RC2NB
ANNUAL REPORT

Universitätsspital Basel

RC2NB

University of Basel

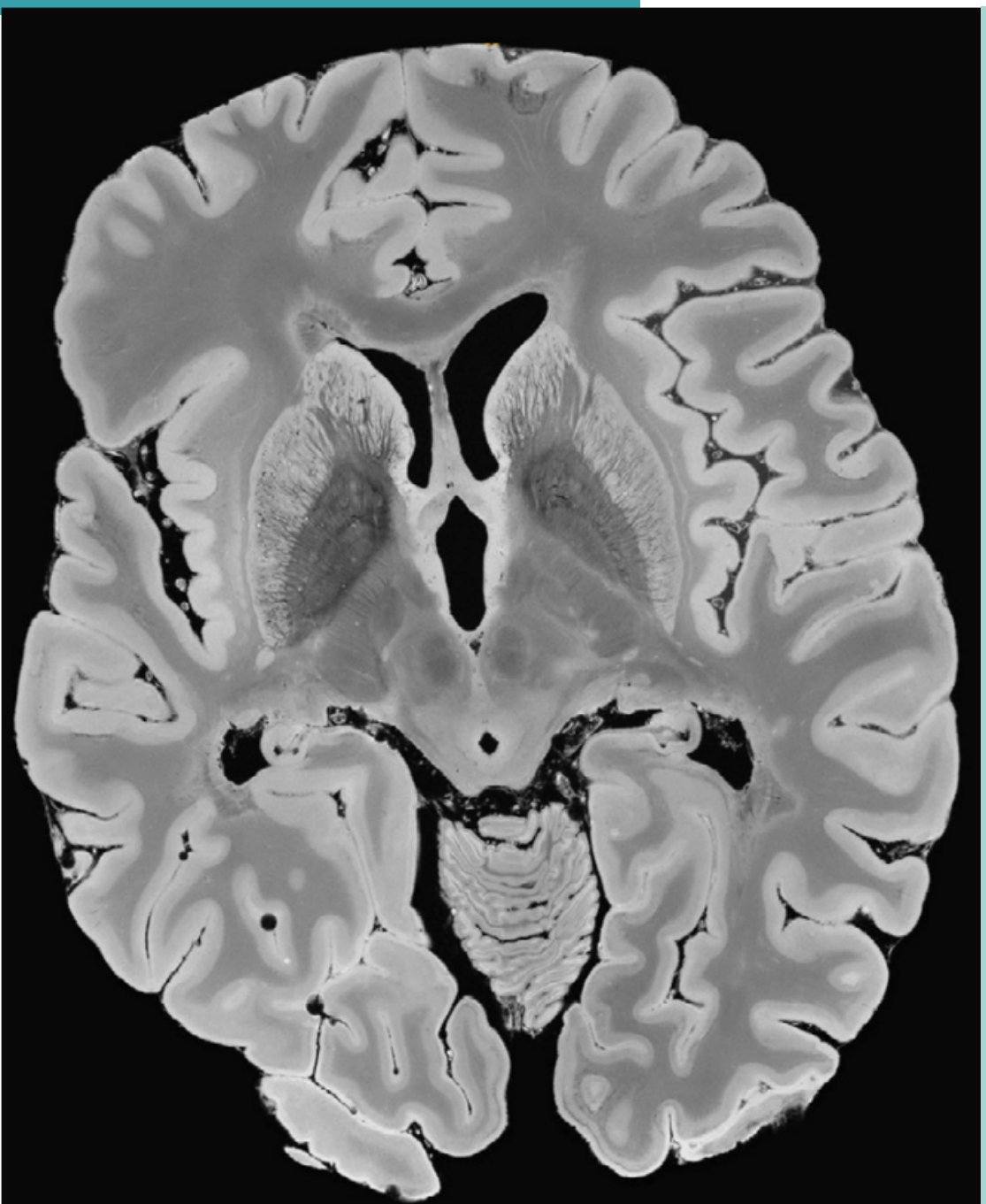
ABOUT US

The Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB) is based on a non-profit foundation. Founded in 2019 by the University Hospital Basel with the participation of the University of Basel the foundation's **mission** is 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 to 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 diagnosis and treatment. 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.

OUR VISION

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.



Content

LETTER OF THE CEOs

2023 has been another year of intense work, growth and new scientific achievements for RC2NB.

We have further developed our research cluster to an incubator of innovation and sustainable research activities. We have pursued our plan for the scientifically sound development and validation of novel digital approaches to holistically measure disease evolution in Multiple Sclerosis (MS) and other neuroimmune diseases. Both at the national and international level, we have fostered collaborative research projects such as MultiSCRIPT and CLINNOVA.

In the following pages we provide an update of ongoing projects in our four workstreams and highlight some of the most significant results of our work in 2023. In 2023 117 peer reviewed original papers, editorials and reviews, were authored or coauthored by RC2NB members.

In workstream 1, dreaMS Validation Study 1 continuously recruits participants out of the Swiss MS Cohort Study and has passed the mark of 200 participants from Basel. Four other Swiss centers (Lugano, Lausanne, Aarau and St Gallen) have already joined the study or are going to join in the first months of 2024. The international dreaMS Validation Study 2 is now in the final stages of regulatory and technological preparation for the first patient in 2024. Neurostatus-UHB Ltd. continued to expand its service portfolio in 2023. More than 30 international phase II and III MS trials are currently using the digital neurostatus version (Neurostatus-eEDSS).

In workstream 2, Jens Kuhle and his group have embarked on a new project funded by the Swiss National Science Foundation and the Progressive MS Alliance aiming to provide evidence that after Neurofilament Light (NfL) a second blood based biomarker, glial fibrillary acidic protein (sGFAP), may add value by better defining the central role of glial activation as a pathogenetic mechanism of disease progression. Cristina Granziera's group (ThINk Basel) 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 (both in vivo and postmortem). Besides, the imaging group has contributed new insights in the pathophysiology of progression independent of relapses as well as novel approaches to diagnose MS. In addition, ThINk Basel pursued the development and validation of AI-based methods for translating novel findings into clinical practice.

In workstream 3, Tobias Derfuss' group concluded a multi-year study of the significance of cell-binding IgM in the CSF of pwMS, continued work on the basic biology of B cell ingress into the CNS, and - together with collaborators in Zürich - secured a four-year, multi-lab Sinergia grant to investigate the role of Epstein Barr virus in MS.

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 deciphering the role of IgA producing cells in the regulation of autoimmunity in MS along the gut-brain axis, Anne-Katrin Pröbstel's experimental neuroimmunology group 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.

In workstream 4, we elaborated through a Delphi process expert-based consensus on how to use sNFL values to guide therapeutic recommendations. In MultiSCRIPT, a pragmatic 3-year randomized trial within the framework of the Swiss MS Cohort Study that is financed by the Swiss National Science Foundation we are now applying these consented algorithms and testing the value of NfL as a biomarker in the care of patients with MS.

CLINNOVA, an international project involving Luxembourg, Region Est in France, Baden Württemberg in Germany and Basel in Switzerland has also gained momentum through a generous financial support of the Canton Basel-City. In this project, we are collecting very advanced datasets in exemplary chronic inflammatory disorders (including MS), as well as developing the infrastructure to perform federated learning – an approach to data analysis that bypasses privacy and data ownership issues by developing a central network that accesses to data locally. The MS part of the project is coordinated by RC2NB under the lead of Cristina Granziera.

In December 2023 we organized "RC2NB 4.0" a well-attended international symposium with prominent international speakers stimulating innovation and transformative thinking toward a better understanding and treatment of MS.

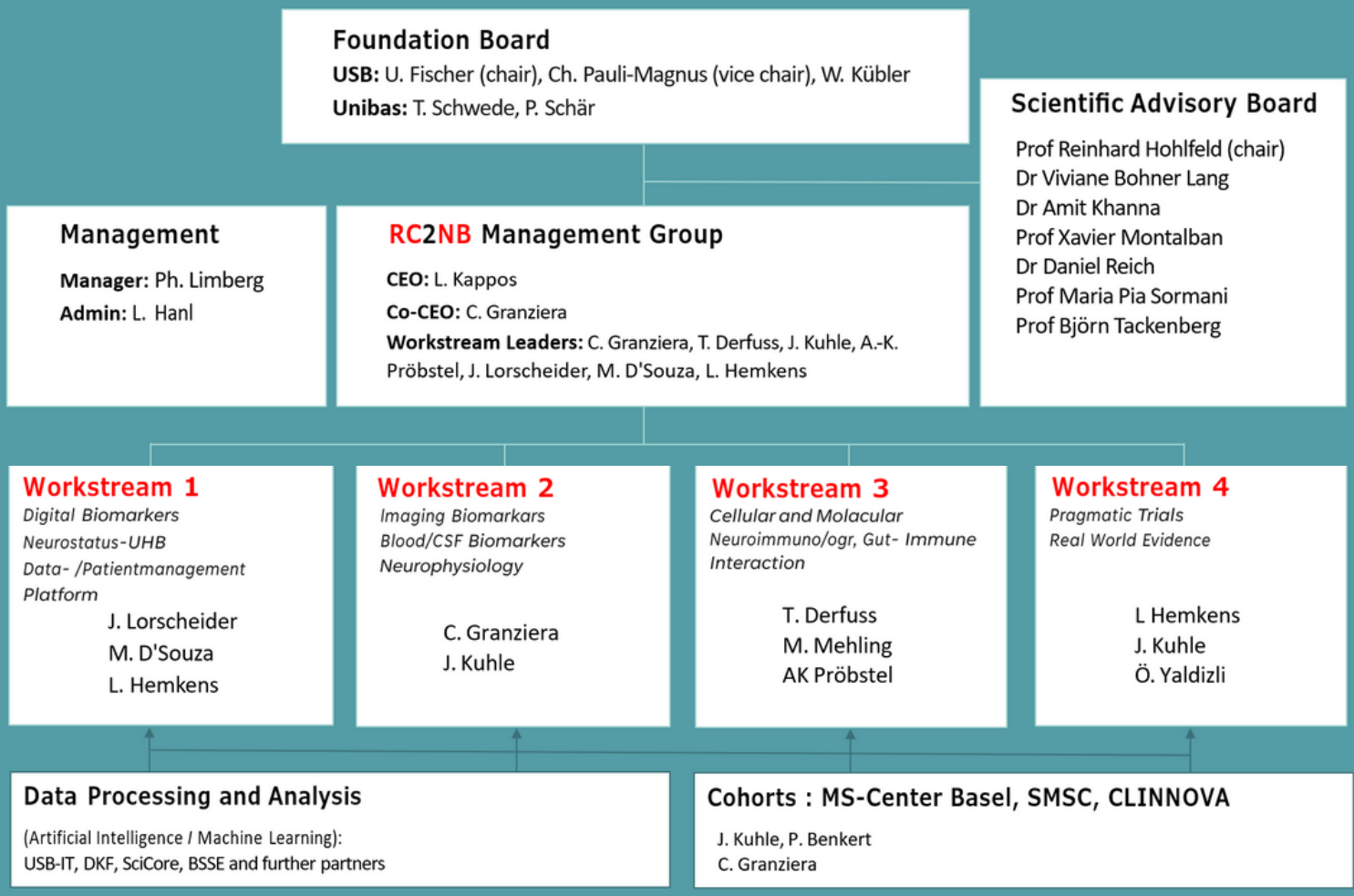
On the administrative and staff levels Lea Hanl joined us in the function of assistant of the management board. Philipp Limberg is now fully employed by RC2NB and also covers the role of project manager of dreaMS validation study 2. Cristina Granziera was elected co-director of RC2NB. The process of establishing a neuroimmunology professorship as a major step towards better embedding of RC2NB in its academic environment is close to its completion, foreseen in the first half of 2024.

In our transformative journey, all of us at RC2NB are very grateful 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

CRISTINA GRANZIERA
CO-CEO

Governance Bodies



Quote from the SAB report issued after its meeting in Basel in December 2023

"The SAB is impressed by the progress made over the past year since its last meeting. As stated in previous reports, the critical importance of the unique research environment in Basel cannot be overemphasised. It is this unique environment that allows the RC2NB to make the best use of its resources in translational MS research, including well-characterised patient cohorts, extensive experience with clinical trials and innovative tools for clinical phenotyping of the disease, as well as outstanding expertise in neuroimaging of MS tissue, fluid biomarkers and immunological monitoring of therapy."

Foundation Board of Trustees

Prof Urs Fischer - Chair of the Board, Chair Neurology, University Hospital Basel.

Prof Christiane Pauli-Magnus - Vice-Chair of the Board, Head of Operations, Department of Clinical Research, University Hospital Basel.

Dr med Werner Kübler, MBA - CEO University Hospital Basel).

Prof Primo Schär - Dean Medical Faculty, University of Basel.

Prof Torsten Schwede - Vice-president Research, University of Basel.

The Board of Trustees held two meetings, on April 5, 2023 and December 20, 2023.

Scientific Advisory Board

Prof Reinhard Hohlfeld - Chair, Munich, Germany.

Dr Viviane Bohner Lang - Patient representative, Allschwil, Switzerland.

Dr Amit Khanna, Basel, 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 third meeting was held on *December 14th, 2023.*

Management Group

Members of the management group representing the four workstreams of RC2NB and meeting monthly to facilitate continuous exchange on and coordination of ongoing and planned research projects.

Prof Ludwig Kappos

CEO, Workstream 1, 2 and 4

Prof Cristina Granziera

Co-CEO, Workstream 1 and 2

Philipp Limberg

Manager, Workstream 1

Lea Hanl

Admin. Assistant

PD Dr Marcus D'Souza

Workstream 1

Prof Jens Kuhle

Workstream 2 and 4

Prof Tobias Derfuss

Workstream 3

PD Dr Lars Hemkens

Workstream 1 and 4

PD Dr Johannes Lorscheider

Workstream 1

Prof Anne-Katrin Pröbstel

Workstream 3

SCIENTIFIC ACHIEVEMENTS 2023

FOUR WORKSTREAMS - ONE VISION

Four closely linked workstreams pursue the common goal of RC2NB. Interdisciplinary research 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.

WORKSTREAM 1: DIGITAL FUTURE

Research Group Leaders

Prof Cristina Granziera
dreaMS

PD Dr Johannes Lorscheider
dreaMS

PD Dr Marcus D'Souza
Neurostatus-UHB

PD Dr Lars Hemkens
dreaMS

In pursuing our mission to advance the digital future for MS care and research the year 2023 was a year of great progress.

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

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

A completely redesigned dreaMS app was released in Summer 2023. The design improvements were based on our experience and feedback in the feasibility study and was a joint effort of the teams at RC2NB and our collaboration partner INDIVI (formerly Healios AG).

A more detailed analysis of the cognitive games suite used in the feasibility study demonstrated strong correlations between features derived from these games and predefined comparators, established paper and pencil-based reference tests. All games were significantly correlated with their established comparators and were perceived as enjoyable and meaningful by the study participants, a crucial aspect to retain long-term adherence (Pless et al., 2023). These findings encouraged us to develop 6 new gamified smartphone tests with multiple difficulty levels that are better customized to the key cognitive domains affected in people with MS.

Figure 1. dreaMS app in new modern design displaying the home screen

These gamified tests are now implemented in the ongoing dreaMS Validation Study 1. As part of the development of these cognitive tests we conducted the CoGames study that included 76 healthy volunteers to investigate reliability and acceptance of these new tests and establish a comparator for the grading of change within and across the different difficulty levels of these adaptive gamified tests (Pless, manuscript in preparation).

In a separate analysis of our feasibility study data, we found that smartwatch-derived activity measures but also sleep, and heart rate features added value in discriminating people with MS with moderate disability from healthy volunteers (Woelfle et al., 2023).

In dreaMS validation study 1 (NCT05009160) we have recruited close to 200 participants by the end of December 2023. By including only participants from the Swiss MS Cohort Study (SMSC), we have the ideal condition that we can compare the sensitivity to change over time of dreaMS digital measures with the high-quality and well-standardized clinical, laboratory and imaging markers of disease severity and progression obtained within the SMSC. To strengthen the validity of the results and accelerate recruitment, we have joined forces and initiated the study in other centers participating in the SMSC, starting with Lugano (EOC) and Lausanne (CHUV). Aarau (KSA), St.Gallen (KSG) and Zurich (USZ) are following in early 2024.

The second key element in our scientific validation strategy is the international dreaMS Validation Study 2 (VS2).

This is a multinational cohort study that will include about 600 participants and is planned to begin enrollement in Q2 2024. This study aims to independently replicate the results of Validation Study 1, with a stronger focus on patient-centered outcomes and optimal generalizability of the findings. In pursuit of these goals, we organized an investigator meeting with our international collaborators at this year's ECTRIMS conference in Milan and as of December 2023, are finalizing the application for regulatory and ethical approval in the participating centers, starting with Germany. Once this milestone is reached, we will onboard all other 22 sites from 10 countries in the European Union. In parallel, we are very grateful for the excellent support from five leading centers in the United States and Canada, who will join forces with us as further study sites in 2024.

As we aim to use dreaMS in both clinical trial and in every day patient care settings, our collaboration partner INDIVI (formerly Healios AG) reached a significant milestone with the filing of dreaMS as a medical device class IIa under MDR. The certification is expected for Q2 2024 paving the path for the use in clinical care settings in unison with its further scientific validation in the two pivotal dreaMS validation studies.

In the field of health care professional based standardized neurological assessment Neurostatus-UHB Ltd. continued and expanded its research activities and service portfolio. During 2023, the Neurostatus-EDSS was licensed to 96 active phase II/III MS trials.

More and more (currently, already 30) of these trials are using the digital version (Neurostatus-eEDSS), which has shown to reduce noise, by significantly improving consistency of assessments. The Neurostatus-eEDSS used in RCTs is implemented in collaboration with established eCOA (electronic clinical outcome assessment) providers under a non-exclusive license. In these collaborations, the Neurostatus-UHB team is responsible for the quality control of the Neurostatus-(e)EDSS and provided over 15'000 expert- reviews for RCTs in 2023. Other activities in 2023 included: (1) SMARTCARE (NCT05575843), an investigator initiated and led study supported by Novartis comparing quality and reliability of Neurostatus-e-EDSS assessments by trained neurologists vs other trained Health Care Professionals (HCPs) completed phase one with 101 first visits, and over 70 follow up visits of phase two. The final analysis is scheduled in first half of 2024.;

(2) In an analysis of a complete Neurostatus-eEDSS data set from a secondary progressive MS trial (Kappos L et al 2018) including more than 13'000 Neurostatus-eEDSS assessments of more than 1'600 pwMS we demonstrated that analysing Neurostatus-eEDSS subscore patterns is more informative than analyzing just EDSS steps or Functional System and Ambulation Scores. Patients with the same EDSS step, have distinct subscore patterns. These findings have implications for recruitment strategies in RCTs but also for guiding clinical care (Greselin M et al., SFCNS 2023); (3) Establishment of an independent adjudication committee (IAC) for MS relapses in three Phase III studies; (4) further adjustment of the internal Quality Management System (QMS), to meet the qualification criteria for ISO 13485 certification, and the requirements for providing consulting to other academic or corporate bodies.

WORKSTREAM 2: INNOVATIVE IMAGING AND ANALYSIS OF BODY FLUIDS

Research Group Leaders

Prof Cristina Granziera

Translational Imaging in Neurology- ThINk Basel

Prof Jens Kuhle

Swiss MS Cohort Study and Laboratory of Clinical Neuroimmunology

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

Our main research focus is the understanding of multiple sclerosis (MS) physiopathology (damage and repair processes), the identification of biomarkers of MS progression and therapy response and the development of new computational models of MS disease impact and evolution. The group is funded through a Professorship of the Swiss National Science Foundation (SNSF), the European Research Council (ERC) (Horizon2020), the Hasler Foundation, the Stiftung zur Förderung der gastroenterologischen und allgemeinen klinischen Forschung, intramural funding of the University of Basel and corporate research grants.

In 2023, we reached some major milestones in the understanding of mechanisms underlying progression independent of relapses, the identification of focal remyelination and features associated with cortical lesions, and in the application of novel imaging biomarkers for MS diagnosis. Exploringn the pathophysiologic substrates of MS progression, in a large study of patients included in the Swiss Multiple Sclerosis Cohort, MS patients experiencing progressive disability accumulation without any clinical signs of inflammatory activity exhibited significantly increased cervical spinal cord atrophy and increased number of paramagnetic rim lesions - a biomarker of chronic focal inflammatory activity- compared to stable patients (Cagol et al., Neurology 2023). As a contribution to increase the specificity of the current criteria for MS diagnosis, we explored the diagnostic value of cortical lesions and the central vein sign in a large MAGNIMS study involving more than 1000 MS patients (Cagol A. et al., JAMA Neurol

2023). We have also recently identified which advanced qMRI measures are most sensitive to identifying remyelinated lesions using a sophisticated postmortem MRI-histopathology approach: quantitative T1 (qT1) and MTR are particularly sensitive and specific for remyelinated lesions in white matter, whereas qT1 only appears to differentiate focal remyelination from demyelination in the cortex (Galbusera et al., Brain Path 2023 and ECTRIMS 2023).

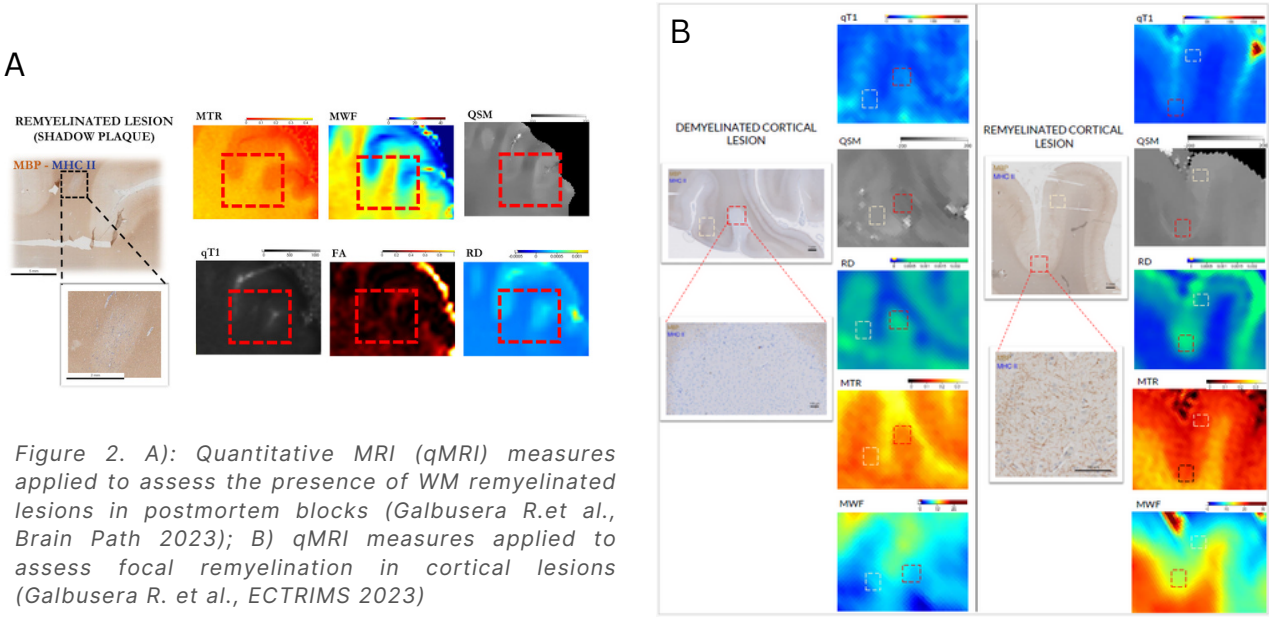


Figure 2. A): Quantitative MRI (qMRI) measures applied to assess the presence of WM remyelinated lesions in postmortem blocks (Galbusera R.et al., Brain Path 2023); B) qMRI measures applied to assess focal remyelination in cortical lesions (Galbusera R. et al., ECTRIMS 2023)

Using an in vivo and postmortem validation method, we have also identified a novel feature of some subpial cortical lesions: arim of increased susceptibility in quantitative susceptibility maps, representing activated microglia cells. (Galbusera R. et al., Annals of Neurol 2023).

The Laboratory of Clinical Neuroimmunology lead by Jens Kuhle focuses on the discovery, development and validation of body fluid biomarkers and is responsible for the blood and cerebrospinal fluid biobank of the Department of Neurology and for the national coordination of the SMSC.

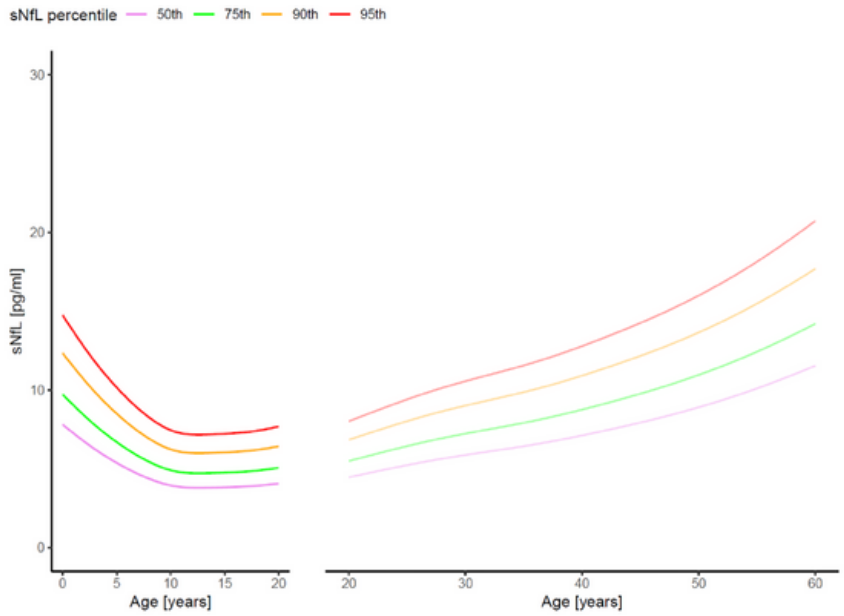
In 2023, the group received a new 4-year project grant focusing on quantifying progression in MS by serum glial fibrillary acidic protein (sGFAP) for personalised medicine and identification of novel targets from the Swiss National Science Foundation, and National MS Society (USA).

The SMSC is meanwhile in its 11th year of existence providing high quality clinical and imaging data as well as biosamples from more than 13’800 time points for translational medicine research and the definition of novel precision medicine tools.

It is a key resource for clinical and translational research projects at RC2NB and the MS Centre at the University Hospital Basel and for numerous national and international collaborations. The group's productivity is exemplified by authorship or co-authorship in 64 original articles in 2023.

Key achievements in 2023 were the generation of a sNfL reference database covering neonatal age to adolecence using serum samples from 2667 healthy controls from Europe and North America. Age-adjusted sNfL Z scores showed higher effect size metrics (Cohen's d) compared with the application of raw sNfL concentrations (Abdelhak et al., Lancet Neurology 2023; Figure 3).

Figure 3. sNfL percentiles reference curves in the paediatric and adult population



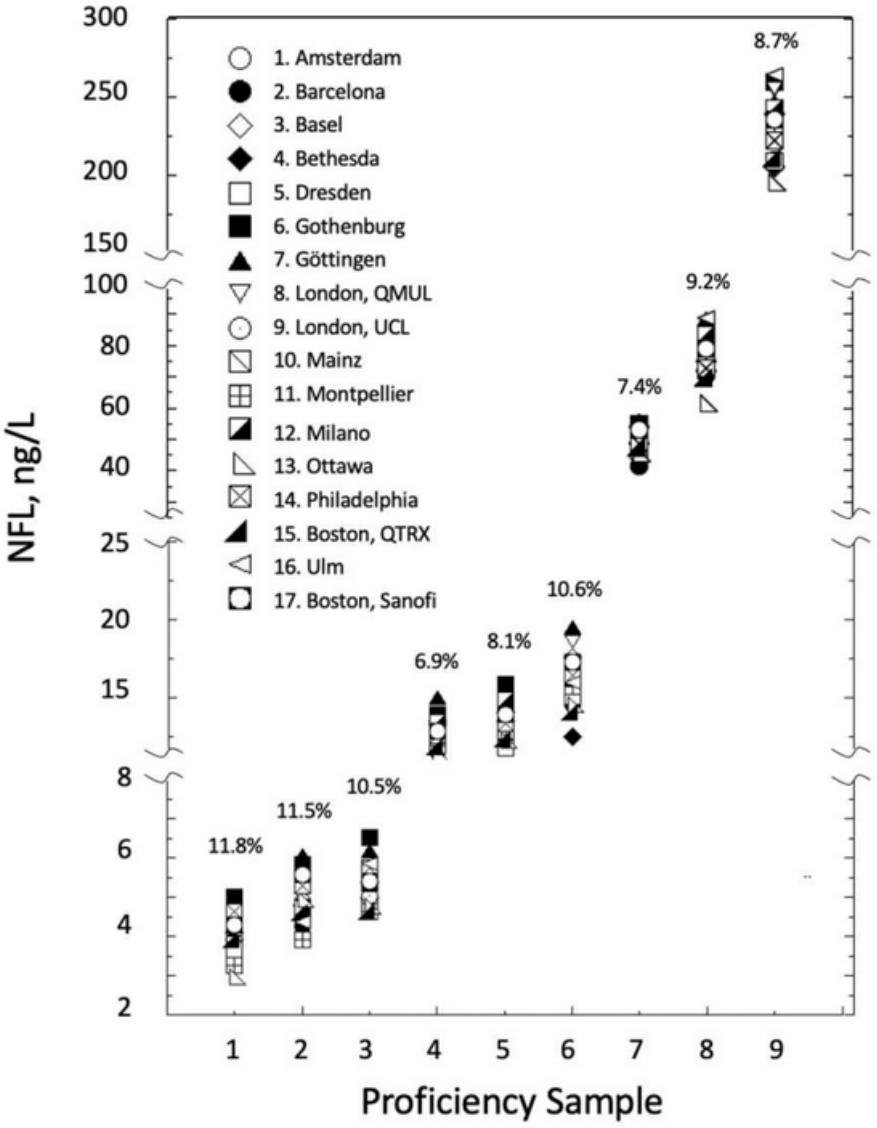
Legend: Combined sNfL percentiles reference curves in paediatric and adult populations (Benkert et al., Lancet Neurology, 2022) show smooth continuity between the proposed cut-offs for sNfL percentiles in the two independent reference populations. A generalized additive model for location, scale, and shape (GAMLSS) was used to model the non-linear association of sNfL concentration (pg/mL) in controls and age (from birth to 20 years of age (left) and until the age of 65 (right, Benkert et al., 2022).

By combining two of the largest observational cohorts (EPIC, University of California San Francisco and SMSC) involving 1899 participants with over 12000 longitudinal visits we showed that sNfL concentrations increased sharply between 12 and 26 months before the diagnosis of confirmed disability progression.

However, at the time disability progression was detected, sNfL concentrations were no longer elevated compared to patients with stable disease, suggesting that sNfL reflects dynamic changes indicative of actual disease processes earlier than physical examination (Abdelhak et al., JAMA Neurology, 2023).

The team further led a large multi-site analytical validation of the Simoa NF-light assay in serum from patients with MS in 17 centres in Europe and the United States. All centres performed measurements using a standardized assay protocol and common materials provided by us to evaluate precision, sensitivity, and parallelism for the Simoa NfL assay. Importantly the between-laboratory imprecision was below 10% across all sites (Kuhle et al., Clin Chem Lab Med, 2023; Figure 4).

Figure 4. Variation in results for each blinded serum sample across 17 sites



Legend: Total coefficients of variation of the NfL results for each sample are depicted. Inter-laboratory consistency of sNfL results with samples from normal and MS patients was examined in a round-robin study with 9 blinded samplescentrally prepared and shipped.

WORKSTREAM 3: RECORDING AND UNDERSTANDING THE DYSREGULATED IMMUNE SYSTEM

Research Group Leaders

Prof Tobias Derfuss

Cellular and Molecular Neuroimmunology

Prof Anne-Katrin Pröbstel

Experimental Neuroimmunology

Prof Matthias Mehling

Immunosenescence, Protective Immunity under DMT

The Clinical Neuroimmunology Lab (Prof 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 project grants and a Sinergia grant from the SNF, the Swiss Personalized Health Initiative, and grants from industry and private foundations.

In 2023 the group concluded and published a multi-year study on the significance of cell-binding IgM in the CSF of pwMS (Callegari et al., 2023a, summarized in Figure 5). This project started in 2017 with the observation that CSF from a sub-population of patients contained IgM that bound to live cells from a primitive neuroectodermal cell line (Figure 5A). Unlike IgG, this signal was specific to patients with MS or CIS, and independent from the global concentration of IgM in the CSF.

Monoclonal antibodies from B cells found in the CSF of a patient with this signature were cloned and investigated, and using a combination of immunoprecipitation mass spectrometry and transcriptional analysis, the target of one of them was identified as SCARA5 (Figure 5B), an iron-transporting scavenger protein that is expressed on some gabaergic neurons, and particularly by cells of the choroid plexus and cerebral blood vessels. Anti-SCARA5 antibodies injected into the brains of mice exacerbate the ingress of encephalitiogenic T cells, providing a possible mechanism by which these autoantibodies might contribute to disease progression (Figure 5C).

As a spin-off of this project, the group also adapted the high-throughput live cell flow cytometry technique that was used for screening the cohorts for the IgM signature for the purpose of monitoring spillover of therapeutic antibodies into non-blood anatomical compartments, particularly CSF and breast milk (Callegari et al., 2023b). Nearing completion are studies of the basic mechanisms governing B cell ingress into the CNS (manuscript in preparation).

Looking further ahead, the successful collaboration with immunologists and computational biologists in Zürich has been extended by securing a four-year, multi-lab Sinergia grant from the SNF to investigate the role of Epstein Barr virus in MS etiology.

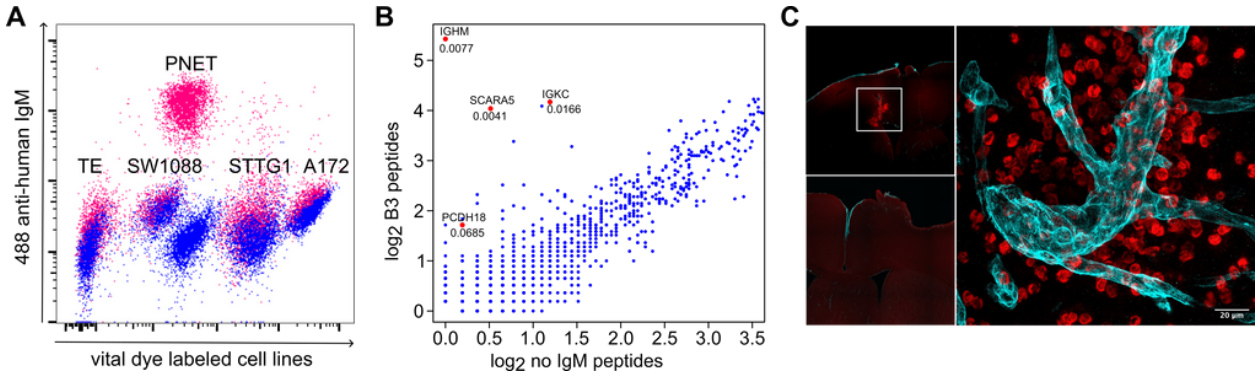


Figure 5. The significance of IgM antibodies targeting SCARA5 in MS. (A) Exemplary flow cytometry plot showing detection in CSF of IgM binding to 5 cell lines including priminitive neuroectodermal tumor cells (PNET, 3rd from left). Red dots show binding of IgM (vertical axis) detected with an anti-human IgM secondary. Blue plots are cells labeled with secondary only. (B) Identification of PNET-binding patient-derived monoclonal IgM target antigen by immunoprecipitation and mass spectrometry. (C) Impact of anti-SCARA5 antibodies in the mouse striatum. Large image on right is a confocal micrograph showing T cells (red) that have infiltrated the brain parenchya surrounding a blood vessel (cyan) under the influence of the injected antibody. Smaller images on left are lower power micrographs showing the location of this lesion in the mouse brain.

The overall aim of the research group "Experimental Neuroimmunology" (Prof Pröbstel) at the Departments of Biomedicine and Clinical Research is understanding the functional diversity and specificity of B cells and their interaction with gut microbiota in central nervous system inflammation including MS, MOGAD, autoimmune encephalitis and neurolupus.

Ultimately the group strives to foster immune regulatory responses and achieve tailored depletion of immune cell subpopulations through targeted manipulation of the gut microbiome. Current research focuses on three main topics: (I) deciphering microbial-immune cell crosstalk in MS, (II) decoding pathogenic B cell and antibody profiles in MOGAD, (III) identifying microbial and immune signatures associated with treatment (non-) response.

Achievements in 2023 include: (1) Identification of anti-MOG-IgA as a novel autoantibody in a clinically distinct subgroup of patients with demyelinating CNS disease seronegative for MOG-IgG and AQP4-IgG (Gomes*, Kulsvehagen* et al. JAMA Neurology 2023; Lipps*, Gomes*, Kulsvehagen* et al. JAMA Neurology 2023) (Figure 6). Among patients double-seronegative for AQP4-IgG and MOG-IgG (n=1126/1339; 84%), isolated MOG-IgA was identified in 6% (n= 3/50) of patients with NMOSD, in 2% (n=5/228) of patients with other CNS demyelinating disease, and in 1% (n=10/848) of patients with multiple sclerosis (MS) but in none of the HC (n=0/110).
The most common disease manifestation in isolated MOG-IgA seropositive patients was myelitis (65%), followed by more

frequent brainstem syndrome (44%, p=0.048), and infrequent manifestation of ON (27%, p=0.02) compared to MOG-IgG patients. MOG-IgA was associated with less frequent type II oligoclonal bands (OCBs) (38%) compared to MOG-IgG/IgA seronegative MS patients (93%, p<0.0001).
Further, most patients with isolated MOG-IgA presented events of demyelination after recent infection/vaccination (64%). These findings suggest that MOG-specific IgA might serve as a novel diagnostic biomarker for patients with CNS demyelination in a subgroup of AQP4-/MOG-IgG double-seronegative patients.

(2) In a joint effort with the groups of Prof Gommermann (Toronto) and Prof Zipp (Mainz) and contributions from Jens Kuhle (Workstream 1), we demonstrated that elevation of BAFF following B cell depletion therapy offers neuroprotection in MS and EAE (Wang*, Lüssi*, Neziraj*, Pössnecker* et al. Science Translational Medicine, in press) pointing towards a potential novel mode of action of anti-CD20 depleting therapies through immune regulatory responses. (3) In experimental models Lena Siewert and Elisabeth Pössnecker identified antigen-specific activation of gut originating immune cells as a driver of autoimmune neuroinflammation with implications for the role of the microbiome in triggering autoreactive immune response in MS patients (Siewert et al., under revision).

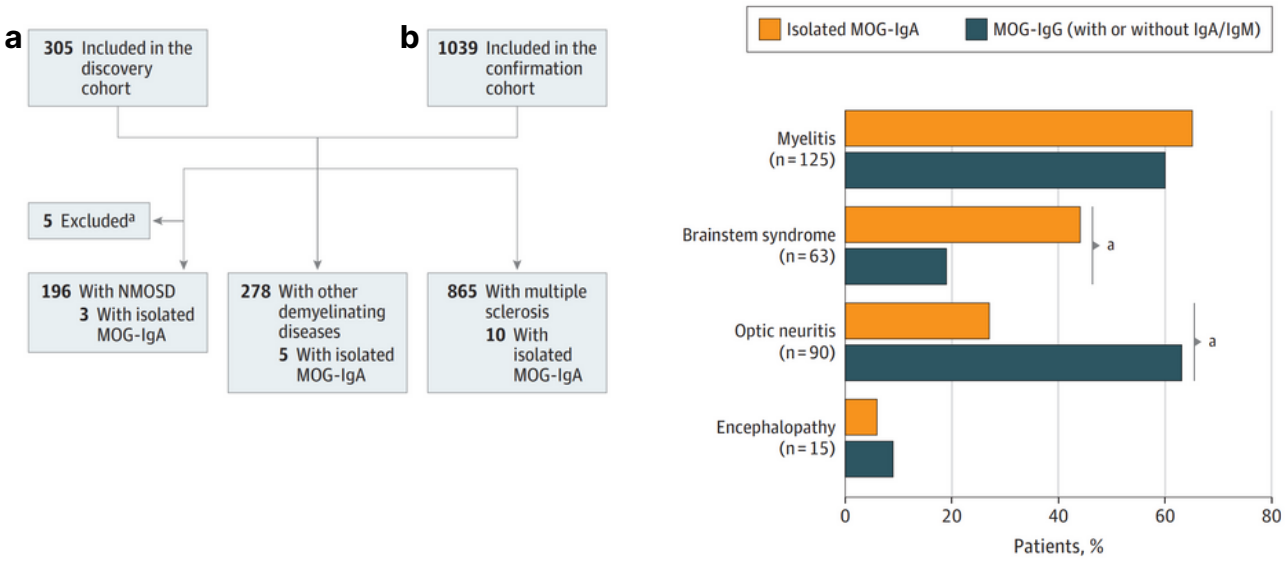


Figure 6. MOG-IgA characterizes a subgroup of patients with central nervous system demyelination. (a) Flowchart of patients in the discovery and confirmation cohort who were screnned for MOG-IgA, MOG-IgG, and MOG-IgM AQP4 was tested as part of the routine clinical diagnosis. (b) Frequency of disease manifestations for patients with isolated MOG-IgA and MOG-IgG.

The group of Prof M. Mehling (Translational Neuroimmunology) at the DBM assessed the role of the atypical chemokine receptor ACKR3 on the formation of inflammatory CNS-lesions. In collaboration with Prof Tim Schroeder (DBSSE/ ETHZ) a single molecule detection assay for ACKR3 and its ligand CXCL12 in mouse brain was established. This allows to link the activity of ACKR3 with histology in EAE lesions and EAE disease course in different ACKR3 genotypes. In the realm of MS treatments, the group aims to comprehend their effects on immunosenescence—a phenomenon characterized by age-related changes in the immune system. To this end, flow cytometry data are linked to clinical, radiological and laboratory data. This revealed differential proportions of immunosenescent T cells in blood of multiple sclerosis patients under specific treatments. The group is currently working on dissecting signaling pathways and cellular interactions to unveil the role of immunotherapies on the aging of the immune system.

WORKSTREAM 4: PRAGMATIC TRIALS AND REAL-WORLD EVIDENCE

Research Group Leaders

PD Dr Lars Hemkens

Senior Scientist
Neurology

Prof Jens Kuhle

Swiss MS Cohort Study and Laboratory of Clinical Neuroimmunology

Prof Özgür Yaldizli

Consultant Neurologist

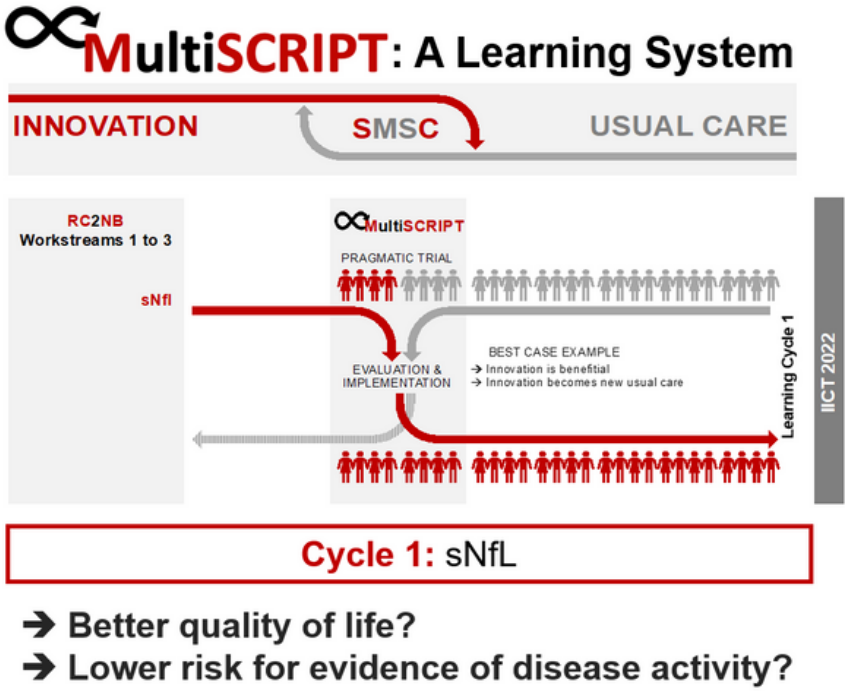


Figure 7. MultiSCRIPT A learning research and care system for people with MS in Switzerland

This workstream provides the framework for translating innovation into research and care. It develops the methodology and structures for the final development stages of RC2NB's diagnostic and therapeutic innovations. The aim is to assess their clinical meaningfulness and the benefits to patients, ensuring these innovations not only meet but exceed current healthcare standards.

The Swiss MS Cohort (SMSC), led by Prof Kuhle, with its standardized procedures and high-quality data collection, is an integral asset to merging pragmatic randomized trial methodology with real-world data collection.

This is catalyzed by MultiSCRIPT (Multiple SClerosis pRagmatIc Platform Trial), a project initiated in 2022 and funded by the Swiss National Science Foundation and embedded in the SMSC, we focused on personalized medicine in Multiple Sclerosis. MultiSCRIPT is a learning care system for persons with MS, dedicated to continuously evaluating innovative treatment strategies emerging from other RC2NB workstreams, aiming to constantly learn and develop more personalized treatment approaches with minimal but necessary intervention.

In 2023, we completed the integration of MultiSCRIPT into the SMSC, including preparations for continuous patient randomization within the SMSC, streamlined informed consent procedures within routine care, adapted data collection with digital tools, selected appropriate quality of life measurement instruments, and implemented these changes in the routine clinical care at the MS Center.

In MultiSCRIPT's first cycle led by Prof Oezguer Yaldizli (co-PI Prof Jens Kuhle and PD Dr Lars Hemkens, scientific coordination by Dr Perrine Janiaud), we compare in a randomized trial design personalized treatment decisions based on additional information provided by serum neurofilament light chain values against the current standard of care.

We aim at recruiting over 900 SMSC patients, with the first patient randomized in January 2024. 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 shown to be superior, NfL monitoring will become the new standard of care, and the next promising care strategy will be evaluated in the next learning cycle.

Integral to this workstream is the Pragmatic Evidence Lab (led by PD Dr Hemkens), which is situated at the intersection of clinical research, evidence-based medicine, and digital health. The lab provides a robust methodological foundation for integrating research into routine care using digital measures and real-world data. To inform the design and conduct of the RC2NB flagship projects MultiSCRIPT, SMSC, dreaMS, and various other studies in workstreams 1,2 and 3, in 2023, the lab's team evaluated all pragmatic randomized trials in multiple sclerosis, conducted systematic analyses of all published validation studies of digital apps for MS, assessed the concepts and definitions of digital biomarkers in biomedical literature, and performed systematic analyses of all patient-reported outcomes and quality of life instruments used in clinical trials of MS disease-modifying treatments. Moreover, synergistically drawing upon the diverse clinical, technological, and methodological expertise within RC2NB, the lab explored the application of artificial intelligence (large language models) in the context of evidence appraisal.

SYMPOSIUM RC2NB 4.0

BREAKING BOUNDARIES: RC2NB 4.0 SYMPOSIUM TRANSFORMS MS RESEARCH WITH FLAIR

The **RC2NB Symposium**, under the theme "Transforming Research in Multiple Sclerosis (MS) and Neuroimmunology" unfolded on December 15, 2023, within the **Biozentrum Lecture Hall** in Basel. This symposium was well attended and served as an exemplary forum, facilitating the exchange of innovative methods and approaches to address central questions and unmet needs in MS and Neuroimmunology.

Commencing early on a Friday morning, the event attracted a diverse audience of more than 350 medical doctors, basic scientists, physicists, and engineers from both academia and the MedTech/pharmaceutical industry. The symposium showcased the interdisciplinary collaboration between medical research, digital innovation, and healthcare, providing a comprehensive overview of the current state and future directions of research in MS and Neuroimmunology through inspirational talks, engaging discussions as well as selected poster presentations from renowned international experts.

Tobias Heimann (Erlangen) started the symposium by sharing insights from the health digital twin in cardiology - a personalized physiological model updated continuously with each scan and exam. Then, we deep-dived into the neuroimmunology realms, with an inspiring overview of the current understanding of MS immunology by Amit Bar-Or (Philadelphia)

Tobias Derfuss (Basel) presented recent findings about how B cells may trigger autoimmunity in healthy people and can enter the brain during a central nervous system (CNS) infection. Starting with a review of the effects of B-cell depletion **Stephen Hauser** (San Francisco) gave a visionary lecture on how these effects can be further improved and how, accounting for its complexity MS might even become a curable disease.

In the session on biomarkers, **Jens Kuhle** presented the diagnostic and prognostic power of fluid biomarkers such as neurofilament light chain protein (NfL) and glial fibrillary acidic protein (GFAP); **Johanna Oechtering** (Basel) highlighted the role of IgM and complement in accelerating damage and progression in multiple sclerosis (MS). **Daniel S. Reich** (Bethesda) shared thoughts and data about how low-field MRI could provide reliable and low-cost traditional biomarkers for the care of MS patients. **Alessandro Cagol** (Basel) gave examples of how neuroimaging can reveal the mechanisms associated with progression independent of relapse activity (PIRA). **Cristina Granziera** (Basel) provided a glimpse into the future through novel approaches in advanced quantitative MRI, both in vivo and postmortem.

The session on "*Clinical Trials and Disease Monitoring in MS*" was opened by **John Ioannidis** (Stanford), who highlighted the vital need for conducting systematic research with scientific rigor, transparency, and large-scale collaboration.

Lars Hemkens (Basel) emphasized the critical role of pragmatic trials and urged the use of digital health technologies to unlock their untapped potential in advancing MS diagnostic and treatment strategies.

Last, in the session entitled “Towards Digital Twins in Neuroimmunology” **Jan Hillert** (Stockholm) highlighted the need for high-quality large cohorts of MS data to gain knowledge about Serious Adverse Events (SAEs). **Björn Tackenberg** (Basel) showcased the transformative impact of federated learning as a novel approach to comprehending biological and clinical data, particularly in the context of the era of big data. Lastly, **Amit Khanna** (Basel) shared with the audience learnings acquired through the integrated analysis of pooled data from large-scale randomized controlled clinical trials and their extensions.





TRANSFORMING RESEARCH

IN MS AND NEUROIMMUNOLOGY

SYMPOSIUM






FINANCIAL STATEMENT FOR 2023

FINANCIAL STATEMENT 2023

	2023	2022
Income from research contributions	3 740 764 CHF	3 469 454 CHF
Income from other sources	2 083 037 CHF	263 667 CHF
Total Operating Income	**5 823 801 CHF**	**3 733 121 CHF**
Technical Development incl. expenses for third party services	-873 268 CHF	-1 046 691 CHF
Personnel	- 1 818 044 CHF	-1 031 898 CHF
Aministration and other expenses	-158 535 CHF	-233 068 CHF
Total Operating Expenses	**-2 849 847 CHF**	**-2 311 657 CHF**
Financial Income	1377 CHF	887 CHF
Financial Expenses	679 CHF	-6951 CHF
Financial Result	698 CHF	-6064 CHF
Ordinary Result before allocation to restricted funds	**2 974 652 CHF**	**1 415 400 CHF**
Assets allocated to restricted funds	-1 355 670 CHF	NA [1]
Ordinary Result after allocation to restricted funds	**1 618 982 CHF**	**1 415 400 CHF**

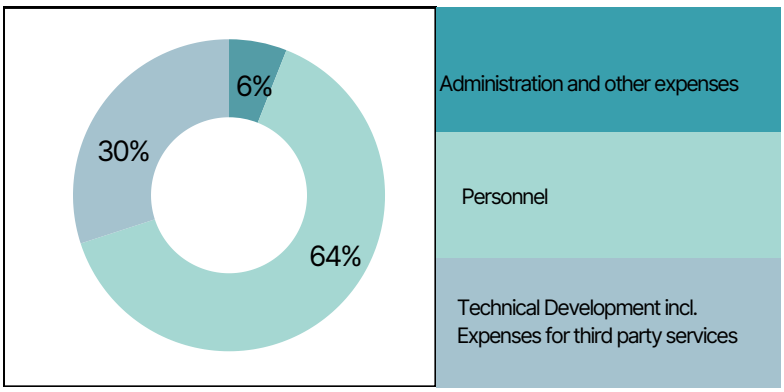


Figure 8. Expenses 2023

[1] Fund allocation to restricted and unrestricted was introduced in 2023

EXPENSES BY COST CENTERS

RC2NB's Financial Statement 2023 was reviewed and approved by the auditor BDO AG. Most projects of research groups in the RC2NB workstreams 2, 3 and 4 are currently funded independently and managed by the University Hospital or the University of Basel and therefore, not part of RC2NB's financial statement.

	Personnel	Consumable and other lab services	Technical Development	Administration and other expenses	Total
WS1	-882 567 CHF	-87 070 CHF	-785 382 CHF	-50 315 CHF	**-1 805 333 CHF**
WS2	-401 440 CHF	0 CHF	0 CHF	- 1 467 CHF	**-402 907 CHF**
WS3	-73 480 CHF	0 CHF	0 CHF	0 CHF	**-73 480 CHF**
WS4	-77 019 CHF	0 CHF	0 CHF	-4 400 CHF	**-81 419 CHF**
Data Storage and Analysis	-95 953 CHF	-6 993 CHF	0 CHF	74 785 CHF	**-28 160 CHF**
Management/ Administration	-214 979 CHF	0 CHF	0 CHF	-180 873 CHF	**-396 565 CHF**
Research Funds	-22 304 CHF	0 CHF	0 CHF	-39 695 CHF	**-61 984 CHF**
Total	**-1 767 741 CHF**	**-94 062 CHF**	**-785 382 CHF**	**-202 662 CHF**	**-2 849 847 CHF**

EQUITY

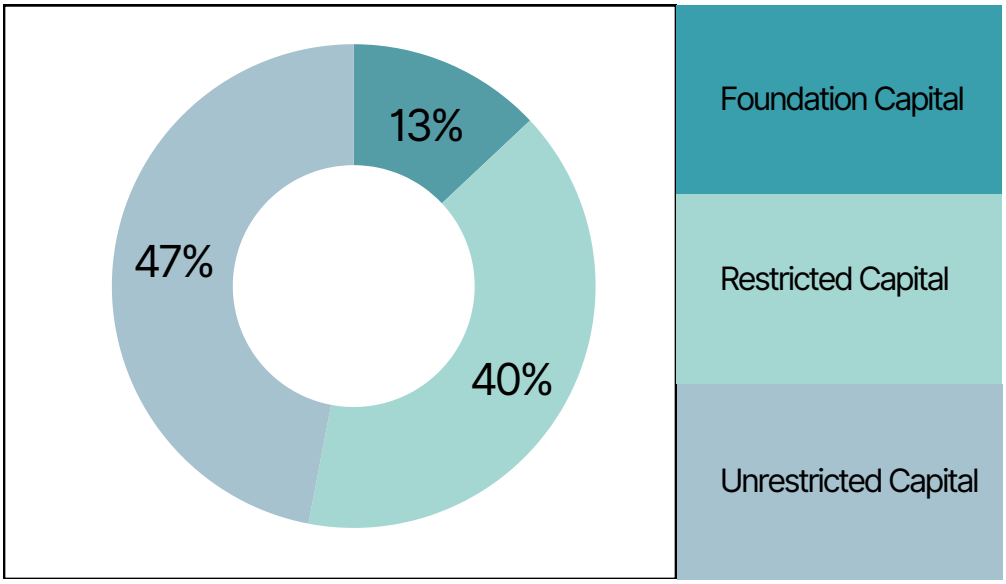


Figure 9. Equity Structure of Foundation
Foundation Capital: Capital reserves as per legal requirement
Restricted Capital: Capital allocated for technical development, conduct of dreaMS Validation Study 1 and dreaMS Validation Study 2
Unrestricted Capital: Capital available to assign in accordance with foundation mission

	2023	2022
Equity as of 01.01	**4 697 473 CHF**	**3 282 073 CHF**
Income	5 824 499 CHF	3 734 008 CHF
Expenses	-2 849 847 CHF	-2 318 608 CHF
Equity as of 31.12	**7 672 125 CHF**	**4 697 473 CHF**
Foundation Capital	1 000 000 CHF	NA
Restricted Capital	3 094 073 CHF	NA
Unrestricted Capital	3 578 052 CHF	NA

Main Partnering Institutions and Research Support

Thank you for supporting us in 2023!

Our work is only possible thanks to the broad support of our institutional donors. We consider ourselves very fortunate to have received very generous donations and to be able to build on our long-standing partnerships with our supporters.

Universitätsspital Basel

University of Basel

Healios *rebranded to* Indivi

Roche

NOVARTIS

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Schweizerischer Nationalfonds

MS Schweizerische Multiple Skleros Gesellschaft

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Innosuisse – Schweizerische Agentur für Innovationsförderung

Neurostatus-UHB AG

MEMBERS AND COLLABORATORS OF RC2NB BY WORKSTREAMS

WORKSTREAM 1

Group Members and Collaborators

dreaMS and digital health:
Caroline Brunner (study nurse)
Sibylle Kolb (study nurse)
Rossella Sala, MSc (study nurse)
Jasmin Hatanek (management assistant)
Melanie Lacalamita (study coordinator)
Philipp Limberg, MSc (project management)
Vera Müller, MSc (Regulatory)
Marko Obradovic, MSc (software engineer)
Vanny Phavanh (study nurse)
Silvan Pless, MSc (neuropsychologist, PhD student)
Melanie Haag, PhD (Project Management)
Dörthe Hansen (Project Management)
Bebeka Cosandey, PhD (Scientific Project Manager)
Dr Andrea Wiencierz (statistician)
Dr Tim Wölfle, MSc (physician-scientist, PhD student)
Thomas Bezençon (medical student)
Lea Hanl (management assistant)
Kathleen Herrgott (scientific collaborator and videographer)
Claudia Saupper, MSc (Data Architect)
Cathrine Axfors, PhD (Scientific Coordinator)
Claudia Becherer (Regulatory Affairs)
Madeleine Vollmer (Regulatory Affairs)
Guilhem Dupont, Corne de Jong, Juan Collado, James Lunt, Óscar Reyes (Healios/INDIVI; other employees of Healios (now INDIVI Ltd involved in dreaMS are not individually mentioned)

Neurostatus-UHB LtD
Dr Ioanna Athanasopoulou (neurologist)
Dr Ilaria Callegari (neurologist)
Dr Lisa Dinsenbacher (neurologist)
Barbara Forman (operations & legal affairs)
Evy Fricker (COO)
Nuria Alicia Cerdá Fuertes (neurologist)
Eddy Garcia (operations lead)
Marcos Gamez (IT)
Martina Greselin (PhD student)
Gabriel Hug (student/IT)
Jasmina Ivanovic (executive assistant)
Prof Christian Kamm (neurologist)
Jakob Kel (IT)
Joanne Sim Joo Li (operations)
Dr Giulia Mallucci (neurologist)
Dr Magdalena Mroczek (neurologist lead)
Vanessa Müller (operations)
Steven Njuguna (IT)
Thomas Trouillet (IT)
Colleen Waiz (operations)
Simon Wunderlin (IT)
Andrea Zimmer (MA Nursing Science, study coordinator)

WORKSTREAM 2

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)
Riccardo Galbusera (PhD student)
Antonia Wenger (PhD student)
Martina Greselin (PhD student)
Sara Bosticardo (PhD student)
Federico Spagnolo (PhD student)
Selina Leber (master student, Medicine)

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)
MSc Sabine Schädelin (statistician)
Dr Dimitrios Gkotsoulias (research fellow)
Dr Xinjie Chen (PhD student)
Osman Hatipoglu (master student, Biomed Engineering)
Igor Schneider (master student, Medicine)
Elisabetta Giacomelli (master student, biomedical engineering)
Marguerite Limberg (research assistant)
Aida Suljakovic (personal assistant)

PD Dr Athina Papadopoulou team:
Dr Federico Burget Villena (MD)
Dr Katerina Ebner (MD)
Dr Shaumiya Sellathurai (MD)
Dr Nuria Cerdá Fuertes (MD)
Dr Jenni Kuhlmann (MD)

Prof Özgür Yaldizli team:
Tim Sinnecker (research fellow)
Jannis Müller (research fellow)
Gizem Tan (master student)
Sophia Reinmann (master student)
Laurent Baumann (master student)

Prof 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)

Prof Jens Kuhle team:
Swiss MS Cohort Study and Clinical Neuroimmunology - Fluid Biomarker Laboratory)
Dr Pascal Benkert (Head of SMSC datacentre, statistician)
Caroline Brunner (study nurse)
Lilian Demuth (study coordinator)
Juan Vilchez Gomez (research technician)
Ulrich Gress (study coordinator)
Melanie Lacalamita (study nurse)
Prof David Leppert (senior postdoc)
Marguerite Limberg (study nurse)
Aleksandra Maleska Maceski, MSc (bioengineer)
Dr Johanna Oechtering (senior neurologist/postdoc)
Dr Annette Orleth (postdoc)
Miriam Rhyner (study nurse)
Sabine Schaedelin, MSc (statistician)
Daniela Stanojevic (study coordinator)
Suvitha Subramaniam, MSc (data scientist)
Dr Eline Willemse (postdoc)
Amar Zadic (research technician)
Genevieve Schmid (study nurse)
Ghislaine Billot (study nurse)
Vanny Phavanh (study nurse)
Suzana Miteva (study nurse)

WORKSTREAM 3

Group Members and Collaborators

Prof Tobias Derfuss Team:
Sebastian Holdermann, MSc (PhD student)
Dr Nicholas Sanderson (postdoc)
Mika Schneider, MSc (PhD student)
Dr Edoardo Galli (postdoc)
Hong Chang (undergraduate student)

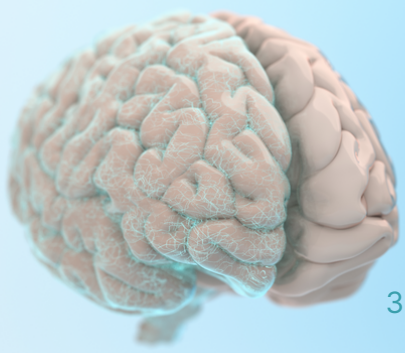
PD Dr Matthias Mehling team:
Mali Coray (MD-PhD student)
Dr Varenka Epple (MD)
Annika Frentzel, BSc (master student)
Dr Jakob Fuhrmann (MD)
Dr Klara Ivanek (postdoc)
Melanie Kaech, BSc (master student))

Prof Anne-Katrin Pröbstel team:
Miriam Beyerle (MD Doctoral Student)
Felix Bosch (MD Doctoral Student)
Paula Cullen (personal assistant)
Tim Dürrenberger (doctoral student)
Julia Flammer (resident/postdoc)
Ana Beatriz Gomes (PhD student)
Julia Gutzwiller (clinical study coordinator)
Marco Häfelfinger (medical student)
Laila Kulsvehagen (PhD student)
Anne-Cathérine Lecourt (lab manager/technician)
Jasmine Lerner (master student)
Patrick Lipps (MD Doctoral Student)
Luc Lutz (master student)
Aida Munoz (Research Associate)
Dr med Tradite Neziraj (postdoc)
Maximilian Otto (undergraduate student)
Elisabeth Pössnecker (PhD student)
Roxanne Pretzsch (postdoc)
Florine Scherhag (master student)
Dr Lena Siewert (postdoc)
Stijn Swinnen (Guest scientist)
Angéline Wettig (undergraduate student)
Nora Wetzel (MD PhD student)

WORKSTREAM 4

Group Members and Collaborators

PD Dr Lars Hemkens
Pragmatic Evidence Lab:
Dr Perrine Janiaud (scientific coordinator, research fellow)
Dr Julian Hirt (research fellow)
Dr Cathrine Axfors (scientific coordinator, research fellow)
Dr Kim Boesen (research fellow)
Pascal Düblin (application developer)
Kinga Dembowska (master student, epidemiology)
Ada Sison (master student, epidemiology)
Thao Vy Nguyen (master student, epidemiology)
Ana Karen Macias Alonso (master student, biomedical engineering)
Maximilian Beer (medical master student)



Awards, distinctions, memberships, completed PhD and Master theses in 2023

P. Benkert and **St. Meier** received the Morgens and Wilhelm Ellermann Award for "Serum neurofilament light chain for individual prognostication of disease activity in people with multiple sclerosis: a retrospective modelling and validation study", Lancet Neurol. 2022 Mar;21(3):246-257

T. Derfuss and **J. Kuhle** received the first MS research award of the Swiss MS society.

T. Derfuss was nominated as honorary member of ECTRIMS.

E. Galli, Research Group Cinical Neuroimmunology, received a grant by the Swiss Neurological Society for his project "Immunomonitoring of Therapy Escalation in MS" .

C. Granziera was elected chair of the prestigious White Matter (WM) group at the International Society of Magnetic Resonance Imaging. She still holds the co-presidency of the Medico-Scientific Advisory Board of the Swiss MS Society (together with Prof B. Engelhard), she is 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 ourstanding 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.

According to ISI statistics based on citations in their field in 2023 **J. Kuhle** and **L. Kappos** were the two top 1% highly cited researchers from the University Hospital Basel.

A-K Pröbstel received the Early Career Award from the Swiss Society of Allergy and Immunology as well as the Alumni Award from the Medical Faculty of the University of Basel.

A-K Pröbstel has been appointed as member of the scientific board of the Schilling Foundation and the Neuromyelitis optica Study Group (NEMOS). Several members of her group are supported with prestigious fellowships by international and Swiss institutions (Swiss Academy of Medicine Young Talents in Clinical Research Fellowship to Roxanne Pretzsch, Goldschmidt-Jacobson Foundation Doctoral Fellowship to Felix Bosch, Travel grant from the Research Fund Flanders to Stijn Swinnen).

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 Biomedicine)
Hye-In Kim, PhD (Department of Biomedicine)
Julia Flammer, MD Doctoral degree (Departments of Biomedicine and Clinical Research)
Janina Wendebourg, PhD (Department of Biomedical Engineering)
Patrick Lipps, MD Doctoral degree (Departments of Biomedicine and Clinical Research)
Laura Rieder, Msc (Department of Biomedicine)
Kinga Dembowska (Department of Clinical Research & Swiss TPH)
Thao Vy Nguyen (Department of Clinical Research & Swiss TPH)
Stephanie Meier, PhD (Department of Clinical Research)

Major competitive project and career grants awarded in 2023

A.-K. Pröbstel was awarded with a Horizon EU consortium grant (1.2 million €, 8.2 million to 10 other EU centers) as well as a 2-year funding from the Swiss MS society.

Together with **Dr Tradite Neziraj**, resident and postdoctoral fellow in her lab, **A.-K. Pröbstel** received funding from the US Department of Defense.

J. Kuhle received a 4-year project grant funding (715k CHF) from the Swiss National Science Foundation ("Quantifying progression in multiple sclerosis: serum glial fibrillary acidic protein (sGFAP) for personalised medicine and identification of novel targets") (2023 – 2027).

The Swiss MS Society decided to further support the SMSC with a 1.2 million CHF grant for 2023-2025.

J. Kuhle and **D. Leppert** received 2-year research grant funding from National MS Society (USA; Progressive MS Alliance) ("Neurofilament light chain and glial fibrillary acidic protein as tools to prognosticate the clinical course, and to quantify drug response in progressive multiple sclerosis") (2023 – 2025).

Publications in peer reviewed journals

*Highlighted papers are displayed in red ink and bold letters
*Authors displayed in blue ink ar members of RC2NB working groups

1. Abdelhak A, Antweiler K, Kowarik MC, Senel M, Havla J, Zettl UK, Kleiter I, Skripuletz T, Haarmann A, Stahmann A, Huss A, Gingele S, Krumbholz M, **Benkert P, Kuhle J**, Friede T, Ludolph AC, Ziemann U, Kümpfel T, Tumani H. Serum glial fibrillary acidic protein and disability progression in progressive multiple sclerosis. Ann Clin Transl Neurol. 2023 Dec 19;

2. Abdelhak A, Barba L, Romoli M, **Benkert P**, Conversi F, D'Anna L, Masvekar RR, Bielekova B, Prudencio M, Petrucelli L, Meschia JF, Erben Y, Furlan R, De Lorenzo R, Mandelli A, Sutter R, Hert L, **Epple V**, Marastoni D, Sellner J, Steinacker P, Aamodt AH, Heggelund L, Dyrhol-Riise AM, Virhammar J, Fällmar D, Rostami E, Kumlien E, Blennow K, Zetterberg H, Tumani H, Sacco S, Green AJ, Otto M, **Kuhle J**, Ornello R, Foschi M, Abu-Rumeileh S. Prognostic performance of blood neurofilament light chain protein in hospitalized COVID-19 patients without major central nervous system manifestations: an individual participant data meta-analysis. J Neurol. 2023 Jul;270(7):3315–28.

3. Abdelhak A, Benkert P, Schädelin S, Boscardin WJ, Cordano C, Oechtering J, Ananth K, Granziera C, Melie-Garcia L, Montes SC, Beaudry-Richard A, Achtnichts L, Oertel FC, Lalive PH, Leppert D, Müller S, Henry RG, Pot C, Matthias A, Salmen A, Oksenberg JR, Disanto G, Zecca C, D'Souza M, Du Pasquier R, Bridel C, Gobbi C, Kappos L, Hauser SL, Cree BAC, Kuhle J, Green AJ, UCSF, MS EPIC, and the SMSC Study Teams. Neurofilament Light Chain Elevation and Disability Progression in Multiple Sclerosis. JAMA Neurol. 2023 Dec 1;80(12):1317–25.

4. Abdelhak A, Kuhle J, Green AJ. Challenges and Opportunities for the Promising Biomarker Blood Neurofilament Light Chain. JAMA Neurol. 2023 Jun 1;80(6):542–3.

5. Abdelhak A, Petermeier F, Benkert P, Schädelin S, Oechtering J, Maleska Maceski A, Kabesch M, Geis T, Laub O, Leipold G, Gobbi C, Zecca C, Green A, Tumani H, Willemse E, Wiendl H, Granziera C, Kappos L, Leppert D, Waubant E, Wellmann S, Kuhle J. Serum neurofilament light chain reference database for individual application in paediatric care: a retrospective modelling and validation study. Lancet Neurol. 2023 Sep;22(9):826–33.

6. Abu-Rumeileh S, Abdelhak A, Foschi M, D'Anna L, Russo M, Steinacker P, **Kuhle J**, Tumani H, Blennow K, Otto M. The multifaceted role of neurofilament light chain protein in non-primary neurological diseases. Brain. 2023 Feb 13;146(2):421–37.

7. Achtnichts L, Zecca C, Findling O, **Kamm CP**, Mueller S, **Kuhle J**, Lutterotti A, Gobbi C, Viviani C, Villiger-Borter E, Nedeltchev K. Correlation of disability with quality of life in patients with multiple sclerosis treated with natalizumab: primary results and post hoc analysis of the TYSabri ImPROvement study (PROTYS). BMJ Neurol Open. 2023;5(1):e000304.

8. Amrein M, **Meier S**, Schäfer I, **Schaedelin S**, **Willemse E**, **Benkert P**, Walter J, Puelacher C, Zimmermann T, Median D, Egli C, **Leppert D**, Twerenbold R, Zellweger M, **Kuhle J**, Mueller C. Serum neurofilament light chain in functionally relevant coronary artery disease and adverse cardiovascular outcomes. Biomarkers. 2023 May;28(3):341–51.

9. Andreasson U, Gobom J, Delatour V, Auclair G, Noam Y, Lee S, Wen J, Jeromin A, Arslan B, Maleska Maceski A, Willemse E, Zetterberg H, Kuhle J, Blennow K. Assessing the commutability of candidate reference materials for the harmonization of neurofilament light measurements in blood. Clin Chem Lab Med. 2023 Jun 27;61(7):1245–54.

10. Ayroza Galvão Ribeiro Gomes AB, Kulsvehagen L, Lipps P, Cagol A, Cerdá-Fuertes N, Neziraj T, Flammer J, Lerner J, Lecourt AC, de Oliveira S Siebenborn N, Cortese R, Schaedelin S, Andreoli Schoeps V, de Moura Brasil Matos A, Trombini Mendes N, Dos Reis Pereira C, Ribeiro Monteiro ML, Dos Apóstolos-Pereira SL, Schindler P, Chien C, Schwake C, Schneider R, Pakeerathan T, Aktas O, Fischer U, Mehling M, Derfuss T, Kappos L, Ayzenberg I, Ringelstein M, Paul F, Callegaro D, Kuhle J, Papadopoulou A, Granziera C, Pröbstel AK. Immunoglobulin A Antibodies Against Myelin Oligodendrocyte Glycoprotein in a Subgroup of Patients With Central Nervous System Demyelination. JAMA Neurol. 2023 Sep 1;80(9):989–95.

11. Bar-Or A, Thanei GA, Harp C, Bernasconi C, Bonati U, Cross AH, Fischer S, Gaetano L, Hauser SL, Hendricks R, Kappos L, Kuhle J, Leppert D, Model F, Sauter A, Koendgen H, Jia X, Herman AE. Blood neurofilament light levels predict non-relapsing progression following anti-CD20 therapy in relapsing and primary progressive multiple sclerosis: findings from the ocrelizumab randomised, double-blind phase 3 clinical trials. EBioMedicine. 2023 Jul;93:104662.

12. **Barakovic M**, Pizzolato M, Tax CMW, Rudrapatna U, Magon S, Dyrby TB, **Granziera C**, Thiran JP, Jones DK, Canales-Rodríguez EJ. Estimating axon radius using diffusion-relaxation MRI: calibrating a surface-based relaxation model with histology. Front Neurosci. 2023;17:1209521.

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