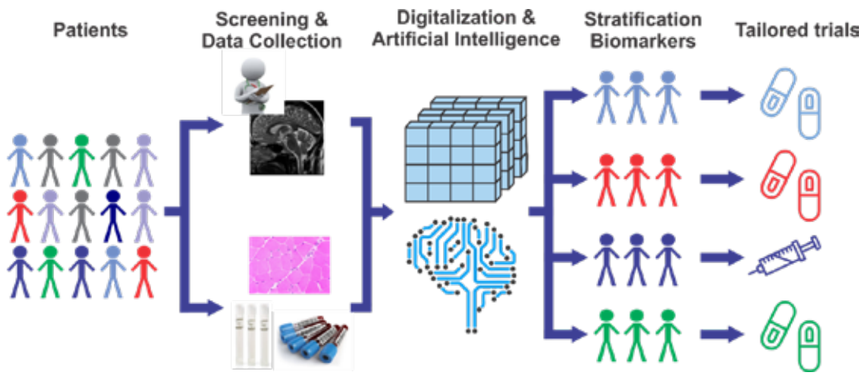


Figure: Neuro-SysMed pipeline

Innovation

Neuro-SysMed acknowledges the value of innovation in medical application, and seeks to be in the forefront of applying new technologies and methods, both in research projects and in therapy approaches. In 2020, the centre continued work on the MED.hjelper project, and also established projects with two new industry partners, as a result of a cooperation with the Norwegian Smart Care Cluster. Additionally, the centre has continued and expanded its work to establish a state-of-the-art online storage and analysis solution, in cooperation with Helse Vest IKT and Microsoft, see the previous page.

MED.hjelper

In collaboration with the Technology Transfer Office of Western Norway (VIS), Neuro-SysMed has worked on designing MED.hjelper, an online solution that will make it easier for patients and their supporters to identify and participate in appropriate clinical trials. This will be useful for Neuro-SysMed to improve patient recruitment in ongoing trials, and in addition, the centre aims at building a solution that will work for trials in other diseases. A supplier has been selected for building the technical platform, and the solution is expected to be launched during 2021. Additionally, the project has been accepted as a pre-incubation candidate by the Bergen Health Incubator, and the intention is to establish it as a spin-off during 2021. This system will provide commercial services to academic or industry researchers who need to recruit patients into clinical trials. Tone Skår at VIS has been the driving force behind this development.

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 negative pressure and atmospheric pressure cycles. The treatment is currently approved, and is used, 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 will perform a pilot study aiming at validation of these anecdotal reports.

Project Ipsilon

The Dutch-Japanese technology company Project Ipsilon has developed an iPad-based software application that aims to detect early signs of cognitive decline. The centre has established a cooperation with the company and aims to pilot this tool in the STRATPARK study to explore whether it is suitable to detect early cognitive decline in this patient population.

Research School in Translational Neuroscience

The Neuro-SysMed Research School in Translational Neuroscience was in the planning phase through 2020 to get the formal approval at the University of Bergen, and will be officially launched during spring 2021. The main 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.

The Research School aims at providing PhD candidates with relevant courses to fulfill obligatory credit points for the PhD training program at the University of Bergen. Another important objective for the Research School is to provide an inspiring and ambitious environment for the stimulation of future research among junior scientists as well as the established seniors. The Neuro-SysMed Research School in Translational Neuroscience is directed by Nina Grytten Torkildsen in collaboration with the Neuro-SysMed director and co-director.

Currently, the Research School offers PhD courses, which will run once a year in collaboration with the Centre for Cancer Biomarkers CCBIO.

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

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

Courses established and available in autumn 2021:

- **CCBIONEUR911: Clinical Trials.** This course is designed to prepare the participants to accomplish clinical trials in humans, and is conducted by Professor Øivind Grytten Torkildsen and Professor Line Bjørge. The first course is due 29. September to 1. October, 2021, and attendees are awarded 2 ECTS credits.

- **CCBIONEURO910: Patient and public involvement in medical and health research.** The aim of the course is to provide knowledge on how to involve user participations in clinical trials, and is conducted by Tone Skår, VIS, and Associate Professor Nina L. Jebsen. The first course is due November 3-5, 2021, and attendees are awarded 2 ECTS credits.

- **CCBIONEUR912: Health innovation.** The course will provide attendees with the necessary knowledge on how to succeed with innovation in health, and is conducted by Magnus Alvestad and Agnete Engelsen. The course will be established during April. The first course is due November 8-9 and December 2-3, 2021, and attendees will be awarded 4 ECTS credits.

Illustration: colourbox.com

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 embedded in all activities at the centre.

The centre provides research training in a broad spectrum of topics, encompassing mechanistic understanding of fundamental disease processes, epidemiological research, big-data analyses and bioinformatics, and the 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 presents 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 page) is an overarching structure of the research training. The school will organize seminars, symposiums and specific courses that award the attendees ECTS credits needed for the research educational programs.

Photo: Thor Brødreskift

Completed Academic Degrees

Researcher education at all levels is central for Neuro-SysMed. Three PhD candidates and one Master student successfully defended their theses during 2020. Their work were initiated prior to the start of the centre, but the topics were within the core activity of the centre.

Gerd Haga Bringeland June 5, 2020 successfully defended her PhD thesis "A mass cytometry receptor occupancy study of natalizumab therapy in multiple sclerosis" at the University of Bergen. Main supervisor was Researcher Sonia Gavasso, and co-supervisors were Professor Christian A. Vedeler and Professor Kjell-Morten Myhr.

In her PhD project, Bringeland aimed to develop a method for reliable natalizumab receptor occupancy (RO) measurement with high-parameter mass cytometry, and to study natalizumab RO and clinical characteristics in relapsing remitting multiple sclerosis (RRMS) patients treated with natalizumab.

The thesis is available here:
https://bora.uib.no/bora-xmlui/handle/1956/22314

Agnes Elisabeth Nystad June 12, 2020 successfully defended her PhD thesis "Effects of calcitriol and fingolimod on remyelination in the cuprizone model" at the University of Bergen. Main supervisor was Professor Øivind Torkildsen, and co-supervisor was PhD Stig Wergeland.

In her PhD project, Nystad aimed to investigate different strategies to improve remyelination and mitigate axonal damage in the cuprizone model, an animal model for de- and remyelination. The goal was to determine the effect of biologically active vitamin D (calcitriol) on remyelination and axonal damage. Moreover, she investigated the effect of the MS-medication fingolimod on remyelination and axonal damage in the cerebellum. Finally, she assessed the impact of fingolimod in the cerebrum.

The thesis is available here:
https://bora.uib.no/bora-xmlui/handle/1956/22329

Omar Hikmat September 25, 2020 successfully defended his PhD thesis "The phenotypic spectrum of polymerase gamma (POLG) disease from birth to late adulthood" at the University of Bergen. Main supervisor was Professor Laurence A. Bindoff, and co-supervisor was Professor Charalampos Tzoulis.

The aim of this PhD project was to study the clinical spectrum and natural course of POLG disease in a large cohort of patients in order to provide a reliable clinical classification that was useful in both paediatric and adult populations, and to identify robust diagnostic and prognostic biomarkers across neurodegenerative diseases.

The thesis is available here:
https://bora.uib.no/bora-xmlui/handle/1956/24119

Atefeh Kianian June 24, 2020 successfully completed her master's degree in the MMN group, working on mitochondrial biogenesis and function in glial astrocytes derived from iPSCs with POLG mutation. These cell-models will help us decipher the role of mitochondrial dysfunction in Parkinson's disease and other neurodegenerative disorders.

Supervisors were Laurence Bindoff and Kristina Xiao Liang. Atefeh is now applying for the PhD program in the MMN group.

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 key publications from the group.

The Multiple Sclerosis Research Group

Improved and tailored therapies for patients with multiple sclerosis

PI: Kjell-Morten Myhr

Myhr is senior consultant and professor of neurology, and has since 2001 directed the Multiple Sclerosis (MS) Research Group at Haukeland University Hospital and the University of Bergen (https://www.uib.no/fg/kgj-ms). He has previously chaired the first KG Jebsen Centre for Medical Research, focusing on MS-biomarkers (2011-2016), and has since 2019 been the director of the Norwegian Centre for Clinical Treatment Research in Neurology, Neuro-SysMed (https://neuro-sysmed.no/).

The project activities of the Multiple Sclerosis (MS) Research Group aim to support and meet the main objective of Neuro-SysMed to generate improved and tailored treatment strategies for patients with MS. Some projects are a direct result from the Neuro-SysMed funding, and others are a part of the long-term commitment of the group for improved therapy and care for MS patients, and thus are important prerequisites for the Neuro-SysMed centre.

The group is currently recruiting patients into four investigator sponsored clinical trials. The RAM-MS study evaluates the safety and efficacy of autologous hematopoietic stem cell transplantation (HSCT) compared to high-efficacy disease modifying therapies (DMT) in relapsing-remitting MS (RRMS) patient with breakthrough disease activity. The OVERLORD-MS study evaluates and compares the efficacy and safety of rituximab and ocrelizumab in newly diagnosed RRMS patients. The COVID-19 vaccine response study evaluates the impact of various DMTs on the vaccination response in MS patients. The SMART-MS study aims to evaluate the regenerative effect of mesenchymal autologous stem cells in progressive MS. This latter study has received approval from the Norwegian Medical Agency and the Ethical Committee, but the start is put on hold due to COVID-19 restrictions for the partner in Ulm, Germany. The group is however pre-screening patients to be ready for the start-up. In addition, they are also national coordinator for three industry sponsored multicentre randomized clinical trials, and recruiting site for another.

In collaboration with the biomarker group, the MS group is currently phenotyping stem cells and immune cells from patients included in the ongoing clinical trials, aiming to identify biomarkers for tailored dosing or patient selection. In other studies, they have evaluated biomarkers of treatment response of natalizumab as well as dimethyl fumarate and teriflunomide. Similarly, the use of neurofilament (NFL) and magnetic resonance imaging (MRI) are used to evaluate treatment response and disease progression. The impact of modifiable lifestyle factors are also evaluated, related to treatment efficacy and long-term prognoses, aiming for improved and personalised treatment strategies in MS.

A sensitive and clinical practical screening instrument for early detection of disabling symptoms like cognitive dysfunction is another important research focus with direct impact for the clinical trial efficacy endpoints. Thus, the Norwegian translation of the brief international cognitive assessment for multiple sclerosis (BICAMS) is currently included in the clinical trials.

Registry and epidemiological studies to evaluate possible risk factors and comorbidities have been a long-term commitment for the research group. Recent data on cancer frequency in MS calls for further studies both on the aetiology of the disease, and risk stratification for immunotherapy.

Preclinical studies evaluating effects from vitamin D on remyelination (repair) in animal models, as well as biomarker discovery studies in these animal models and the cerebrospinal fluid from MS patients are other prioritized projects in the group. They also use animal models in feasibility studies of mesenchymal stem cells as a regenerative therapy in progressive MS.

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The Neuromics Research Group

Biomarkers and tailored therapies for Parkinson's disease

PI: Charalampos Tzoulis

Professor Tzoulis is an expert in neurodegeneration, neurogenetics and mitochondrial medicine. His research group, "Neuromics" (http://www.neuromics.org/#research), comprises more than 20 members and integrates molecular, computational and clinical neuroscience, with the overarching aim to decipher the role of mitochondrial dysfunction in Parkinson's disease (PD), and develop novel biomarkers for patient stratification and tailored therapies.

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

During 2020, Professor Tzoulis' group made key-advances in their research projects:
The NAD-PARK study, a phase-I randomized trial of NAD-supplementation therapy with nicotinamide riboside (NR) in PD is completed and shows promising results, including conclusive evidence that NR penetrates the brain and impacts the cerebral metabolic profile.

The NO-PARK study, a phase-II randomized trial of NR in PD, is initiated in four out of seven centres and has already recruited nearly 100 patients. When completed, this study will provide a definite answer to whether NR-therapy can delay the progression of PD.

The STRAT-PARK initiative was also initiated in 2020. STRAT-PARK is a cohort study aiming to stratify PD according to clinical and biological variation, provide mechanistic insight into disease subtypes, and develop clinical biomarkers for patient stratification. So far, approximately 15 patients and controls have been recruited in Bergen, and the project is now starting at partner-centres in Trondheim and London Ontario, Canada.

The ParkOme initiative aims to map the multi-omic profile of PD at the individual and single-cell level. So far, the group has analyzed the genome, DNA-methylome, histone-acetylome (for selected markers), transcriptome, and proteome, for ~100 brain samples. In addition, they mapped the transcriptome in a total of ~1,000 brain samples. Analyses of the ParkOme data have generated novel insights into the genetics and gene-expression profile of PD. Moreover, in the first histone-acetylome-wide study in PD, the group showed that the brain of individuals with PD is characterized by a profound, genome-wide dysregulation of H3K27 acetylation and decoupling from transcription.

Single-cell transcriptomics, using the dedicated 10X-Chromium platform, are also well-underway. The methodology has been established and the data from the first pilot experiments in blood cells and nuclei from brain tissue are currently being analyzed. The group is also experimenting with the potential of long-read sequencing to map "obscure" areas of the genome, assess DNA-methylation natively, and evaluate RNA-splicing. The first samples have been analyzed and the group's bioinformatics team is currently establishing the analyses pipelines.

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

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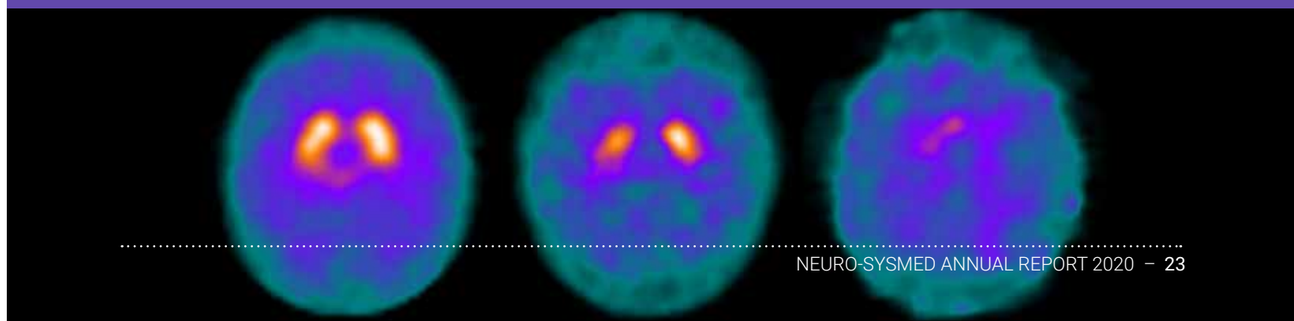

The Bergen Dementia Research Group

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 Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). The group aims at identifying novel biomarkers for dementia and stratifying dementias according to underlying molecular patterns.

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 the 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. In 2021, they will start a new cohort study – STRAT-COG. This study aims to establish a comprehensive biomarker panel for dementia by combining existing biomarkes for Alzheimer's 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. STRAT-COG will include a brain donation program.

In 2020, the Bergen Dementia Research Group started recruiting individuals with mild cognitive impairment to the ongoing Dementia Disease Initiation (DDI) project (PI: Tormod Fladby).

The Bergen Dementia Research Group is a partner in the ANeED study: Ambroxol in New and Early Dementia with Lewy Bodies (PI: Arvid Rongve). The ANeED study is a national multicentre phase III RCT clinical intervention study with Ambroxol in prodromal and mild DLB in Memory Clinics in Norway. Patient inclusion will start in 2021.

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SELECTED KEY PUBLICATIONS

1. Gaare JJ, Nido G, Dölle C, Sztromwasser P, Alves G, Tysnes OB, Haugarvoll K, Tzoulis C. Meta-analysis of whole-exome sequencing data from two independent cohorts finds no evidence for rare variant enrichment in Parkinson disease associated loci. PLoS One. 2020 Oct 1;15(10):e0239824. PMID: 33002040
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12. Tzoulis C, Zayats T, Knappskog PM, Müller B, Larsen JP, Tysnes OB, Bindoff LA, Johansson S, Haugarvoll K. HTRA2 p.G399S in Parkinson disease, essential tremor, and tremulous cervical dystonia.Proc Natl Acad Sci U S A. 2015 Mar 30. pii: 201503105. PMID: 25825781

Photo: Ingrid Færøyvik/Haraldsplass Diakonale Sykehus

Clinical Treatment for ALS

PI: Ole-Bjørn Tysnes

Ole-Bjørn Tysnes is 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.

Initial presentation of ALS varies between affected individuals, and typically presents as spinal-onset disease (muscle weakness of the limbs), or bulbar-onset disease (difficulty with speech and swallowing). Sporadic ALS (sALS) accounts for 90% of cases and has no clear 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 (Riluzole package insert 2016), prolonging survival by 2-3 months (Miller et al. 2012). Edaravone, approved in the US in 2017, is administered in courses intravenously and shows efficacy in only a small subset of patients with ALS.

Recent research by the group and others indicates that boosting the activity of the histone deacetylate enzymes known as sirtuins, via a combination of nicotinamide riboside (NR) and pterostilbene, has neuroprotective effects in ALS and may delay clinical disease progression.

Based on these preliminary findings, 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 this hypothesis, they 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 our power estimates, a total of 180 patients will be recruited from all over Norway. The study was started in October 2020. By end of February 2021, 20 patients are included in the study. All study centres will be recruiting by end of March 2021.

This novel 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.

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2020 PUBLICATIONS

1. Association of SNCA Parkinson's Disease Risk Polymorphisms With Disease Progression in Newly Diagnosed Patients. Szwedo AA, Pedersen CC, Ushakova A, Forsgren L, Tysnes OB, Counsell CE, Alves G, Lange J, Macleod AD, Maple-Grødem J. Front Neurol. 2021 Feb 10;11:620585. doi: 10.3389/fneur.2020.620585. eCollection 2020.PMID: 33643180 Free PMC article.
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Illustration: colourbox.com

Centre for Elderly and Nursing Home Medicine

PI: Bettina Husebø

The Centre for Elderly and Nursing Home Medicine (SEFAS) is a part of the Department of Global Public Health and Primary Care at the Faculty of Medicine, University of Bergen. The centre is led by Professor Bettina Husebø, established in collaboration with the GC Rieber Foundations and financed by the Norwegian Government. The group's focus is research, teaching and implementation of research results based on national and international multidisciplinary collaboration.

SEFAS is a part of the Section for Elderly Medicine, Social Pharmacy and Interprofessional Work-Place Learning (FEST). SEFAS staff currently counts five permanent positions funded by a grant from the Norwegian Directorate of Health, with administrative and research functions including co-research and user representation. The remaining positions are related to ongoing projects, constituting a vibrant research environment with a total of five postdoctoral researchers, nine PhD candidates, and three master students, in 2020. Most positions are financed by the Research Council of Norway (RCN).

SEFAS is directly linked to Neuro-SysMed by the DIGI.PARK project. Other national collaboration partners include the Alrek Health Cluster, the municipality of Bergen, Western Norway University of Applied Sciences, the Centre for International Health, and the Norwegian Smart Care Cluster, among others. The group has ongoing international collaboration with researchers from USA (Yale University; Harvard Medical School, McLean Hospital), the Netherlands (University of Leiden), Austria (Joanneum Research, Graz), Romania (Politehnica University of Bucharest), and Japan (Tohoku University), among others. In 2020, this resulted in three applications for project funding led by SEFAS and submitted to EU Horizon 2020, ERC, and the RCN.

Despite the COVID-19 related restrictions, SEFAS held high activity levels during 2020; their annual report is available at www.uib.no/sefas. SEFAS also figured among the top 10 from the Faculty of Medicine, UiB, most frequently featured in media communications in 2020 (Faculty's Annual Communications Report). Further, two international students have won awards after their stay in Bergen and publications based on COSMOS data. Erika Ito, Tohoku University, investigated the impact of psychotropic drug use on quality of life in people with dementia. Paulien van Dam, University of Leiden, investigated analgesic treatment and quality of life in this population. As a cultural highlight, the group contributed to the Bergen Festival's opening day with the Bergen International Summit. The focus of this day was on culture, activity, and health in elderly care.

SEFAS currently has two major ongoing research projects. LIVE@Home.Path is a mixed-method stepped wedge randomized controlled trial including home-dwelling persons with dementia and their informal caregivers (dyads) in Bergen, Bærum and Kristiansand. Funded by the RCN, the trial investigates the impact of a complex intervention to improve resource utilization and caregiver burden.

In the initial phase of the COVID-19 restrictions, SEFAS nested a new study, PAN.DEM (PANdemic in people with DEMentia) into the ongoing LIVE@Home.Path trial and interviewed caregivers on their perceptions of the situation and how the pandemic influences the health care service, neuropsychiatric symptoms, use of assistive technology, and social contact. Several articles are published or in preparation, and the research group is actively related to the newly established Pandemic Centre at UiB. Results were also presented digitally at the Technology in Psychiatry Summit, McLean Hospital (28.-30.10.2020): www.vimeo.com/470492759

2020 also marks the initial steps of the ActiveAgeing approach, a collaborative effort between SEFAS, Neuro-SysMed, the GC Rieber Foundations and Helgetun Living Lab. Helgetun is a senior housing project aiming to promote mental, social and physical activity, creativity and healthy ageing, consisting of 31 apartments in rural surroundings near Bergen. ActiveAgeing will investigate the current possibilities for enhanced activity and quality of life in healthy elderly and people with e.g. Parkinson's disease (PD). Using innovative home-based sensors, the ActiveAgeing project will produce big data to develop AI-based algorithms that can describe and predict function and activity in elderly people. ActiveAgeing also aims to determine how smart housing and health systems can be used to promote healthy ageing and empower individuals to stay active in health and disease. In DIGI.PARK, the group investigates the use of wearable and sensor technology to determine symptom trajectories and prognosis in people with PD, working closely with Neuro-SysMed and including participants in parallel with the planned STRAT-PARK study. Collaboration with the Group for Artificial Intelligence, UiB, and the upcoming Incubator, UiB, is established.

GROUP MEMBERS

Group members involved in Neuro-SysMed projects:

Professor Bettina Husebø, MD, PhD, Professor, Centre Leader
Guro Akre, Adviser, Coordinator
Ane Erdal, PhD, Researcher
Rune Samdal, Co-Researcher (user representative)
Line I. Berge, MD, PhD, Postdoc
Juan Carlos Torrado, PhD, Postdoc
Haakon Reithe, PhD Candidate

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Photo: Silje K. Robinson

The Biorecognition Unit

PI: Aurora Martinez

Aurora Martinez leads the Biorecognition Unit at the Department of Biomedicine, UiB. This group investigates the molecular basis of disease, notably in inborn errors of metabolism with neurological impairment such as parkinsonisms, phenylketonuria and porphyria. The research of the group has a special focus on therapy development, including screening of large compound libraries, novel drug design and drug repurposing.

A key focus in the lab is studies of proteins involved in dopamine synthesis and transport. The projects combine biochemical, biophysical and structural studies of isolated proteins and protein complexes with assays in cellular and animal models, elucidating the pathogenic role of dysfunctional biomolecular interactions and loss of protein stability on genotype-correlations and gain-of-function comorbidities. The group is also increasing its research- and innovation focus on drug discovery and development, and contributes to Nor-Openscreen and EU-Openscreen (Eric and Drive) infrastructure projects for high-capacity screening, chemical biology and drug design, focusing on low molecular weight drug candidates (figure 1). Furthermore, the Martinez lab investigates the characterization and optimization of interactions with selected proteins, notably tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine, for enzyme stabilization and improved cellular uptake, aiming at development of enzyme replacement therapies (see key publications to the right).

Within the Neuro-SysMed centre, the research of the group is integrated in translational projects with clinical partner groups, focusing on molecular mechanisms involved in the development and progression of Parkinson's disease, and on the concomitant discovery and evaluation of specific mechanistic-based therapies. The use of high-throughput screening methods and facilities are essential in these projects. Towards this end, the Martinez lab has initiated projects to understand and develop therapies to correct (i) dysfunctional protein-protein interactions involved in dopamine synthesis and vesicular transport, (ii) proteostasis dysregulation, and (iii) neuronal respiratory complex I deficiency and impaired mitochondrial DNA homeostasis, collaborating with Neuro-SysMed partners Trond Riise, Charalampos Tzoulis and Laurence A. Bindoff.

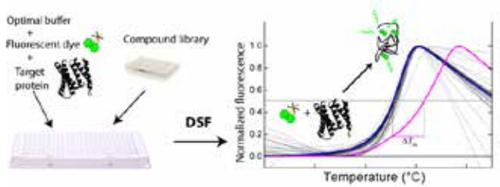

Figure 1. Protocol for high-throughput screening of compound libraries by differential scanning fluorimetry (DSF), based on target stabilization by ligand binding. This protocol can be used to discover ligands for both soluble and membrane proteins. From Brennecke et al. (2019) EU-OPENSCREEN: A novel collaborative approach to facilitate chemical biology. SLAS Discov 24, 398-413.

GROUP MEMBERS

Aurora Martinez, PhD, Professor, Group Leader
Svein I. Støve, PhD, Postdoc, UiB
Marte I. Flydal, PhD, Researcher, HUH
Karina S. Prestegård, Industrial PhD, RCN/Pluvia
Kunwar Jung KC, MS, PhD Candidate, UiB
Mary Dayne Sia Tai, MS, PhD Candidate, UiB

The group includes 14 members in total. The above participate in projects related to Neuro-SysMed.

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The Mitochondrial Medicine and Neurogenetics Research Group (MMN)

PI: Laurence Bindoff

The MMN group performs clinical and basic research primarily focussed on mitochondria and their role in disease. To this end, the group studies primary mitochondrial diseases such as those caused by mutations in POLG and mitochondrial DNA, and 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 and neurodegeneration so that no one mechanism prevails. This suggests that either mitochondrial dysfunction is a "common" final pathway for all forms of neurodegeneration, or that mitochondrial promiscuity, i.e. their involvement in almost any cellular process, means that these changes are secondary, and are either not involved in the disease process or only partly so.

The group has established a robust model system to investigate disease related changes in mitochondrial function. Reprogramming patient fibroblasts to induced pluripotent stem cells (iPSC) provides a substrate from which any cell type/tissue can be generated. For example, the group has generated neuronal lineages including dopaminergic neurones, motor neurones, glial cells such as astrocytes and oligodendrocytes and mesenchymal cells such as cardiomyocytes. MMN's role in Neuro-SysMed is to provide this expertise in generating stem cell models in appropriate cell lineages (e.g. neuronal or glial). MNN is now extending its work into generating complex structures called organoids. The group has successfully generated cortical organoids ("brains in dish") from patients with mitochondrial disease and controls.

The group's studies with stem cell models show that it is possible to replicate findings such as respiratory chain complex I deficiency and mtDNA depletion in neural stem cells (NSC), progenitors committed to the neuronal lineage, but with retained ability to divide. The group published their findings in NSC with POLG mutations in EMBO Molecular Medicine. They have also submitted work showing that astrocytes from POLG patients also manifest a phenotype, but more interestingly, they become toxic for neurones. Astrocyte involvement in neurodegeneration is an exciting new area and these groundbreaking 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. This work is under review. Lastly, the group has been looking at various candidate compounds for treating mitochondrial dysfunction.They found that N-acetylcysteine amide was able to reduce oxidative stress and improve mitochondrial function in iPSC derived dopaminergic neurones. This was published in Experimental Neurology.

The MMN group has also generated cardiomyocytes from iPSC and done this in a 96 well format. This method was published in Scientific Reports. The importance of this work is that it confirms our ability to generate a wide range of differentiated cell types, something that can be important in the future.

The group's recent clinical work has focussed on greater understanding of POLG related disease and the elaboration of biomarkers with which to diagnose and follow mitochondrial diseases. Studies of POLG related disease have used the POLG registry that now contains >180 patients, both living and dead. This unique material has allowed them to generate a simplified classification of POLG related disease, to investigate the impact of gender and pregnancy on disease course and outcome, and to study mental health and quality of life in affected individuals. Intriguingly, they found clear gender differences: males tended to present and die earlier than females and onset and worsening in females was associated with onset of menarche and pregnancy.

The search for biomarkers has focussed on two areas: novel mitochondrial disease markers and studies to investigate how best to use known biomarkers. Neurofilament light chain (NF-L) released by damage to neurones has been used as a marker to follow disease progression in multiple sclerosis. The group asked the question whether it could be useful also in mitochondrial disease, and performed a study comparing it with other known mitochondrial biomarkers, namely FGF21 and GDF15. In their pilot study, they showed that NF-L could be useful in detecting central nervous system involvement in patients with systemic mitochondrial disease. In those with disease restricted to skeletal muscle, FGF21 and GDF15 were more sensitive. They also investigated the detection of mtDNA deletions and showed that urine sediment cells were an appropriate source of DNA, thus obviating the need for muscle biopsy in these patients.

GROUP MEMBERS

Laurence Bindoff, Professor, Group Leader
Kristina Xiao Liang, PhD, Senior Researcher
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Sepideh Mostafavi, MS, PhD Candidate
Cecilie Kristensen, MS, PhD Candidate
Anbin Chen, MS, PhD Candidate
Omar Hikmat, MD, PhD Candidate
(Successfully defended September 25, 2020. Postdoc as of January 1, 21)
Kristin Nielsen Varhaug, MD, PhD Candidate
Atefeh Kianian, Master Student (successfully completed June 23, 20)

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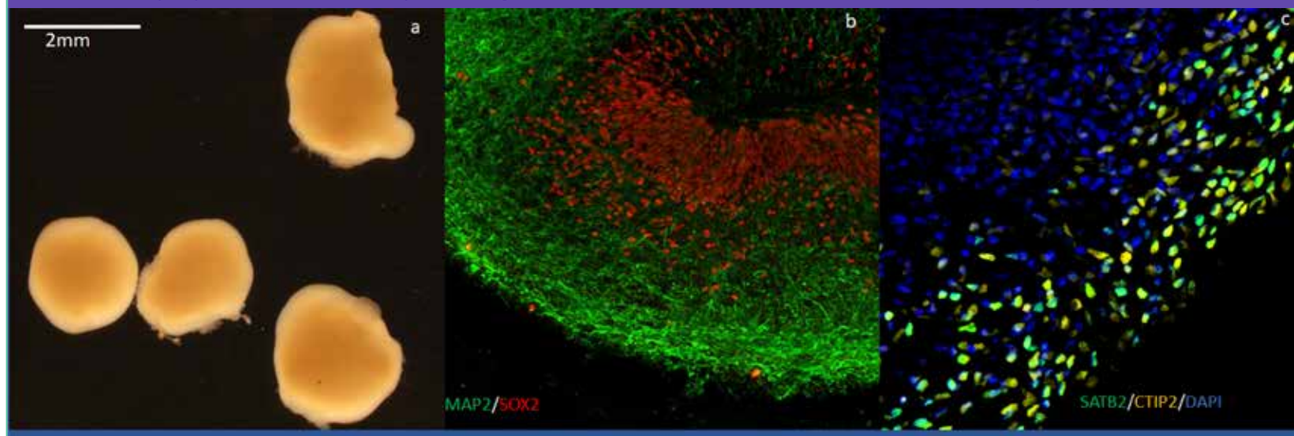

Brain organoids. a) whole organoid. b) neurones & progenitors. c) showing different subtypes of neurones

Images: Prof. Laurence Bindoff and Dr. Yu Hong.

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.

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 group propose that therapies promoting mitochondrial function via replenishing the NAD+ pool can shield neurons against the neurodegenerative processes and delay disease progression. Nicotinamide riboside (NR) is a well-established precursor which effectively elevates NAD+ synthesis and is non-toxic in animals and humans. It is fully approved for human use, has good oral bioavailability, crosses the blood-brain barrier and has been shown to extend lifespan in yeast and to have strong neuroprotective effects in animals. Therefore, the group believes that NR is an excellent candidate for correcting NAD+ deficiency and rectifying the metabolic impairment in neurodegeneration.

Using various cell systems and state-of-the-art metabolomics approaches, the group is studying the impact of NAD+ deficiency on major cellular bioenergetics and signalling systems. Previously, they have been able to set up the analytical technologies to measure the NAD+ metabolome and its dynamics in biological samples. They have established cellular NAD+ turnover rates in human cell lines and identified metabolic adjustments evoked by chronic NAD+ deficiency. These measurements require the use of stable isotope-labeled NAD+ precursors and high-resolution mass spectrometry. In turn, the group needed to develop suitable algorithms enabling appropriate correction for naturally occurring isotopes. This has been achieved in a way applicable to a wide range of biomolecules (preprint Dietze et al., https://doi.org/10.1101/2020.10.31.361725).

In cellular model systems, the group has mimicked age-dependent decline of NAD levels using genetic engineering to introduce NAD consuming enzyme activities into various subcellular compartments. Phenotypic and mechanistic studies revealed a tight regulation of total cellular NAD turnover, independent of the organelle targeted and the actual total cellular NAD concentration. Based on cell biological analyses, fluxomics and mathematical modelling, they propose that mitochondria serve as cellular NAD buffer. This function requires a mitochondrial NAD carrier as well as a mitochondrial enzyme which reversibly converts NAD to NMN and ATP (preprint vanLinden et al., doi.org/10.21203/rs.3.rs-116850/v1). A key contribution to develop this hypothesis was the discovery of a mitochondrial NAD carrier to which the group made major contributions (Luongo et al.).

The group will now extend their efforts and use the developed methodology to analyze the potential metabolic effect of NR supplementation in patients with Parkinson's disease as part of the NAD-PARK and NOPARK clinical studies.

GROUP MEMBERS

Mathias Ziegler, MD, PhD, Professor, Group Leader
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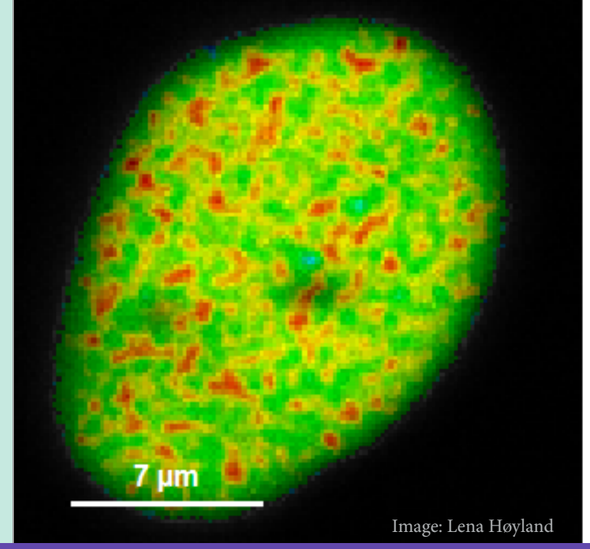

Image: Lena Høyland

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Photos: Marc Niere

The Neuroimmunology and Biomarker Group

PI: Christian Vedeler

Professor Christian Vedeler is Professor of Neurology and Neuroimmunology at the University of Bergen and Haukeland University Hospital. He is the Director of the Neuroimmunology 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 neuroimmunology, biomarker establishment, autoimmunity and neurodegeneration.

The Biomarker Group currently focuses on translational single cell omics research 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).

The group is developing quality controlled diagnostic and biomarker assays based on state of the art technologies. They use mass cytometry 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 neurofilamant (NFL) and IgG bands. Based on quanterix technology, they measure NFL-light chain in serum samples from patients to monitor treatment response and disease progression in neurological diseases. In collaboration with the Department of Medical Biochemistry and Pharmacology, they have established a very sensitive capillary gel electro-phoresis method that substantially increased sensitivity and specificity of oligoclonal immuno-globulins in CSF of patients with MS and other neuroinflammatory diseases. Currently, they are establishing a method to test pharmacological profiles of drugs and anti-drug antibodies of biological medications, such as for anti-CD20 antibodies used to treat patients with MS.

The group contributes with standard operating procedures for laboratory manuals in clinical trials and has optimized standard protocols for biobanking of patient materials in clinical trials at Neuro-SysMed.

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. These proteins will be further characterized as potential biomarkers for neurodegenerative diseases.

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.

GROUP MEMBERS

Senior Researchers
Christian Vedeler, MD, PhD, Professor, Group Leader
Sonia Gavasso, MSc, PhD

PhD Candidates
Gerd Haga Bringeland, MD
Torbjørn Kråkenes, MSci
Ida Herdlevær, MSci
Eirik Solheim, MSci
Margrethe Raspotnig

**Core personnel of Neuro-SysMed*

Pre-PhD projects
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Kjell Inge Erikstad (Stud.Med.)

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Kamal Mustafa, MSc, PhD
Bjørn Tore Gjertsen, MD, PhD
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Nima Agaheepour, MSc, PhD
Brice Gaudilliere, MD, PhD

Associated Postdoctoral Fellow
Christopher Elnan Kvistad, MD, PhD

Associated PhD Candidate
Kristin N Varhaug, MD

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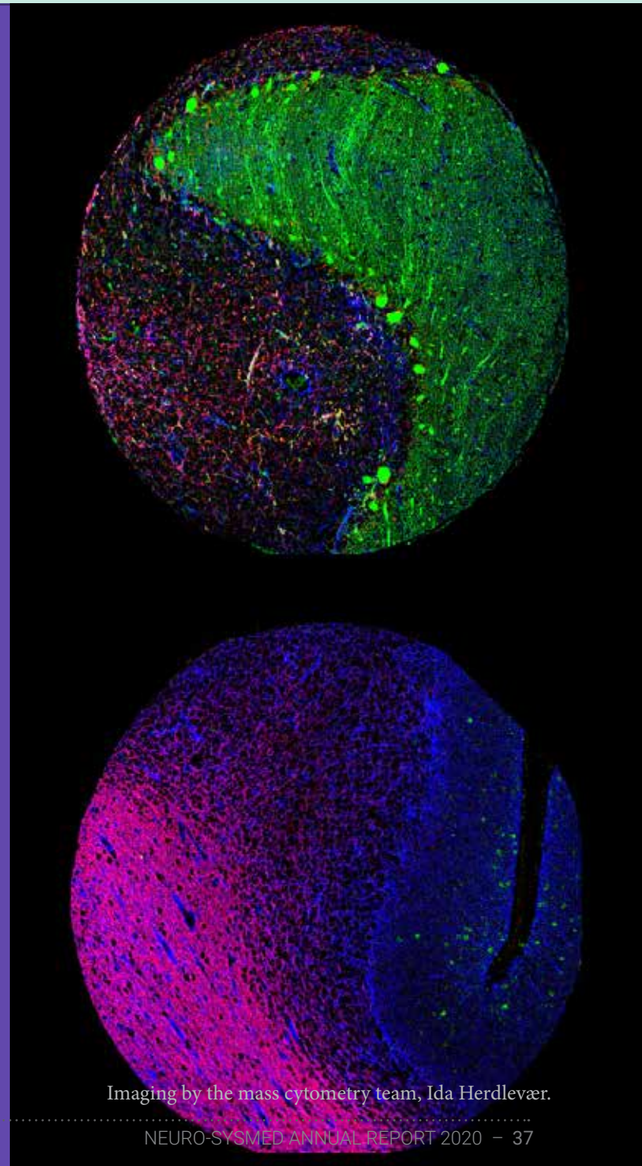


Imaging by the mass cytometry team, Ida Herdlevær.

Motion Biomechanics and Biomarkers in Parkinson's Disease

PI: Mandar Jog

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

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

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.

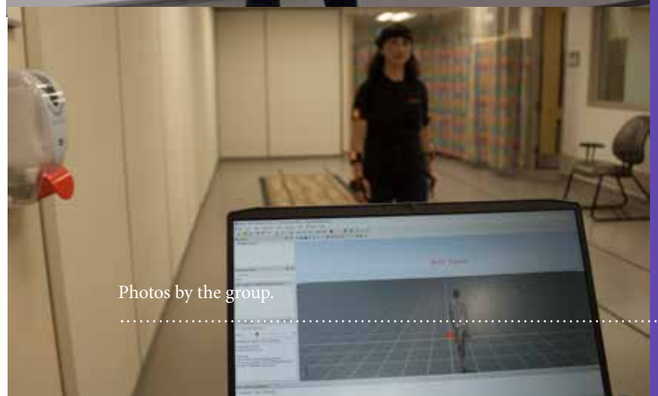
Prominent examples of Professor Jog's work include using spinal cord stimulation for gait dysfunction treatment in Parkinson's disease, with impressive results.

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

Professor Jog has a key role in the design and implementation of clinical cohort studies as well as randomized clinical trials for PD, such as the ongoing NO-PARK, NAD-PARK and STRAT-PARK studies. These trials employ innovative approaches for objective patient assessment, which are enabled by technologies developed by Professor Jog's lab, such as wireless whole-body wearable sensors with accompanying computational algorithms.

GROUP MEMBERS

Mandar Jog, MD, FRCPC, Professor, Group Leader
Soumya Sharma, MD, DM, Postdoc
Jacky Ganguly, MD, DM, Postdoc
Dinkar Kulshreshtha, DM, Postdoc
Mellany Tuesta, MD, Postdoc
JiaRen Chai, MD, Postdoc
Sourabh Bansal, MD, DM, Postdoc
Heather Russell, RN, Clinical Nurse
Sima Soltani, PhD, Postdoc Associate
Olivia Samotus, MSc, PhD Candidate
Yokesh Tamilselvam, MSc, PhD Candidate
Dorian Aur, PhD, Research Analyst



Photos by the group.

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12. Page AD. et al. Exploring the Psychosocial Impact of Botulinum Toxin Type A Injections for Individuals With Oromandibular Dystonia: A Qualitative Study of Patients' Experiences. Am J Speech Lang Pathol. 2021 Feb 25:1-15. doi: 10.1044/2020_AJSLP-20-00124. Epub ahead of print. PMID: 33647215.

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
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Julia Romanowska, PhD, Bioinformatician
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Akash Kapali, PhD Candidate (MS)
Julia Axiina Tuominen, PhD Candidate (PD)
Kjetil Bjørnevik, MD, PhD, Supervisor, Harvard School of Public Health
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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

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Illustration: colourbox.com

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 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 Computational Biology Unit, UiB
Kjell Petersen, Researcher, PhD, Head of the Service Group at the Computational Biology Unit, UiB

SELECTED KEY PUBLICATIONS

1. X Zhang, I Jonassen, RASflow: an RNA-Seq analysis workflow with Snakemake, BMC bioinformatics 21 (1), 1-9
2. Gonzalo S Nido, Fiona Dick, Lilah Toker, Kjell Petersen, Guido Alves, Ole-Bjørn Tysnes, Inge Jonassen, Kristoffer Haugarvoll, Charalampos Tzoulis, Common gene expression signatures in Parkinson's disease are driven by changes in cell composition, Acta neuropathologica communications 8, 1-14
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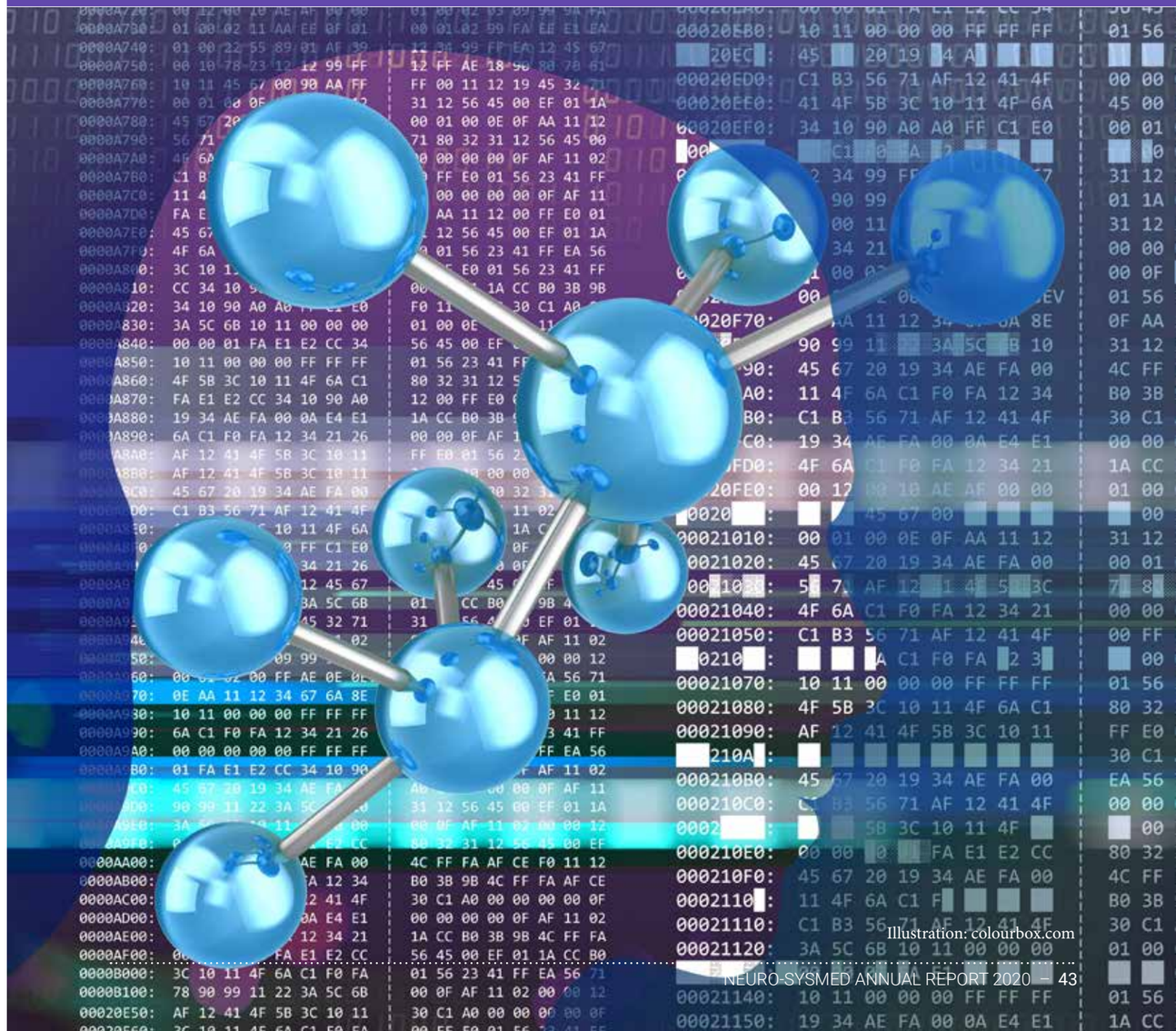

Illustration: colourbox.com

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. In his affiliation to Neuro-SysMed, his project will contribute to a better understanding of philosophical issues in precision medicine in severe chronic neurological diseases. A central issue which will be studied is the concept of suffering. Developing new perspectives on suffering, the group will use this concept as a frame for developing novel interdisciplinary approaches to understanding the characteristics of suffering in patients with severe chronic neurological diseases and how these can be alleviated.

The project will focus on the four diseases studied at Neuro-SysMed: Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). To enable more precise articulations of the philosophical problems to be studied, the aim is to establish and develop collaborations across the various groups and activities at the centre.

The philosophical and methodological issues to be studied are:

1. Issues related to the nature of severe chronic neurological diseases with a special focus on the problems of heterogeneity and complexity in disease stratification and classification.
2. Issues related to the limits and goals of the systems / precision medicine paradigm in severe chronic neurological diseases with a special focus on the intersection between data and algorithmic driven science, clinical research, and clinical practice.
3. Issues related to conceptualization of suffering and the nature and characteristics of suffering in patients with severe chronic neurological diseases, including their co-sufferers, e.g. next of kin.
4. Issues related to broader societal aspects, expectations, and concerns with regard to precision medicine in severe chronic neurological diseases, including the models for studying these broader aspects (e.g., ethical legal and social aspects (ELSA), responsible research and innovation (RRI), technology assessment (TA), and ethics of science and technology)

The group plans to organize interdisciplinary discussion and reflection fora at Neuro-SysMed that will seek integration across the different groups. Here, topical philosophical, societal, and ethical issues in relation to the centre's activities will be discussed. The group will contribute to public understanding and debate about these issues.

The activities of the group in 2020 have been restricted by the fact that the PI has been on two consecutive sabbaticals, the first was a research sabbatical committed to a project at SVT during the spring and the second was a parental leave during most of the fall. However, important progress was made at the conclusion of the year in relation to understanding foundational aspects of the concept of suffering, and a new research project was articulated, i.e. "The philosophy of severe chronic neurological diseases". The PI will continue this work while awaiting the employment of a postdoc to this project. The concept of suffering will serve as a key analytic frame and heuristic entry point of this research project.

During 2020, the group established contact with a recognized international publishing house for writing a book based on this research project. The book proposal will be written in cooperation with the postdoc. Before the March 12th lockdown, Jan Reinert Karlsen contributed to a popular science debate about philosophical aspects of the science of aging organized by The Students' Society of Bergen. After the lockdown, the Interdisciplinary Seminar about Suffering was reorganized as a 'peripathetic seminar' (i.e. walk–think–talk' seminars) on a weekly basis. These ambulating seminars continued throughout 2020.

GROUP MEMBERS

Jan Reinert Karlsen, Cand. Philol., PhD, Associate Professor, Group Leader
Roger Strand, Dr. Scient., Professor, Group Leader of the ELSA-team at the Centre for Cancer Biomarkers (CCBIO)

Affiliated members through the Interdisciplinary Seminar about Suffering
Caroline Benedicte Nitter Engen, MD, PhD, Researcher
Berge Osnes, Cand. Psychol., PhD, Associate Professor
Håvard Øritsland Eggestøl, PhD, Senior advisor, The Norwegian Biotechnology Advisory Board

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2. Karlsen, JR; Solbakk, JH; Holm, S. Ethical Endgames: Broad Consent for Narrow Interests; Open Consent for Closed Minds. Cambridge Quarterly of Healthcare Ethics 2011;20(4) p. 572-583
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Image below: *Landscape with the Fall of Icarus* by Pieter Bruegel the Elder: In the right-low corner, a boy (Icaros) has fallen into the sea. Does the painting show the human position of suffering by depicting how people and the world turn away from the personal disasters of others, or by showing how life must continue despite such disasters?

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 Studies

Multiple sclerosis (MS) is an immune mediated disease of the central nervous system (CNS) characterized by repeated episodes of dysfunction from the CNS. In the microscope and on magnetic resonance imagining (MRI), we can see accumulation of widespread inflammatory lesions with demyelination (damage of the nerve insulation sheets) and axonal damage (damage of the nerves). The disease has huge impact on patients' function and quality of life, as well as financially, both for patients and society.

Head of Research, Kjell-Morten Myhr

Most patients (85-90%) experience repeated episodes of dysfunction 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).

The disease is a result of a complex interplay between genetic and environmental factors. More than two-hundred normal gene-variants (polymorphisms) seem to influence the risk of MS. Some of the most important environmental factors include Epstein-Barr virus infections, low levels of Vitamin D, smoking and overweight.

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 treatments, the aim of treatment has changed dramatically during the last decades, from simply reducing relapse rates and slowing of disability progression to preventing all evidence of new disease activity.

Early initiation of highly effective therapy 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 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 a major challenge in MS. The MS group at Neuro-SysMed aims to explore treatment strategies for progressive MS (PMS) in two studies. SMART-MS is a pilot study to evaluate whether treatment with autologous bone marrow derived mesenchymal stem cells is feasible, safe and can promote neural repair in PMS. In another study, the groups aims to evaluate whether an increase in neuronal NAD levels can improve mitochondrial function and rescue neuronal dysfunction and death seen in PMS.

Tailored symptomatic therapy and rehabilitation to reduce potential disabling symptoms to improve overall functioning are important as well. The group therefore performs a pilot study to explore a new treatment strategy for spasticity in MS.

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

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

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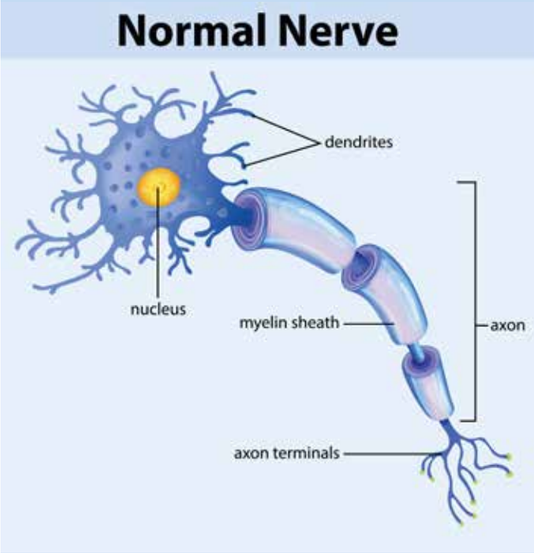
Norwegian collaborators

- **Dr. Linn H. Steffensen**, University Hospital of North Norway, Tromsø
- **Professor Margitta Kampman**, University Hospital of North Norway, Tromsø
- **Professor Karl Bjørnar Alstadhaug**, Nordland Hospital Trust, Bodø
- **Dr. Per Lopen**, Namsos Hospital, Namsos
- **Dr. Kathrine Lian**, St. Olavs University Hospital, Trondheim
- **Dr. Åse Hagen Morsund**, Molde Hospital, Molde
- **Dr. Johannes Willumsen**, Molde Hospital, Molde
- **Dr. Kristin Lif Breivik**, Førde Hospital
- **Dr. Ineke HogenEsch**, Haugesund Hospital
- **Dr. Alok Bhan**, Stavanger University Hospital
- **Professor Elisabeth Farbu**, Stavanger University Hospital
- **Dr. Åslaug Rudjord Lorentzen**, Sørlandet Hospital Trust, Kristiansand
- **Dr. Gro Owren Nygård**, Oslo University Hospital
- **Professor Hanne F Harbo**, Oslo University Hospital
- **Professor Mona Beyer**, Oslo University Hospital
- **Professor Trygve Holmøy**, Akershus University Hospital, Lørenskog



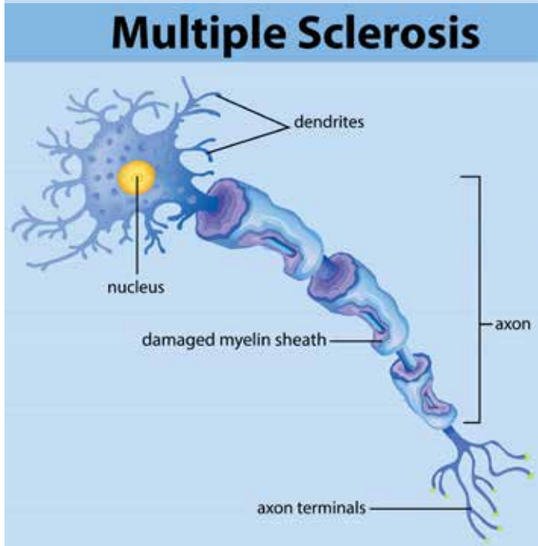


Illustration: colourbox.com

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).

HCT 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 (https://clinicaltrials.gov/ct2/show/NCT03477500). The trial is multidisciplinary and involves a close collaboration between 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).

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 proportion of patients with no evidence of disease activity (NEDA) after 2 years (96 weeks) and further after 5 years (240 weeks).

Until now, 51 patients have been enrolled in the study, and enrollment 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 (UNN), St. Olavs Hospital (St. Olavs), Akershus University Hospital (Ahus), and Haukeland University Hospital (HUH). 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 patients are primarily followed for two years and further for another 3 years in the extension phase, for a total of 5 years.

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

Norwegian webpage: https://helse-bergen.no/ram-ms

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

Trial: B-cell depletion therapy form onset of 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 very recent Norwegian HTA indicate similar treatment effects from rituximab and ocrelizumab – but clearly, state that more data, preferably from a RCT is needed (https://nyemetoder.no/Documents/Rapporter/disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab-hta-rapport-2019.pdf). Rituximab has been used for the treatment of rheumatologically diseases and haematological cancers since 1998, and due to patency expire, costs only a fraction of ocrelizumab. If rituximab 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 timepoint. In this study, the group therefore aims to compare the efficacy and safety of rituximab to ocrelizumab for early treatment in 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 15 patients have been enrolled in the study. More than 10 hospitals plans to participate.

Detailed description is available at https://clinicaltrials.gov/ct2/show/NCT045786394

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

Funding
- KLINBEFORSK
- 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 (SMART-MS).

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

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

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, Akershus University Hospital in Lørenskog, St Olav's Hospital in Trondheim, and the University Hospital of North Norway, Tromsø.

The study has received approval from the Regional Committees for Medical and Health Research Ethics Western Norway, and the Norwegian Medicines Agency. The first patient was planned for inclusion late 2020 or early 2021, but the study is put on hold, due to COVID-19 restrictions for the partner in Ulm, Germany.

Detailed description is available at
https://clinicaltrials.gov/ct2/show/NCT04749667

SUPPORT:

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

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

Trial: The COVID-19 vaccination response in MS patients

PI: Kjell-Morten Myhr

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

Several studies have concluded that vaccination in general is safe in MS. Evidence have shown that 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 (DMTs).

Vaccination response and immunity is another challenge related to vaccination of MS-patients receiving DMTs. These medications have immunomodulatory or immunosuppressive effects and may therefore reduce the immune response to various vaccines. Although limited data are available, the group has previously shown that interferon-beta therapies do not influence the vaccination response, whereas glatiramer acetate, natalizumab, fingolimod, and especially mitoxanthrone 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 the limited data on vaccine response in MS-patients receiving DMTs, and the current challenge of COVID-19 vaccination, the group aims 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 therapy, compared to healthy population controls not receiving immunotherapy.

This is a collaborative project, chaired by Professor Rebecca Cox at the Influenza Centre, University of Bergen. Other participants include Oslo University Hospital and Sørlandet Hospital Trust. PI for the MS-arm of the study is Kjell-Morten Myhr and the project is included in the thesis of PhD Candidate Hilde Marie Torgauten. The Ethical Committee has approved the research protocol and parent recruitment has started. Blood samples are drawn prior to and at specific intervals after vaccination. Preliminary results are expected in Q3/Q4 2021.

SUPPORT:

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

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

Trial: Spasticity therapy in MS

PI: Kjell-Morten Myhr

A pilot study to evaluate a novel treatment strategy for spasms in multiple sclerosis.

The treatment of pain and spasticity in multiple sclerosis (MS) is often challenging due to suboptimal effects, and realistic 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 to increase blood circulation in the lower extremities, called "FlowOx". A pressure chamber is sealed around the patient's legs just below the knee, and this applies negative pressure and atmospheric pressure cycles. The treatment is currently approved and used for selected patients with arterial insufficiency that causes intermittent claudication or diabetes-related leg ulcers. Several MS patients who reported of 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 has reviewed patient reports, that all describe 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, which could possibly modulate signal transmission at the spinal cord level with a consequent 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 aims to perform an explorative pilot study of 10 patients to evaluate whether improvement of symptoms can be measured.

This user-initiated treatment trial aims to include 10 patients for six months with open label therapy with FlowOx. **The main objective** is to evaluate whether patients' reported spasticity is reduced after one months of therapy. Several other secondary and tertiary endpoints are included. 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 is prepared, and the study has received conditional approvals from the Regional Committees for Medical and Health Research Ethics Western Norway, and the Norwegian Medicines Agency. The estimated study start is Q2 2021.

SUPPORT:

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

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

Research: Genetic susceptibility in MS

PI: Stig Wergeland

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

The cause of multiple sclerosis (MS) is unknown, but there is strong evidence for involvement of both genetic and environmental factors. There is a clear heritability in MS, but the genes and variants involved are largely unknown. GWAS studies have provided some insight by identifying genetic markers (> 200) associated with a modified risk for MS. These have generally small effects and mark loci rather that specific genes. Therefore, the genes and biological pathways involved remain largely unmapped. To overcome this limitation, 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 novel genetic risks of MS and possible biomarkers for diagnosis and disease progression, and further exploit the obtained insight of disease mechanisms to identify novel therapeutic targets.

DNA samples from about 2500 MS patients in the Norwegian MS Registry and about 3000 controls, mainly from the HUSK-study (https://husk-en.w.uib.no/) will be analysed by whole exome sequencing and data will be available for analyses from Q4 2020. 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 postponed due to some regulatory evaluations and some practical issues related to transportation of samples to the group's collaborator in the USA. The study is approved by the Regional Committee for Medical and Health Research Ethics Western Norway, and contract for collaboration with HUSK and the exome sequencing providers is finalized. All formal approvals are thus available and the data are available for further analyses in Q3/Q4 2021.

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

Trial: Nicotinamide Riboside in progressive MS

PI: Kjell-Morten Myhr

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 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. We therefore aim to investigate if oral nicotinamide riboside (NR), a NAD precursor, can improve neuronal NAD deficiency and mitochondrial dysfunction in patients with PMS.

More detailed information about mitochondrial dysfunction and nicotinamide riboside (NR) is given in the 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 study has been postponed for at least six months 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 Q2-2021 and estimated study start is Q3/Q4 2021.

SUPPORT:

Participating Centres
- Haukeland University Hospital, Bergen
- Stavanger University Hospital, Stavanger
- Haugesund Hospital, Haugesund
- Førde Hospital, Førde
- Other 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
- Participating hospitals
- University of Bergen

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

Based on these observations, the 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 biomarker (neurofilament, B-cell counts) evaluations.

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

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

The study is postponed for about six months 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 Q2-2021 and estimated study start is Q3/Q4 2021.

SUPPORT:

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

Funding
- The Research Council of Norway, Neuro-SysMed
- 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 (1-4), and during 2020, four new studies have been added (5-8).

1. Tysabri observation Trial in RRMS, Phase IV, 2007. Long-term safety and efficacy observational study of natalizumab (Biogen) (KM Myhr national coordinator) https://clinicaltrials.gov/ct2/show/NCT00493298

2. Ocrelizumab vs Interferon beta-1a sc. trice weekly in RRMS, the OPERA trial Phase III, 2011. Open label extension (Roche) (KM Myhr national coordinator) https://clinicaltrials.gov/ct2/show/NCT01412333

3. Orelizumab (open label) in RRMS – safety and efficacy extension study, the LIBERTO study Phase IV, 2018 (Roche) (KM Myhr national coordinator) https://clinicaltrials.gov/ct2/show/NCT03599245

4. 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) https://clinicaltrials.gov/ct2/show/NCT03961204

5. Primary Progressive Multiple Sclerosis (PPMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168) (PERSEUS) (Sanofi) (Ø Torkildsen national coordinator) https://clinicaltrials.gov/ct2/show/NCT04458051

6. Nonrelapsing Secondary Progressive Multiple Sclerosis (NRSPMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168) (HERCULES) (Sanofi) (Ø Torkildsen national coordinator) https://clinicaltrials.gov/ct2/show/NCT04411641

7. Study of Evobrutinib in Participants With Relapsing Multiple Sclerosis (RMS) (evolutionRMS2) (Merck) (Sanofi) (Ø Torkildsen national coordinator) https://clinicaltrials.gov/ct2/show/NCT04338061

8. An Open-label Study Evaluating Ofatumumab Treatment Effectiveness and PROs in Subjects With RMS Transitioning From Dimethyl Fumarate or Fingolimod to Ofatumumab (ARTIOS) (Novartis) (KM Myhr PI at Haukeland University Hospital) https://clinicaltrials.gov/ct2/show/NCT04353492

Illustration: colourbox.com

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 for PD 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 the greatest challenges facing science and society today, and a top priority for healthcare and biomedical research.

Ongoing PD research at Neuro-SysMed

PD research at Neuro-SysMed has three primary aims:

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

In addition to the described trials and research on the following pages, Neuro-SysMed also contributes on a industry sponsored trial in PD:

- REASON: a phase 1 single- and multiple-ascending-dose study to assess the safety, tolerability, and pharmacokinetics of BIIB094 administered intrathecally to adults with Parkinson's disease. Sponsor: Biogen.

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

- 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.
- Professor Leonidas Stefanis, University of Athens, Greece.
- Professor Gabor G. Kovacs, University of Toronto, Canada.
- Professor Ellen Gelpi-Mantius, Medical University of Vienna, Austria.

In Norway

- Professor Mathias Toft, Oslo University and Ullevål University Hospital, Oslo.
- Professor Christofer Lundqvist, Akershus University Hospital (AHUS), Oslo.
- Dr. Kari Anne Bjørnaråa, Drammen Hospital (DH), Drammen.
- Professor Jan Aasly, St. Olavs University Hospital (St. Olavs), Trondheim.
- Dr. Karen Herlofson, private practice and Arendal Hospital (AH), Arendal.
- Dr. Stig Hegrestad, Førde Central Hospital (FCH), Førde.

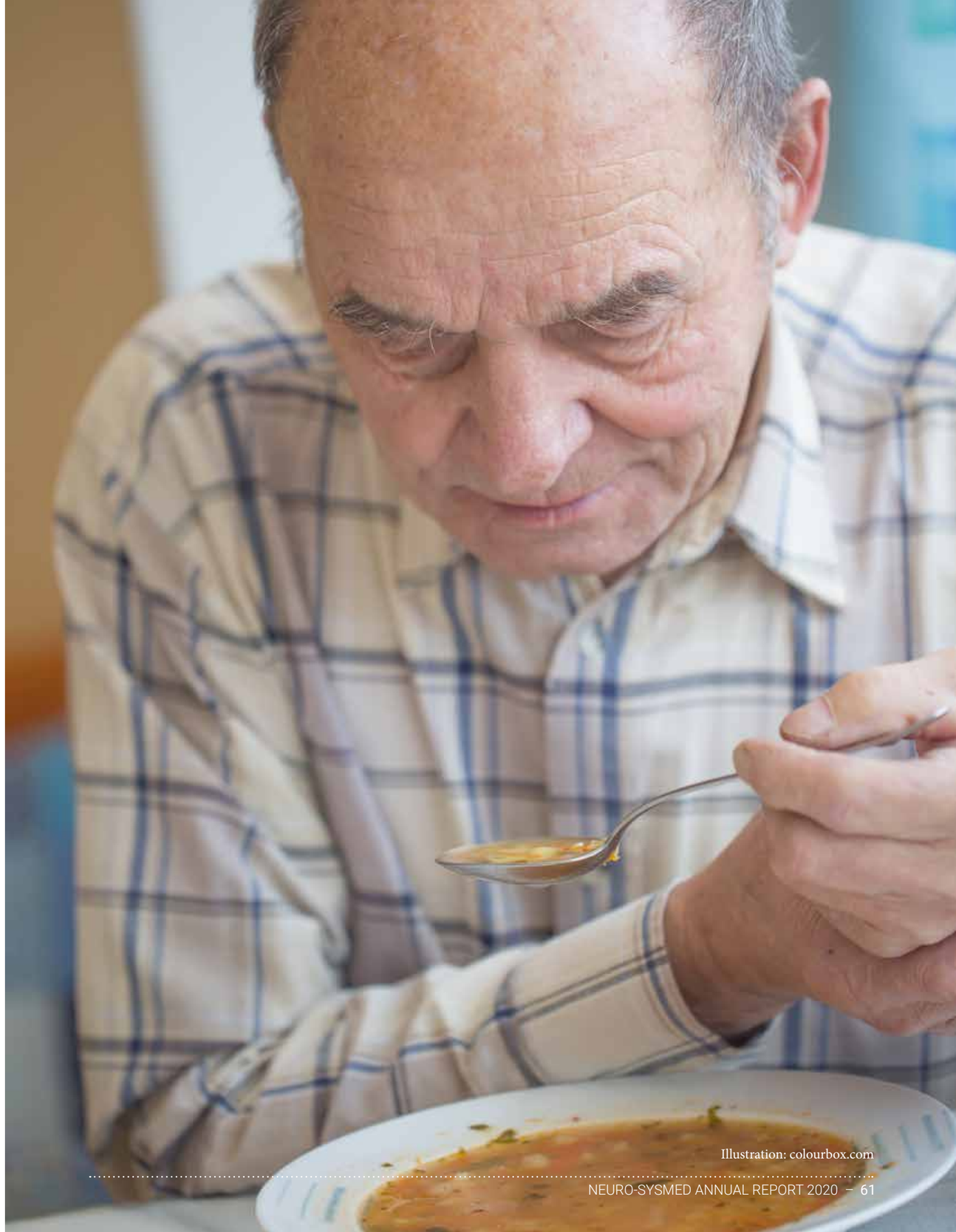


Illustration: colourbox.com

Trial: NAD-PARK

PI: Charalampos Tzoulis

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

Background: Mitochondrial dysfunction plays a key role in the pathogenesis of PD. The Tzoulis group and others have shown that impaired mitochondrial DNA homeostasis and defective mitochondrial respiration, particularly affecting complex I, occur in neurons of individuals with PD. Impaired mitochondrial respiration is predicted to have profound effects on neuronal metabolism and survival, including ATP deficiency and a decline in the NAD+/NADH ratio. Decreased NAD+ levels would further compromise neuronal function and survival, due to a combination metabolic compromise, impaired DNA repair, altered signalling and dysregulation of histone acetylation leading to aberrant control of gene expression. While NAD+ levels cannot be reliably measured in postmortem brain samples, breakthrough research by our group showed that the PD brain is, indeed, characterized by genome-wide increase in histone acetylation, which is likely to be due to decreased activity of the NAD-dependent deacetylase enzymes known as sirtuins.

Taken together, these findings nominate NAD supplementation as a potential neuroprotective therapy for PD. In humans, NAD is either produced *de novo* from tryptophan or via salvage pathways from three NAD precursor compounds: nicotinamide, nicotinic acid and nicotinamide riboside (NR). NR is the only known precursor that both effectively boosts NAD synthesis, increases sirtuin activity and is non-toxic in animals and humans. Thus, NR holds potential as NAD-supplementation therapy in PD and other neurodegenerative disorders.

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: target engagement as measured by cerebral NAD-levels (31P-MRS) and glucose utilization (FDG-PET).

Status: The NAD-PARK trial is completed. 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. The study is completed, and the report is being drafted, to be submitted for publication in April 2021. Key results are summarized below:

1. NR har excellent compliance and tolerability in PD and shows no signs of toxicity or adverse side effects.
2. NR upregulates mitochondrial respiration in patient blood and muscle.
3. NR penetrates the brain and leads to a significant increase in cerebral NAD.
4. NR impacts cerebral glucose metabolism ameliorating striatal hypermetabolism.
5. NR is associated with a small but significant reduction in UPDRS.

The current conclusion of the study is that NR is a safe and well-tolerated therapy in PD and leads to substantial NAD supplementation in the brain, the target organ of the disease. Moreover, these results are highly encouraging for the larger NO-PARK study (see next section).

SUPPORT:

Participating Centres
- Haukeland University Hospital, 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 be 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 seven centres across all four health regions of Norway: 1) Haukeland University Hospital (HUH, leading site), Bergen; 2) Akershus University Hospital (AHUS), Akershus, Oslo; 3) Ullevål University Hospital (UUH), Oslo; 4) Rikshospitalet (RH), Oslo; 5) Drammen Hospital (DH), Drammen; St. Olavs University Hospital (St. Olavs), Trondheim; 6) Dr Karen Herlofson Practice and Arendal Hospital (AH), Arendal; 7) Førde Central Hospital (FCH), Førde. 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 of oral NR delays disease progression in PD measured by MDS-UPDRS. Secondary & tertiary endpoints include to determine whether high dose of 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. In 2020, four out seven centres were initiated and recruitment approaches 100 patients.

Detailed description is available at
https://clinicaltrials.gov/ct2/show/NCT03568968

Haukeland University Hospital website:
https://helse-bergen.no/kliniske-studier/parkinson-sykdom-behandling-med-nikotinamid-nopark-studien

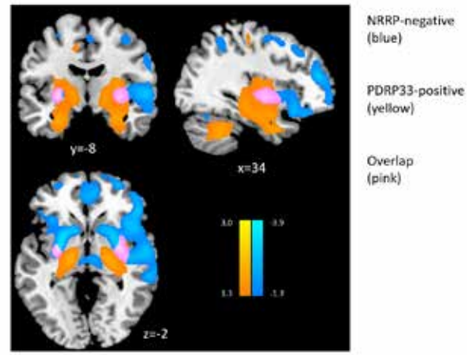


Figure: Overlapped regions in posterior putamen/globus pallidus

SUPPORT:

Participating Centres/Partners
- Haukeland University Hospital, Bergen
- Akershus University Hospital, Oslo
- Ullevål University Hospital, Oslo
- Rikshospitalet, Oslo
- Drammen Hospital, Drammen
- St Olav's University Hospital, Trondheim
- Dr. Karen Herlofson and Arendal Hospital, Arendal
- Førde Central Hospital, Førde

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

Research: The ParkOme – a multidimensional molecular atlas of PD

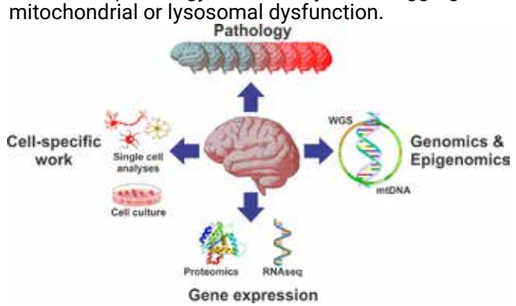
PI: Charalampos Tzoulis

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 about 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 reflect human disease. Thus, the most accurate source of information 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, 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 the 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 groups is interrogating the ParkOme using a combination of powerful supervised and unsupervised computational analyses (including AI). Molecular signatures defining PD and its subclasses will be identified and translated into: 1) Disease models recapitulating subclasses of human disease, 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 Neuro-SysMed. 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: So far, the group has analyzed the genome, DNA-methylome, histone-acetylome, transcriptome, and proteome for ~100 brain samples. In addition, they mapped the transcriptome in a total of ~1,000 brain samples. Single-cell transcriptomics, using the dedicated 10X-Chromium platform, are also well-underway. The methodology has been established and the data from the first pilot experiments in blood cells and nuclei from brain tissue are currently being analyzed. The group is also experimenting with the potential of long-read sequencing to map "obscure" areas of the genome, assess DNA-methylation natively, and evaluate RNA-splicing. The first samples have been analyzed and the bioinformatics team is currently establishing the analyses pipelines.

Analyses of the ParkOme data during 2020 generated novel insights into the genetics and gene-expression profile of PD – described in several original publications. Moreover, in the first histone-acetylome-wide study in PD, the group showed that the brain of individuals with PD is characterized by a profound, genome-wide dysregulation of H3K27 acetylation and decoupling from transcription.

SUPPORT:

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

Research: Cohort study STRAT-PARK

PIs: Charalampos Tzoulis and Mandar Jog

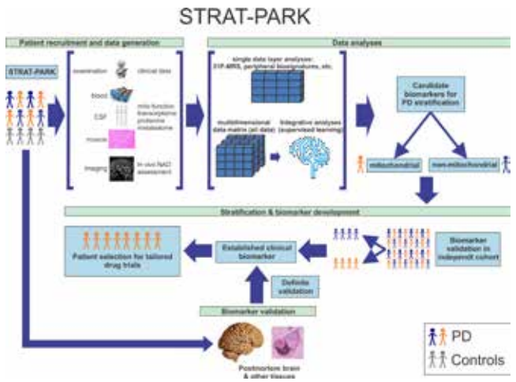
A population-based cohort study from three centres across Norway and Canada.

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: The group is establishing a population-based cohort from three centres across Norway and Canada. They 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, the group will apply state-of-the-art computational analyses to perform multidimensional integration of the database and identify biomarkers for molecular stratification of PD. 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 (HUH) 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. As part of the clinical



characterization, the group will implement novel methods of objective motor assessment using body suits with integrated movement sensors, implemented in collaboration with co-PI **Professor Mandar Jog**, who is a leading world expert in motion biomechanics for PD and related movement disorders.

Status: Participant recruitment started in Bergen in 2020 and a total of 15 patients and controls have been included. Recruitment is now starting in Trondheim and London during April 2021.

SUPPORT:

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

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

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. Neurodegenerative dementias have profound impact on both patients and families. In addition, they present a formidable challenge to society as a whole, especially as neurodegenerative dementias become more frequent in the aging population.

Head of Research, Kristoffer Haugarvoll

More than 100,000 individuals are estimated to suffer from dementia in Norway, and 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). In the majority of cases, however, a mixture of pathologies can be identified in the very same brain. This is indicating that our current diagnostic scheme, that bases the diagnosis on clinical syndromes, is too simplistic and fails to reflect the complexity that is occurring in the brain.

Key knowledge gaps, nationally and internationally, are our limited understanding of the causes and molecular pathogenesis of dementia. These mechanisms need to be elucidated in order to identify novel therapeutic targets that can prevent disease progression. The contribution of several molecular etiologies is a further issue when considering the molecular etiology of dementia. 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-morten 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 (STRAT-COG). In STRAT-COG, the group aims at identifying predictors for prognosis and to identify subgroups of dementia patients that may benefit form personalized treatments in the future. They also participate in trials of novel dementia treatments (ANeeD).

National and international collaborators

- Professor Dag Årsland, King's College London, UK and Stavanger University Hospital, Norway
- Professor Tormod Fladby, Dept. of Neurology, Akershus University Hospital and Institute of Clinical Medicine, University of Oslo, 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

Cohort Study: STRAT-COG Biomarkers for Improved Treatment of Dementia

PI: Kristoffer Haugarvoll

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

Neurodegenerative progressive dementias such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are leading causes of disability and mortality. The prevalence of Alzheimer's disease is about one percent at age 65 and increases dramatically to between 20-50% in those older than 85 years. Dementia with Lewy bodies is the second most common type of progressive dementia in older individuals after Alzheimer's disease. Pathological verification remains the gold standard for diagnosing neurodegenerative dementias. The pathological hallmarks of Alzheimer's disease are extracellular accumulation of amloid β (Aβ) peptide in the brain ("senile plaque", SP) and by intraneuronal accumulation of hyperphosphorylated tau protein in neurofibrillary tangles (NFT). This is accompanied by synaptic and neuronal losses. However, it is becoming increasingly clear that most dementia patients have an overlap between different molecular pathologies.

Improved diagnosis and treatment for neuro-degenerative dementias is pivotal. To achieve this, it is important to base the diagnosis of dementia on underlying biological mechanisms rather than simplistic clinical syndromes. This will also enable us to study the effects of overlapping pathologies in individual patients.

Clinical studies on cognitive decline and dementia are located at Haraldsplass Deaconess Hospital. Postdocs Ragnhild Eide Skogseth, MD, PhD and Lasse Melvær Giil, MD, PhD are instrumental in these studies.

The objectives of the study are to establish a comprehensive biomarker panel for dementia by combining existing biomarkes for Alzheimer's pathology with biomarkers for neuronal loss and α-synuclein pathology. This will enable us to elucidate how the mixture of different molecular pathologies affects prognosis and to stratify individual patients suffering from dementia based on underlying biological processes. STRAT-COG will include a brain donation program.

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

Photo: Joergen True / C.F. Moller Architects

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 central nervous system (CNS) result in muscle weakness, atrophy, paralysis and ultimately death within 2-3 years from the onset of symptoms.

Head of Research, Ole-Bjørn Tysnes

Initial presentation of ALS varies between affected individuals, and typically presents as spinal-onset disease (muscle weakness of the limbs), or bulbar-onset disease (difficulty with speech and swallowing).

Sporadic ALS (sALS) accounts for 90% of cases and has no clear 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 (Riluzole package insert 2016), prolonging survival by 2-3 months (Miller et al. 2012). Edaravone, approved in the US in 2017, is administered in courses intravenously and shows efficacy in only a small subset of patients with ALS.

Recent research by the Neuro-SysMed ALS group and others indicates that boosting the activity of the histone deacetylate enzymes known as sirtuins, via a combination of nicotinamide riboside (NR) and pterostilbene, has neuroprotective effects in ALS and may delay clinical disease progression.

Based on these preliminary findings, 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, they are now running a phase-II, multi-center, double-blinded randomized clinical trial of oral NR and pterostilbene in early ALS (NO-ALS study). Based on the group's power estimations, a total of 180 patients will be recruited from entire Norway. The study was started in October 2020. By end of February 2021, 20 patients are included in the study. All study centers will be active by end of March 2021.

In addition to the NO-ALS study, the ALS study group in Neuro-SysMed is planning 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 is also currently performing a questionnaire study to record the use of off-label therapies, as well as supplement use of vitamins and other compounds.

RESEARCH GROUP AND NATIONAL COLLABORATORS

Ole-Bjørn Tysnes, PhD, M.D, Professor, Head of the Study
Marit Renså, Study Nurse
Tiina Rekand, PhD, Professor
Tale Litlere Bjerknes, Study Physician, PhD
Tina Taule, PhD, Researcher

Collaborators:
Trygve Holmøy, PhD, MD, Professor
Ola Nakken, Study Physician, PhD
Hilde Nilsen, PhD, Professor
Evandro Fei Fang, PhD, Researcher

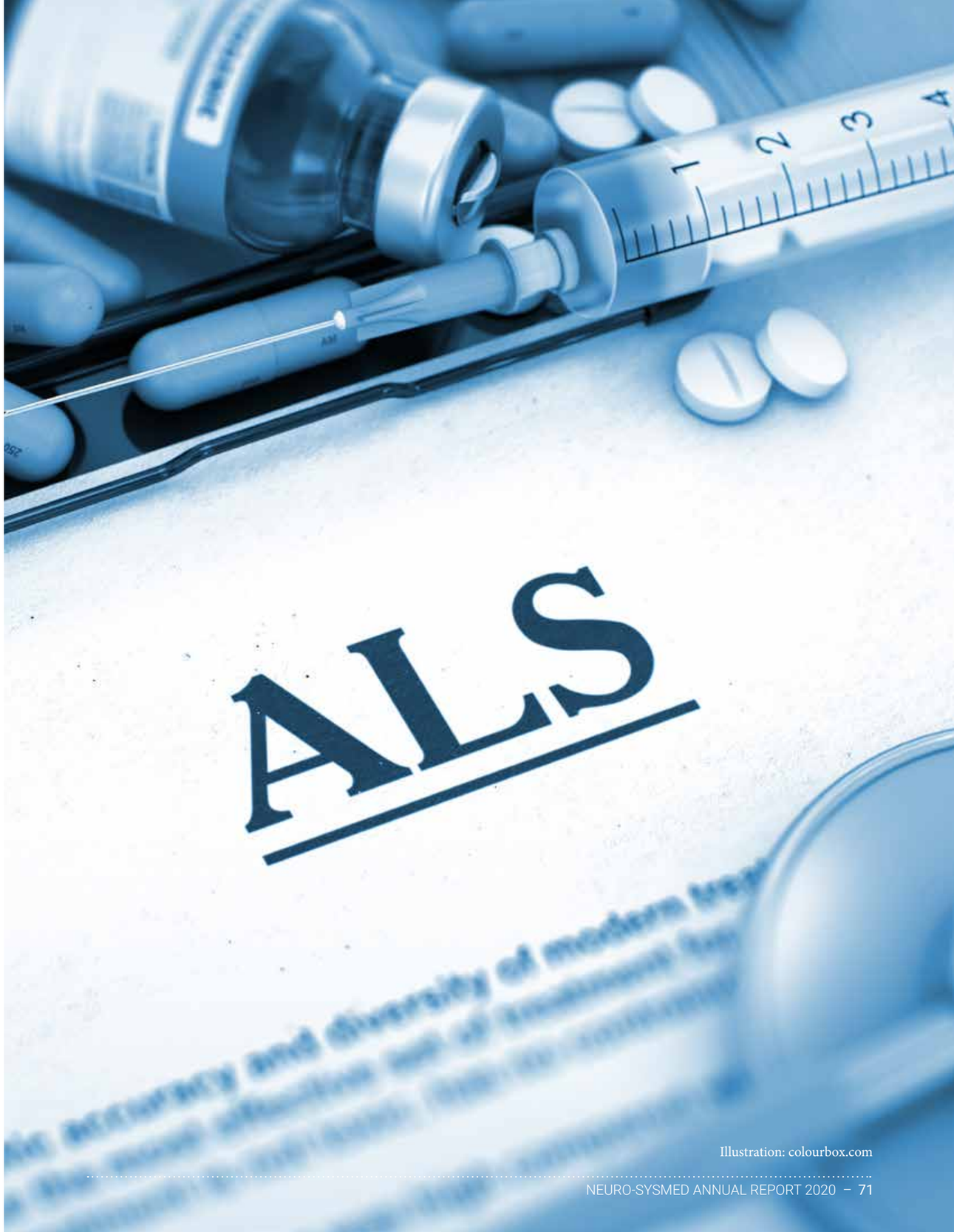


Illustration: colourbox.com

Trial: NO-ALS

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 (NO-ALS study).

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

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

Patients have been included since October 2020. By March 21, 24 patients are included. The study is expected to close by the end of 2022.

SUPPORT:

Participating Centres
- Haukeland University Hospital, Bergen
- Akershus University Hospital, Lørenskog
- Oslo University Hospital, Oslo
- Drammen Hospital, Vestre Viken
- St Olav's University Hospital, Trondheim
- Stavanger University Hospital, Stavanger
- University Hospital of North Norway, Tromsø
- Førde 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

This trial was focus of a TV2 news story in October 2020:

Survey on off-label drug use

PI: Ole-Bjørn Tysnes

Questionnaire-study on the use of off-label drugs and nutrition supplements among patients with amyotrophic lateral sclerosis in Norway.


Illustration: colourbox.com

Riluzole (Rilutek®) is the only approved drug in the treatment of amyotrophic lateral sclerosis (ALS) in Norway. The United States and Japan have also approved Edaravone (Radicava®) as a drug in the treatment of ALS. In recent years, several other existing drugs have been suggested as possible treatments against ALS. Among them is the anti-diabetic drug Metformin, which has shown promising results against some forms of ALS in animal models.

We have little knowledge on whether patients in Norway use other drugs than Rilutek® against ALS, so called "off-label use". In this questionnaire survey, the group aims to shed light on the use of off-label drugs and supplements against ALS among Norwegian ALS-patients. The patients are asked to fill out an anonymous survey on whether they are using off-label drugs and supplements against ALS. The questionnaire also include standardized questions concerning respondent's quality of life.

The study is conducted by medical student **Gard Aasmund Skulstad Johanson** with professor **Ole-Bjørn Tysnes** and Dr. **Tale Litleré Bjerknes** as supervisors.

PARTNERS:

- Haukeland University Hospital, Bergen
- The University of Bergen

Research: 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. The screening performed during 2020 has identified 31 specific drugs that are reducing the risk of developing PD after controlling for multiple testing. They will during spring 2021 finish the sub-studies estimating the dose-response effect of these drugs, the variation of effect according to number of years prior onset to PD and whether these findings are caused by PD patients having a condition prior to disease onset (prodromal phase) that somehow reduces the chances of being prescribed these drugs. Before initiating validation studies using experimental models at a molecular level, the group will perform expansion studies estimating the effect of drugs that are targeting the same receptors or proteins.

Any of the drugs that have been identified and 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

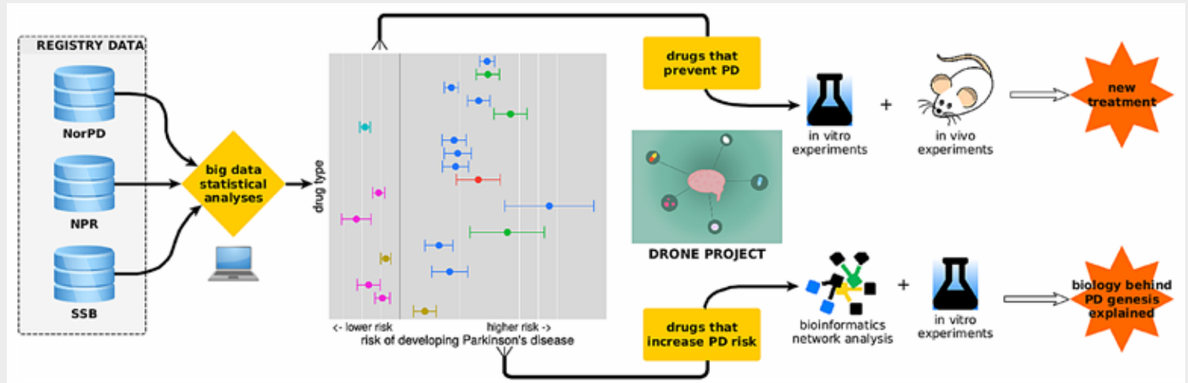


Illustration: colourbox.com

Neuro-SysMed in the News

News stories featuring Neuro-Sysmed in 2020 in the media.

Apr. 30, 2020, it-praten, "Moderne skyteknologi : – Vi er med på noe viktig", on the use of IT platforms in Neuro-SysMed.

Aug. 27, 2020, Dagens Medisin, "Slår alarm: – MS-behandlingen i Norge er ikke «faglig forsvarlig»", interview with Lars Bø and Kjell-Morten Myhr regarding national decisions on MS drug approvals.

Sept. 12, 2020, Dagens Medisin, "Får viktig finansiering til MS-studie", interview with Kjell-Morten Myhr, regarding received financing of the OVERLORD study.

Sept. 19, 2020, iTromsø, "Bare forskning kan stoppe demens!", referral to Neuro-SysMed and dementia research. The same article is also in other media: Sunnmøringen, Sandnesposten, Dagens Medisin and Tønsbergs blad.


Dagens Medisin Nyheter Debatt Pharma DM Arena DMTV Om oss

Blogger

Anette Storsteins blogg Publisert 2020-09-23

Hvorfor trenger vi mer hjerneforskning?

Del:

Det er mange gode grunner til at vi trenger mer hjerneforskning. En av tre i Norge vil få sykdom eller skade i hjernen og nervesystemet gjennom livet. Hjernesykdom blir derfor den neste store helseutfordringen i Norge. Demens er en av våre hyppigste dødsårsaker. Ca 100 000 nordmenn er rammet av denne sykdommen, og forekomsten vil dobles frem mot 2040. Psykiske lidelser er en hovedårsak til ung uførhet. Hodepine er alene grunnen til to millioner fraværsdager fra skole og jobb hvert år. Vi kjenner fortsatt ikke årsaken til den fryktede sykdommen ALS, og hjernekreft, en svært alvorlig kreftform, har ikke nytt godt av kreftbehandlingens fremskritt. Både i Europa og resten av verden ser vi det samme: hjernesykdommene er nå en ledende årsak til funksjonstap og død.

ANETTE STORSTEIN

Anette Storstein er spesialist i nevrologi og overlege ved Nevrologisk avdeling, Haukeland universitetssykehus, med hovedfokus på kroniske lidelser i nervesystemet. Hun har lang erfaring fra arbeid som tillitsvalgt i Legeforeningen og i Norsk Nevrologisk forening og sitter som styremedlem i Hjernerådet.

Sept. 23, 2020, Dagens Medisin, "Hvorfor trenger vi mer hjerneforskning?", opinion piece on the need for brain research and the importance of Neuro-SysMed, from Senior Consultant Anette Storstein.

Oct. 19, 2020, TV2, "Her tennes håpet for ALS-syke Vivian (40)", patient case and interview with Ole-Bjørn Tysnes.


2 Nyheter Sporten Sumo Meny

Skal teste ALS-medisin på firebarnsmor Vivian Brosvik

Her tennes håpet for ALS-syke Vivian (40)

For fem år siden fikk firebarnsmoren Vivian Brosvik dødsdommen. Nå blir hun den første i Norge som deltar i en studie der man tester ut en ny medisin mot ALS.

Oct. 22, 2020, Dagens Medisin, "Nye MS-pasienter skal få rituksimab eller okrelizumab i Bergen", interview with Kjell-Morten Myhr and Øivind Torkildsen regarding startup of the OVERLORD study.


Dagens Medisin Nyheter Debatt Pharma DM Arena DMTV Om oss

HAR VENTET: Spesialist Øystein Rasch Omdal Haugstad, leder Kjell-Morten Myhr ved forskningssenteret Neuro-SysMed og professor Øivind Torkildsen ved Universitetet i Bergen har vært på at studien som vanntilsiger rituksimab med okrelizumab, skal komme i gang. Foto: Marit Hommedal

Foto: Marit Hommedal

Nye MS-pasienter skal få rituksimab eller okrelizumab i Bergen

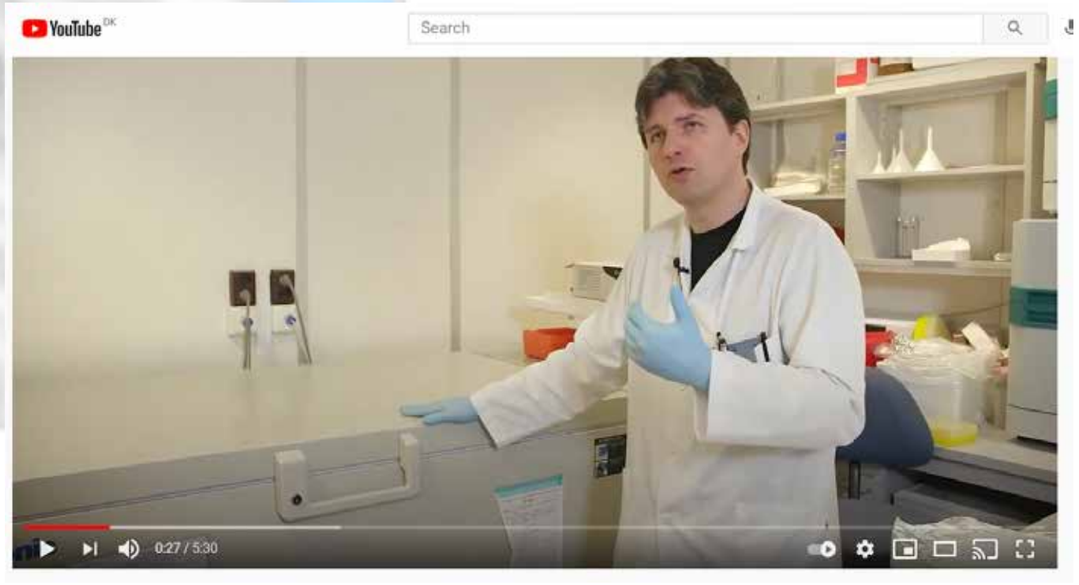
Haukeland universitetssjukehus starter nå en studie som skal gi pasienter med multippel sklerose (MS) okrelizumab eller rituksimab

Lasse Mjør

Publisert: 2020-10-22 — 08:24

Social media example

Sept. 17, 2020, YouTube, shared in other social media, "På labben med Charalampos "Haris" Tzoulis", entry for the digital Norwegian Research Fair. Haris explains Neuro-SysMed's work with frozen brains.


YouTube DK Search

0:27 / 5:30

Publication list 2020

Relevant publications from the Neuro-SysMed PIs in 2020.

1. Bringeland GH, Blaser N, Myhr KM, Vedeler CA, Gavasso S. Wearing-off at the end of natalizumab dosing intervals is associated with low receptor occupancy. Neurol Neuroimmunol Neuroinflamm. 2020;7:e678. PMID: 32019768

2. Bringeland GH, Myhr KM, Vedeler CA, Gavasso S. Wearing-off at the end of natalizumab dosing interval and risk of MS disease activity: A prospective 1-year follow-up study. J Neurol Sci 2020;415:116880. PMID: 32413799

3. Butzkueven H, Kappos L, Wiendl H, Trojano M, Spelman T, Chang I, Kasliwal R, Jaitly S, Campbell N, Ho PR, Licata S; Tysabri Observational Program (TOP) Investigators. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). J Neurol Neurosurg Psychiatry 2020;91:660-668. PMID: 32234967.

4. Cortese M, Munger KL, Martínez-Lapiscina EH, Barro C, Edan G, Freedman MS, Hartung HP, Montalbán X, Foley FW, Penner IK, Hemmer B, Fox EJ, Schippling S, Wicklein EM, Kappos L, Kuhle J, Ascherio A; BENEFIT Study Group. Vitamin D, smoking, EBV, and long-term cognitive performance in MS: 11-year follow-up of BENEFIT. Neurology 2020;94:e1950-e1960. PMID: 32300060

5. De Vries MC, Brown DA, Allen ME, Bindoff L, Gorman GS, Karaa A, Keshavan N, Lamperti C, McFarland R, Ng YS, O'Callaghan M, Pitceathly RDS, Rahman S, Russel FGM, Varhaug KN, Schirris TJJ, Mancuso M. Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus. Inherit Metab Dis 2020;43:800-818. PMID: 32030781

6. Dick F, Nido GS, Alves GW, Tysnes OB, Nilsen GH, Dölle C, Tzoulis C. Differential transcript usage in the Parkinson's disease brain. PLoS Genet 2020;16:e1009182. PMID: 33137089

7. Erga AH, Alves G, Tysnes OB, Pedersen KF. Evolution of impulsive-compulsive behaviors and cognition in Parkinson's disease. J Neurol 2020;267:259-266. PMID: 31628533

8. Erga AH, Alves G, Tysnes OB, Pedersen KF. Impulsive and compulsive behaviors in Parkinson's disease: Impact on quality of and satisfaction with life, and caregiver burden. Parkinsonism Relat Disord 2020;78:27-30. PMID: 32679528

9. Fløtnes IH, Ricken G, Klotz S, Lang A, Ströbel T, Dölle C, Kovacs GG, Tzoulis C. Mitochondrial respiratory chain deficiency correlates with the severity of neuropathology in sporadic Creutzfeldt-Jakob disease. Acta Neuropathol Commun 2020;8:50. PMID: 32299489

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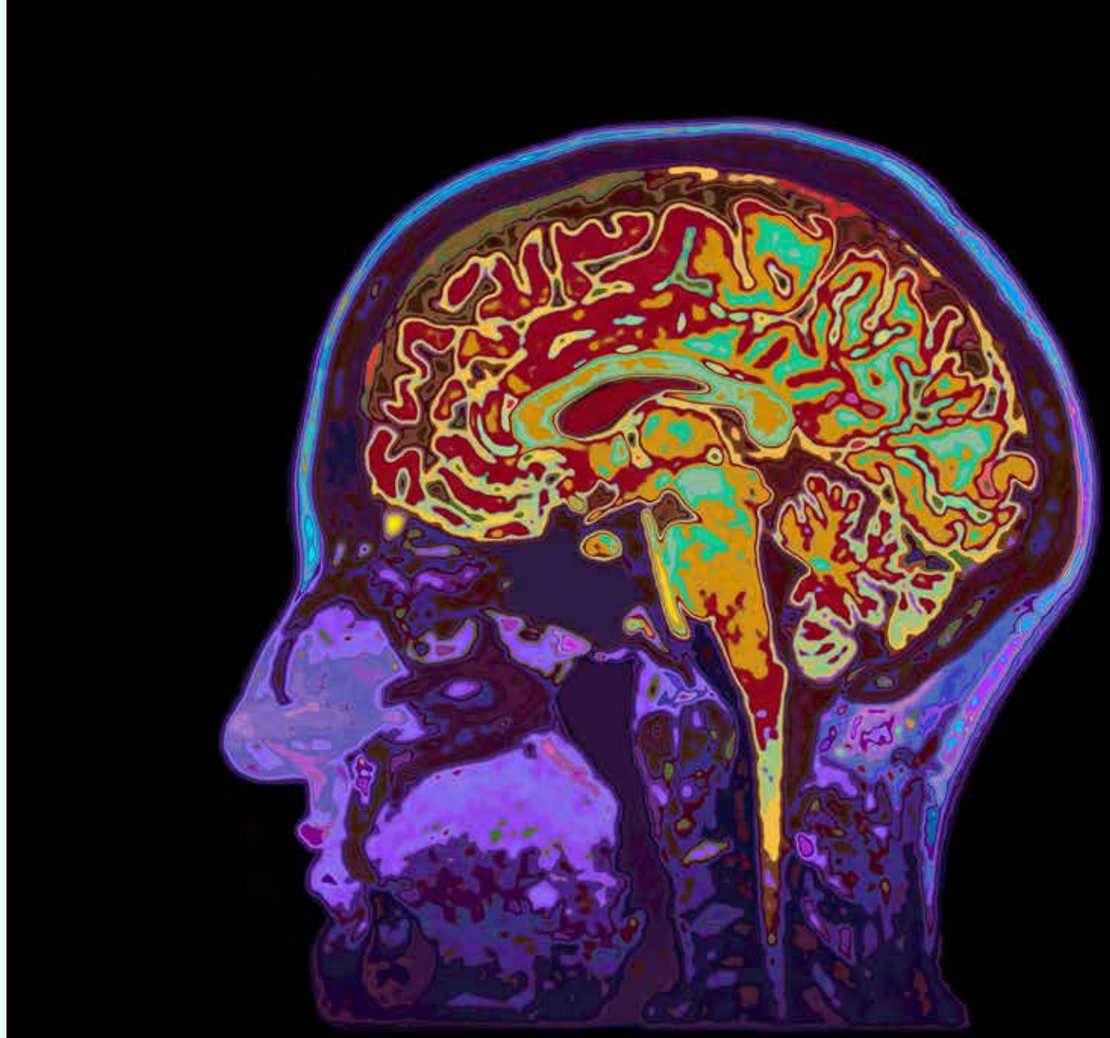

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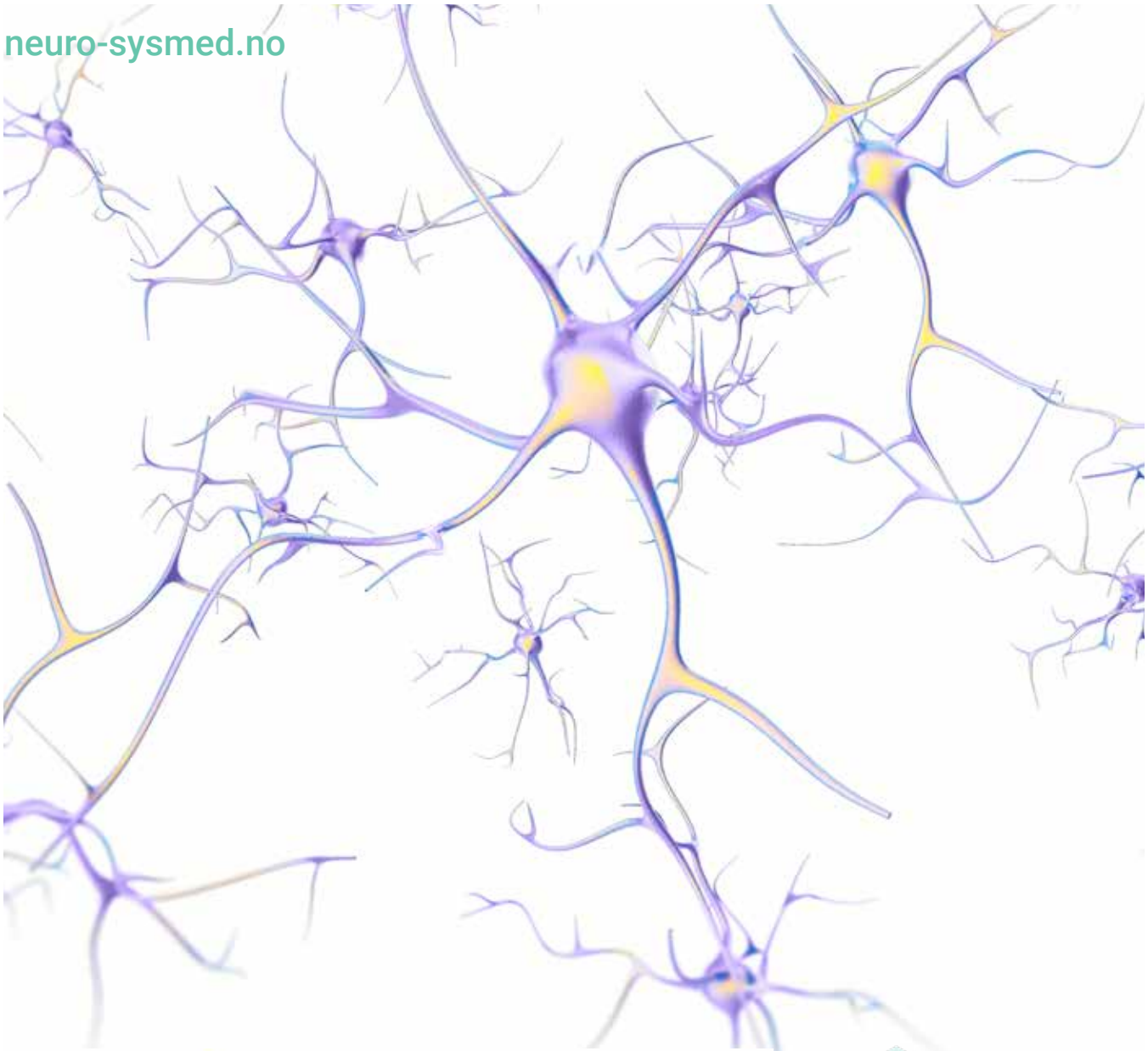

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