Multiple Sclerosis 2023
Brain Health Alliance

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WU LAB
NEUROIMMUNOLOGY

Disclosures

- Research
  - NIH, VA, NMSS, EMD Serono, Biogen, Roche
- Consulting
  - Sage, Progentec, Sangamo, Novartis, Roche, Alumis, Vulcan Biosciences
- Speaking
  - EMD Serono
- Editorial
  - Neurology Neuroimmunology & Neuroinflammation Journal of Neuroimmunology
- Testimony
  - Department of Justice

Outline

- MS Overview
- Adaptive Immunity in MS
- Example of Current Therapies
- CSF Investigations
- Emerging MS Therapies
- Questions

The “Father of Multiple Sclerosis”

Sclerose en plaque

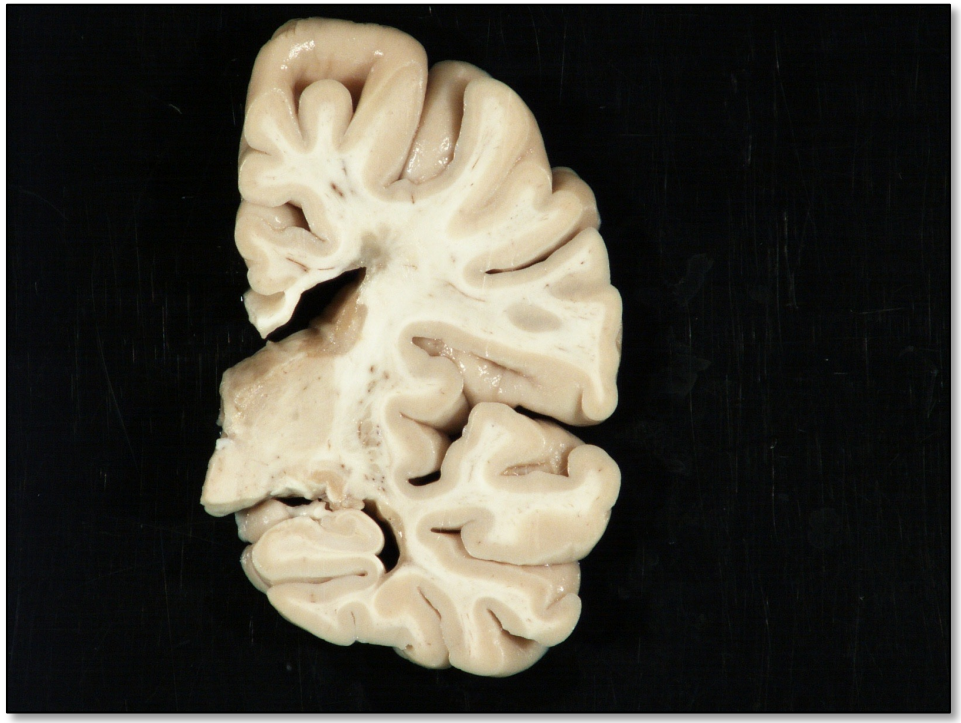
Jean Martin Charcot
(1825–93)

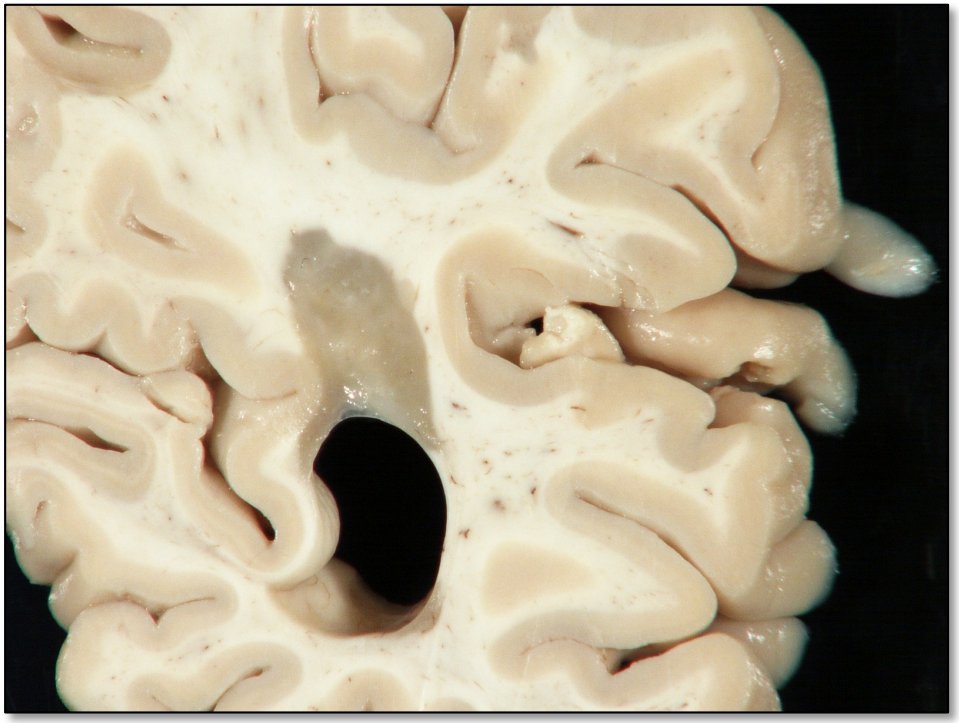
Triad:

- Nystagmus
- Intention Tremor
- Dysarthria

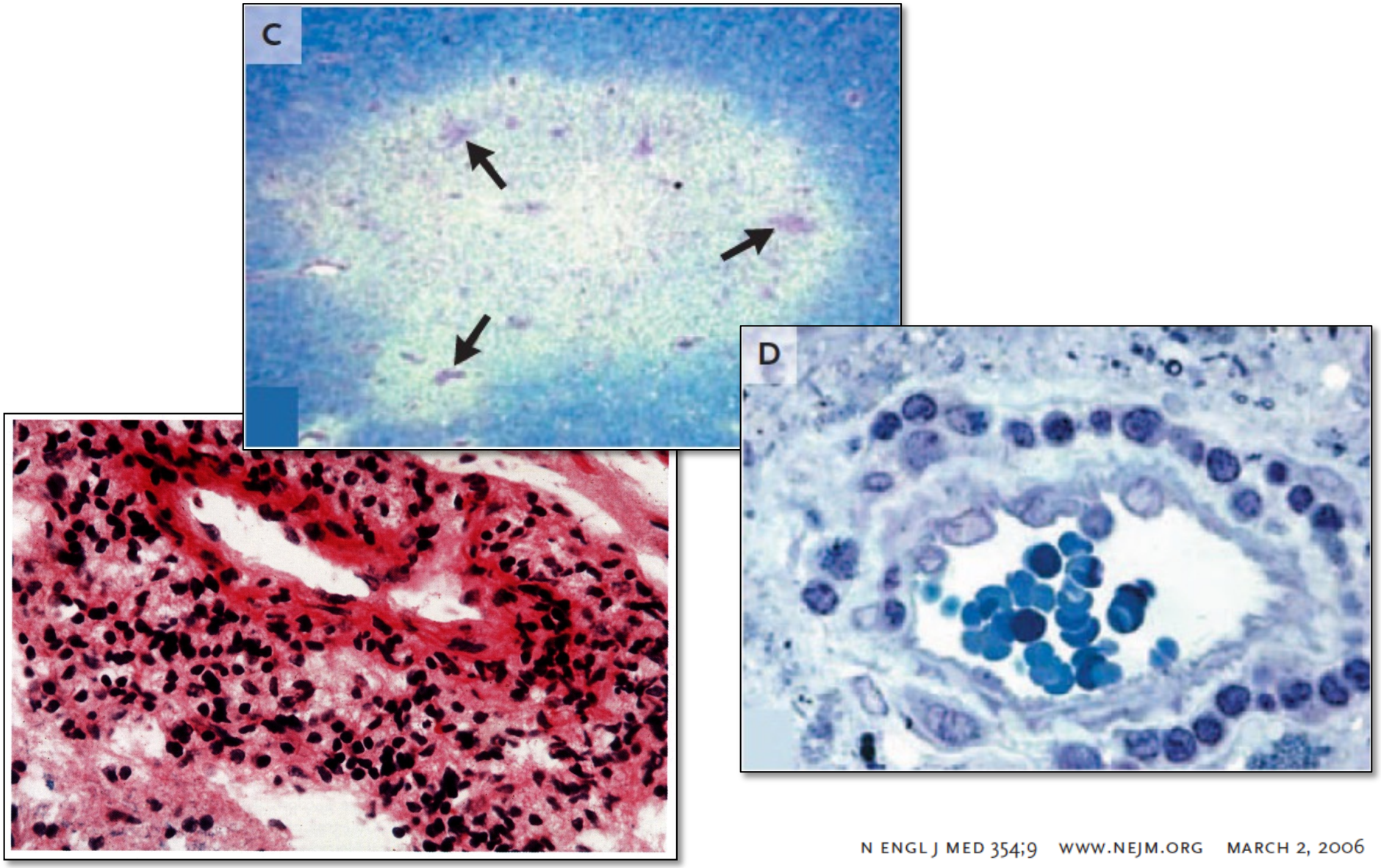
Zalc, B. Brain 2018:
141; 3482–3488

Gross examination
(autopsy)





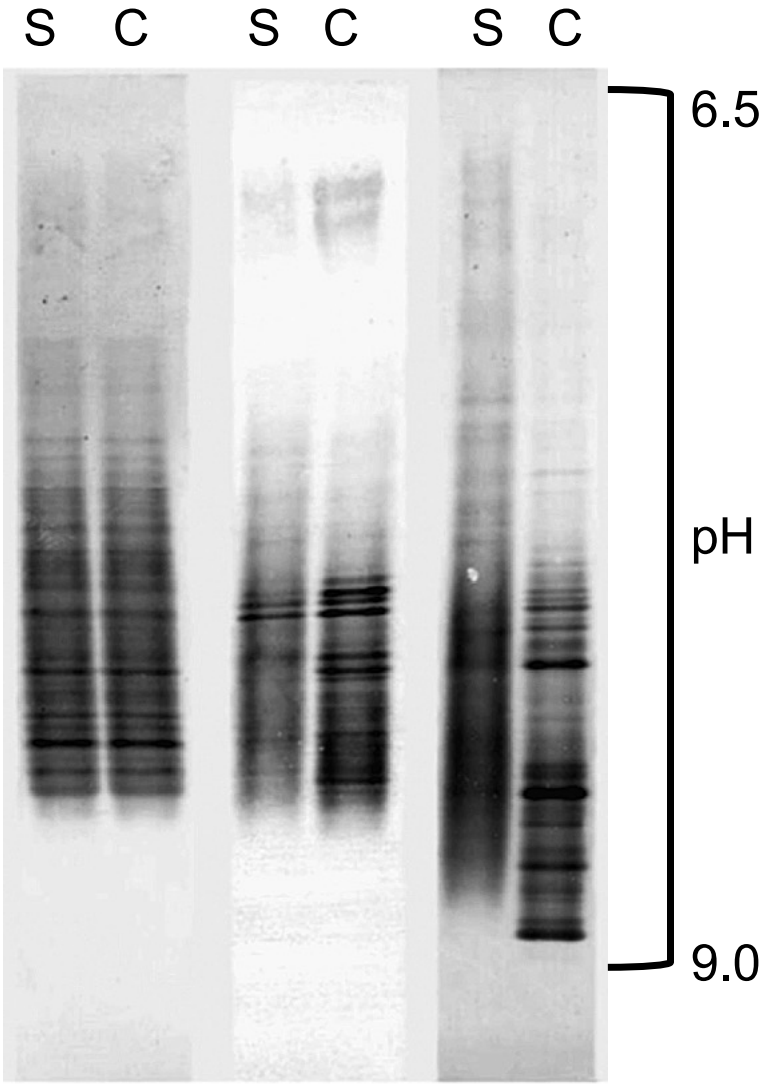
Microscopic examination

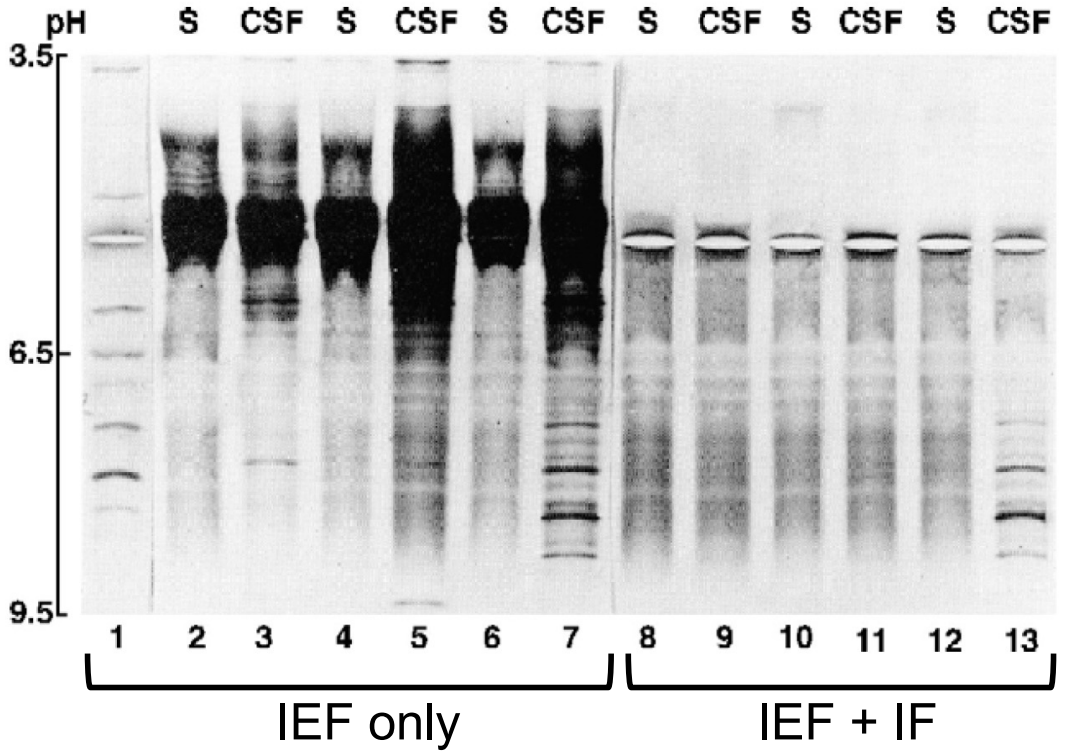


CSF Analysis in MS

- Cell count (typically < 50 WBC)
- WBC differential (typically ~ 80-90% L)
- "Trotter studies"
  - IgG Index
  - Albumin Index
  - IgG synthesis rate
  - Oligoclonal bands
- Other routine values for exclusion of other diseases (protein, VDRL, etc.)

Isolelectric Focusing & Immuno-fixation



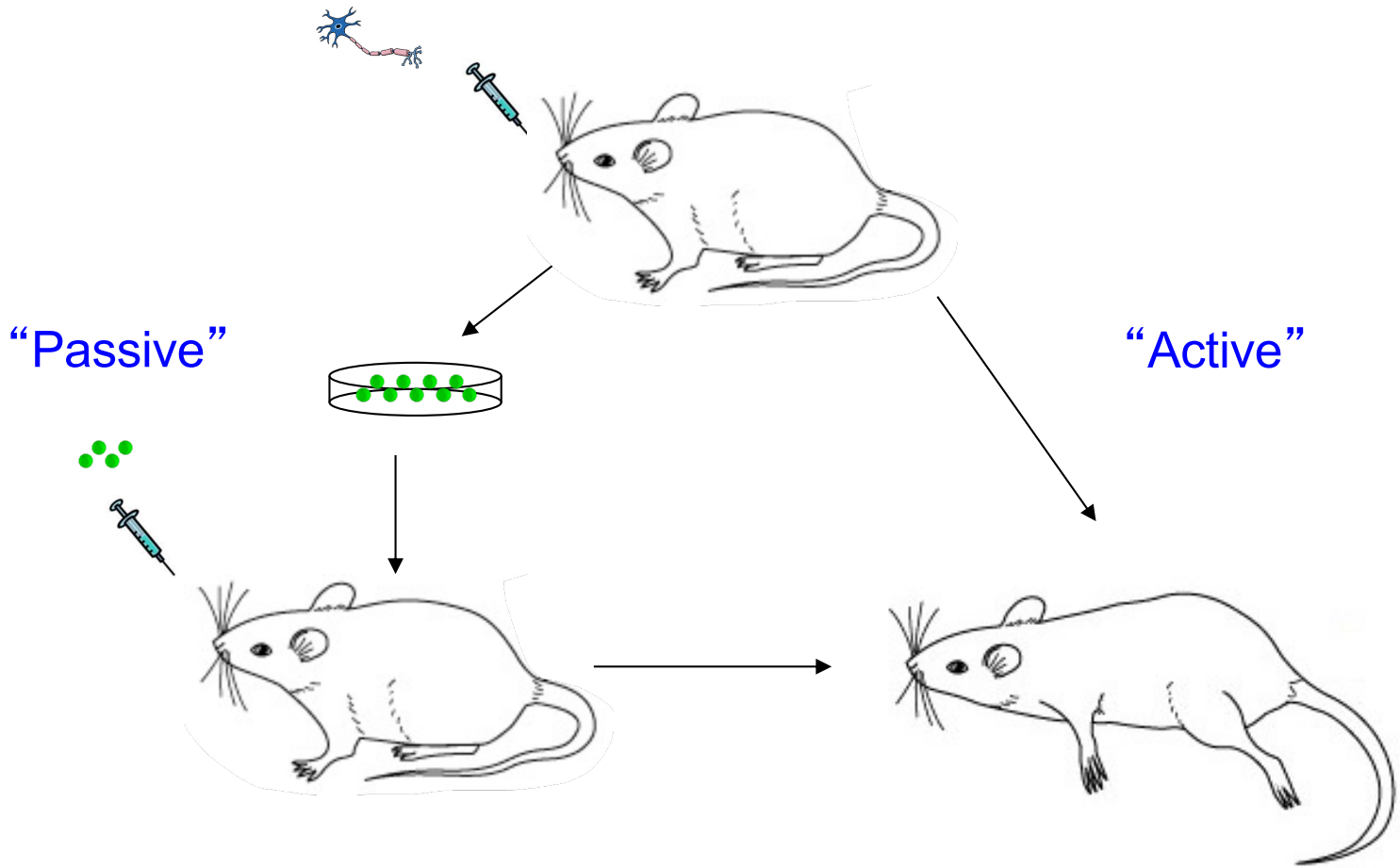


2 and 3: Hyperaesthesia
4 and 5: Myopathy of unknown cause
6 and 7: MS

Freedman, Multiple Sclerosis 2004; 10: S31¡/S35

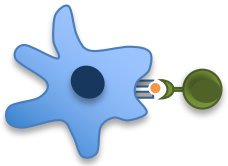
H. Link, Y.-M. Huang / Journal of Neuroimmunology 180 (2006) 17–28

A Model for Multiple Sclerosis: Experimental Autoimmune Encephalomyelitis (EAE)

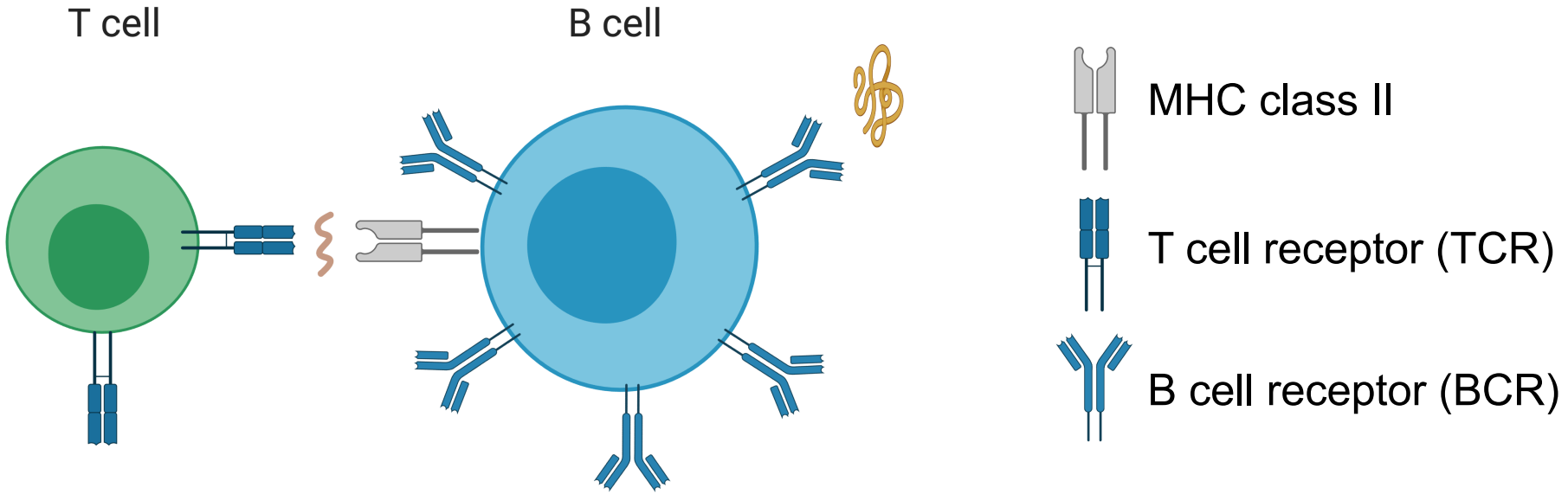


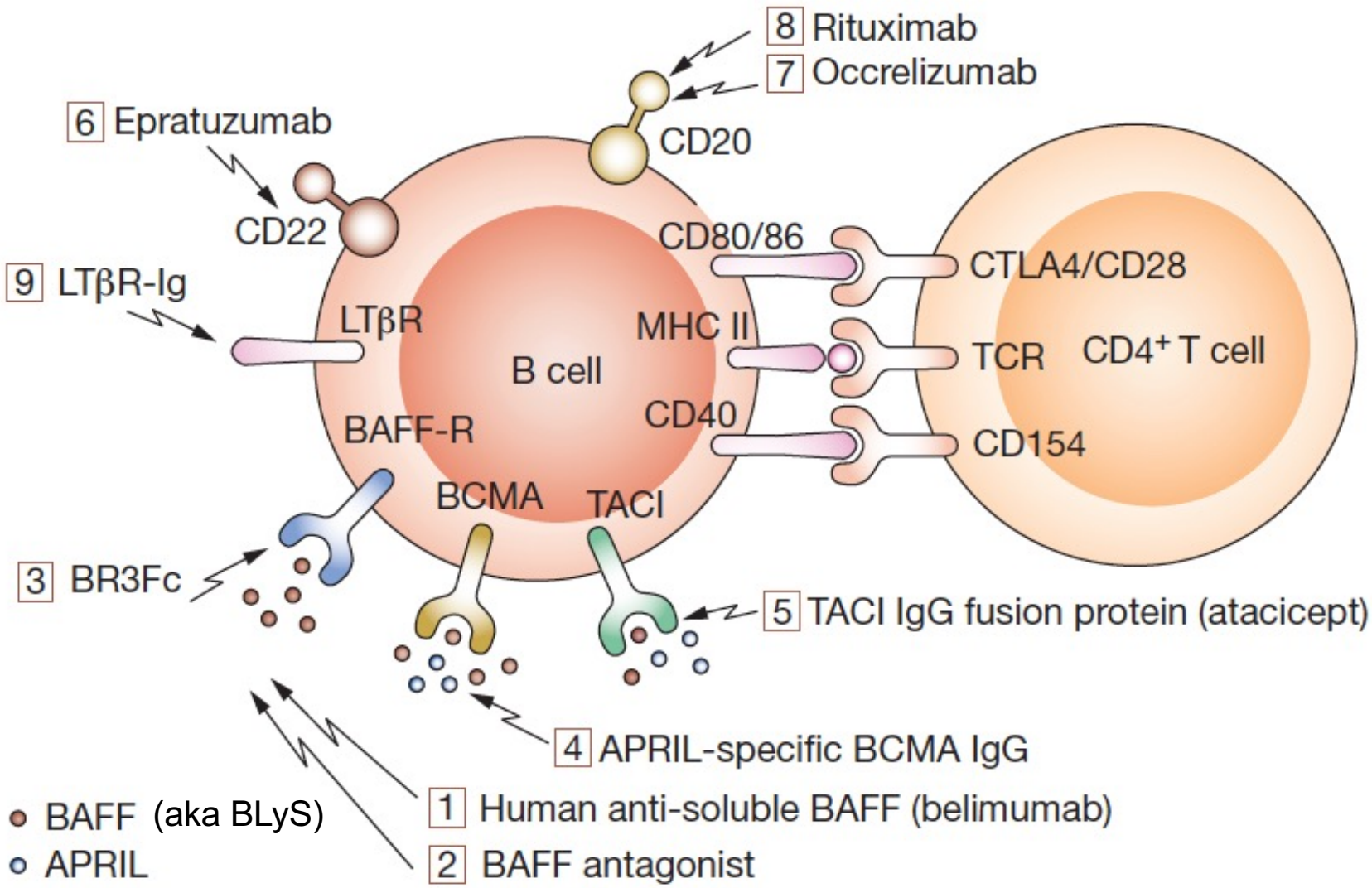
Current Protocols in Neuroscience (2001) 9.7.1-9.7.11

ACTIVATION



Adaptive Immunity





Dalaka, Nature Clinical Practice Neurology; 2008 vol 4 no 10

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

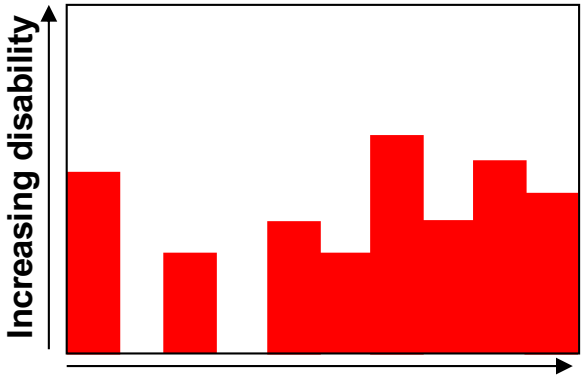
Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D., Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D., Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D., Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D., and Craig H. Smith, M.D., for the HERMES Trial Group*

Table 3. (Continued.)

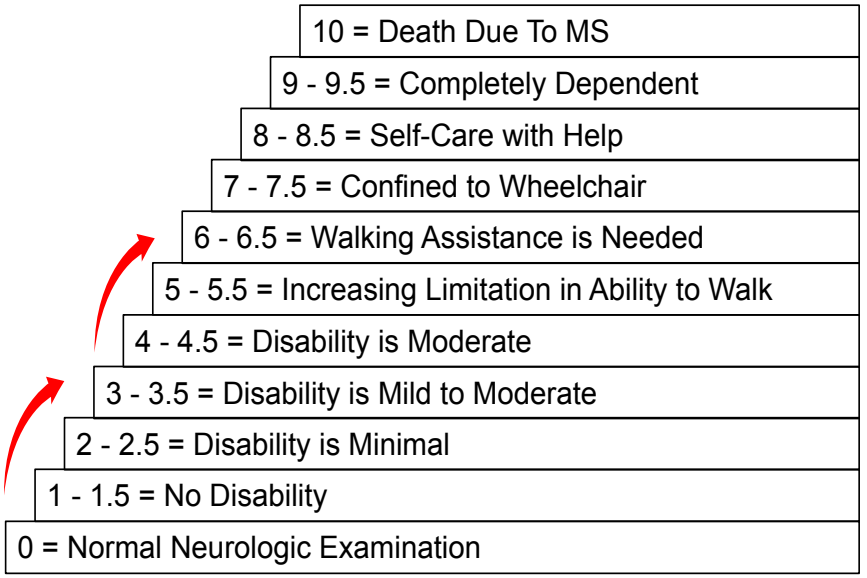
End Point	Placebo (N=35)	Rituximab (N=69)	P Value
Clinical			
Relapses between wk 0 and wk 48 — no. of patients (%)			
0 relapses	21 (60.0)	55 (79.7)	
1 relapse	11 (31.4)	8 (11.6)	
2 relapses	1 (2.9)	5 (7.2)	
≥3 relapses	2 (5.7)	1 (1.4)	
Mean no. of relapses (range)	0.54±0.82 (0–3)	0.30±0.67 (0–3)	
Annualized rate of relapse from wk 0 to wk 24			
Total no. of relapses	13	11	
Total subject-years of follow-up	15.9	31.3	
Unadjusted rate	0.8	0.4	
Adjusted rate (90% CI)**	0.8 (0.53–1.31)	0.4 (0.23–0.60)	0.04††
Mean‡‡	0.8±1.20	0.3±0.86	
Median	0	0	
Annualized rate of relapse from wk 0 to wk 48			0.08††
Total no. of relapses	19	21	
Total subject-years of follow-up	27.2	59.7	
Unadjusted rate	0.7	0.4	
Adjusted rate (90% CI)**	0.7 (0.46–1.12)	0.4 (0.24–0.57)	
Mean‡‡	0.7±1.05	0.4±0.81	
Median	0	0	

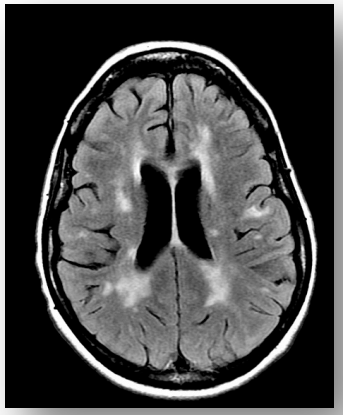
Outcome Measures in MS Trials

Relapse Rate

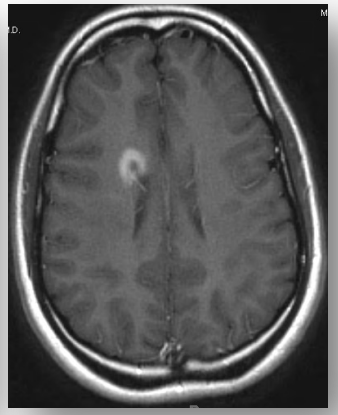


EDSS





T2 lesion volume



Gd+ lesions

1. Timed 25-Foot Walk (T25FW)
2. 9-Hole Peg Test (9HPT)
3. Paced Auditory Serial Addition Test (PASAT)

} MSFC (z-score)

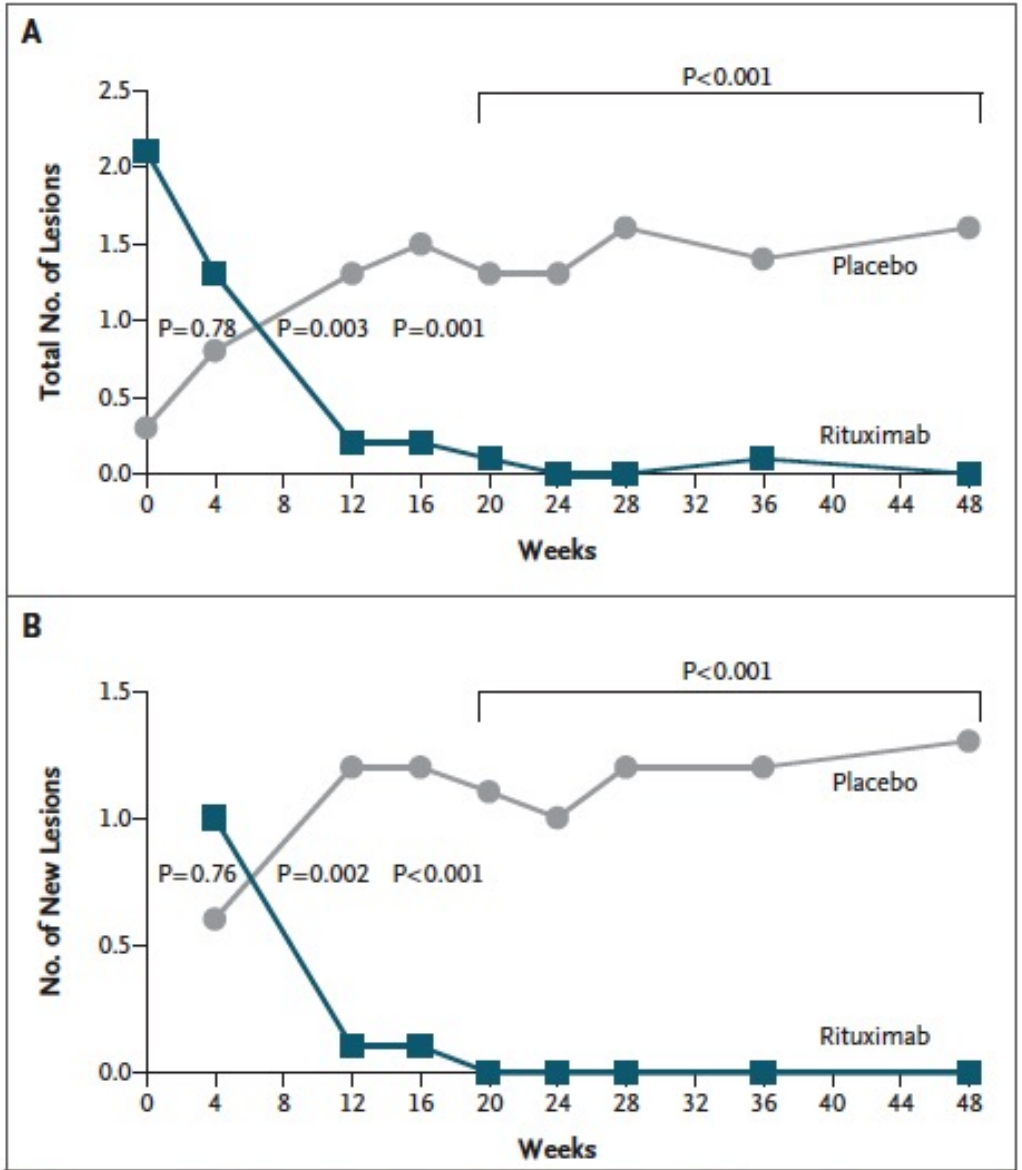
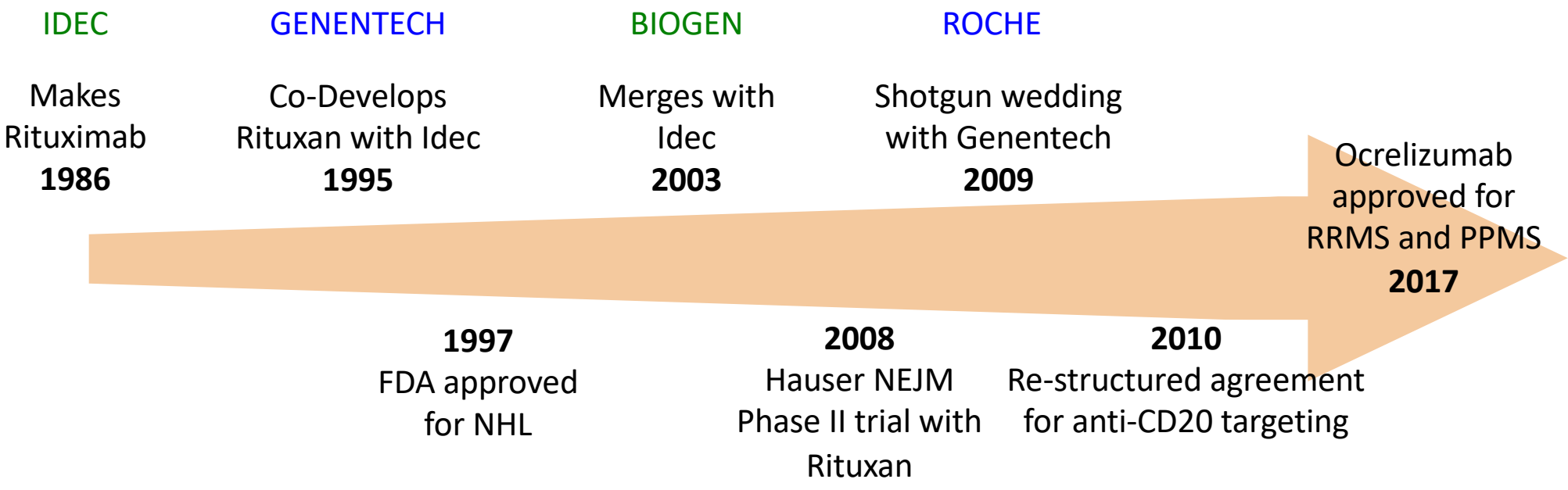


Figure 2. Gadolinium-Enhancing Lesions in Each Study Group from Baseline to Week 48.

Panel A shows the mean total number of gadolinium-enhancing lesions by week, and Panel B shows the mean number of new gadolinium-enhancing lesions by week. Missing values were imputed by averaging the available data. The baseline MRI was obtained at week −4.

B Cell Depletion Therapy in MS



Rituxan – patent expired in 2015
Ocrelizumab – patent ?

Phase I: Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

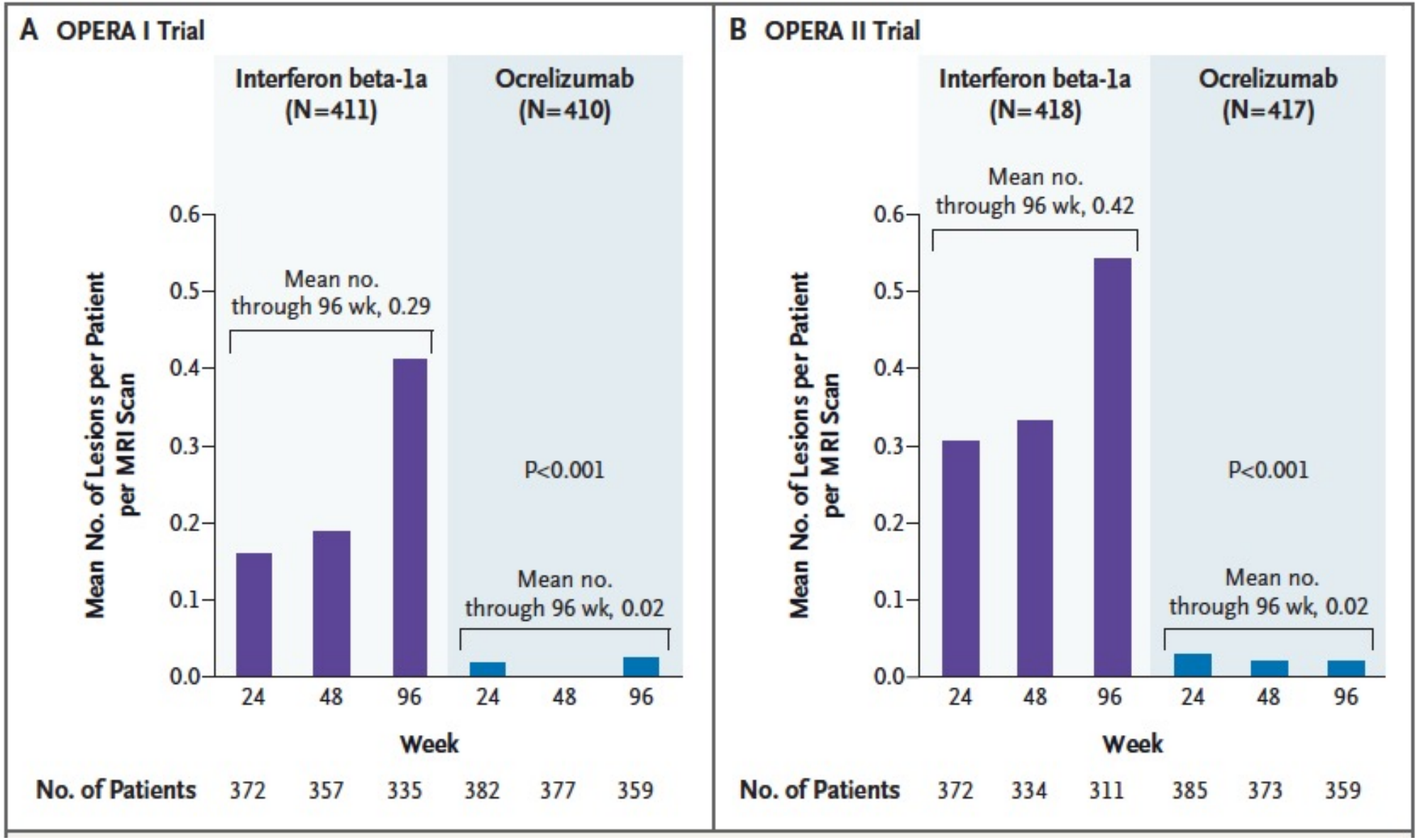
Phase II: The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

Phase III: The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

ORIGINAL ARTICLE

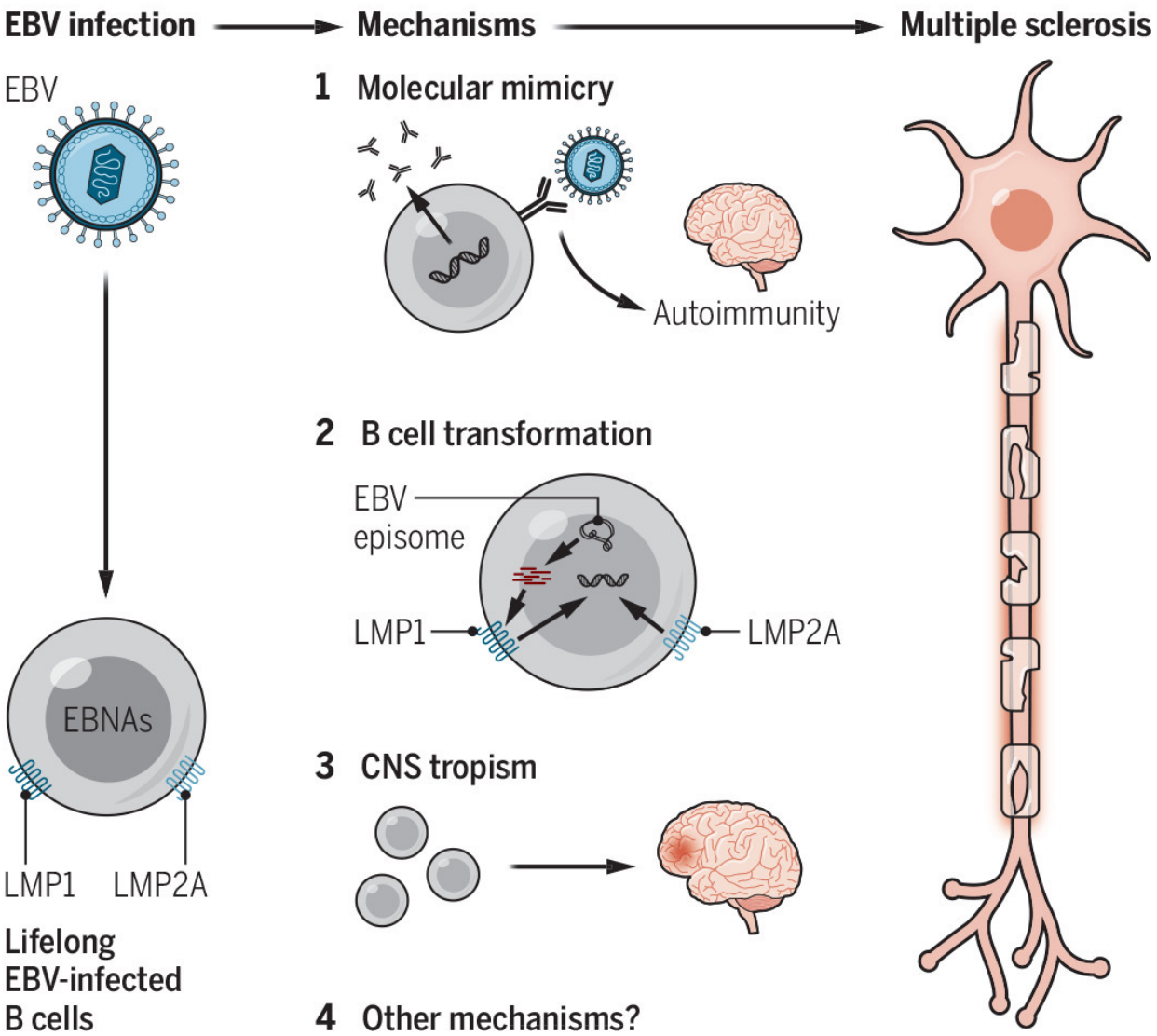
Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis

S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee, J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura, S. Belachew, P. Chin, N. Mairon, H. Garren, and L. Kappos, for the OPERA I and OPERA II Clinical Investigators*

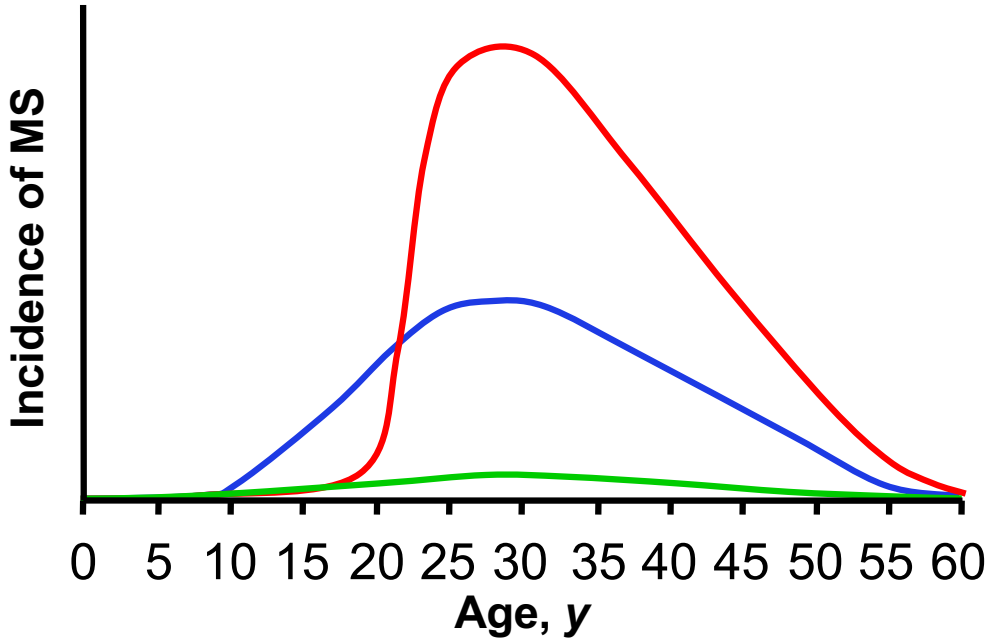


Hauser et al, N Engl J Med. 2017 Jan 19;376(3):221-234

Epstein-Barr Virus & MS



Age of EBV Infection and MS Risk



Late EBV infection with IM

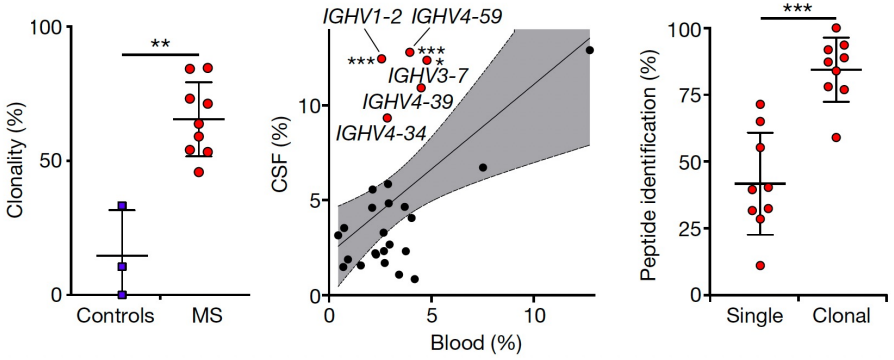
Early EBV infection without IM

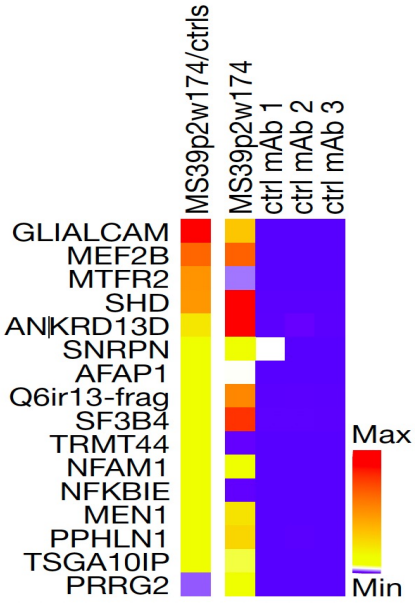
No EBV infection

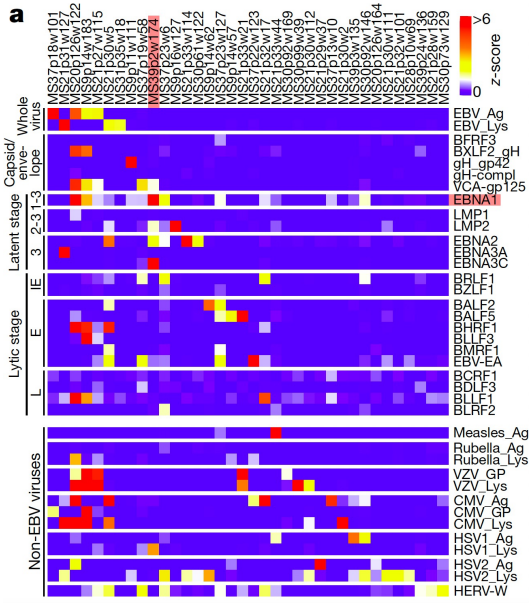
IM = infectious mononucleosis.

Ascherio A and Munger KL. Ann Neurol. 2007;61:288-299.

Immuno-pathophysiology of MS







Nature (2022) 603:321-7

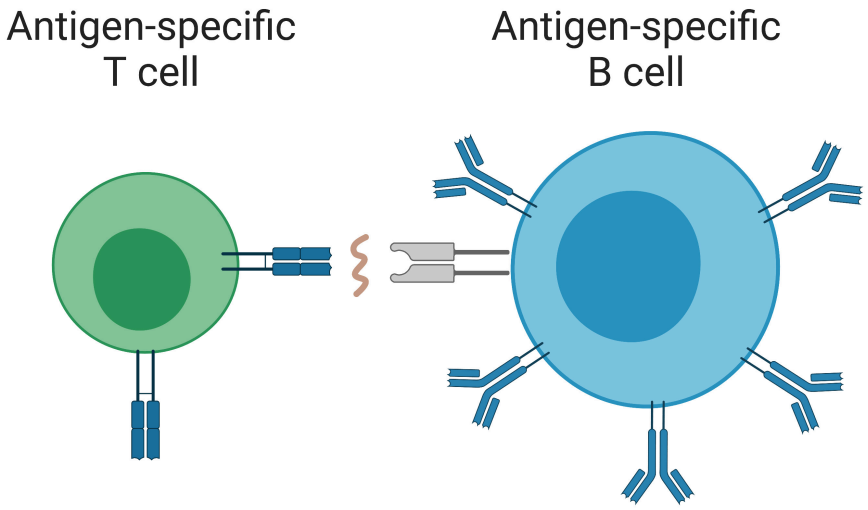
Causality vs Therapy/Prevention

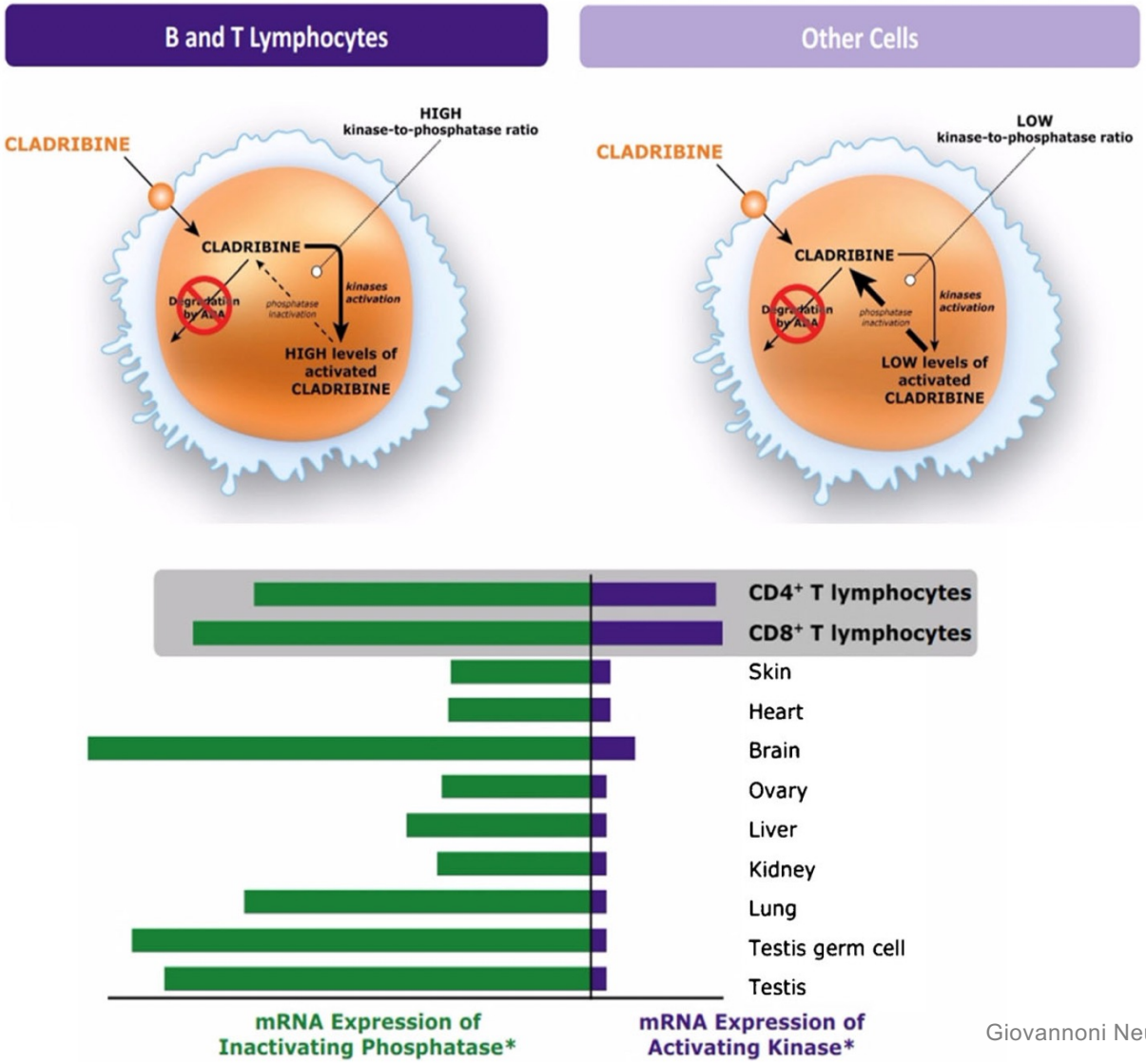
"Moderna Starts Human Trials Of mRNA Vaccine For Virus That Likely Causes Multiple Sclerosis"

"…most cases of MS could be prevented by stopping infection with EBV, as well as opening up the possibility of a cure for MS by 'targeting EBV'"

https://www.forbes.com/sites/roberthart/2022/01/14/moderna-starts-human-trials-of-mrna-vaccine-for-virus-that-likely-causes-multiple-sclerosis/?sh=4ca948c51a04

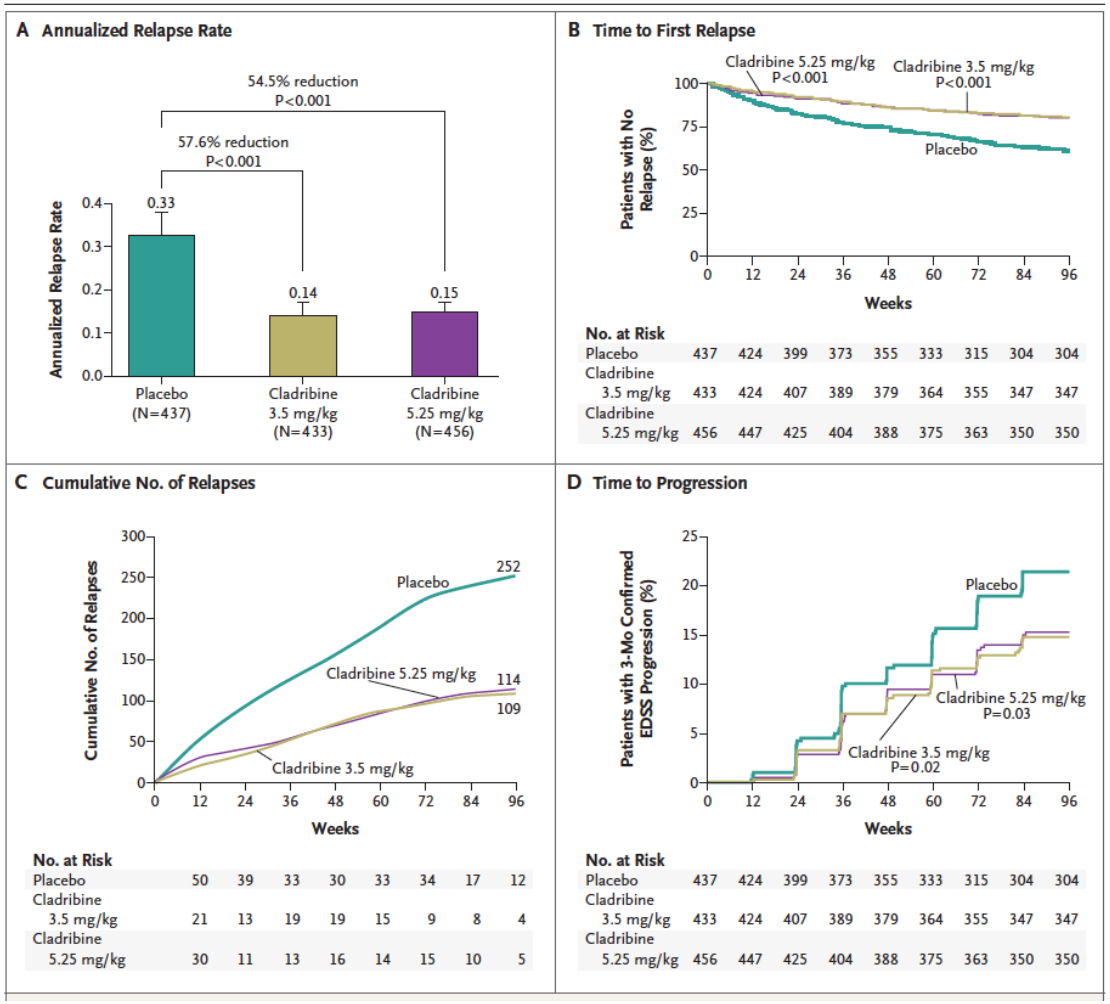
Immuno-pathophysiology of MS



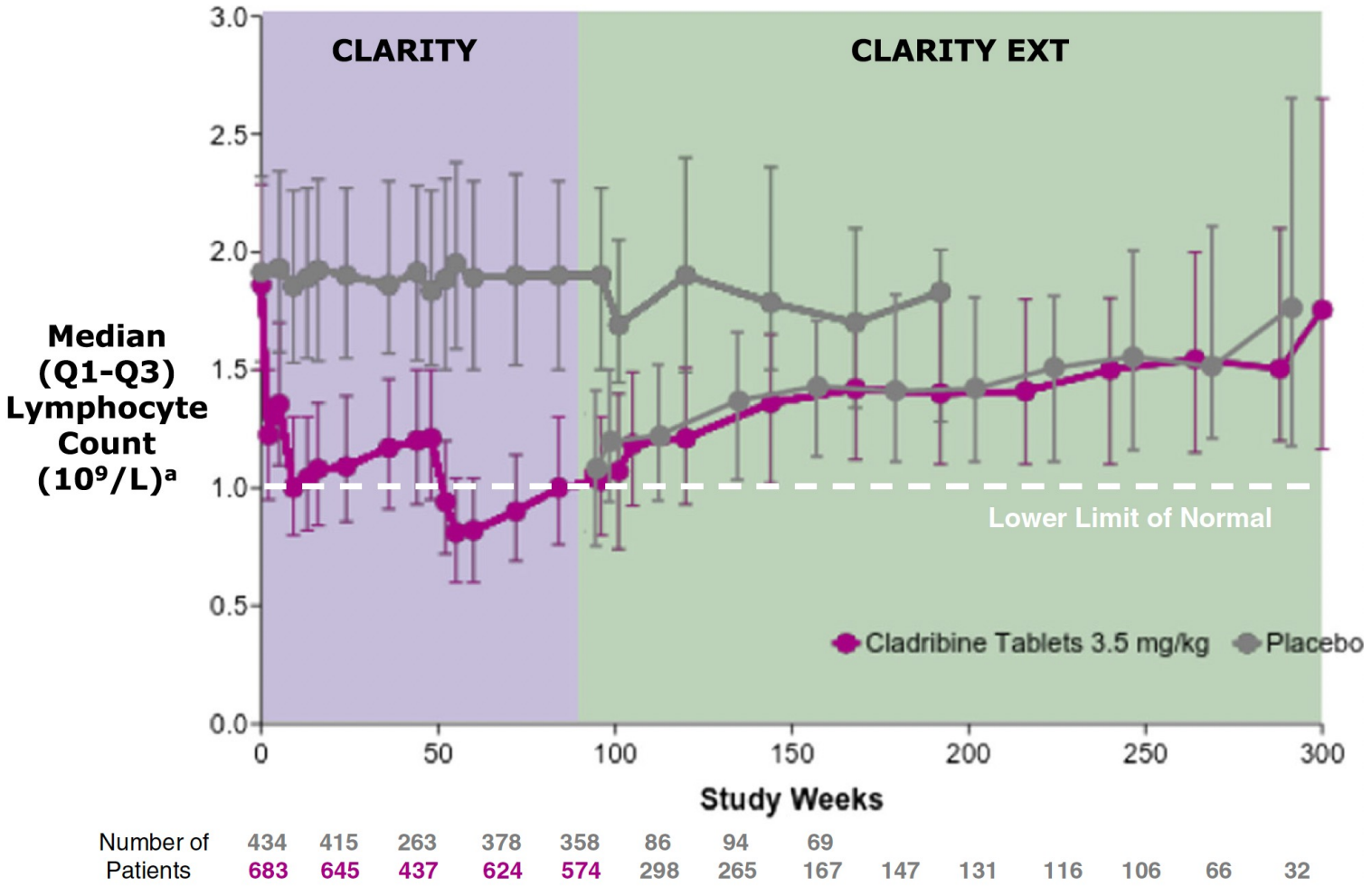


Giovannoni Neurotherapeutics (2017) 14:874–887

Cladribine Efficacy for Relapsing MS

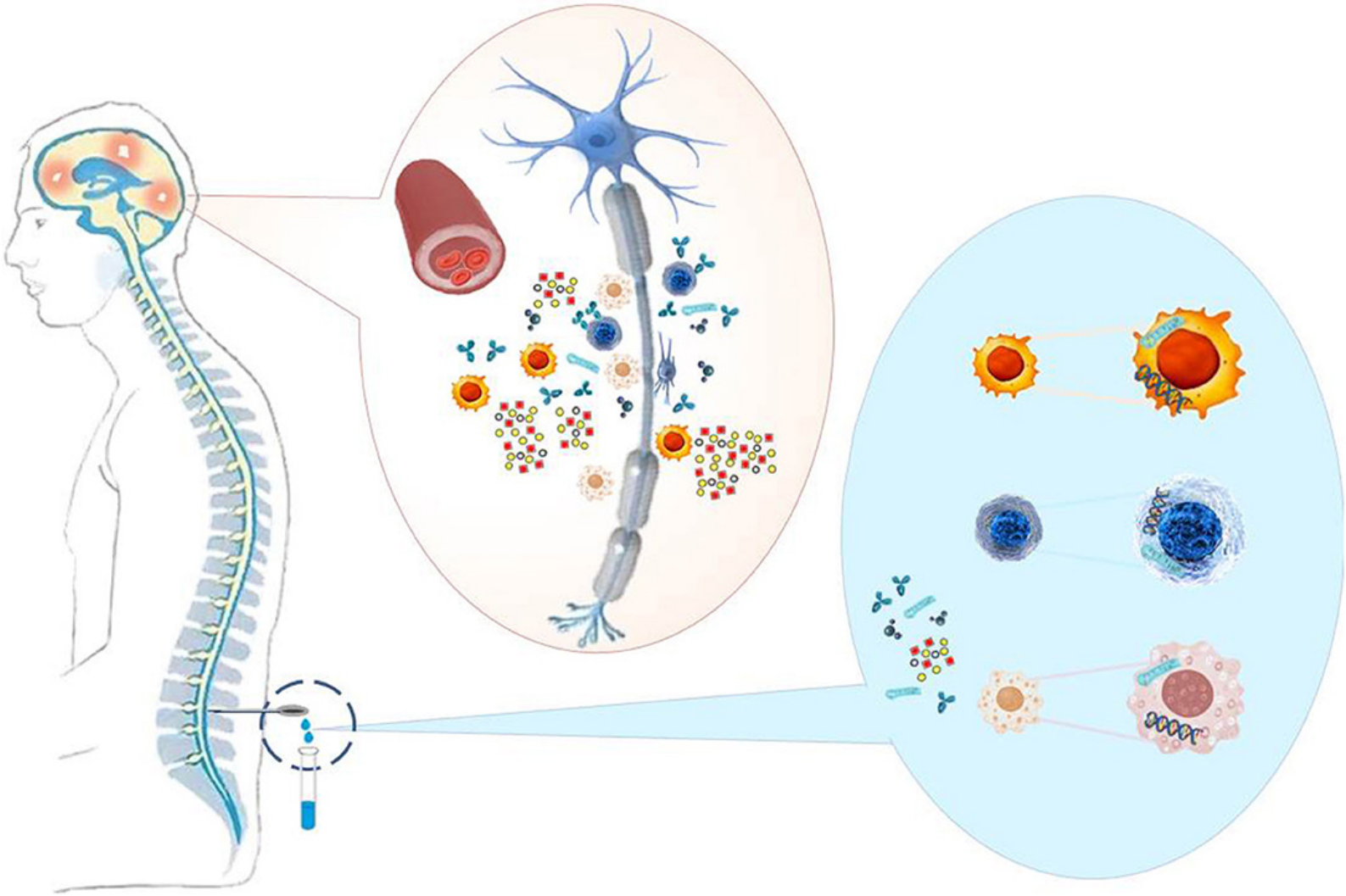


Giovannoni, et al. N Engl J Med 2010;362:416-26.

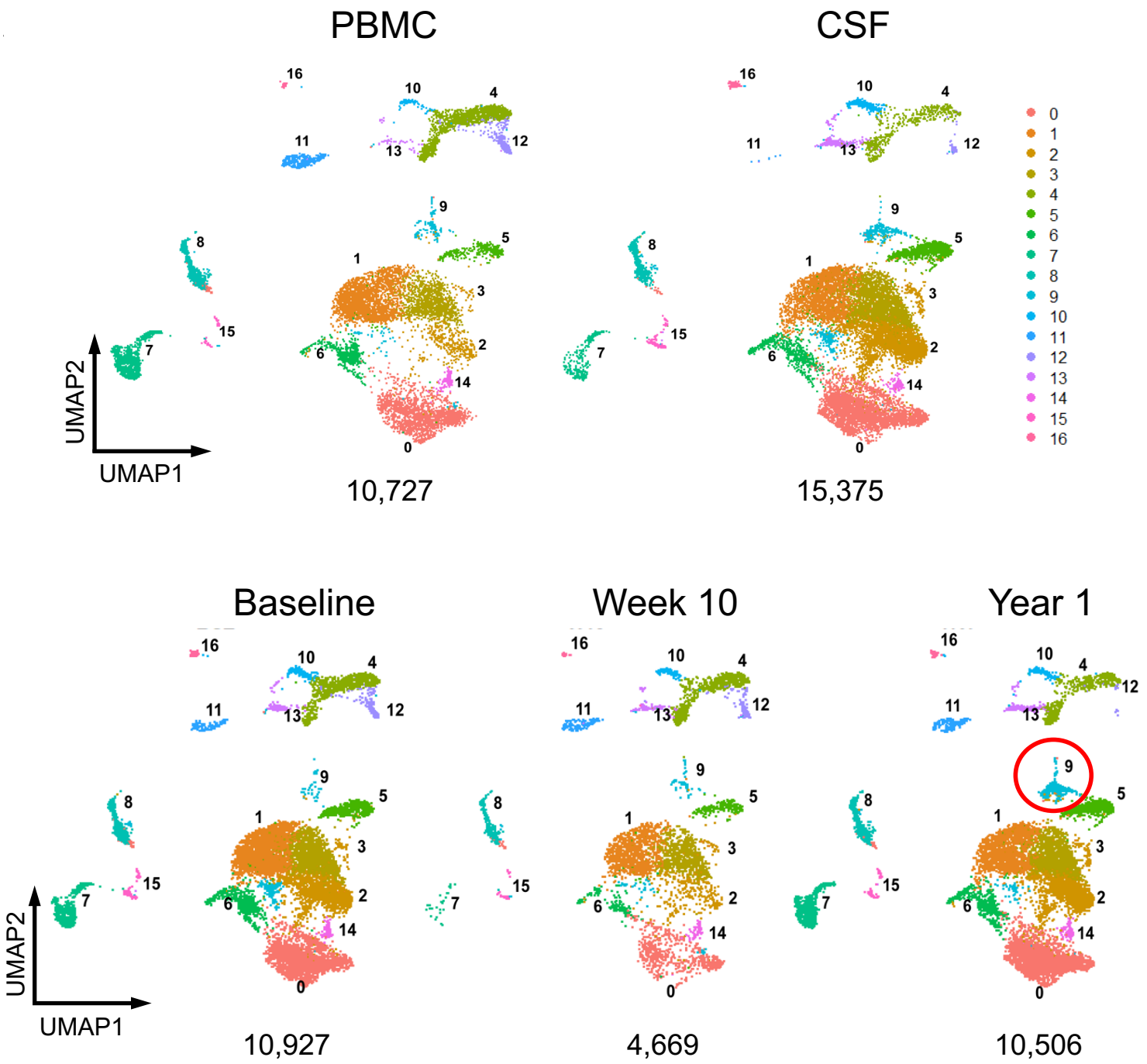


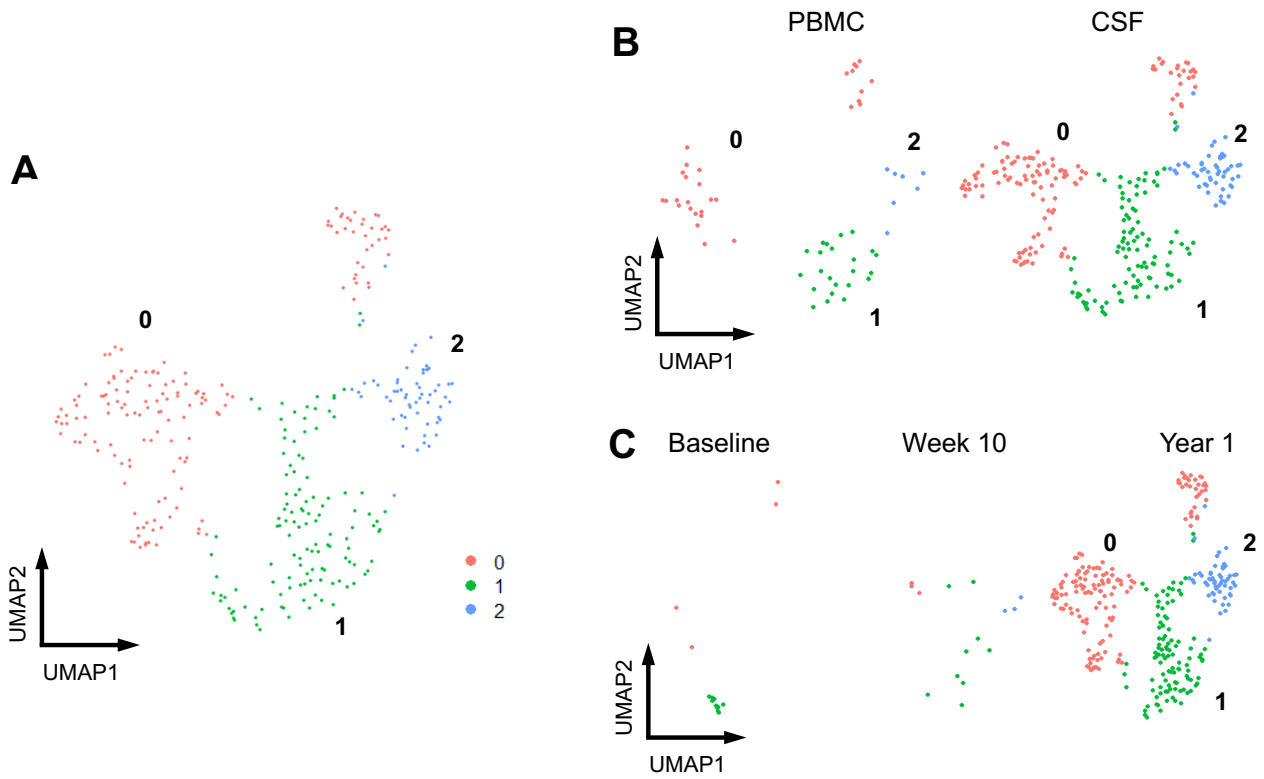
[a]Pooled data from CLARITY, CLARITY EXT, and PREMIERE; figure includes treatment gap. Visits with sample size ≥30 are displayed.

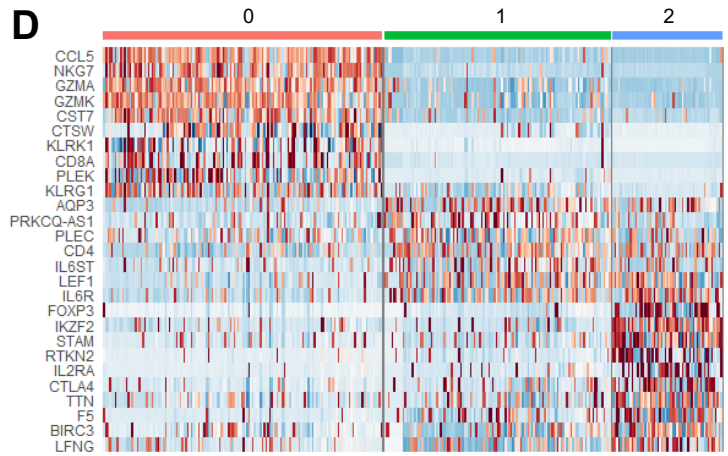
Giovannoni. Neurotherapeutics (2017) 14:874–887



Deisenhammer et al Frontiers Immunol. (2019) 10 | Article 726


PBMC
CSF
Baseline
Week 10
Year 1
UMAP2
UMAP1
10,727
15,375
10,927
4,669
10,506
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16


A
0
1
2
UMAP2
UMAP1
B
PBMC
CSF
C
Baseline
Week 10
Year 1


D
0
1
2
CCL5
NKG7
GZMA
GZMK
CST7
CTSW
KLRK1
CD8A
PLEK
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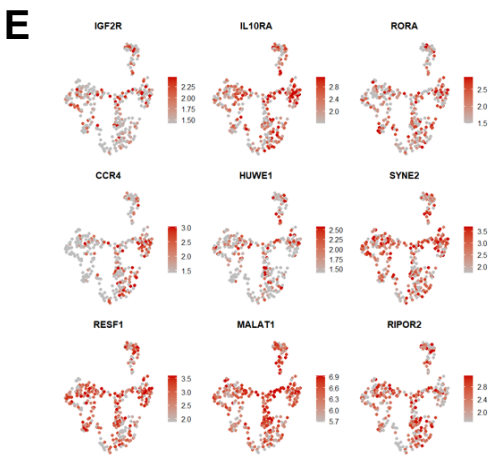
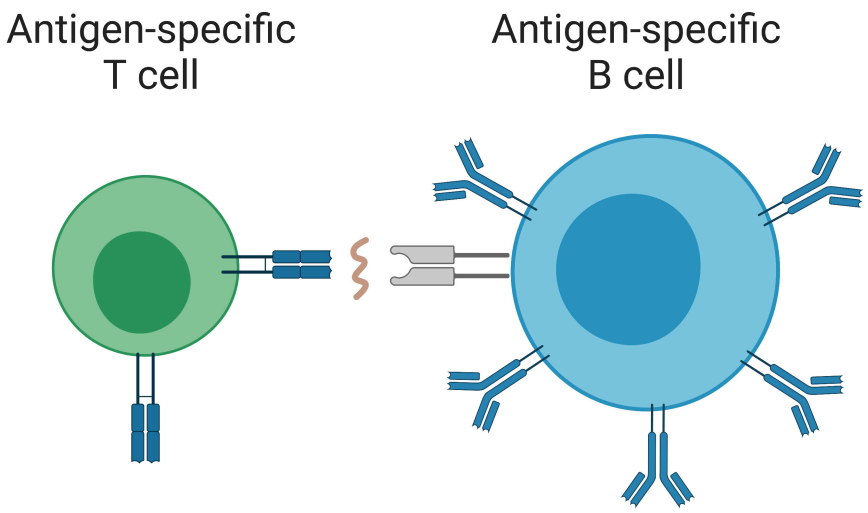
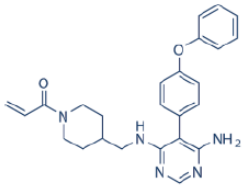
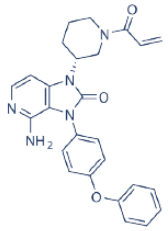
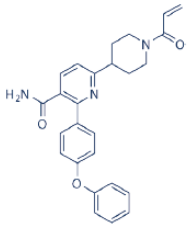
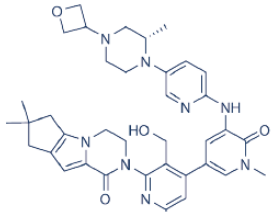
AQP3
PRKCQ-AS1
PLEC
CD4
IL6ST
LEF1
IL6R
FOXP3
IKZF2
STAM
RTKN2
IL2RA
CTLA4
TTN
F5
BIRC3
LFNG


E
IGF2R
IL10RA
RORA
CCR4
HUWE1
SYNE2
RESF1
MALAT1
RIPOR2

Immuno-pathophysiology of MS



Bruton's Tyrosine Kinase Inhibition

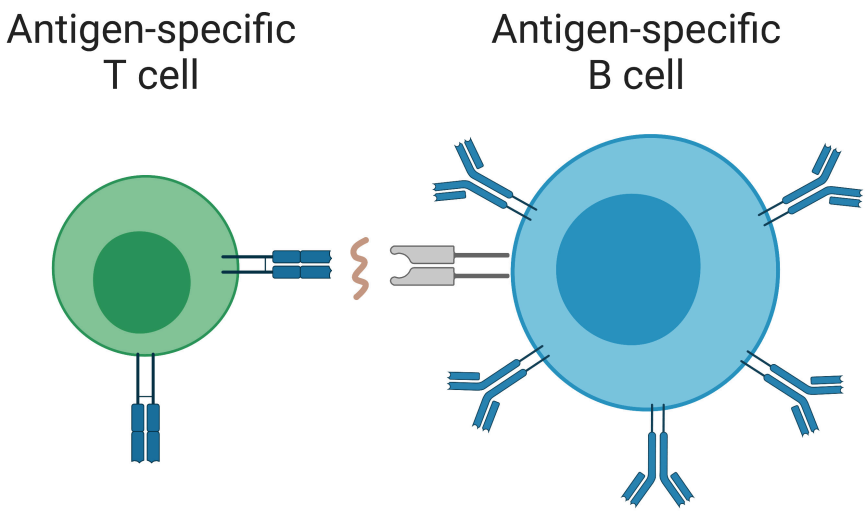
TABLE. COMPARISON OF BRUTON TYROSINE KINASE INHIBITOR PHARMACOLOGY				
	Evobrutininb (M-251) (PRN2246)	**Tolebrutinib (SAR442168)**	**Orelabrutinib (ICP-022)**	**Fenebrutinib (GDC-0853)**
Structure				
Molecular weight	429.51[24]	455.51[24]	427.9[25]	664.80[24]
Chemical bond with BTK10	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible	Noncovalent, reversible
Inhibition site	Kinase domain C481 residue	Kinase domain C481 residue	Kinase domain C481 residue	SH2 domain K430 residue, kinase domain M 477 and D539 residues
IC50 (nM)[a]	37.97	0.4-0.79	1.6	2.37
Inhibition of other tyrosine kinases	Minimal, targets BTK selectively[7]	Binds 12 of 250 tyrosine kinases at 1 mcMol[9]	Best selectivity, BTK only; > 90% inhibition[25]	Targets 2 of 286 kinases[7]
Abbreviations: BTK, Bruton tyrosine kinase; BTKI, BTK inhibitor; IC50, half-maximal concentration. [a]The IC50 for the BTKIs of interest vary depending on the type of used cells to determine the inhibition constant; however different papers report comparable values.				

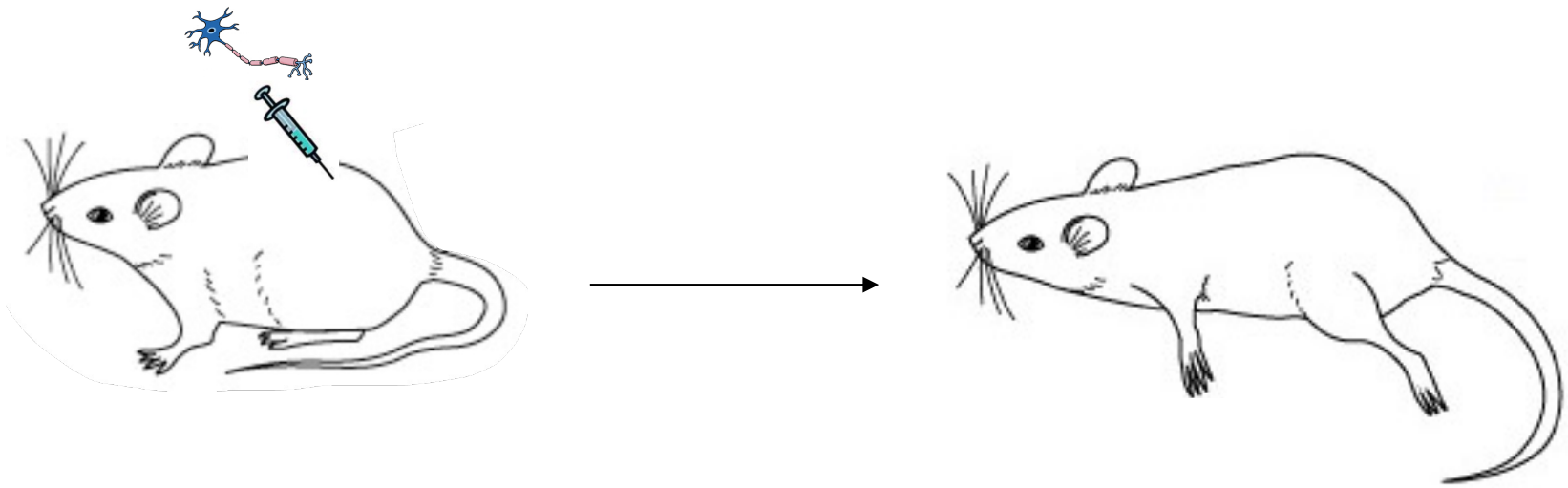
Hendriks RW. Nature Chemical Biology volume 7, pages4–5 (2011)

Bruton's Tyrosine Kinase Inhibition

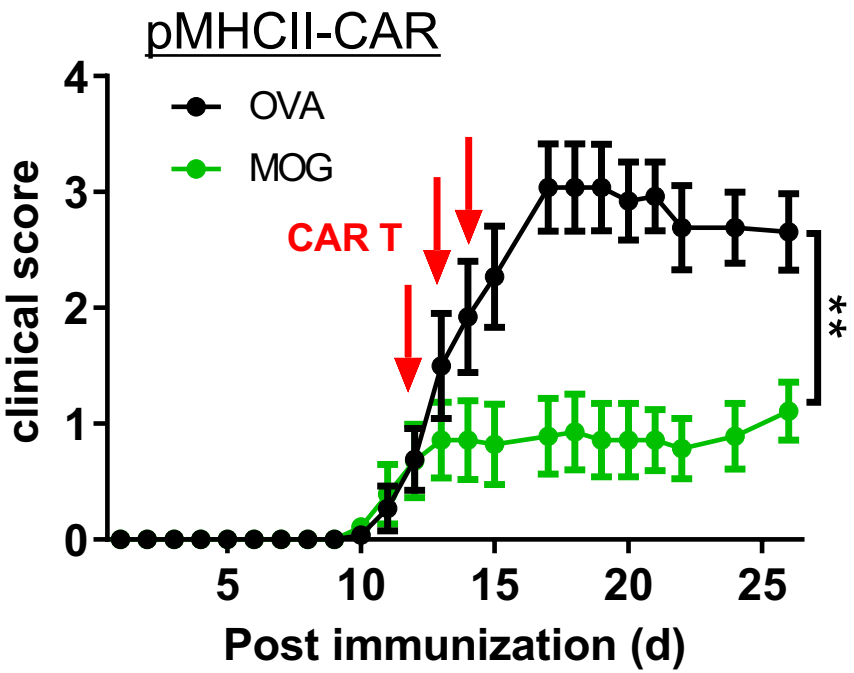
OLE period	Statistics	Dose received in the DBP[a]					
		Placebo/ Evobrutinib 25 mg QD (n=39)	Evobrutinib 25 mg QD (n=39)	Evobrutinib 75 mg QD (n=42)	Evobrutinib 75 mg BID (n=44)	DMF (n=49)	Total (n=213)
OLE W0 to switch from evobrutinib 75 mg QD to 75 mg BID dose[b]	**ARR**	**0.30**	**0.22**	**0.13**	**0.16**	**0.15**	**0.19**
	95% CI	0.15–0.53	0.09–0.43	0.04–0.31	0.07–0.34	0.05–0.32	0.13–0.26
From time of switch to evobrutinib 75 mg BID until OLE W132[b]	**ARR**	**0.10**	**0.13**	**0.07**	**0.11**	**0.10**	**0.10**
	95% CI	0.03–0.22	0.05–0.27	0.02–0.18	0.04–0.23	0.04–0.22	0.07–0.14
OLE W0 to OLE W132	**ARR**	**0.18**	**0.17**	**0.09**	**0.13**	**0.12**	**0.14**
	95% CI	0.10–0.29	0.09–0.28	0.04–0.18	0.07–0.22	0.06–0.21	0.11–0.17

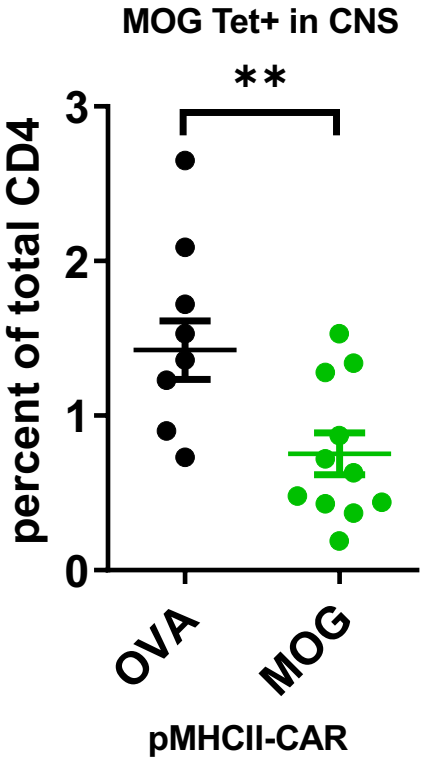
Immuno-pathophysiology of MS





Efficacy of pMHCII-CAR T cells in EAE

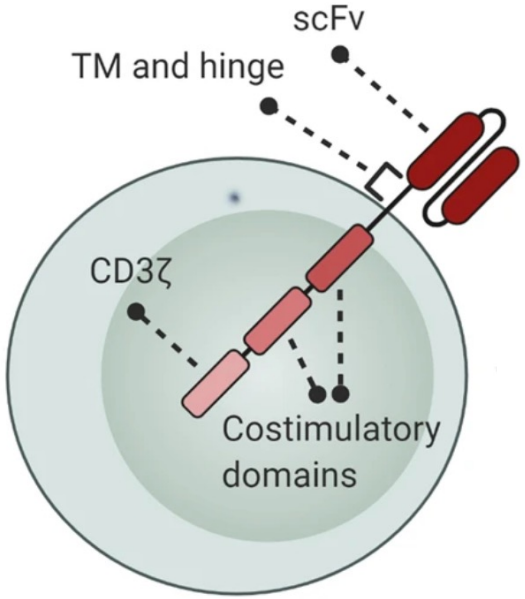




MOG_{35-55} pMHCII-CAR T cells can ameliorate EAE

Chimeric Antigen Receptor (CAR) T Cell Therapies

Traditional CAR T cells



- Specificity
- Potent killing

Table 1. The list of clinical trials of chimeric antigen receptor (CAR)-T cell therapy beyond oncology.

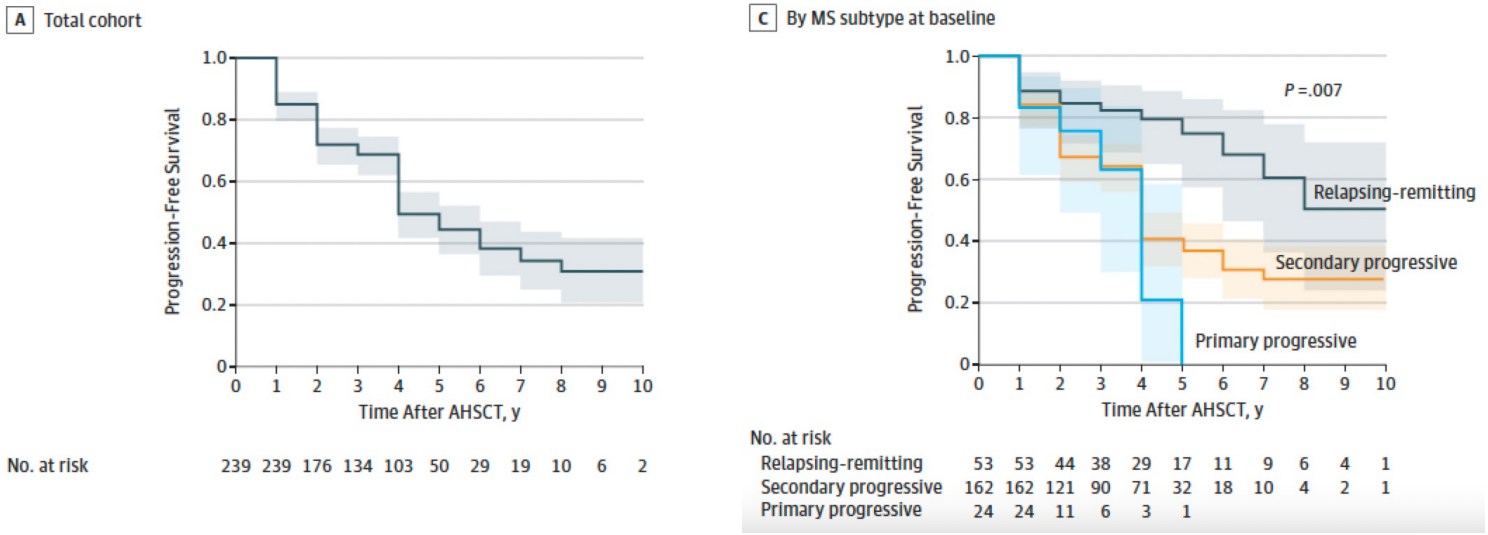
Disease	Target/Approach	NCT, Current Status
Mucosal-Dominant Pemphigus Vulgaris	Clone-specific anti-Dsg3 CAAR-T	NCT04422912, Phase I recruiting
Generalized Myasthenia Gravis	Non-specific anti-BCMA CAR-T	NCT04146051, Phase I, II recruiting
Systemic Lupus Erythematosus	Non-specific anti-CD19 CAR-T	NCT03030976, Phase I, unknown
Neuromyelitis Optica Spectrum Disorder	Non-specific tandem anti-CD19 and anti-CD20 CAR-T	NCT03605238, Phase I, withdrawn
	Non-specific anti-BCMA CAR-T	NCT04561557, Phase I recruiting
Human Immunodeficiency Virus	Anti-gp120 BNAbs based CAR-T	NCT03240328, Phase I recruiting
		NCT03980691, Phase I recruiting
	Anti-gp120 dual CAR-T	NCT04648046, Phase I not yet recruiting
COVID-19	Bispecific anti-ACE2 and anti-NKG2D CAR-NK	NCT04324996, Phase I, II recruiting

Poorebrahim et al Oncogene 40: 421-35 (2021)

Zmievskaya et al. Biomedicines. 2021;9(1):59.

Bone marrow transplantation for MS

- “Stem cell therapy”



- BEAT-MS Trial: compares ‘best available’ therapy

Summary

- MS is a heterogeneous disease
- Abundant disease-modifying therapies are available
- Reverse-translation of MS medications sheds light on pathophysiology
- Numerous emerging therapies for MS are on the horizon

Mechanisms of EBV

“The researchers say that the association between EBV and MS risk was too strong to be explained by any other known MS risk factors. The findings strongly suggest that EBV is part of the chain of events that leads to most cases of MS. However, EBV in itself is not sufficient to trigger MS.”

“Epstein-Barr virus does not cause MS, but the immune response to this virus is different in MS patients, and our hypothesis is that the altered immune response contributes to the development and progression of the disease.”

“Professor Alberto Ascherio stressed that EBV is necessary, but not sufficient, for someone to develop MS. In other words, you have to be infected with EBV to get MS, and the other risk factors associated with MS only become relevant in the presence of EBV.”

https://www.nih.gov/news-events/nih-research-matters/study-suggests-epstein-barr-virus-may-cause-multiple-sclerosis#:~:text=The%20researchers%20say%20that%20the,not%20sufficient%20to%20trigger%20MS.
https://doi.org/10.1016/j.msard.2022.104158