



Progressive MS: A Major Unmet Need

Mechanisms, role of EBV and Biomarkers

Sept 10, 2024

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Outline

Progressive biology of MS: an under-estimated unmet need

Mechanisms contributing to progressive MS biology

Emerging roles of EBV

How to measure relevant biologies: key to providing biological proof-of-principle insight

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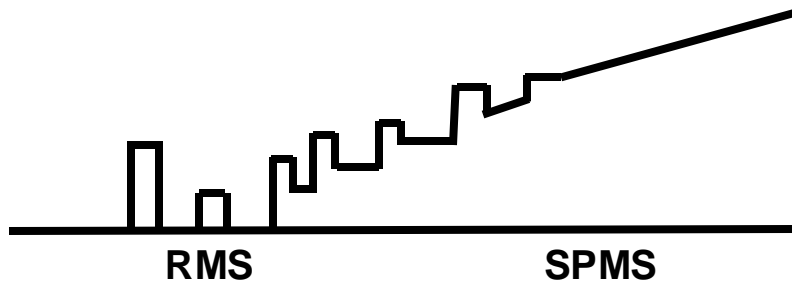
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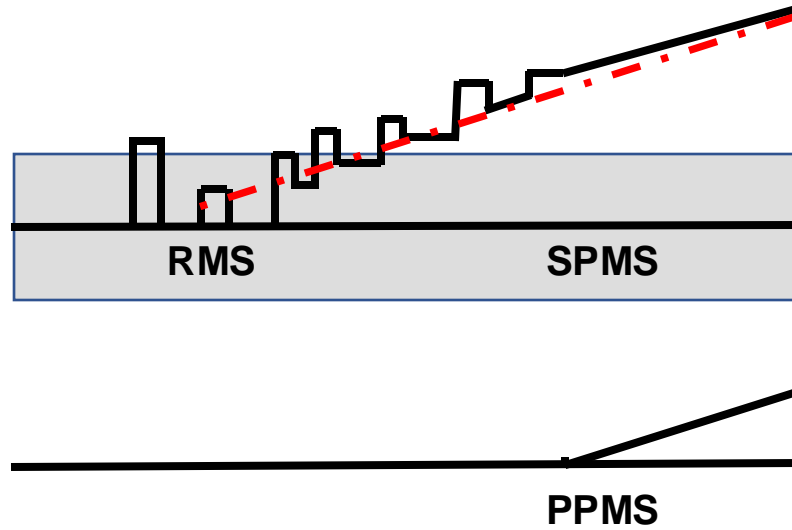
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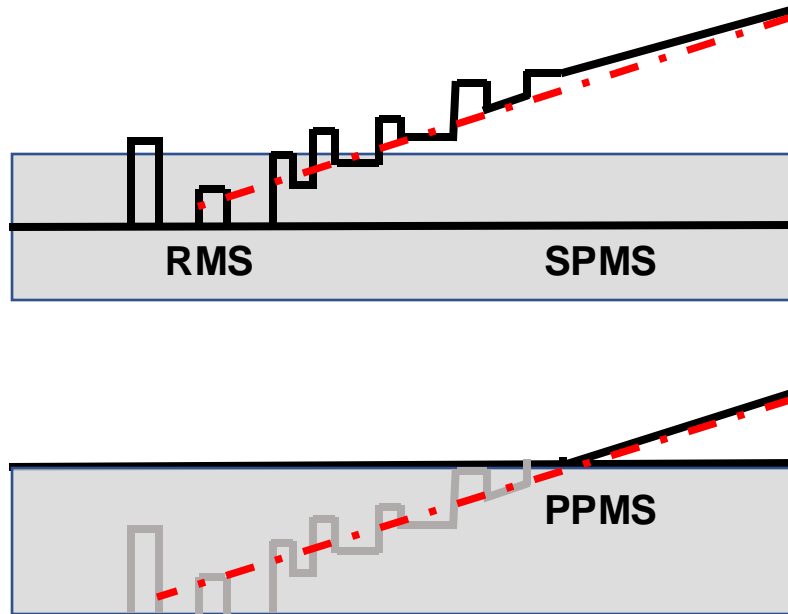
Revisiting the Clinical Spectrum of MS



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Both 'Relapsing' and 'Progressive' biologies exist across MS spectrum

Both mostly sub-clinical, and exhibit substantial clinical heterogeneity

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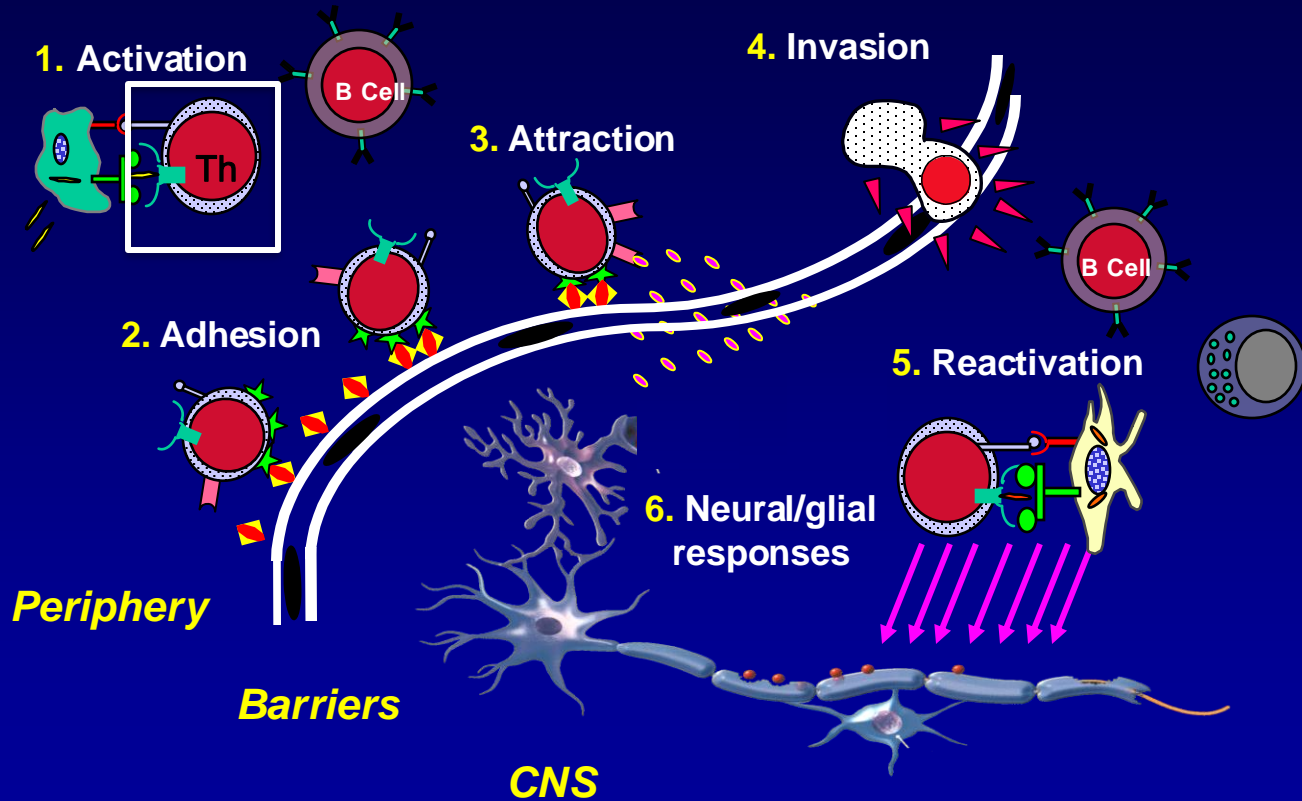
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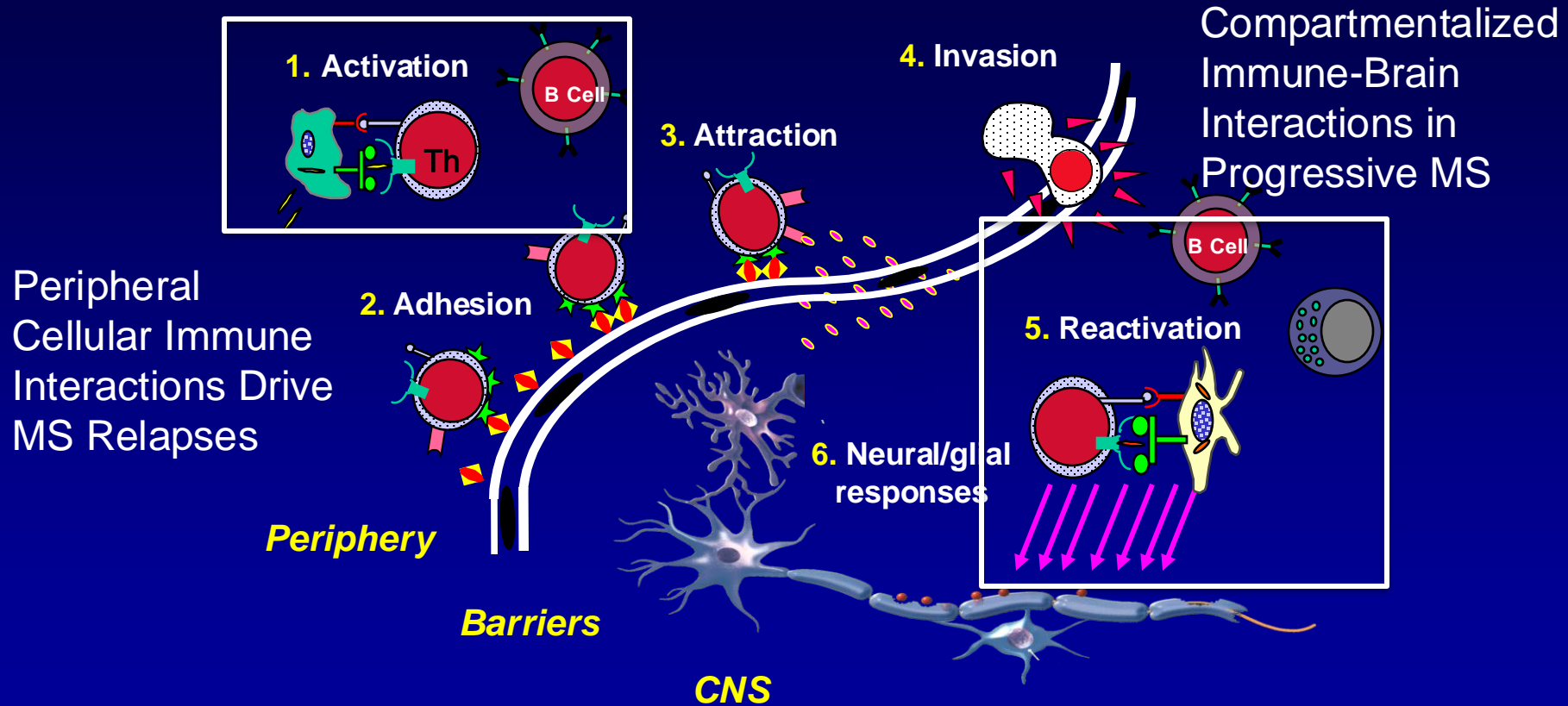
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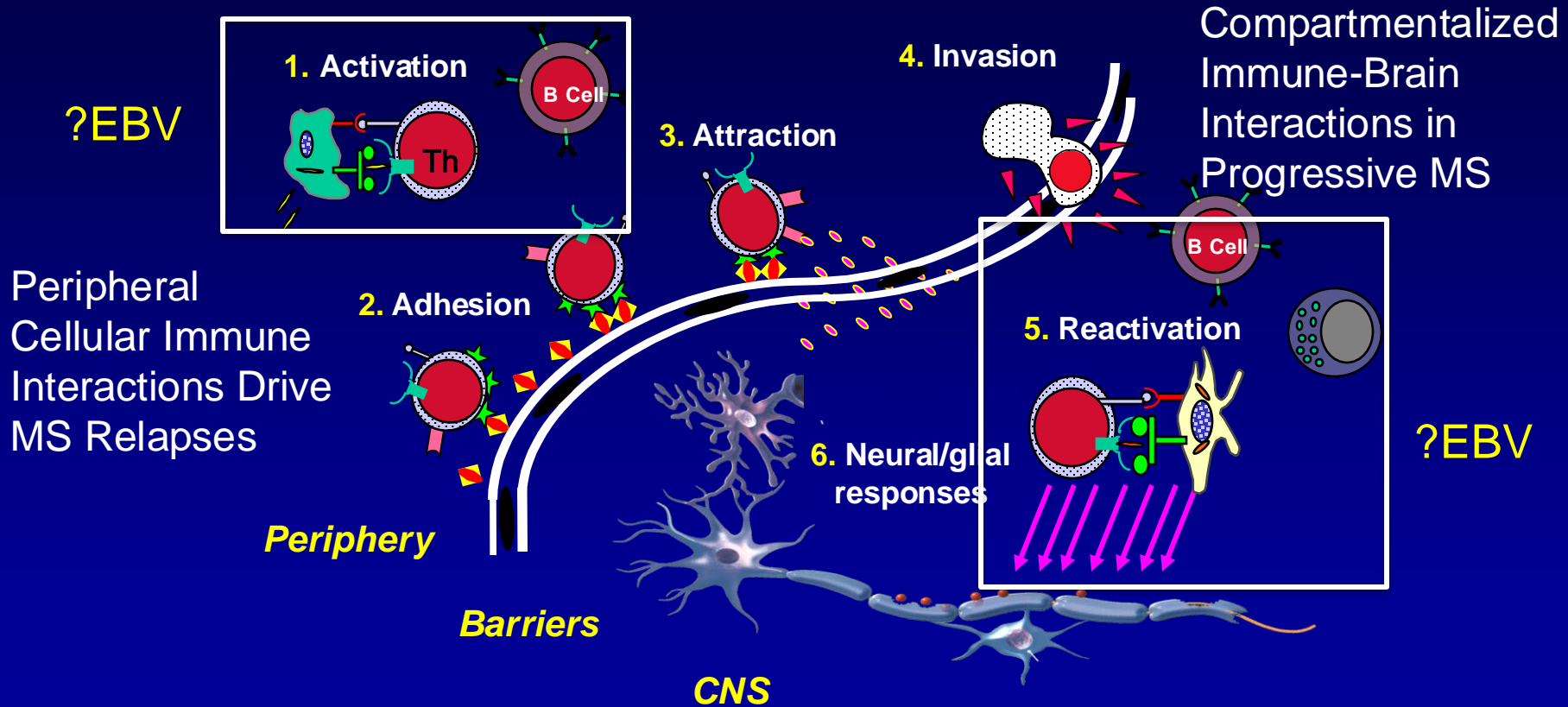
Simplified model of MS Immune Pathogenesis



Simplified model of MS Immune Pathogenesis



Treatments impacting only peripheral inflammation: modest efficacy at best for progressive MS



Elucidating mechanisms of Progressive ('non relapsing') MS

Potential underlying mechanisms:

Inflammation: meningeal; sub-ependymal; perivascular; diffuse microglial

Bidirectional Immune:CNS interactions propagate injury

Mitochondrial (hypoxia; demand > supply; innate/adaptive immunity)

'Toxic substances': glutamate; oxygen, nitrogen species, thrombin

Ion channels: 'functional channelopathies'

Neural-glia uncoupling; functional networks

Loss of compensatory mechanisms

Normal aging + comorbidities (esp. vascular)

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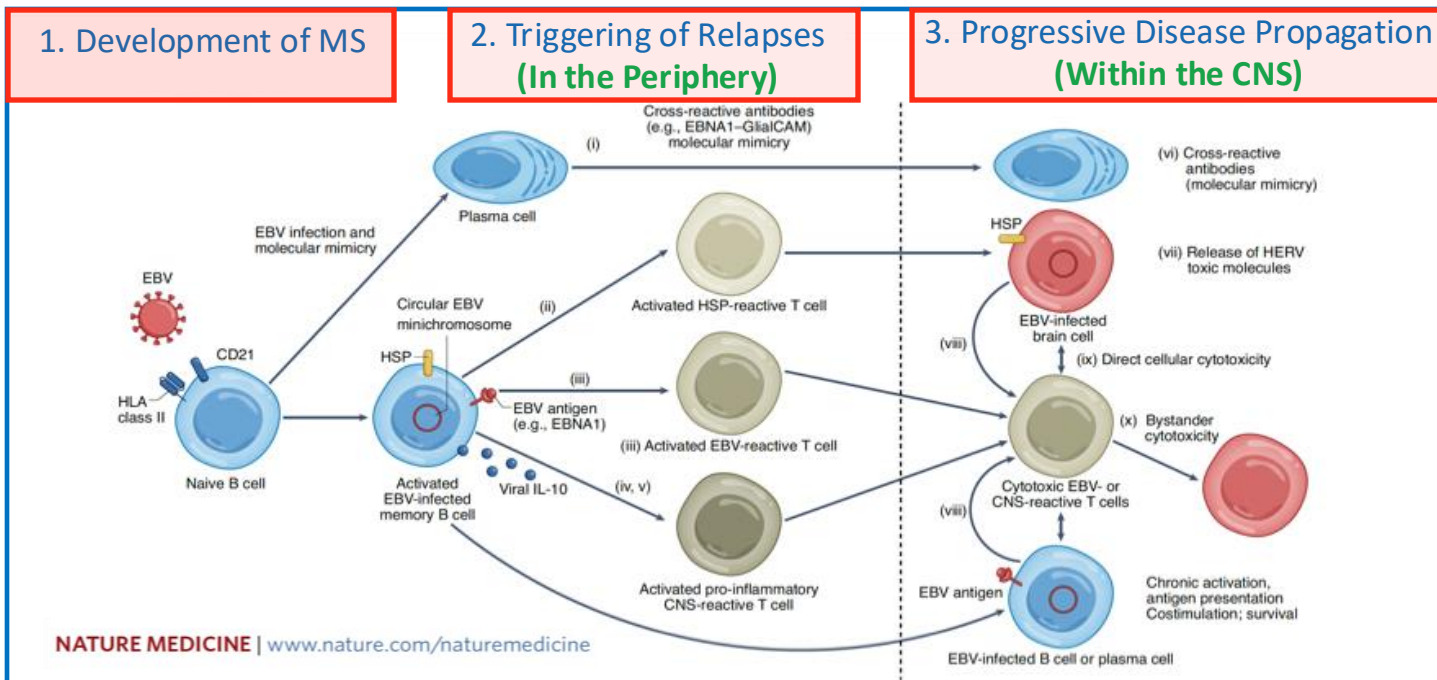
Reinvigorated interest in EBV role/s across MS spectrum

MULTIPLE SCLEROSIS

Guilty by association: Epstein-Barr virus in multiple sclerosis

Two new studies provide robust epidemiological evidence and a mechanistic link, with potential implications for strategies that target Epstein-Barr virus.

Amit Bar-Or, Brenda Banwell, Joseph R. Berger and Paul M. Lieberman Nat Med, 2022



Ineffective control of Epstein-Barr-virus-induced autoimmunity increases the risk for multiple sclerosis

Cell 186, 1–14, December 21, 2023

Hannes Vietzen,^{1,5,*} Sarah M. Berger,¹ Laura M. Kühner,¹ Philippe L. Furlano,¹ Gabriel Bsteh,^{2,3} Thomas Berger,^{2,3} Paulus Rommer,^{2,3,4} and Elisabeth Puchhammer-Stöckl^{1,4}



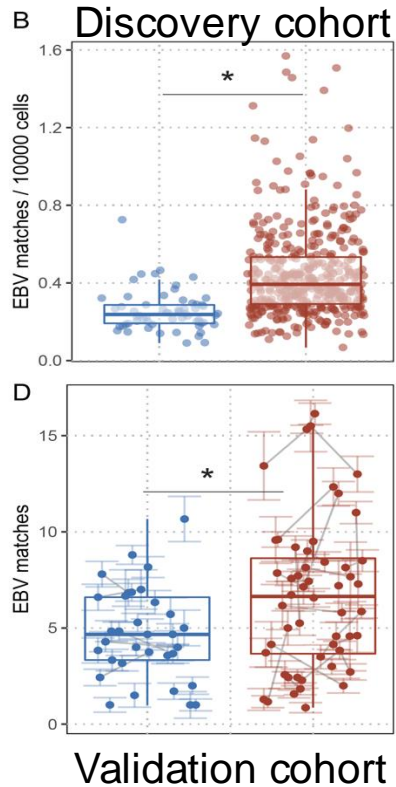
BRIEF DEFINITIVE REPORT

Broader Epstein-Barr virus-specific T cell receptor repertoire in patients with multiple sclerosis

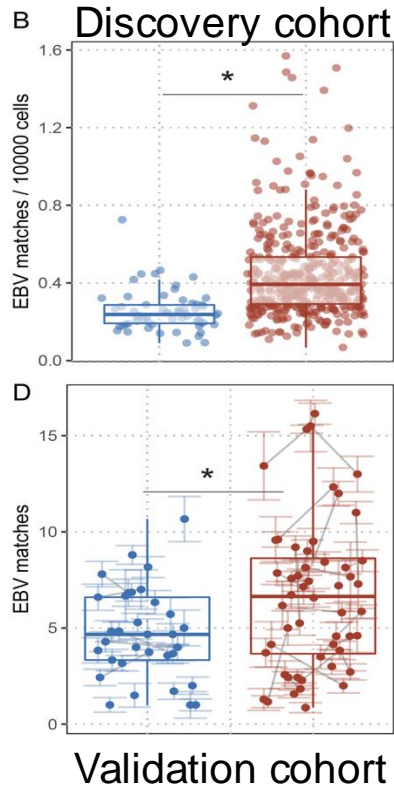
Tilman Schneider-Hohendorf^{1*}, Lisa Ann Gerdes^{2,3,4*}, Béatrice Pignolet^{5*}, Rachel Gittelman⁶, Patrick Ostkamp¹, Florian Rubelt⁷, Catarina Raposo^{8,9}, Björn Tackenberg^{8,9}, Marianne Riepenhausen¹, Claudia Janoschka¹, Christian Wünsch¹, Florence Bucciarelli⁵, Andrea Flierl-Hecht^{2,3,4}, Eduardo Beltrán^{2,3,4}, Tania Kümpfel^{2,3,4}, Katja Anslinger¹⁰, Catharina C. Gross¹, Heidi Chapman⁶, Ian Kaplan⁶, David Brassat⁸, Hartmut Wekerle^{2,11}, Martin Kerschensteiner^{2,3,4}, Luisa Klotz¹, Jan D. Lünemann¹, Reinhard Hohlfeld^{2,3}, Roland Liblau^{5*}, Heinz Wiendl^{1*}, and Nicholas Schwab^{1*}

Schneider-Hohendorf et al., JEM, 2022

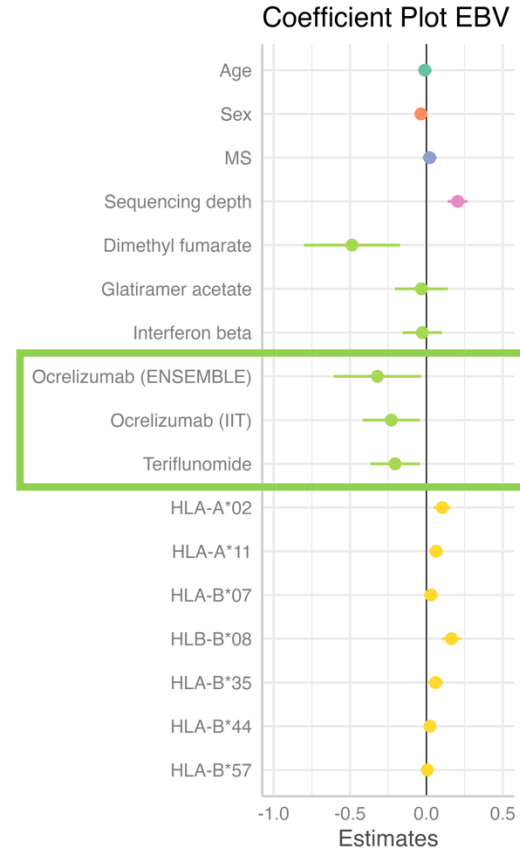
Broader EBV T cell repertoire in MS and Treatment Responses



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Schneider-Hohendorf et al., JEM, 2022



Schneider-Hohendorf et al., Brain, 2024

Assessing effect of therapies on (MS-implicated) EBV biology

Need to measure EBV 'biology/state' broadly:

ie. study both EBV-infected B cells and EBV-reactive T cells

Assays to detect EBV and EBV infected B-cells

ddPCR (EBV DNA viral load)

RTddPCR (EBV RNA viral transcripts: lytic + latent)

PrimeFlow (Flow-FISH)

LCLs (lymphoblastoid cell lines)

Assays to detect EBV-specific T-cell responses:

T cell repertoire

AIM assays (CD4, CD8)

Multiplexed custom HLA-tetramers (CD8)

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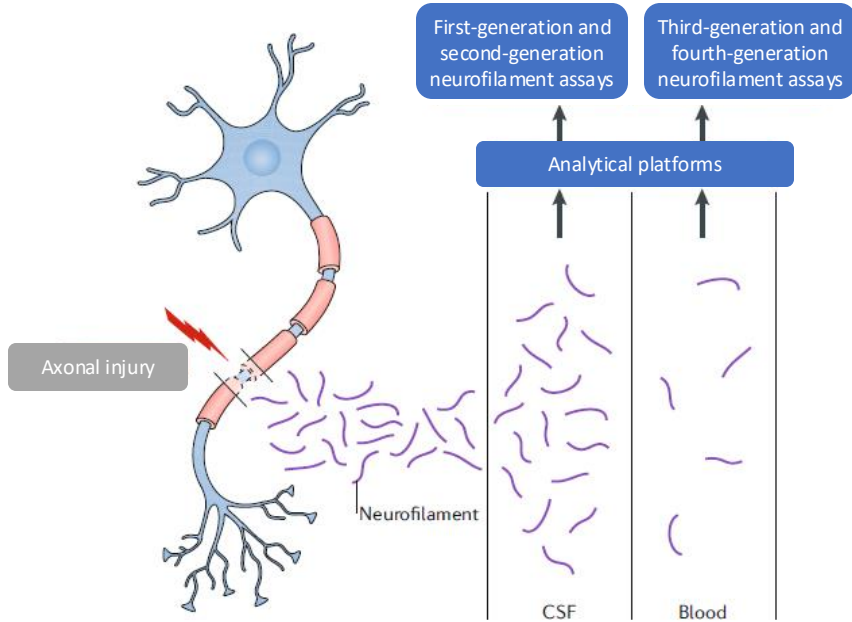
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NfL: neurofilament light chain; GFAP: glial fibrillary acidic protein
... fluid biomarkers of injury and progression in MS

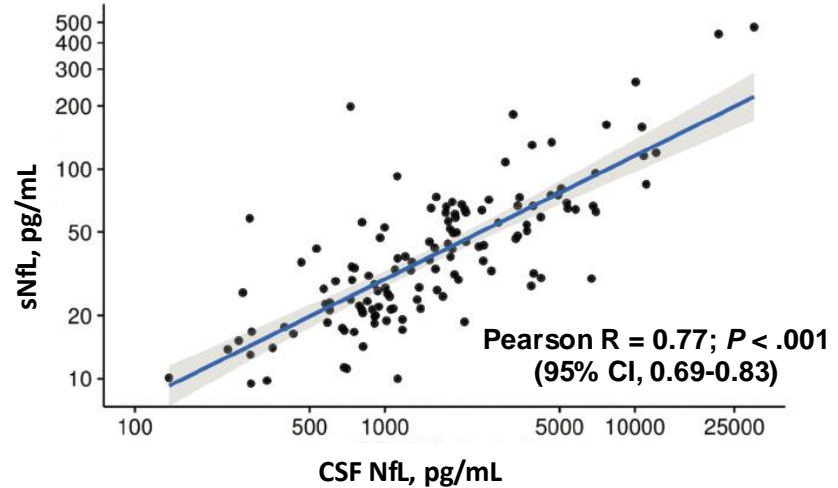
Neurofilament Light Chain (NfL)

Non-specific marker of neuroaxonal injury ¹⁻⁷

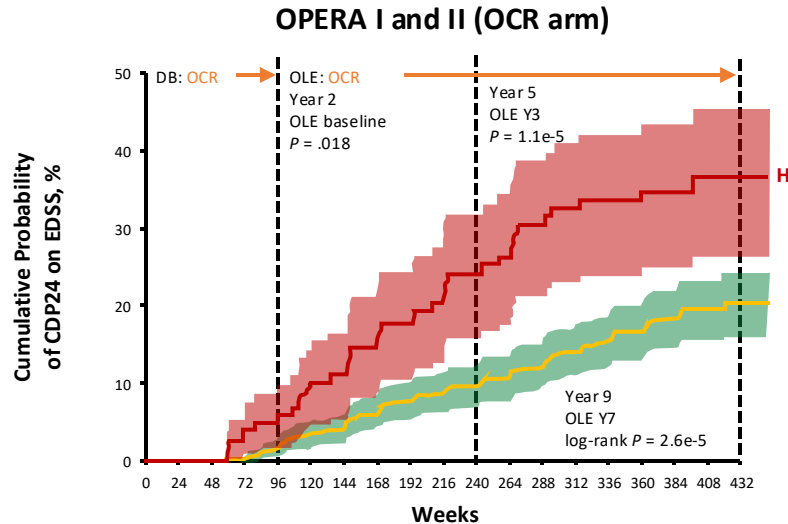
Neuroaxonal Source: Structural Cytoskeleton Component



Neuroaxonal damage → elevated NfL (MS, AD, ALS, PD, and Trauma)



NfL elevation in MS Patients on High Efficacy Therapy reflect injury from progressive MS biology

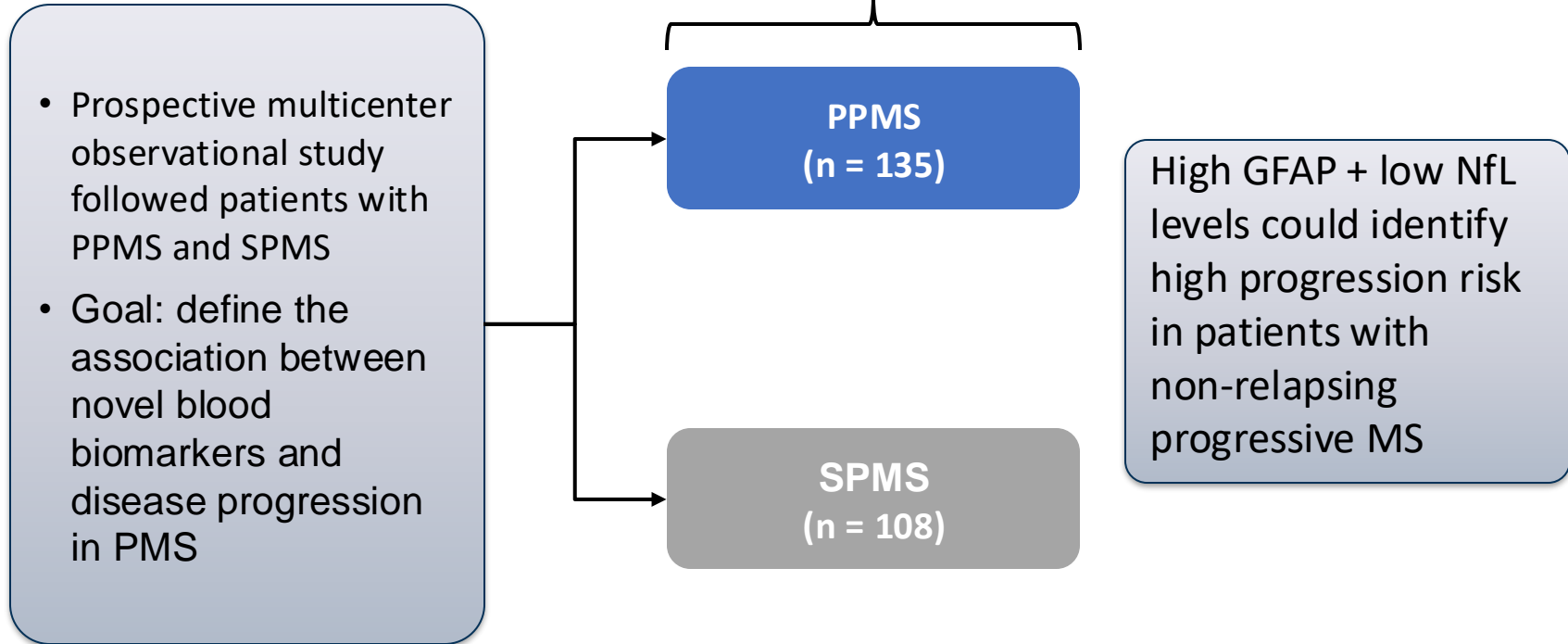


W48 sNFL	No. at Risk																			
Low	533	533	533	526	503	471	457	435	419	408	400	390	379	365	358	338	311	224	96	
High	124	124	124	118	113	103	99	91	88	84	78	72	67	62	59	56	51	35	12	

Nfl in a state of MS free of focal inflammation is a good predictor of future disability risk.-

GFAP + NfL: Results of EmBioProMS¹

Patients followed over a mean of 29.3 months



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