

Emerging Molecular and Cellular Biomarkers in NMOSD



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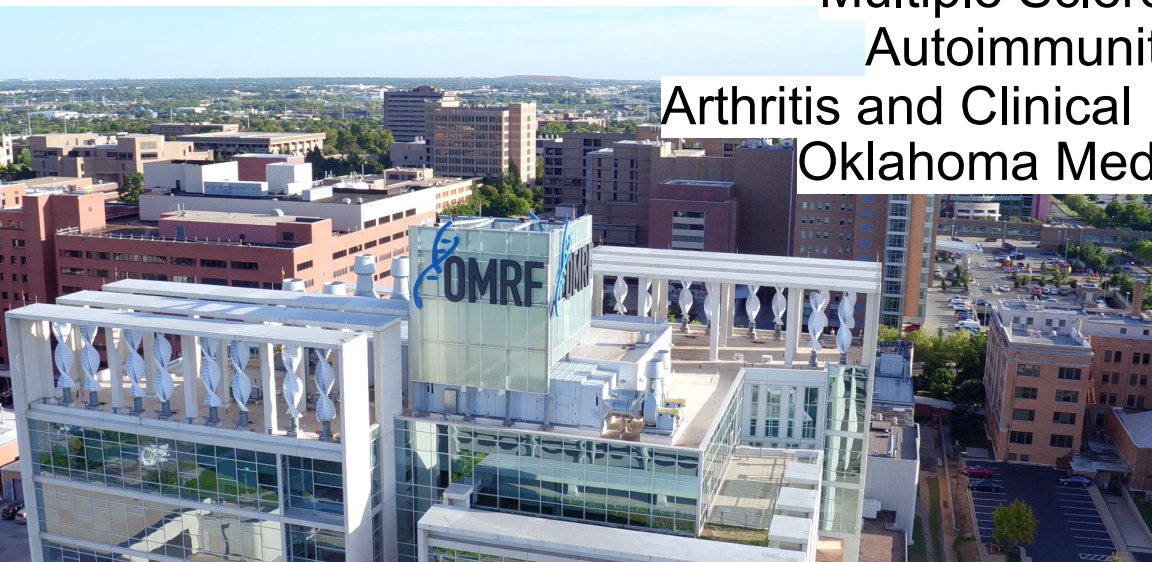
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Multiple Sclerosis Center of Excellence

Autoimmunity Center of Excellence

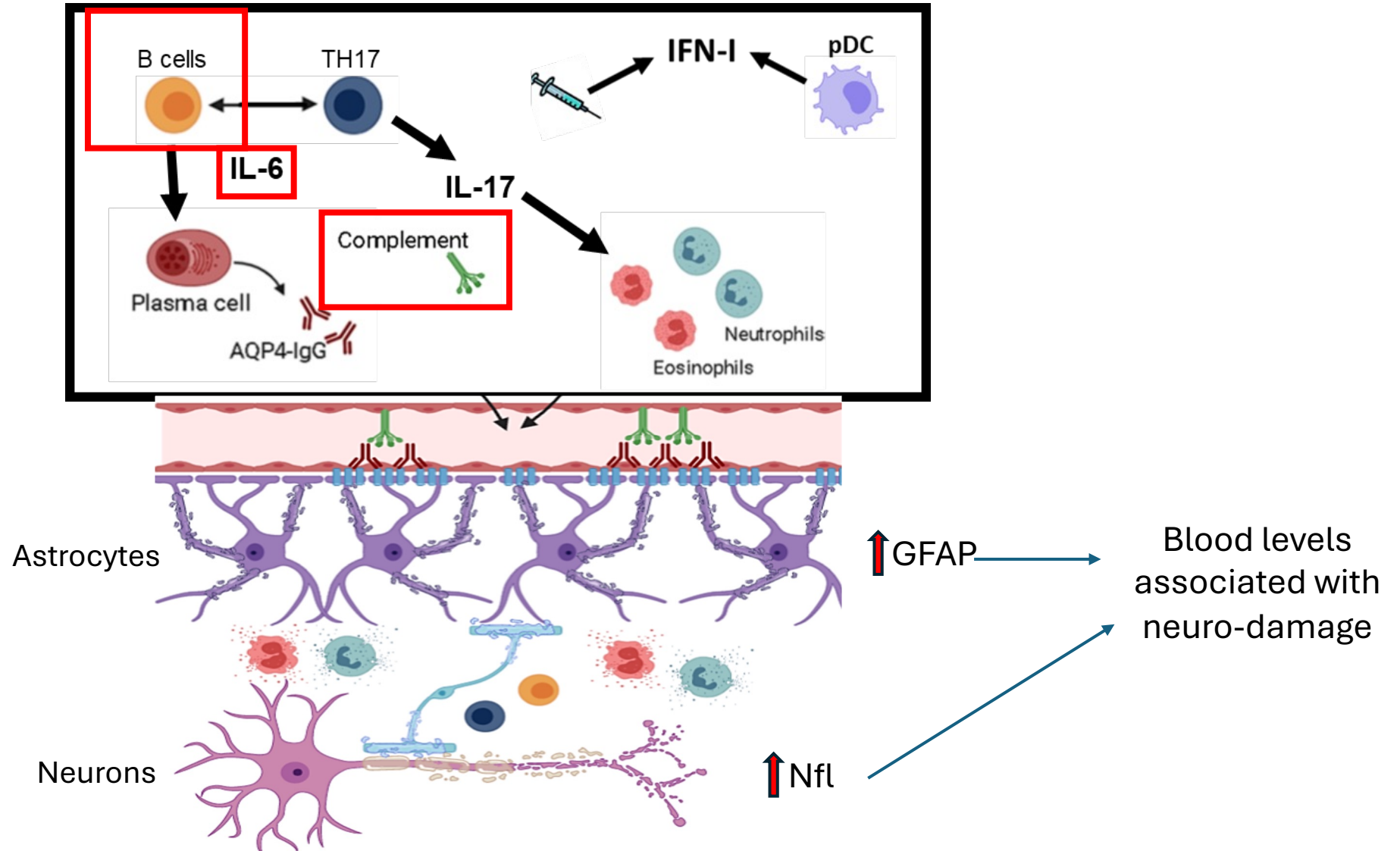
Arthritis and Clinical Immunology Research Program

Oklahoma Medical Research Foundation

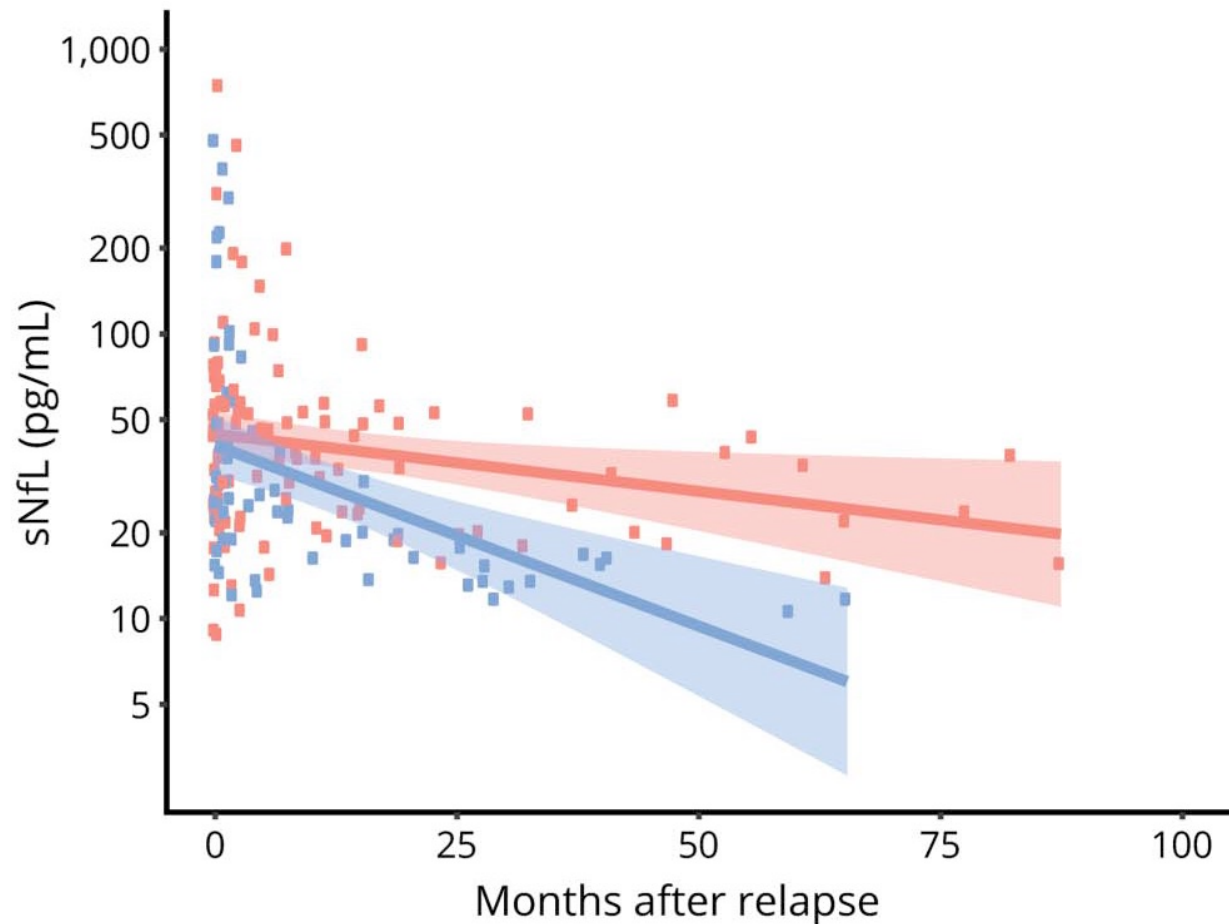
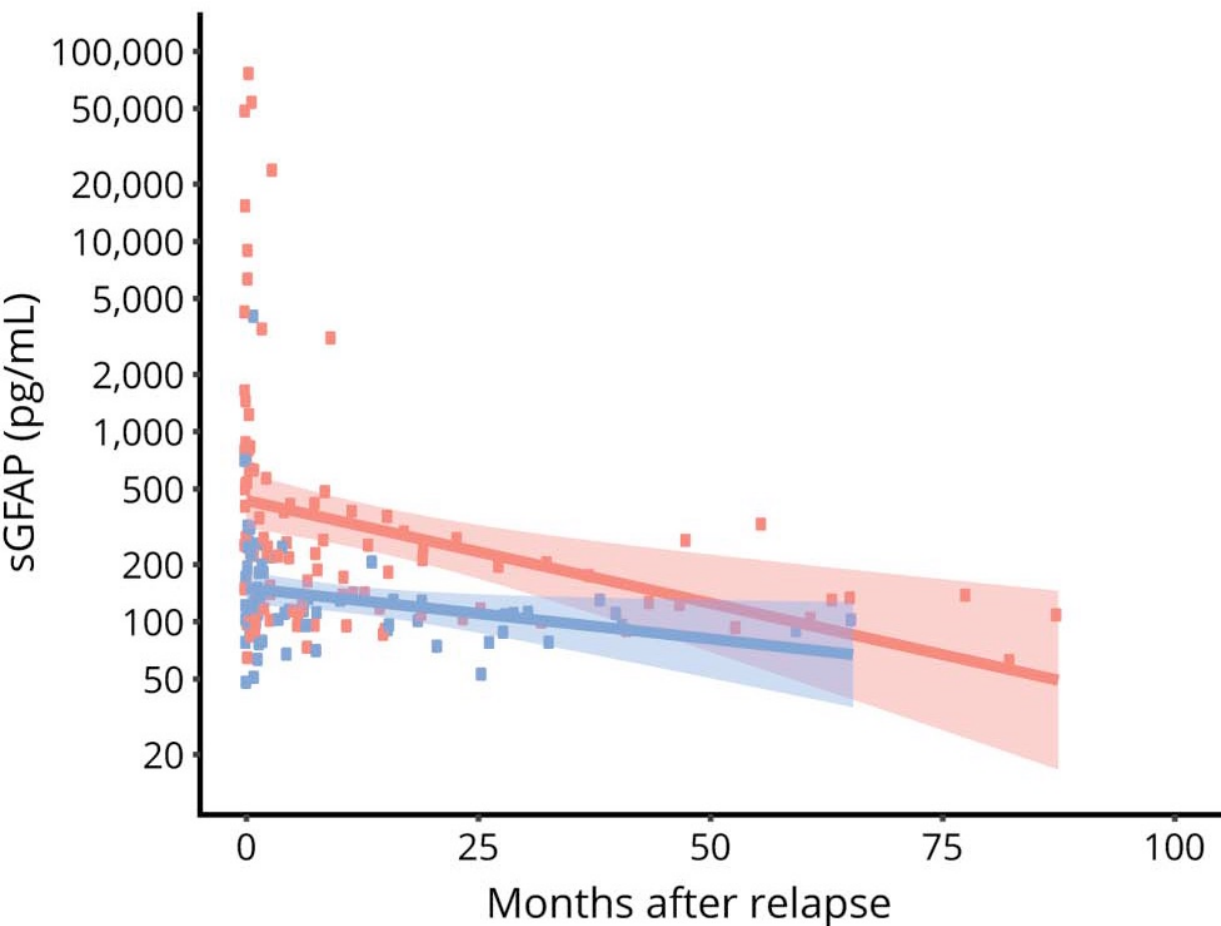


DISCOVERIES THAT MAKE A DIFFERENCE

Immune pathogenesis of NMO

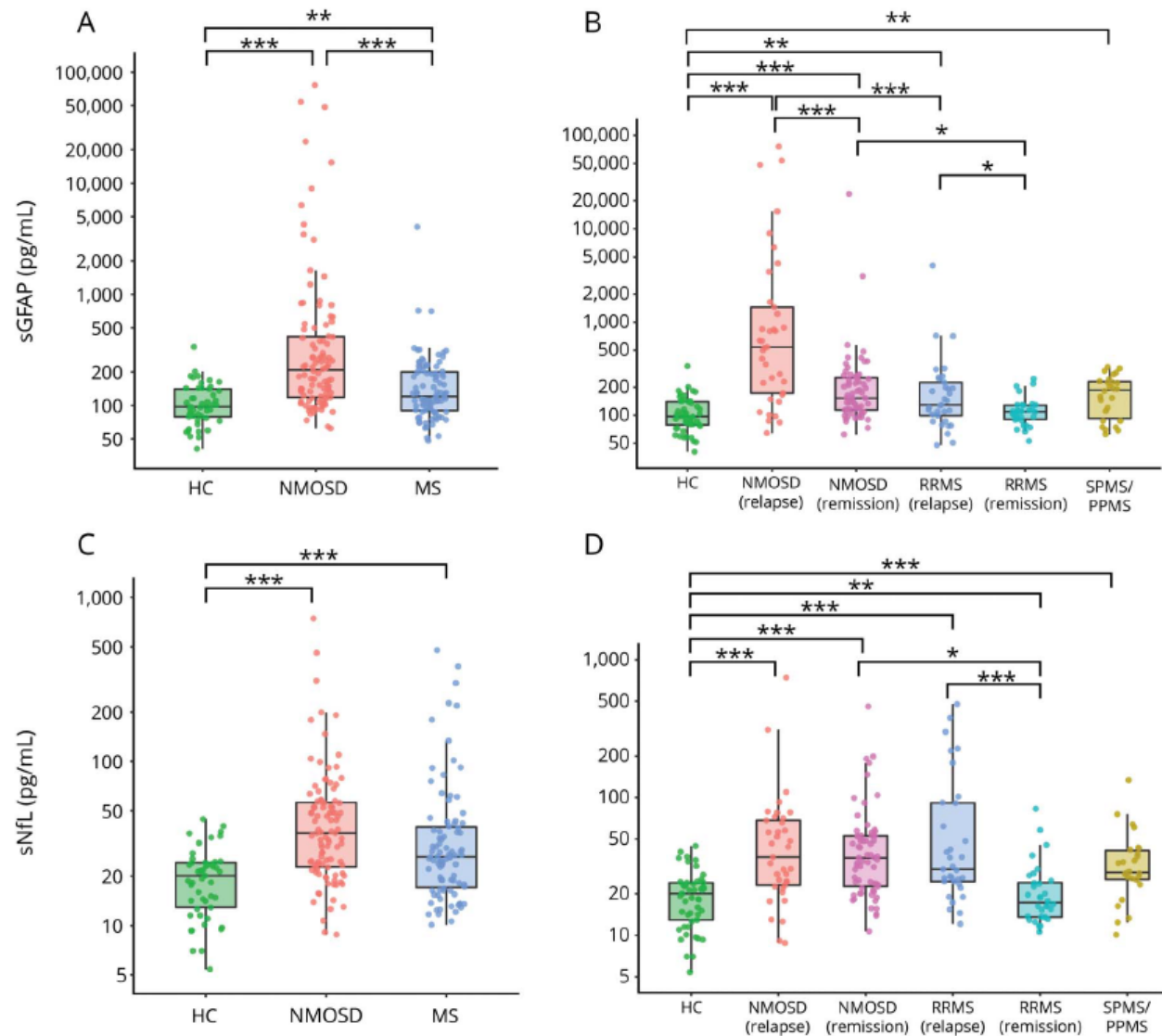


Longitudinal Changes in GFAP and NFL after relapse



MS
NMO

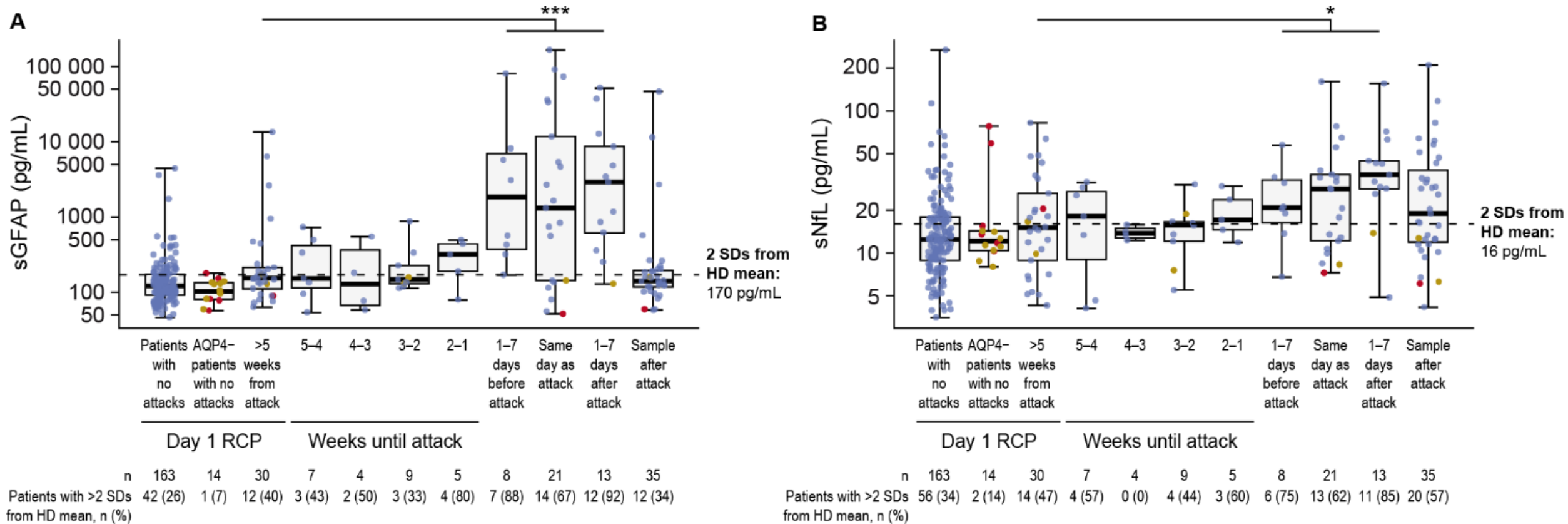
GFAP levels are reduced during remission in NMO



GFAP levels are associated with EDSS and relapse

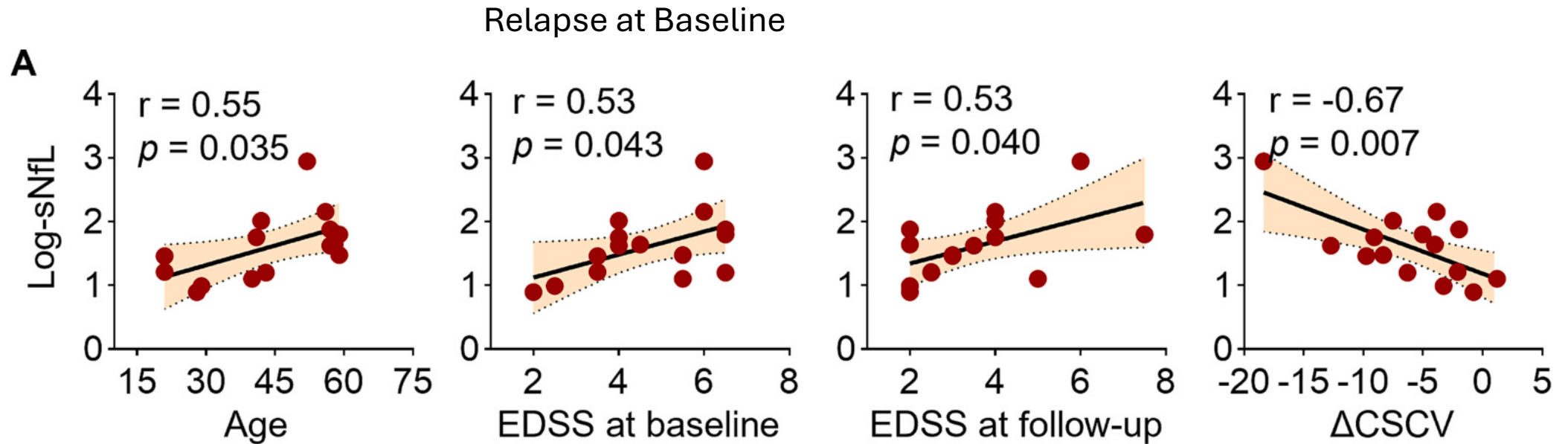
NFL levels are associated with EDSS not relapse

GFAP (not NFL) tracks with relapse



Aktas O et al. N-Momentum study, JNNP 2023

Nfl associated with EDSS and spinal cord atrophy during remission



Treatments : rituximab, tocilizumab

Follow up is 1 year.

Are there molecular and cellular signatures in NMO patients?

Collaborators

Dr. Friedemann Paul, *Charité Universitätsmedizin, Berlin*

Dr. Robert Axtell, *OMRF*

- **Proteomics:** Serum protein profiling of patients
- **Transcriptomics:** Whole blood RNA profiling

Study design for NMOSD biomarkers



96 NMOSD patients

- 53 AQP4+
- 25 MOG+
- 18 DN

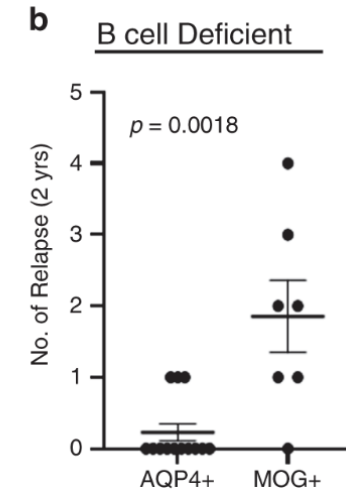
49 Healthy Controls



Serum proteomics

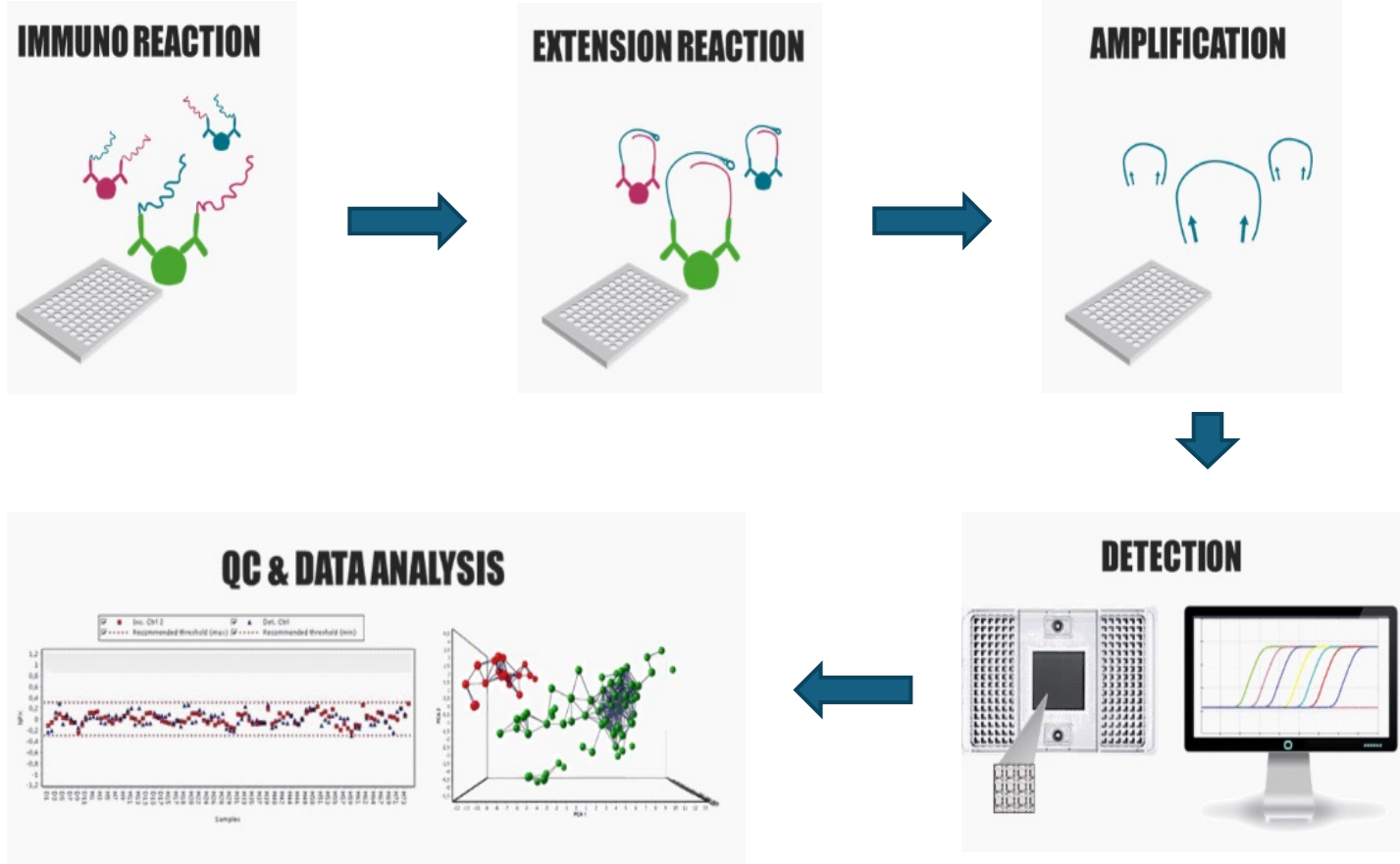


Distinguish between AQP4+, MOG+ and DN-NMOSD patients



Differences in effect of BCD in AQP4+, MOG+ and DN-NMOSD patients

Proximity Extension Assay (PEA) - Olink Proteomics

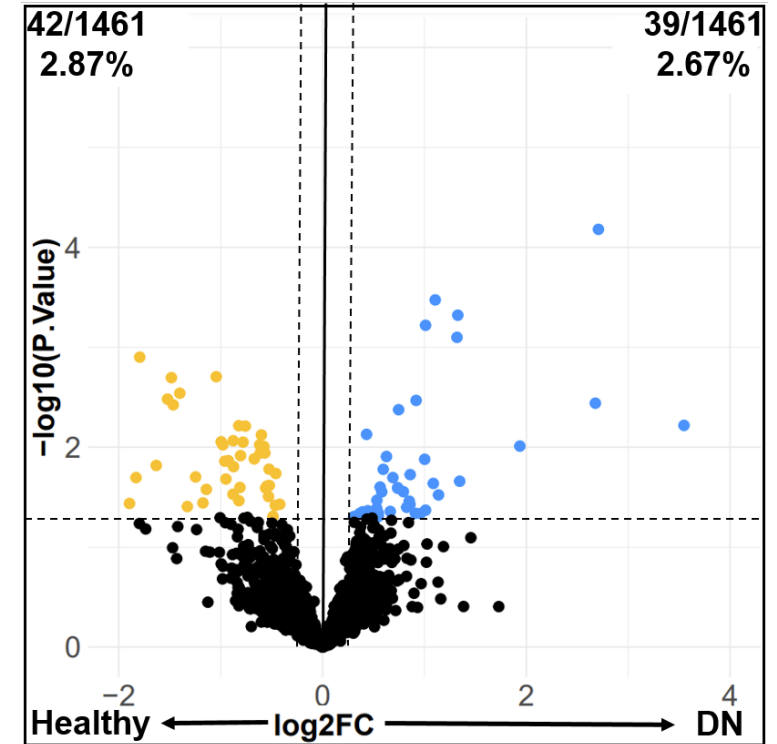
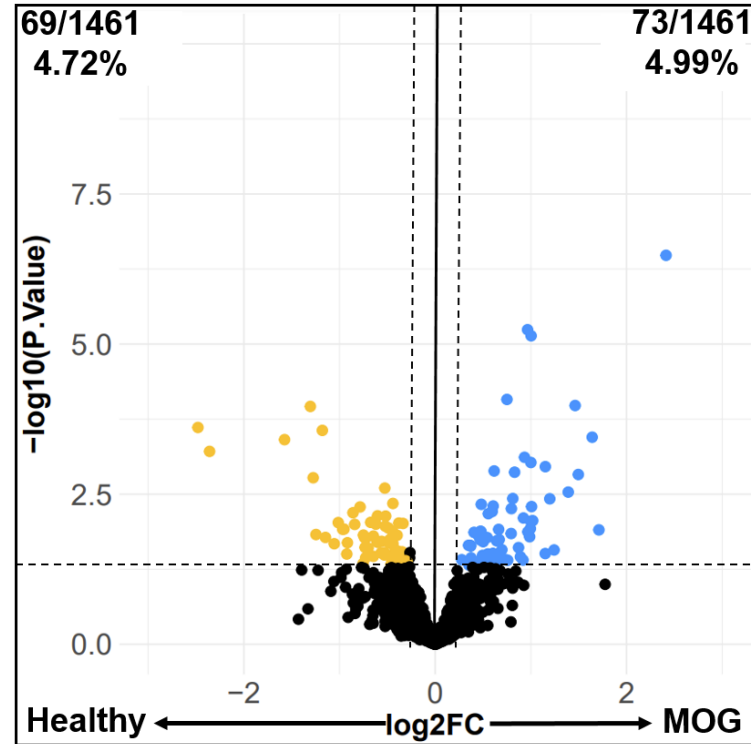
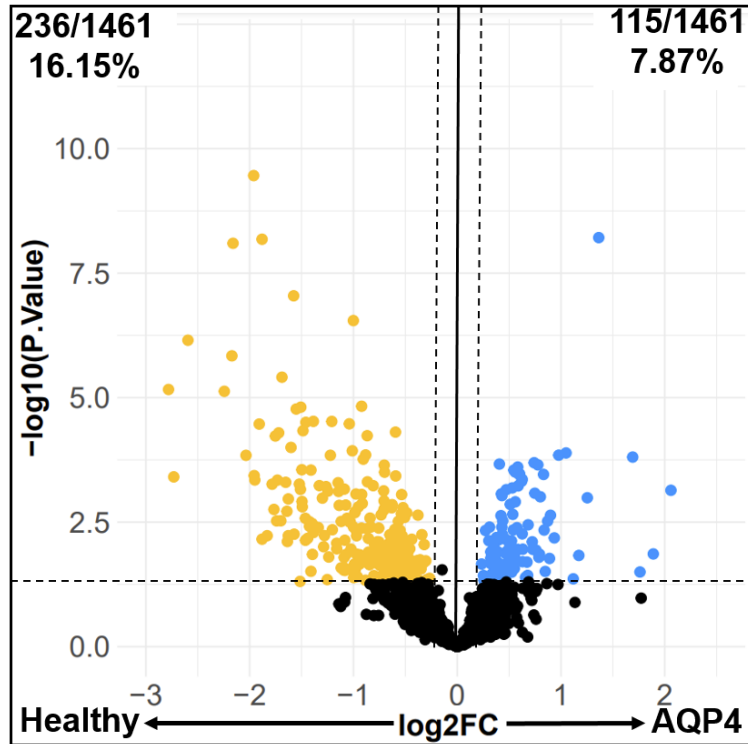


Why use PEA?

1. Highly sensitive compared to standard ELISAs
2. Low chance of antibody cross-reactivity compared to other multiplexing assays
3. Requires very little sample volume

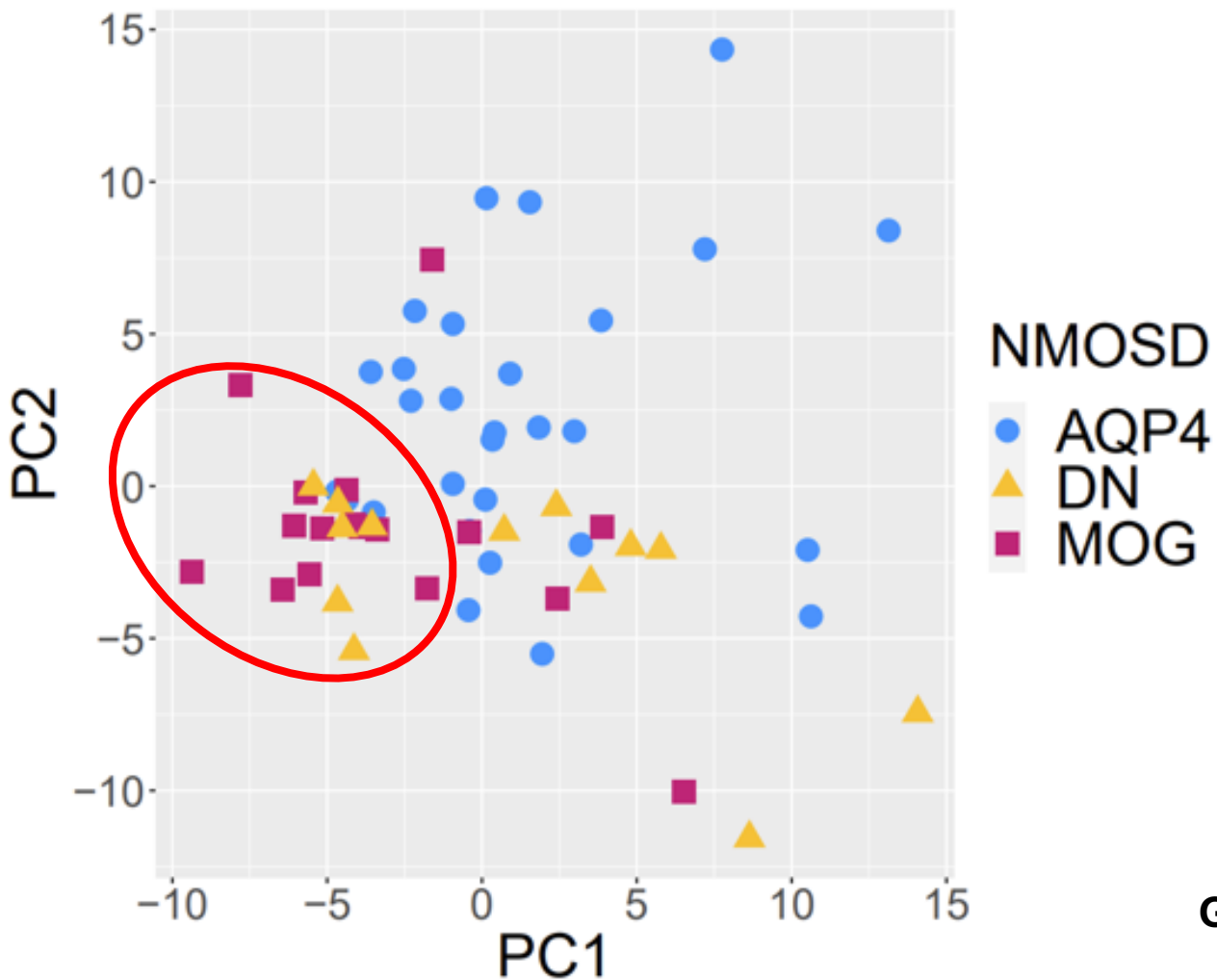
4. Measures over 1500 serum proteins in one aliquot of sample

Serum protein profiles distinguish NMOSD subgroups from healthy controls



Gawde S et al. Neurol Neuroimmunol Neuroinflamm 2024

Serum protein profiles distinguish between NMOSD subgroups

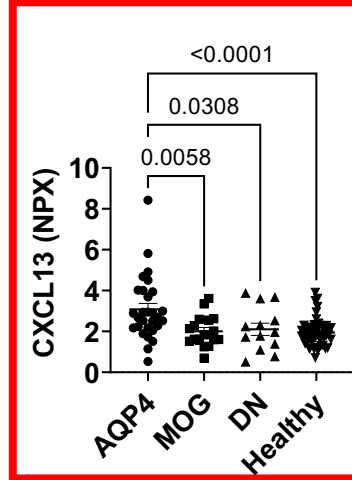


- Overall serum protein profiles can distinguish NMOSD subgroups.
- Overlap between serum protein profiles of MOG-NMOSD and DN-NMOSD patients

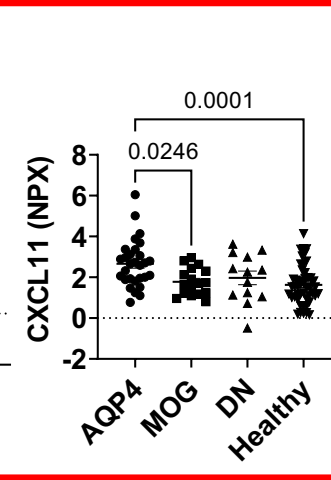
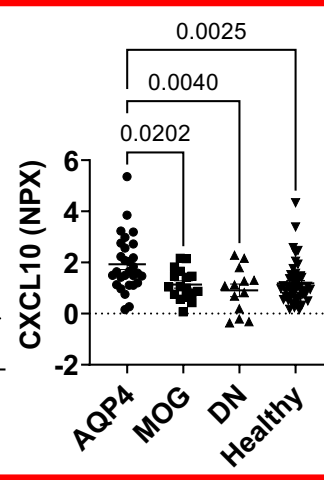
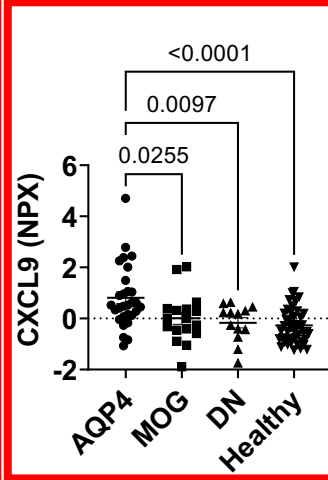
Serum protein profiles distinguish NMOSD subgroups from healthy controls

AQP4-NMOSD

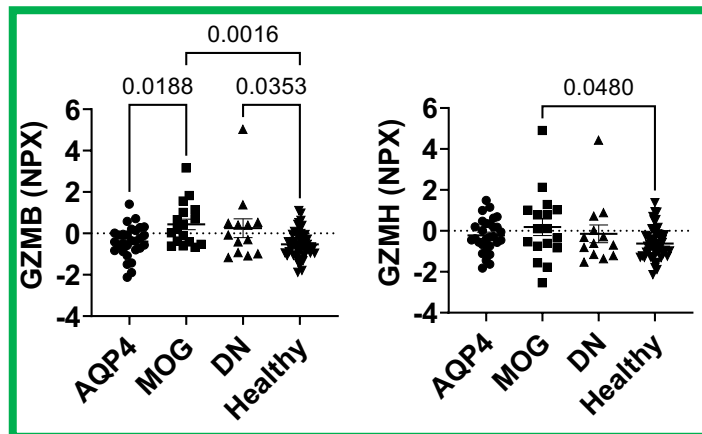
TFH/ B cell chemokine



Type I IFN chemokines

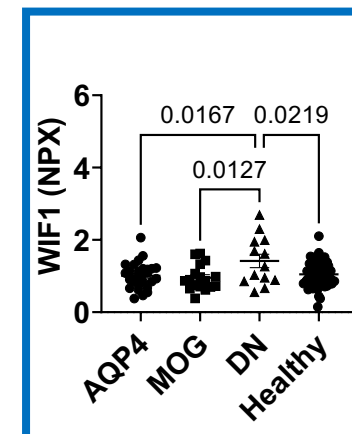


Granzymes



MOG-NMOSD

Wnt inhibitory factor 1



DN-NMOSD

Short Summary

- Type I IFN-induced chemokines CXCL9, CXCL10 and CXCL11 are elevated in AQP4-NMOSD.
 - Indicate that pathogenic processes in AQP4-NMOSD are driven by type I IFN

- CXCL13, which is a T follicular helper (TfH)/ B cell chemokine, is elevated in AQP4-NMOSD.
 - Indicate that these cells are involved in pathogenesis of AQP4-NMOSD

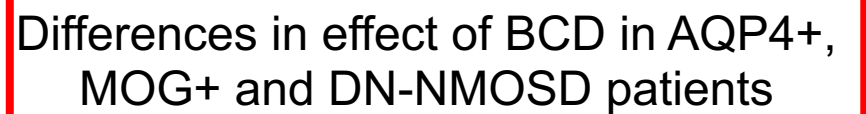
- Granzyme B and H levels are increased in MOGAD.
 - MOG-reactive CD8+ T cells could be involved in MOGAD pathogenesis

- Serum protein profiles of DN-NMOSD are more similar to MOGAD than AQP4-NMOSD

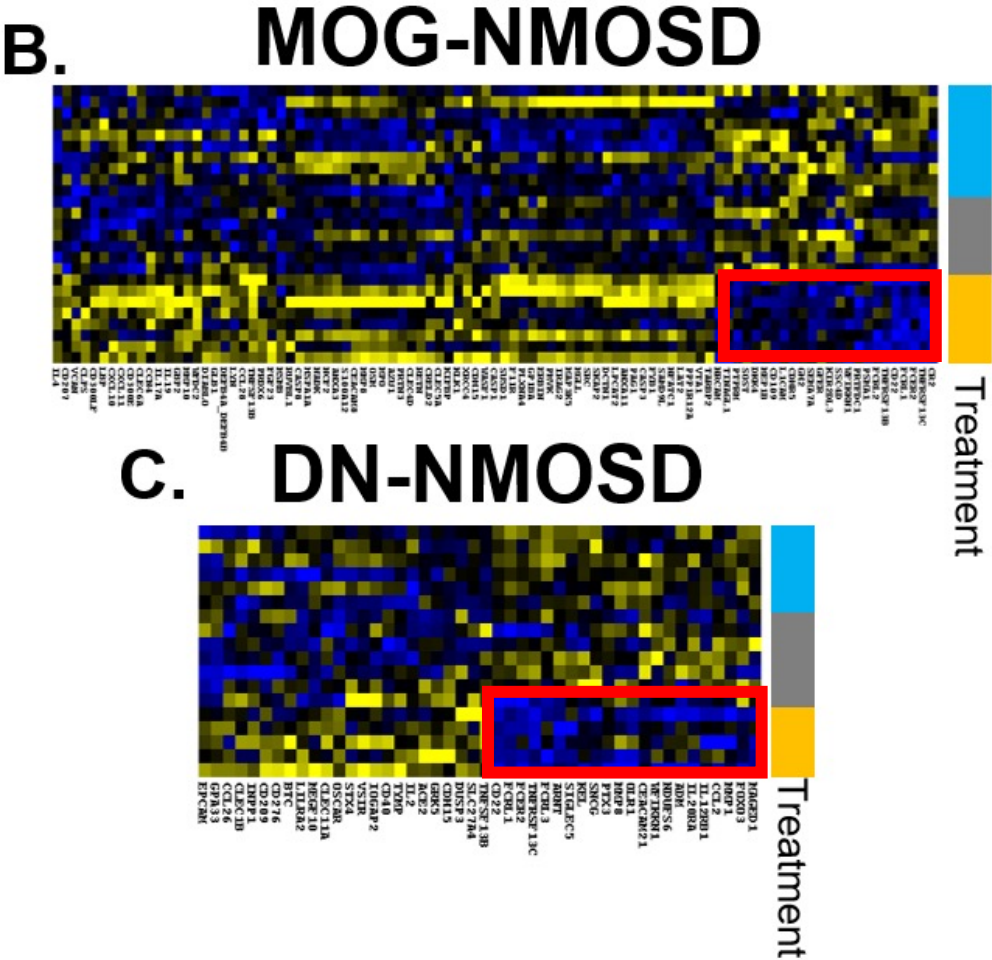
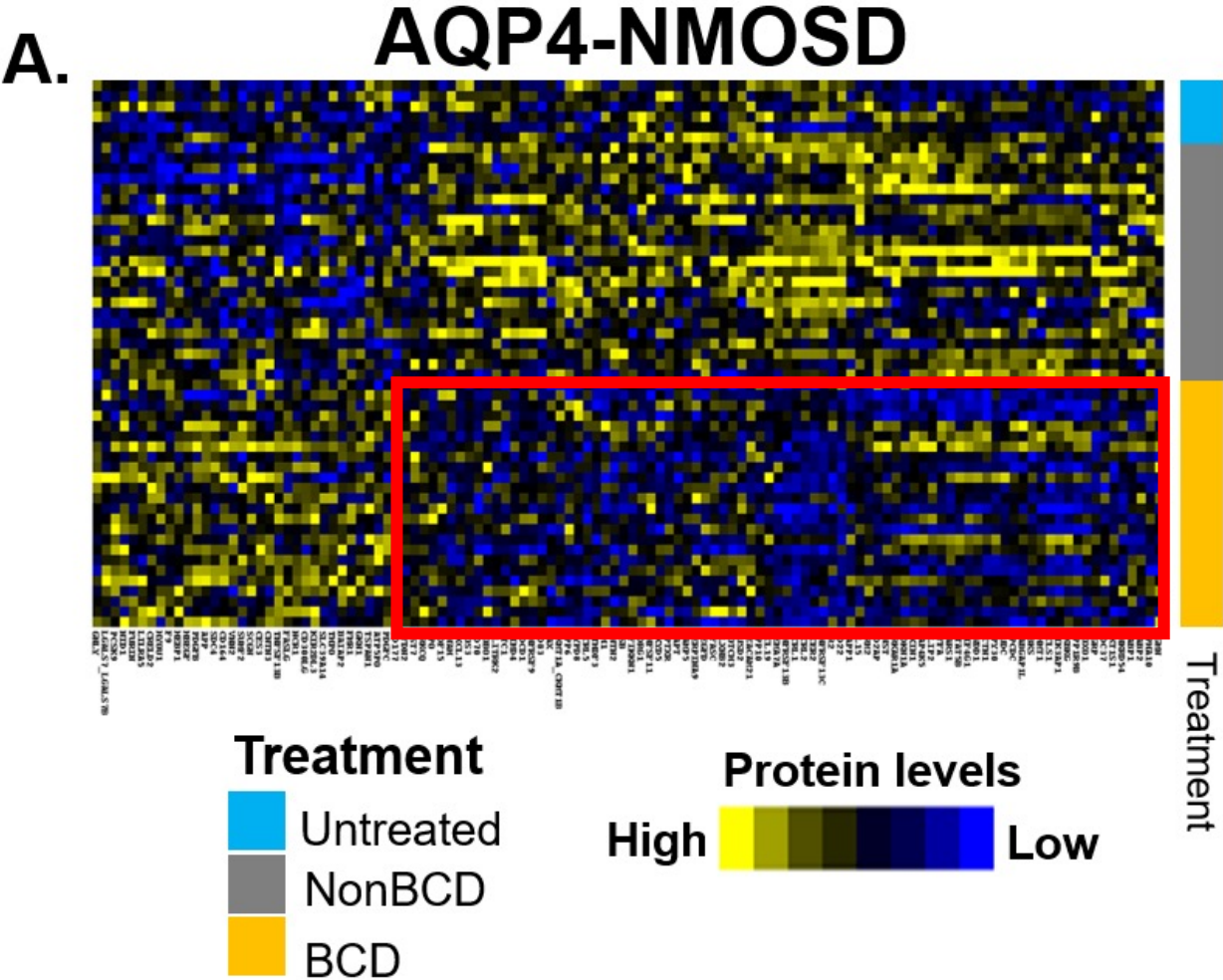


- 53 AQP4
- 25 MOG
- 18 DN

49 Healthy Controls

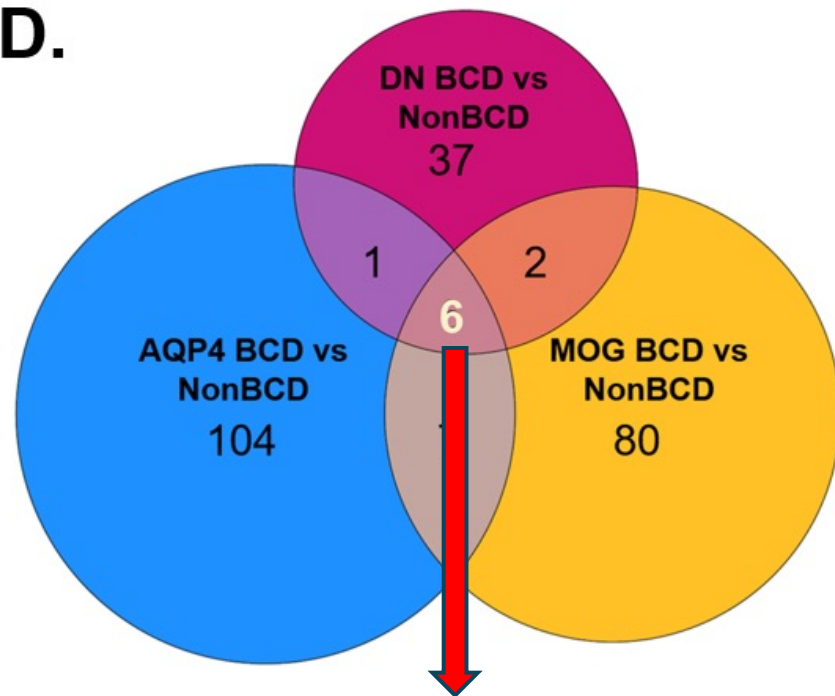


BCD alters serum protein profiles of NMOSD subgroups



Serum proteins indicate B cell depletion in NMOSD subgroups

D.



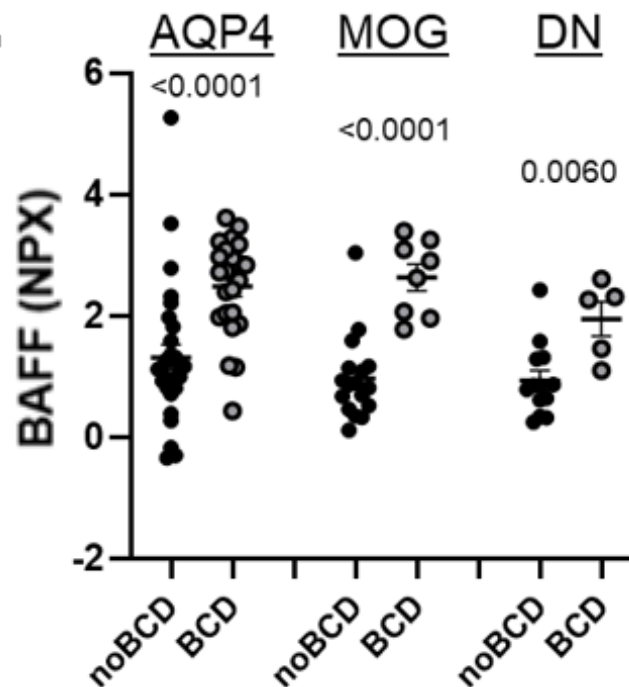
Common proteins

BAFF → ↑ with BCD

FCER2
TNFRSF13C
WFIKKN1
FCRL1
CD22 } ↓ with BCD

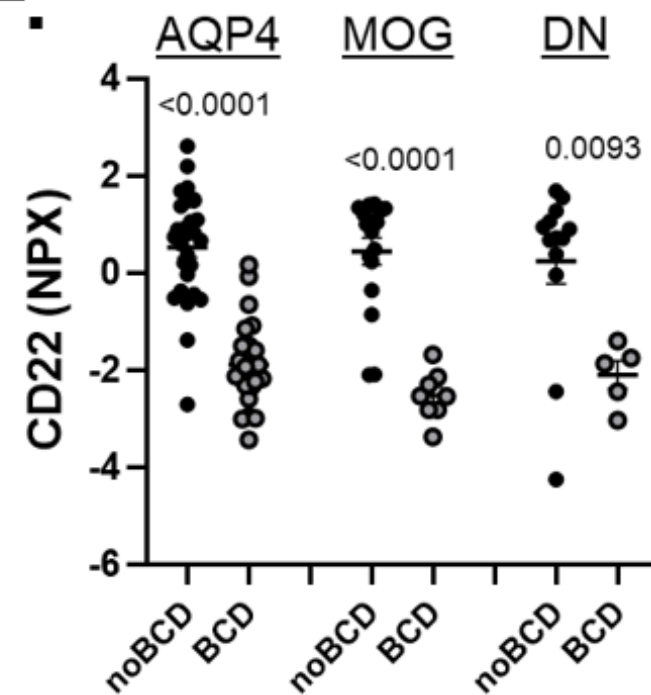
B cell
associated
proteins

G.



B cell survival factor
(BAFF)

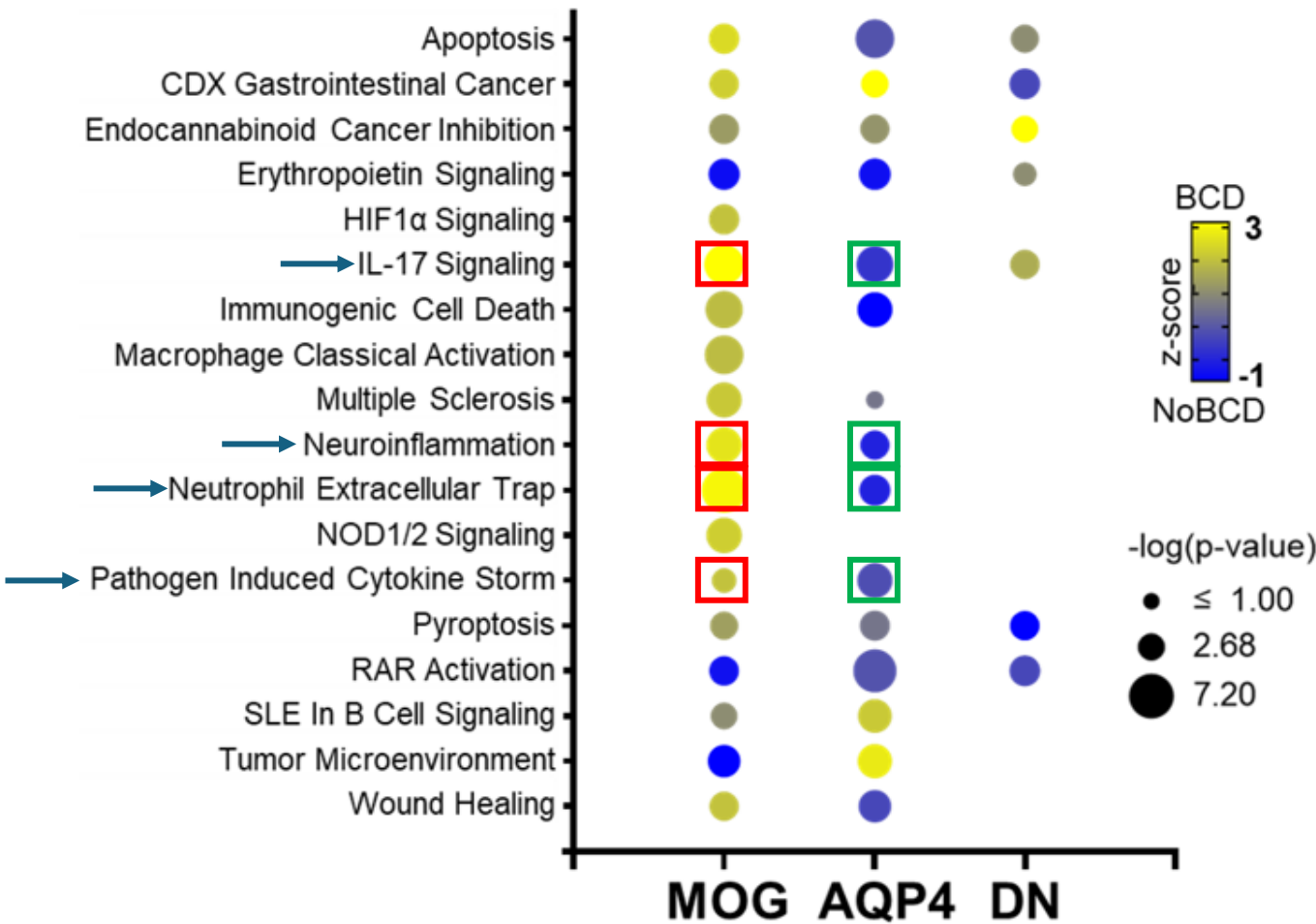
F.



Expressed on B cells

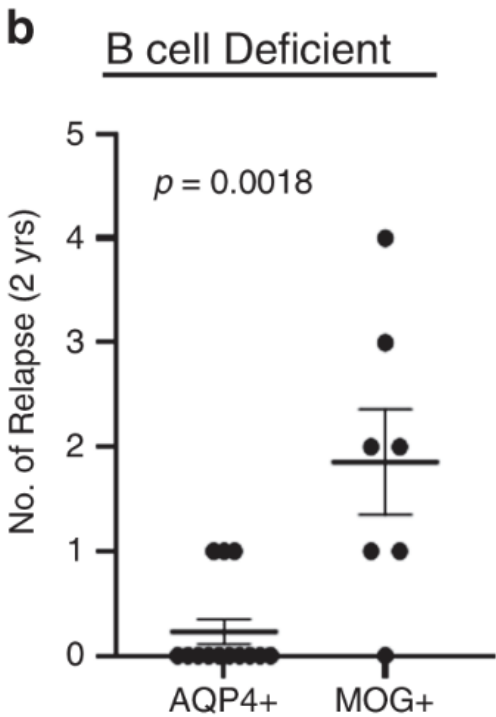
BCD differentially modulates inflammatory pathways in AQP4 and MOG-NMOSD patients

H. Pathways Altered by BCD



MOG-NMOSD

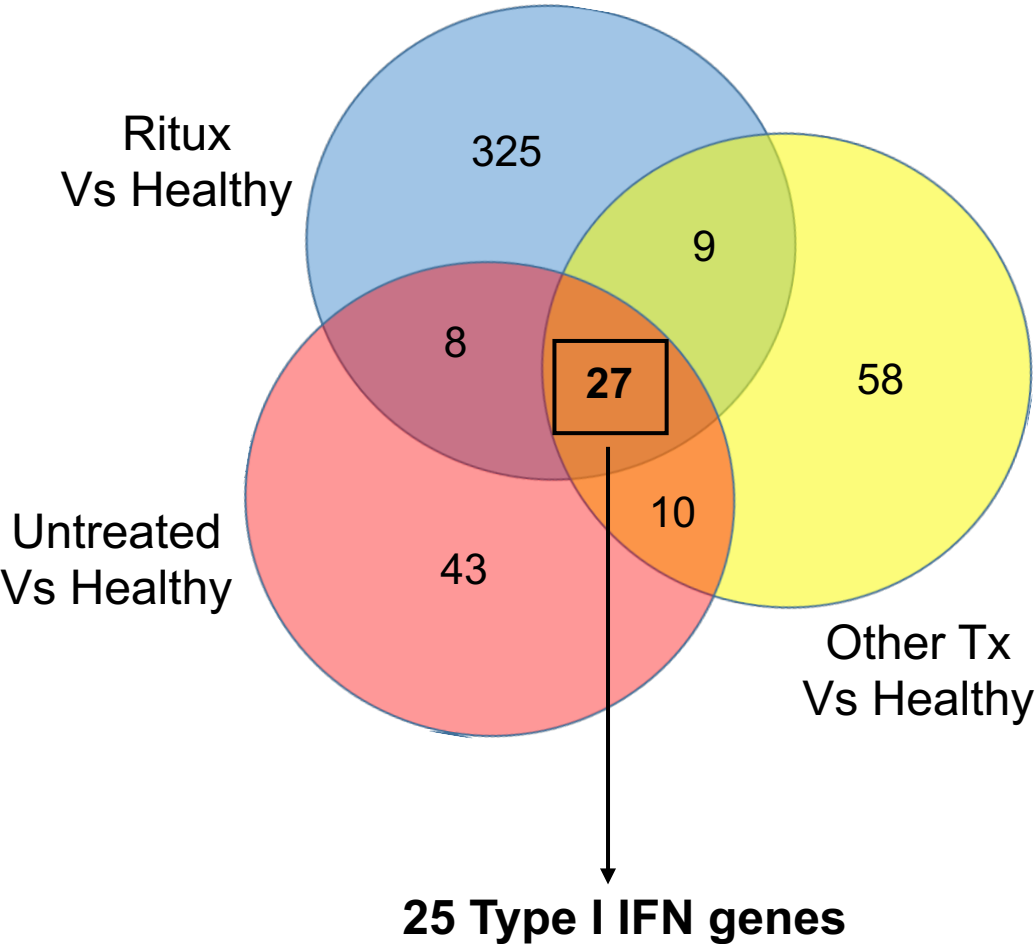
AQP4-NMOSD



Short Summary

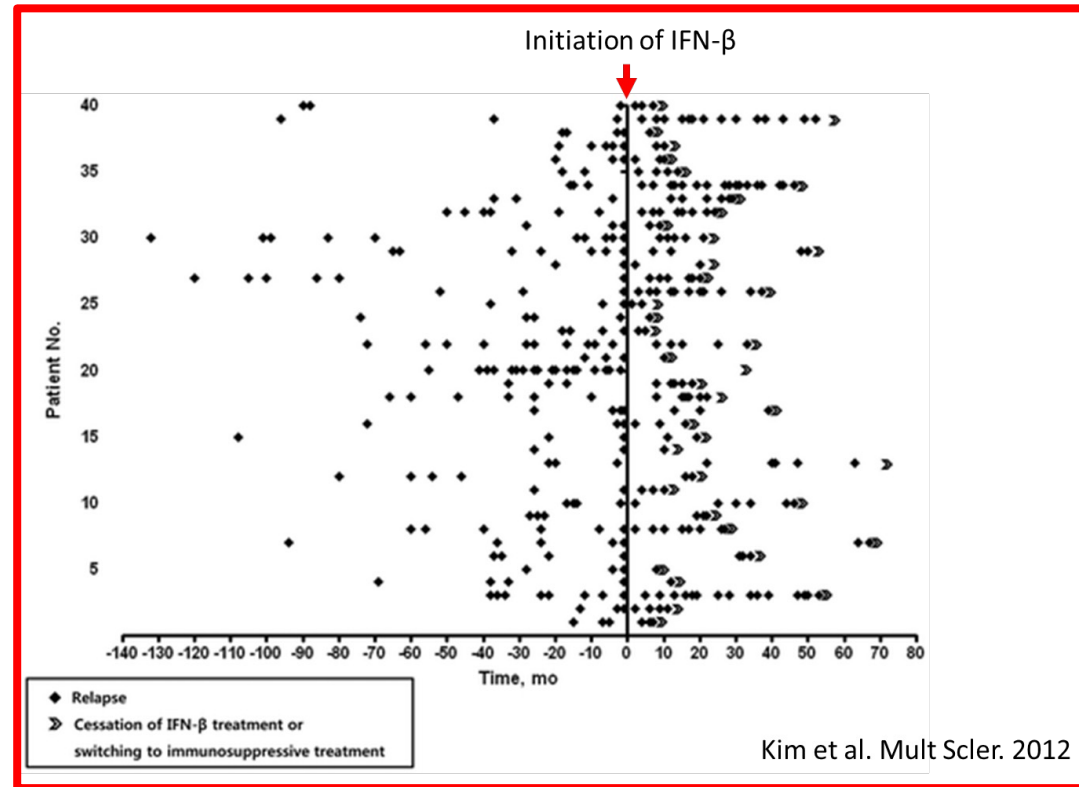
- Type I IFN-induced chemokines CXCL9, CXCL10 and CXCL11 are elevated in AQP4-NMOSD.
- Granzyme B and H levels are increased in MOGAD.
- Serum protein profiles of DN-NMOSD are more similar to MOGAD than AQP4-NMOSD
- Anti-CD20 BCD differentially modulates inflammatory signaling pathways in AQP4-NMOSD and MOGAD.

RNA profiles of NMO patients



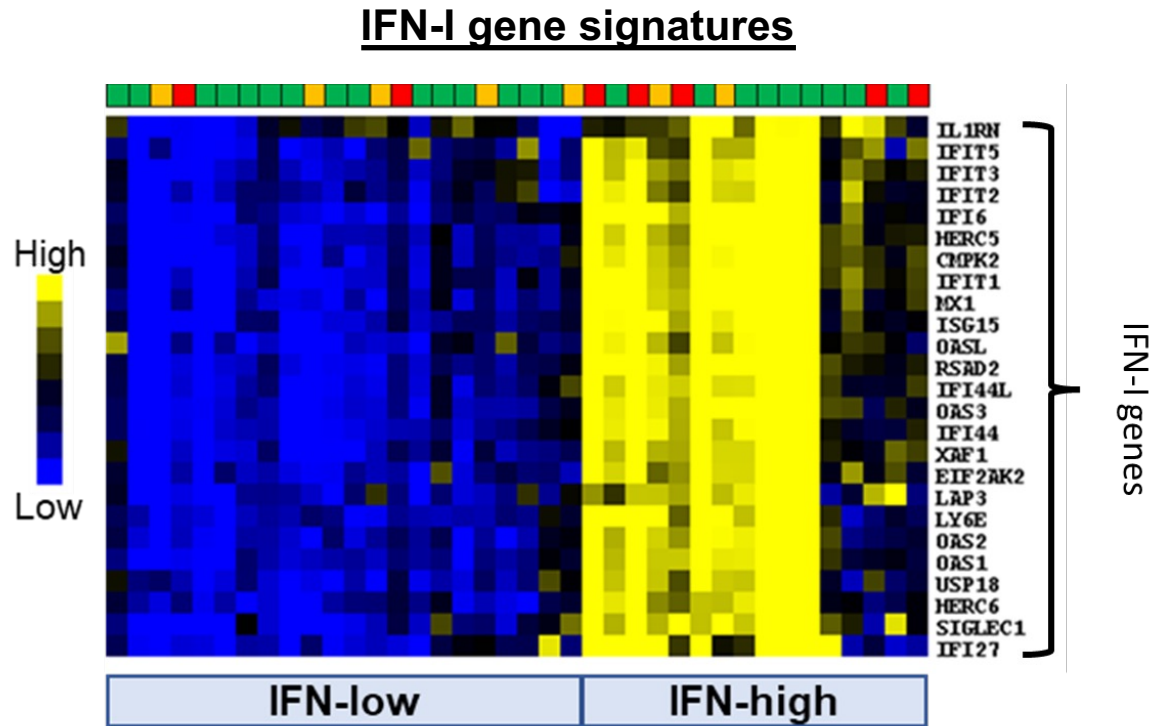
Recombinant Type I IFN treatment induces NMO relapses

- **Interferon Beta (Type I IFN)** (FDA approved for Multiple sclerosis) **worsens NMOSD**

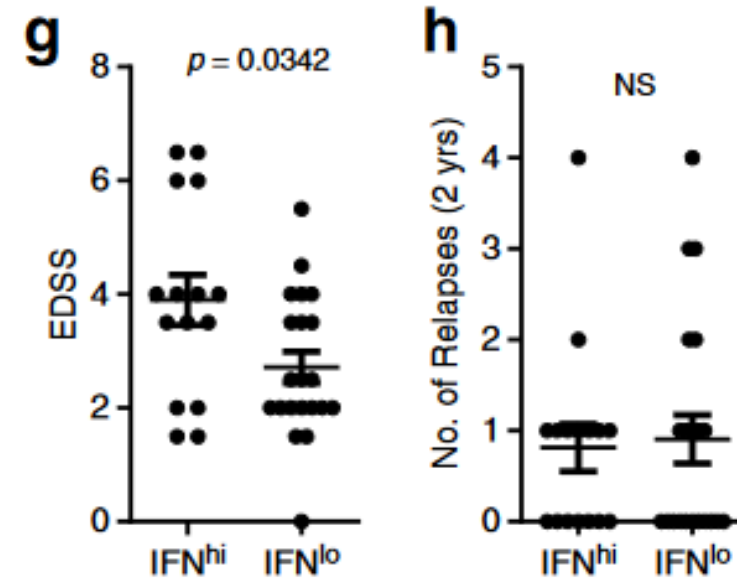


Endogenous Type I IFN is associated with severe persistent disability in NMO

Transcriptomics (IFN-signatures)



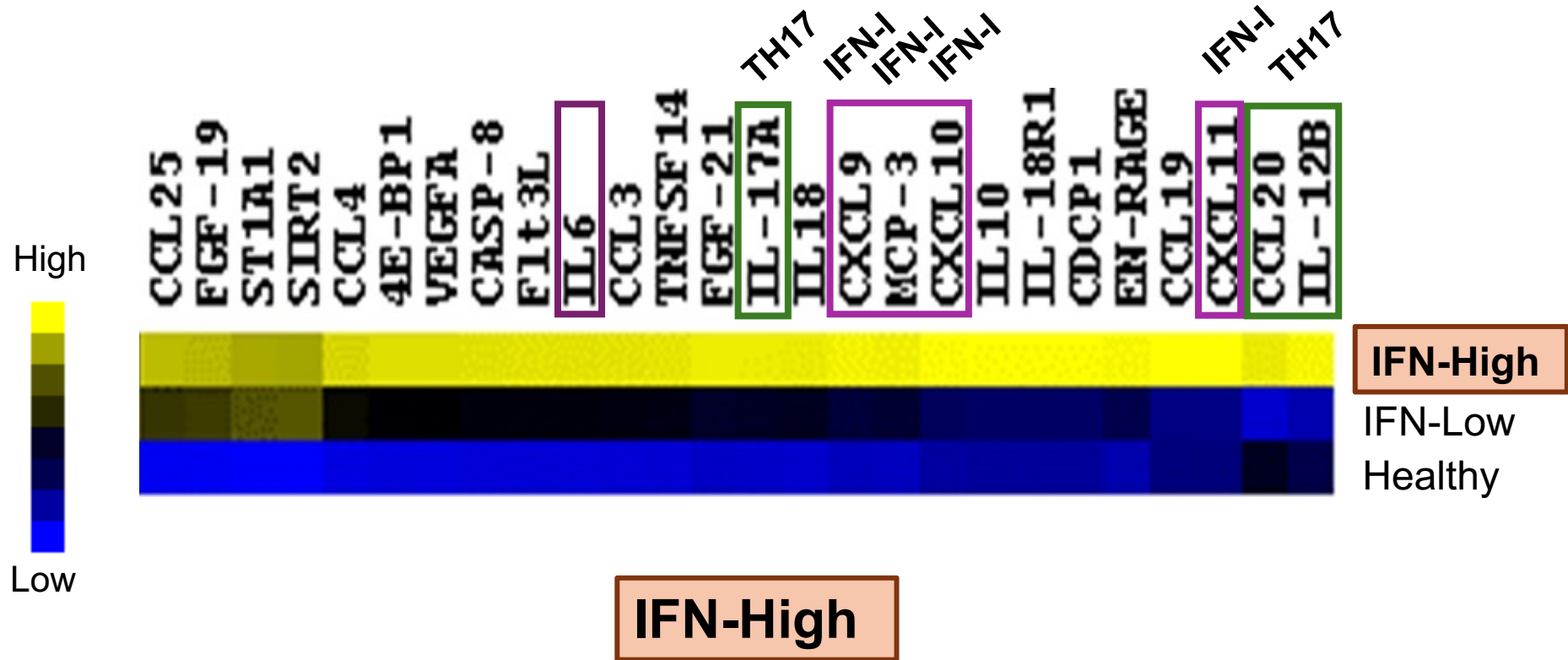
Clinical Outcomes



Findings

- Interferon signatures are elevated in NMOSD.
- IFN signatures can stratify NMOSD: IFN-high and IFN-low
- IFN-high patients had $\uparrow$ serum IL-17 cytokines and IL-6.
- IFN-high patients had severe disability (but not relapses)

IFN-High NMO is characterized by elevated IL-6 and TH17 responses



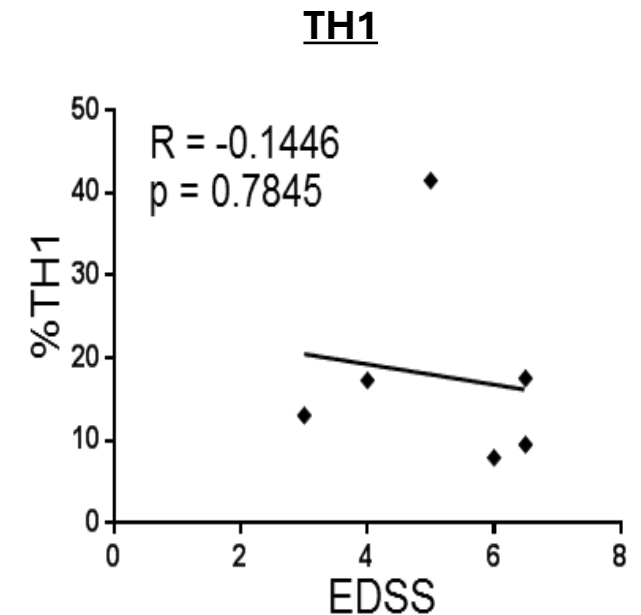
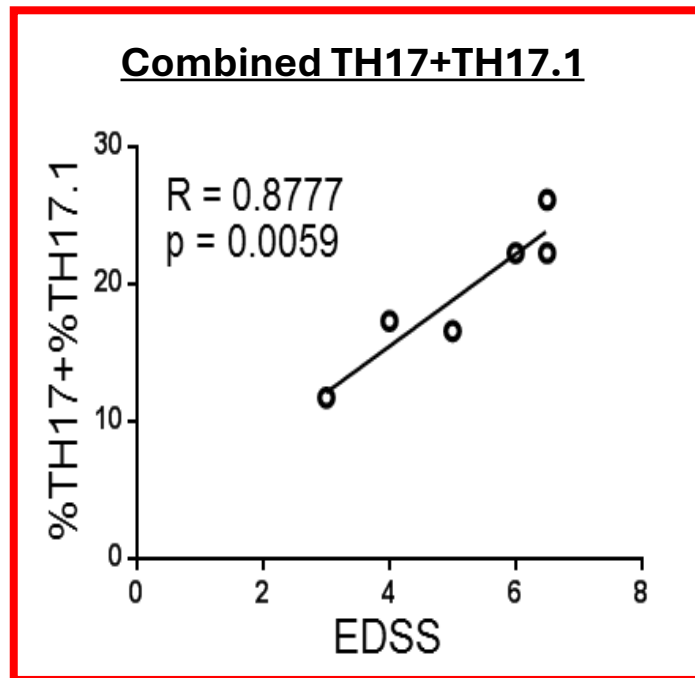
TH17 responses – ↑IL-17A, ↑IL-12p40, ↑CCL20

IFN-I signatures – ↑MCP-3, CXCL9, CXCL10, CXCL11

IFN-I/TH17 signatures – ↑IL-6

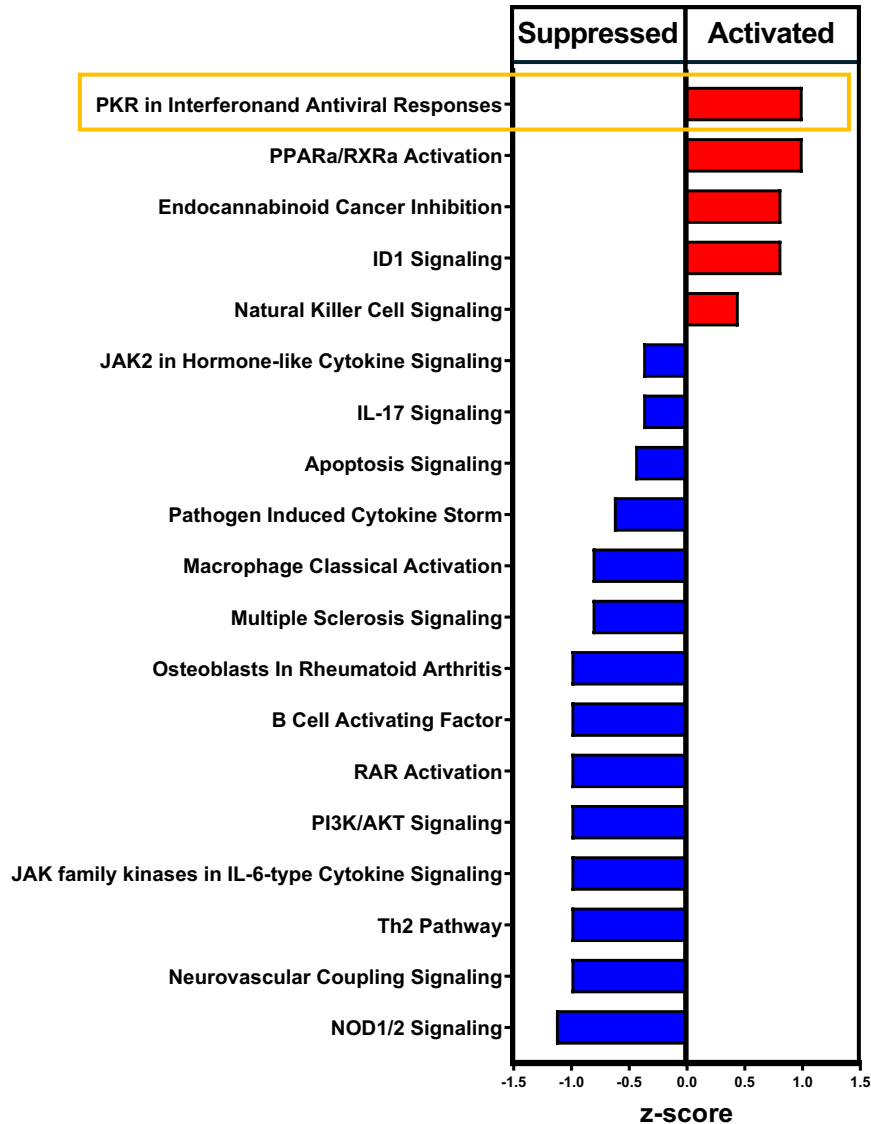
TH17 cells in PBMCs are correlated with EDSS

Variables	NMOSD
Total no.	6
Age, year, mean (SD)	45.6 (17.3)
Sex F/M (%F)	4/2 (67.7)
Serological status, N (%)	
AQP4-Ig+	6 (100)
MOG-Ig+	0 (0)
Treatment, N (%)	
None	6 (100)
EDSS, mean (range)	5.2 (3 - 6.5)

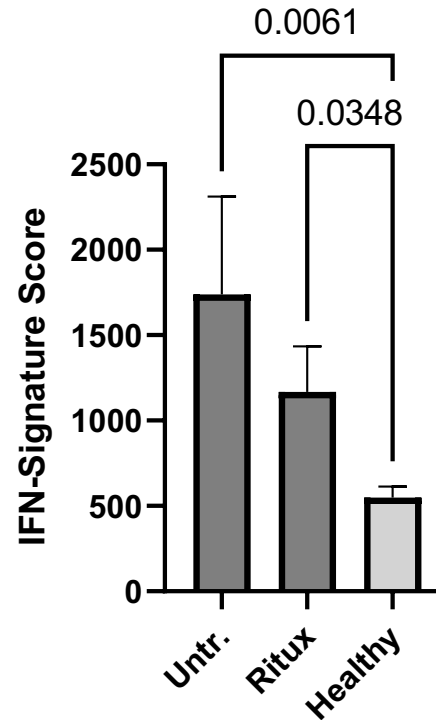


B cell depletion does not reduce IFN-signatures in NMO

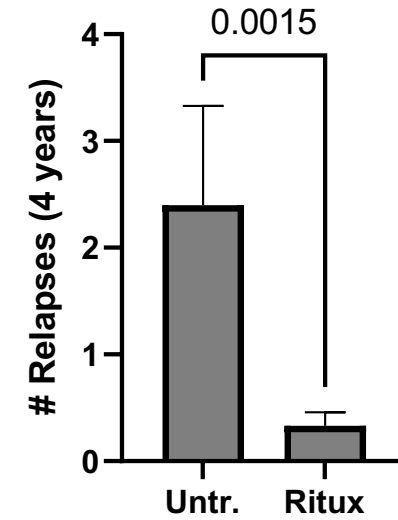
Serum Proteomics signatures affected by BCD



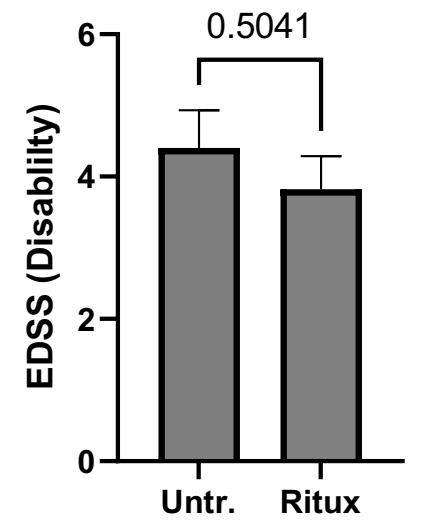
Transcriptomics



Little effect on IFN-Sig.



Reduce Relapses



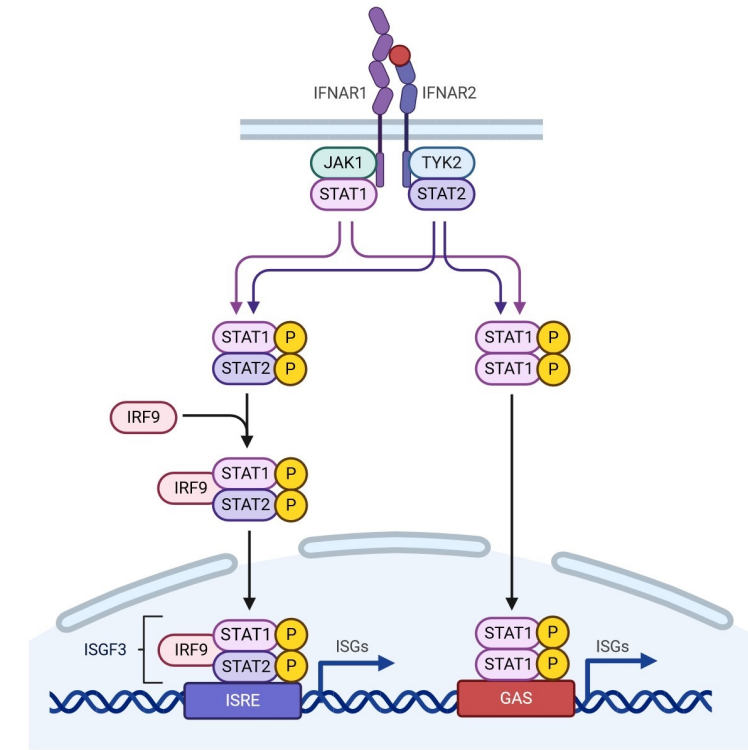
Little effect on EDSS

Blockade of Type I IFN in NMO

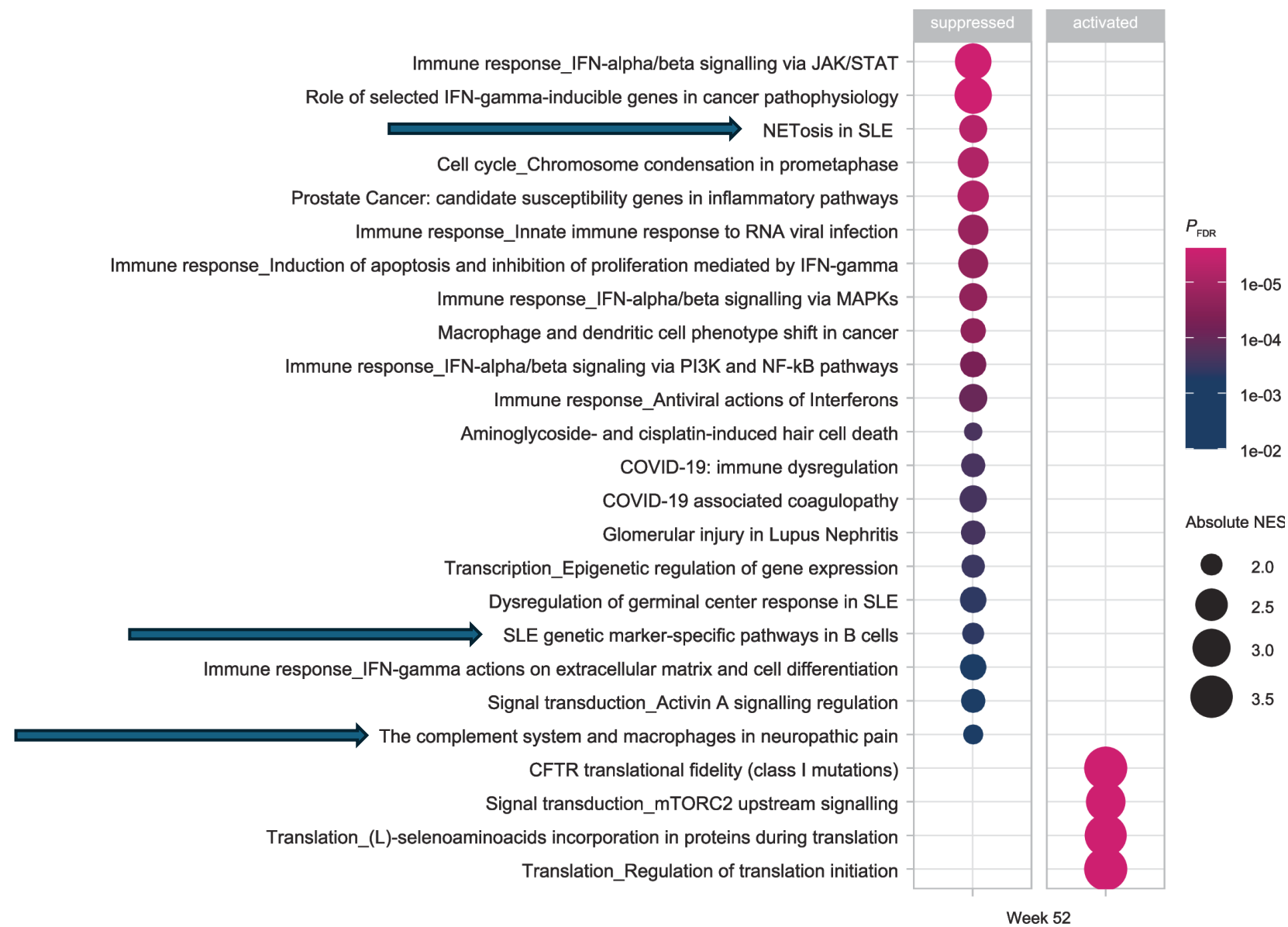
- Type I IFN is elevated in NMO and is associated with worse disability and neuro-damage.
- Current DMTs continue to have worsening symptoms/disability.
- Current DMTs (anti-CD20) do not reduce IFN-gene signatures.
- **Could the addition of anifrolumab to standard of care benefit patients?**

Anifrolumab-IFN receptor blocker

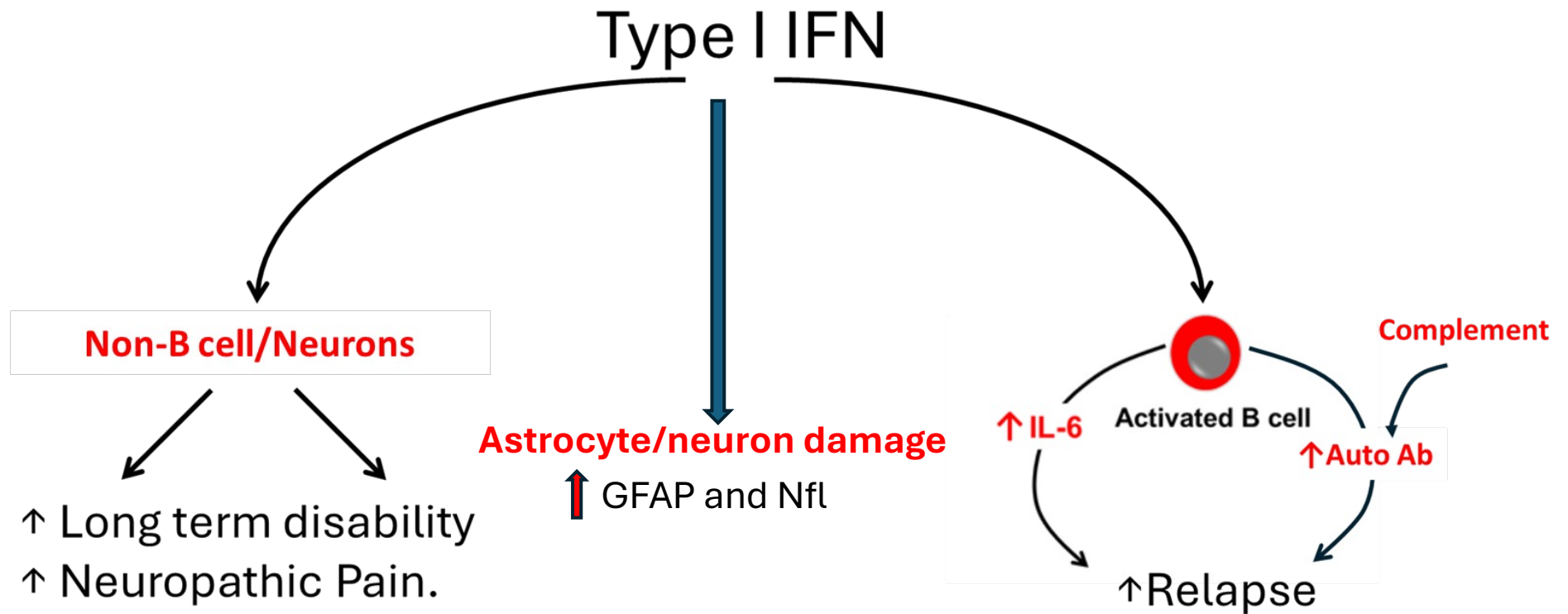
- Anifrolumab is an antibody that binds and blocks the type I IFN receptor.
- It is approved for treating systemic lupus erythematosus (SLE)
- Proteomic studies of SLE trials (TULIP1 and TULIP2) show anifrolumab reduces several biological pathways implicated in NMO pathology.



Anifrolumab Downregulates the Complement System, Neutrophil Activity, B cell activity in SLE



Hypothesis: anifrolumab will reduce severity of relapses AND may attenuate long-term disability in NMO



Current approved NMOSD therapies target B cell/antibody functions.
Type IFN modulates B cell activity/function and drive neuronal hypersensitivity (pain).
IFN blockade could offer multimodal therapy benefits for NMOSD.

OMRF NIAID ACE Project 2024-2029: NASCAR Clinical Trial for NMO

Double-Blind, Placebo Controlled Trial in Neuromyelitis Optica of Anifrolumab to Standard of Care for Acute Relapses and Worsening Symptoms

- OMRF—central site
 - Chair: Yang Mao-Draayer, MD, PhD, Professor and Director of Clinical and Experimental Therapeutics
 - Mechanistic Chair: Robert Axtell, PhD, Associate Professor
- Other potential trial sites: Washington U., UAB, NYU, U Chicago, Cleveland Clinic, University hospital Cleveland, Henry Ford, U Wisconsin, U Mass, Swedish, Hackensack Meridian Health, Mount Sinai, USC, Cornell, U Rochester
- AstraZeneca
- Rho and NIH/NIAID

Acknowledgements

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Thank you note

- Our patients and family members...

