ECTRIMS 2022

Congress Report | Pathogenesis

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

26 – 28 October 2022
Amsterdam, The Netherlands

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Day 1

Pathogenesis Session 1
Hot Topic 4: New ways of imaging MS pathology

Wednesday, 26 October 10:00–11:00 CEST
Speakers: Bart Eggen, Valeria Ramaglia, Francisco Quintana
Chairs: Inge Huitinga, Patrick Vermersch

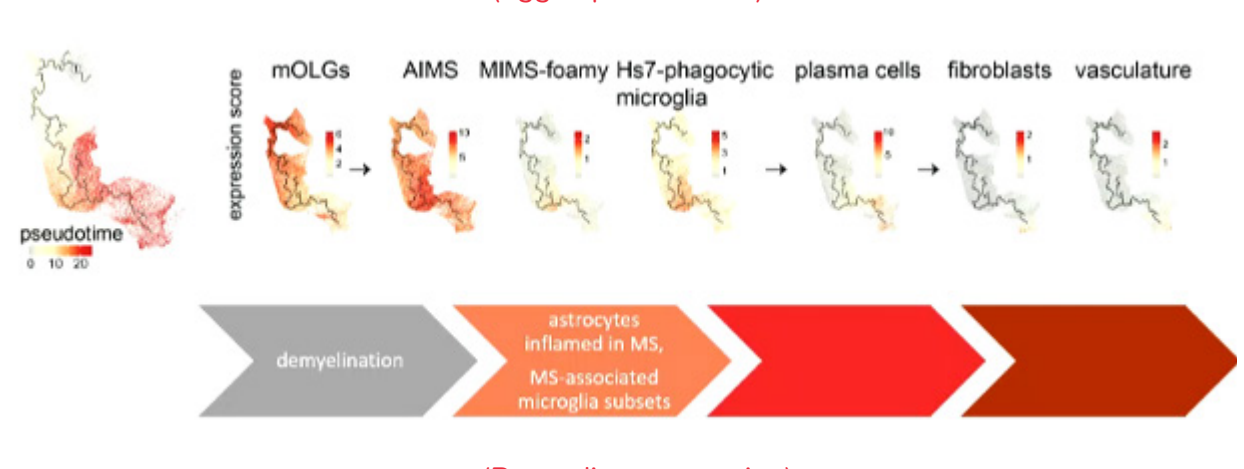
Conclusion: Novel imaging methods improve our understanding of the molecular mechanisms involved in MS lesion progression and development. These imaging techniques have highlighted the role of specific genes and certain cell subpopulations in lesion development, with the potential for these to become novel therapeutic targets.

What's New: Focusing on lesion rims and using spatial gene activity profiling, in situ sequencing confirmed apolipoprotein C1 (APOC1), secreted phosphoprotein 1 (SPP1) and ferritin light chain (FTL) as rim markers in mixed active/inactive and active lesions, with higher expression levels in such lesions than in control white matter. Looking at these lesion rims in an attempt to predict lesion evolution, it became apparent that not all normal-appearing white matter is in fact normal, and that there is an overlap in the gene signatures seen in different lesion types.

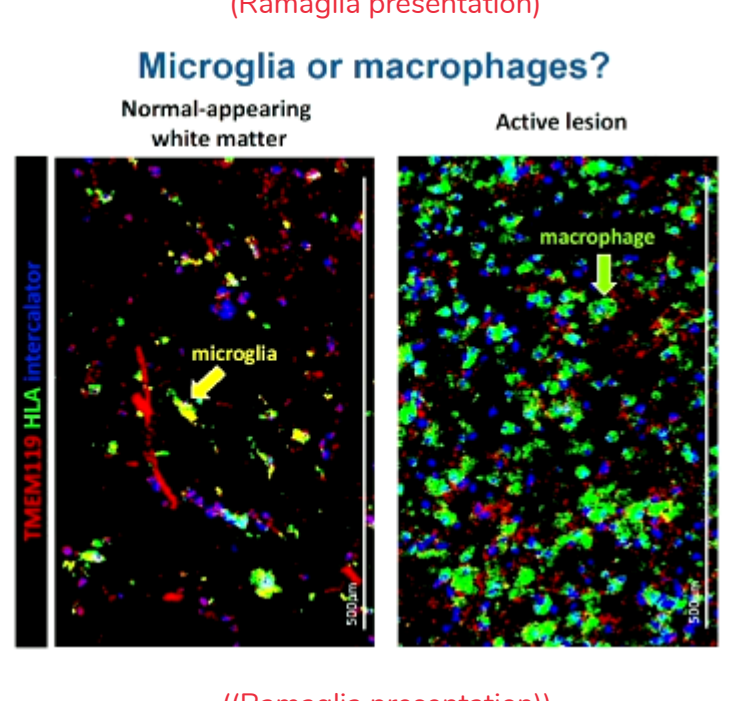
Imaging mass cytometry (IMC) is another novel imaging technique, reproducing immunofluorescence-equivalent staining patterns. It can discriminate demyelinating macrophages from the resident microglial pool and identify types of lymphocytes present, as well as subsets of T and B cells. This quantitative approach is a promising one for increasing the understanding of how meningeal inflammation relates to cortical pathology in MS patients, with the potential to identify novel therapeutic targets. Focusing on microglia-astrocyte communication, a new imaging technique, called FIND-seq (Focused Interrogation of cells by Nucleic acid Detection and Sequencing) allows characterisation of pathogenic subsets of astrocytes. Initially, using a zebrafish model, SigmaR1-IRE1-XBP1s was identified as a driver of pathogenic astrocytes. This new technique captures all the cDNA and DNA of the cell and was able to show that the mineralocorticoid receptor (NR3C2) is a negative regulator of XBP1-driven astrocytes, and that nuclear receptor co-repressor 2 (Ncor2) signalling is a negative regulator, limiting XBP1-driven pathogenic astrocytes. FIND-seq enables in-depth investigation of rare cell subsets of interest based on the expression of nucleic acid markers.

Background: The processes underlying MS lesion initiation, progression and remyelination are poorly understood. Moreover, the neuropathological and immunopathological appearance of lesions in the central nervous system in multiple sclerosis is heterogeneous. Novel imaging techniques will allow more precise characterisation of the specific cells and cellular processes involved in lesion development and progression in MS.

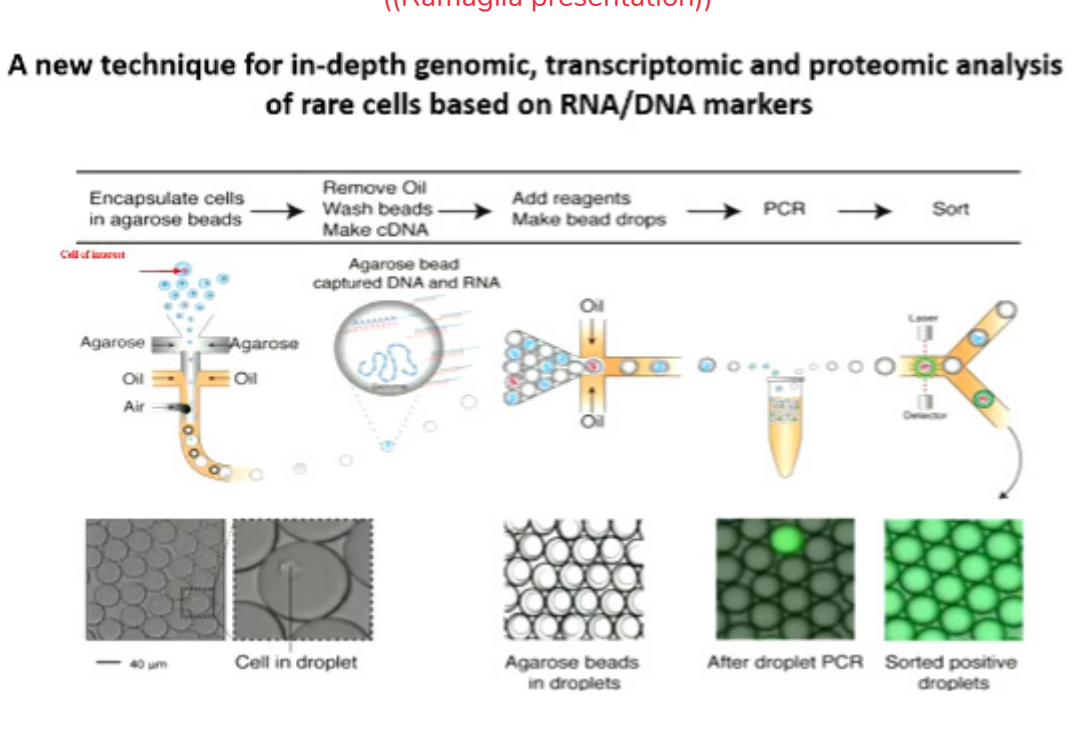
(Eggen presentation)



(Ramaglia presentation)



((Ramaglia presentation))



Pathogenesis Session 2
Young Scientific Investigators' Session 1: Immune profiling

Wednesday, 26 October 14.30 – 15.30 CEST
Speakers: Stephanie Zandee, Dimitrios Ladakis, Annalisa Colombi, Ilaria Callegari, Sarah Dybowski
Chairs: Franziska Di Pauli, Kjell Morten Myhr

Conclusion: Latest research in MS includes the development of improved approaches for disease characterisation and associated brain pathology such as multi-modular screening for detailed immune cell profiling of brain tissue. The metabolomic profiles of MS lesions were characterised as harbouring extensive changes in lipid metabolism compared with controls, and distinctive cerebral spinal fluid (CSF) inflammatory profiles were identified in patients with chronic active lesions, consistent with innate and adaptive immune activation. B-cell activity in MS remains paramount with CSF immunoglobulin (Ig)M suggested to target multiple central nervous system (CNS) antigens, and the sequential combination of Bruton's tyrosine kinase (BTK) inhibition with B-cell depletion facilitated the repopulation of B cells with their pathogenic function dampened.

What's New: Immune cell profiling by immunofluorescence is limited by the number of biomarkers that can be explored simultaneously. A novel multi-modular approach using single cell, spatial and bulk RNA sequencing, confocal microscopy, flow cytometry and lesion classification by histology and histochemistry, facilitated phenotypic analysis of infiltrating immune cells and CNS resident cells within isolated MS brain lesions. Multi-dimensional characterisation provides an unprecedented view into the disease processes underlying lesion formation and evolution in MS, with CD6 on T cells highlighted as a molecule of interest.

The circulating metabolome is altered in MS, characterised by immune-mediated demyelination and consecutive axonal loss. Whether these changes reflect metabolic changes in the affected CNS tissue is not clear. Metabolomic profiling of MS brain tissue revealed extensively altered myelin lipids compared with control white matter, with significant differences in lesions, particularly increased levels of inflammatory sphingolipid and amino acid metabolites, and reductions in anti-inflammatory polyunsaturated fatty acids, endocannabinoid, monoacylglycerol and energy metabolites. Lipid alterations may have utility as biomarkers of inflammation and neurodegeneration in MS.

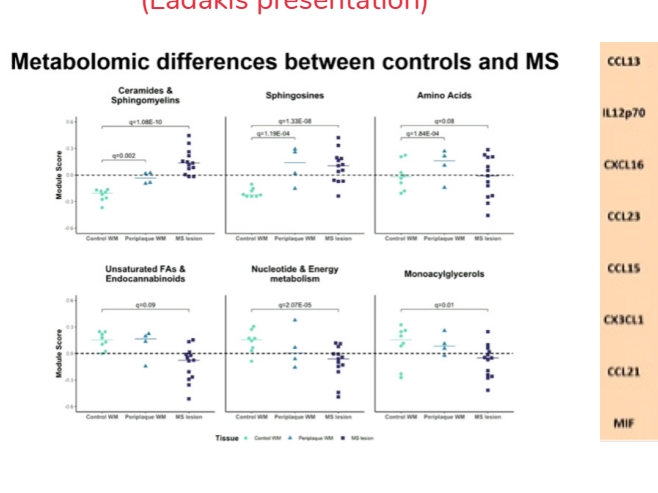
In addition to demyelination, chronic active lesions in MS, identified as paramagnetic rim-positive lesions, are associated with accrual of disability over time. Assessment of 85 treatment-naïve patients with relapsing-remitting MS at the time of diagnosis confirmed a unique inflammatory CSF molecular profile associated with chronic active lesions, consistent with and supporting the key role of innate and adaptive immune activation since the initial stage of the disease.

Intrathecal Ig production, particularly IgG, is a hallmark of MS, with up to 25% of patients showing additional persisting intrathecal IgM synthesis associated with spinal cord manifestation, higher disease activity and a high degree of somatic hypermutation, suggesting antigen-driven production. The target antigenic stimulus that initiates/perpetuates B cell activation of intrathecally produced CSF IgM in MS is not known. Cellular screening suggested that intrathecal IgM synthesis in MS may be a sign of an increased inflammatory response and an antigenic trigger. Investigations into the identification of the target antigen of one IgM clone (M16) are ongoing.

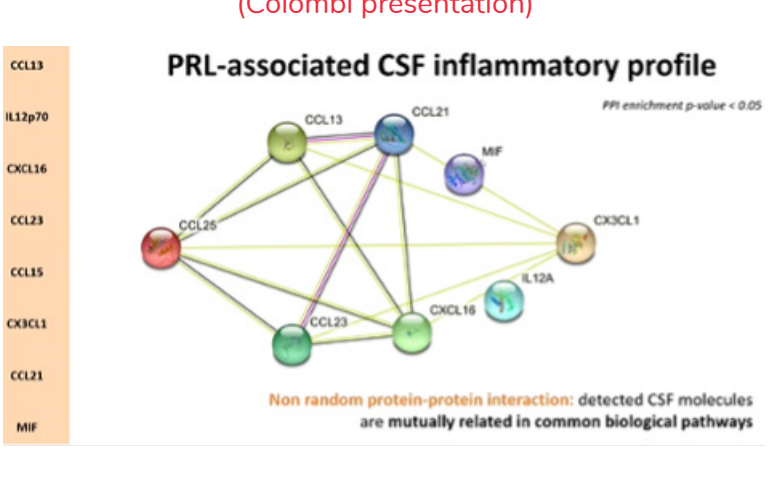
B cells are important pathogenic drivers in MS and cell-depletion is a therapeutic strategy; however, long-term anti-CD20 mediated B-cell depletion results in negative immunologic effects. Upon the cessation of anti-CD20, B cells reappear with an overly activated phenotype under inflammatory conditions. In a mouse model of MS, a novel sequential therapeutic approach of B-cell depletion followed by a BTK inhibitor provided clinical effects along with a delay in B-cell maturation. In the repopulated B cells, pro-inflammatory differentiation and activation were controlled and anti-inflammatory properties were maintained.

Background: Although MS is recognised as a chronic inflammatory, demyelinating and neurodegenerative disorder of the CNS, there is still no cure for the disease, with only options for treating symptoms and reducing the risk of relapse and progression. An increased understanding of the immune profile in MS provides novel insights into the pathophysiology of the disease and may facilitate the identification of new pharmacological targets, immunotherapies and tailored treatment strategies to halt disease progression.

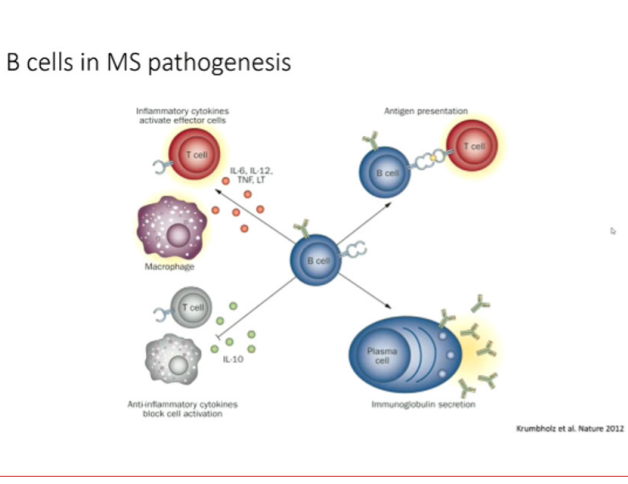
(Ladakis presentation)



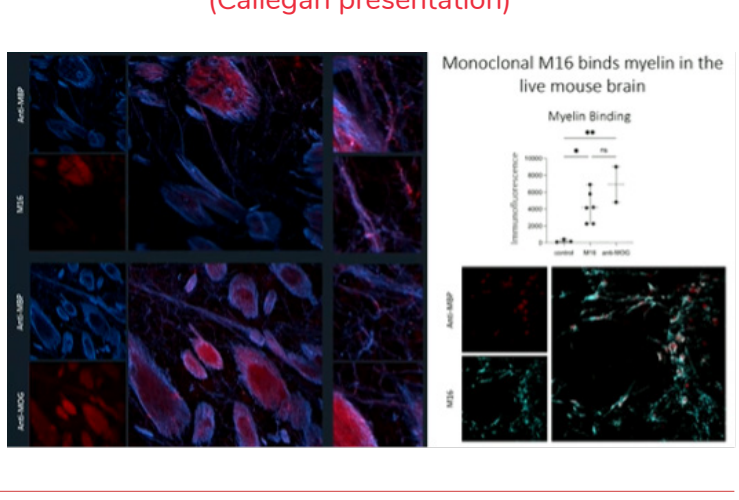
(Colombi presentation)



(Dybowski presentation)



(Callegari presentation)



Pathogenesis Session 3
Remyelination

Wednesday, 26 October 14:30 – 16:00 CEST
Speakers: Cristina Granziera, Catherine Lubetzki, Jody de Jong, Lidia Stork, Hannah Kapell, Amir Ziaee
Chairs: Wia Baron, Tanja Kuhlmann

Conclusion: Advances in imaging techniques, along with increasing knowledge of the various players in both the demyelination and remyelination processes, provide an important basis for targeting remyelination in a clinical setting in MS.

What's New: Extracellular matrix (ECM) surface structures have a different appearance in demyelinated lesions, compared with non-demyelinated tissues. There are distinct properties of the acellular ECM in multiple sclerosis and in cuprizone-induced lesions, with white matter MS lesions having a greater abundance of heparan sulphate proteoglycan 2 (HSPG2) and less abundant brevican than in normal white matter ECM. Additionally, several ECM-associated proteins, including regulators of microglia behaviour, were found in cuprizone-induced lesions, but were absent in white matter lesions.

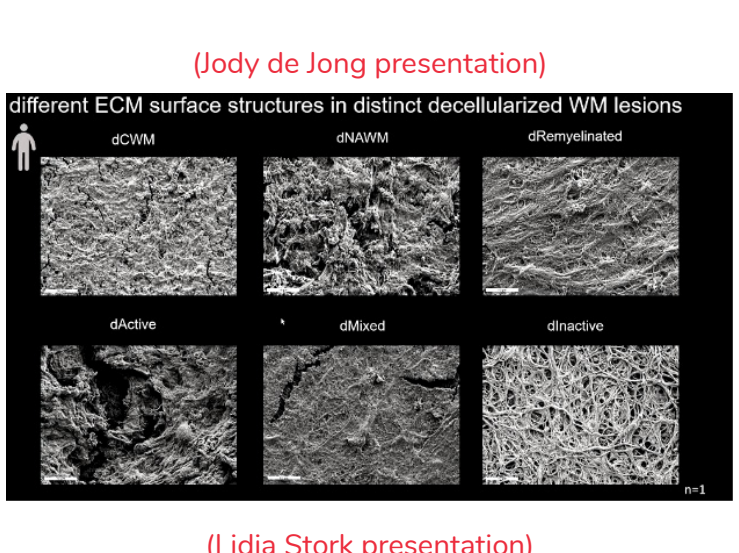
In patients with late-onset MS, remyelination may be less effective than in normal-onset MS. The number of mature and active myelinated oligodendrocytes in normal and perilesional white matter is lower in late-onset MS; notably, cells of both populations decline with patient age. In patients with late-onset MS, but not those with normal-onset MS, a higher disability score was associated with lower numbers of oligodendrocytes in active lesions. The reduced number of mature and active oligodendrocytes in late-onset MS may partially explain the progressive disease course and the higher disability level.

Modulation of the homeostasis of potassium ion channels around the node of Ranvier may represent a novel therapeutic approach in inflammatory demyelination. Activation of Kv7 neuronal ion channels was found to attenuate symptoms in experimental autoimmune encephalomyelitis (EAE), to increase survival, to have neuroprotective effects and to preserve oligodendrocyte Kir4.1 channels in EAE. Kv7 activation with retigabine may be a novel treatment strategy to counteract progressive neurodegeneration in MS patients.

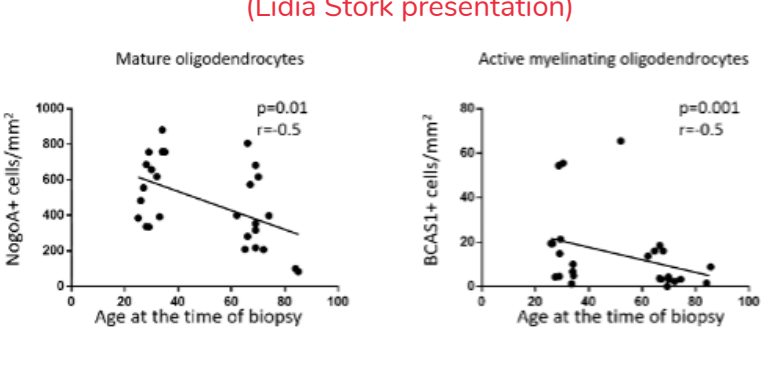
Neuregulin-1 (Nrg-1) plays numerous diverse roles in the central nervous system, with recent work demonstrating that treatment with Nrg-1 promotes maturation of oligodendrocyte progenitor cells and remyelination in MS-like demyelinating lesions. Nrg-1 treatment enhanced myelin phagocytosis in activated microglia, and accelerated the accumulation of free cholesterol in activated microglia. Nrg-1 treatment also accelerated the accumulation of neutralised lipids in activated microglia exposed to myelin debris and facilitated their release over time.

Background: Multiple sclerosis lesions are characterised by persistent demyelination. Promotion of remyelination, and thus prevention of neurodegeneration, is necessary to promote recovery in MS, which is perhaps the biggest challenge that remains to be overcome in this disease. MS lesions have a distinct cellular component, with oligodendrocyte progenitor cells required for remyelination. The age of onset of MS is a key contributor to disease phenotype, with normal onset MS presenting at 20–40 years, and usually follows a relapsing–remitting disease course for 10–15 years before becoming progressive. In contrast, late onset MS (age >50 years) is three times more likely to be progressive at onset or to have faster disease progression, which may be related to differences in remyelination. We now have improved imaging techniques that allow us to identify remyelination and demyelination in vivo.

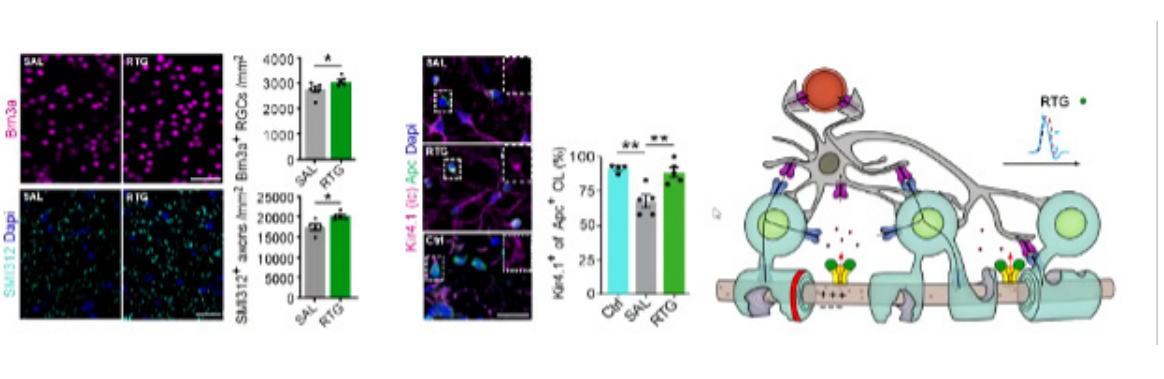
(Jody de Jong presentation)



(Lidia Stork presentation)



(Hannah Kapell presentation)



Day 2

Pathogenesis Session 1
Scientific Session 8: Immune cell trafficking into the CNS

Thursday, 27 October 11:30 – 13:00 CEST
Speakers: Alexandre Prat, Jonathan Kipnis, Fabienne van Puijfelik, Rose-Marie Rébillard, Jeen Engelenburg, Stephane Rodriguez
Chairs: Maria Pia Amato, Giancarlo Comi

Conclusion: The cells most reactive to inflammation are venous endothelial cells, and these may allow access of immune cells into the central nervous system (CNS). Changes in immune responses may also be facilitated by altered communication between the cerebrospinal fluid (CSF) and skull bone marrow. The expanding availability of CNS and peripheral blood phenotype datasets, including those specific to different regions of the brain, may be useful tools for better characterising the immune changes in MS and provide a better understanding of the distinct immune signatures across brain regions in the MS brain.

What's New: Following the COVID-19 pandemic, there has been an increasSingle-cell RNA sequencing has shown that there is heterogeneity of endothelial cells across brain regions. Endothelial cells, particularly venous and capillary venous CNS endothelial cells, are the most reactive to inflammation. Up-regulated DICAM (a dual immunoglobulin-like molecule), a novel adhesion molecule expressed by CD4 TH17 lymphocytes, in the peripheral blood of patients with MS was identified as a potential therapeutic target to reduce migration of immune cells across vascular brain structures.

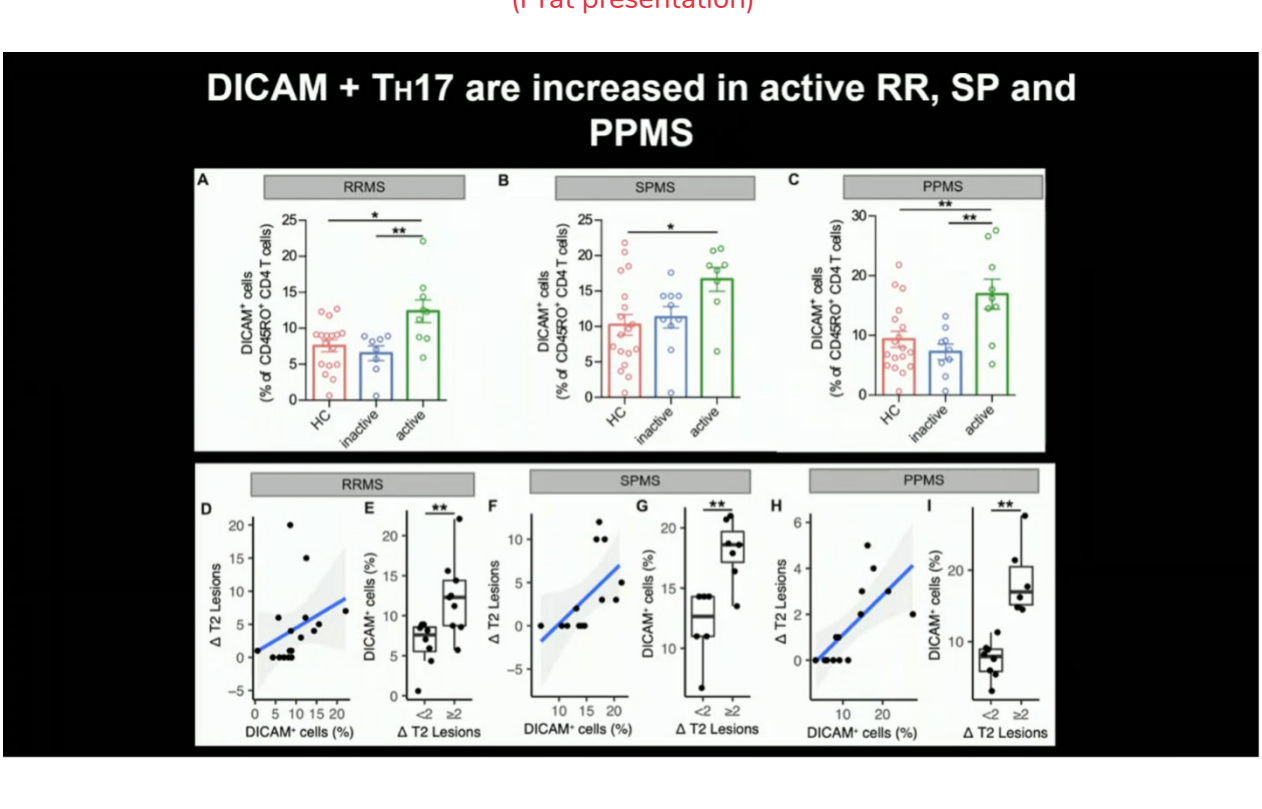
The immune system at the brain borders is specialised, and impaired lymphatics or dysfunctional border macrophages could interfere with glymphatics and affect immune surveillance. In MS, it is possible that CSF-delivered signals to skull bone marrow are also affecting immune responses.

When cell types involved in the pathogenesis of MS are considered, CD4+ and CD8+ T-cell subsets, with a cytotoxic profile that likely contributes to their preferential recruitment to the CNS, are characterised by co-expression of RUNX3 and EOMES but not T-bet in patients with MS. Mass cytometry identified a subset of individuals with relapsing-remitting MS (RRMS) who had high frequencies of these CD206+CD209+CCR5+ classical monocytes (named MyX and comprising >2% of myeloid cells). These patients were significantly more prone to present an active disease and to develop a higher disability score, suggesting a role of this immune cell population in the RRMS disease course. Investigation of the phenotypic and functional profile of brain T cells in non-MS and MS white and grey matter identified a TRM-cell phenotype that abundantly expresses two proteins: SPP1 (osteopontin) and MS4A1 (CD20). In MS lesions, these TRM-cells produce fewer cytokines upon activation possibly because of compartmentalisation.

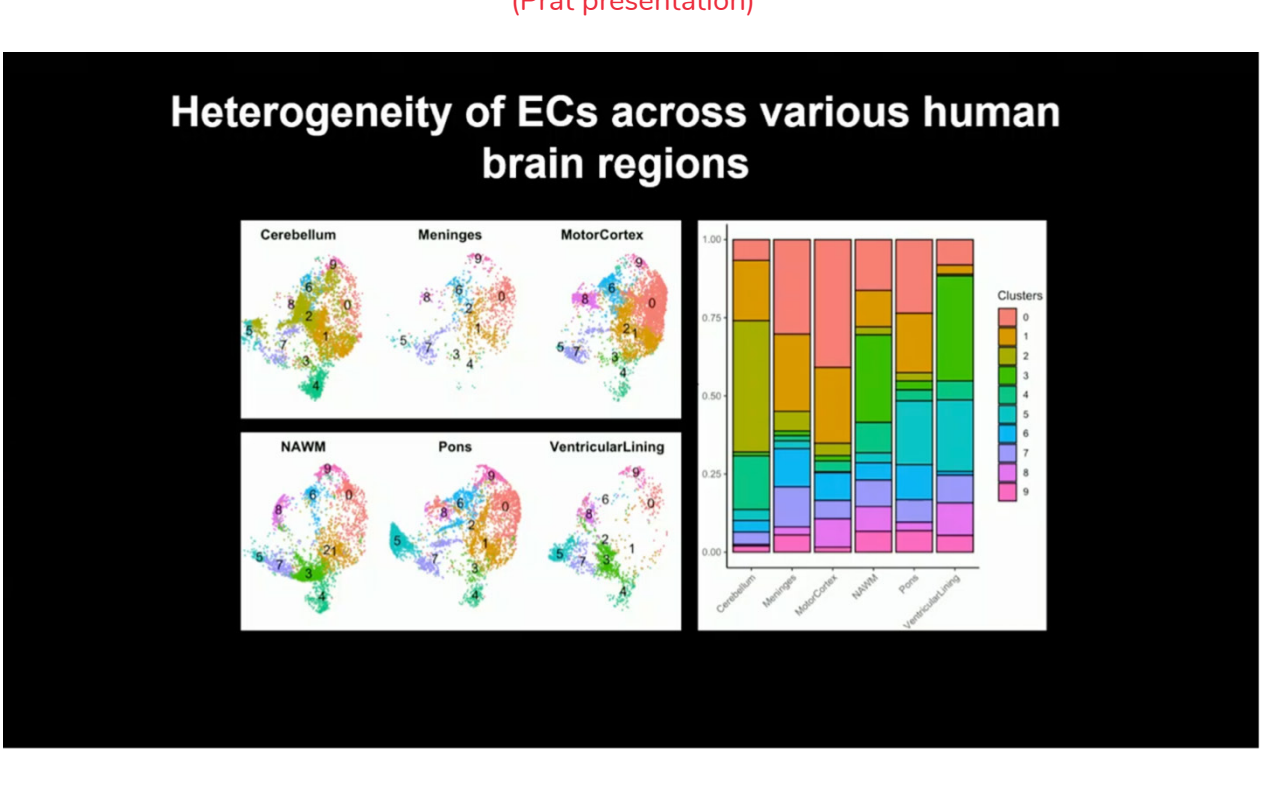
High-dimensional single cell characterisation of immune cells in the CNS revealed regional heterogeneity of blood-borne immune cells in the CNS of patients with MS. These cells have a signature that is distinct from those of patients with other neurological diseases.

Background: MS is a prototypical idiopathic neuroinflammatory disorder. Immune cell trafficking into the CNS is a key hallmark of MS pathogenesis. The role and route of entry – be it across the blood–brain barrier, the blood–cerebrospinal fluid barrier or the blood–meningeal barrier – and the precise cells involved may help our understanding of the pathogenesis of MS and provide new leads for diagnostic tools or disease intervention strategies.

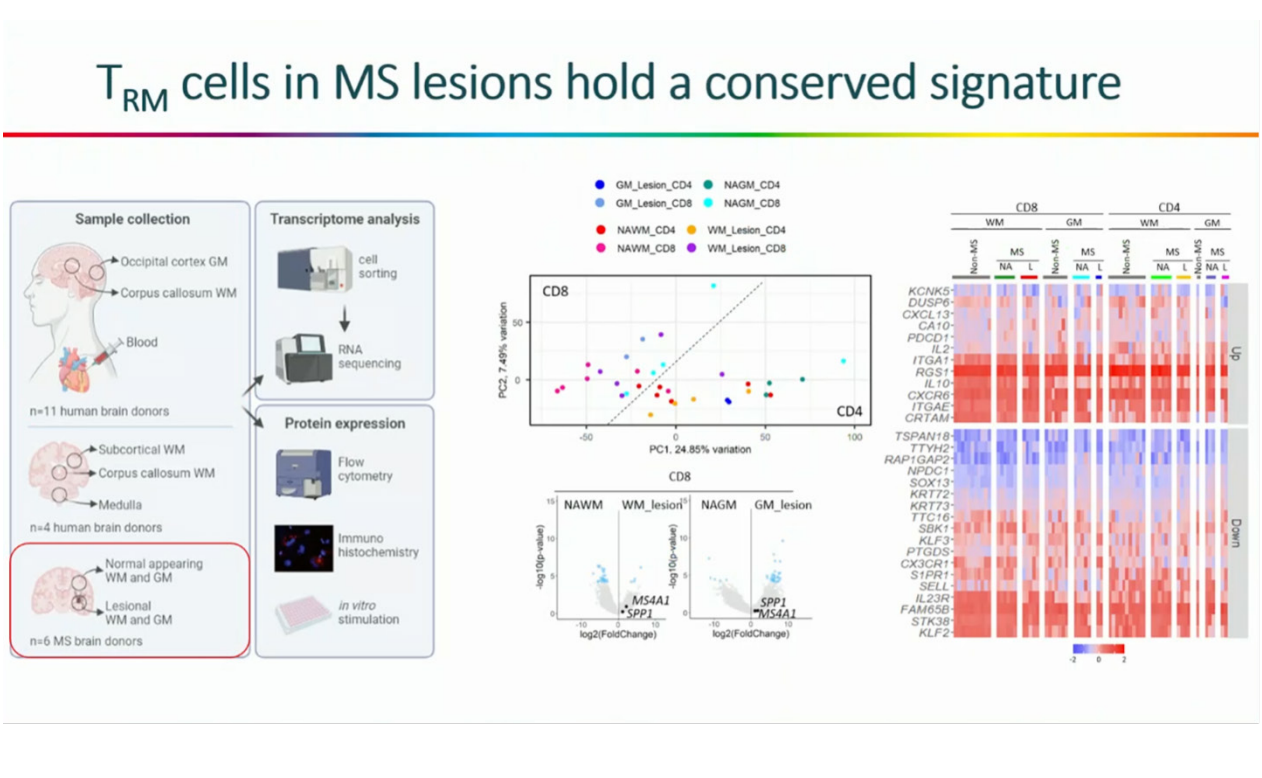
(Prat presentation)



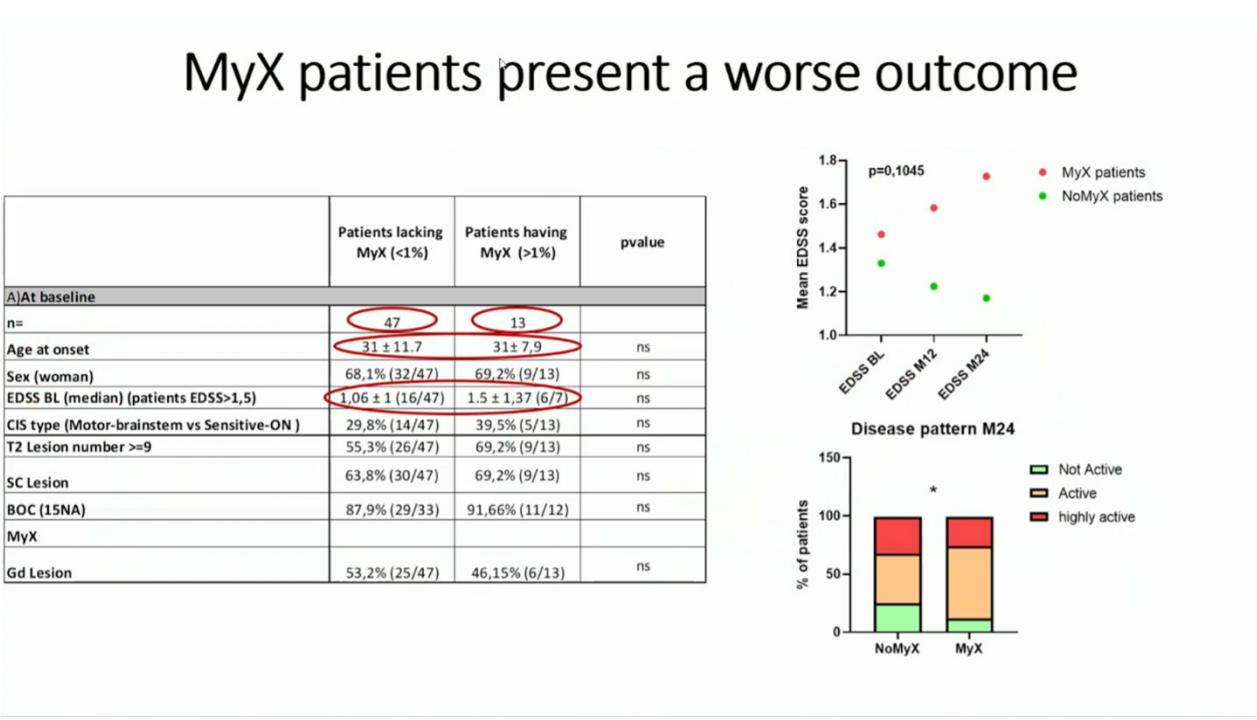
(Prat presentation)



(Engelenburg presentation)



(Rodrigues presentation)



Pathogenesis Session 2
Scientific Session 10: B and T cells

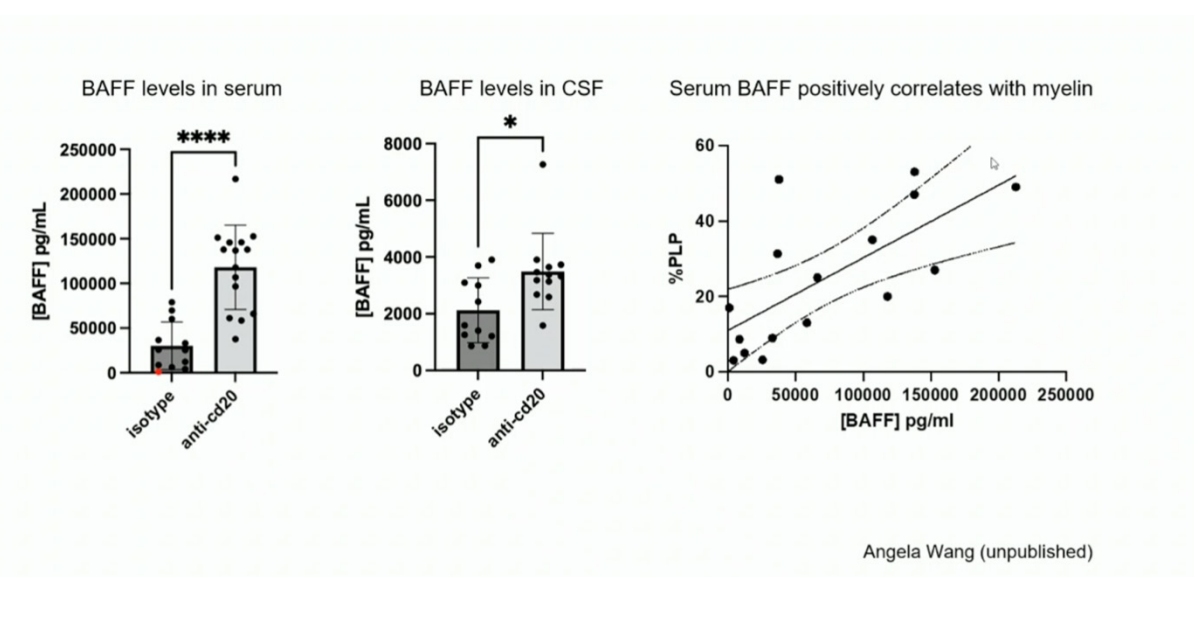
Thursday, 27 October 15:00 – 16:30 CEST
Speakers: Jennifer Gommerman, Klaus Dornmair, Stefanie Bock, Diego Espinoza, Silke Häusser-Kinzel, Hye In Kim
Chairs: Joost Smolders, Frauke Zipp

Conclusion: Novel approaches and concepts regarding lymphocyte-involvement in MS may shape the direction of this field. For example, pharmacological targeting of two-pore-domain potassium channel K2P18.1 modulates the number of developing thymus Treg cells and may thus represent a new therapeutic strategy in autoimmunity. Better targeted therapy for children with acquired inflammatory demyelinating syndromes may be possible with better elucidation of the underlying immune mechanisms leading to MS and myelin oligodendrocyte glycoprotein (MOG)-associated disease (MOGAD). In MS, B cells may have immunoregulatory properties with the potential to control central nervous system (CNS)-intrinsic inflammation associated with clinical progression, but these cells may also mediate the pathogenesis of the disease when T cells are also present.

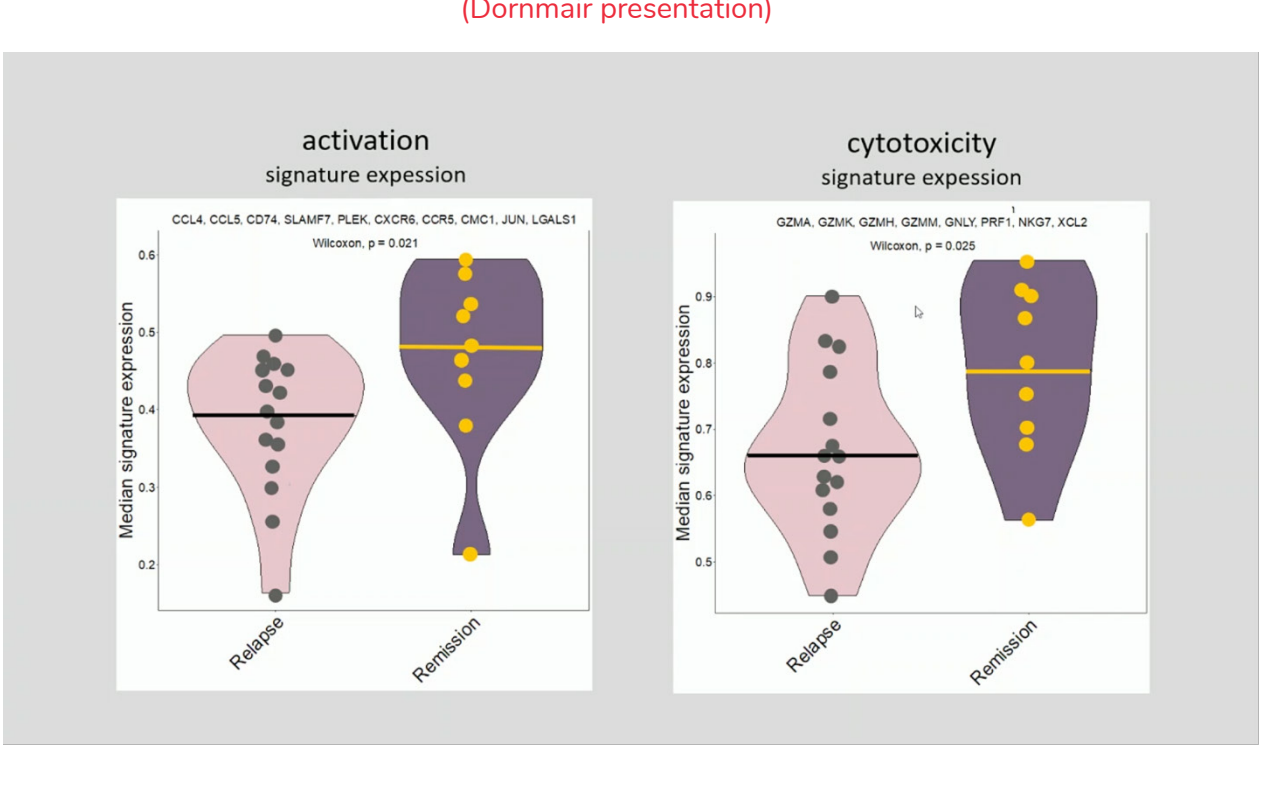
What's New: CNS-resident gut-derived plasma cells that produce immunoglobulin A (IgA) during inflammation interleukin (IL)-10–dependently inhibit experimental autoimmune encephalomyelitis. IgA+ IL-10 producing plasma cells mobilised from the gut play a role in suppressing neuroinflammation and increasing the B cell survival factor BAFF, which is associated with protection against demyelination in the CNS. Depletion of B cells with anti-CD20 spares grey matter concomitant with elevated serum BAFF levels. When considering T cells, there are detectable differences in immunological signatures based on the clinical state of untreated patients with very early MS. Patients with MS in relapse versus remission have strong clonal expansion of CD8+ T cells with downregulated cytotoxicity markers and activation markers, and upregulated egress markers (i.e. cells have higher mobility). The K2P18.1, which is regulated via intracellular Ca 2+/calcineurin is expressed on T cells and has a role in T-cell receptor signalling during thymus Treg development, translating the receptor signal into thymus Treg development in mice and humans. Comparing children with MS versus those with MOGAD revealed that MS is associated with a CD4 T-cell compartment enriched for a memory population with a Th1-like (STAT4+ and CXCR3+/CCR6-) phenotype and CD8 memory T cells enriched for the checkpoint-molecule TIGIT. Regulatory B-cell functions are preserved in patients with MS. As B-cell-derived IL-10 modulates myeloid phagocytes and microglia in an anti-inflammatory manner, B cells within the CNS may not be exclusively pathogenic. However, a model has been developed that potentially links B cells to brain infection, which, in combination with T cells, induce an autoimmune response and significant demyelination.

Background: The role and source of plasma cells in the CNS of patients with MS remains unclear. Previous research shows that there are detectable differences in the immunological signatures of patients with prodromal and established MS, that alterations in Treg numbers or function contribute to the pathogenesis of autoimmunity and that thymus-derived Treg development includes Ca2+ signalling cascades. Children with MS and MOGAD have different responses to treatment, suggesting differences in the immune mechanisms leading to these diseases. The role of B cells in the pathogenesis of CNS requires clarification.

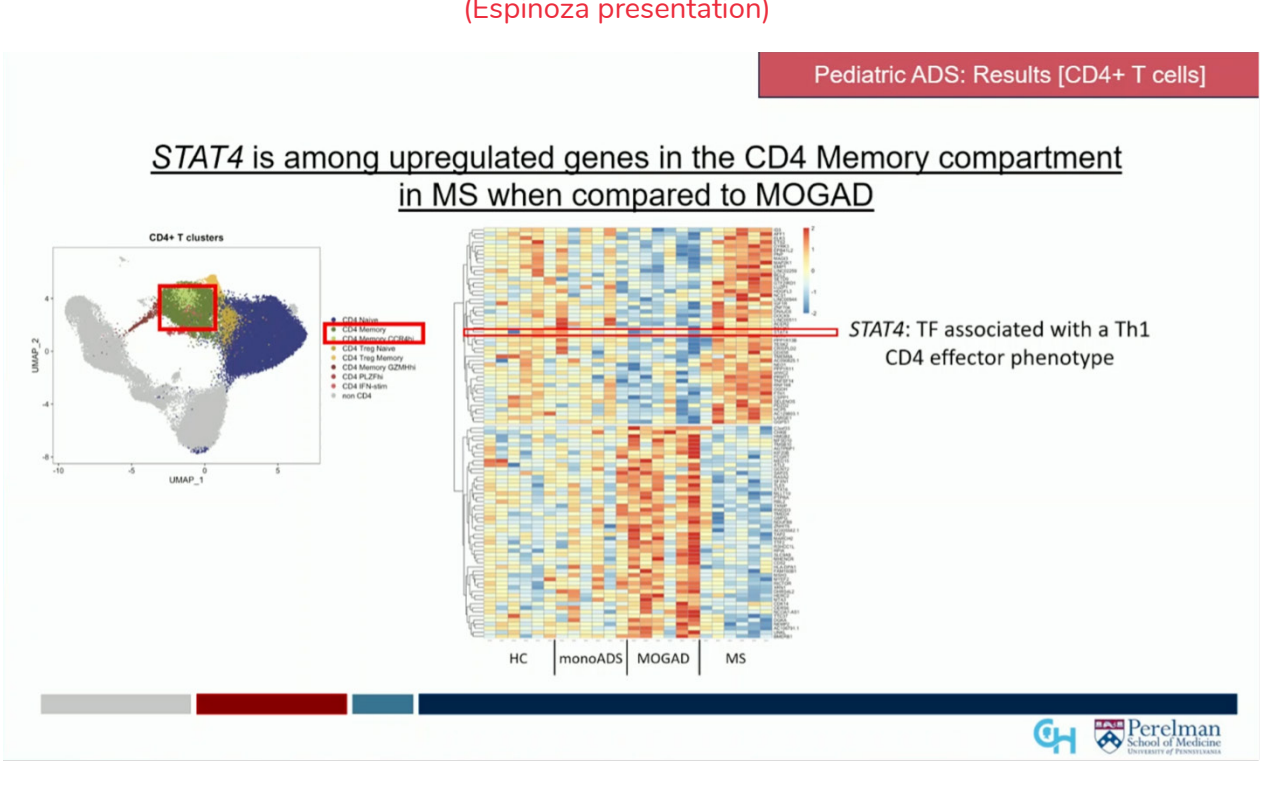
(Gommerman presentation)



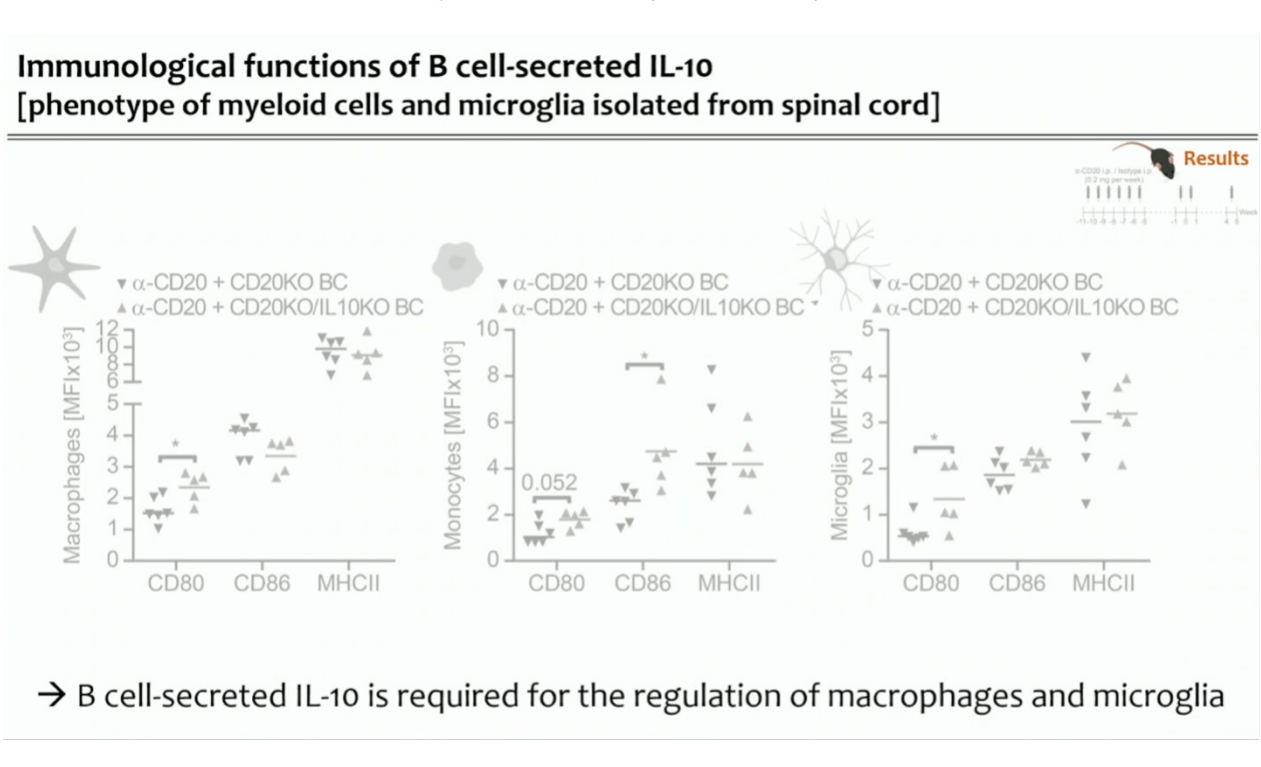
(Dornmair presentation)



(Espinoza presentation)



(Häusser-Kinzel presentation)



Pathogenesis Session 3
Scientific Session 12: The Earliest Events in MS

Thursday, 27 October 15:00–16:30 CEST
Speakers: Richard Reynolds, Peter Stys, Vicki Maltby, Alberto Ascherio, Daniel Jons, Gavin Sowa
Chairs: Luke Healy, Christine Stadelmann-Nessler

Conclusion: Evidence is accumulating to suggest an important role for early (pre)-inflammatory changes in MS. In particular, the Epstein–Barr virus (EBV) appears to play a key part in early MS pathology, and serological responses to EBV viral peptides may precede neuroaxonal damage. Some MS patients also develop autoantibodies to a serine arginine repeat motif, which may be present years before disease onset. Work is ongoing to increase knowledge around these earliest events in MS, which will lead to better understanding of overall disease pathology and open up new therapeutic pathways and targets.

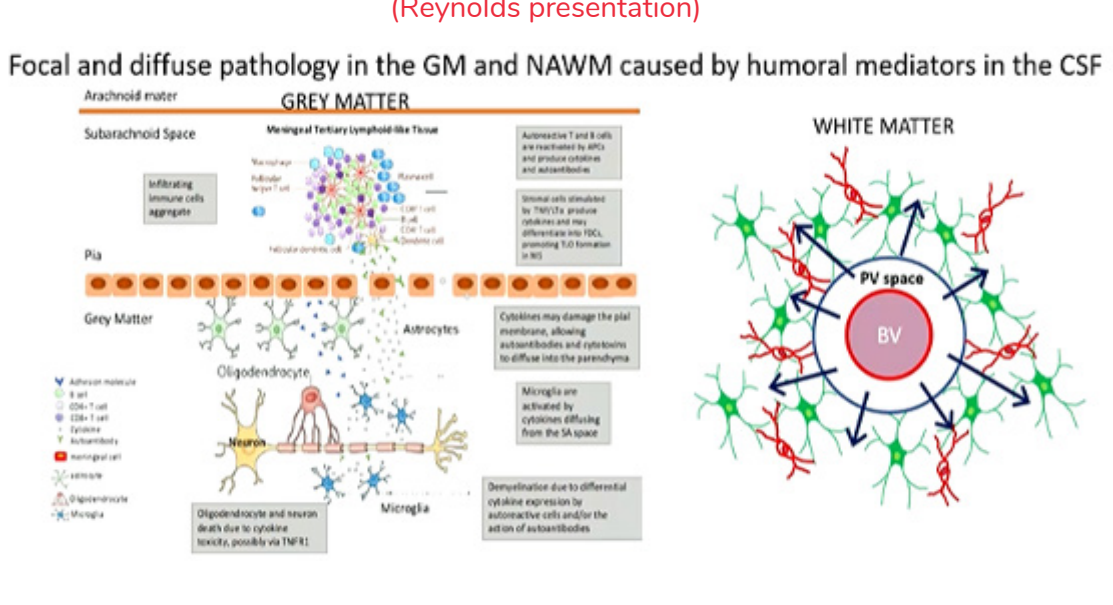
What's New: Focal and diffuse pathology can be seen in both the grey matter and normal-appearing white matter caused by humoral mediators in the cerebrospinal fluid (CSF). This occurs in the absence of T and B cells in the parenchyma or perivascular spaces, which suggests both direct and indirect mechanisms of early inflammatory events in MS. Data are also emerging to support the idea of an 'inside-out' pathology to MS, in which primary degenerative factors potentially occur very early in the MS brain. According to this model, autoimmune inflammatory reactions to an underlying degenerative process cause myelin injury and generate epitopes and antigens to which a primed immune system continues to react in a recurrent manner, leading to ongoing inflammatory relapses until the patient enters a progressive disease phase.

A large body of evidence already supports EBV as a leading risk factor for MS and a potential necessary condition for early disease development. Increases in EBV serologies are detectable 10–15 years before the clinical debut of MS and may precede neuroaxonal damage in pre-symptomatic patients. Potential mechanisms of EBV infection include molecular mimicry leading to autoimmunity, and work is ongoing to determine if serological response to EBV peptides can discriminate MS status. Other autoantibodies with a proven role in early MS pathology are those that develop to a serine-arginine repeat motif. These may be present years before disease onset and patients enriched in this motif also show higher neurofilament light (NfL) levels, suggestive of increased inflammation.

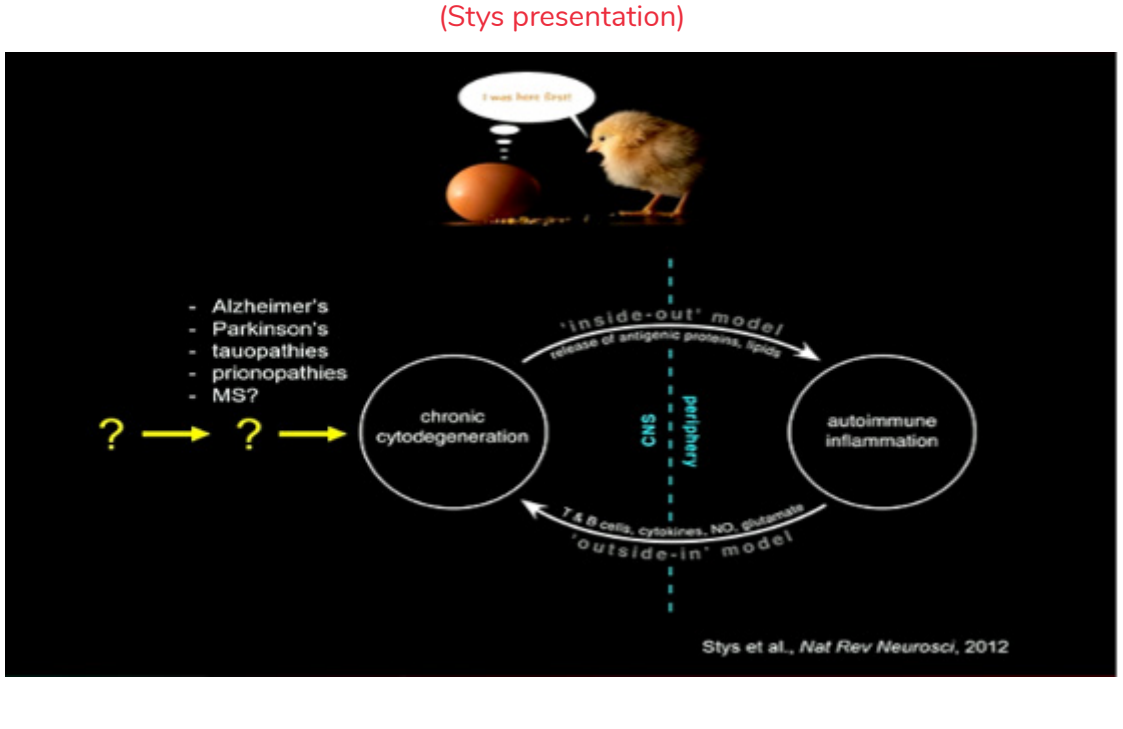
Finally, B cells from MS patients show a marked epigenetic age acceleration of over 5 years versus controls. This indicates that B-cell function, rather than abundance, may be associated with MS disease development.

Background: The question of how MS begins remains one of the most pressing areas of MS research and answers may lie in the inflammatory changes seen early in the disease course. Pro-inflammatory and cytotoxic factors are present in the central nervous system from the early stages of MS and are associated with increasing severity of MS pathology and an accelerated clinical course.

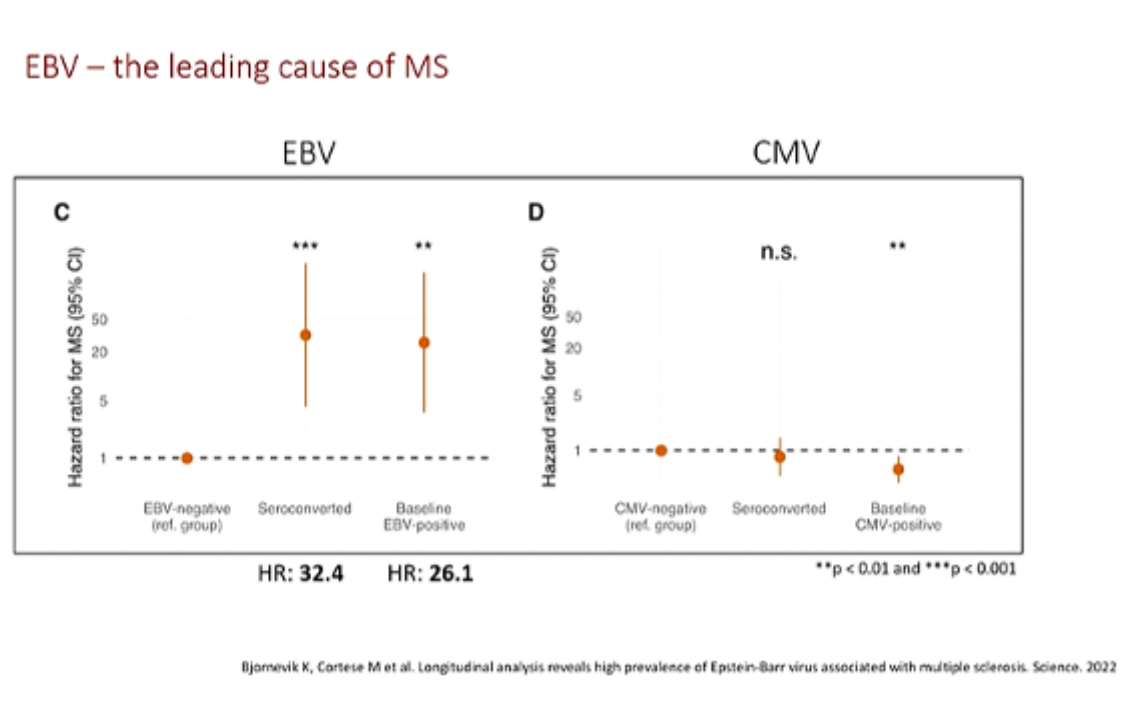
(Reynolds presentation)



(Stys presentation)



(Ascherio presentation)



Day 3

Pathogenesis Session 1
Hot Topic 10: Emerging Role of Lipids in MS

Friday, 28 October 12:00 – 13:00 CEST
Speakers: Jerome Hendriks, David Hafler, Gesine Saher
Chairs: Valbona Mirakaj, Gijs Kooij

Conclusion: Lipid mediators in the central nervous system (CNS) have the capacity to modulate neuro-inflammatory responses and may provide new avenues for exploration as novel diagnostic and or therapeutic modalities in MS. Lipid metabolism is a major determinant of CNS remyelination and approaches targeting the lipid-immune axis have shown potential in promoting lesion repair and fostering endogenous remyelination in MS. Lipids have also demonstrated a favourable impact on the suppressive function of T-regulatory cells (Tregs), which is known to be impaired in patients with MS.

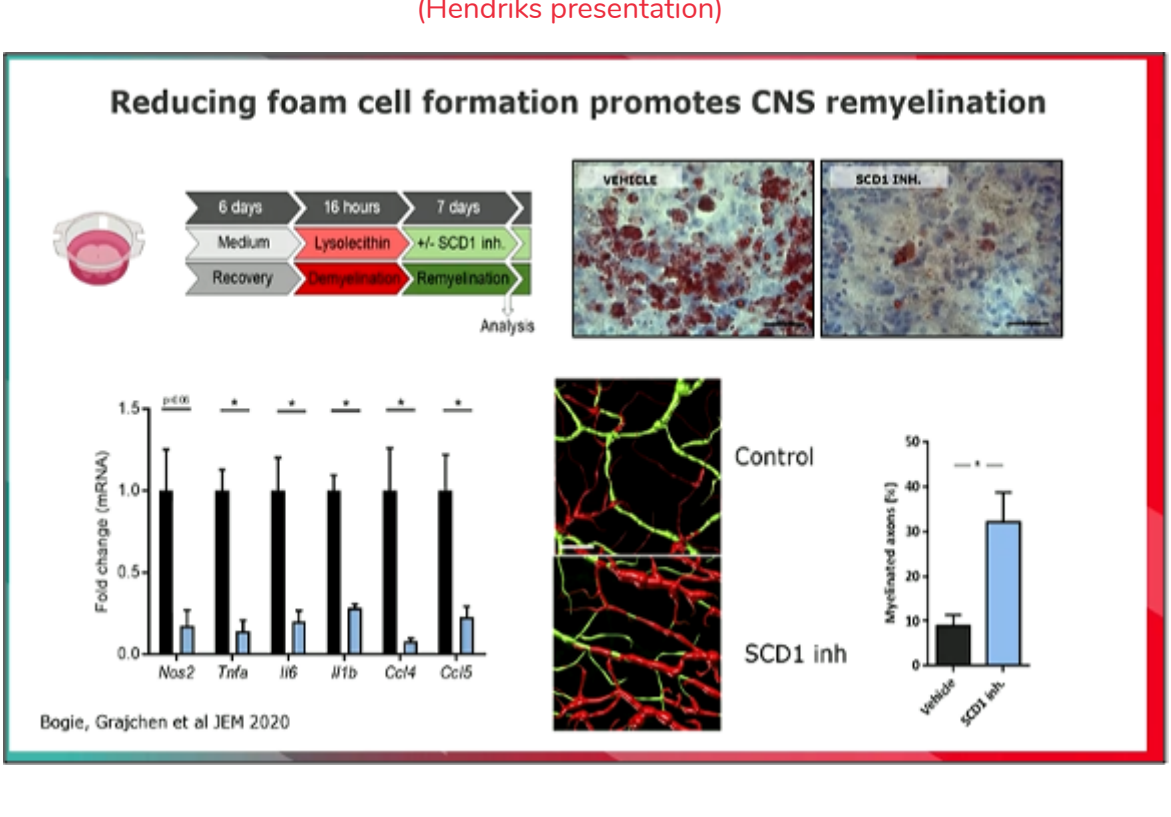
What's New: Recent research has demonstrated that lipid processing and efflux is disrupted in foamy macrophages in MS. In these experiments, lipid accumulation in phagocytes was shown to induce an inflammatory lesion-promoting phenotype, while stimulation of lipid efflux resolved inflammation and promoted remyelination. Targeting foamy macrophages may therefore represent a promising strategy to attenuate lesion progression in the CNS and induce lesion repair.

Tregs play a key role in MS pathology and patients typically show defects in Treg suppression. Recent data have demonstrated the existence of a basal state of inflammation related to Treg dysfunction in MS adipose tissue, with alterations in the regulation of long-chain fatty acid storage. Lipids, notably oleic acid, have demonstrated the ability to partially restore this Treg suppressive capacity in MS patients. A newly discovered molecular mechanism responsible for the loss of Treg function in MS centres on the PRDM1 short-form isoform.

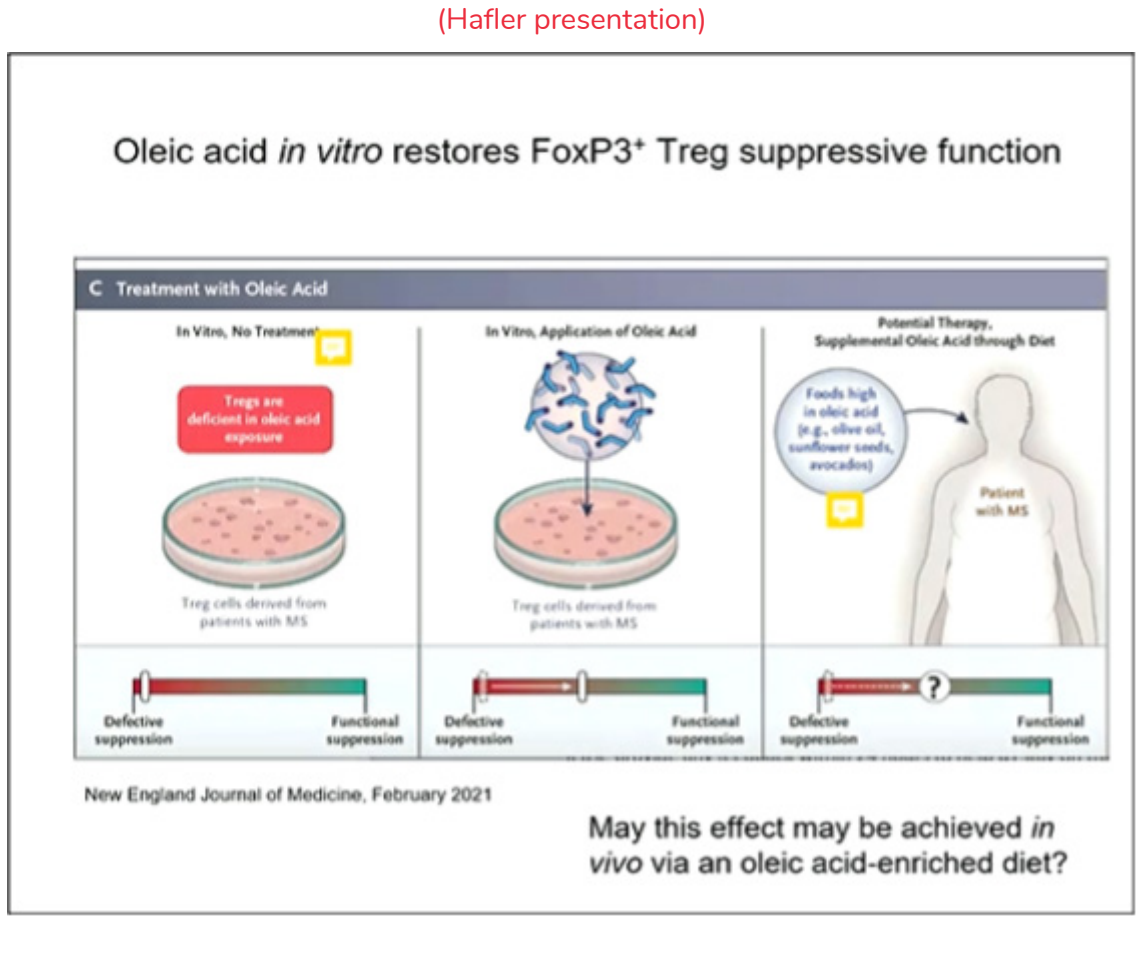
Lipid metabolism is critically involved in the endogenous repair of demyelinated lesions, which occurs early in the MS disease course. However, MS is associated with systemic metabolic perturbations caused by neuroinflammation, leading to an imbalance between peripheral and CNS energy metabolism and causing CNS starvation and neurone damage. Research has shown that feeding a lipid-promoting ketogenic diet may foster the energy metabolism of neurones by providing the missing energy substrate.

Background: Lipids play a major role in modulating CNS physiology and are essential in the regulation of neuro-inflammatory responses. Research is ongoing to exploring how lipids and lipid mediators contribute to MS pathology and their role in remyelination and repair in the CNS.

(Hendriks presentation)



(Hafler presentation)



(Hafler presentation)