RC2NB
ANNUAL REPORT
2022
About RC2NB

The Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB) is based on a non-profit foundation. It was founded in 2019 by the University Hospital Basel with the participation of the University of Basel to continue and enhance the long-standing commitment and internationally renowned, clinically oriented research for patients with multiple sclerosis and other neuroimmunological diseases. Within and across four Workstreams RC2NB coordinates and supports several competitively funded research groups, dedicated to improving the clinical, imaging, biochemical, molecular, and cellular characterization of the disease process and understanding the benefits and side effects of newly developed therapies. Switzerland’s largest MS center, the established high-quality patient cohorts coordinated from here, the local, national, and international networks as well as academic partner institutions and collaborating industry provide optimal conditions for RC2NB’s mission. With its interdisciplinary team and its alignment of basic research, clinical research, and patient care, RC2NB aims at the rapid translation of research results into advances of patient treatment and diagnosis. Main activities of RC2NB include the development of innovative digital biomarkers, the establishment of structures and expertise for managing and processing large volumes of highly complex data, and the application of cutting-edge analytic approaches, including artificial intelligence.

Vision

RC2NB’s mission is to strengthen internationally recognized expertise and innovative research projects to improve the clinical, imaging, biochemical, molecular, and cellular characterization of the disease process in Multiple Sclerosis and other neuroimmunological diseases and understanding the benefits and side effects of newly developed and future therapies. RC2NB coordinates and complements these projects with the development and validation of digital biomarkers and their integration with innovative methods of information processing and artificial intelligence. Improving the life of people with MS and neuroimmunological diseases through the development of innovative tools that comprehensively characterize the disease process, facilitate the development and implementation of better treatments and enable personalized disease management.

Mission

Improving the life of people with MS and neuroimmunological diseases through the development and integration of innovative tools that comprehensively characterize the disease process, facilitate the development and implementation of better treatments and enable personalized disease management.
1 | Introduction

2022 has been a year of further important transformation and growth for RC2NB.

Our approach towards a multidimensional, holistic, and deep in-vivo characterization of Multiple Sclerosis (MS), this exemplary complex autoimmune and neurodegenerative disease of the central nervous system, gains momentum and attractiveness for local and international collaborators and sponsors.

This attraction is based on the creativity and still increasing productivity of the research groups contributing to the RC2NB workstreams, which is accelerated by the experience of working together as part of an excellent collaborative research cluster providing so many opportunities for synergies and setting the ground for strong internal and local collaborations.

Selected 2022 achievements of the research groups are highlighted in part 3 of this report and reflected in the 135 peer reviewed original papers, editorials and reviews, authored or co-authored by RC2NB members. To increase your appetite for further reading of our report (and the respective publications) let me very briefly mention a few of these highlights:

In workstream 1, the development of dreaMS is continuing according to our plans. Whilst Validation Study 1 continuously recruits participants out of the Swiss MS Cohort Study, soon also from other Swiss centers, the preparatory work for the international Validation Study 2 had a jump start with a most successful meeting with selected representatives of leading MS centers at ECTRIMS.

In workstream 2, Jens Kuhle and his group continued establishing the value of neurofilament light as a specific marker of neuroaxonal damage in general and more and more at the individual level. The group expanded their focus and is now providing evidence that another novel biomarker, sGFAP, may allow to better define the central role of glial activation in slow progression as opposed to acute inflammatory damage in MS. Cristina Granziola’s group was able to show the value of advanced quantitative MRI not only in depicting myelin damage but also in differentiating efficient from failing myelin repair.

In workstream 3, Tobias Derfuss’ group used a machine-learning-based computational analytical pipeline for cells obtained from pwMS treated with the oral medication dimethyl fumarate (DMF) to make important steps towards closer characterizing immune cell subpopulations that have specific roles in the induction and regulation of autoimmunity responses. Further, in a joint effort with Anne-Katrin Pröbstel they identified distinct microbiota as predictors for the development of lymphopenia in patients under DMF. In the course of their highly relevant effort trying to decipher the role of IgA producing cells along the gut-brain axis and regulation of autoimmunity in MS, the newly established experimental neuroimmunology group of Anne-Katrin Pröbstel detected a MOG specific IgA-antibody in patients seronegative for anti-MOG and anti-NMOSD IgG, that seems to be associated with a characteristic disease pattern.

The path to better and more patient-oriented measures of disease evolution that are accepted by the scientific community and health authorities is complicated by a scientific dilemma, which repeatedly emerged in our discussions with EMA,

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FDA, and other stakeholders as a “contradictio in adiecto”: We are requested to provide evidence for a high correlation with established measures, well knowing that this correlation must be getting worse, the better we outperform them. There is no way out of this dilemma than to provide evidence for the meaningfulness of new measures to patients with the disease. Providing methodologically sound evidence that implementation of such measures into healthcare decision algorithms improves outcomes is the most convincing proof of their clinical value and meaningfulness. Randomized pragmatic trials are an approach that gains more and more attention in this respect. We are therefore very grateful to the Swiss National Science Foundation for awarding one of its prestigious Investigator-Initiated Clinical Trial grants for MultiSCRIPT, a pragmatic 3-year randomized trial within the framework of the Swiss MS Cohort Study.

MultiSCRIPT will in a first cycle explore the value of sNFL, as addition to established decision algorithms for treatment escalation and de-escalation in relapsing MS. To better focus our respective activities, and encouraged by this IICT grant, we newly established “Pragmatic Trials and Real World Evidence” as RC2NB’s workstream 4. More about WS 4 and MultiSCRIPT in part 3 of this report!

On the administrative and personnel levels the decision of Yvonne Naegelin, who was COO and co-founder and leader of the dreaMS project, to leave the group and engage in a leading position with Swissmedic induced or accelerated several rearrangements. The role of the management group as scientific leadership of RC2NB and its members’ responsibility for enhanced communication and crossfertilization across the workstreams was strengthened. Philipp Limberg was engaged as RC2NB- and dreaMS manager and Lars Hemkens and his clinical epidemiology group engages in the dreaMS project and is responsible for integrating and scaling up activities on pragmatic trials and real-world evidence. Last but not least: Cristina Granziera increasingly engaged in WS 1 and joined Jens Kuhle as deputy CEO of RC2NB. A major step towards better embedding of RC2NB in its academic environment was achieved in by the final decision of the University to create and advertise together with RC2NB a new structural professorship for Clinical Neuroimmunology at the Medical Faculty. In our transformative journey all of us at RC2NB are very greatful for the continued trust and support by the University Hospital, the University, national and international research organizations, our corporate sponsors, and all our cooperation partners.

Ludwig Kappos  
CEO
2.2 | Board of Trustees

Members
Prof Urs Fischer (president of the Board, Chairman Neurology, University Hospital Basel)
Prof Christiane Pauli-Magnus (vice president of the Board, Head of Department of Clinical Research, University Hospital Basel)
Dr med Werner Kübler, MBA (CEO University Hospital Basel)
Prof Primo Schar (Dean Medical Faculty, University of Basel)
Prof Torsten Schwede (Vice-president Research, University of Basel)

The Board of Trustees held three meetings, on January 6th, June 30th and November 29th 2022.

2.3 | Scientific Advisory Board

Members
Prof Reinhard Hohlfeld (chair), Munich, Germany
Dr Viviane Bohner Lang (patient representative), Allschwil, Switzerland
Prof Xavier Montalban, Barcelona, Spain
Prof Daniel Reich, Bethesda, United States of America
Prof Maria Pia Sormani, Genova, Italy
Prof Björn Tackenberg, Basel, Switzerland

The international RC2NB Scientific Advisory Board (SAB) meets annually and independently reviews the work and provides advice to the RC2NB. The second - and first in-person meeting was held on June 22nd 2022.

Quote from the SAB report issued after this meeting:
“RC2NB draws from the unique local structures, experiences, and expertise in translational MS research. Assets include well-characterized patient cohorts, most notably the Swiss MS cohort, which is central to all RC2NB activities; extensive experience with clinical trials, including innovative tools for clinical phenotyping of the disease; and outstanding expertise in neuroimaging of MS tissue, fluid biomarkers and immunological monitoring of therapy. The SAB is impressed how productively RC2NB makes use of this excellent research environment, as evidenced by a number of outstanding recent publications, as well as submitted and unpublished papers. The SAB considers it highly commendable that the research of RC2NB involves intense collaboration between different teams from the different workstreams. The integration of complementing expertise from a broad spectrum of areas is an important distinguishing feature of RC2NB, fostering full realization of its research potential.”

2.4 | Management Group

Members
Prof Ludwig Kappos, CEO, Workstream 1, 2 and 4
Prof Tobias Derfuss, Workstream 3
PD Dr Marcus D’Souza, Workstream 1
Prof Cristina Granziera, Workstream 1 and 2
PD Dr Lars Hemkens, Workstream 1 and 4
Prof Jens Kühle, Workstream 2 and 4
Philipp Limberg, Workstream 1
PD Dr Johannes Lorscheider, Workstream 1
Prof Anne-Katrin Pröbstel, Workstream 3
Jasmin Hatanek, Admin. Assistant

Members of the management group represent the four workstreams of RC2NB and meet monthly to facilitate continuous exchange on and coordination of ongoing and planned research projects.
Three workstreams - One vision

Four closely linked workstreams pursue the common goal of the RC2NB. Interdisciplinary teams collaborate within and across the workstreams to develop innovative tools for monitoring the health of patients with MS, better understand the disease process, enable personalized disease management, and find better treatments.

The year 2022 has been very fruitful for workstream 1, which has the mission to advance the digital future for MS care and research.

With “dreaMS”, we aim to establish and validate smartphone-based digital measures for MS.

The group received a starting grant by Innovate – Schweizerische Agentur für Innovationsförderung – and further funding by various grants to and by the Foundation for Clinical Neuroimmunology and Neuroscience Basel.

In the past year, the outcomes of the first feasibility study were published in the Journal of Neurology (Woelfle et al., 2022). This study with 31 persons affected by MS and 31 healthy volunteers proved that smartphone-derived measurements of motor function, dexterity, vision, and cognition are technically feasible and reliable. Moreover, the tests achieved an excellent user acceptance and were perceived as very meaningful for people affected by MS.

In addition to a digital version of the Symbol Digit Modalities Test, we explored the assessment of various cognitive domains by a suite of cognitive games (Pless et al., oral presentation AAN 2022, submitted). Here, we found strong correlations of features derived from these games with established paper and pencil-based reference tests as predefined comparators. These findings suggest that adaptive cognitive games may be useful measures of cognition. All games were perceived as enjoyable and meaningful, which is crucial for long-term adherence.

Based on these encouraging feasibility study results, we started with Validation Study 1 in March 2022 (NCT05009160). By end of year 2022, more than 90 of expected 300-400 persons affected by MS and healthy volunteers have been enrolled. By restricting recruitment to pwMS from the Swiss MS Cohort Study (SMSC), we have ideal conditions to compare the validity and sensitivity for change over time of the new digital metrics derived from dreaMS with the high-quality and well-standardized clinical, laboratory and imaging markers of disease severity and progression obtained in the SMSC. To accelerate recruitment, we are preparing the extension of the study to other Swiss centres participating in the SMSC and plan to enroll the first study participants from centers outside Basel in the second quarter of 2023.

In terms of broadening the geographic scope of the project beyond Switzerland and further validating the outcomes of Validation Study 1...
in independent cohorts, the preparations for the international Validation Study 2 are also well underway. This study’s objective is the independent validation of the results of Validation Study 1 in a multinational cohort of approximately 600 patients. To achieve this goal, a meeting with selected potential international collaborators was held at this year’s ECTRIMS conference in Amsterdam, which sparked a lot of interest among the audience. So far 22 sites from 8 European countries, the United States and Canada have confirmed their willingness to participate in the study. As quality management is key in a project of this scope, an important achievement of our technology partner Healis AG was their certification according to ISO 13845 standard.

Neurostatus-UHB AG was incorporated as a stock corporation established under Swiss law as a 100% USB subsidiary in November 2021. In 2022, the Neurostatus team managed to meet all the challenges of this transformation without interrupting or reducing ongoing activities. During this year Neurostatus-EDSS was licensed to 96 active phase II/III MS trials, of which more than 30 are using the digital version (Neurostatus-eEDSS), which has been shown to significantly improve consistency of assessments. The Neurostatus-eEDSS used in randomized controlled trials (RCTs) is implemented in collaboration with currently four different established eCROs (electronic clinical outcome assessment) companies with non-exclusive licenses. In addition to the guidance and substantial support during implementation in the respective environments of these eCROs, the team of Neurostatus-UHB AG is responsible for the continuous quality control and provided more than 12’000 individual expert-reviews for RCTs in 2022. Other achievements in 2022 included: (1) the development and validation of an EDSS-calculator, allowing a synoptic EDSS consistency check in RCTs still using the paper and pencil version (based on Functional System Scores (FSS) and the Ambulation Score (AS)); (2) the first releases of the academic Neurostatus-eEDSS version within the UHB environment, allowing a real time online consistency check of Neurostatus-EDSS assessments (mandatory subscories, FSS, AS and EDSS step); (3) development of a support webpage for Neurostatus-eEDSS users; (4) start of SMARTCARE - an investigator initiated and lead study conducted within workstream 1 and supported by Novartis Pharma AG, Basel. This study aims to explore whether Non-Neurologist Health Care Professionals (HCPs) are able to perform standardized (e) EDSS assessments of similar quality and reliability as trained neurologists, thus allowing to increase the pool of licensed HCPs performing the Neurostatus-eEDSS. This study combines a new Neurostatus-EDSS training for HCPs and telemedicine (see Figure 2 Study design SMARTCARE study). Figure 2 Smartcare Study comparing standardized Neurostatus-EDSS assessments by trained HCPs and Neurologists - Design

3.2 Workstream 2: Innovative imaging and analysis of body fluids

Research Group Leaders

Prof Cristina Granziola (advanced neuroimaging research –ThINK Basel)

Prof Jens Kuhle (Swiss MS Cohort Study and Body Fluid Biomarker Laboratory)

The Translational Imaging in Neurology (ThINK) Basel group consists of 5 principal investigators (Prof Cristina Granziola, PD Dr Athina Papadopoulou, PD Dr Katrin Parmar, PD Dr Regina Schläger, and PD Dr Özgür Yaldızlı) and their respective teams for a total of 47 people.

Our main research focus is the understanding of multiple sclerosis (MS) physiopathology, the identification of biomarkers of MS progression and therapy response, the development of new computational models of MS disease impact and evolution as well as the investigation of mechanisms of structural remodeling/regeneration within the central nervous system of MS patients. To achieve these goals we exploit the sensitivity and specificity of advanced quantitative magnetic resonance imaging and modern analysis methods including classical machine-learning techniques and deep-learning networks. The group is funded through a Professorship of the Swiss National Science Foundation (SNSF), the European Research Council (ERC) (Horizon 2020), the Hasler Foundation, the Stiftung zur Förderung der gastroenterologischen Forschung, intramural funding of the Università of Basel and corporate research grants.

In 2022, we achieved some major milestones in the understanding of MS pathophysiology and in the identification of novel imaging biomarkers. In a large study of patients included in the SMSC, MS patients that show progressive disability accumulation without any clinical or radiological signs of inflammatory activity exhibited significantly increased brain atrophy and cortical loss compared to stable patients (Cagol et al., JAMA Neurol 2022). We have also recently identified novel biomarkers of remyelination in quantitative susceptibility maps (QSM), a finding that opens the perspective of in vivo assessing therapies with potential remyelinating and/or neuroprotective effects in people with MS (Rahmanzadeh et al., Annals Neurol 2022). Specifically, in this study, exploiting a dual approach based both on in vivo imaging and postmortem imaging-histopathology we showed that QSM hypo- and iso-intense lesions correspond to completely remyelinated plaques (“shadow” plaques, Figure 3).

The Laboratory of Clinical Neuroimmunology led by Jens Kuhle focuses on the discovery, development and validation of body fluid biomarkers and is responsible for the blood and cerebrospinal fluid bio-bank of the Department of Neurology and the SMSC. The group is funded through two project grants of the Swiss National Science Foundation, grants from the National MS Society (USA), Swiss MS Society as well as corporate research funding.

Through the SMSC more than 270’000 biofluid samples from more than 12’000 time points are available for translational medicine research and the definition of precision medicine tools. The growing number of biofluid samples and the accompanying high quality standardized clinical and imaging data are a key resource for the research of the group, RC2NB, and numerous national and international
Optimised cut-offs of serum (s) GFAP and sNfL Z-scores from ROC analysis were associated with a 4-fold (HR: 4.09 [2.04-8.18], p<0.001) increased risk of CDW compared to sGFAP-P bew/sNfL-placement. The combination of sGFAP-P bew/sNfL-placement showed a slightly reduced risk (2.32 [0.99-4.52], p=0.05). The combination of sGFAP-P bew/sNfL-placement on the other hand did not show an increased risk of CDW (1.03 [0.30-3.53], p=0.97).

Evidence that the presence of intrathecal IgM synthesis is associated with a higher amount of neuronal damage (Oechtering et al, Ann Neurol 2022) in early phases of MS, highlights the value of collection of cerebrospinal fluid in the SMSC enabling progress in translational medicine to improve therapeutic decision making in MS.

3.3 | Workstream 3: Recording and understanding the dysregulated immune system

The Clinical Neuroimmunology Lab (Prof Tobias Derfuss) studies the biology of multiple sclerosis and related diseases from two approaches. The top-down approach depends on observational studies of immunologic parameters in patients, both in response to treatment, and in the natural history of the disease. The bottom-up approach involves in vitro and in vivo experimental modeling of plausible hypothetical mechanisms to explain the observations. The group is funded by SNF project grants, the Swiss Personalized Health Initiative and industry grants.

In 2022 we continued to publish and expanded the two of the components of our ongoing collaboration in the framework of the Swiss Personalized Health Initiative, in which we studied the impact of the oral medication dimethyl fumarate. Occasional failure of this treatment, lymphopenia. By addressing this issue, we have made advances in the cloning and characterization of antibodies of the IgM class from single human B cells (Callegari et al., 2022) and have also made the important observation that monoclonal antibodies from patients with autoantibody-driven neurological diseases can cause massive tissue damage via activation of the complement system in combinations of two or more antibodies of different epitope specificity but seem to be harmless if...
present as single antibodies only (Rose et al., 2022). In parallel to completion and publication of both experimental projects we are proceeding with our study on the role of Epstein Barr virus infection in circumventing B cell tolerance checkpoints.

The overall aim of the research group “Experimental Neuroimmunology” (Prof Anne-Katrin Pröbstel) at the Departments of Bio- medicine and Clinical Research lies in understanding the functional diversity and specificity of B cells and their interaction with gut microbiota in central nervous system inflammation expanding the focus from MS to MOGAD, autoimmune encephalitis and neurolupus. Ultimately the group strives to develop strategies to foster immune regulatory responses and achieve tailored therapeutic interventions.

Achievements in 2022 include: (I) Identification of microbial signatures associated with MS disease activity as well as with relevant side effects (lymphopenia) under immune modulating therapy in a patient subgroup (Diebold et al. Gut microbes 2022) (Figure 6: Mounting evidence points towards a pivotal role of gut microbiota in multiple sclerosis (MS) pathophysiology. Yet, whether disease-modifying treatments alter microbiota composition and whether microbiota shape treatment response and side-effects remain unclear. In this prospective observational pilot study, we assessed the effect of dimethyl fumarate (DMF) on gut microbiota and on host/microbial metabolomics in a cohort of 20 MS patients. Combining state-of-the-art microbial sequencing, metabolome mass spectrometry, and computational analysis, we identified longitudinal changes in gut microbiota composition under DMF-treatment and an increase in citric acid cycle metabolites suggesting gastrointestinal microbiota as a novel key therapeutic target for metabolic properties of DMF beyond immune cells. Notably, DMF-induced lymphopenia, a clinically relevant safety concern, was correlated with distinct baseline microbiome signatures in MS patients. By characterizing gut microbial composition as a candidate risk factor for DMF-induced lymphopenia, we provide novel insights into the role of microbiota in mediating clinical side-effects. (Diebold et al. Gut microbes 2022) (2) Discovery of a novel mucosal originating myelin-reactive autoantibody in a clinically distinct subgroup of patients with atypical demyelination (Gomes*, Kulsvehaugen* et al. under review): Little is known about the presence and clinical relevance of IgA autoantibodies against myelin targets in CNS demyelination. Here, we identified a myelin-reactive antibody in a subgroup of patients with MOG-IgG and AQP4-IgG seronegative demyelination presenting with myelitis and brainstem syndrome but less frequent optic neuritis. Ongoing work aims to decipher the underlying pathogenesis. (3) Identification of an immune trafficking signature in patients with MOGAD for which currently a therapeutic blocking antibody is evaluated in pre-clinical models (unpublished).

The group of PD Dr Matthias Mehling (Translational Neuroimmunology) at DBM assessed the impact of MS-immunotherapies on protective immunity. Together with Prof Jens Kuhle and the SMSC collaborators they systematically collected data on SARS-CoV-2 infections; severity of COVID-19 according to the WHO scale and SARS-CoV-2 vaccines were prospectively documented with specifically developed questionnaires over two years amongst SMSC participants. A sub-study conducted in 2022 including 242 pwMS was devoted to determining the rate of Omicron breakthrough infections and severity of COVID-19 in pwMS under treatment with different DMTs and to estimating the impact of SARS-CoV-2-specific antibody levels on breakthrough infection risk were included into this sub-study. Omicron breakthrough infections were reported in 57 pwMS and severity on the WHO scale ranged from 1-10. Patients with antibody levels >150 U/ml after the second vaccination had a 64% lower risk for Omicron breakthrough-infection compared to patients with antibody levels <0.7 U/ml. Our findings support the assumption that a higher humoral immune response after the second SARS-CoV-2 vaccination is associated with a lower Omicron breakthrough infection rate, contrasting reports from the general population that described lacking or rather minor association of antibody response with protection from Omicron infection.

![Figure 5](image1.png)

**Figure 5** Influence of antibody combination on pathogenicity in an experimental myasthenia gravis rat model. The effect of two single, patient-derived acetylcholine receptor (AChR)-specific, monoclonal antibodies was compared with the combination of both. Rats were injected with PBS, a beta-subunit AChR specific antibody (bG402-G1), an alpha-subunit specific AChR specific antibody (aG101) or a combination of both. The effect on the neuromuscular endplates was measured in cryosections of gastrocnemius muscle at 36 h after antibody injection. The endplates were visualized with bungarotoxin staining (red) and the presynaptic side of the synapse was stained with SV2A. The combination of antibodies lead to a significant destruction of the endplate and the presynaptic membrane (seen on the right image).

![Figure 6](image2.png)

**Figure 6** Microbiota composition predisposes to DMF-associated lymphopenia. (a) Non-metric multidimensional representation (NMDS) of the gastrointestinal microbiota composition of samples from individuals with (red) or without (turquoise) subsequent DMF-associated lymphopenia. Circles represent confidence interval of 95% (stress: 0.17). (b) Graphical summary of findings from this study and the recent literature.
This new workstream, launched in Spring 2022, provides the framework for translation of innovation to research and care. In our strategy it will develop the methodology and structures for the final steps in RC2NB’s development of diagnostic and therapeutic innovations by evaluating their clinical value and meaningfulness for patients. We aim to provide robust evidence that implementation of such innovative measures into healthcare decision making truly improves patient-relevant outcomes, i.e., that the innovations not only are on par with the current standard, but consistently outperform and improve the current standard of care. This workstream lays the foundation for methodologically robust real-world evidence generation. We take advantage of the unique combination of interdisciplinary clinical and methodological expertise with long-standing experience in clinical trial design and conduct, apply new methods and build novel research and data infrastructures for pragmatic, decentralized, and remote clinical trials using real world data. Our goal of concurrent evaluation and implementation ensures rapid integration of research findings into care.

The SMSC with its standardized procedures and high-quality data collection offers a unique opportunity to merge pragmatic randomized trial methodology with real-world data collection. Indeed, in 2022 we received an Investigator-Initiated Clinical Trial grant by the Swiss National Science Foundation for *MultiSCRIPT: personalized medicine in Multiple Sclerosis – pRagmatIc Plat-form Trial embedded within the Swiss MS Cohort (SMSC)*.

*MultiSCRIPT* aims to continuously assess innovative treatment strategies emerging from other RC2NB workstreams (Figure 7). This will allow us to continuously learn and generate new strategies that are more personalized aiming to treat patients as little as possible but as much as necessary at the right time. Before each learning cycle, a systematic Delphi process involving national and international experts and patient consultants is conducted, to optimize the clinical application of the novel treatment decision strategies.

In the first cycle of *MultiSCRIPT* (PI: PD Dr Özgür Yaldızlı), we plan to compare an intensive biomarker monitoring strategy using serum neurofilament light chain (sNfL) values to inform more personalized treatment decisions (e.g., escalation or de-escalation of treatments) against the current usual care without sNfL-monitoring. More than 900 eligible SMSC patients will be included. The novel treatment strategy will be considered superior to usual care if either more patients have no evidence of disease activity (NEDA3), or their health-related quality of life increases. If it is shown to be superior, intensive biomarker monitoring will become the new standard of care, and the next promising strategy will be evaluated in a next learning cycle.

For the structured Delphi process preceding the first *MultiSCRIPT* cycle, we invited 18 national and 10 international MS experts and 3 patient consultants to develop treatment decision algorithms to implement the information of sNfL into routine care. The Delphi process was completed end of January 2023 with a final in-person discussion in Lucerne, generating broad consensus among all *MultiSCRIPT* centers to implement common approaches to the use of sNfL information in supporting treatment decisions.
Several activities of research groups in the RC2NB workstreams are managed independently and therefore not part of RC2NB's financial statement. No expenses covered by RC2NB for workstream 4 in 2022.

RC2NB’s Financial Statement 2022 was reviewed and approved by the auditor BDO AG.
5 | Main Partnering Institutions and Research Support

6 | Members and Collaborators of RC2NB by Workstreams

Workstream 1

Research Group Leaders
PD Dr Marcus D’Souza (Neurostatus-UHB)
Prof Cristina Granziola (dreaMS, CLINNOVA)
PD Dr Lars Hemkens (dreaMS, CLINNOVA)
PD Dr Johannes Lorscheider (dreaMS)

Group Members and Collaborators
dreaMS and digital solution:
Caroline Brunner (study nurse)
Jasmin Hatanek (management assistant)
Melanie Lacalamita (study coordinator)
Philipp Limberg, MSc (project management)
Vera Müller, MSc (study nurse)
Marko Obidovic, MSc (software engineer)
Vanny Phavanh (study nurse)
Silvan Pless, MSc (neuropsychologist, PhD student)
Dr Andrea Wilencierz (statistician)
Dr Tim Wällfie, MSc (physician-scientist, PhD student)
Guilhem Dupont, Corne de Jong, Juan Collado, James Lunt, Óscar Reyes (Healios; other employees of Healios Ltd involved in dreaMS are not individually mentioned)

Neurostatus-UHB Ltd:
Dr César Alvarez-González (neurologist)
Dr Ioanna Athanasopoulou (neurologist)
Elena Bürlin (IT specialist/IT Lead)
Barbara Forman (operations)
Evy Fricker (COO)
Nuria Alicia Cerdá Fuertes (neurologist)
Eddy García (operations lead)
Marcos Gomez (IT)
Joel Götti (student/IT)
Gabriel Hug (student/IT)
Jasmína Ivanovic (executive assistant)
Dr Christian Kamm (neurologist)
Dr Giulia Mallucci (neurologist)
Vanessa Müller (operations)
Dominik Nguyen (IT)
Steven Njuguna (IT)
Svetlana Orlova (IT specialist/IT)
Thomas Trouillet (programme/IT)
Colleen Waiz (operations)
Simon Wunderlin (IT)
Andrea Zimmer (study coordinator)
Workstream 2

Research Group Leaders
Prof Cristina Granziera (advanced neuroimaging research – ThINk Basel)
Prof Jens Kuhle (Swiss MS Cohort Study and Clinical Neuroimmunology)

Group Members and Collaborators

ThINk Basel
Prof Cristina Granziera team:
Dr Matthias Weigel (senior researcher)
Dr Lester Melie Garcia (senior researcher)
Dr Mario Alberto Pineda (research fellow)
Dr Muhamed Barakovic (research fellow)
Dr Alessandro Cagol (research fellow)
Dr Jannis Müller (research fellow)
Dr Gretel Sanabria Diaz (research fellow)
Dr Po-Jui Lu (research fellow)
Dr Ilaria Callegari (research fellow)
Dr Esther Ruberte (senior researcher)
Dr Nina Siebenborn (neuroradiologist)
Dr Alexandra Todea (neuroradiologist)
MSc Sabine Schädelin (statistician)
Xinjie Chen (PhD student)
Riccardo Galbusera (PhD student)
Antonia Wenger (PhD student)

Reza Rahmanzadeh (PhD student)
Sara Bosticardo (PhD student)
Federico Spagnolo (PhD student)
Osman Hatipoglu (master student, Biomed Engineering)
Selina Leber (master student, Medicine)
Igor Schneider (master student, Medicine)
Martina Greselin (master student, Biomed Engineering)
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Lara Rustemi (master student, psychology)
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PD Dr Athina Papadopoulou team:
Dr Cesar Alvarez (MD)
Dr Katerina Ebner (MD)
Dr Nuria Cerde Fuertes (MD)
Dr Jenni Kuhlmann (MD)

PD Dr Özgür Yaldızlı team:
Tim Sinnecker (research fellow)
Jannis Müller (research fellow)
Gizem Tan (master student)
Sophia Reinmann (master student)
Laurent Baumann (master student)

PD Dr Regina Schläger team:
Dr med Janina Wendebourg (PhD student)
Dr med Laura Sander (PhD student)
Dr Eva Kesenheimer (PhD student)
Valentina Crepulja (master student)

PD Dr Katrin Parmar team:
Dr Charidimos Tsagkas (research fellow)

Swiss MS Cohort Study and Clinical Neuroimmunology - Fluid Biomarker Laboratory

Prof Jens Kuhle team:
Dr Ahmed Abdelhak (postdoc)
Dr Pascal Benkert (Head of SMSC datacentre, statistician)
Caroline Brunner (study nurse)
Lilian Dernuth (study coordinator)

PD Dr Özgür Yaldızlı team:
Leyla Develioğlu (technician)
Juan Vilchez Gomez (research technician)
Ulrich Gress (study coordinator)
Melanie Lcalamita (study nurse)
Prof David Leppert (senior postdoc)
Marguerite Limberg (study nurse)
Alessandra Maleska, MSc (bioengineer)
Stephanie Meier (PhD student)
Dr Johanna Oechtering (senior neurologist/postdoc)
Dr Annette Orleth (postdoc)
Miriam Rhyner (study nurse)
Monika Röthlisberger (study nurse)
Sabine Schaedelin, MSc (statistician)
Daniela Stanoevíc (study coordinator)
Suxitha Subramaniam, MSc (data scientist)
Dr Eline Willemse (postdoc)
Nancy Wlochek (study nurse)
PD Dr Özgür Yaldızlı (senior neurologist/postdoc)
Amar Zadic (research technician)
Workstream 3

Research Group Leaders
Prof Tobias Derfuss (Cellular and Molecular Neuroimmunology)
PD Dr Matthias Mehling (Immunosenescence)
Prof Anne-Katrin Pröbstel (Experimental Neuroimmunology)

Group Members and Collaborators

Prof Tobias Derfuss team:
Dr Ilaria Callegari
(PhD student)
Sebastian Holdermann, MSc
(PhD student)
Dr Nicholas Sanderson
(postdoc)
Mika Schneider, BSc
(master student)
Dr Edoardo Galli
(postdoc)
Noemi Vazquez
(undergraduate student)

PD Dr Matthias Mehling team:
Mali Coray
(MD-PhD student)
Dr Varenka Epple (MD)
Annika Frentzel, BSc
(master student)
Dr Jakob Fuhrmann (MD)
Dr Klaara Ivanek
(postdoc)
Melanie Kaech, BSc
(master student)

Prof Anne-Katrin Pröbstel team:
Miriam Beyerle
(MD Doctoral Student)
Tim Dürrenberger
(phd student)
Julia Flammer
(resident/postdoc)
Ana Beatriz Gomes
(PhD student)
Laila Kulevshagen
(PhD student)
Anne-Cathérine Lecourt
(lab manager/technician)
Jasmine Lerner
(undergraduate student)
Patrick Lips
(MD Doctoral Student)
Luc Lutz
(master student)
Dr med. Tadite Neziraj
(postdoc)
Maximilian Otto
(undergraduate student)
Elisabeth Pössnecker
(PhD student)
Roxanne Pretzsch
(postdoc)
Dr Lena Sievert
(postdoc)
Lea Volken
(undergraduate student)
Angéline Wettig
(undergraduate student)

Workstream 4

Research Group Leaders
PD Dr Lars Hemkens MPH
Prof Jens Kühle
PD Dr Özgür Yaldızlı

Group Members and Collaborators

PD Dr Lars Hemkens

Pragmatic Evidence team:
Dr Perine Janiaud
(research fellow)
Dr Julian Hirt
(research fellow)
Dr Amanda Herbrand
(research fellow)
Pascal Dublin
(application developer)
Anurima Bhattacharjee
(master student, epidemiology)
Kings Dembowska
(master student, epidemiology)
Thao Vy Nguyen
(master student, epidemiology)
Ana Karen Macias Alonso
(master student, biomedical engineering)
C. Granziera was elected vice-chair of the prestigious White Matter (WM) group at the International Society of Magnetic Resonance Imaging, co-president of the Medico-Scientific Advisory Board of the Swiss MS Society, member of the International Advisory Committee on Clinical Trials in MS, and member of the Executive Board of the Department of Biomedical Engineering at the University of Basel.

C. Granziera received the Robert Bing Prize for her outstanding work on advanced neuroimaging of novel biomarkers of damage and repair in MS, which promise to improve diagnostic, therapeutic monitoring and prognostic procedures in MS care.


J. Kuhle was nominated as co-chair of the BioMSeu Consortium for CSF biomarker research and as a member of the Grants committee of the Swiss MS Society.

According to ISI statistics based on citations in their field in 2022 J. Kuhle and L. Kappos were two of the three top 1% highly cited researchers from the Department of clinical research.

A.-K. Pröbstel received the Sobek Young Investigator Award for her work on B cells and antibodies and their interaction with microbiota in MS. Several members of her group are supported with prestigious fellowships by international and Swiss institutions.

Completed PhD and Master theses:
Po-Jui Lui, PhD (Department of Biomedical Engineering)
Reza Rahmanzadeh, PhD (Department of Biomedical Engineering)
Ilaria Callegari, PhD (Department of Biomedical Engineering)
Hye-In Kim, PhD (Department of Biomedical Engineering)
Laura Rieder, MsC (Department of Biomedical Engineering)
Arunima Bhattacharjee (Department of Clinicial Research & Swiss TPH)

C. Granziera received a 1.6 million CHF grant for 3 years from the Stiftung zur Förderung der Gastroenterologischen und allgemeinen klinischen Forschung sowie der medizinischen Bildauswertung, to pursue her work in the field of advanced imaging of brain repair.

A.-K. Pröbstel was awarded with a 1.8 million CHF Starting Grant from the SNSF (Swiss substitute funding for the ERC grants).

J. Kuhle received a 4-year project grant funding from the Swiss National Science Foundation (“Quantifying progression in multiple sclerosis: serum glial fibrillary acidic protein (gGFAP) for personalised medicine and identification of novel targets”). The Swiss MS Society decided to further support the SMSC with a 1.2 million CHF grant for the next 3 years.

J. Kuhle, L. G. Hemkens and Ö. Yaldızlı (PI) received an Investigator Initiated Clinical Trial (IICT) grant over 1.95 million CHF for the MultiSCRIPT Study by the Swiss National Science Foundation for the next 4.5 years.

J. Kuhle was nominated as co-chair of the BioMSeu Consortium for CSF biomarker research and as a member of the Grants committee of the Swiss MS Society.


Comment: In this work, we created a reference database for serum NfL based on 10,133 blood samples from 5,030 people. In MS patients from the SMMSC, sNfL percentiles and Z scores indicate a gradually increased risk for future acute (relapse and lesion formation) and chronic (disability worsening) disea-se activity. The longitudinal course of sNfL Z score values decreased to those seen in the control group with use of monoclonal antibodies (ie, alemtuzumab, natalizumab, ocrelizumab, and rituximab) and, to a lesser extent, oral therapies (ie, dimethyl fumarate, fingolimod, siponimod, and teriflunomide). Results were fully supported in the validation cohort (n=4341) from the Swedish Multiple Sclerosis registry. We showed that sNfL percentiles and Z scores allow for identification of MS patients at risk for a detrimental disease course and suboptimal therapy response beyond clinical and MRI measures, specifically in people with disability-free status. Additionally, sNfL might be used as an endpoint for comparing effectiveness across drug classes in pragmatic trials.


Comment: Here we tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military. 965 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.


The aim of this study was to determine whether disability progression independent of relapse activity in multiple sclerosis. JAMA Neurol. 2022;79(7):682-92.


In this prospective observational pilot study, we assessed the effect of dimethyl fumarate (DMF) on gut microbiota and host/microbial metabolomics in a cohort of 20 MS patients. Combining state-of-the-art microbial sequencing, metabolome mass spectrometry, and computational analysis, we identified longitudinal changes in gut microbiota composition under DMF treatment and an increase in citric acid cycle metabolites. Notably, DMF-induced lymphopenia, a clinically relevant safety concern, was correlated with distinct baseline microbiome signatures in MS patients. By characterizing gut microbiota composition as a candidate risk factor for DMF-induced lymphopenia, we provide novel insights into the role of microbiota in mediating clinical side-effects.


Here we show outcomes of a cross-sectional clinical study (NCT04472013) including clinical and imaging data and corresponding multivariable characterization of immune mediators in the cerebrospinal fluid (CSF) and plasma of patients belonging to different Neuro-COVID severity classes. The most prominent signs of severe NeuroCOVID are blood-brain barrier (BBB) impairment, elevated microglia activation markers and a poly-clonal B cell response targeting self-antigens and non-self-antigens. Collectively, we identify several potentially actionable targets to prevent or intervene with the neurological consequences of SARS-CoV2 infection.


In this work, we aimed to (i) identify qMRI measures that distinguish histological lesion types in postmortem multiple sclerosis (MS) brains, especially the remyelinated ones; and to (ii) investigate the relationship between those measures and quantitative histological markers of myelin, axons, and astrocytes in the same experimental setting. Our study provides new information on the discriminative power of qMRI in differentiating MS lesions—especially remyelinated ones—as well as on the relative association between multiple qMRI measures and myelin, axons and astrocytes.


69. Kuhlmann T, Moccia M, Coetzee T, Cohen JA, Correa J, Graves J, Mairi RA, Montalban X, Yong YY. Blood Neurofilament Light in Progressive Multiple Sclerosis (SPMS 49%), and 6-month disability progression (SPMS 26%, PPMS 48%), earlier wheelchair dependence (SPMS; EXPAND) and primary progressive multiple sclerosis (PPMS; INFORMS) using siponimod and fingolimod, respectively, as active compounds was performed. Independent of treatment, high vs low baseline pNfL levels were associated with significantly higher risks of confirmed 3-month (SPMS 32%, PPMS 197%), cognitive decline (SPMS 41%), and higher rates of brain atrophy. pNfL levels were lower in patients treated with sponimod or fingolimod vs placebo-treated patients and higher in those having experienced disability progression. In conclusion, pNfL was reduced by treatment and may be a meaningful outcome measure in PMS studies.


77. Lam KH, van Munster CEP, Derfuss DG, Granziela G, Abbotta M, Bach Cuadra M. Correlation of the pNfL level with disease activity and treatment response in progressive multiple sclerosis (PPMS) with and without acute disease activity in 2 placebo-controlled, phase 3 studies in secondary progressive multiple sclerosis (SPMS; EXPAND) and primary progressive multiple sclerosis (PPMS; INFORMS) using siponimod and fingolimod, respectively, as active compounds was performed. Independent of treatment, high vs low baseline pNfL levels were associated with significantly higher risks of confirmed 3-month SPMS (32%), PPMS (49%) and 6-month disability progression (SPMS 26%, PPMS 48%), earlier wheelchair dependenc


Comment: In this study we investigated whether an intrathecal IgM production (IgMIF +) is associated with spinal cord manifestation and neuronal injury in early MS. Patients with a spinal syndrome had a 8.36-fold higher odds of IgMIF + (p < 0.01). Each spinal T2w lesion and contrast enhancing lesion in Multiple Sclerosis. Ann Neurol. 2022;91(6):814-20.

Intrathecal IgM Synthesis Is Associated with Spinal Cord Manifestation and Neuronal Injury in Early MS. Neurology. 2022. We performed 3 studies: (1) a cross-sectional study in a prospective cohort of 115 patients with MS and 76 healthy controls, who underwent 3T magnetic resonance imaging (MRI) for quantitative susceptibility mapping (QSM), myelin water fraction (MWF), and neurite density index (NDI) maps. White matter (WM) lesions in QSM were classified into 5 WM lesion types (iso-intense, hypo-intense, hyperintense, lesions with hyperintense rims, and lesions with paramagnetic rim lesions [PRLs]); (2) a longitudinal study of 40 patients with MS to assess the accuracy of QSM classification to identify advanced MRI Biomarker for Remyelinated Lesions in Multiple Sclerosis. Ann Neurol. 2022;92(3):486-502. We present the first evidence that it is possible to distinguish chronic MS lesions in a clinical setting, hereby supporting with new biomarkers to develop and assess remyelinating therapies.


Investigation of the extent, pattern, and clinical relevance of spinal cord (SC) gray and white matter atrophy in vivo in MS patients. Data showed that MS patients show clinically relevant cervical SC atrophy in the anterior horn, which is more pronounced in progressive MS and at the level of cervical SC enlargement.


In this feasibility study, we demonstrated that smartphone-based monitoring of people with multiple sclerosis is technically feasible. The test results had a good test-retest reliability and the tests thems elves were well accepted and perceived as meaningful by people affected by multiple sclerosis.


