Universität Basel

Faculty of Medicine

Universitätsspital Basel

RC2NB

ANNUAL REPORT

2022

RC2NB | Research Center for Clinical Neuroimmunology and Neuroscience Basel

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.

Contents

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 Granziera'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 autoimmune 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,

FDA, and other stakeholders as a "contradictio in adjecto": 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.

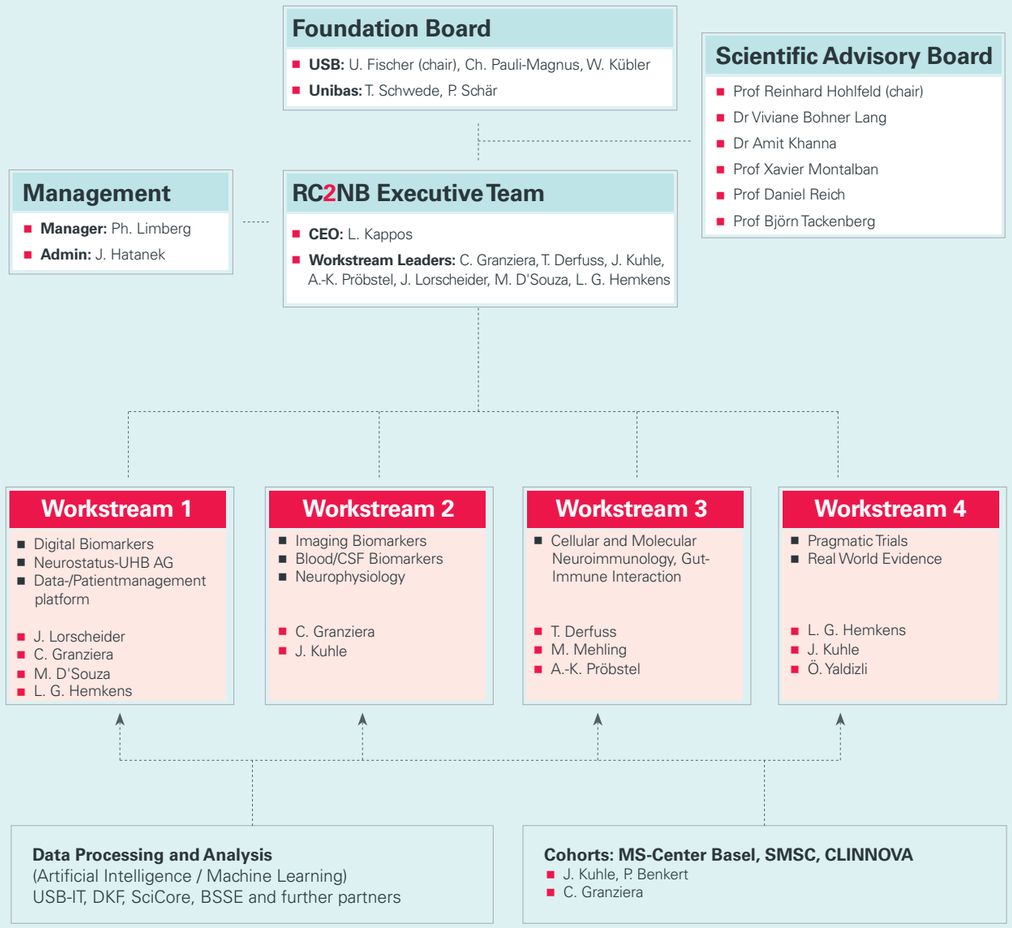
MultiSCRIPT will in a first cycle explore the value of sNFL, as addition to established decision algorithms for treatment escalation and de-escalation in relapsing MS. To better focus our respective activities, and encouraged by this IICT grant, we newly established "Pragmatic Trials and Real World Evidence"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

On the administrative and personel 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 | Governing Bodies

2.1 | Organizational Chart



2.2 | Board of Trustees

Members
Prof Urs Fischer (president of the Board, Chairman Neurology, University Hospital Basel)
Prof Christiane Pauli-Magnus (vicepresident of the Board, Head of 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)

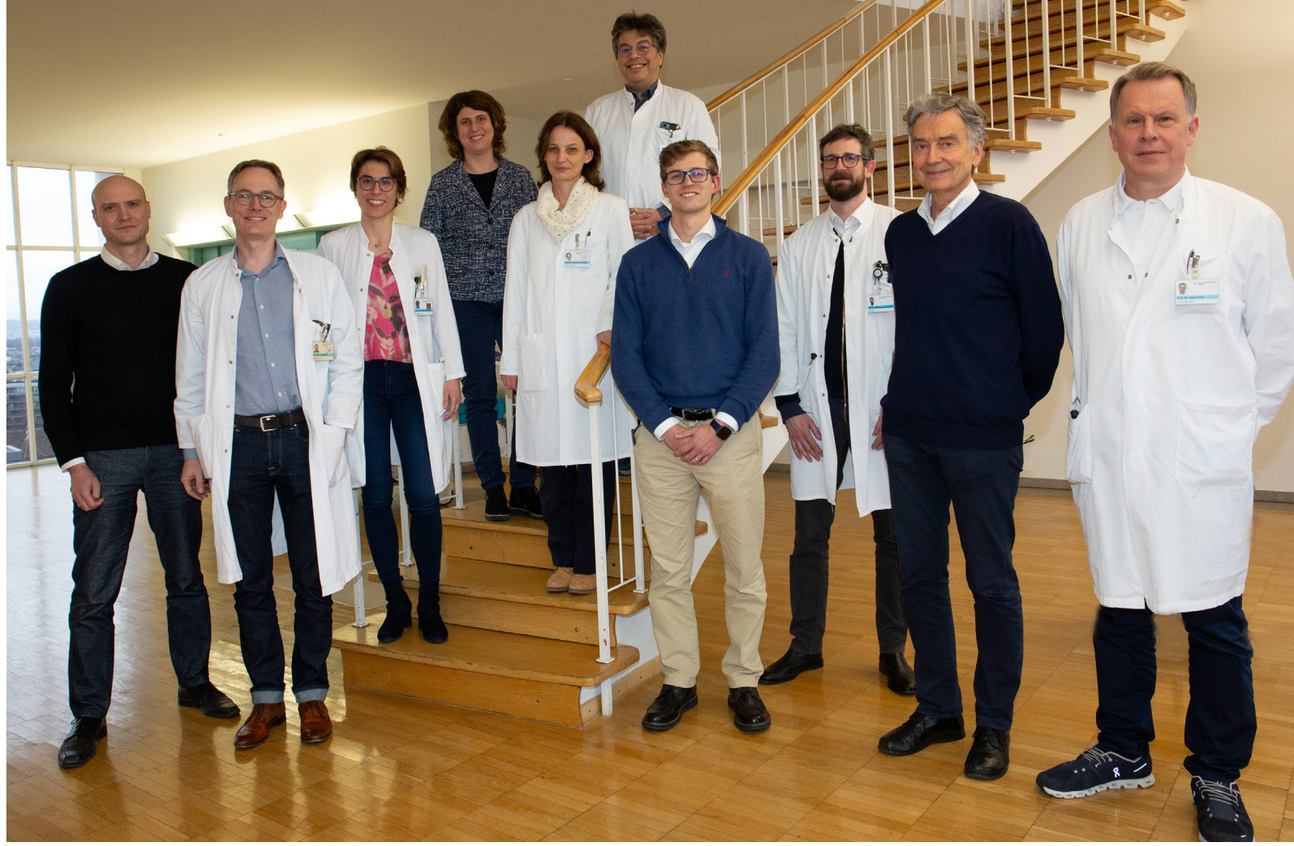
The Board of Trustees held three meetings, on January 6th, June 30th and November 29th 2022.

2.3 | Scientific Advisory Board

Members
Prof Reinhard Hohlfeld (chair), Munich, Germany
Dr Viviane Bohner Lang (patient representative), Allschwil, Switzerland
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 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."



Management Group (from left to right): Lars Hemkens, Tobias Derfuss, Anne-Katrin Pröbstel, Jasmin Hatanek, Cristina Granziera, Marcus D'Souza, Philipp Limberg, Johannes Lorscheider, Ludwig Kappos, Jens Kuhle

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 Kuhle, 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.

3 | Scientific Achievements

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.

DreaMS Study Team – (from left to right): Guilhem Dupont (Healios), Corne de Jong (Healios), Rossella Sala, Thomas Bezençon, Vanny Phavanh, Silvan Pless, Perrine Janiaud, Cristina Granziera, Vera Müller, Ludwig Kappos, Tim Wölfle, Philipp Limberg, Johannes Lorscheider, Lars Hemkens

3.1 | Workstream 1: Digital future

Research Group Leaders

PD Dr Marcus D'Souza (Neurostatus-UHB AG)
PD Dr Lars Hemkens (dreaMS, since 01.04.2022)
PD Dr Johannes Lorscheider (dreaMS)
PD Dr Yvonne Naegelin (dreaMS, until 30.03.2022)
Prof Cristina Granziera (dreaMS, since 01.02.2022)

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 Innosuisse – 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

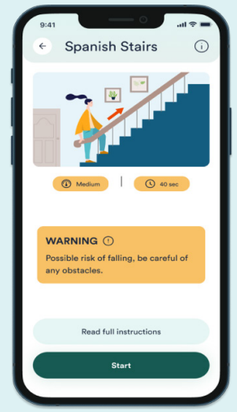
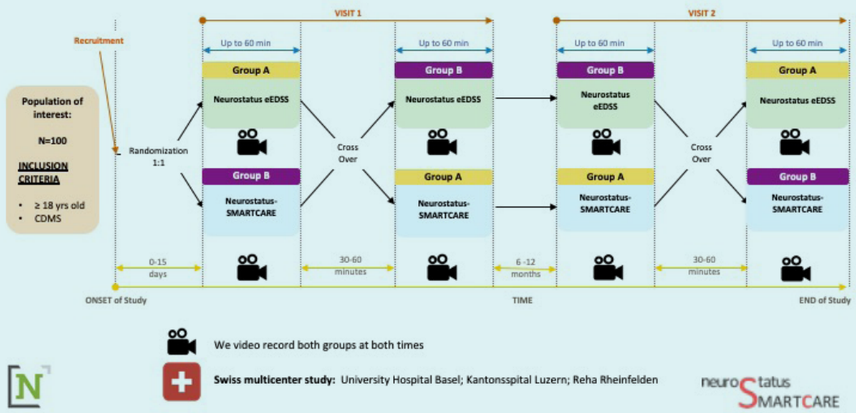


Figure 1 example of dreaMS challenge: excercise "climbing stairs" – one of the best performing and best accepted in the feasibility study

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 Healios 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 eCOA (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 subscores, FSS, AS and EDSS step); (3) development of a support webpage for Neurostatus-(e)EDSS 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-(e)EDSS. This study combines a new Neurostatus-EDSS training for HCPs and telemedicine (see Figure 2 Study design SMARTCARE study (NCT05575843)).

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 Granziera (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 Granziera, PD Dr Athina Papadopoulou, PD Dr Katrin Parmar, PD Dr Regina Schläger, and PD Dr Özgür Yaldizli) 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) (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 2022, we achieved some major milestones in the understanding of MS pathophysiology and in the indentification 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-histhopathology we showed that QSM hypo- and isointense 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 biobank 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

collaborations. In addition to attracting important funding, the group's productivity is underlined by the authorship or co-authorship of 53 original and 8 review papers or editorials in 2022. Key achievements in 2022, were the demonstration that serum glial fibrillar acidic protein (GFAP) is a better predictor of disability in MS (Meier et al., JAMA N, in press; ECTRIMS 2022 Young Investigator Award; Figure 4) in addition to and independently of serum neurofilament light chain (NfL) concentrations (Benkert et al., Lancet N 2022; in 2022 the group received the reknown Viollier price for this publication). Based on such findings GFAP now appears as a promising second blood biomarker at the doorstep of guiding personalized medicine choices. The further study of the proteomic linkage of sGFAP with other candidate markers and the creation of normative values and its broad examination in the entirety of the SMSC for clinical use will be further accelerated by a four-year SNF-project grant received in October 2022.

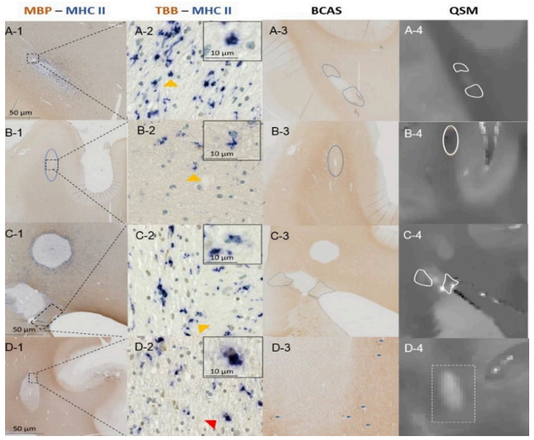


Figure 3 Histopathology and postmortem Quantitative Susceptibility Mapping (QSM) of remyelinated lesions, from Rahmanzadeh R. et al., Annals Neurol 2022). A1–D1: MBP (brown)-MHC II (blue) double IHC in exemplary fully (B-1) or partially (A1, C1, D1) remyelinated lesions. A2–D2: DAB-enhanced TBB (brown) - MHC II (blue) staining showing macrophages/activated microglia containing (D1; red arrow) or lacking iron (A1–C1; yellow arrow); A3–D3: BCAS1 IHC showing non-compact myelin and, in D-3, newly formed myelinating oligodendrocytes; A4–D4: postmortem QSM showing fully (B-1) or partially (A1, C1, D1) remyelinated lesions.

Optimised cut-offs of serum (s) GFAP and sNfL Z-scores from ROC analysis were used to dichotomize patient groups.

$sGFAP_{high}/sNfL_{high}$ was associated with a 4-fold (HR: 4.09 [2.04-8.18], p<0.001) increased risk of CDW compared to $sGFAP_{low}/sNfL_{low}$. The combination of $sGFAP_{high}/sNfL_{low}$ showed a slightly reduced risk (2.32 [0.99-5.42], p=0.05). The combination of $sGFAP_{low}/sNfL_{high}$ 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.

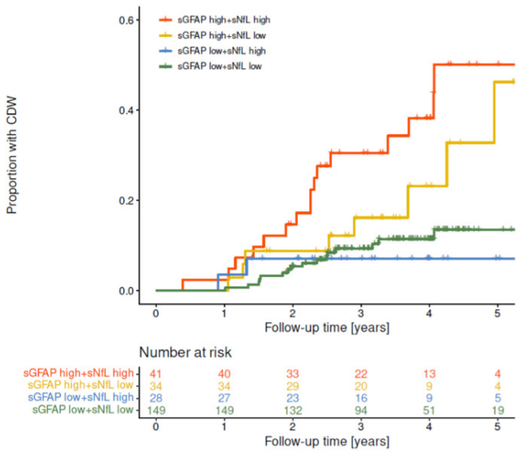


Figure 4 Kaplan-Meier curves using serum GFAP and serum NfL to predict time to confirmed disease worsening (CDW) in 252 patients treated with B cell depleting therapy in the SMSC (Jama Neurology, in press).

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

Research Group Leaders

Prof Tobias Derfuss (Cellular and Molecular Neuroimmunology)

PD Dr Matthias Mehling (Immunosenescence, Protective Immunity under DMT)

Prof Anne-Katrin Pröbstel (Experimental Neuroimmunology)

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 concluded and published 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. In the first, more clinically-oriented study, we sought to define immunological biomarkers that would predict the occurrence of an important adverse effect of treatment, lymphopenia. By subjecting blood cell data from Cytometry by Time of Flight (CyTOF) to a machine-learning-based computational analytical pipeline, we determined that the best predictor was a population of CCR4-expressing T cells (Diebold et al., 2022A). The second study also leveraged the CyTOF platform, but for the more basic-science question which immune cell types are most likely to be involved in the pathogenesis of the disease. Studying algorithmically extracted cell populations based on expression of surface markers, transcription factors and cytokines, we identified a subgroup of T effector memory cells expressing GM-CSF, TNF-alpha, and CXCR3, whose abundance was reduced by effective treatment with dimethyl fumarate. Occasional failure of this depletion was associated with treatment non-response and the abundance of the cell type was also correlated with levels of serum neurofilament light chain, a measure of CNS damage (Diebold et al., 2022B). As part of our bottom-up experimental studies we have further explored the possible involvement of antibodies in MS. This approach has involved testing of hypotheses to explain why B cell depleting therapies are so effective and focused on the trafficking of B cells into the CNS and the cell biology of antibody production. First results of these research lines were presented at ECTRIMS 2022. In the course of developing techniques that we believe are necessary for this project, 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 Biomedicine 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 depletion of immune cell subpopulations through targeted manipulation of the gut microbiome. Current research in the group 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 and is funded through an SNF Excellenza professorship, EU-Horizon and NationalMS society grants and an SNF Research Starter Grant.

Achievements in 2022 include: (1) 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

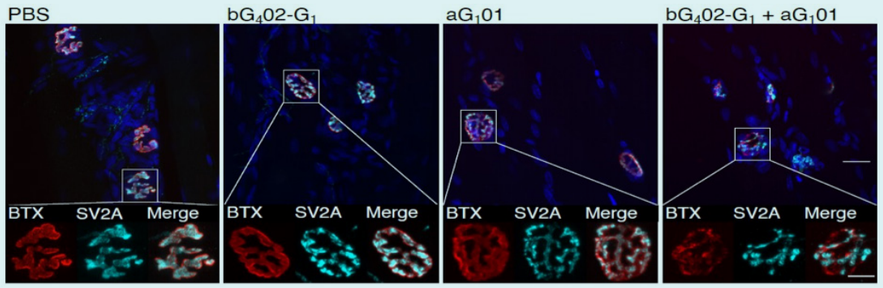


Figure 5 Influence of antibody combination on pathogenicity in an experimental myasthenia gravis rat model. The effect of two single, patient-derived acetylcholine receptor (AChR)-specific, monoclonal antibodies was compared with the combination of both. Rats were injected with PBS, a beta-subunit AChR 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).

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*, Kulsvehagen* et al. under review): Little is known about the presence and clinical relevance of IgA autontibodies 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 systemtically 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 substudy completed 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.

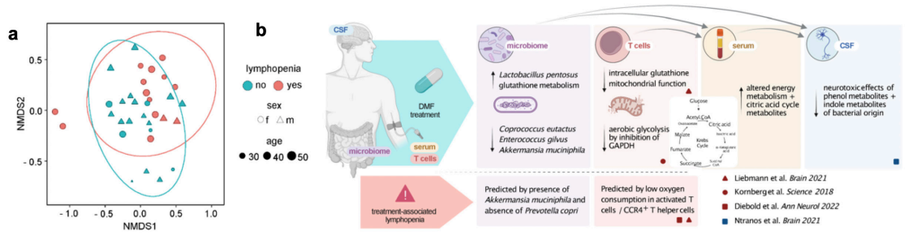


Figure 6 Microbiota composition predisposes to DMF-associated lymphopenia. (a) Non-metric multidimensional representation (NMDS) of the gastrointestinal microbiota composition of samples from individuals with (red) or without (turquoise) subsequent DMF- associated lymphopenia. Circles represent confidence interval of 95% (stress: 0.17). (b) Graphical summary of findings from this study and the recent literature.

3.4 | Workstream 4: Pragmatic Trials and Real-World Evidence

Research Group Leaders

PD Dr Lars Hemkens

Prof Jens Kuhle

PD Dr Özgür Yaldizli

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 Swiss Multiple Sclerosis Cohort (SMSC) has been a longstanding flagship of several translational projects of the MS Center at University Hospital Basel and is now also a cornerstone of WS4. Since 2021, SMSC has continued to grow with now 1'615 patients prospectively recruited (median follow-up time 6.2 years of 12'078 visits). The participating centers have developed critical expertise in the standardization and integration of high quality clinical data (i.e., patient examinations are performed by Neurostatus® certified examiners in >90% of the cases), and imaging data (as of 2022/12: 7'273 cranial MRI scans were acquired and evaluated according to a pre-defined standard protocol across all centers), and over 270'000 biofluid samples from 98% of all visits have been banked.

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 Platform 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 Yaldizli), 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.

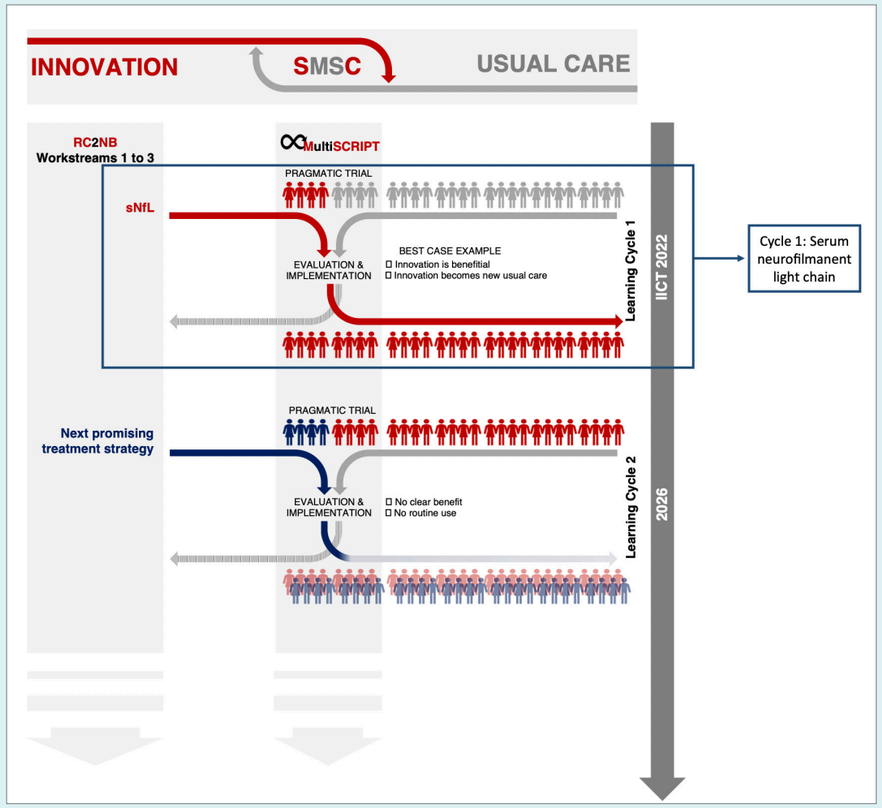


Figure 7 MultiSCRIPT - A learning research and care system for people with MS in Switzerland

4 | Financial Statement

Financial Statement	2022	2021
Research contributions	3'469'454.41	3'750'000.00
Other income	264'553.65	333'176.12
Total Income	**3'734'008.06**	**4'083'176.12**
Technical development incl. expenses for third party services	-1'046'690.88	-1'304'270.21
Personnel	-1'031'898.02	-798'372.45
Administration and other expenses	-240'018.76	-127'646.78
Total Expenses	**-2'318'607.66**	**-2'230'289.44**
Ordinary result for the period	**1'415'400.40**	**1'852'886.68**

Equity	2022	2021
Equity as of 01.01.	3'282'072.70	1'429'186.02
Income	3'734'008.06	4'083'176.12
Expenses	-2'318'607.66	-2'230'289.44
Equity as of 31.12.	**4'697'473.10**	**3'282'072.70**

RC2NB's Financial Statement 2022 was reviewed and approved by the auditor BDO AG.

Expenses by Cost Centers

	Workstream 1	Workstream 2
Personnel	-381'120.57	-251'359.85
Consumables and other lab services	-68'824.65	0.00
Technical development	-1'015'497.68	0.00
Administration and other expenses	-22'905.65	-2'133.33
Total Expenses	**-1'488'348.55**	**-253'493.18**

	Workstream 3	Workstream 4[1]
Personnel	-62'563.45	0.00
Consumables and other lab services	0.00	0.00
Technical development	0.00	0.00
Administration and other expenses	0.00	0.00
Total Expenses	**-62'563.45**	0.00

	Data Storage and Analysis	Management/ Administration	Total
Personnel	-139'474.45	-191'379.70	-1'025'898.02
Consumables and other lab services	0.00	0.00	-68'824.65
Technical development	0.00	0.00	-1'015'497.68
Administration and other expenses	-55'423.75	-127'924.58	-208'387.31
Total Expenses	**-194'898.20**	**-319'304.28**	**-2'318'607.66**

[1]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.

5 | Main Partnering Institutions and Research Support

Universitätsspital Basel

Universität Basel

Healios

NOVARTIS

Roche

euresearch

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Innosuisse – Schweizerische Agentur für Innovationsförderung

Swiss National Science Foundation

MS Schweizerische Multiple Sklerose Gesellschaft

6 | Members and Collaborators of RC2NB by Workstreams

Workstream 1

Research Group Leaders

PD Dr Marcus D'Souza (Neurostatus-UHB)
Prof Cristina Granziera (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 Obradovic, MSc (software engineer)
Vanny Phavanh (study nurse)
Silvan Pless, MSc (neuropsychologist, PhD student)
Dr Andrea Wiencierz (statistician)
Dr Tim Wölfle, 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 Álvarez-González (neurologist)
Dr Ioanna Athanasopoulou (neurologist)
Elena Börlin (IT specialist/IT Lead)
Barbara Forman (operations)
Evy Fricker (COO)
Nuria Alicia Cerdá Fuertes (neurologist)
Eddy Garcia (operations lead)
Marcos Gomez (IT)
Joel Götti (student/IT)
Gabriel Hug (student/IT)
Jasmina 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 (programmer/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)

Tejeswini Jayakumar
(master student, biomedical engineering)

Panitda Huynh
(master student, psychology)

Lara Rustemi
(master student, psychology)

Marguerite Limberg
(research assistant)

Aida Suljakovic
(personal assistant)

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 Yaldizli 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 Demuth
(study coordinator)

Leyla Develioglu
(technician)

Juan Vilchez Gomez
(research technician)

Ulrich Gress
(study coordinator)

Melanie Lacalamita
(study nurse)

Prof David Leppert
(senior postdoc)

Marguerite Limberg
(study nurse)

Aleksandra 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 Stanojevic
(study coordinator)

Suvitha Subramaniam, MSc
(data scientist)

Dr Eline Willemse
(postdoc)

Nancy Wochnik
(study nurse)

PD Dr Özgür Yaldizli
(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 Klara Ivanek
(postdoc)

Melanie Kaech, BSc
(master student)

Prof Anne-Katrin Pröbstel team:

Miriam Beyerle
(MD Doctoral Student)

Tim Dürrenberger
(doctoral student)

Julia Flammer
(resident/postdoc)

Ana Beatriz Gomes
(PhD student)

Laila Kulsvehagen
(PhD student)

Anne-Cathérine Lecourt
(lab manager/technician)

Jasmine Lerner
(undergraduate student)

Patrick Lipps
(MD Doctoral Student)

Luc Lutz
(master student)

Dr med Tradite Neziraj
(postdoc)

Maximilian Otto
(undergraduate student)

Elisabeth Pössnecker
(PhD student)

Roxanne Pretzsch
(postdoc)

Dr Lena Siewert
(postdoc)

Lea Volken
(undergraduate student)

Angéline Wettig
(undergraduate student)

Workstream 4

Research Group Leaders

PD Dr Lars Hemkens MPH

Prof Jens Kuhle

PD Dr Özgür Yaldizli

Group Members and Collaborators

PD Dr Lars Hemkens

Pragmatic Evidence team:

Dr Perrine Janiaud
(research fellow)

Dr Julian Hirt
(research fellow)

Dr Amanda Herbrand
(research fellow)

Pascal Düblin
(application developer)

Arunima Bhattacharjee
(master student, epidemiology)

Kinga Dembowska
(master student, epidemiology)

Thao Vy Nguyen
(master student, epidemiology)

Ana Karen Macias Alonso
(master student, biomedical engineering)

7 | Awards, distinctions, memberships, completed PhD and Master theses in 2022

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 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.

S. Meier (Clinical Neuroimmunology, Kuhle) won the Young investigator award at ECTRIMS 2022 for the work "Serum glial fibrillary acidic protein compared with neurofilament light chain as biomarker for multiple sclerosis disease progression" and the Viollier prize for "Serum neurofilament light chain for individual prognostication of disease activity in people with multiple sclerosis: a retrospective modelling and validation study". (2022): The Lancet. Neurology, 2, 246-257.

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 Biomedicine)

Hye-In Kim, PhD (Department of Biomedicine)

Laura Rieder, MsC (Department of Biomedicine)

Arunima Bhattacharjee (Department of Clincial Research & Swiss TPH)

8 | Major competitive project and career grants awarded in 2022

C. Granziera received a 1.5 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 (sGFAP) 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. Yaldizli (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.

9 | Publications in peer reviewed journals (*highlighted papers)

1. Abdelhak A, Cordano C, Boscardin WJ, Caverzasi E, **Kuhle J**, Chan B, Gelfand JM, Yiu HH, Oertel FC, Beaudry-Richard A, Condor Montes S, Oksenberg JR, Lario Lago A, Boxer A, Rojas-Martinez JC, Elahi FM, Chan JR, Green AJ. Plasma neurofilament light chain levels suggest neuroaxonal stability following therapeutic remyelination in people with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2022.

2. Abdelhak A, Foschi M, Abu-Rumeileh S, Yue JK, D'Anna L, Huss A, Oeckl P, Ludolph AC, **Kuhle J,** Petzold A, Manley GT, Green AJ, Otto M, Tumani H. Blood GFAP as an emerging biomarker in brain and spinal cord disorders. Nat Rev Neurol. 2022;18(3):158-72.

3. 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. 2022.

4. Arnold DL, Piani-Meier D, Bar-Or A, Benedict RH, Cree BA, Giovannoni G, Gold R, Vermersch P, Arnould S, Dahlke F, Hach T, Ritter S, Karlsson G, **Kappos L**, Fox RJ, Investigators EC. Effect of siponimod on magnetic resonance imaging measures of neurodegeneration and myelination in secondary progressive multiple sclerosis: Gray matter atrophy and magnetization transfer ratio analyses from the EXPAND phase 3 trial. Mult Scler. 2022;28(10):1526-40.

5. Arnold DL, Sprenger T, Bar-Or A, Wolinsky JS, **Kappos L**, Kolind S, Bonati U, Magon S, van Beek J, Koendgen H, Bortolami O, Bernasconi C, Gaetano L, Traboulsee A. Ocrelizumab reduces thalamic volume loss in patients with RMS and PPMS. Mult Scler. 2022;28(12):1927-36.

6. Atila C, Loughrey PB, Garrahy A, Winzeler B, Refardt J, Gildroy P, Hamza M, Pal A, Verbalis JG, Thompson CJ, **Hemkens LG**, Hunter SJ, Sherlock M, Levy MJ, Karavitaki N, Newell-Price J, Wass JAH, Christ-Crain M. Central diabetes insipidus from a patient's perspective: management, psychological co-morbidities, and renaming of the condition: results from an international web-based survey. Lancet Diabetes Endocrinol. 2022;10(10):700-9.

7. Battaglini M, Vrenken H, Tappa Brocci R, Gentile G, Luchetti L, Versteeg A, Freedman MS, Uitdehaag BMJ, **Kappos L**, Comi G, Seitzinger A, Jack D, Sormani MP, Barkhof F, De Stefano N. Evolution from a first clinical demyelinating event to multiple sclerosis in the REFLEX trial: Regional susceptibility in the conversion to multiple sclerosis at disease onset and its amenability to subcutaneous interferon beta-1a. Eur J Neurol. 2022;29(7):2024-35.

8. *__Benkert P__, Meier S, __Schaedelin S__, Manouchehrinia A, __Yaldizli O__, __Maceski A__, __Oechtering J__, Achtnichts L, Conen D, __Derfuss T__, Lalive PH, Mueller C, Muller S, __Naegelin Y__, Oksenberg JR, Pot C, Salmen A, __Willemse E__, Kockum I, Blennow K, Zetterberg H, Gobbi C, __Kappos L__, Wiendl H, Berger K, Sormani MP, __Granziera G__, Piehl F, __Leppert D, Kuhle J__, Nf LRDitSMSCSG. Serum neurofilament light chain for individual prognostication of disease activity in people with multiple sclerosis: a retrospective modelling and validation study. Lancet Neurol. 2022;21(3):246-57.

Comment:In this work we created a reference database for serum NfL based on 10 133 blood samples from 5390 people. In MS patients from the SMSC, sNfL percentiles and Z scores indicated a gradually increased risk for future acute (eg, relapse and lesion formation) and chronic (disability worsening) disease 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 disease activity-free status. Additionally, sNfL might be used as an endpoint for comparing effectiveness across drug classes in pragmatic trials

9. *Bjornevik K, Cortese M, Healy BC, __Kuhle J__, Mina MJ, Leng Y, Elledge SJ, Niebuhr DW, Scher AI, Munger KL, Ascherio A. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022;375(6578):296-301.

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, 955 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.

10. Borriello F, Pasquarelli N, Law L, Rand K, Raposo C, Wei W, Craveiro L, **Derfuss T**. Normal B-cell ranges in infants: A systematic review and meta-analysis. J Allergy Clin Immunol. 2022;150(5):1216-24.

11. Bosticardo S, Schiavi S, **Schaedelin S**, Lu PJ, **Barakovic M**, **Weigel M, Kappos L, Kuhle J**, Daducci A, Granziera G. Microstructure-Weighted Connectomics in Multiple Sclerosis. Brain Connect. 2022;12(1):6-17.

12. Buhler A, Wolbers M, Model F, Wang Q, Belachew S, Manfrini M, **Lorscheider J, Kappos L**, Beyersmann J. Recurrent disability progression endpoints in multiple sclerosis clinical trials. Mult Scler. 2022:13524585221125382.

13. Buhmann C, Lezius S, Potter-Nerger M, Gerloff C, **Kuhle J**, Choe CU. Age-Adjusted Serum Neurofilament Predicts Cognitive Decline in Parkinson's Disease (MARK-PD). Mov Disord. 2022;37(2):435-6.

14. Buhmann C, Potter-Nerger M, Schulz R, Gerloff C, **Kuhle J**, Choe CU. Reply to: "Diabetes and Neuroaxonal Damage in Parkinson's Disease". Mov Disord. 2022;37(7):1569-70.

15. Butzkueven H, Spelman T, Horakova D, Hughes S, Solaro C, Izquierdo G, Kubala Havrdova E, Grand'Maison F, Prat A, Girard M, Hupperts R, Onofrj M, Lugaresi A, Taylor B, Group MSS, Giovannoni G, **Kappos L**, Hauser SL, Montalban X, Craveiro L, Freitas R, Model F, Overell J, Muros-Le Rouzic E, Sauter A, Wang Q, Wormser D, Wolinsky JS. Risk of requiring a wheelchair in primary progressive multiple sclerosis: Data from the ORATORIO trial and the MSBase registry. Eur J Neurol. 2022;29(4):1082-90.

16. *__Cagol A, Fuertes NC__, Stoessel M, __Barakovic M, Schaedelin S, D'Souza M__, Wurfel J, Brandt AU, __Kappos L__, Sprenger T, __Naegelin Y, Kuhle J, Granziera G, Papadopoulou A.__ Optical coherence tomography reflects clinically relevant gray matter damage in patients with multiple sclerosis. J Neurol. 2023.

Investigation of the associations among OCT changes, MRI measurements of global and regional brain volume loss, and physical and cognitive impairment in people with MS.

Results showed that, in people with MS, pRNFL and GCIPL reflect the integrity of clinically-relevant gray matter structures, underling the value of OCT measures as markers of neurodegeneration and disability in multiple sclerosis.

17. *__Cagol A, Schaedelin S, Barakovic M, Benkert P__, Todea RA, __Rahmanzadeh R, Galbusera R__, __Lu PJ, Weigel M, Melie-Garcia L, Ruberte E__, Siebenborn N, Battaglini M, Radue EW, __Yaldizli O, Oechtering J, Sinnecker T, Lorscheider J__, Fischer-Barnicol B, Muller S, Achtnichts L, Vehoff J, Disanto G, Findling O, Chan A, Salmen A, Pot C, Bridel C, Zecca C, __Derfuss T,__ Lieb JM, Remonda L, Wagner F, Vargas MI, Du Pasquier R, Lalive PH, Pravata E, Weber J, Cattin PC, Gobbi C, __Leppert D, Kappos L, Kuhle J, Granziera G.__ Association of Brain Atrophy With Disease Progression Independent of Relapse Activity in Patients With Relapsing Multiple Sclerosis. JAMA Neurol. 2022;79(7):682-92.

The aim of this study was to determine whether disability progression independent of relapse activity (PIRA) in patients with RMS is associated with accelerated brain tissue loss. Data showed that patients with RMS and PIRA exhibit accelerated brain atrophy, especially in the cerebral cortex. These results point to the need to recognize the insidious manifestations of PIRA in clinical practice and to further evaluate treatment strategies for patients with PIRA in clinical trials.

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