

# *Pearls in Pathogenesis: NMO, MOGAD & SND*



**Tanuja Chitnis MD, FAAN**

Professor of Neurology, Harvard Medical School

Larsen-Chugg Distinguished Chair in Neurology,

Co-Director, Brigham Multiple Sclerosis Center, Brigham and Women's Hospital

Director, CLIMB Study, Brigham and Women's Hospital

Director, Translational Neuroimmunology Research Center, Brigham and Women's Hospital

Vice Chair, Neuroscience Research, Brigham and Women's Hospital

Director, Mass General Brigham Pediatric MS Center, Massachusetts General Hospital



# NMO, MOGAD, Seronegative NMO (SND)

Pathology

Target tissue/antigen

Immunology

Biomarkers

Therapeutic targets

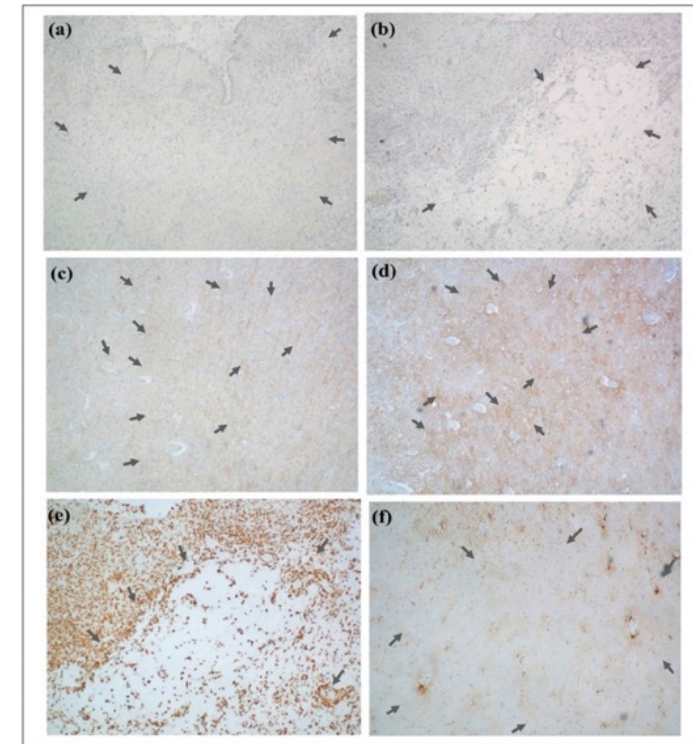
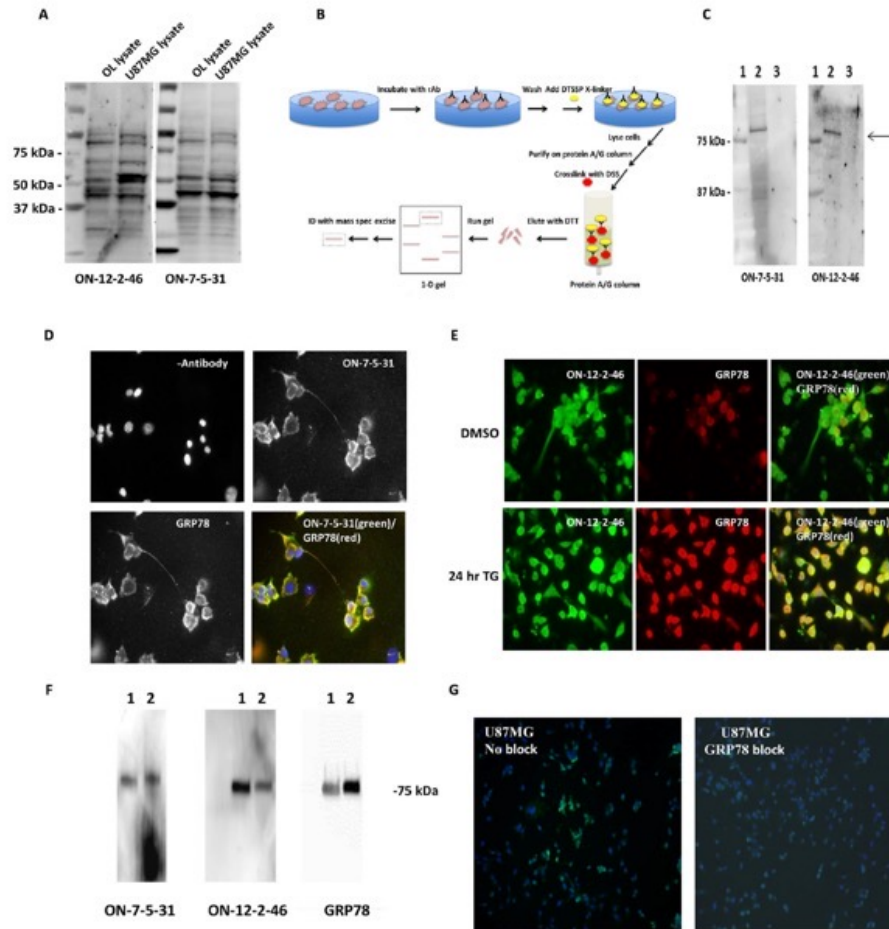
Tolerance

**NMO**  
**(AQP4+ NMO)**



# NMO – Pathology

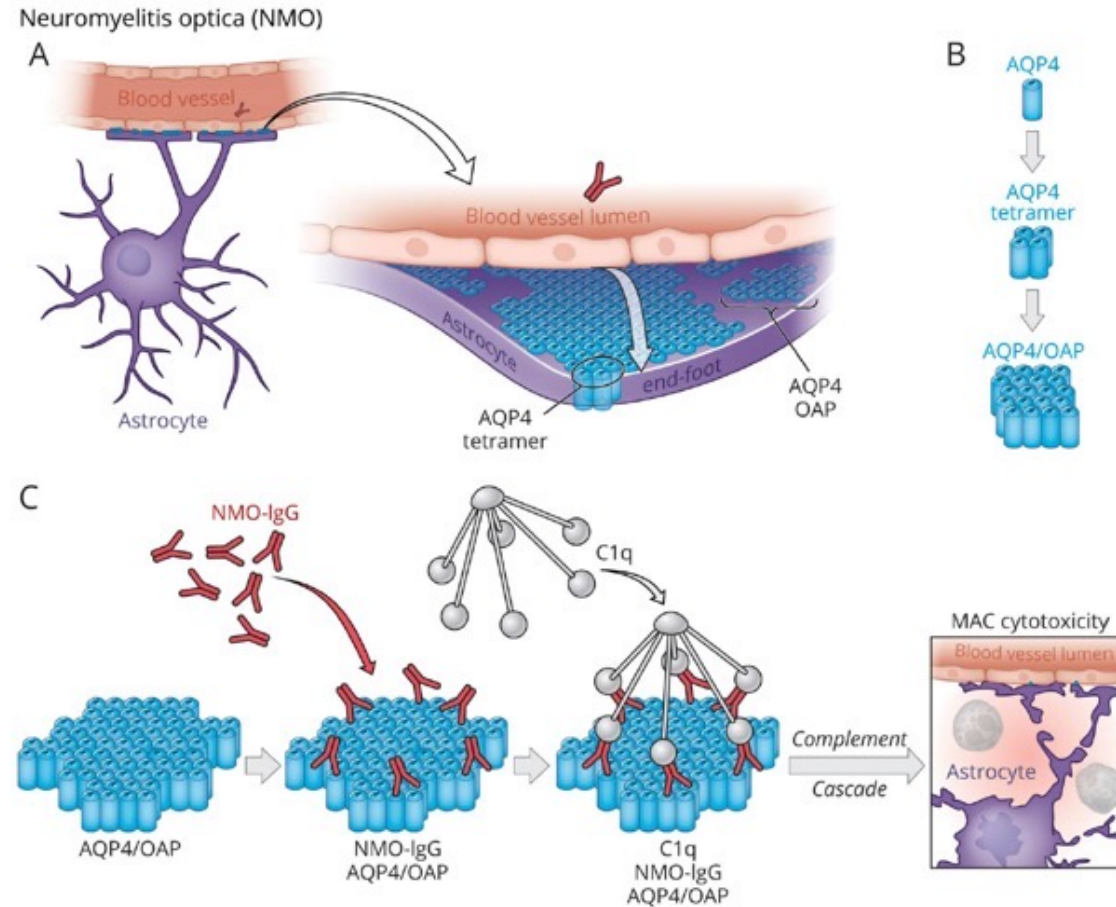
## Endothelial cell dysfunction – allow BBB breakdown?



Microfibril associated protein 4 (MFAP)  
4 co-localizes with AQP4 loss  
*Samadzadeh, MSJ 2023*

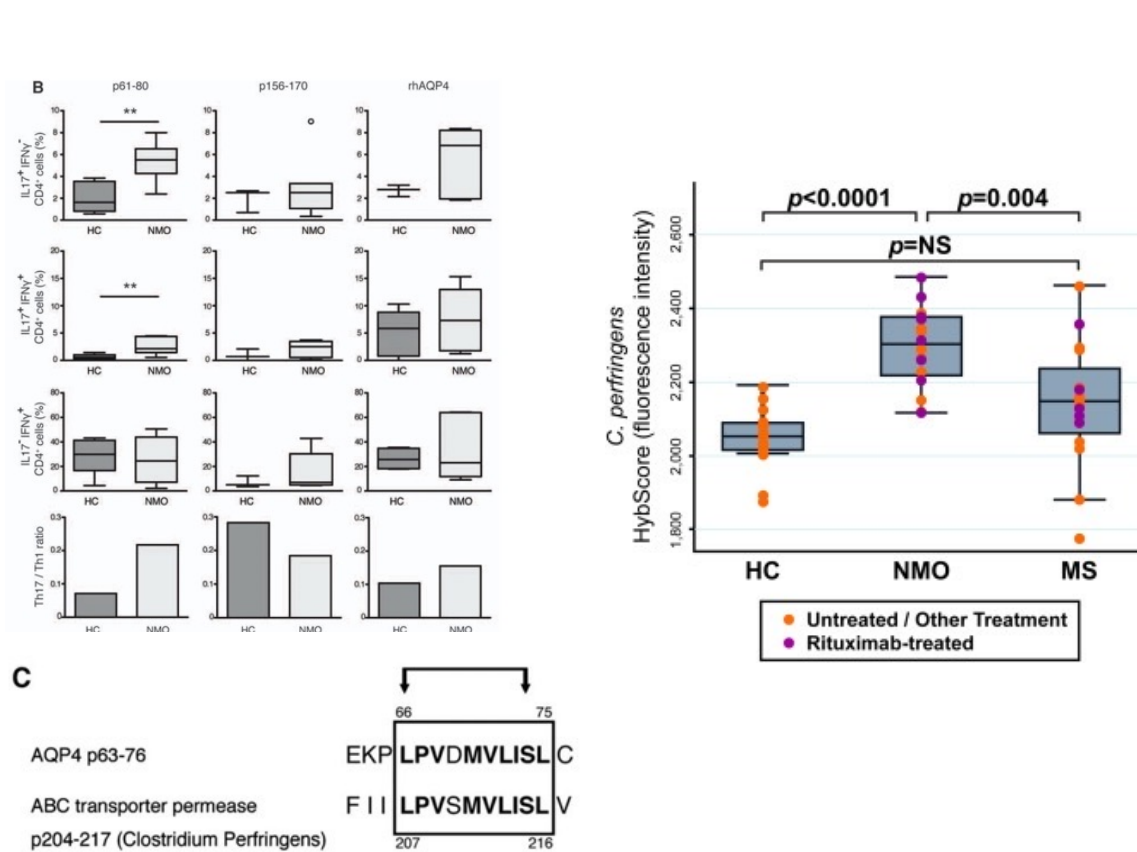
# NMO – Immunology

Antibodies target AQP4 OAP with C' activation



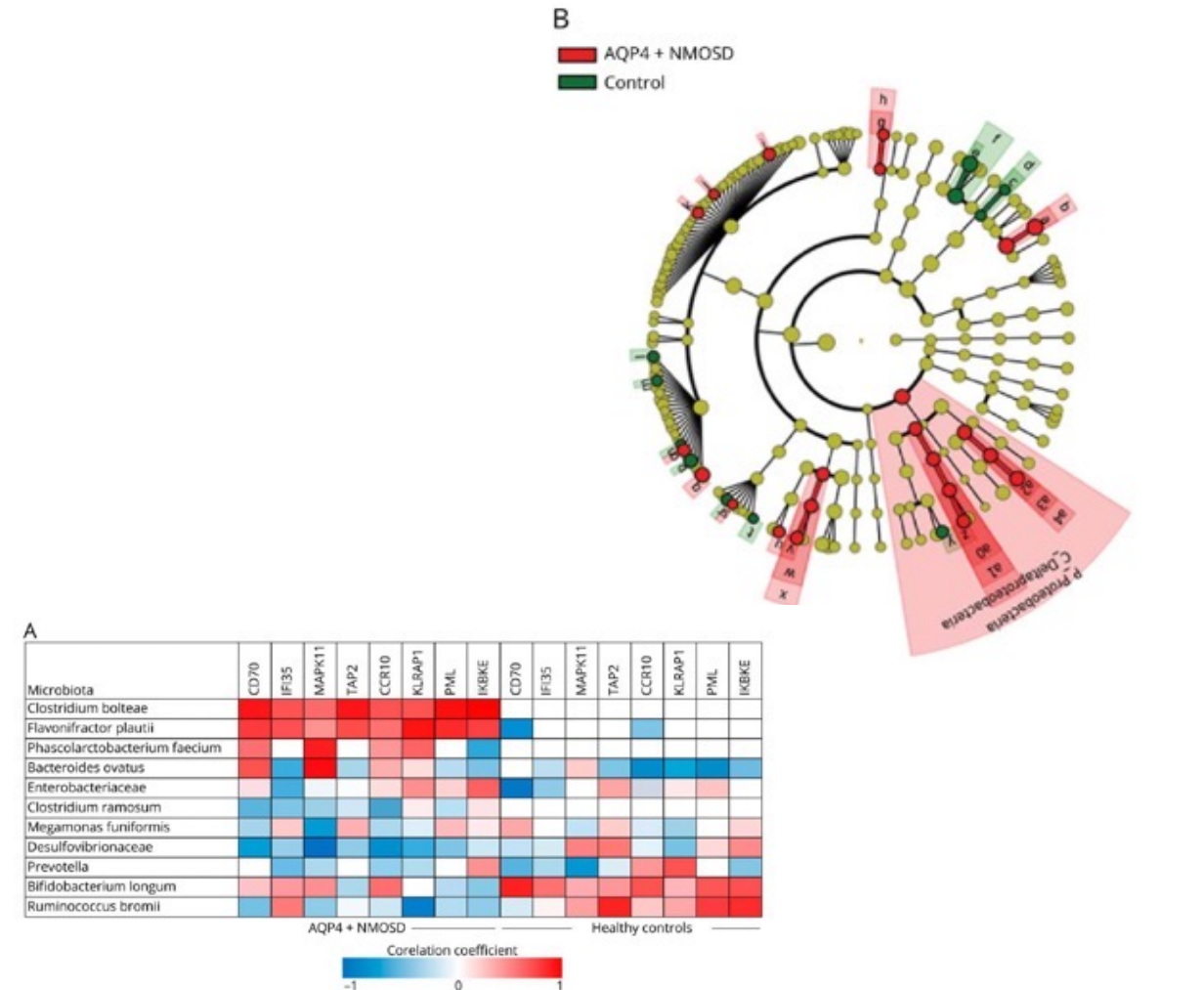
# NMO – Immunology

Th17 cells target AQP4 peptides with Clostridia molecular mimicry which is increased in the gut microbiome in NMO



Varrin-Doyer, Annals of Neurology, 2012

Cree, Annals of Neurology 2016





# NMO - Biomarkers

Rodin and Chitnis, Frontiers in Neurology, 2024

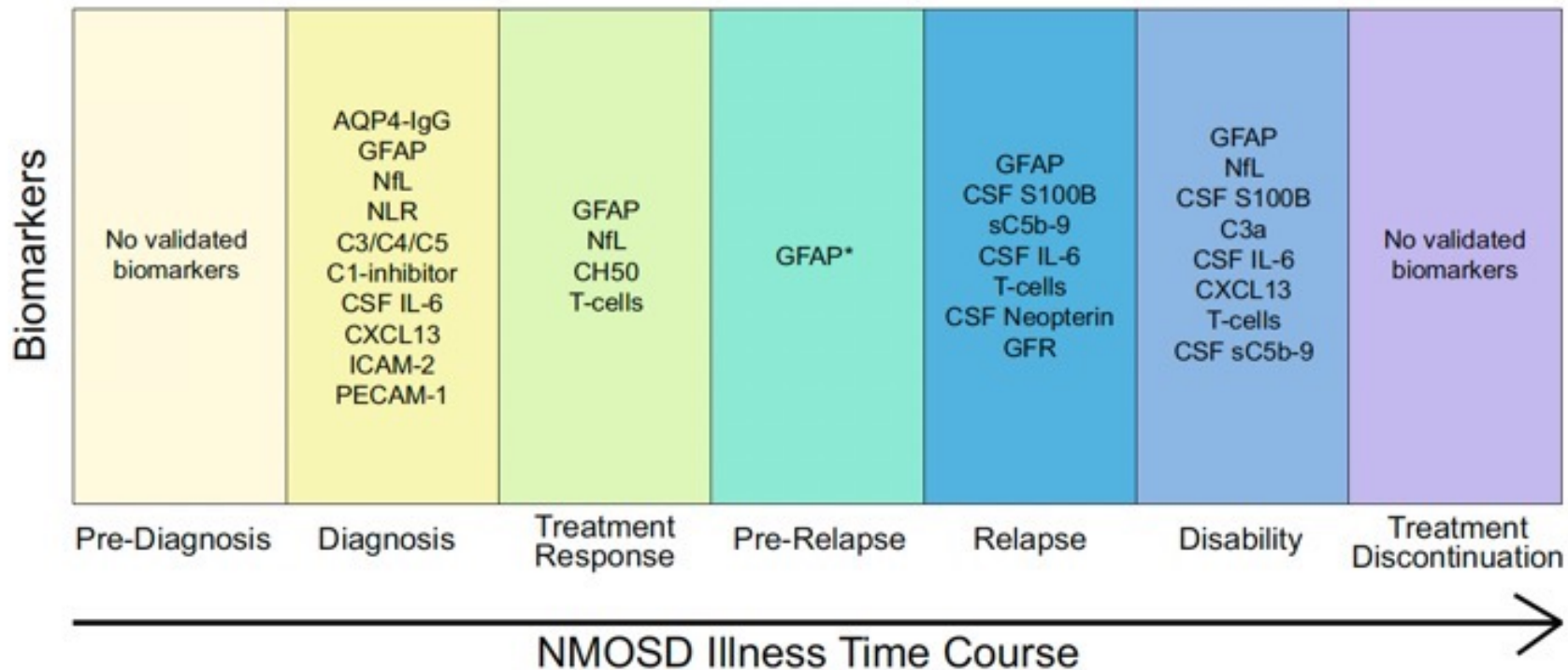
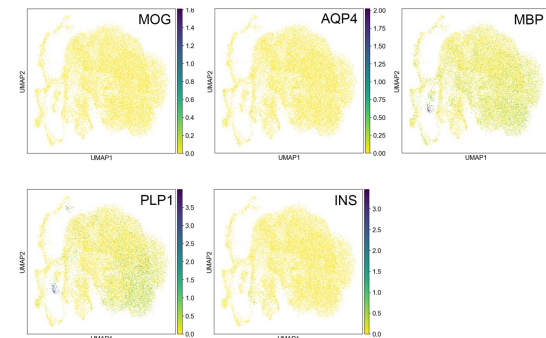
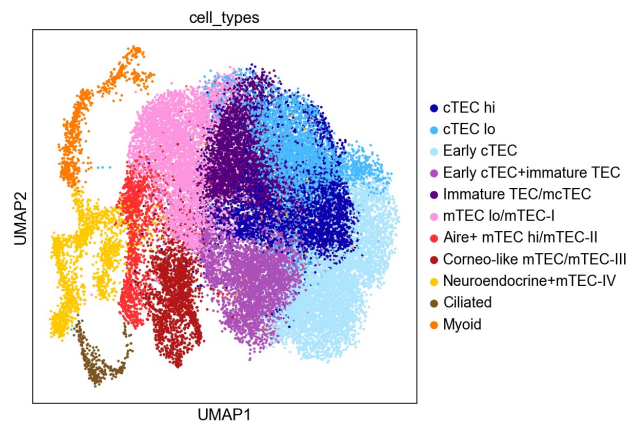
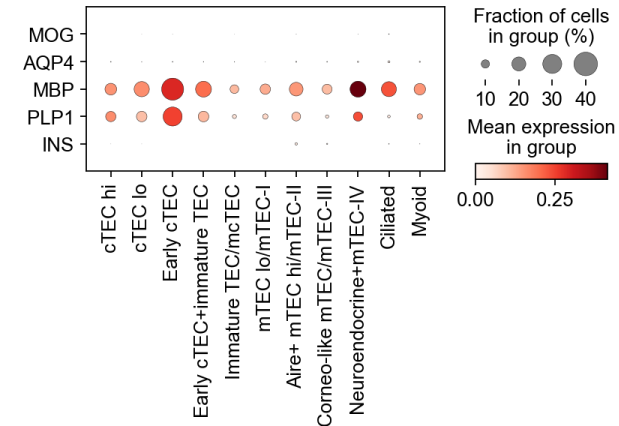
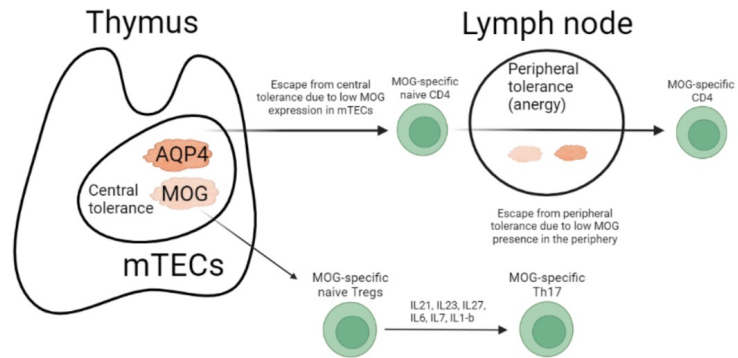


FIGURE 1

Summary of key NMOSD biomarkers and their clinical utility during various stages of disease. Except where indicated, all referenced biomarkers are from serum. \*Relapse prediction for serum GFAP has only been shown within <1 week preceding relapse.

# NMO – Tolerance

Reduced expression of MOG and AQP4 in the thymus may result in loss of central tolerance





# NMO - Advances and opportunities

Complement – end organ

B cells: CD19, CD20, CD27

IL-6R inhibition

Target antigen-specific T and B cells – TCR/BCR?

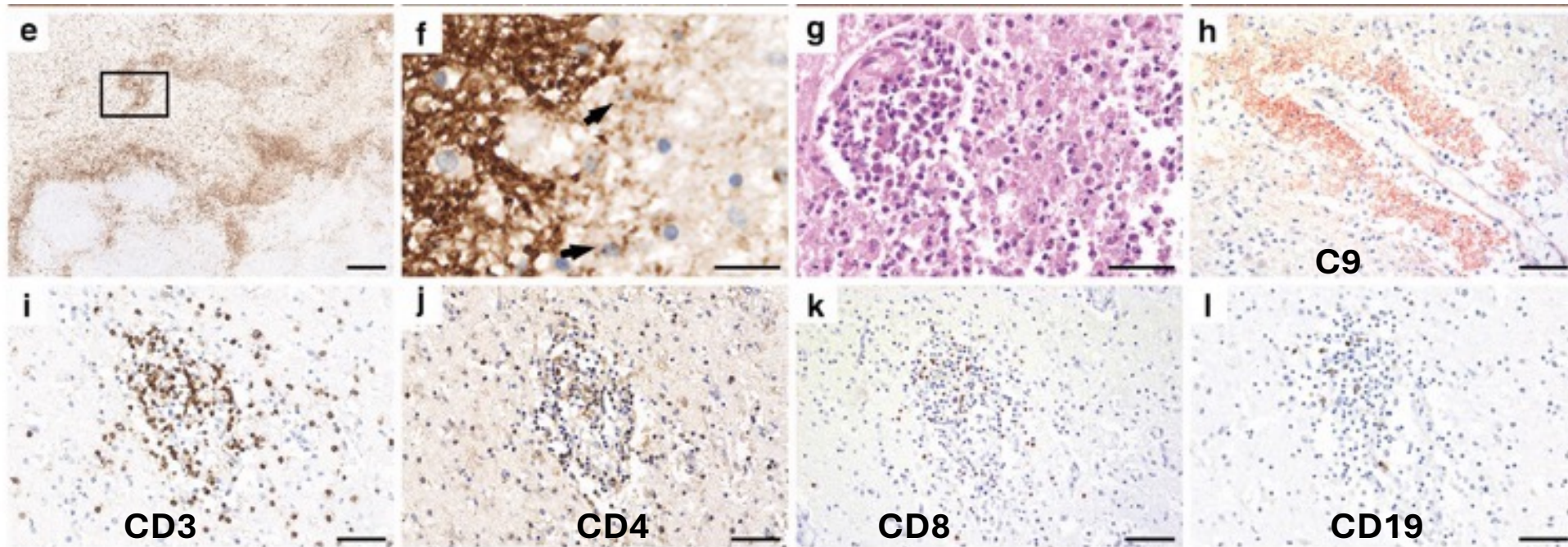
Prevent molecular mimicry?

Boost peripheral tolerance/regulation?

**MOGAD**

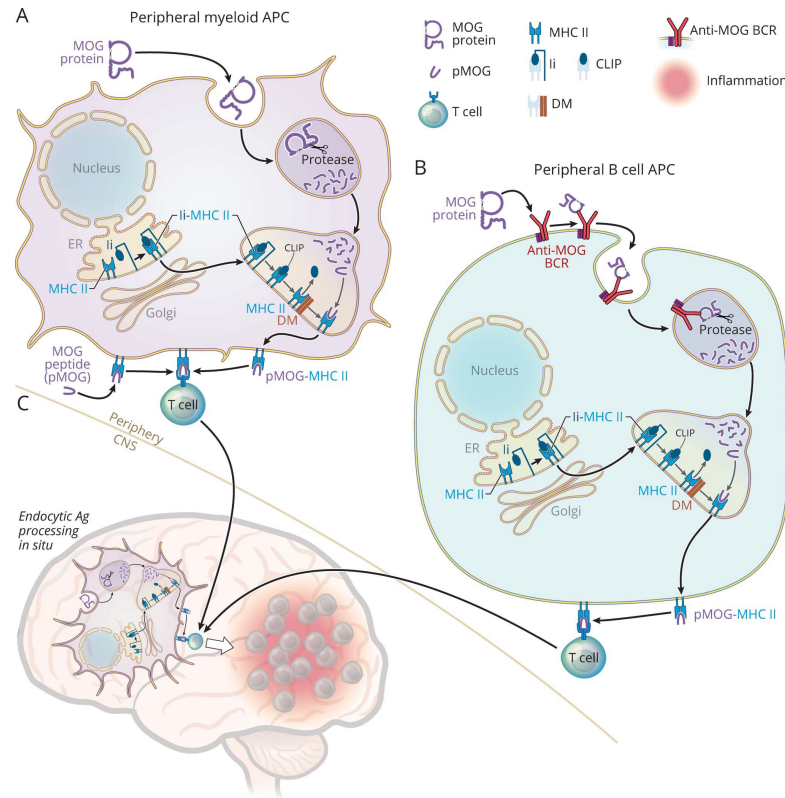
# MOGAD – Pathology

Predominance of CD4 T cells; limited complement activation

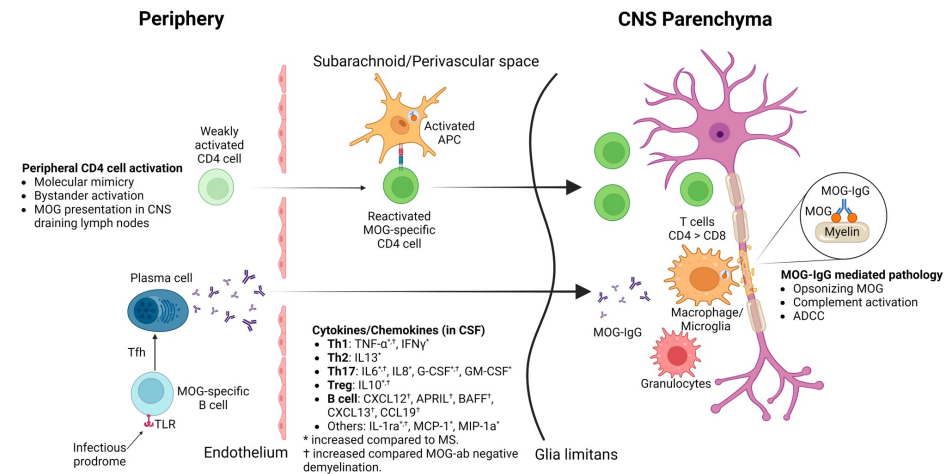


# MOGAD – Immunology

## Role of B cells, antibody and APC presentation of processed MOG to T cells



Moseley et al, N2, 2024

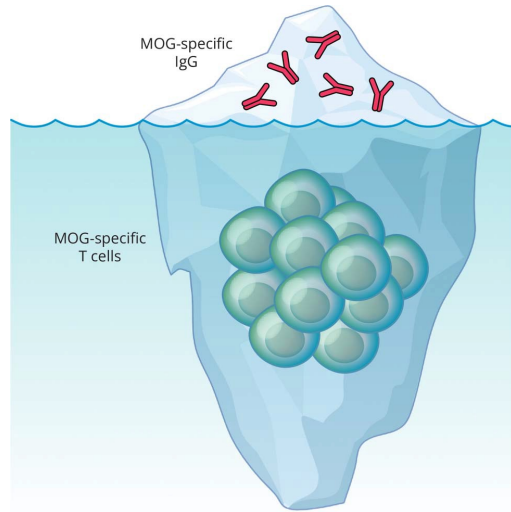


Corbali and Chitnis, Frontiers of Neurology, 2023

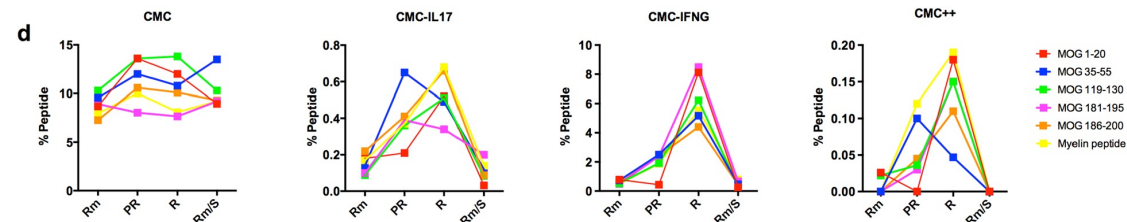
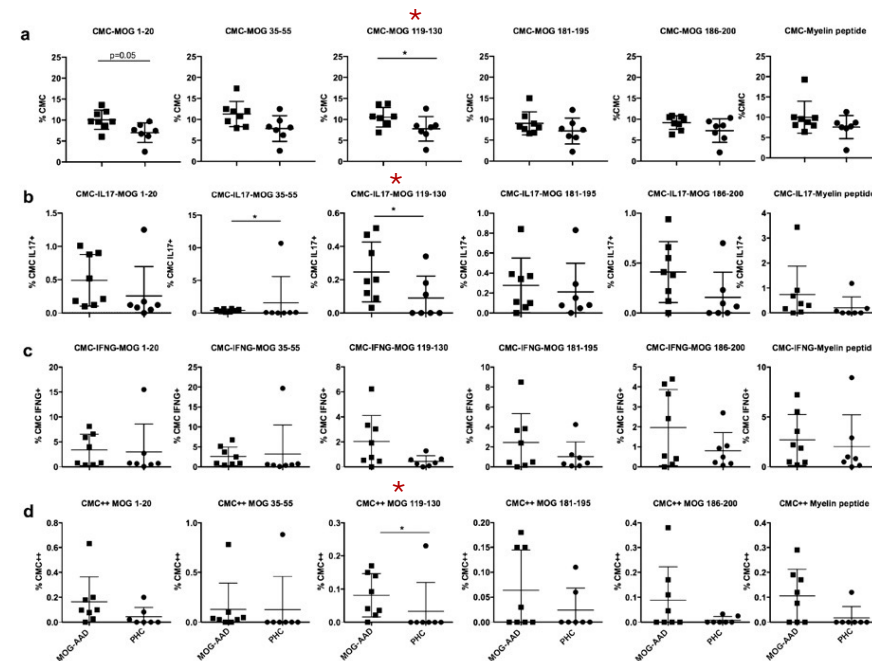


# MOGAD Immunology

## Increased MOG peptide-reactive central memory Th17 cells at relapse and vs. controls



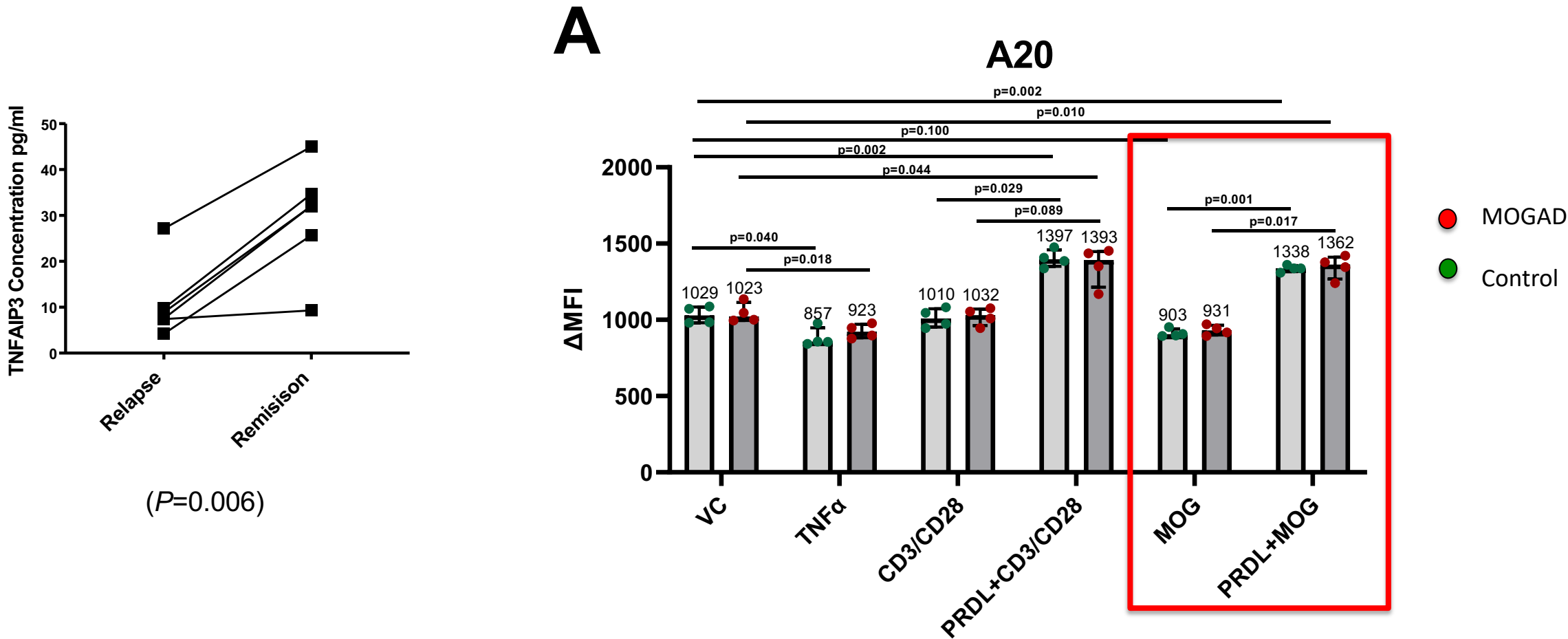
Moseley et al, N2, 2024



Saxena et al, Scientific Reports, 2020

# MOGAD Immunology

A20 (TNFAIP3) is decreased at relapse and increases in T cells with prednisolone treatment in vitro



# MOGAD - Biomarkers

Corbali and Chitnis, Frontiers of Neurology, 2023

Potential biomarkers		MOGAD disease activity	Significance/implications	Therapeutic mechanism
MOG-IgG titer (9, 98, 139)	Serum	High titers required for diagnosis	Seronegative conversion indicates decreased relapse risk	FcRn blockers, IVIG, Plasmapheresis
NfL (140, 141)	Serum	Increased mostly in the first attack, then stay stable throughout the course	Significant axonal damage happens mostly in the first attack	
MBP (60)	CSF	Increased	Marker of demyelination	
GFAP (60, 141)	Serum	Stay stable during relapses	Spared astrocytes	
Tau (141)	Serum	Increased during relapses	Synthesized in axons and oligodendrocytes	
IL6 (72, 73, 113, 142)	CSF, serum	Increased in the CSF during relapses	Increased STAT3 activation could cause increased Th17	IL6 receptor blockers
			Impair BBB	
TNF $\alpha$ (42, 43, 143)	CSF	Increased in the CSF during relapses	May affect BBB through increased cell adhesion molecule expression (such as ICAM-1 and VCAM-1)	
A20/TNFAIP3 (123)	Serum	Decreased in the serum during relapses (individual level)	Increased NF $\kappa$ B activation	Steroids (increase)
	Intracellular		Steroid increase A20 expression in T cells	
N/L ratio blood (128)	Blood	Increased ratio during relapses	Could help differentiating relapse from pseudo-relapse	

# MOGAD – Advances and opportunities

FcRN

IL-6R inhibition

Specific targeting of TCR/BCR?

Antigen-specific tolerance?

Deletion, regulation of autoreactive T cells?

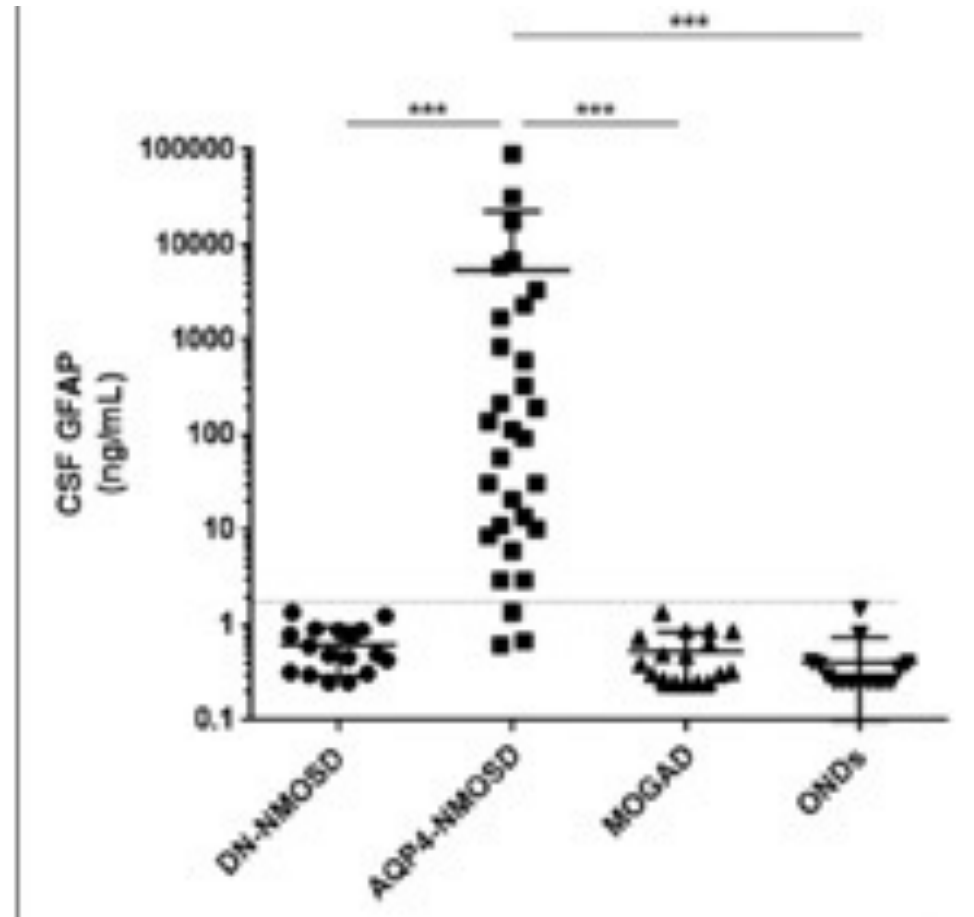
Biomarkers of relapse?



# **Seronegative NMOSD**

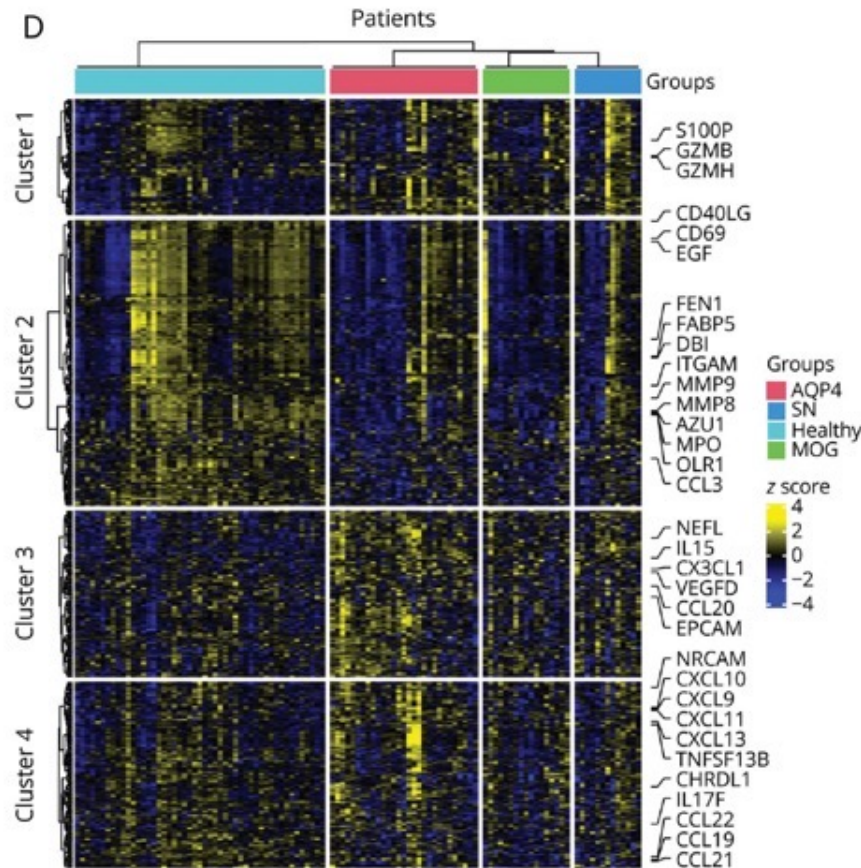
# Seronegative NMOSD – Biomarkers

CSF GFAP levels are low in double seronegative NMOSD



# Seronegative NMOSD - Biomarkers

## WIF1 and DCTN6 are increased in serum of double seronegative NMOSD



- Wnt inhibitory factor 1 (WIF1) levels were significantly increased in SN-NMOSD compared with AQP4-NMOSD and MOGAD patients
- Dynactin-6 (DCTN6) levels were increased in SN-NMOSD compared with AQP4-NMOSD only

# Seronegative NMOSD – advances and opportunities

Improved definition of SND

Biomarker studies informing  
pathogenesis – diagnosis by elimination?

Definitive biomarkers?

->Exploration of pathogenesis and  
potential therapeutic targets



# THANK YOU

