UNITED STATES
DEPARTMENT OF VETERANS AFFAIRS

UT SOUTHWESTERN
MEDICAL CENTER

The role of T lymphocytes in NMO and MS

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Disclosures

- Dr. Stüve served as a consultant for Sanofi-Aventis, EMD Serono, Novartis, Pfizer, Teva Neuroscience, Roche, and Genzyme
- Dr. Stüve is an associate editor for the Archives of Neurology, and Therapeutic Advances in Neurological Disorders
- Dr. Stüve has received grant support from Teva Pharmaceuticals

Circulation

Central Nervous System

T cell

T cell extravasation

T cell

T cell

T cell adhesion

T cell

T cell rolling

T cell

APC

T cell

T cell activation

T cell

Chemoattraction

CNS APC

T cell

T cell re-activation

B cell

T cell

B cell – T cell cross-activation

Plasma cell

Memory B cell

Antibodies & Complement

Inflammatory mediators

MBP

PLP

Oligo-dendendrocyte

Activation of Na^+ channels

K^+ Na^+

NA^+

Ca^{2+} Na^+

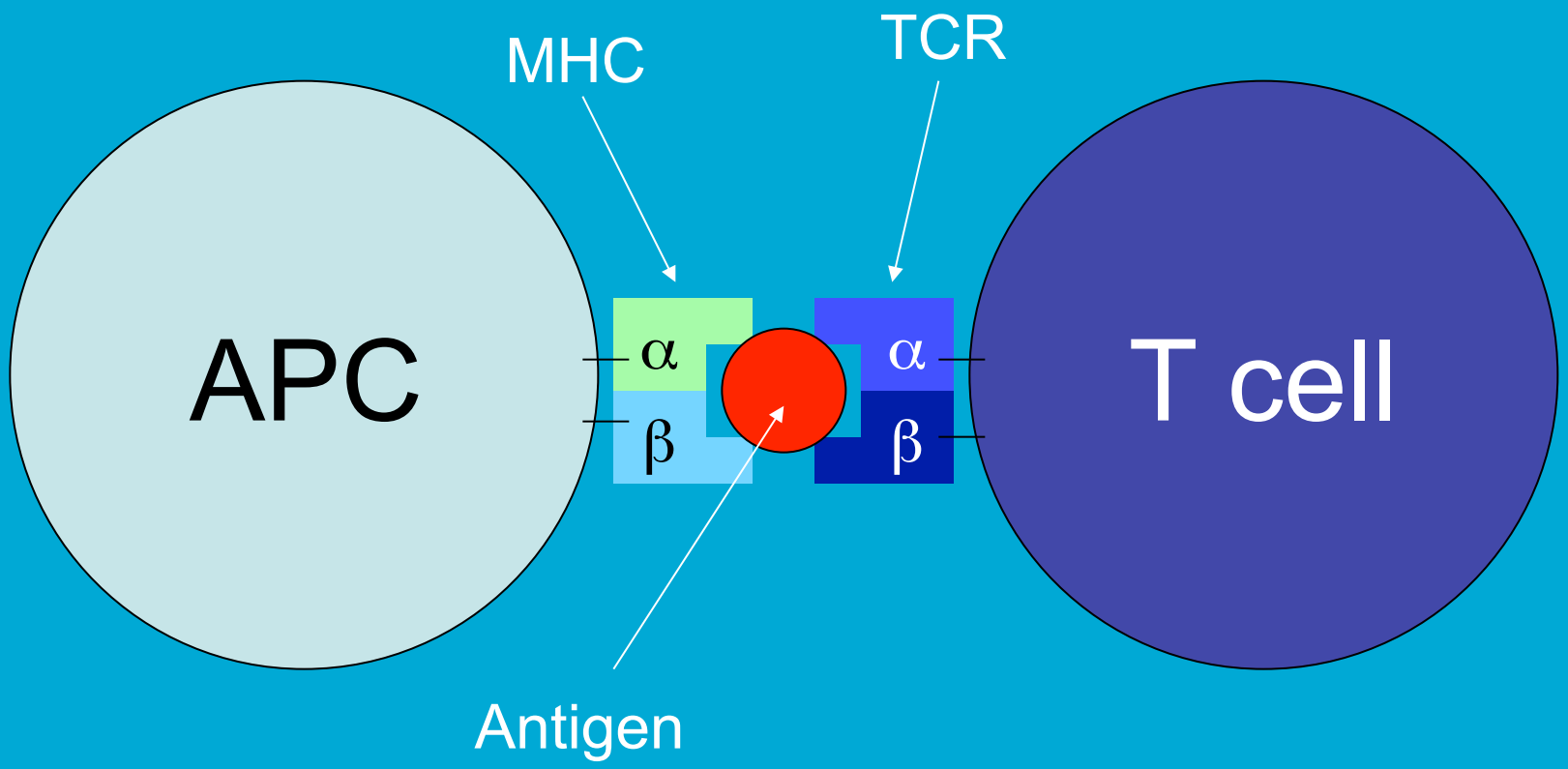
Reverse Na^+ Ca^{2+} exchange

Inflammation

Hypoxia, ischemia

Energy depletion

Failure of Na/K ATPase


MHC
TCR
APC
α
β
α
β
T cell
Antigen

Multiple sclerosis-like illness occurring with human immunodeficiency virus infection

J.R. Berger, MD; W.A. Sheremata, MD; L. Resnick, MD; S. Atherton, PhD; M.A. Fletcher, PhD; and M. Norenberg, MD

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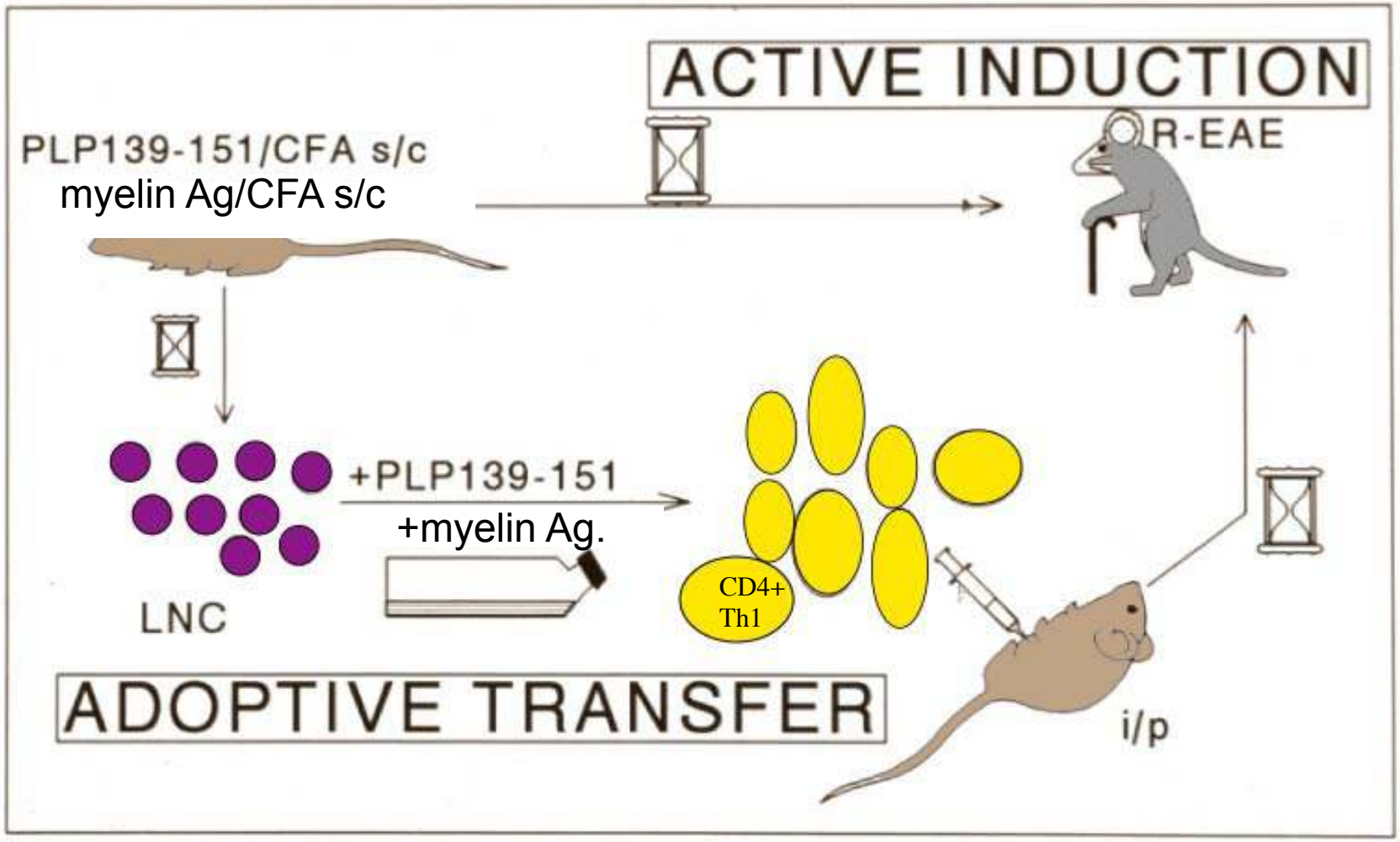
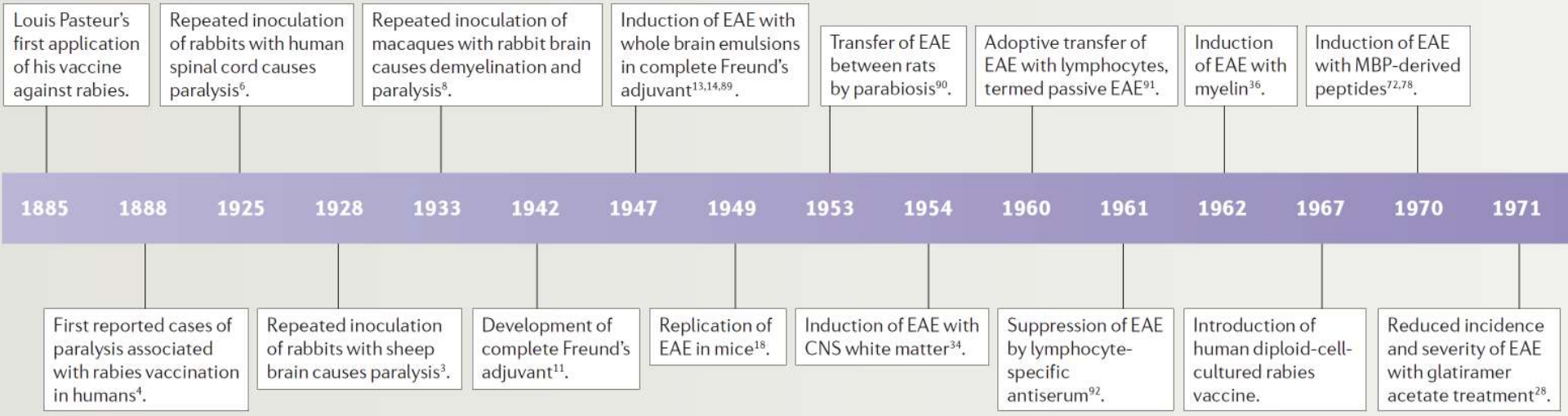
NEUROLOGY 1989;39:324-329



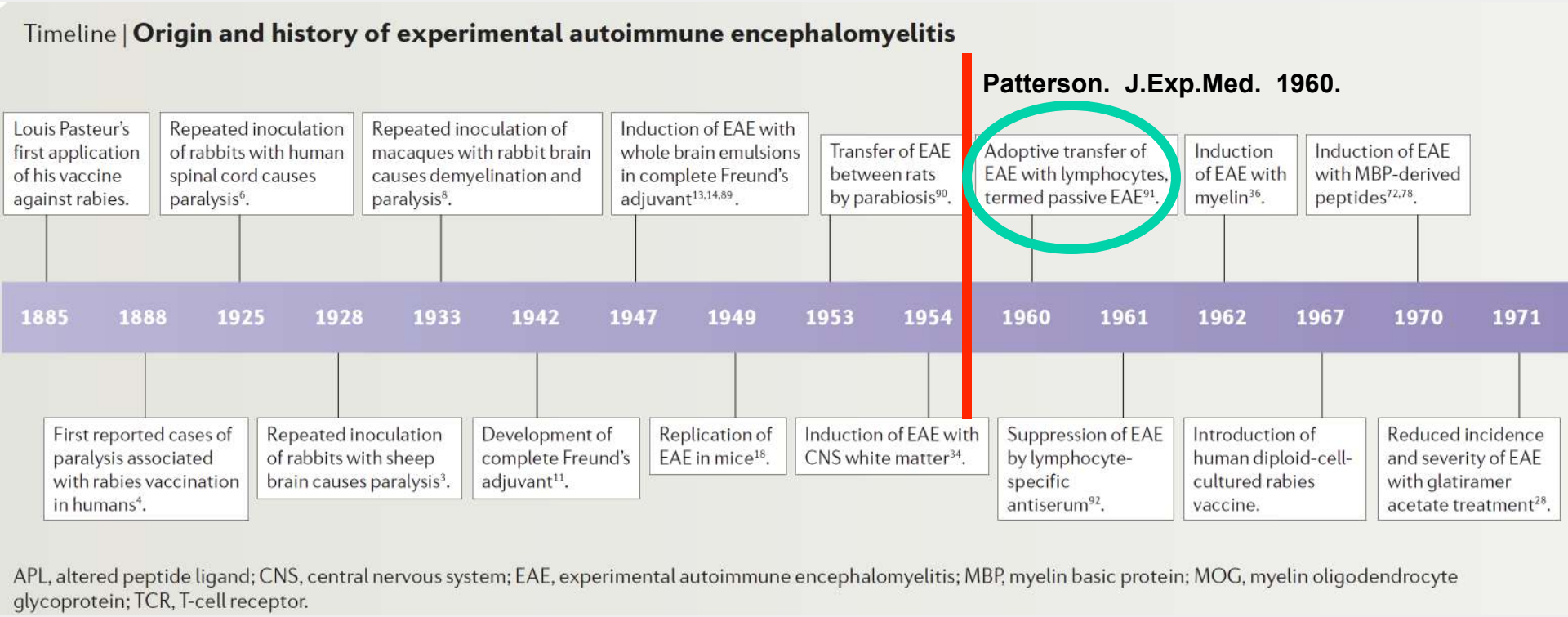
Courtesy of Nitin Karandikar, M.D., Ph.D., UT Southwestern.

Timeline | **Origin and history of experimental autoimmune encephalomyelitis**



APL, altered peptide ligand; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; TCR, T-cell receptor.

Baxter. Nat.Rev.Immunol. 2007.



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Baxter. Nat.Rev.Immunol. 2007.

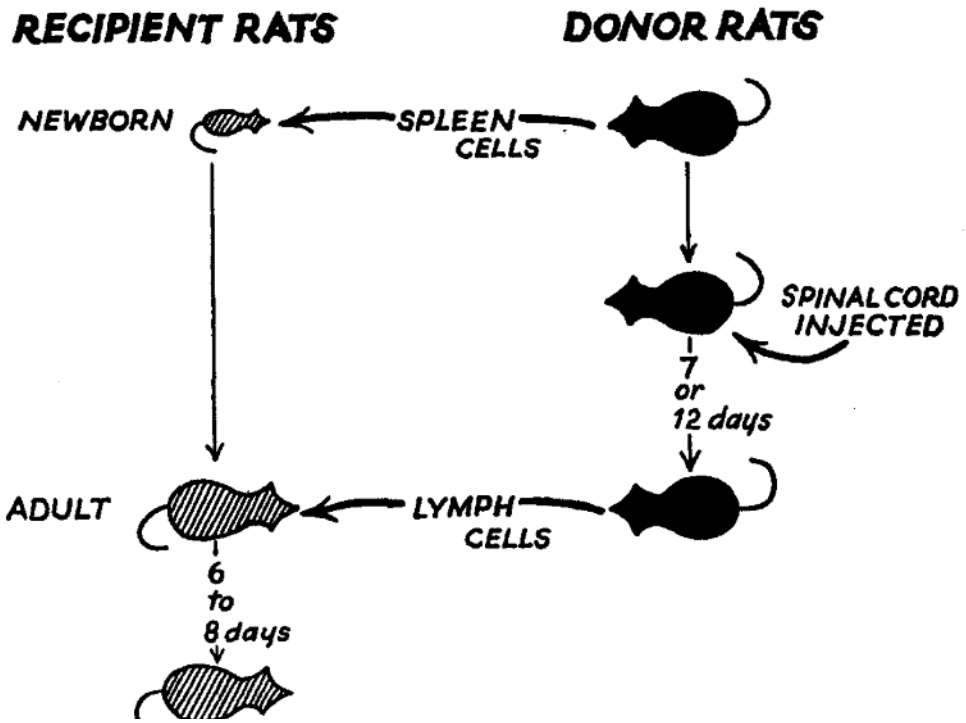
TRANSFER OF ALLERGIC ENCEPHALOMYELITIS IN RATS BY MEANS OF LYMPH NODE CELLS

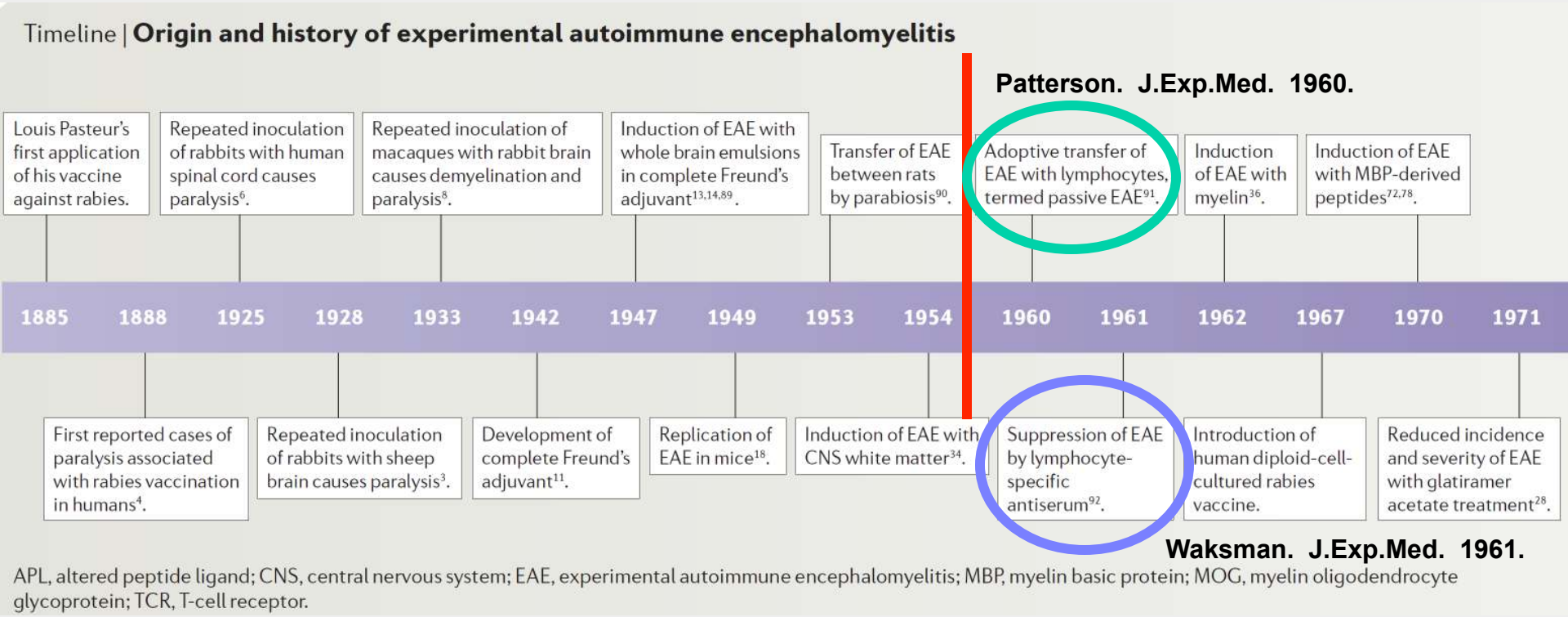
By PHILIP Y. PATERSON, M.D.

(*From the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, and Department of Microbiology, New York University College of Medicine, New York*)

Plates 3 to 6

(Received for publication, August 21, 1959)





Baxter. Nat.Rev.Immunol. 2007.

Cell, Vol. 72, 551–560, February 26, 1993, Copyright © 1993 by Cell Press

Transgenic Mice That Express a Myelin Basic Protein–Specific T Cell Receptor Develop Spontaneous Autoimmunity

Joan Goverman,* Andrea Woods,† Lisa Larson,*
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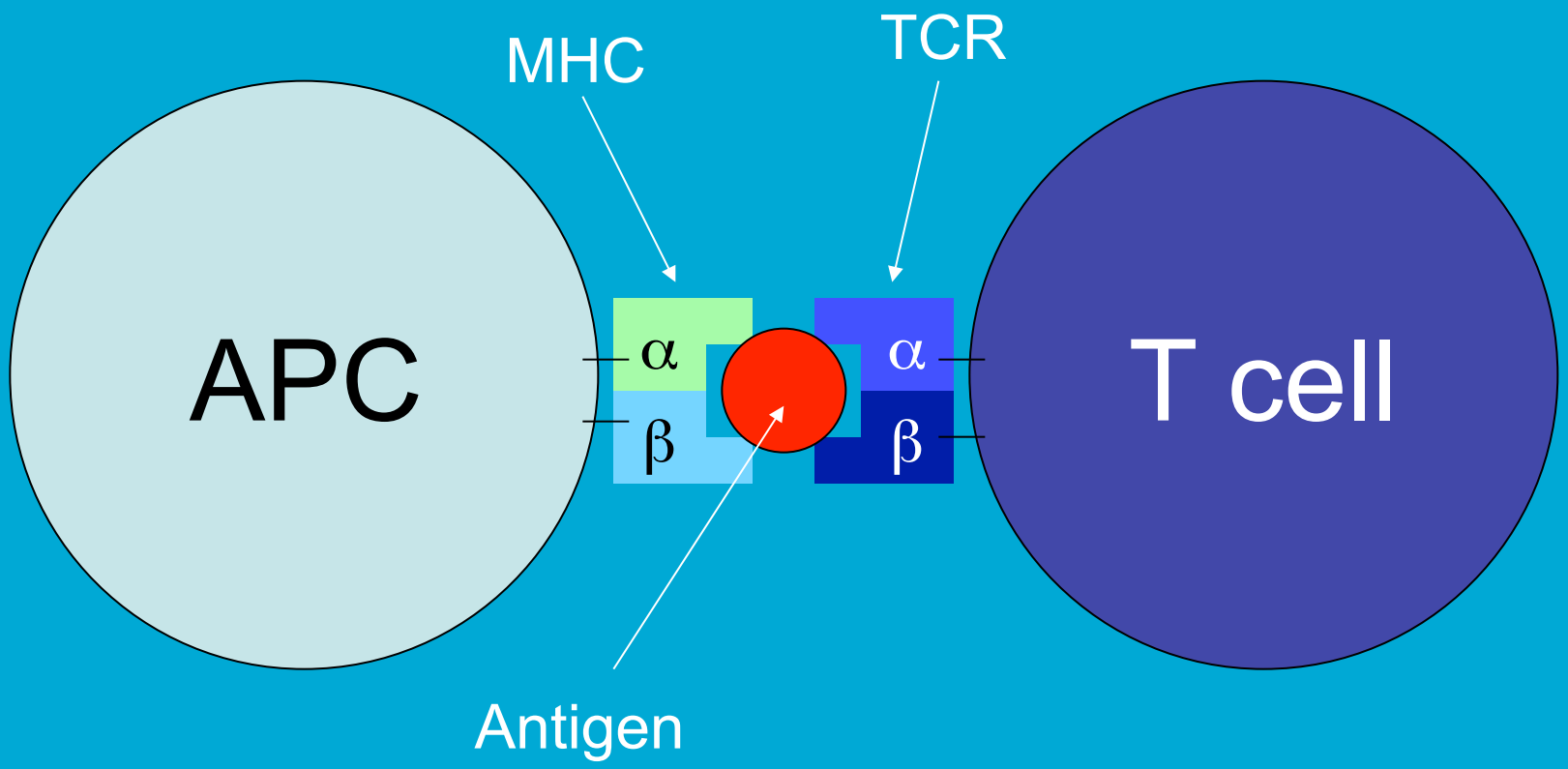
Rahway, New Jersey 07065


MHC
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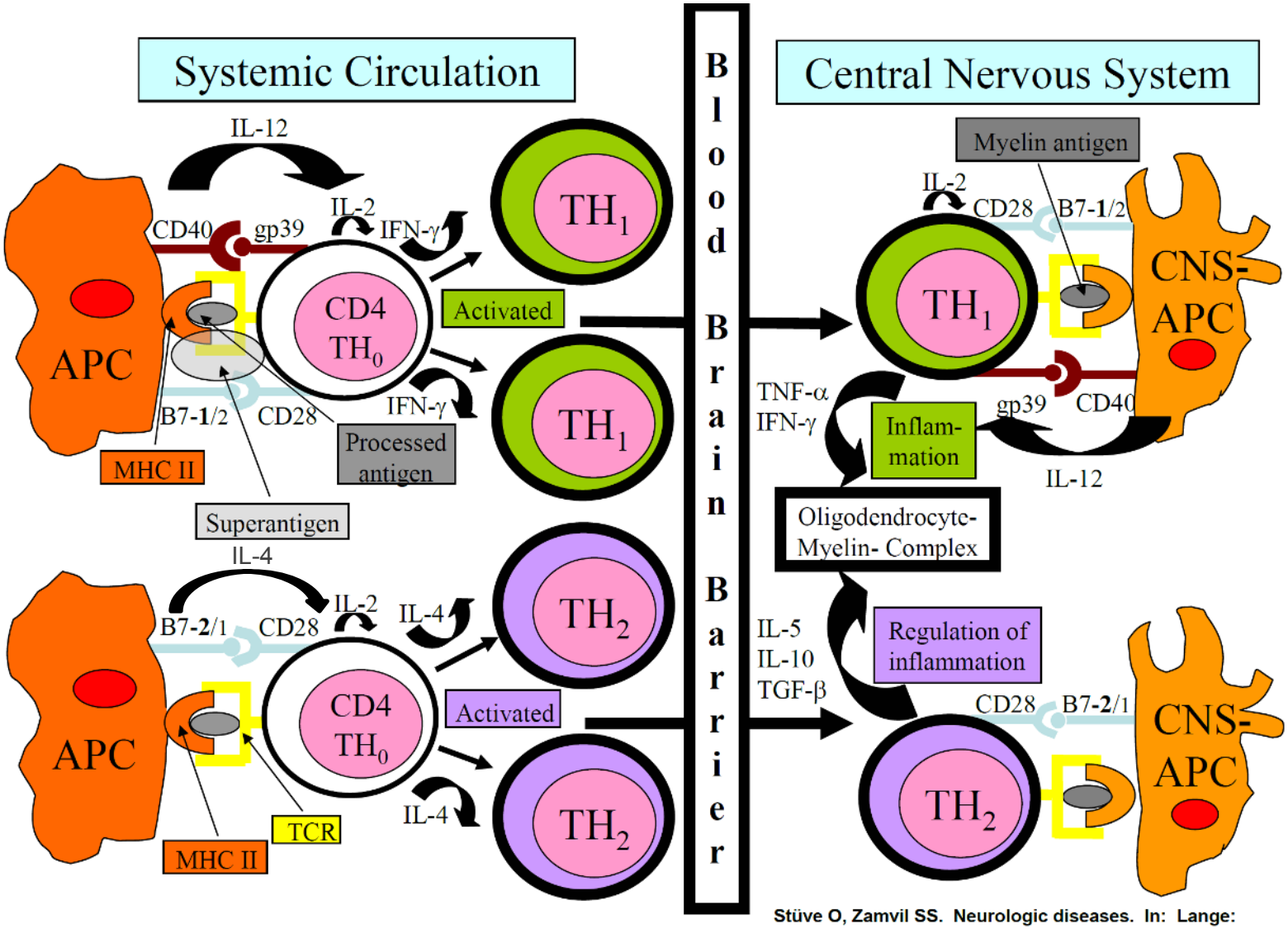
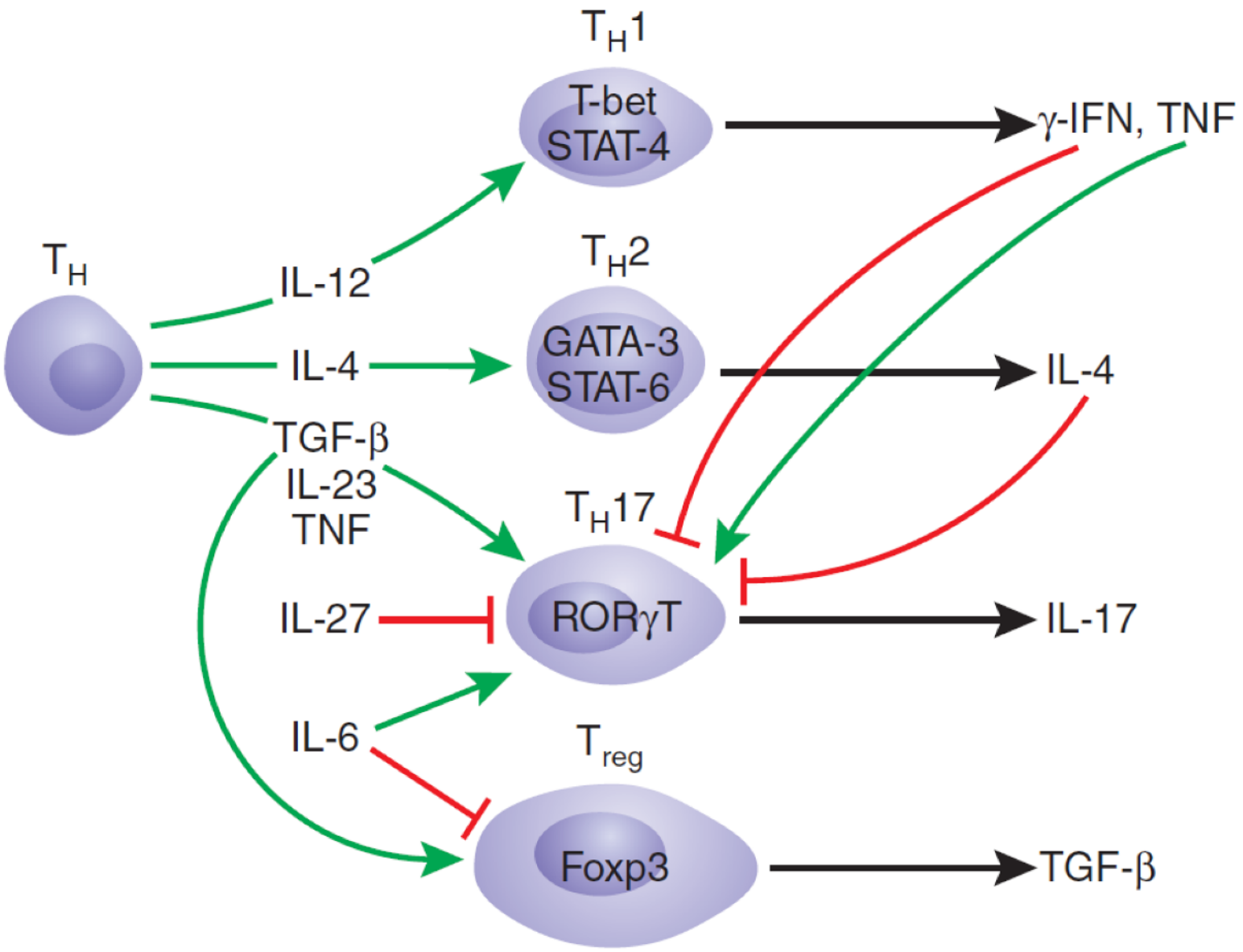


Stüve O, Zamvil SS. Neurologic diseases. In: Lange: Medical Immunology (tenth edition). Eds: Parslow TG, Stites DP, Terr AI, Imboden, JB. *McGraw Hill,* 38:510-526.



Steinman. Nat.Med. 2007.

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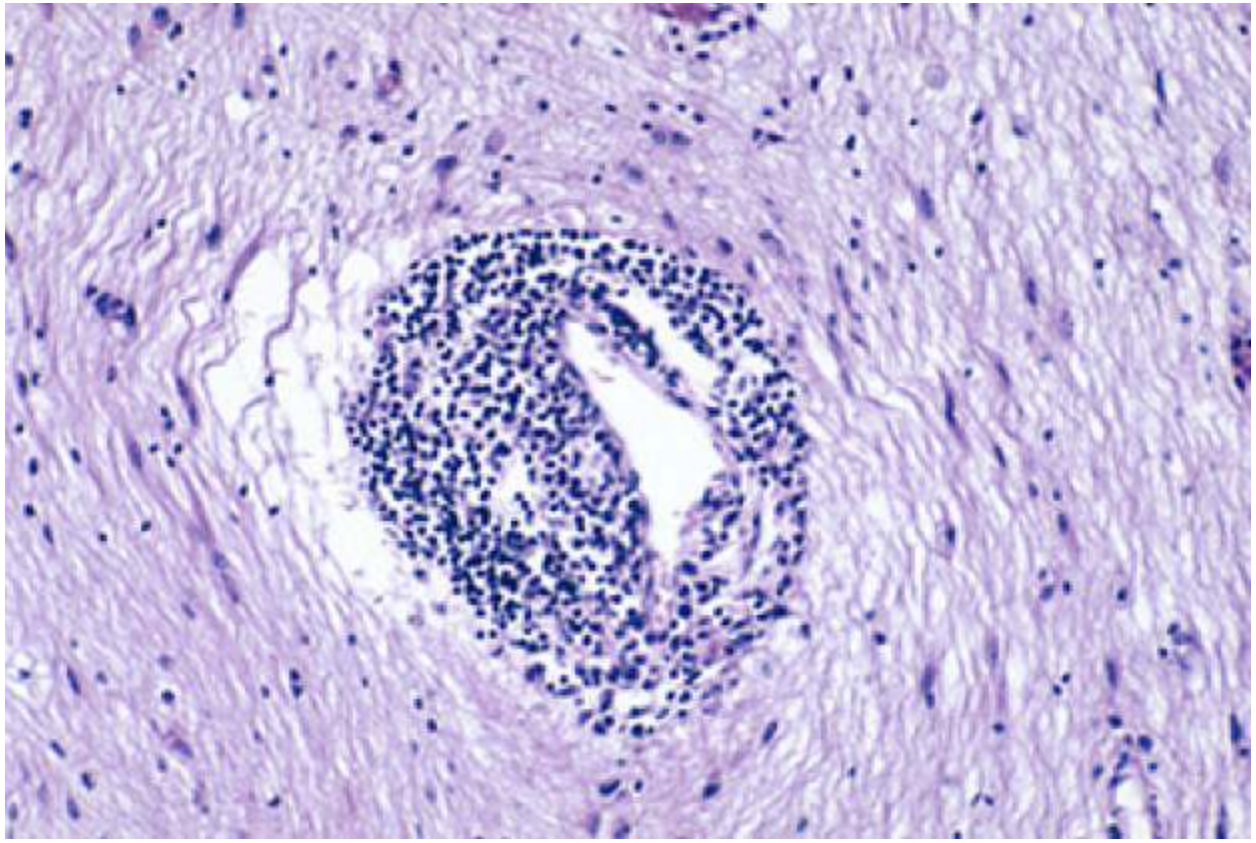
T cells in Multiple Sclerosis

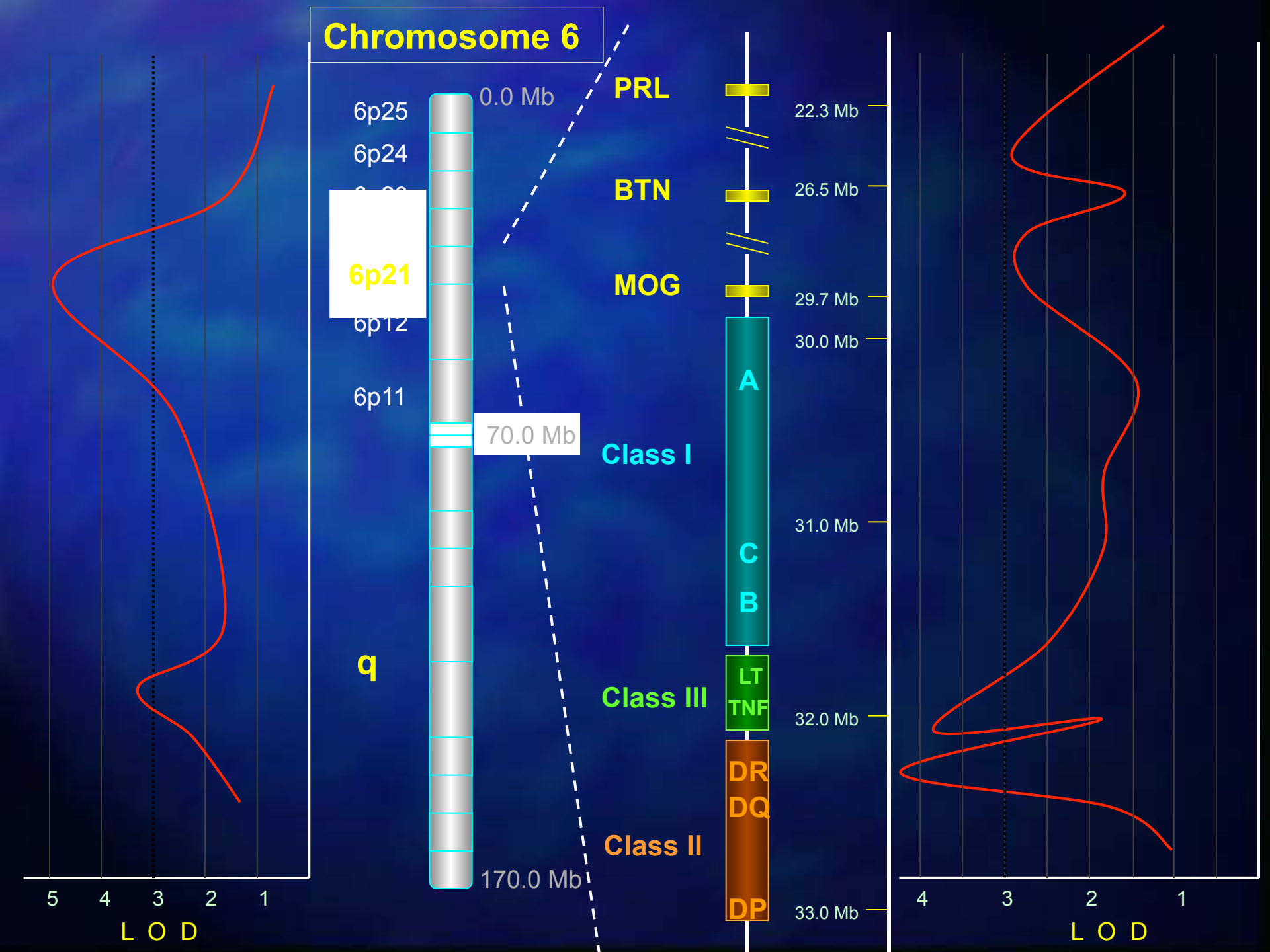


Feature	Pattern I	Pattern II	Pattern III	Pattern IV
Inflammation				
Composition of Infiltrates				
CD3 T cells	197 ± 68	133 ± 18	145 ± 23	134 ± 71
Plasma cells	5.9 ± 1.9	9.3 ± 2.1	5.4 ± 1.6	3.8
Macrophages	1,158 ± 105	931 ± 71	842 ± 91	1,650 ± 30
C9neo	−	++	−	−
Demyelination				
Perivenous pattern	+	+	−	±
Lesion edge	Sharp	Sharp	Ill-defined	Sharp
Concentric pattern	0/10	0/45	8/25	0/3
Oligodendrocytes				
#OG in DM	295 ± 73	249 ± 30	51 ± 24	55 ± 55
DNA frag in OG	±	±	++APO	++PPWM
OG apoptosis	−	−	14–37%	−
Myelin protein loss	Even	Even	MAG ≫ Others	Even
Remyelination				
Shadow plaques	++	++	−	−

Values given in the table represent cells per square millimeter.

#OG = density of oligodendrocytes in inactive demyelinated plaque center; DNA frag in OG = oligodendrocytes showing nuclear DNA fragmentation; OG apoptosis = apoptotic cell death of oligodendrocytes in active lesional areas; MAG = myelin-associated glycoprotein; PPWM = DNA fragmentation in oligodendrocytes in the periplaque white matter.

Lucchinetti et al. Ann Neurol. 2000.


Chromosome 6
6p25
6p24
6p21
6p12
6p11
q
0.0 Mb
70.0 Mb
170.0 Mb
PRL
BTN
MOG
Class I
Class III
Class II
22.3 Mb
26.5 Mb
29.7 Mb
30.0 Mb
31.0 Mb
32.0 Mb
33.0 Mb
A
C
B
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TNF
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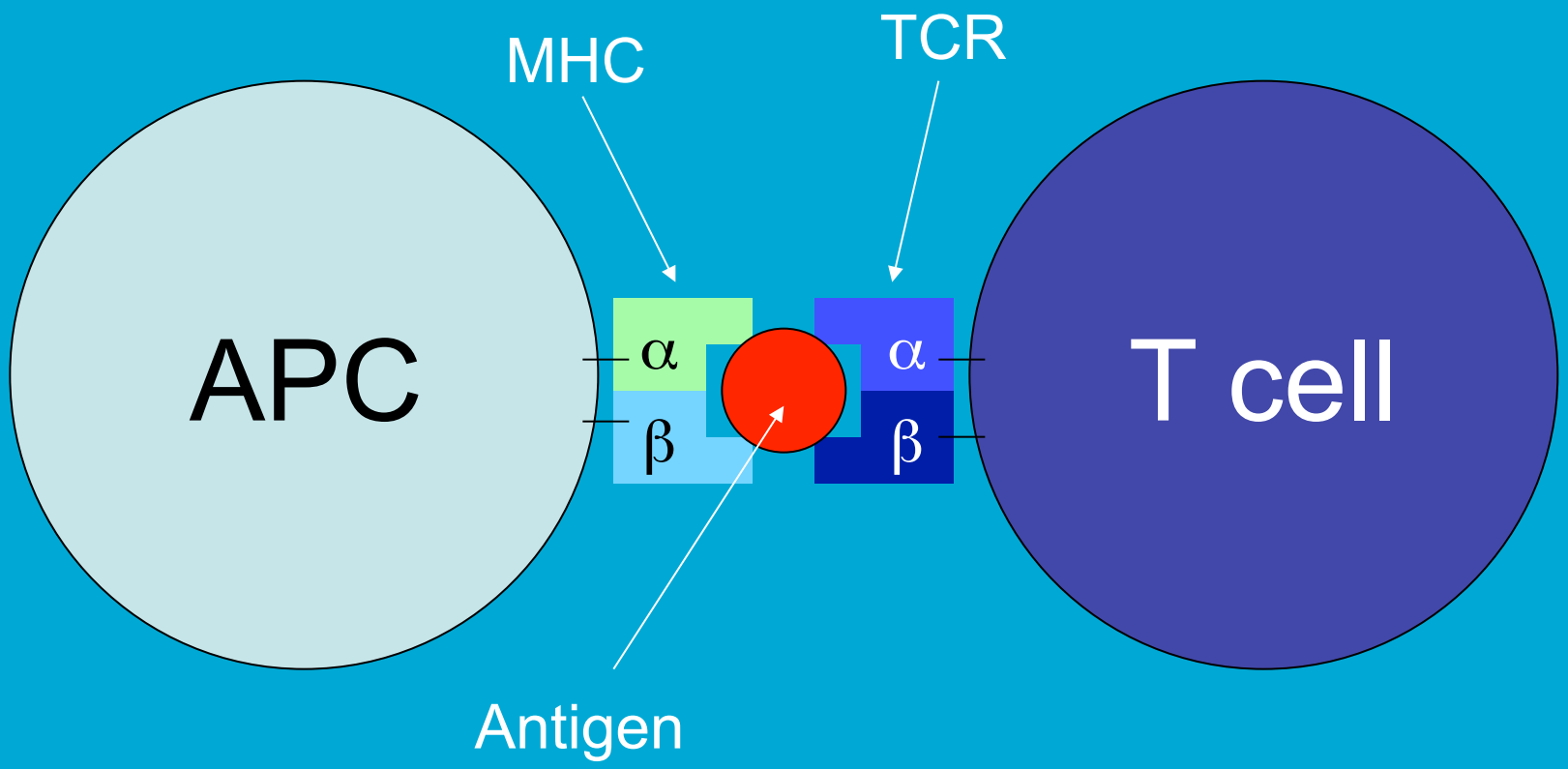
DQ
DP
5 4 3 2 1
L O D
4 3 2 1
L O D


MHC
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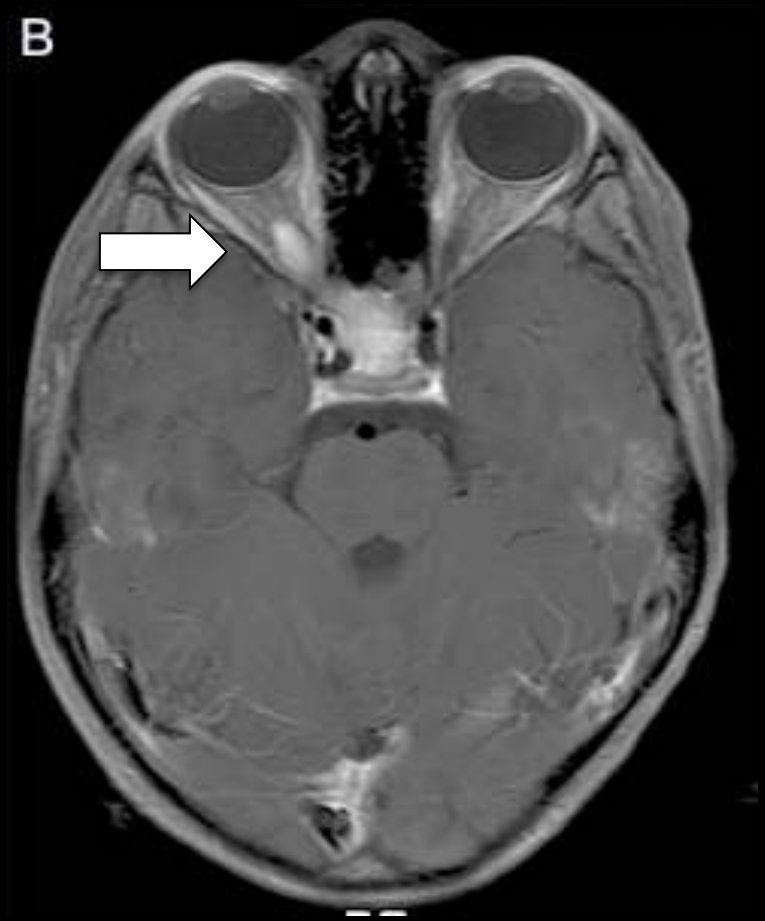
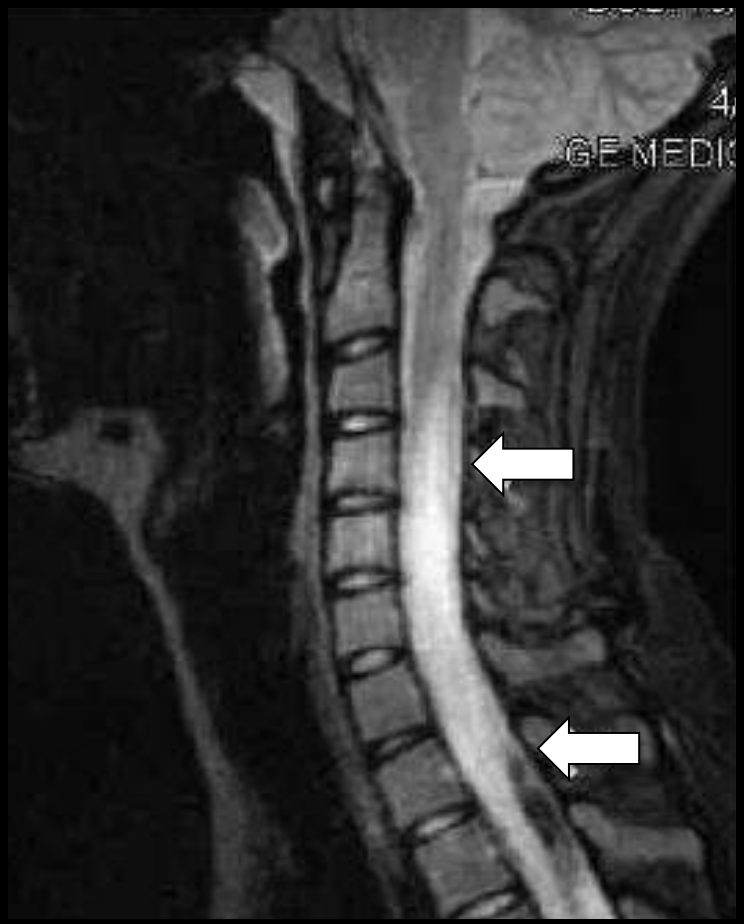
T cells in Neuromyelitis Optica (NMO)

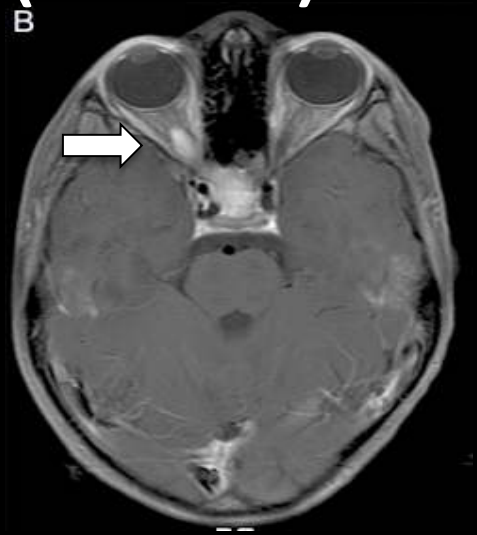
Neuromyelitis Optica (NMO)

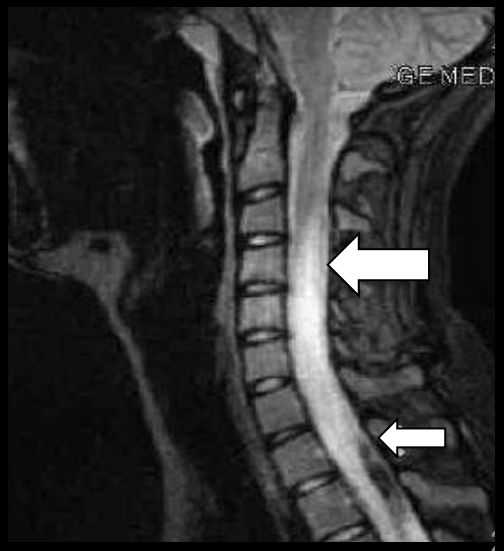




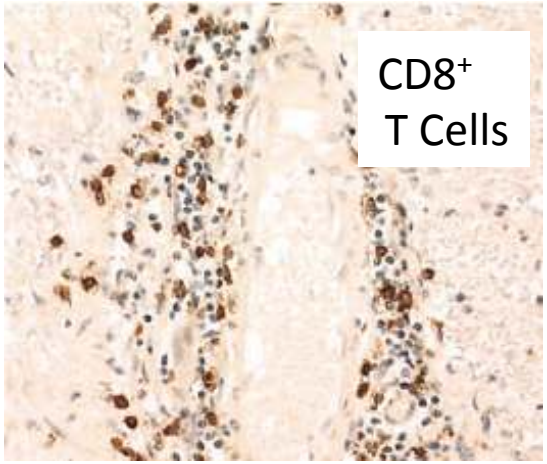
Neuromyelitis Optica (NMO)

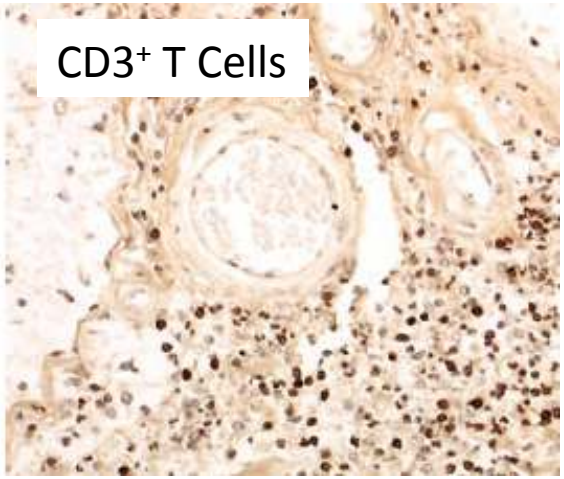
- NMO is a rare syndrome in Western countries: < 1% of CNS demyelinating disease
- Age of onset: Childhood to late adulthood
- Women > men
- Shows a Relapsing Remitting Disease course

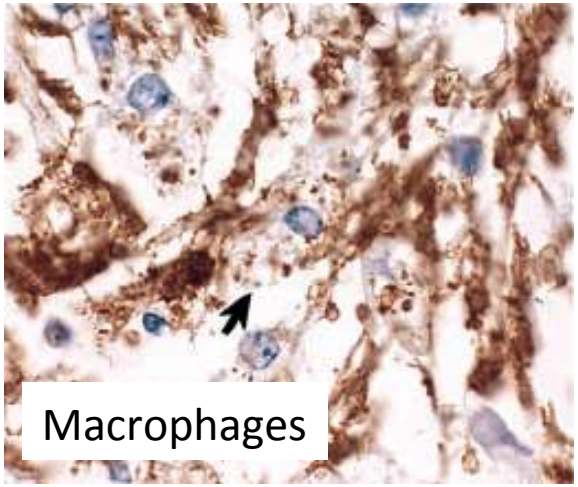


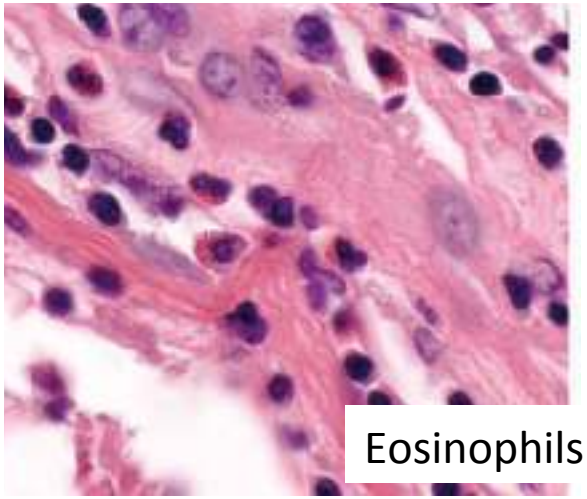


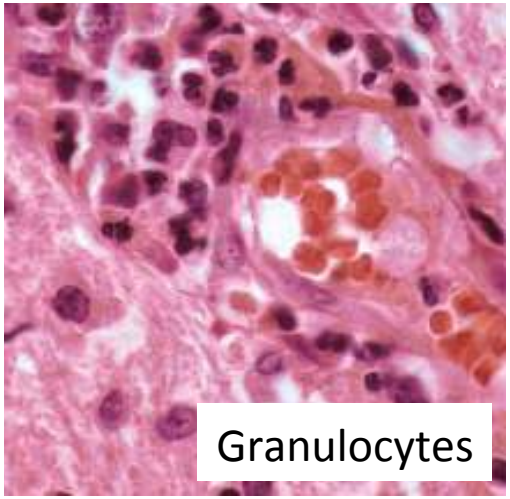
NMO Pathology











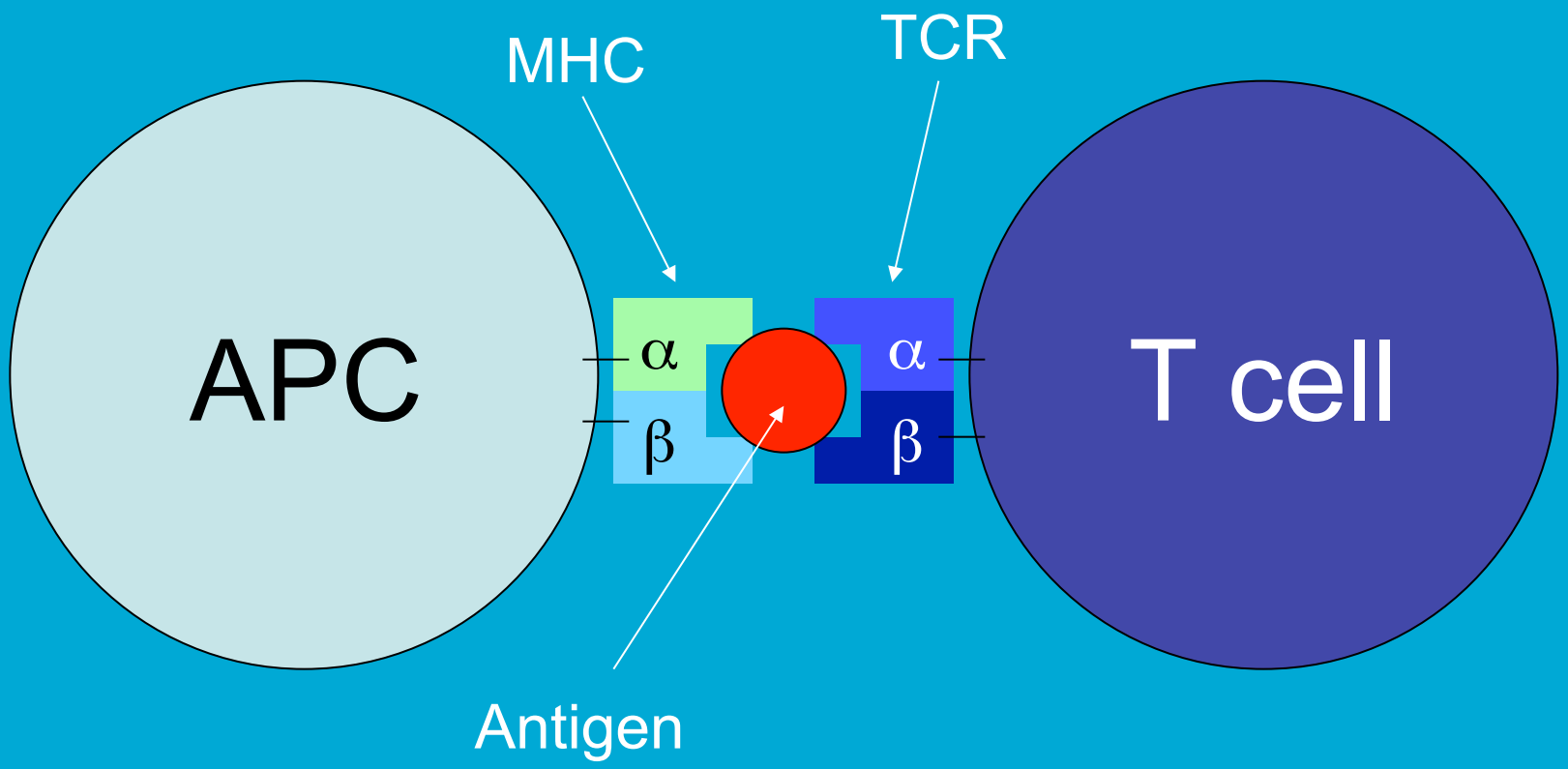
Lucchinetti et al. 2002. Brain.

NMO Human Leukocyte Antigen

Table 2. HLA-DRB allele group frequencies in Brazilian Mulatto patients with neuromyelitis optica spectrum disorders (NMOSD) and in healthy Mulattoes. Significant values ($p < 0.05$) are in boldface

	Mulatto Controls		Mulatto NMO Patients (blanks taken as homozygous)				Mulatto NMO Patients (blanks taken as heterozygous)			
	n^a	Frequency[b]	n^a	Frequecny[b]	p^c	OR (95% CI)[d]	n^a	Frequency[b]	p^c	OR (95% CI)[d]
DRB1										
*01	3	0.0536	9	0.1667	0.0709	3.53 (0.9–13.85)	7	0.1296	0.1985	2.63 (0.64–10.76)
*03	5	0.0893	13	0.2407	**0.0401**	**3.23 (1.07–9.82)**	13	0.2407	**0.0401**	**3.23 (1.07–9.82)**
*04	7	0.1250	4	0.0741	0.5278	0.56 (0.15–2.03)	3	0.0556	0.3212	0.41 (0.1–1.68)
*07	6	0.1071	3	0.0556	0.4897	0.49 (0.12–2.07)	3	0.0556	0.4897	0.49 (0.12–2.07)
*08	6	0.1071	2	0.0370	0.2713	0.32 (0.06–1.66)	2	0.0370	0.2713	0.32 (0.06–1.66)
*09	2	0.0357	0	0.0000	0.4956	0.20 (0.01–4.26)	0	0.0000	0.4956	0.20 (0.01–4.26)
*10	0	0.0000	4	0.0741	0.0548	10.07 (0.53–191.67)	4	0.0741	0.0548	10.07 (0.53–191.67)
*11	5	0.0893	6	0.1111	0.7592	1.28 (0.37–4.45)	5	0.0926	1.0000	1.04 (0.28–3.82)
*12	2	0.0357	0	0.0000	0.4956	0.20 (0.01–4.26)	0	0.0000	0.4956	0.20 (0.01–4.26)
*13	8	0.1429	7	0.1296	1.0000	0.89 (0.3–2.66)	5	0.0926	0.5572	0.61 (0.19–2)
*14	4	0.0714	2	0.0370	0.6790	0.50 (0.09–2.85)	2	0.0370	0.6790	0.50 (0.09–2.85)
*15	7	0.1250	2	0.0370	0.1621	0.27 (0.05–1.36)	1	0.0185	0.0608	0.13 (0.02–1.11)
*16	1	0.0179	2	0.0370	0.6147	2.12 (0.19–24.03)	2	0.0370	0.6147	2.12 (0.19–24.03)
Blank	–	–	–	–	–	–	7	0.1296	–	–
Total	56	1.0000	54	1.0000	**0.0032 ± 0.0014**[e]	–	54	1.0000	**0.0216 ± 0.0011**[e]	–

Brumet al. Multiple Sclerosis Journal. 2010.


MHC
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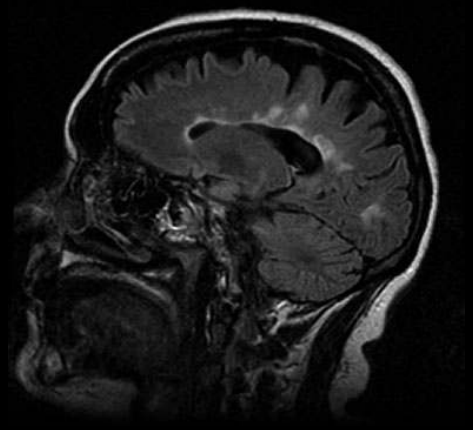
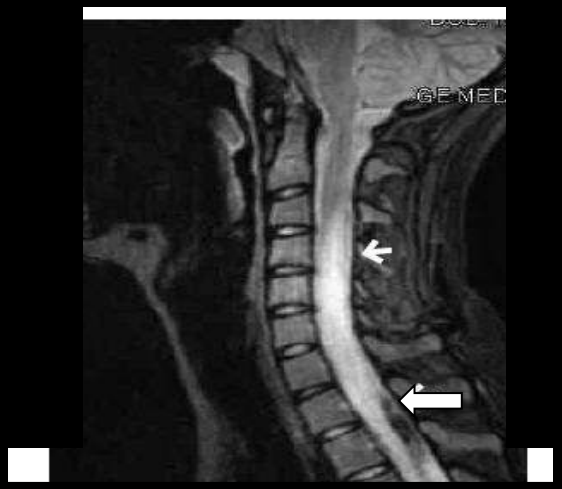
T cell
Antigen

MS VS NMO





- Lesions predominantly in the brain, with lesions extending to the optic nerve and spinal cord
- NMO IgG negative
- Auto-antigen is unknown
- HLA-DRB1*15:01

- Lesions predominantly in the optic nerve and spinal cord
- NMO IgG positive
- Auto-antigen is thought to be AQP4
- HLA-DRB1*03:01

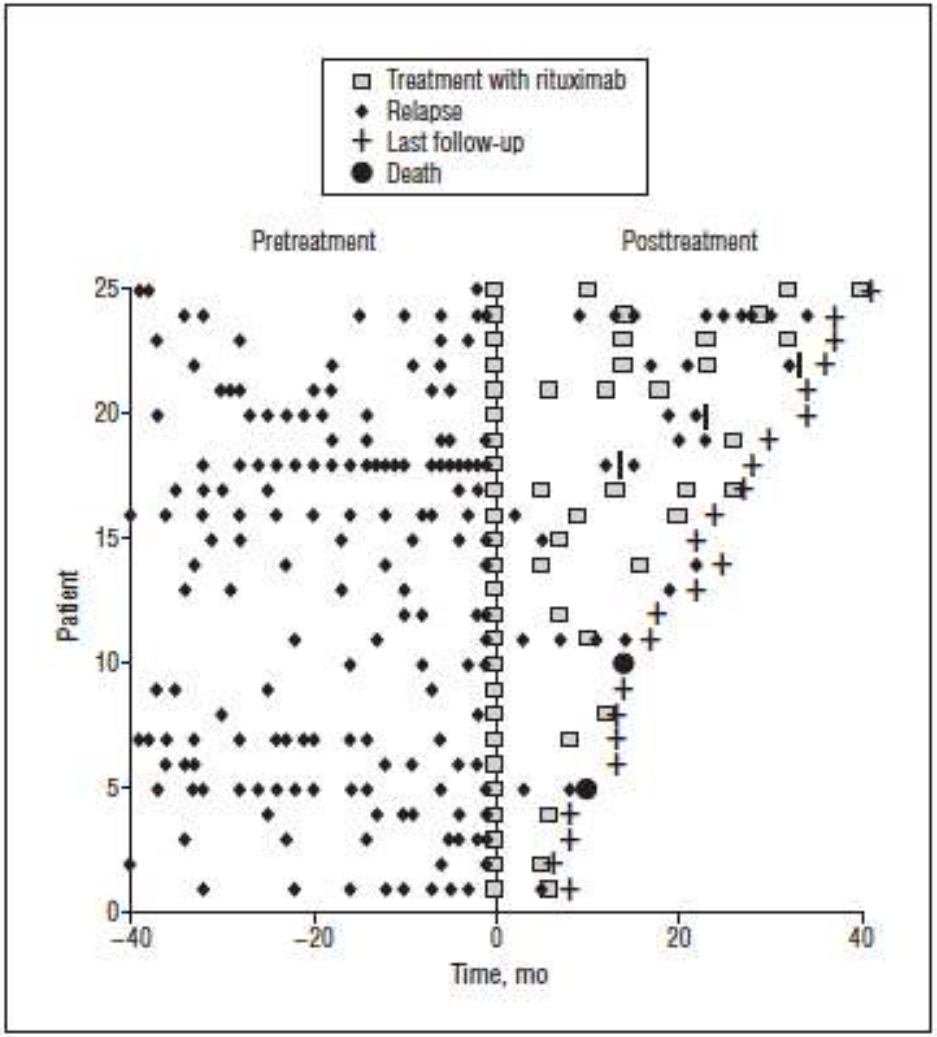
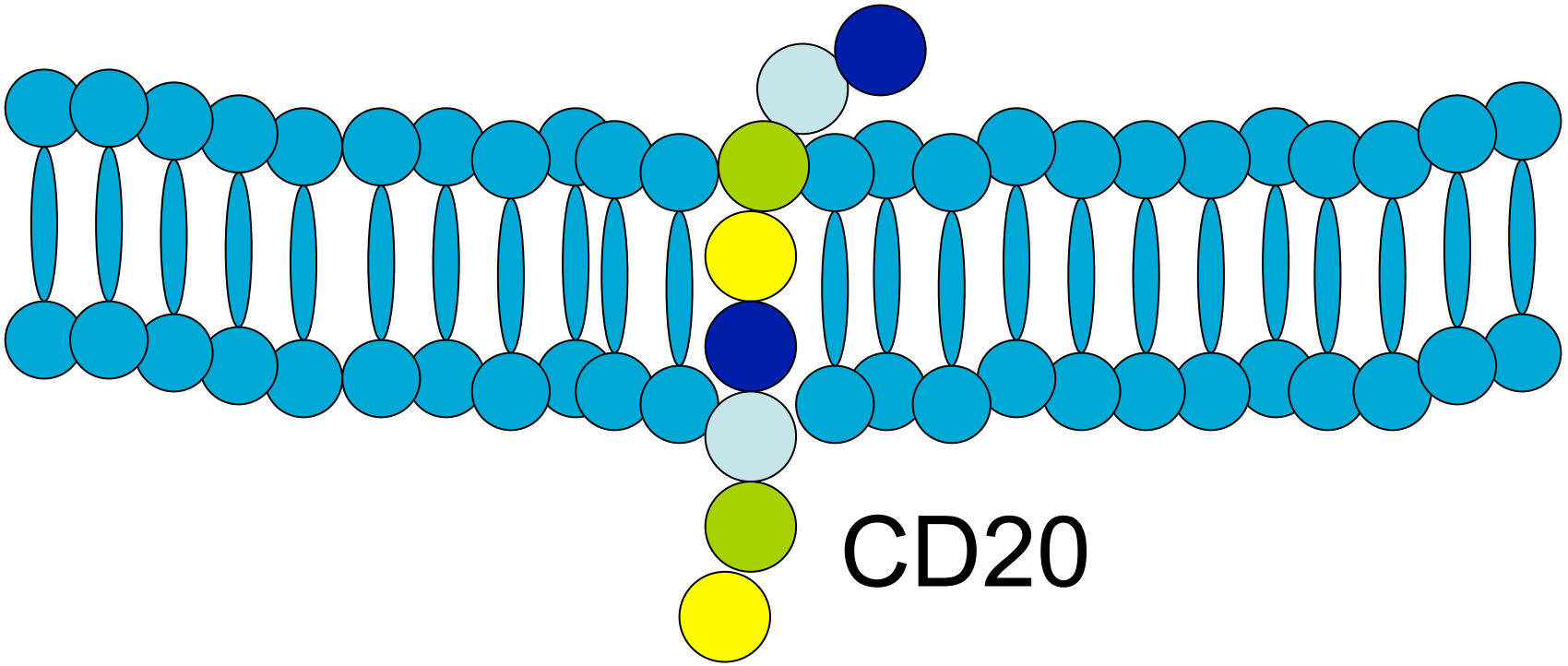
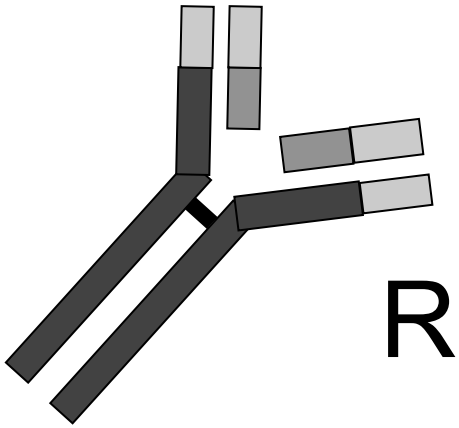


Figure. Relapses in patients with neuromyelitis optica before and after treatment with rituximab.

Jacob et al. Arch Neurol. 2008.





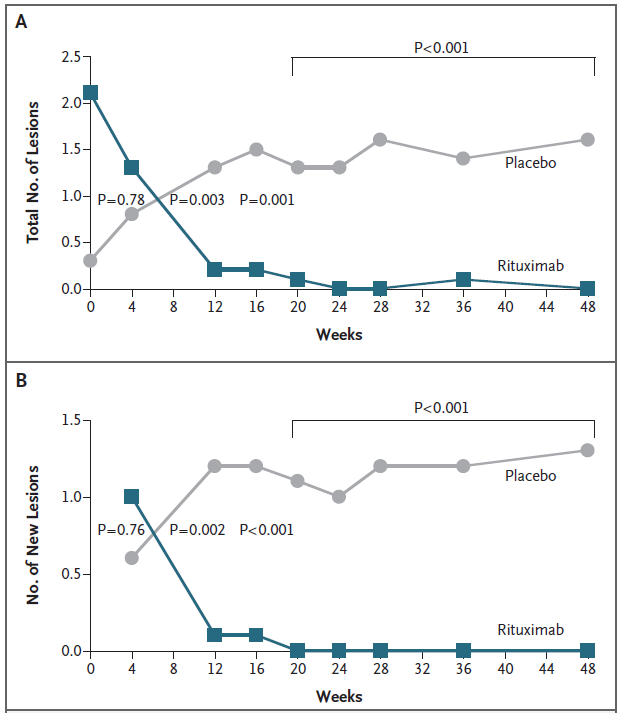
Rituximab

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*



Hauser et al. NEJM. 2008.

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Journal of Neuroimmunology xx (2006) xxx–xxx

Journal of
Neuroimmunology

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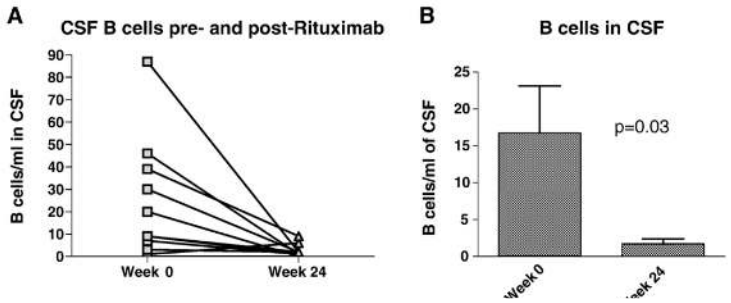
Rituximab reduces B cells and T cells in cerebrospinal fluid of multiple sclerosis patients

Anne H. Cross [a,*], Jennifer L. Stark [a], Joanne Lauber [a], Michael J. Ramsbottom [a], Jeri-Anne Lyons [b]



Cross et al. J Neuroimmunol. 2006.

ELSEVIER

Journal of Neuroimmunology xx (2006) xxx–xxx

Journal of
Neuroimmunology

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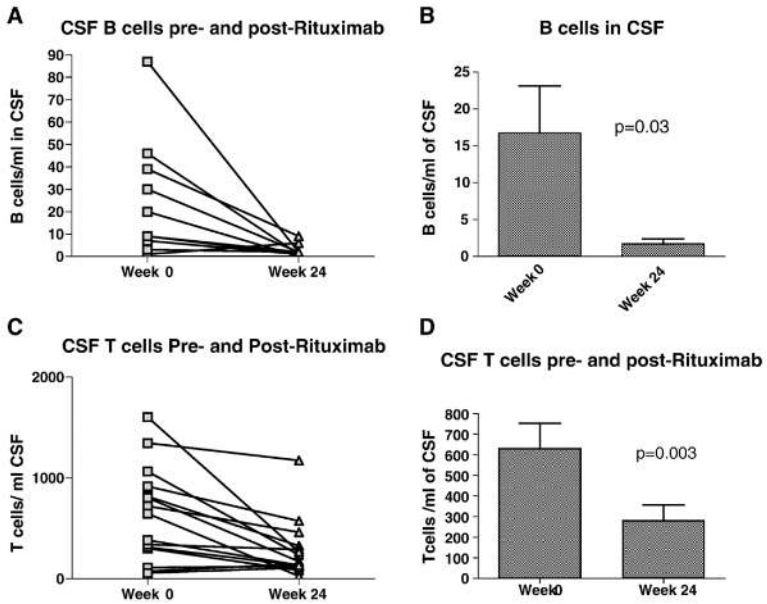


Cross et al. J Neuroimmunol. 2006.

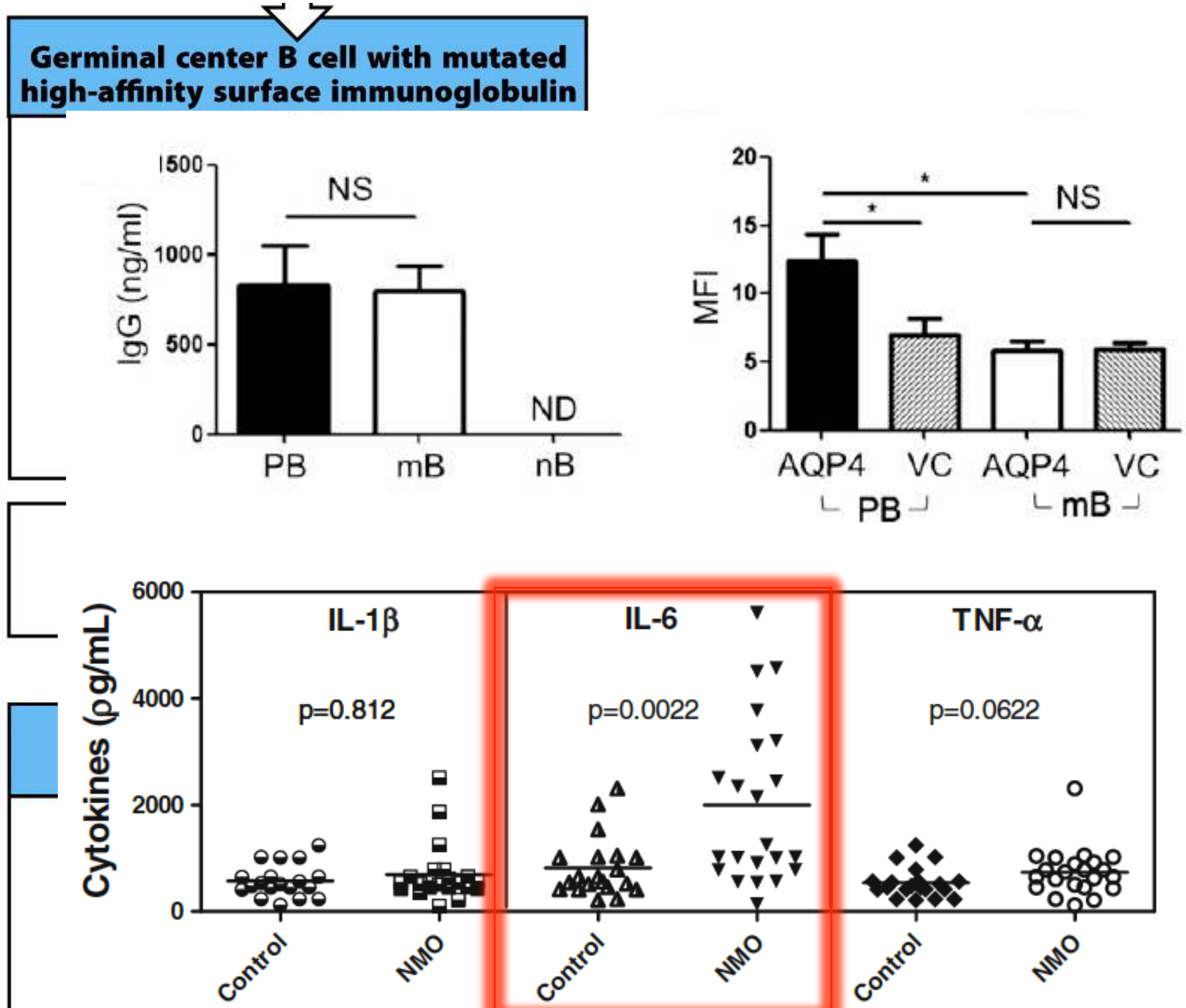
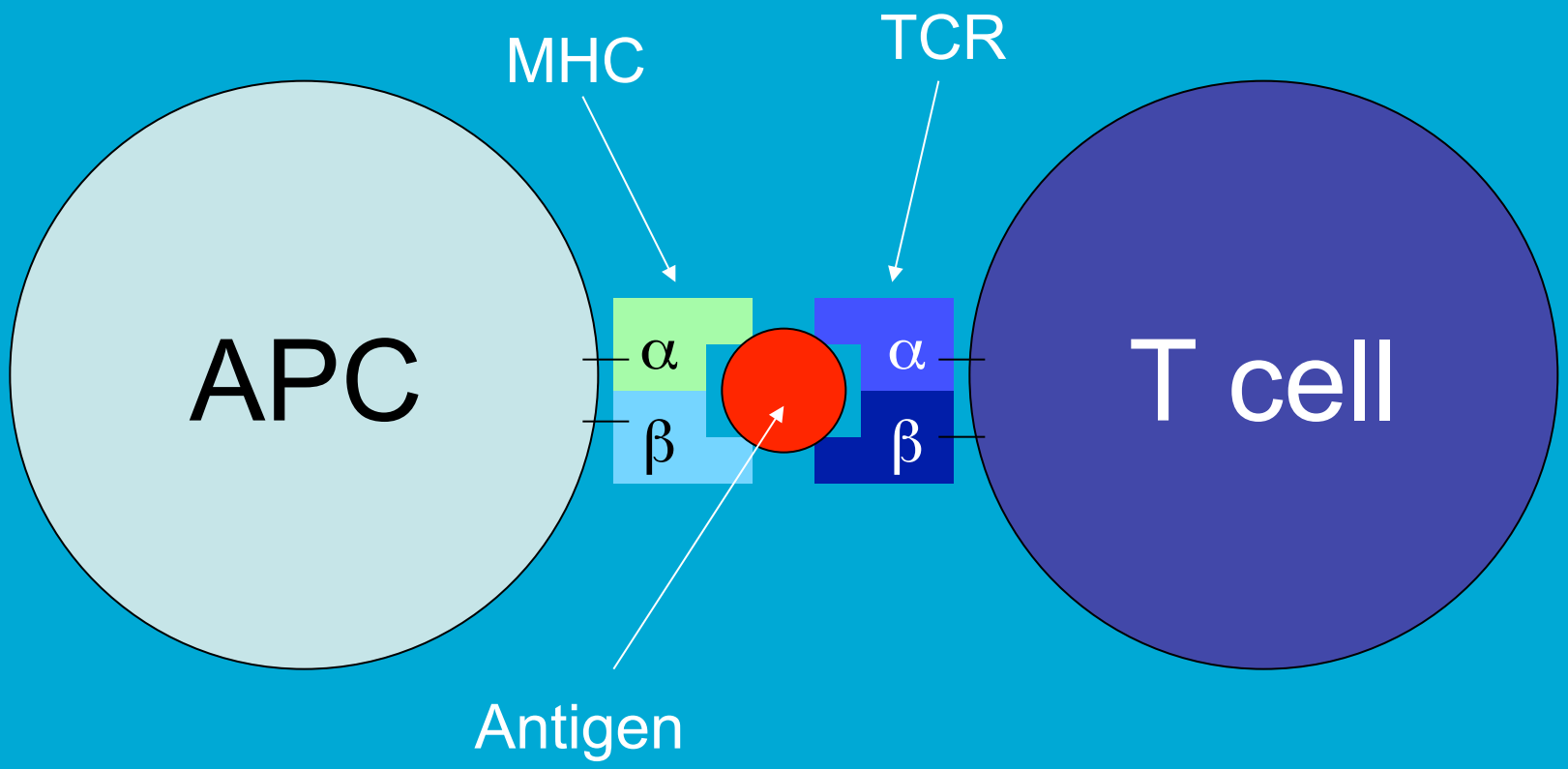


Figure 9-11 part 2 of 2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Antigen

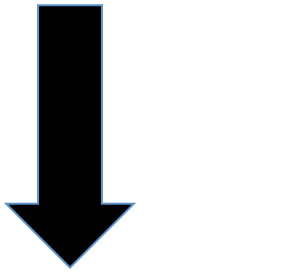
HLA-DRB1 Polymorphism Determines Susceptibility to Autoimmune Thyroiditis in Transgenic Mice: Definitive Association with HLA-DRB1*0301 (DR3) Gene

By Yi-chi M. Kong,* Lesley C. Lomo,* Reinhard W. Motte,‡ Alvaro A. Giraldo,‡ Jean Baisch,§ Gudrun Strauss,‖ Gunter J. Hämmerling,‖ and Chella S. David§

HLA-DRB1*03:01 $^{+/+}$

X

H2Ab$^{-/-}$



HLA-DRB1*03:01 $^{+/+}$ H2Ab$^{-/-}$

Kong et al. J Exp Med. 1996.

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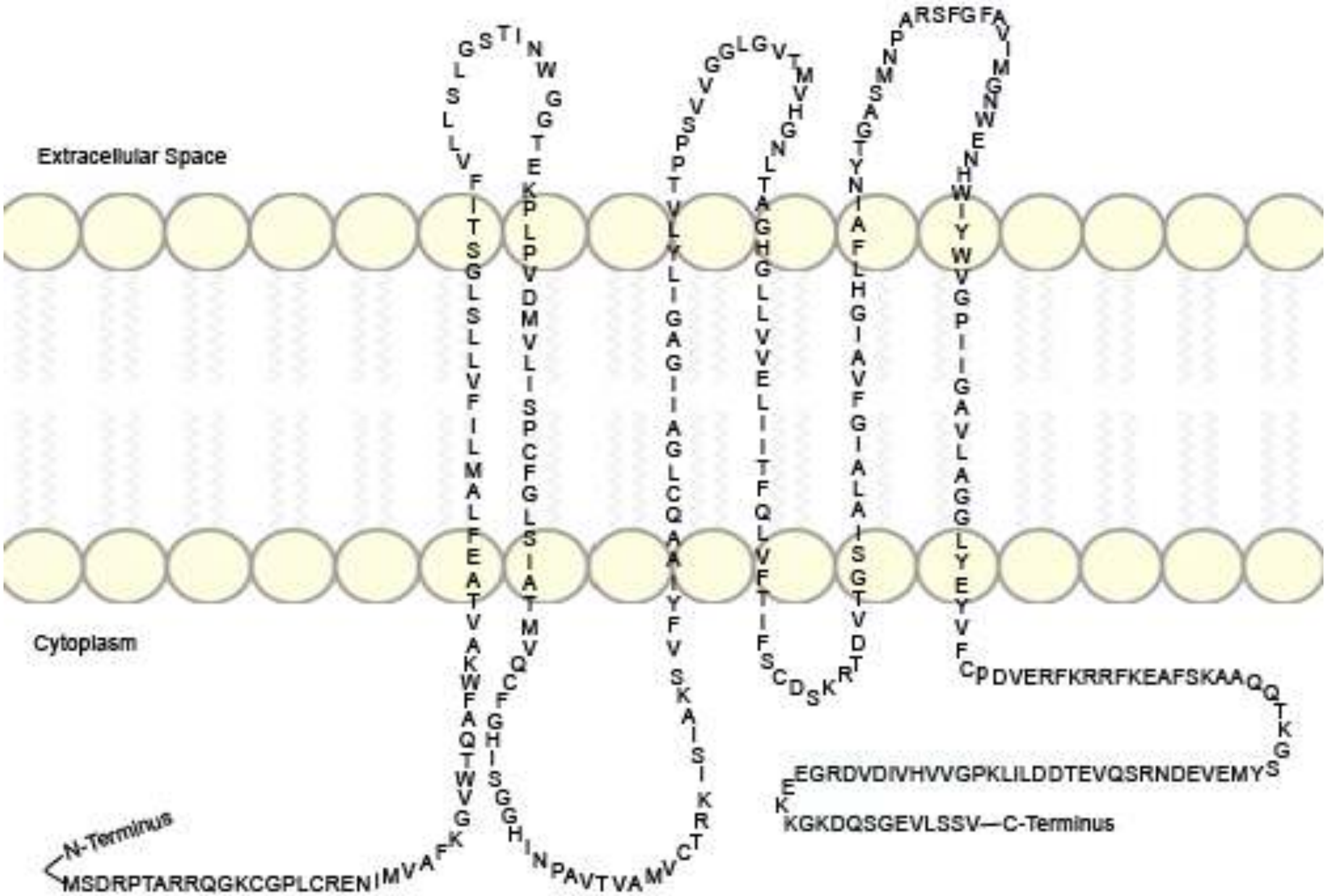
Aquaporin 4



Aquaporin 4 Overlapping, 20-Amino-Acid Long Peptides.

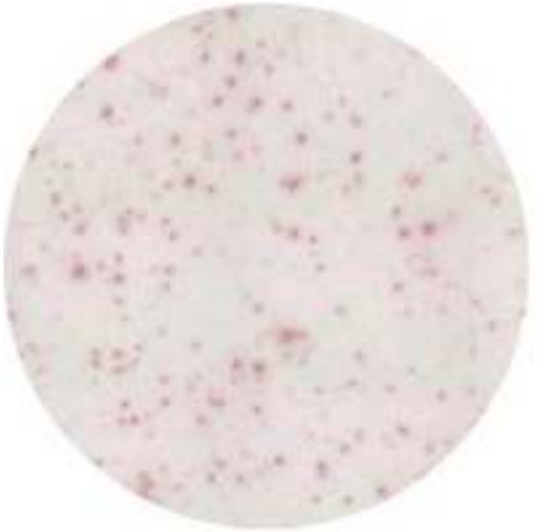
Peptide Number	Sequence	AQP4	Peptide Number	Sequence	AQP4
1	MSDRPTARRWGKCGPLCTRE	1-20	17	LVELIITFQLVFTIFASCDS	161-180
2	GKCGPLCTRENIMVAFKGVW	11-30	18	VFTIFASCDSKRTDVTGSIA	171-190
3	NIMVAFKGVWTQAFWKAVTA	21-40	19	KRTDVTGSIALAIGFSVAIG	181-200
4	TQAFWKAVTAEFLAMLIFVL	31-50	20	LAIGFSVAIGHLFAINYTGA	191-210
5	EFLAMLIFVLLSLGSTINWG	41-60	21	HLFAINYTGASMNPARSFGP	201-220
6	LSLGSTINWGGTEKPLPVDM	51-70	22	SMNPARSFGPAVIMGNWENH	211-230
7	GTEKPLPVDMVLISLCFGLS	61-80	23	AVIMGNWENHWIYWVGPIIG	221-240
8	VLISLCFGLSIATMVQCFGH	71-90	24	WIYWVGPIIGAVLAGGLYEY	231-250
9	IATMVQCFGHISGGHINPAV	81-100	25	AVLAGGLYEYVFCPDVEFKR	241-260
10	ISGGHINPAVTVAMVCTRKI	91-110	26	VFCPDVEFKRRFKEAFSKAA	251-270
11	TVAMVCTRKISIAKSVFYIA	101-120	27	RFKEAFSKAAQQTKGSYMEV	261-280
12	SIAKSVFYIAAQCLGAIIGA	111-130	28	QQTKGSYMEVEDNRSQVETD	271-290
13	AQCLGAIIGAGILYLVTPPS	121-140	29	EDNRSQVETDDLILKPGVVH	281-300
14	GILYLVTPPSVVGGLGVTMV	131-150	30	DLILKPGVVHVIDVDRGEEK	291-310
15	VVGGLGVTMVHGNLTAGHGL	141-160	31	VIDVDRGEEKKGKDQSGEVL	301-320
16	HGNLTAGHGLLVELIITFQL	151-170	32	VDRGEEKKGKDQSGEVLSSV	304-323

100 ugs of whole protein hAQP4 emulsified in Complete Freuds Adjuvant (CFA)

Day 10

Aquaporin 4 Overlapping, 20-Amino-Acid Long Peptides.

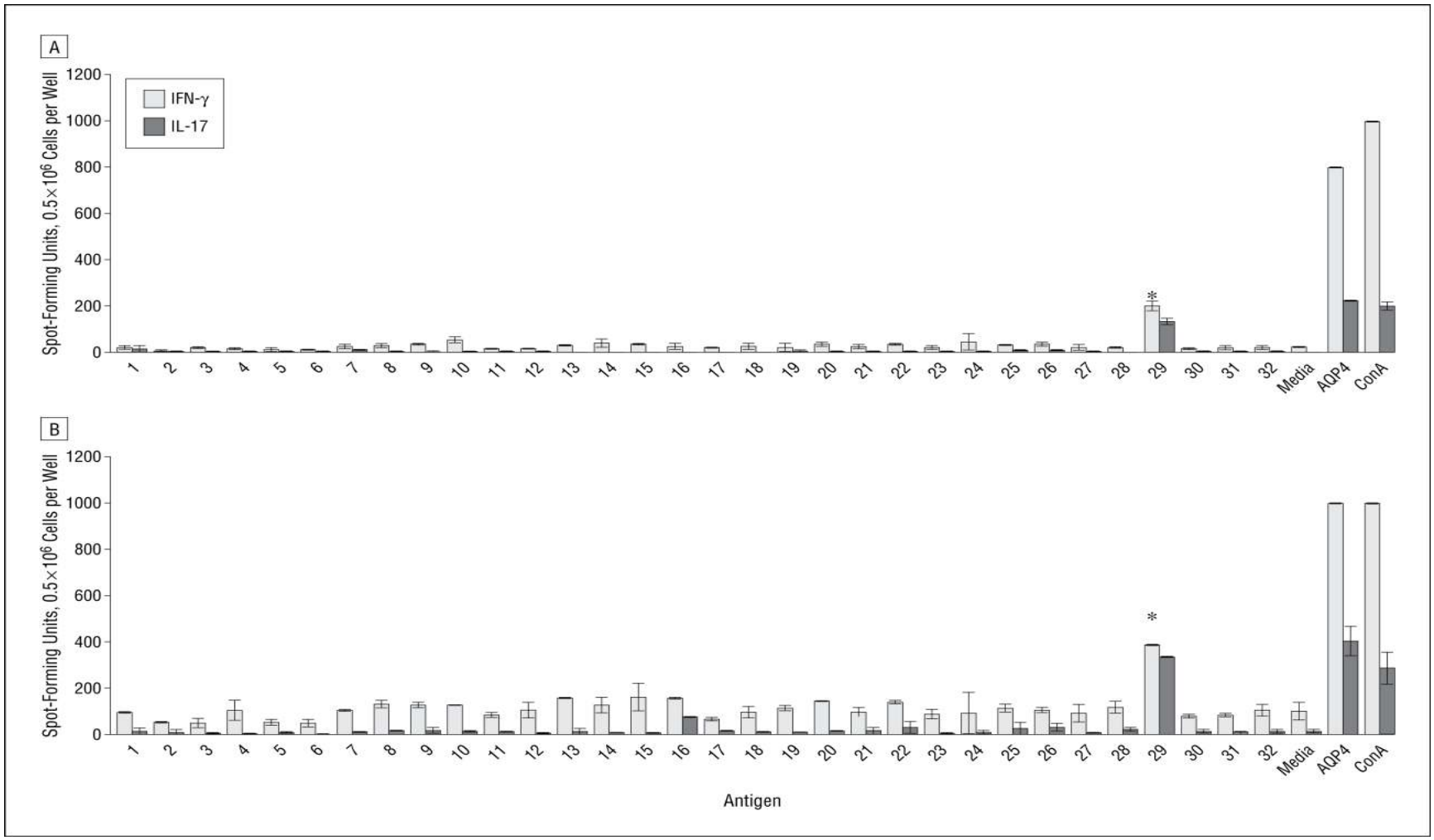
Peptide Number	Sequence	AQP4	Peptide Number	Sequence	AQP4
1	MSDRPTARRWGKCGPLCTRE	1-20	17	LVELIITFQLVFTIFASCDS	161-180
2	GKCGPLCTRENIMVAFKGVW	11-30	18	VFTIFASCDSKRTDVTGSIA	171-190
3	NIMVAFKGVWTQAFWKAVTA	21-40	19	KRTDVTGSIALAIGFSVAIG	181-200
4	TQAFWKAVTAEFLAMLIFVL	31-50	20	LAIGFSVAIGHLFAINYTGA	191-210
5	EFLAMLIFVLLSLGSTINWG	41-60	21	HLFAINYTGASMNPARSFGP	201-220
6	LSLGSTINWGGTEKPLPVDM	51-70	22	SMNPARSFGPAVIMGNWENH	211-230
7	GTEKPLPVDMVLISLCFGLS	61-80	23	AVIMGNWENHWIYWVGPIIG	221-240
8	VLISLCFGLSIATMVQCFGH	71-90	24	WIYWVGPIIGAVLAGGLYEY	231-250
9	IATMVQCFGHISGGHINPAV	81-100	25	AVLAGGLYEYVFCPDVEFKR	241-260
10	ISGGHINPAVTVAMVCTRKI	91-110	26	VFCPDVEFKRRFKEAFSKAA	251-270
11	TVAMVCTRKISIAKSVFYIA	101-120	27	RFKEAFSKAAQQTKGSYMEV	261-280
12	SIAKSVFYIAAQCLGAIIGA	111-130	28	QQTKGSYMEVEDNRSQVETD	271-290
13	AQCLGAIIGAGILYLVTPPS	121-140	29	EDNRSQVETDDLILKPGVVH	281-300
14	GILYLVTPPSVVGGLGVTMV	131-150	30	DLILKPGVVHVIDVDRGEEK	291-310
15	VVGGLGVTMVHGNLTAGHGL	141-160	31	VIDVDRGEEKKGKDQSGEVL	301-320
16	HGNLTAGHGLLVELIITFQL	151-170	32	VDRGEEKKGKDQSGEVLSSV	304-323



Incubate cells taken from the spleen and lymph nodes (LN) with overlapping peptides for 48 hours

→ ELISpot Assays for IFN-gamma, and IL-17

Peptide #29 ($AQP4_{281-300}$) induces a Th_1 and Th17 immune response



Arellano et al. Arch Neurol. 2012.

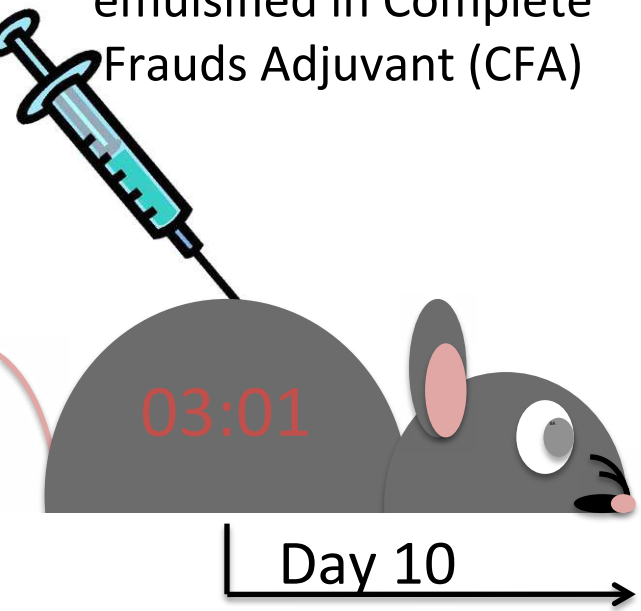
Identifying the immunogenic region of AQP4 $_{281\text{-}300}$

$AQP4_{280\text{-}301}$ Overlapping Peptides

Number	AA	Sequence
1	280-294	VEDNRSQVETDDLIL
2	281-295	EDNRSQVETDDLILK
3	282-296	DNRSQVETDDLILKP
4	283-297	NRSQVETDDLILKPG
5	284-298	RSQVETDDLILKPGV
6	285-299	SQVETDDLILKPGVV
7	286-300	QVETDDLILKPGVVH
8	287-301	VETDDLILKPGVVHV

Arellano et al. Arch Neurol. 2012.

100 ugs of $AQP4_{281-300}$ emulsified in Complete Frauds Adjuvant (CFA)



$AQP4_{280-301}$ Overlapping Peptides

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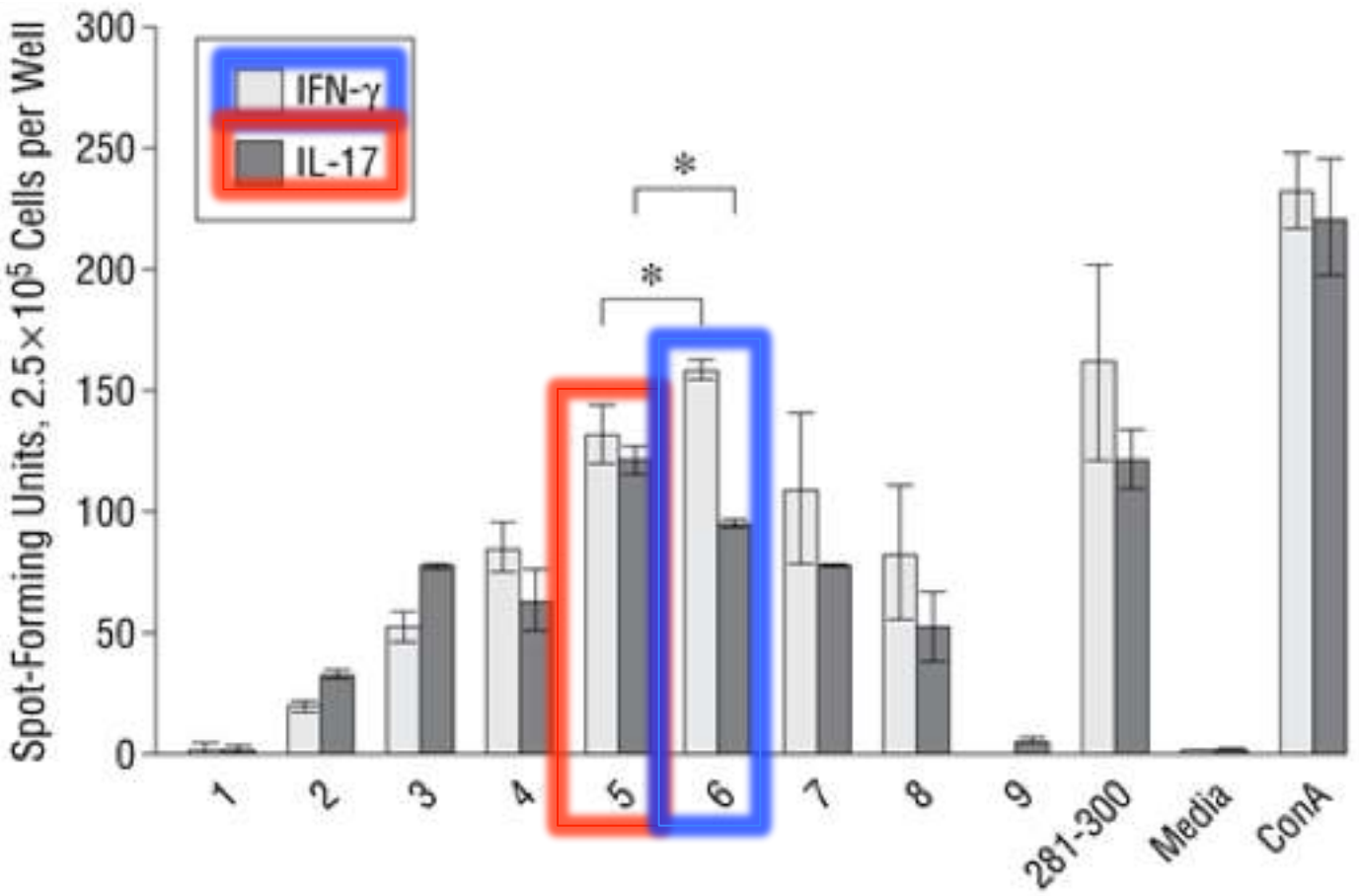
6	285-299	SQVETDDLILKPGVV
7	286-300	QVETDDLILKPGVVH
8	287-301	VETDDLILKPGVVHV

Incubate cells taken from the lymph nodes (LN) with overlapping peptides for 48 hours → ELISpot Assays for IFN-gamma, and IL-17

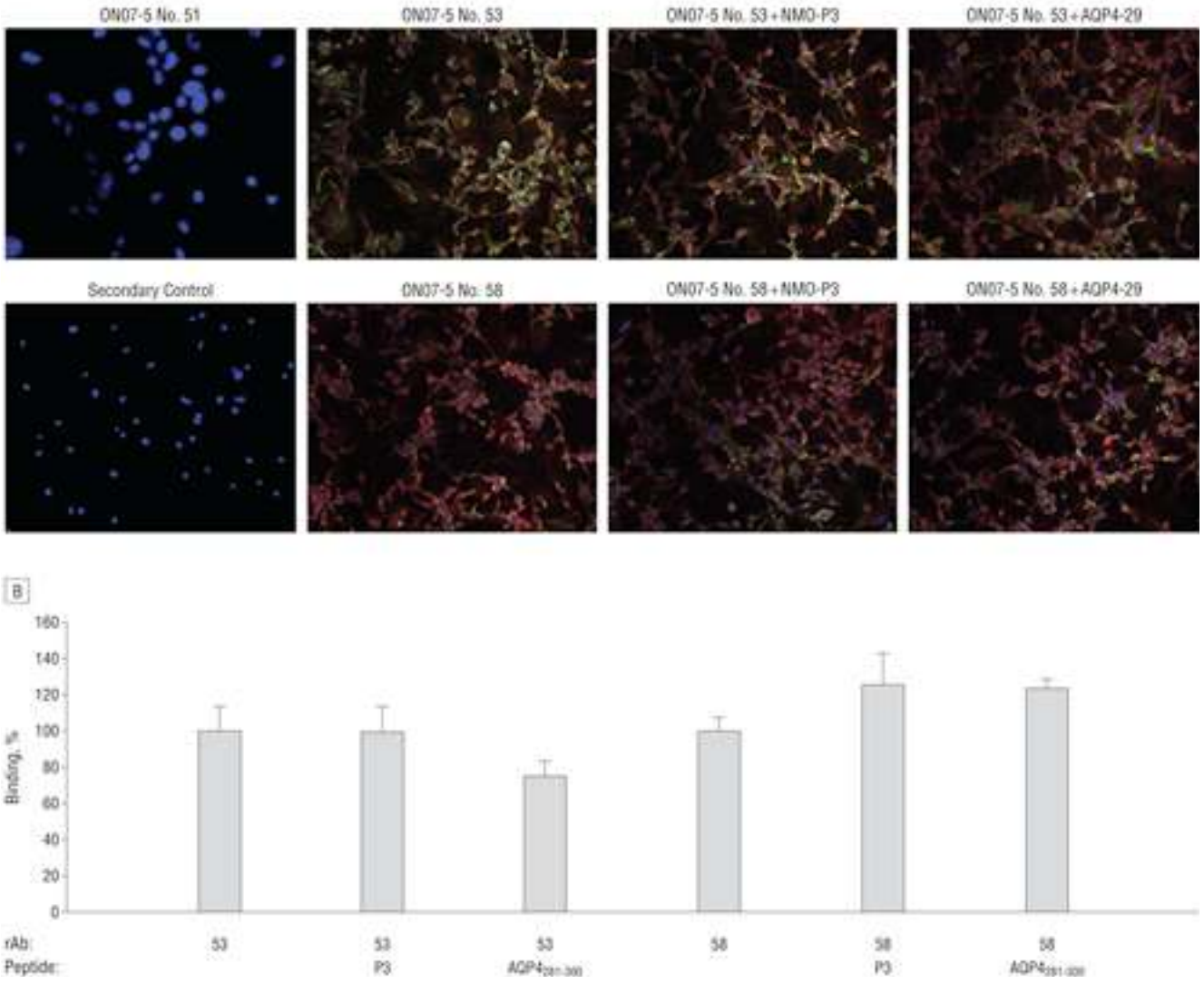
Arellano et al. Arch Neurol. 2012.

$AQP4_{284-299}$ is the immunogenic region of $AQP4_{281-300}$



Arellano et al. Arch Neurol. 2012.

$AQP4_{281-300}$ does not inhibit AQP4 antibody binding



Arellano et al. Arch Neurol. 2012.

Conclusion

- $AQP4_{281\text{-}300}$ is an immunogenic peptide that stimulates a Th_1 and Th_{17} immune response in HLA-DRB1* 03.01 transgenic mice

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- $AQP4_{284\text{-}299}$ is the immunogenic region of $AQP4_{281\text{-}300}$
  - $AQP4_{284\text{-}298}$ leads to a Th_{17} immune response
  - $AQP4_{285\text{-}299}$ leads to a Th_1 immune response

Conclusion

- $AQP4_{281-300}$ is an immunogenic peptide that stimulates a Th_1 and Th_{17} immune response in HLA-DRB1* 03.01 transgenic mice
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- $CD4^+$ T cells proliferate in response to $hAQP4_{284-299}$

Conclusion

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- $AQP4_{284-299}$ is the immunogenic region of $AQP4_{281-300}$
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- $CD4^+$ T cells proliferate in response to $hAQP4_{284-299}$
- $AQP4_{281-300}$ does not inhibit NMO IgG binding to astrocytes

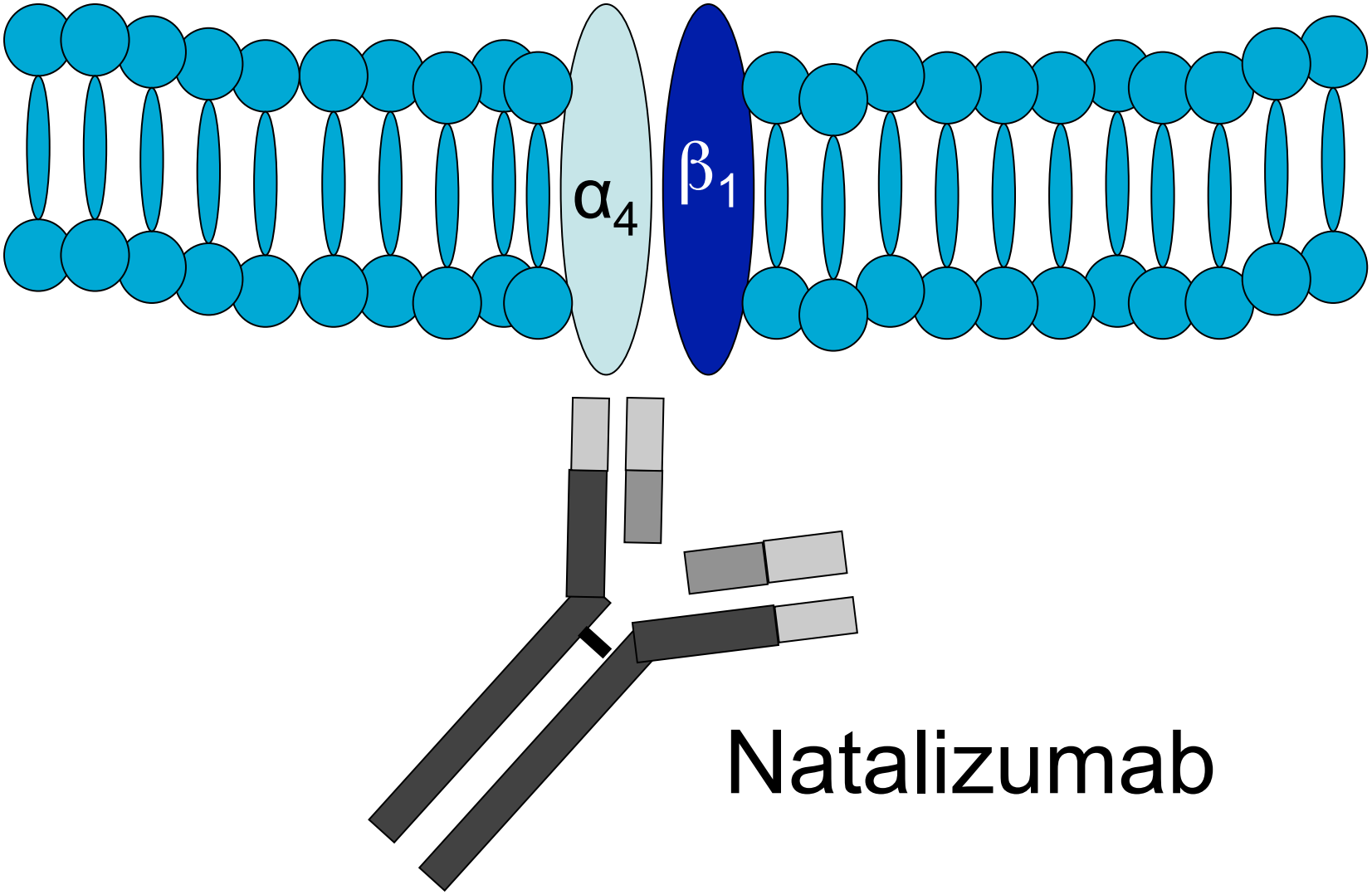
Approved therapies for MS

®Avonex	RRMS	i.m.	qwk
®Betaseron	RRMS	s.c.	qod
®Rebif	RRMS	s.c.	tiw
®Extavia	RRMS	s.c.	qod
®Copaxone	RRMS	s.c.	qdaily
®Novantrone	Relapsing forms	i.v.	q3months
®Tysabri	RRMS	i.v.	qmonth
®Gilenya	RRMS	p.o.	bid
® Aubagio	RRMS	p.o.	qdaily

Approved therapies for MS

®Tysabri	RRMS	i.v.	qmonth

VLA-4



Circulation

Central Nervous System

T cell

T cell

T cell

T cell adhesion

T cell

T cell rolling

T cell

APC

T cell

T cell activation

T cell

B cell

T cell

B cell – T cell cross-activation

Chemoattraction

CNS APC

T cell

T cell re-activation

Plasma cell

Memory B cell

Antibodies & Complement

Inflammatory mediators

MBP

PLP

Oligo-dendendrocyte

Activation of Na^+ channels

K^+ Na^+

NA^+

Ca^{2+} Na^+

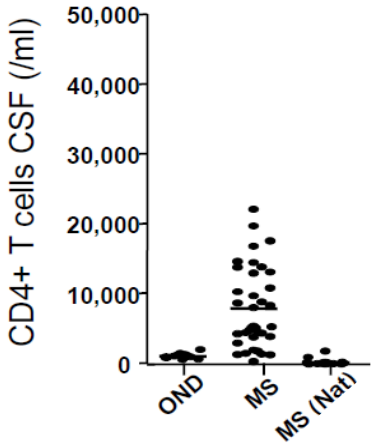
Reverse Na^+ Ca^{2+} exchange

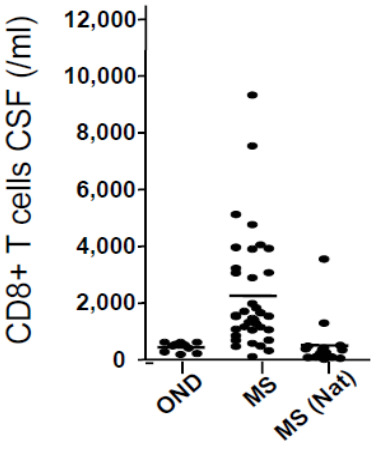
Inflammation

Energy depletion

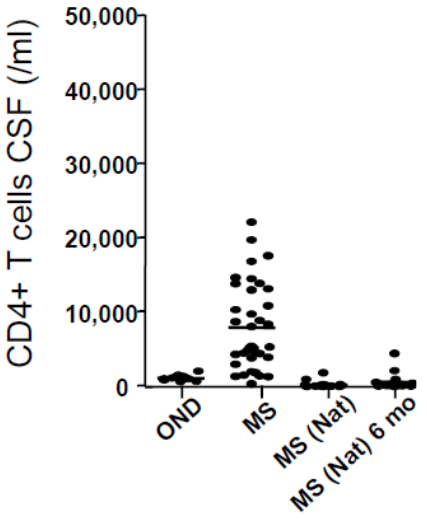
Failure of Na/K ATPase

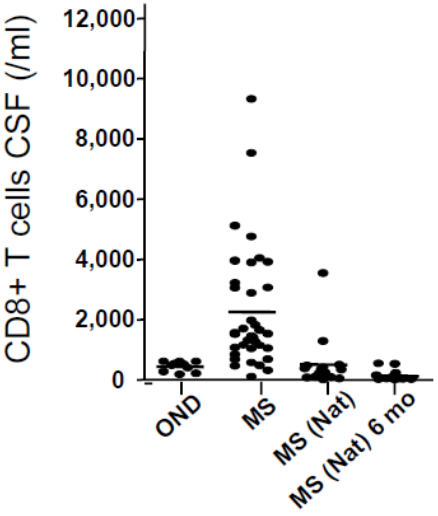
Hypoxia, ischemia





Stuve et al. Neurology. 2009.





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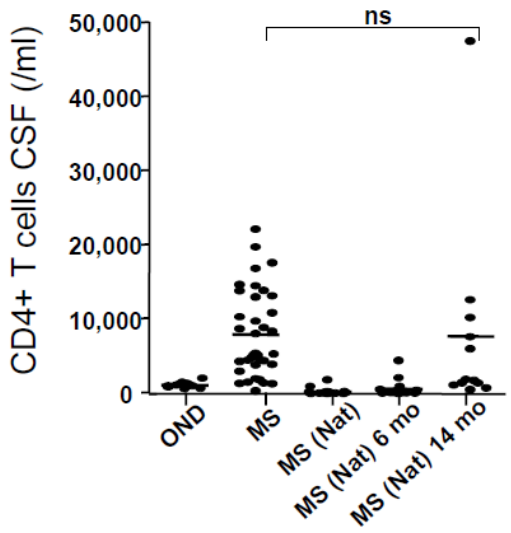

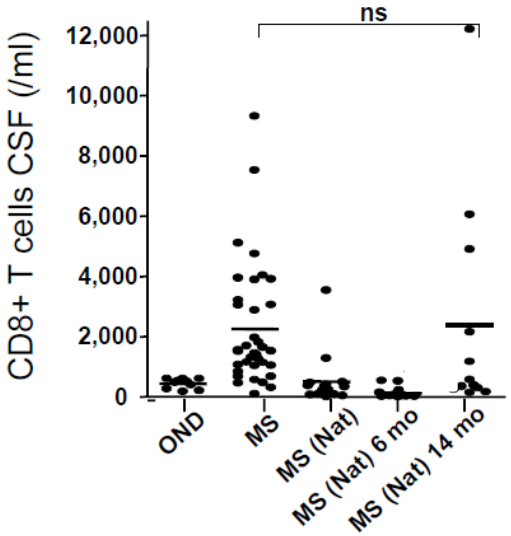

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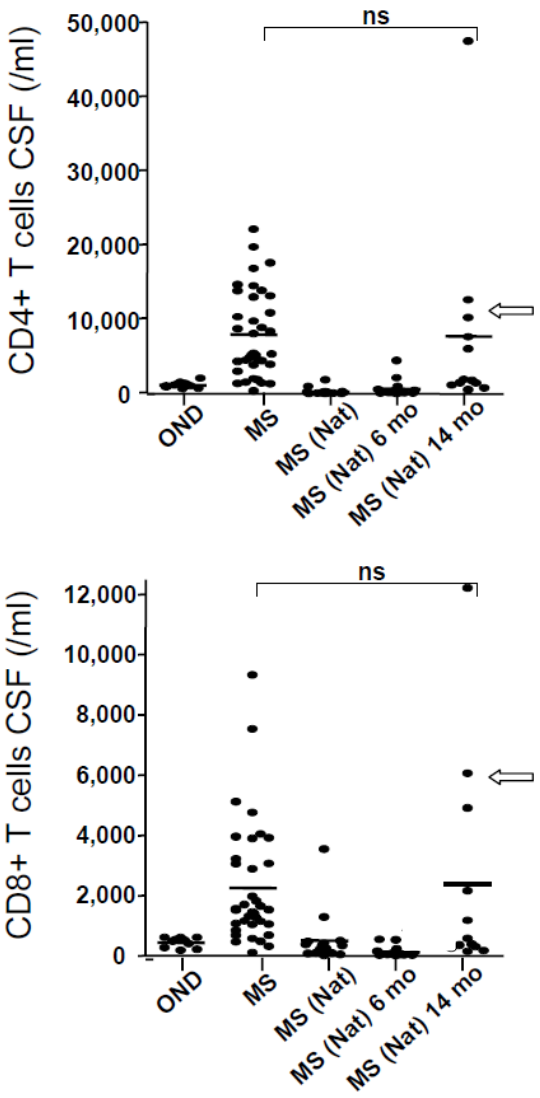
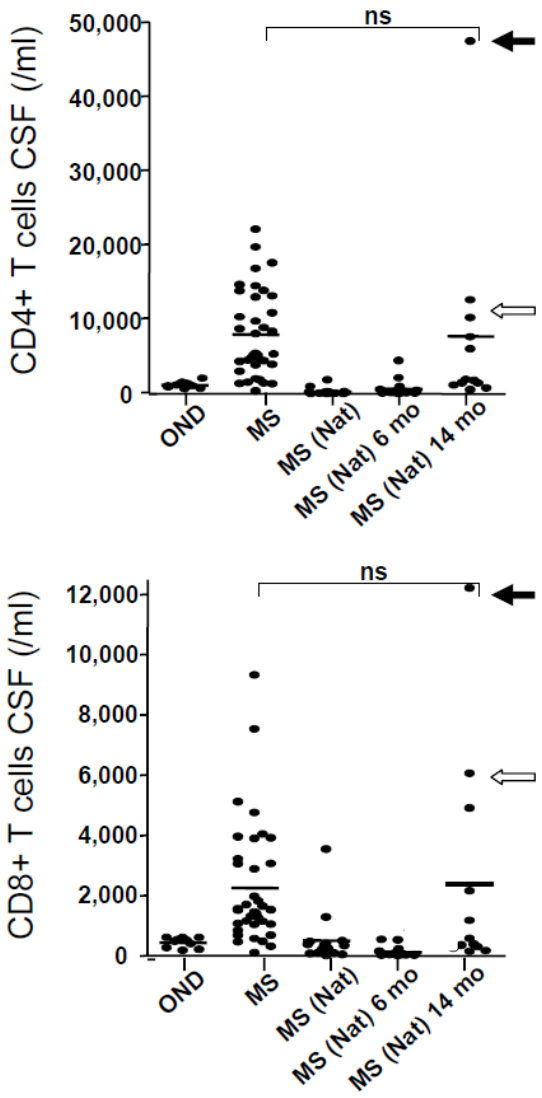


Stuve et al. Neurology. 2009.



Stuve et al. Neurology. 2009.

ORIGINAL CONTRIBUTION

Failure of Natalizumab to Prevent Relapses in Neuromyelitis Optica

Ingo Kleiter, MD; Kerstin Hellwig, MD; Achim Berthele, MD; Tania Kümpfel, MD; Ralf A. Linker, MD; Hans-Peter Hartung, MD; Friedemann Paul, MD; Orhan Aktas, MD; for the Neuromyelitis Optica Study Group

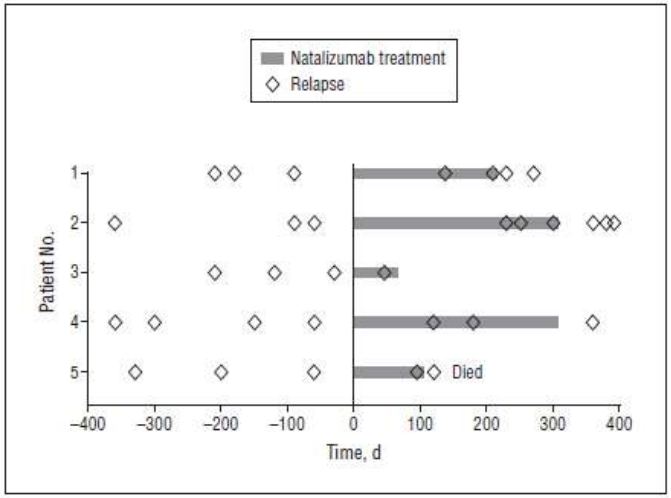


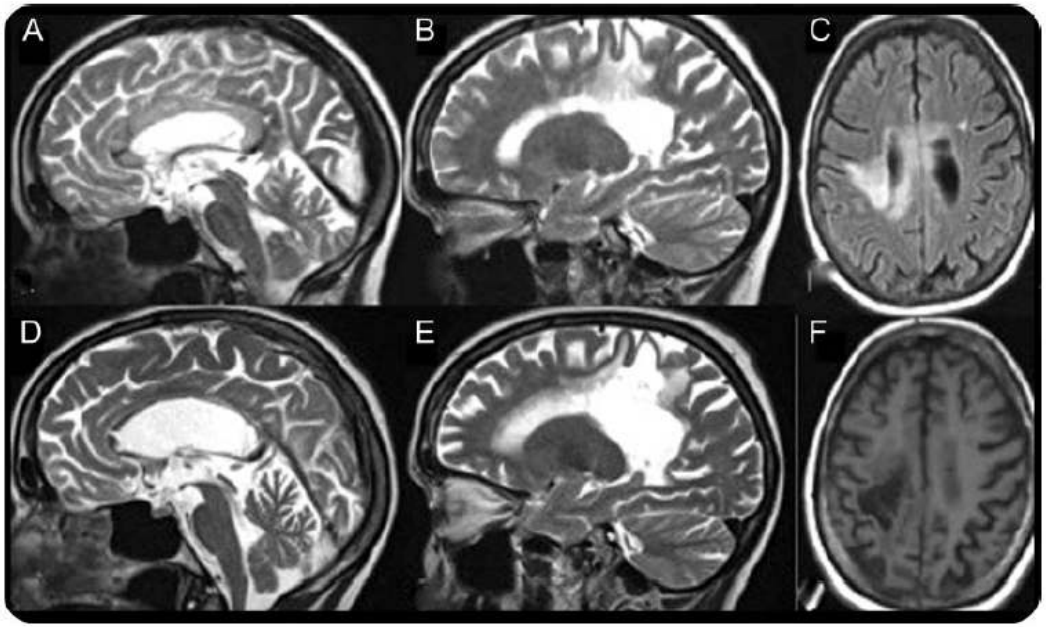
Figure. Relapses in patients with neuromyelitis optica before, during, and after treatment with natalizumab. Shown are all relapses (diamonds) from day –400 to +400 relative to start of medication. Bars depict duration of natalizumab treatment until plasma exchange (patients 1, 2, and 5) or 4 weeks after last infusion (patients 3 and 4).

Kleiter et al. Arch Neurol. 2012.

Clinical/Scientific Notes

Anu Jacob, FRCP
Michael Hutchinson, FRCP
Liene Elsone, MD
Siobhan Kelly, MD
Rehiana Ali, MD
Ivars Saukans, MD
Niall Tubridy, MD
Mike Boggild, MD

DOES NATALIZUMAB THERAPY WORSEN NEUROMYELITIS OPTICA?



Jacob et al. Neurology. 2012.

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MULTIPLE SCLEROSIS JOURNAL | MSJ

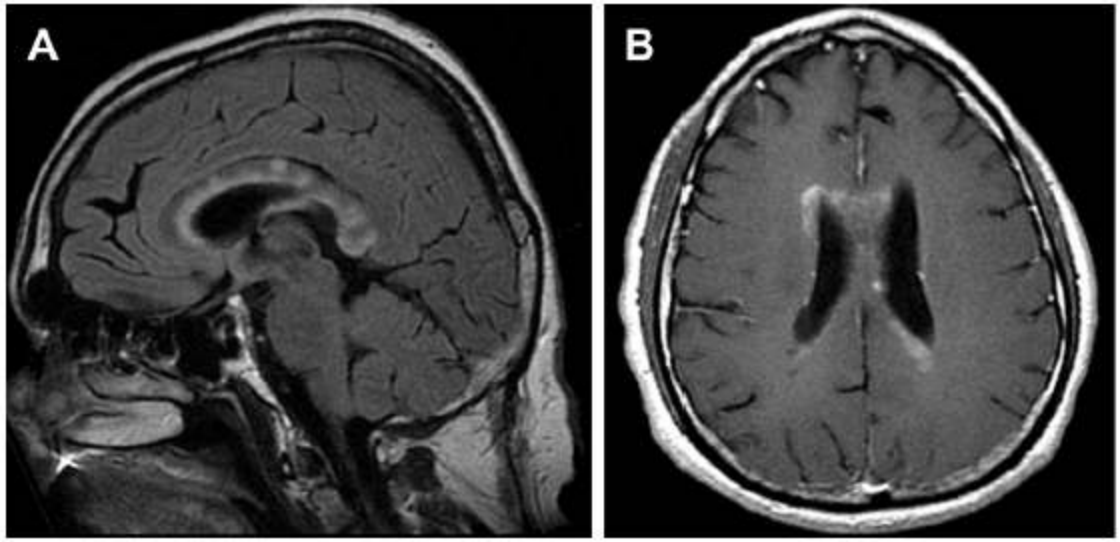
Short Report

Multiple Sclerosis Journal
18(1) 108–112

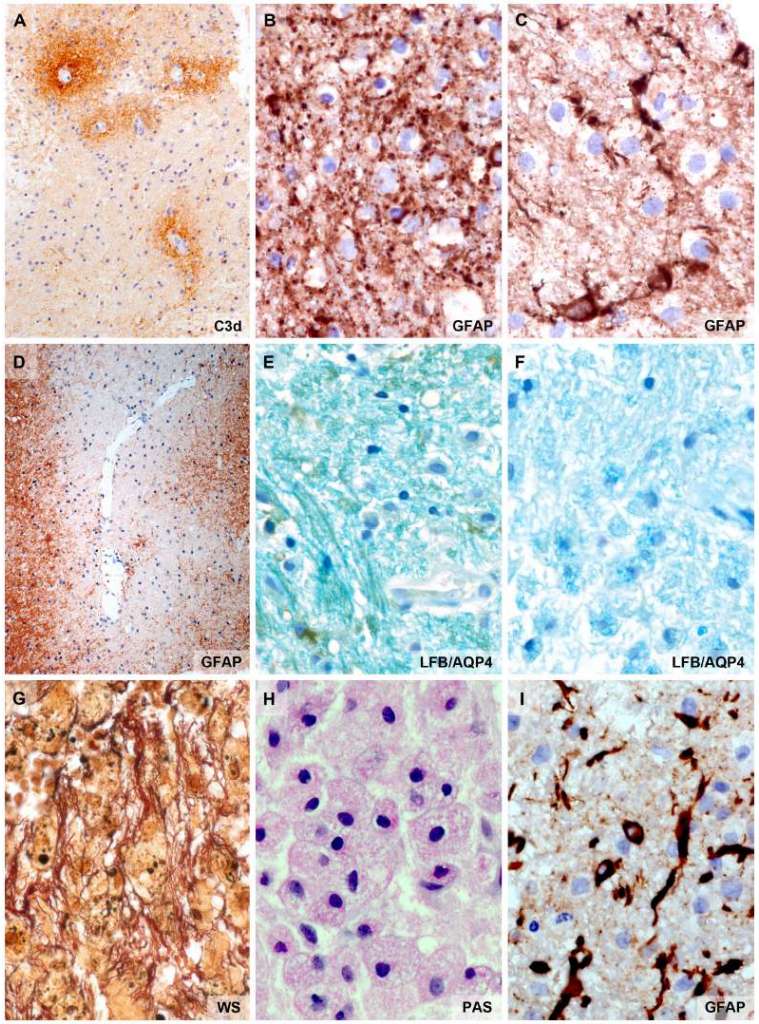
DOI: 10.1177/1352458511421185
msj.sagepub.com
SAGE

Massive astrocyte destruction in neuromyelitis optica despite natalizumab therapy

MH Barnett[1,2], JW Prineas[1,2], ME Buckland[3,4], JDE Parratt[2] and JD Pollard[1]



Barnett et al. Mult Scler J. 2012.



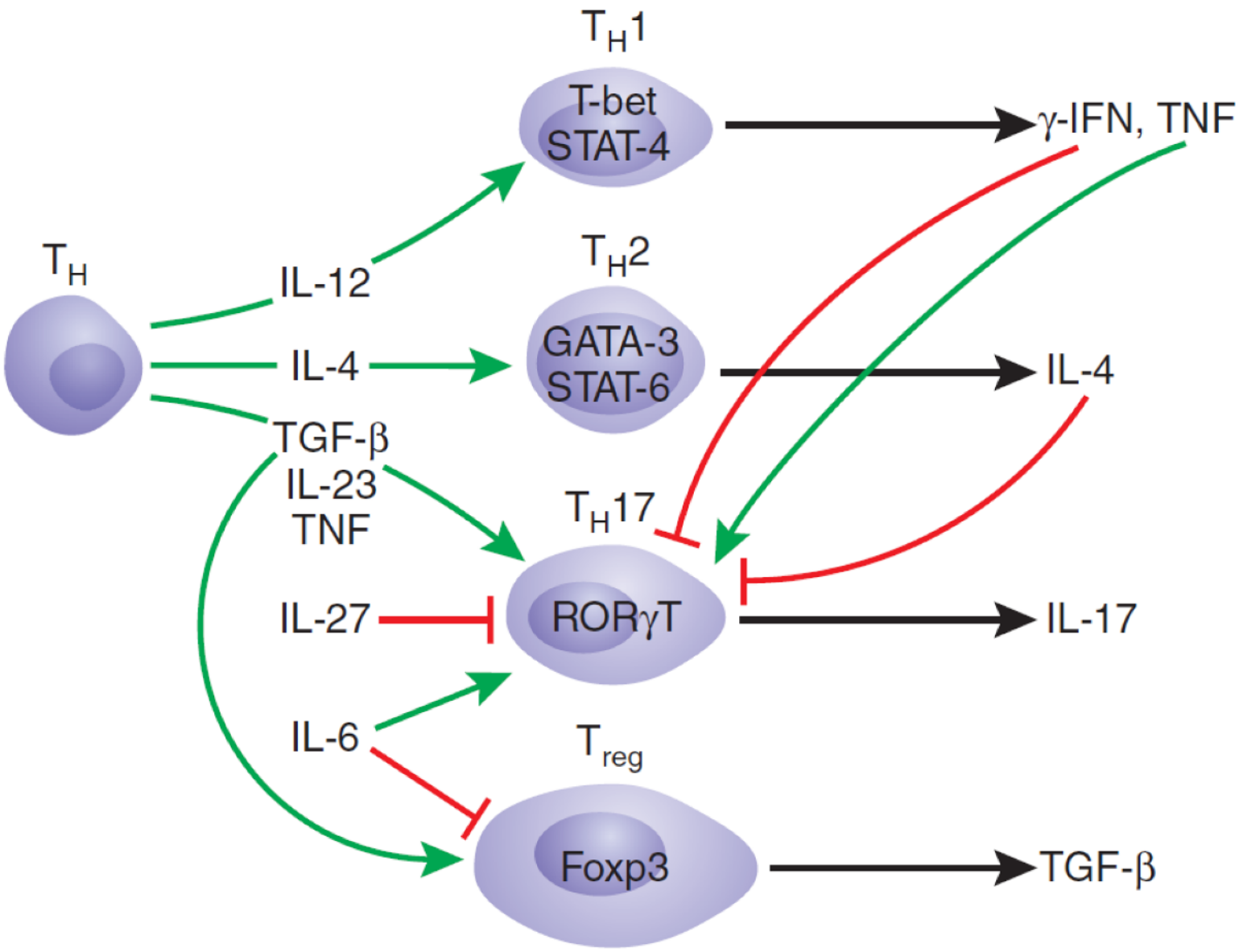
Barnett et al. Mult Scler J. 2012.

Multiple sclerosis-like illness occurring with human immunodeficiency virus infection

J.R. Berger, MD; W.A. Sheremata, MD; L. Resnick, MD; S. Atherton, PhD; M.A. Fletcher, PhD; and M. Norenberg, MD

Article abstract—We describe seven men with a neurologic disease clinically indistinguishable from multiple sclerosis occurring in association with seropositivity for the human immunodeficiency virus, type 1 (HIV-1). Histopathology of the CNS obtained in three patients (2 by brain biopsy, 1 at autopsy) was consistent with MS. The neurologic symptoms preceded the onset of clinically evident immunosuppression in all patients. In three men, HIV-1 seropositivity was demonstrated concomitantly or within 3 months of the onset of their neurologic disease. In the others, features of MS preceded the demonstration of HIV-1 seropositivity by 41 months, 59 months, 11 years, and 18 years, respectively. Despite the superimposition of varying degrees of cellular immunodeficiency associated with HIV-1 infection, six of these men continued to experience relapsing neurologic symptoms.

NEUROLOGY 1989;39:324-329



Steinman. Nat.Med. 2007.

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OBSERVATION

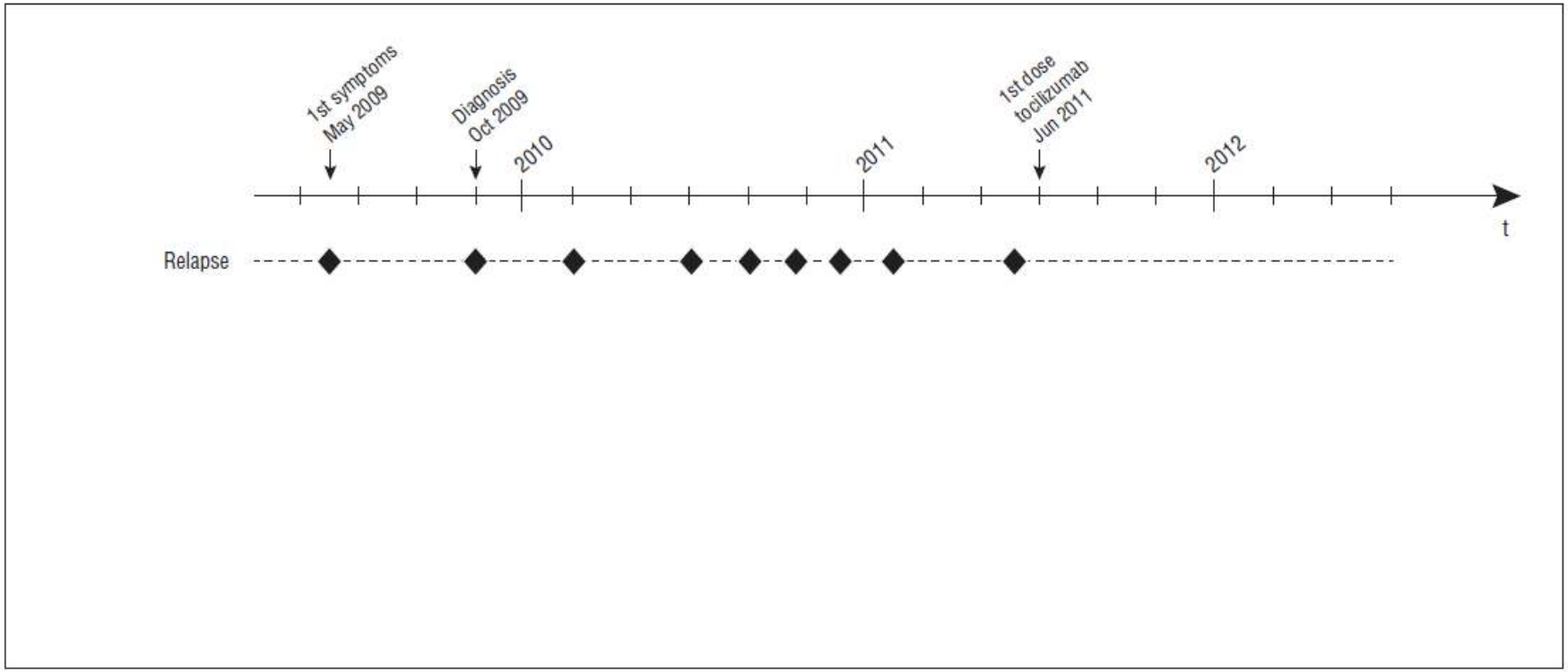
ONLINE FIRST

Disease Amelioration With Tocilizumab in a Treatment-Resistant Patient With Neuromyelitis Optica

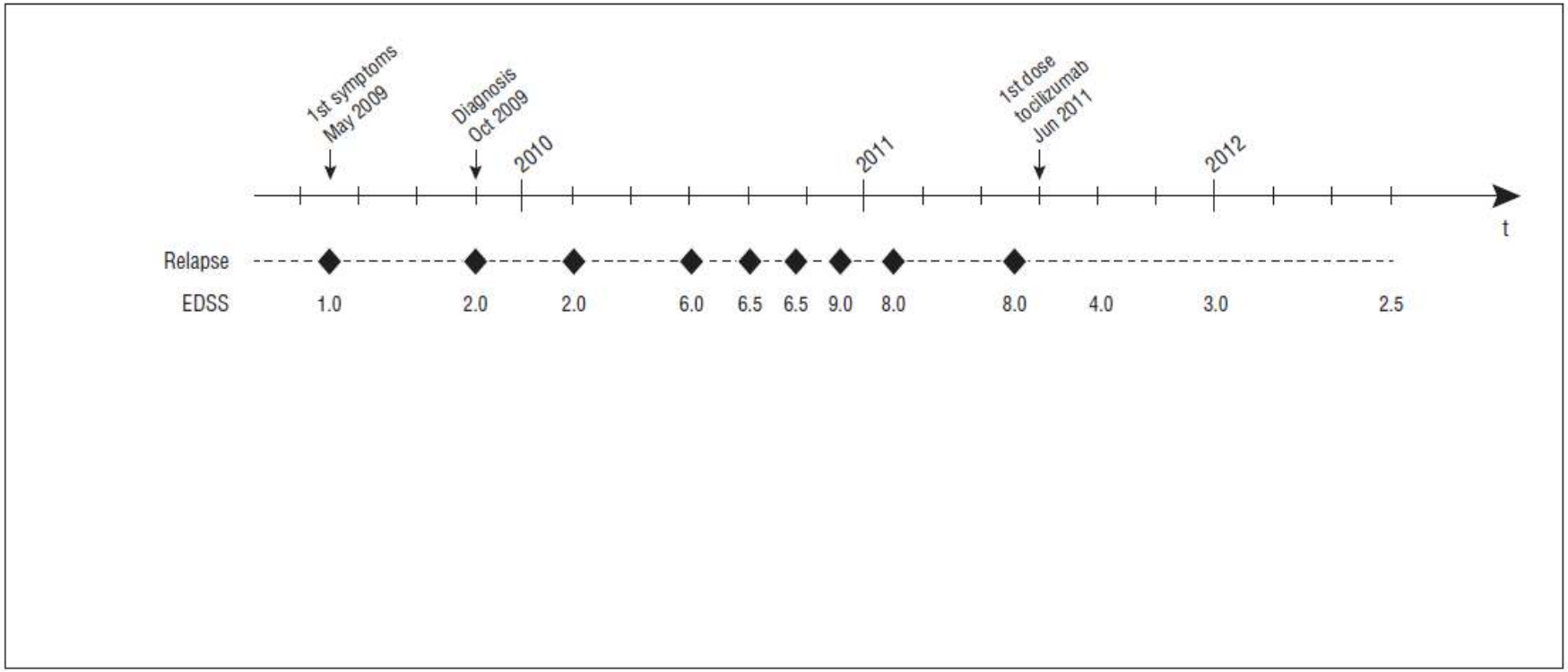
Implication for Cellular Immune Responses

Bernd C. Kieseier, MD; Olaf Stüve, MD, PhD; Thomas Dehmel, PhD; Norbert Goebels, MD; Verena I. Leussink, MD; Anne K. Mausberg, PhD; Marius Ringelstein, MD; Bernd Turowski, MD; Orhan Aktas, MD; Gerald Antoch, MD; Hans-Peter Hartung, MD

Kieseier et al. Arch Neurol. 2012.



Kieseier et al. Arch Neurol. 2012.



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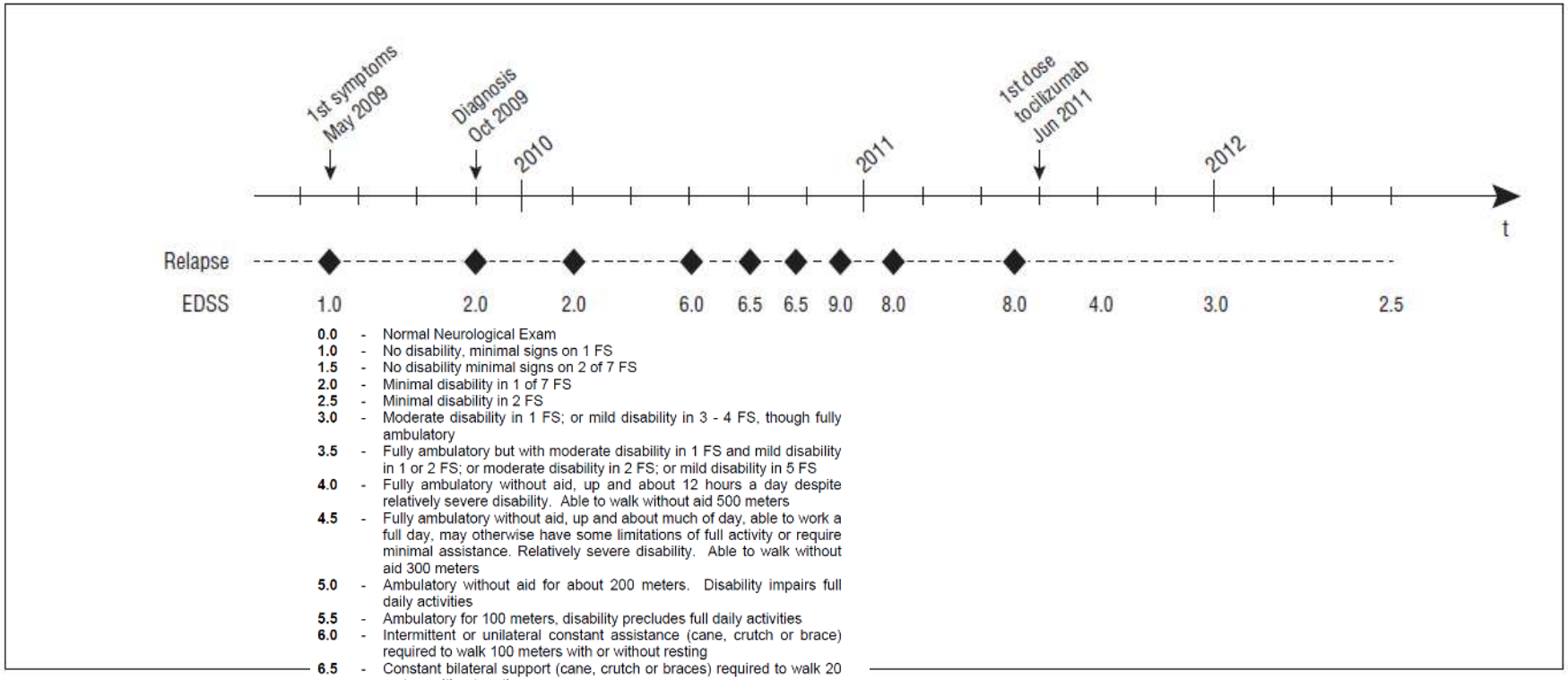
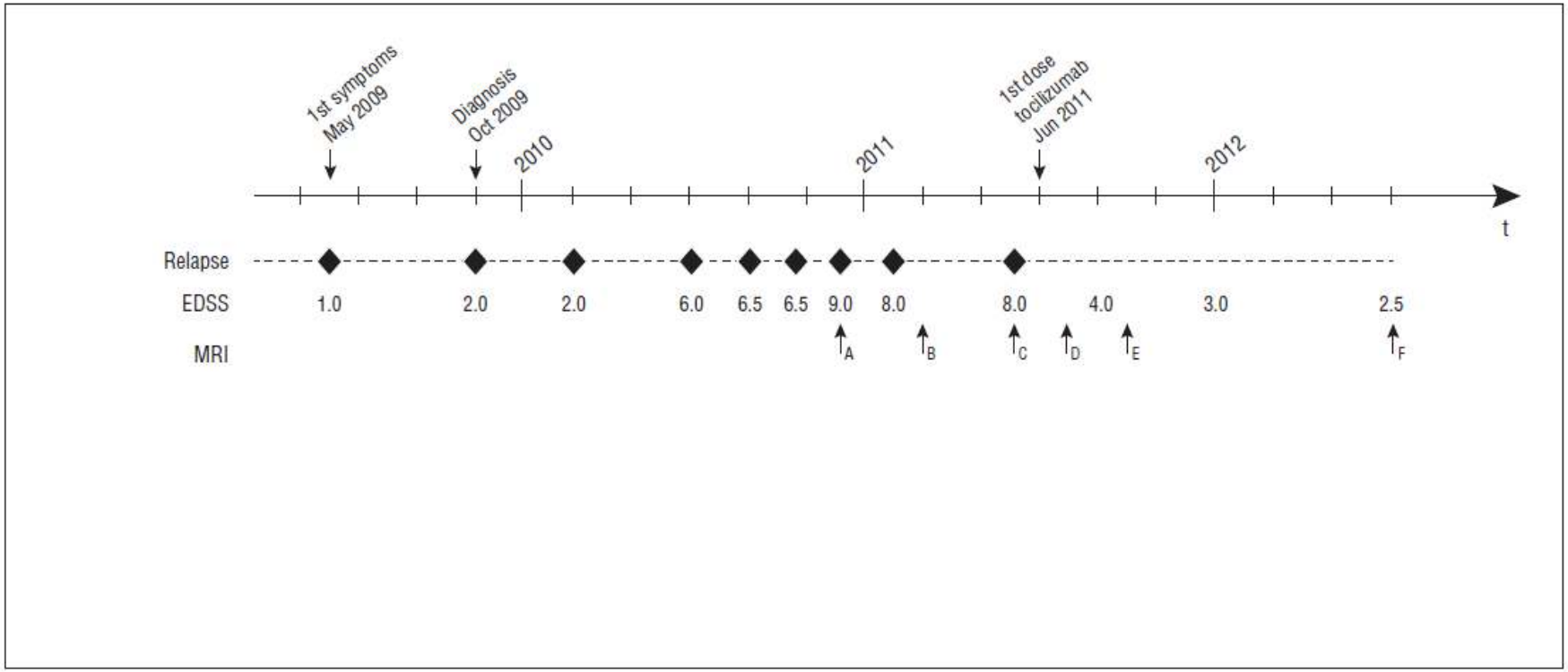


0.0 - Normal Neurological Exam
1.0 - No disability, minimal signs on 1 FS
1.5 - No disability minimal signs on 2 of 7 FS
2.0 - Minimal disability in 1 of 7 FS
2.5 - Minimal disability in 2 FS
3.0 - Moderate disability in 1 FS; or mild disability in 3 - 4 FS, though fully ambulatory
3.5 - Fully ambulatory but with moderate disability in 1 FS and mild disability in 1 or 2 FS; or moderate disability in 2 FS; or mild disability in 5 FS
4.0 - Fully ambulatory without aid, up and about 12 hours a day despite relatively severe disability. Able to walk without aid 500 meters
4.5 - Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid 300 meters
5.0 - Ambulatory without aid for about 200 meters. Disability impairs full daily activities
5.5 - Ambulatory for 100 meters, disability precludes full daily activities
6.0 - Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting
6.5 - Constant bilateral support (cane, crutch or braces) required to walk 20 meters without resting
7.0 - Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day
7.5 - Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorized chair for full day's activities
8.0 - Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self care functions, generally effective use of arms
8.5 - Essentially restricted to bed much of day, some effective use of arms, retains some self care functions
9.0 - Helpless bed patient, can communicate and eat
9.5 - Unable to communicate effectively or eat/swallow
10.0 - Death

Kieseier et al. Arch Neurol. 2012.



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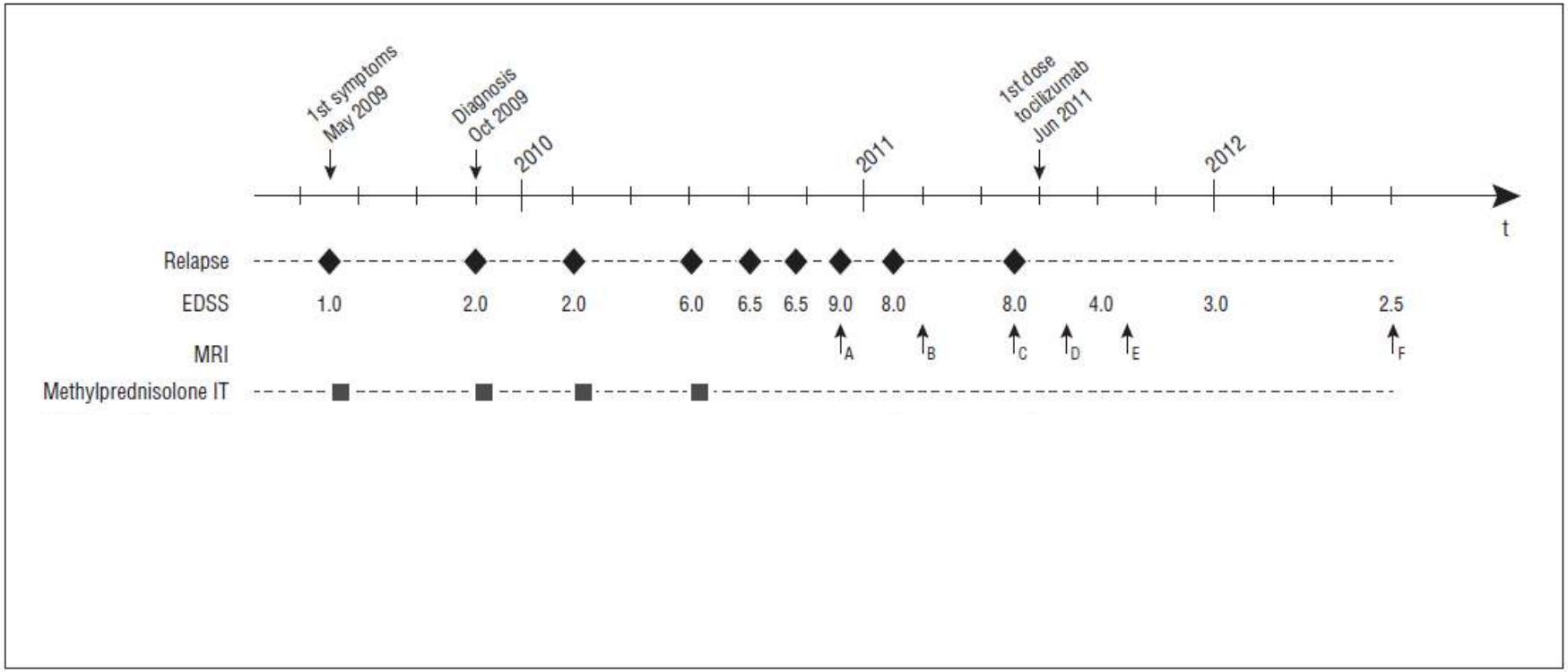

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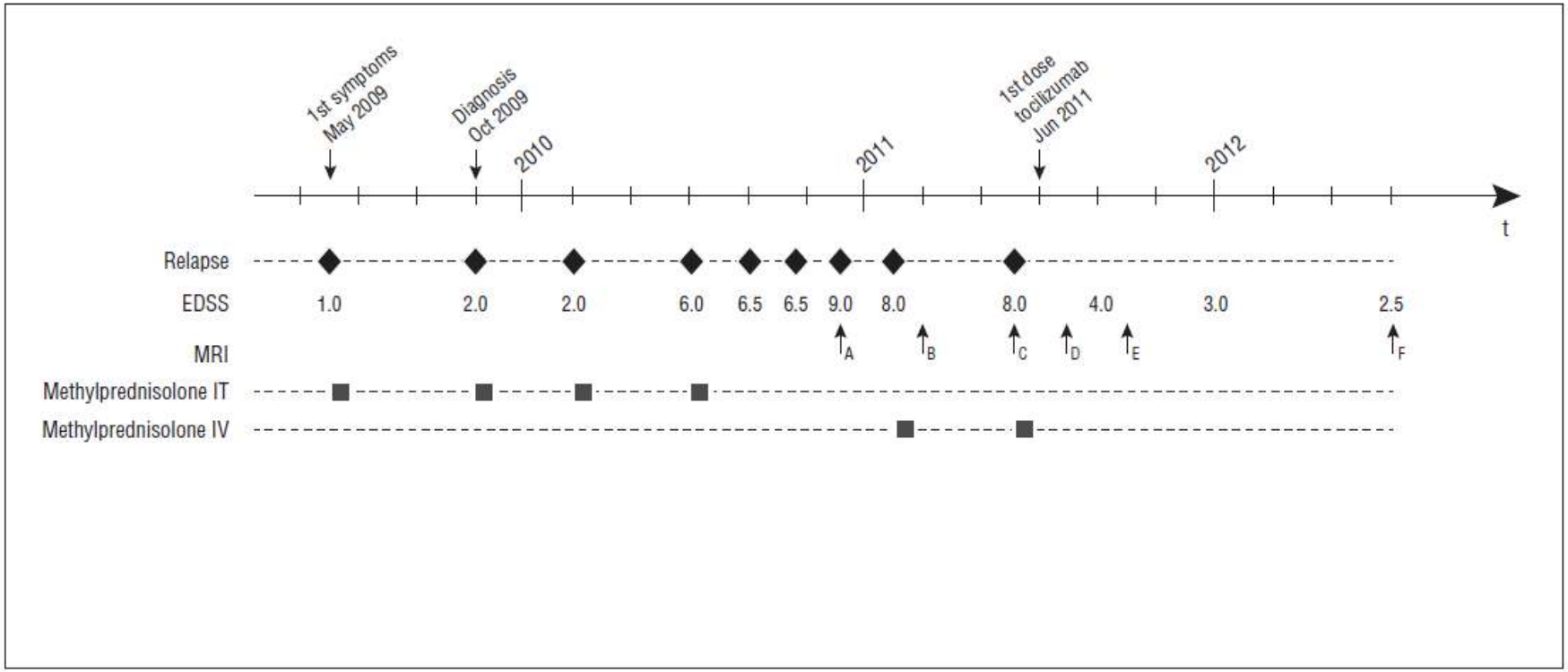
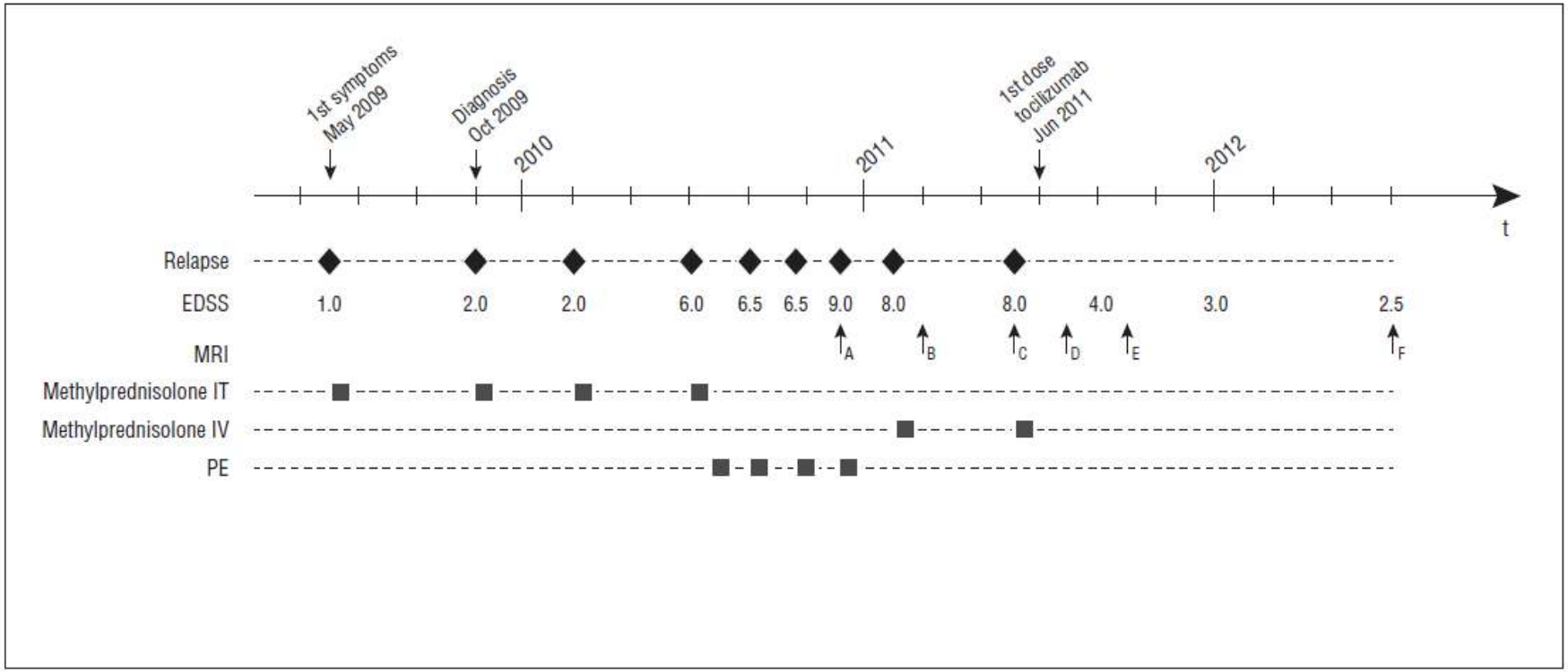


Kieseier et al. Arch Neurol. 2012.



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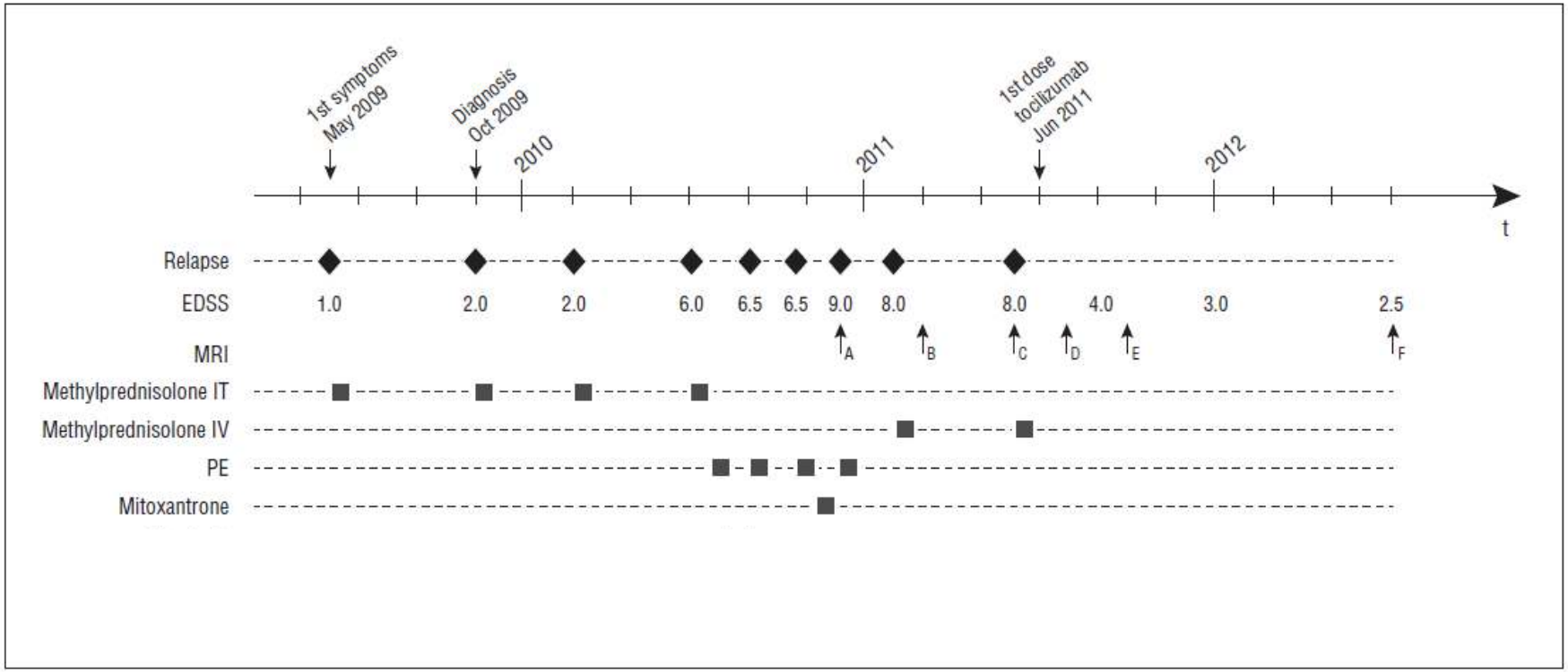
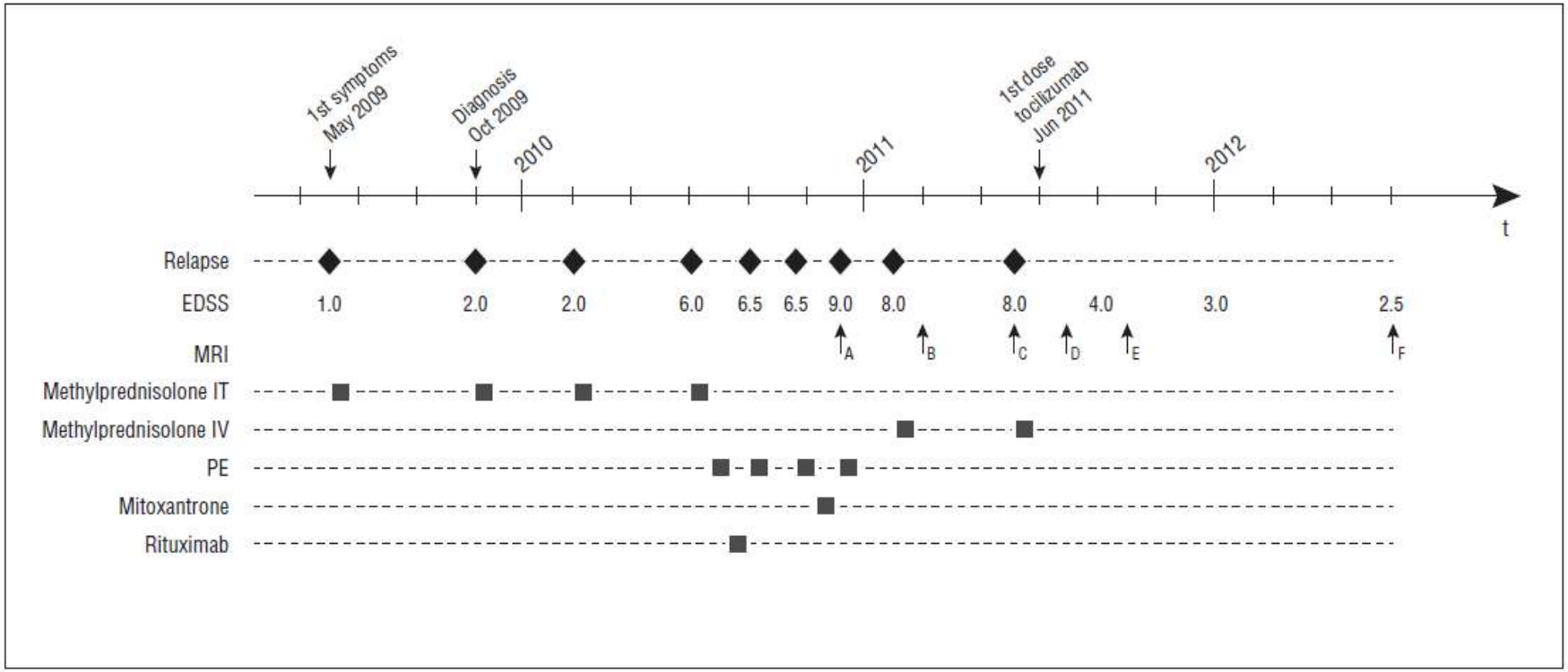


Kieseier et al. Arch Neurol. 2012.



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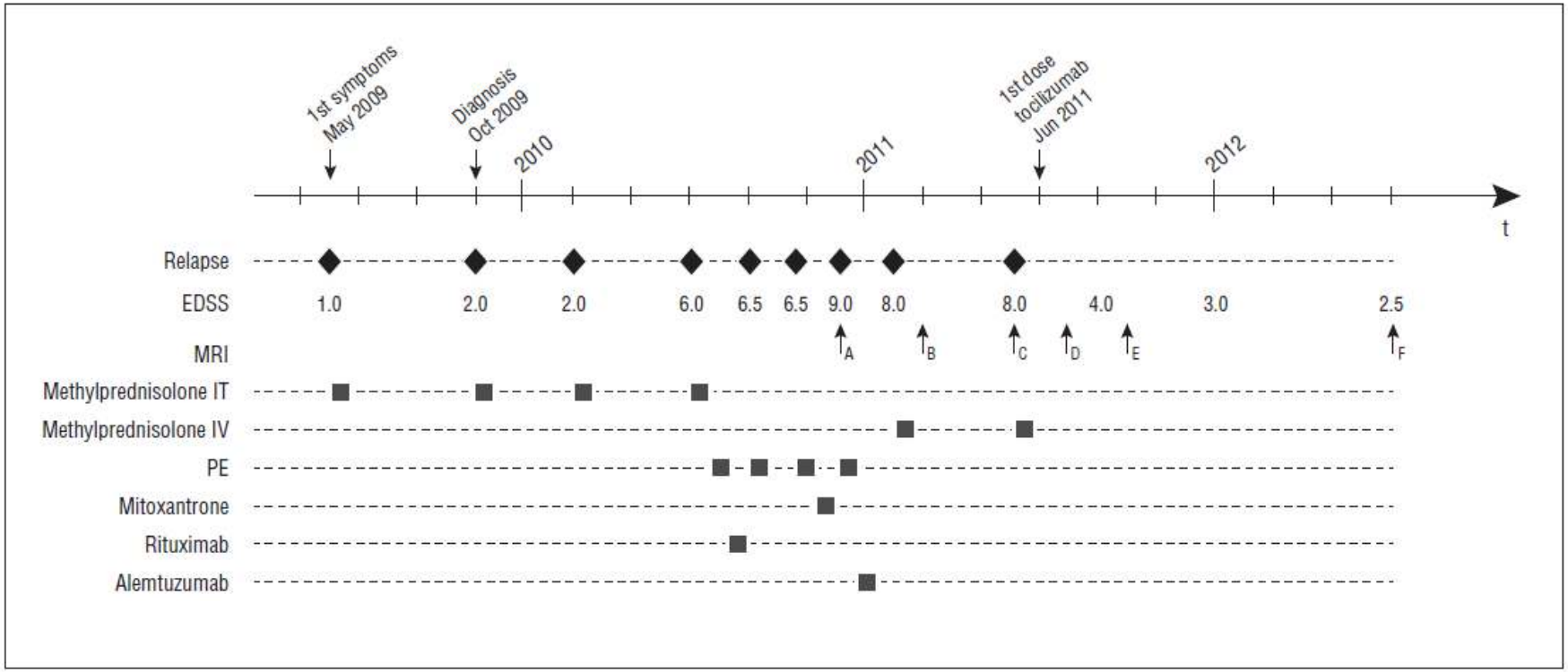


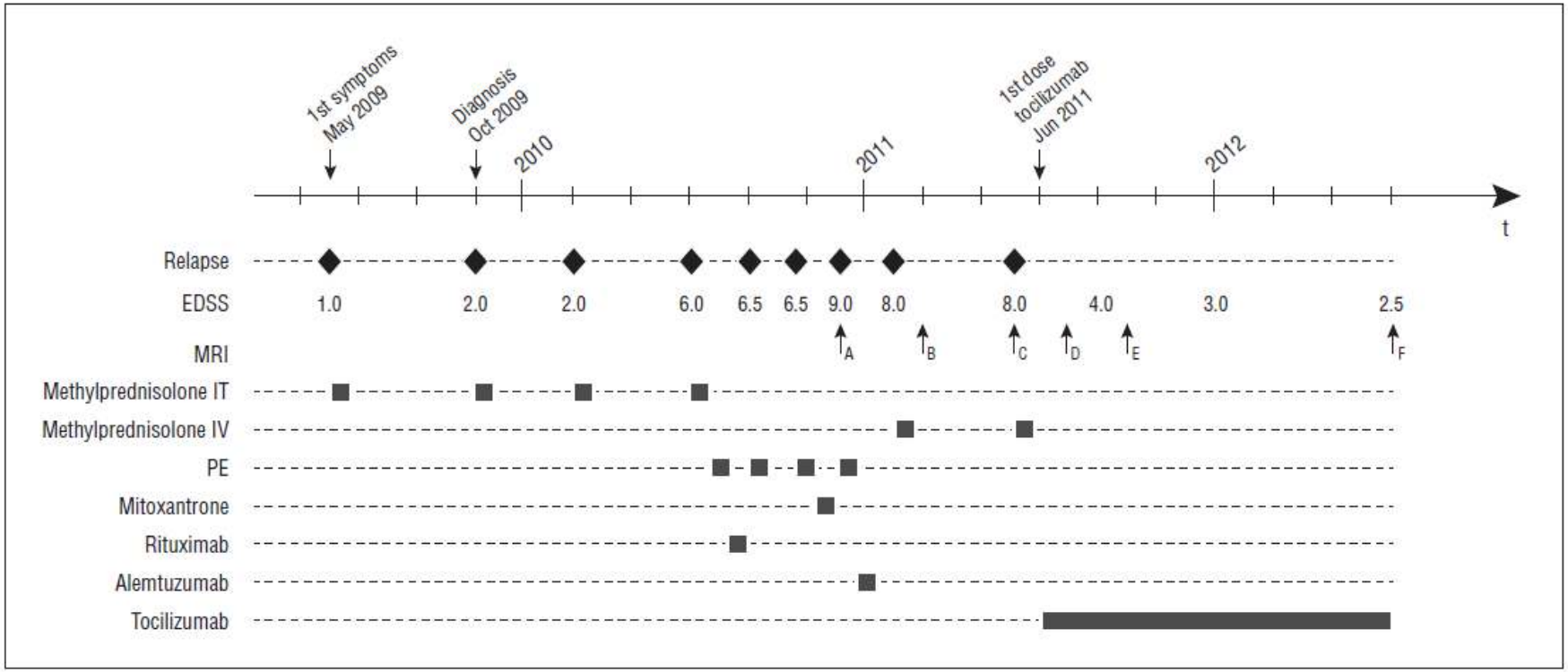
Kieseier et al. Arch Neurol. 2012.

Multiple sclerosis-like illness occurring with human immunodeficiency virus infection

J.R. Berger, MD; W.A. Sheremata, MD; L. Resnick, MD; S. Atherton, PhD; M.A. Fletcher, PhD; and M. Norenberg, MD

Article abstract—We describe seven men with a neurologic disease clinically indistinguishable from multiple sclerosis occurring in association with seropositivity for the human immunodeficiency virus, type 1 (HIV-1). Histopathology of the CNS obtained in three patients (2 by brain biopsy, 1 at autopsy) was consistent with MS. The neurologic symptoms preceded the onset of clinically evident immunosuppression in all patients. In three men, HIV-1 seropositivity was demonstrated concomitantly or within 3 months of the onset of their neurologic disease. In the others, features of MS preceded the demonstration of HIV-1 seropositivity by 41 months, 59 months, 11 years, and 18 years, respectively. Despite the superimposition of varying degrees of cellular immunodeficiency associated with HIV-1 infection, six of these men continued to experience relapsing neurologic symptoms.

NEUROLOGY 1989;39:324-329



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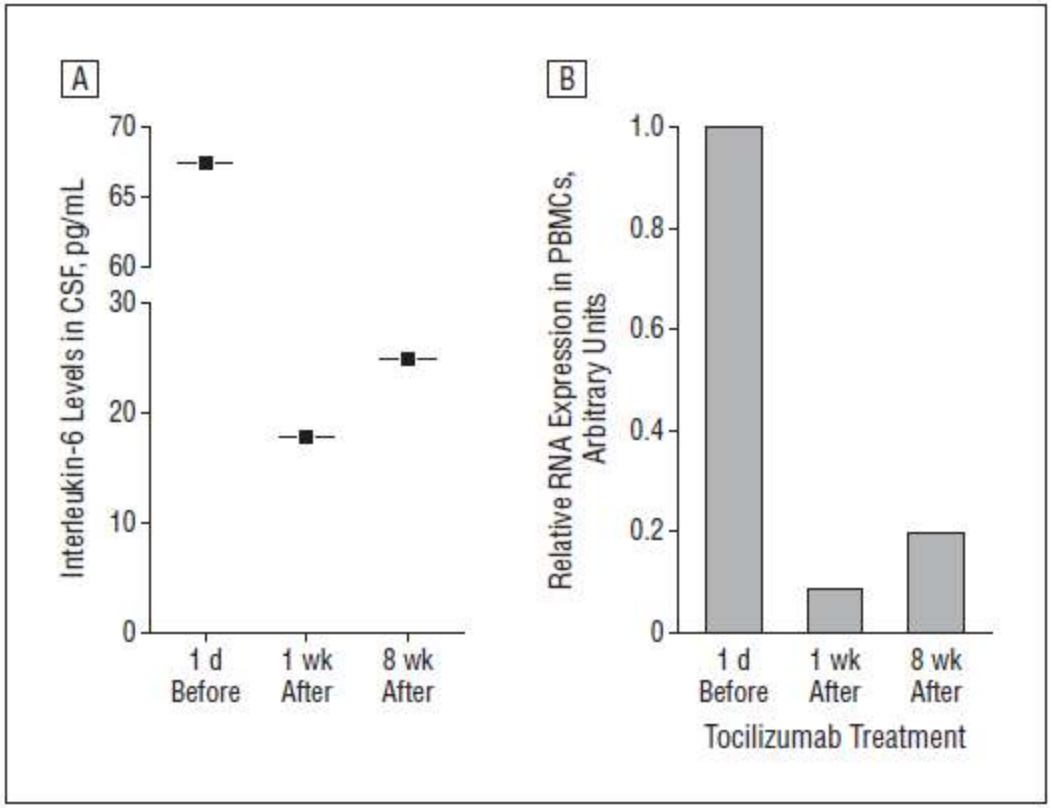
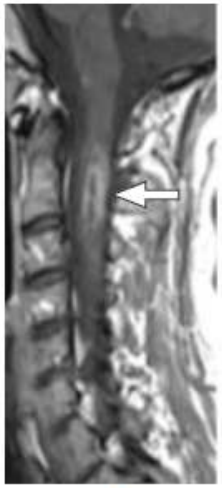


Kieseier et al. Arch Neurol. 2012.

A Nov 2010



4 wk After
Rituximab

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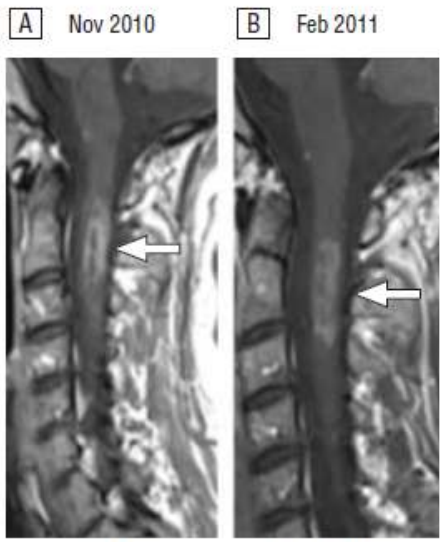

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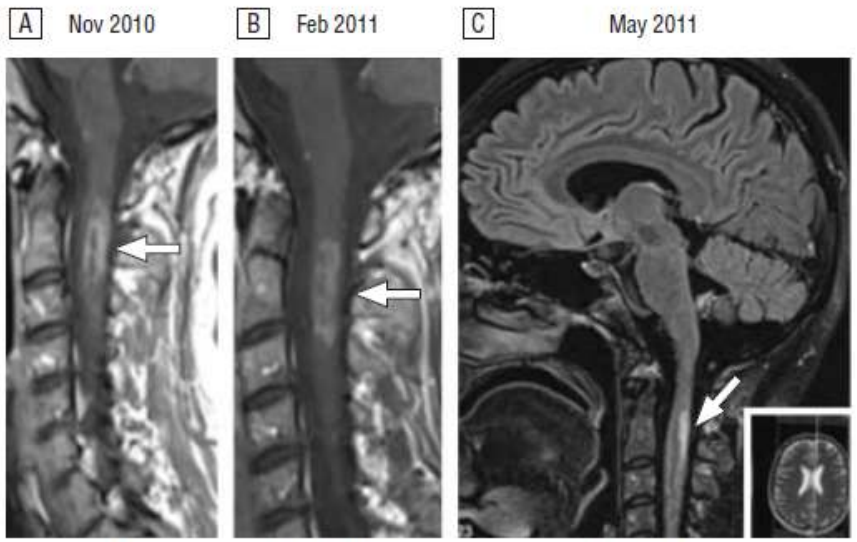

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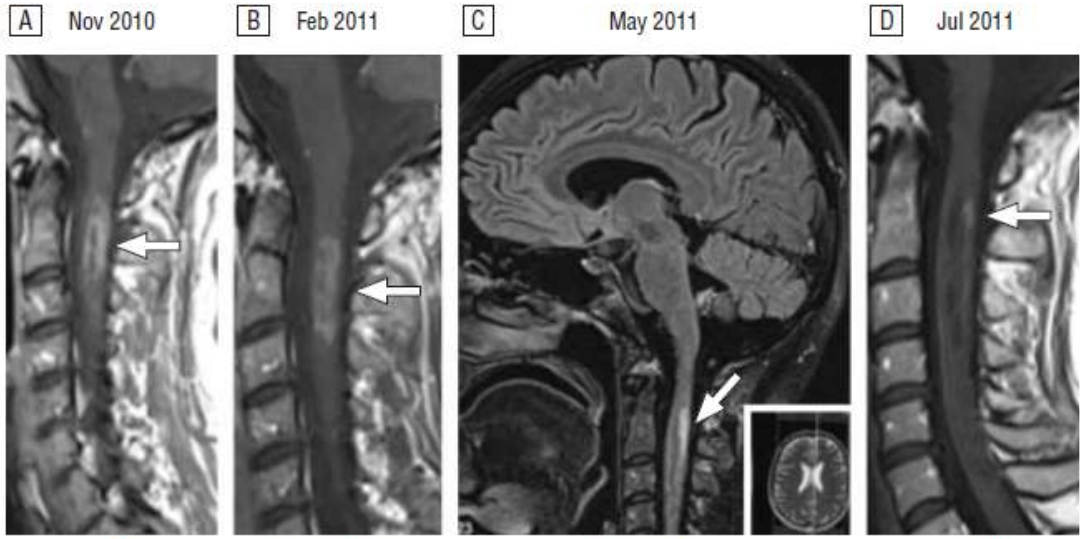

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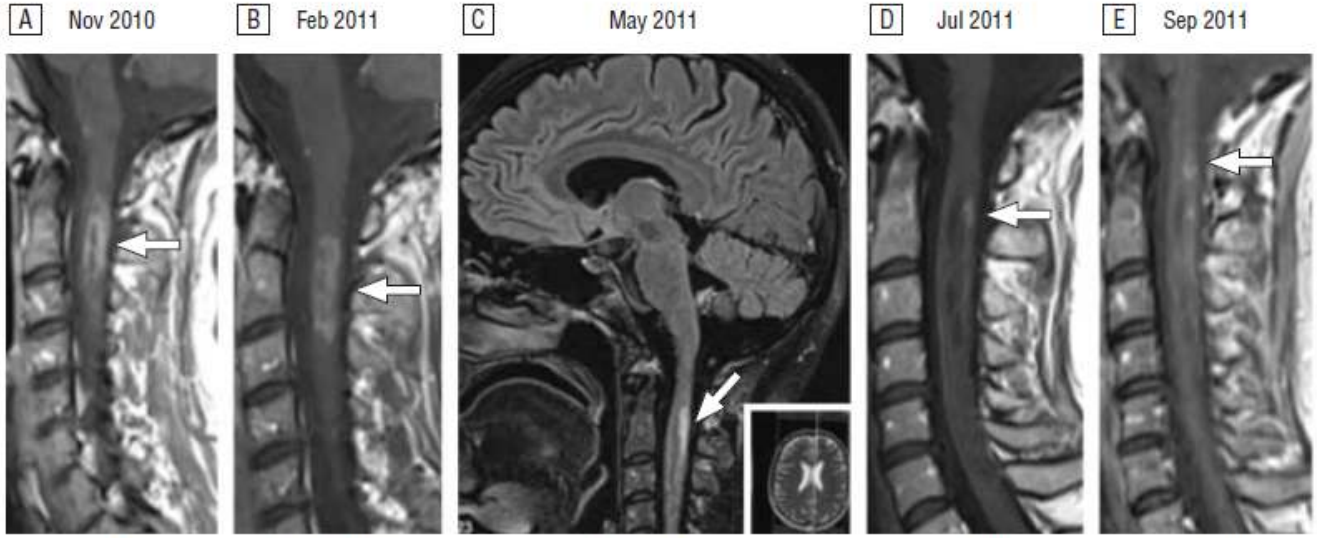

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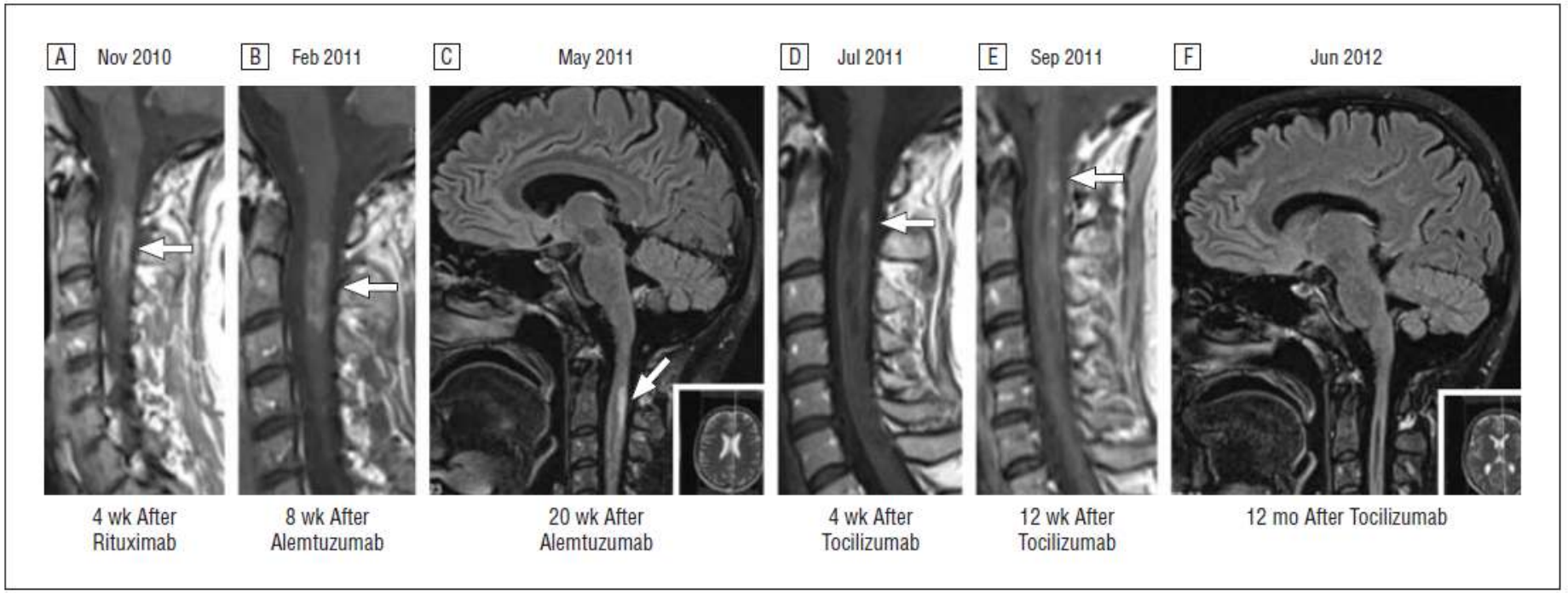

Kieseier et al. Arch Neurol. 2012.

Summary

- The EAE animal model of MS strongly suggests a pathogenic role for T cells in disease pathogenesis of MS and NMO

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- Not all T cells cause disease

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- T cells are abundantly present in NMO lesions
- NMO is associated with HLA-DR1*03:01, suggesting a pathogenic role for $CD4^+$ T cells
- Specific T cells and cytokines will become the target of pharmacotherapies for patients with NMO

UNITED STATES
DEPARTMENT OF VETERANS AFFAIRS

UT SOUTHWESTERN
MEDICAL CENTER

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Acknowledgements

You

The End