Clinical Neuro-immunology

Molecular and immunological analysis of Multiple Sclerosis
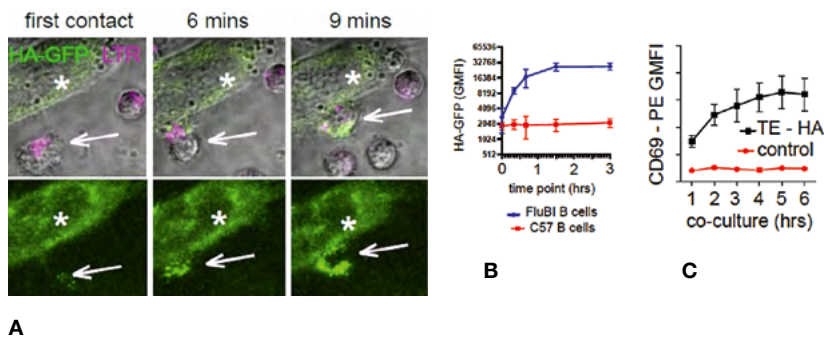
Our research focuses on the molecular and immunological analysis of multiple sclerosis (MS), an inflammatory and neurodegenerative disease of the central nervous system (CNS), and number one cause of neurological disability in young adulthood. We pursue two main research lines: 1) Relevance of B-cells and antibodies in MS pathogenesis. 2) Exploration and validation of biomarkers in cerebrospinal fluid and blood as tools for therapeutic decision making for persons with MS. Both approaches provide novel tools for monitoring the efficacy of current and emerging therapies of MS.

B cells and their targets in MS (Derfuss group)
B-cells have a major role in the pathogenesis of MS. Depletion of B-cells leads to a remarkable amelioration of the disease. The mechanisms by which B-cells impact MS are however incompletely understood. Our research focuses on the identification of novel B-cell autoantigens and the characterization of the interaction of auto-aggressive B-cells with the CNS. We could show that antibodies against native myelin oligodendrocyte glycoprotein (MOG) identify a subset of patients with neuromyelitis optica and are also found in SLE patients with CNS involvement. Using transgenic animal models, we were able to prove a new concept how infection could lead to the development of autoantibodies like those against MOG. We identified the co-capture of membrane antigens by the B cell receptor as a key step in initiating an autoimmune response in the context of an infection. This work is now continued by analyzing the capacity of B cells to migrate to peripheral tissues including the CNS and harvest their cognate and non-cognate antigens from the tissue. The phenomenon of membrane capture can also be used to purify B cells of a certain specificity from blood (Fig. 1) and to identify novel B cell autoantigens in MS.
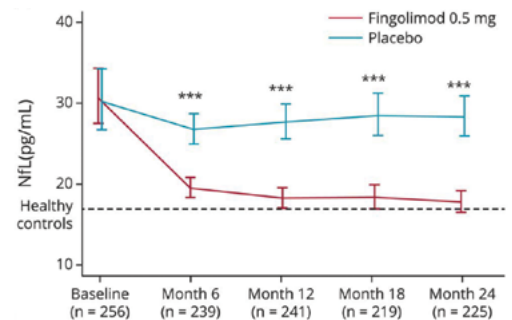
Defining biomarkers for disease progression and therapy response (Kuhle group)
Despite modern MS therapy almost completely suppresses acute disease activity ("relapses"), chronic worsening of neurological functions ("progression") continues to affect almost all persons with MS. Neurofilament light chain (NfL) is a biofluid marker of neuronal damage and has been established by us as a blood-based precision medicine tool to measure disease activity and drug response (Fig. 2), and to predict the long-term outcome of disability on the group level. We pursue now to establish NfL as a diagnostic tool for individual patients for therapeutic decision making. We aim to better characterize the pathophysiology of NfL based on innovative MRI techniques and to establish a normative data base from controls over eight decades of age to be used as reference values for individual testing. Further, we investigate other biofluid markers to contextualise NfL signals with regard to state and stage of MS, and for differential diagnosis vis-à-vis other inflammatory neurological diseases. This project is based on patient information and biological samples from the Swiss MS Cohort Study, a consortium of Swiss academic MS centres founded in 2012, and a number of international collaborations in Europe and the US.

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Fig. 1: Antigen Extraction from Membrane by Cognate B cells
(A) Live Cell Imaging of membrane antigen capture. Hemagglutinin-specific FluBI mouse B cells (white arrows, labeled magenta LTR) are added to cells (white asterisks) expressing a fusion protein of hemagglutinin with a cytoplasmic GFP (HA-GFP, green). Images show the initial contact between a B cell and an antigenic target cell, then the same location at 6 and 9 minutes later. The lower panels show only the GFP channel to show capture of antigen. **(B)** Extraction of membrane expressed HA-GFP by antigen-specific or antigen-irrelevant B cells. HA-specific FluBI B cells were labeled with Cell Trace Violet (CTV), mixed with unlabeled, antigen irrelevant mouse B cells at a ratio of 1:10, and added to an adherent layer of cells stably transfected with membrane-expressed HA-GFP. At the indicated time points, the B cells were retrieved and interrogated by flow cytometry. The FluBI cells were separated from unspecific B cells by CTV label, and GFP levels were compared between the two cell types. Points and bars show mean and standard deviation of the geometric mean GFP fluorescence. **(C)** Time-course of CD69 upregulation. HA-specific FluBI mouse B cells were exposed to HA-expressing TE HA, or HA-non-expressing control cells for the indicated times, and then retrieved, immunolabeled for B220 and CD69 and measured by flow cytometry. Vertical axis shows the geometric mean immunofluorescence intensity and SEM of the anti-CD69

Fig. 2: NfL is the first blood-based measure to quantitate the neuroprotective effect of MStherapy
Geometric means of plasma NfL with 95 % confidence intervals. Dotted line represents plasma NfL concentration in healthy controls. ***$p < 0.0001$. n = number of patients.

Connection to Clinical Practice

Our two research groups are closely connected to the MS centre, the Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB) and the Outpatient Clinic of the Department of Neurology, University Hospital Basel that provides care for more than 1300 MS patients per year. This provides access to a population of MS-patients in different stages and states of disease, treated with all state-of-the-art therapies. The close collaboration with the Translational Imaging in Neurology (ThINk) group at the Department of Biomedical Engineering, the Medical Image Analysis Centre (MIAC) and the Division of Neuroradiology enables characterization of patients with cutting edge neuroimaging techniques. The Clinical MS Research Group plays a key role in conceptualising and conducting international therapeutic trials to bring novel therapies to persons with MS. These trials provide unique possibilities for a translational medicine approach by connecting basic research and clinical studies for a better understanding of disease, and specifically for progressive MS.

The development of biomarkers needs prospective, standardized, and high-quality clinical and neuroradiological data from large patient cohorts to allow for validation on the individual patient level, and hence application in clinical practice as Precision Medicine tools. The Swiss MS Cohort Study (SMSC), initiated in 2012 and coordinated by our MS Group since then, is the mainstay of research efforts in Clinical Neuroimmunology; it provides an internationally unique long-term follow-up of over 1200 Swiss MS patients with clinical and MRI data, and blood and cerebrospinal fluid samples for biomarker research.

Selected Publications

Khalil, M, Pirpamer L, Hofer E, Voortman MM, Barro C, Leppert D, Benkert P, Ropele S, Enzinger C, Fazekas F, Schmidt R, Kuhle J. (2020. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. Nat. Commun., 11, 812.

Kuhle J, Kropshofer H, Haering DA, Kundu U, Meinert R, Barro C, Dahlke F, Tomic D, Leppert D, Kappos I. (2019). Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. Neurology 92, E1007–E1015.

Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, Gattringer T, Barro C, Kappos L, Comabella M, Fazekas F, Petzold A, Blennow K, Zetterberg H, Kuhle J. (2018). Neurofilaments as biomarkers in neurological disorders. Nat. Rev. Neurol. 14, 577–589.

Barro C, Benkert P, Disanto G, Tsagkas C, Amann M, Naegelin Y, Leppert D, Gobbi C, Granziera C, Yaldizli Ö, Michalak Z, Wuerfel J, Kappos L, Parmar K, Kuhle J. (2018) Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. Brain 141,2382–2391.

Disanto G, Barro C, Benkert P, Naegelin Y, Schädelin S, Giardiello A, Zecca C, Blennow K, Zetterberg H, Leppert D, Kappos L, Gobbi C, Kuhle J. (2017). Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. Ann Neurol. 81, 857–870.

Zimmermann M, Rose N, Lindner JM, Kim H, Gonçalves AR, Callegari I, Syedbasha M, Kaufmann L, Egli A, Lindberg RLP, Kappos L, Traggiai E, Sanderson NSR, Derfuss T. (2019). Antigen Extraction and B Cell Activation Enable Identification of Rare Membrane Antigen Specific Human B Cells. Front. Immunol. 10, 829.

Naegelin Y, Naegelin P, von Felten S, Lorscheider J, Sonder J, Uitdehaag BMJ, Scotti B, Zecca C, Gobbi C, Kappos L, Derfuss T. (2019). Association of Rituximab Treatment With Disability Progression Among Patients With Secondary Progressive Multiple Sclerosis. JAMA Neurol. 76, 274–281.

Diebold M, Sievers C, Bantug G, Sanderson N, Kappos L, Kuhle J, Lindberg RLP, Derfuss T. (2018). Dimethyl fumarate influences innate and adaptive immunity in multiple sclerosis. J. Autoimmun. 86, 39–50.

Sanderson NS, Zimmermann M, Eilinger L, Gubser C, Schaeren-Wiemers N, Lindberg RL, Dougan SK, Ploegh HL, Kappos L, Derfuss, T. (2017). Cocapture of cognate and bystander antigens can activate autoreactive B cells. Proc. Natl. Acad. Sci. U S A. 114, 734–739.

Pröbstel AK, Kuhle J, Lecourt AC, Vock I, Sanderson NS, Kappos L, Derfuss T. (2016). Multiple Sclerosis and Antibodies against KIR4.1. N. Engl. J. Med. 374, 1496–1498.