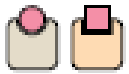
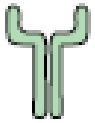
Eisagogi-epanalipsis


Receptors


TCR


Class I MHC molecule


Class II MHC molecule


Cytokine receptor


Antibody (Ab)

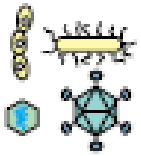

Auto-Ab

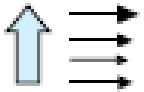

Complement


Thymus


Lymph node


Cellular tissue


Bacteria and viruses


Arrows denoting transportation, effect, and direction


Positive effect


Negative effect


Inhibition

Blockade


Signal


Stem cell


B cell


T cell


Erythrocyte

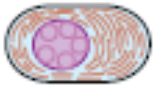

Monocyte


Neutrophil granulocyte


Basophil granulocyte


Eosinophil granulocyte


Basophil mast cell


Plasma cell


Antigen-presenting cell (APC)


Natural killer cell (NK cell)


Macrophage


Megakaryocyte

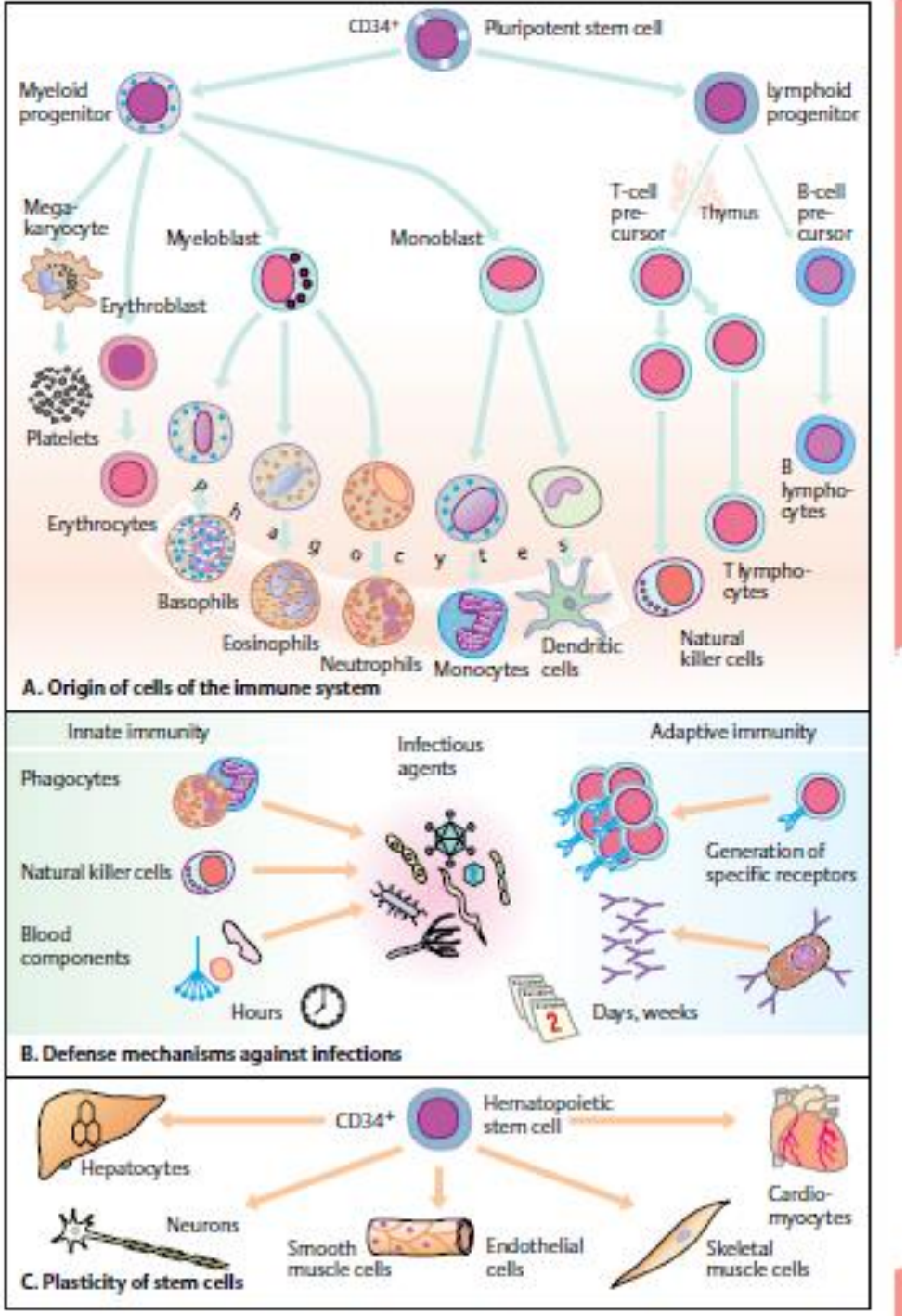

Thrombocytes


Langerhans' cell


Interdigitating dendritic cell


Mature dendritic cell

overview


CD34+
Pluripotent stem cell
Myeloid progenitor
lymphoid progenitor
Mega-karyocyte
Myeloblast
Monoblast
T-cell pre-cursor
Thymus
B-cell pre-cursor
Erythroblast
Platelets
Erythrocytes
Phagocytes
Basophils
Eosinophils
Neutrophils
Monocytes
Dendritic cells
B lympho-cytes
T lympho-cytes
Natural killer cells
A. Origin of cells of the immune system
Innate immunity
Adaptive immunity
Infectious agents
Phagocytes
Natural killer cells
Blood components
Hours
Generation of specific receptors
Days, weeks
B. Defense mechanisms against infections
CD34+
Hematopoietic stem cell
Hepatocytes
Neurons
Smooth muscle cells
Endothelial cells
Cardio-myocytes
Skeletal muscle cells
C. Plasticity of stem cells

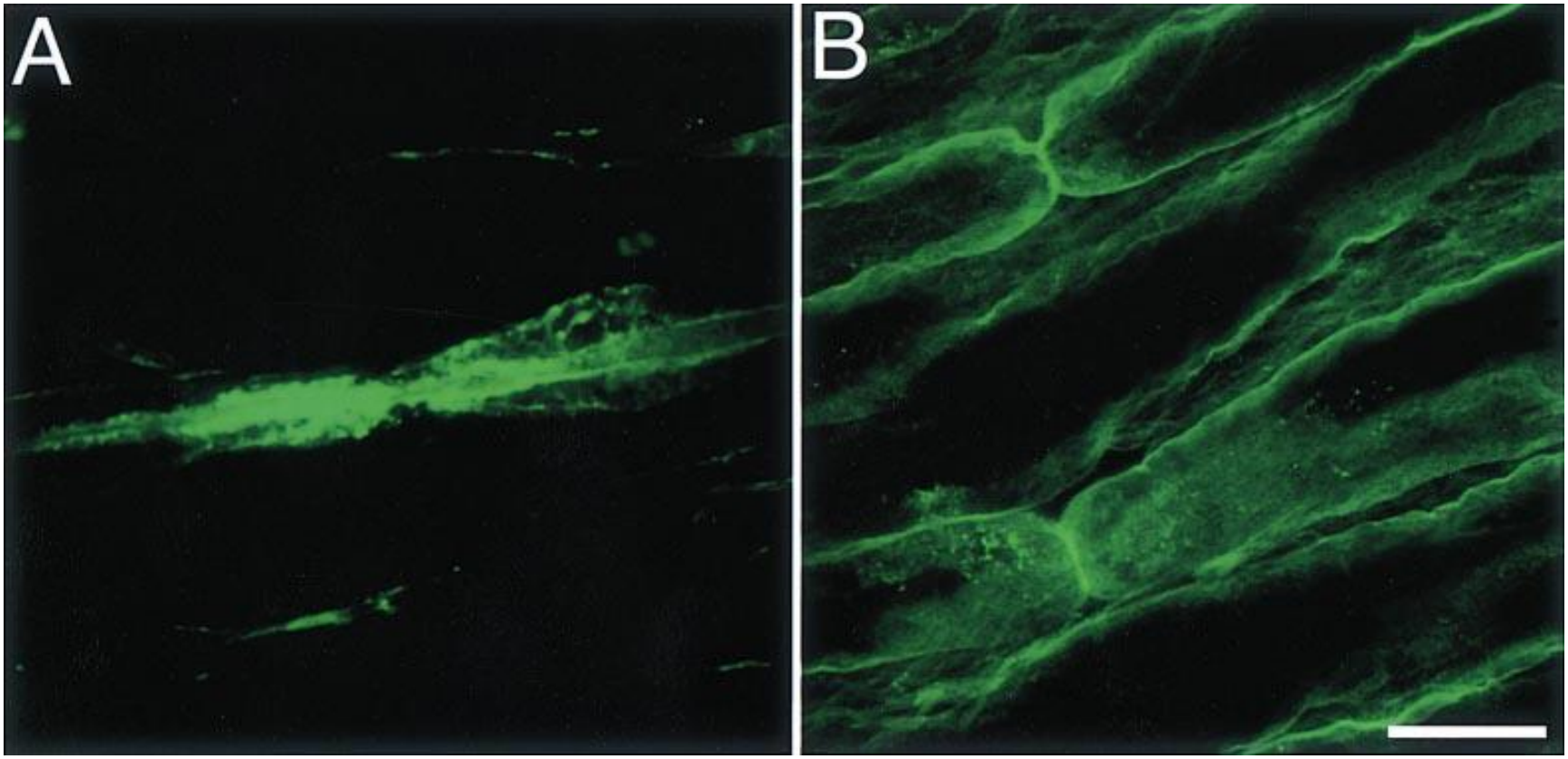
1. Ανίχνευση Αντισωμάτων

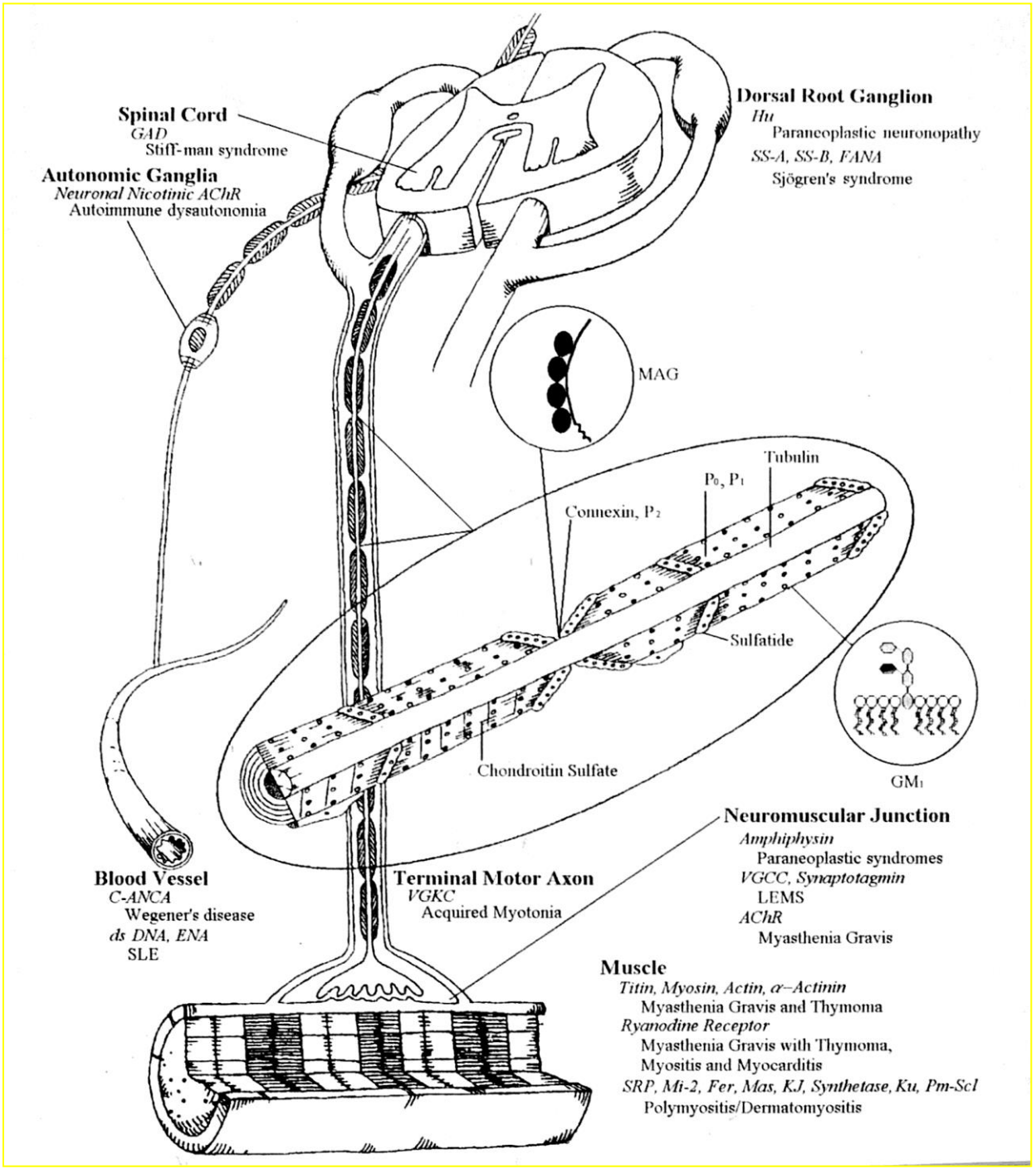
2. Χαρακτηρισμός Αντιγόνου στόχου

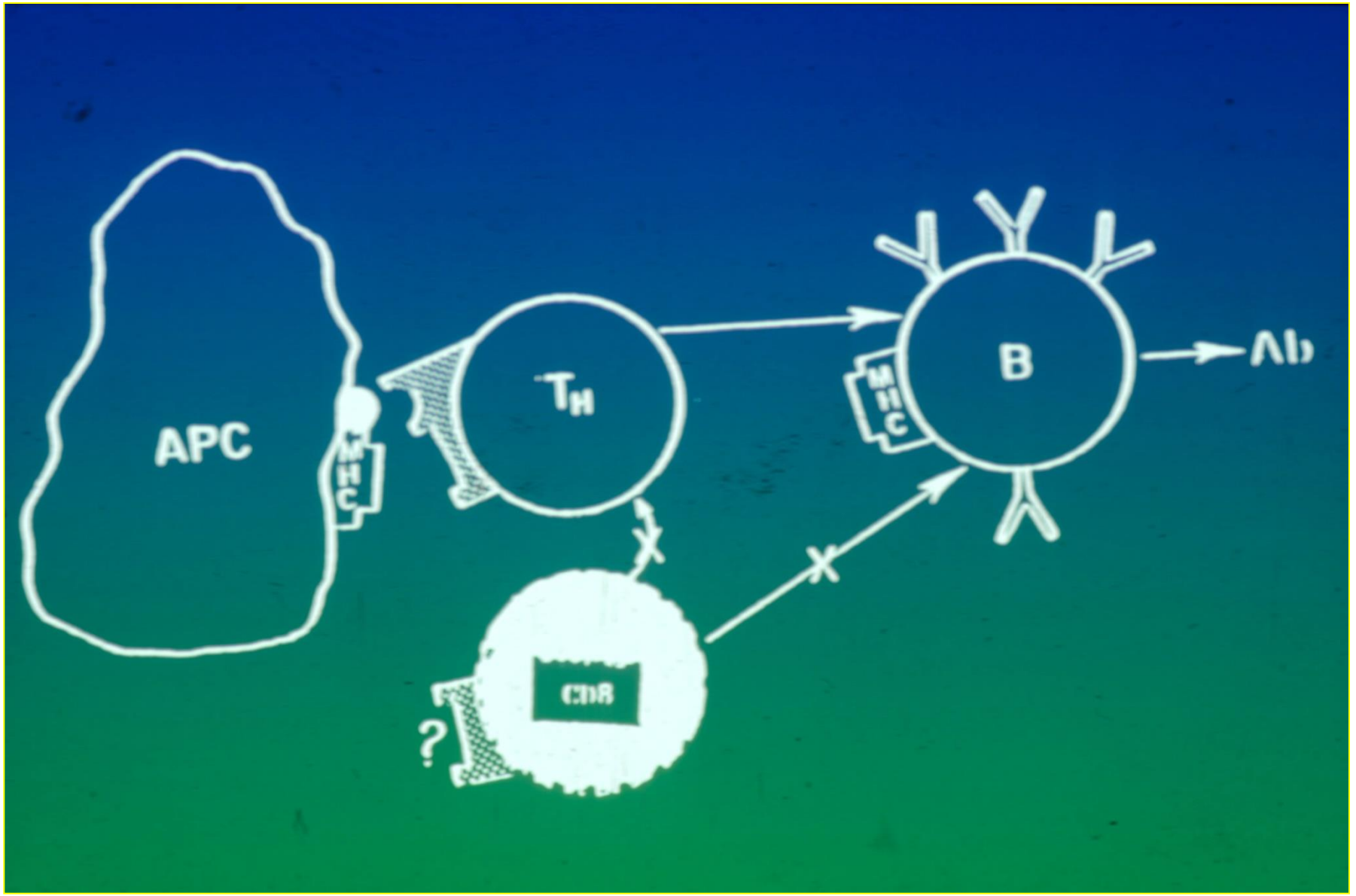
3. Πτώση των τίτλων συνδυάζεται με ύφεση της νόσου

4. Μεταφορά της νόσου σε πειραματόζωο μέσω των χαρακτηρισθέντων αντισωμάτων

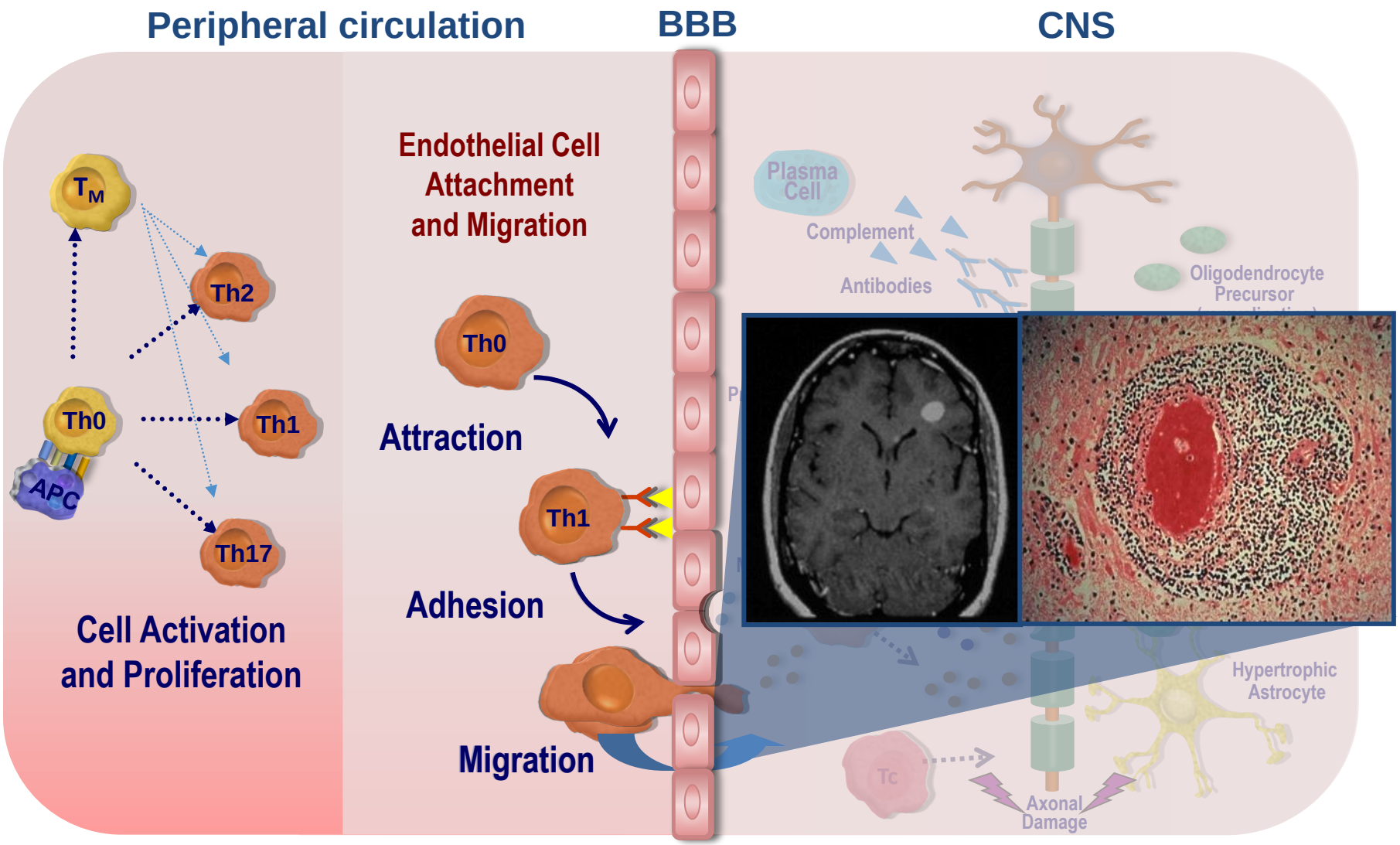
5. Ανοσοποίηση με το χαρακτηρισθέν αντιγόνο προκαλεί πειραματικό μοντέλο της νόσου


A
B


Spinal Cord
GAD
Stiff-man syndrome
Autonomic Ganglia
Neuronal Nicotinic AChR
Autoimmune dysautonomia
Dorsal Root Ganglion
Hu
Paraneoplastic neuronopathy
SS-A, SS-B, FANA
Sjögren's syndrome
MAG
Tubulin
P0, P1
Connexin, P2
Sulfatide
Chondroitin Sulfate
GM1
Blood Vessel
C-ANCA
Wegener's disease
ds DNA, ENA
SLE
Terminal Motor Axon
VGKC
Acquired Myotonia
Neuromuscular Junction
Amphiphysin
Paraneoplastic syndromes
VGCC, Synaptotagmin
LEMS
AChR
Myasthenia Gravis
Muscle
Titin, Myosin, Actin, α–Actinin
Myasthenia Gravis and Thymoma
Ryanodine Receptor
Myasthenia Gravis with Thymoma,
Myositis and Myocarditis
SRP, Mi-2, Fer, Mas, KJ, Synthetase, Ku, Pm-Scl
Polymyositis/Dermatomyositis

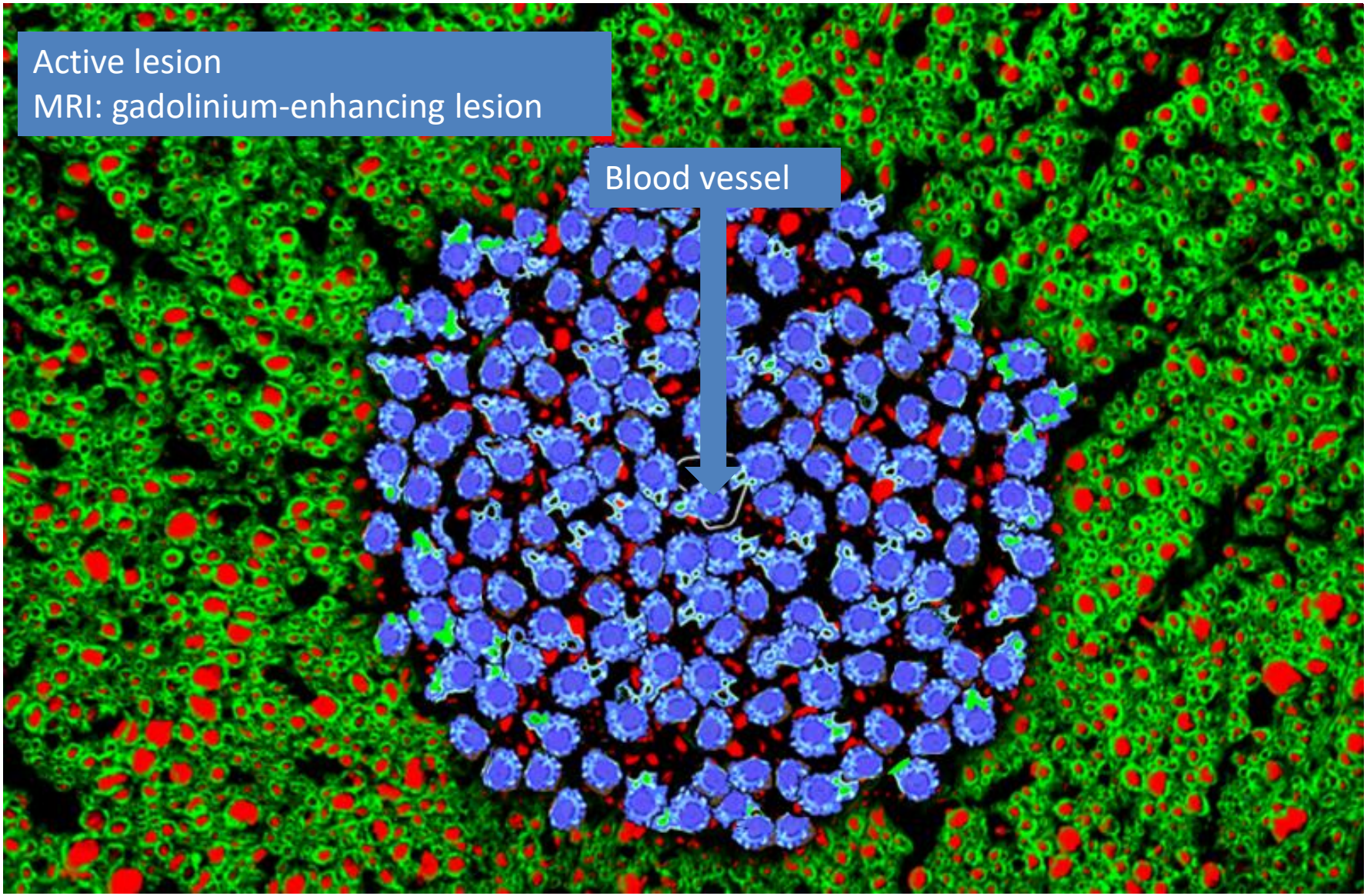

APC
MHC
T_H
B
MHC
Ab
X
X
CD8
?

Immune Cells Migrate into the CNS



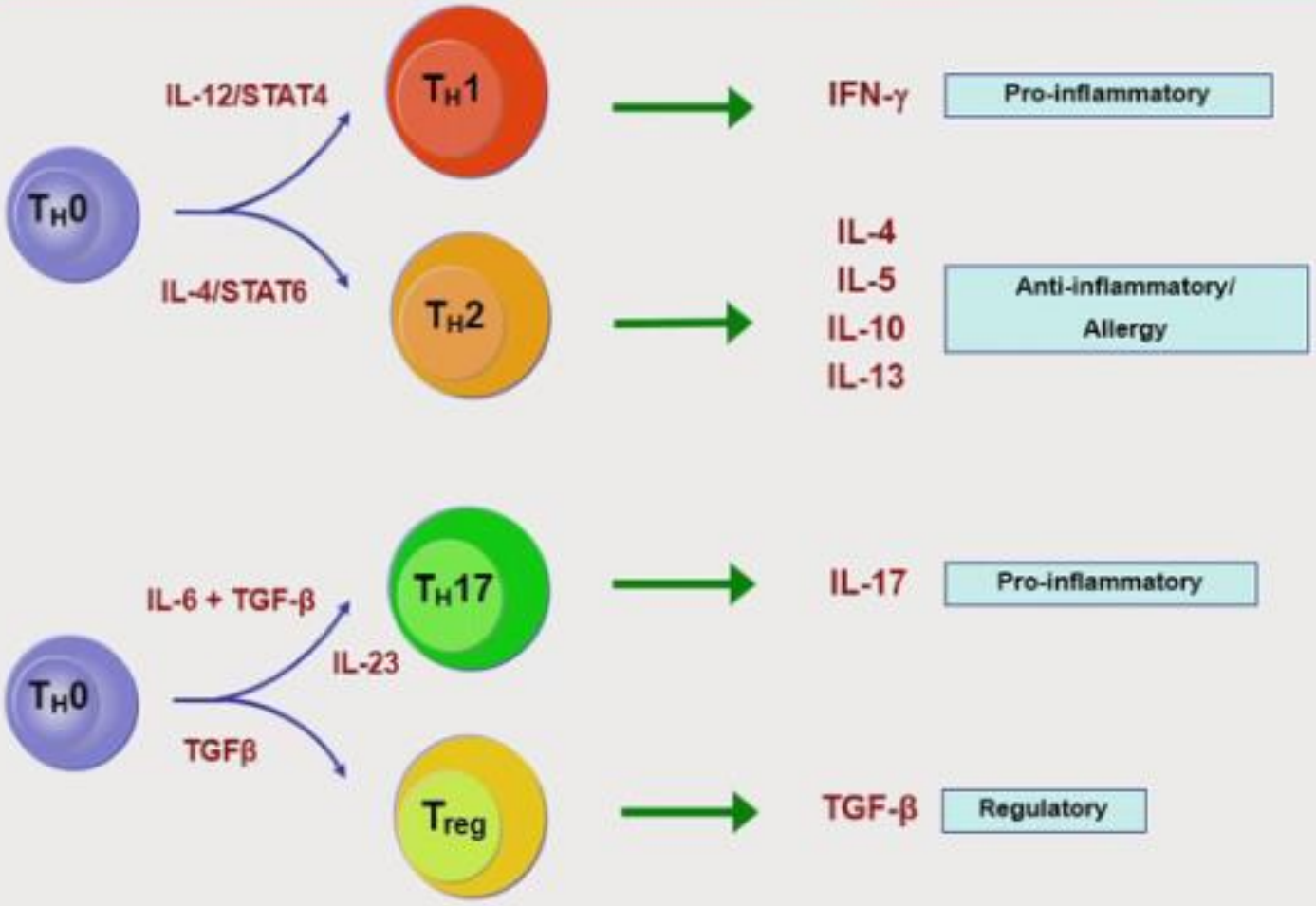
Compston A, et al, eds. *McAlpine's Multiple Sclerosis*. 4th ed. Philadelphia, PA: Churchill Livingstone, Elsevier; 2006;
Frohman EM, et al. *N Engl J Med.* 2006;354(9):942-955; Hawkins BT, Davis TP. *Pharmacol Rev*. 2005;57(2):173-185;
Lopez-Diego RS, Weiner HL. *Nat Rev Drug Discov.* 2008;7(11):909-925; Noseworthy JH, et al. *N Engl J Med*. 2000;343(13): 938-952;
Wong AD, et al. *Front Neuroeng*. 2013;6:7; Wiendl H, Kieseier BC. *Expert Opin Investig Drugs.* 2003;12(4):689-712; Yong VW. *Neurology.* 2002;59(6):802-808.

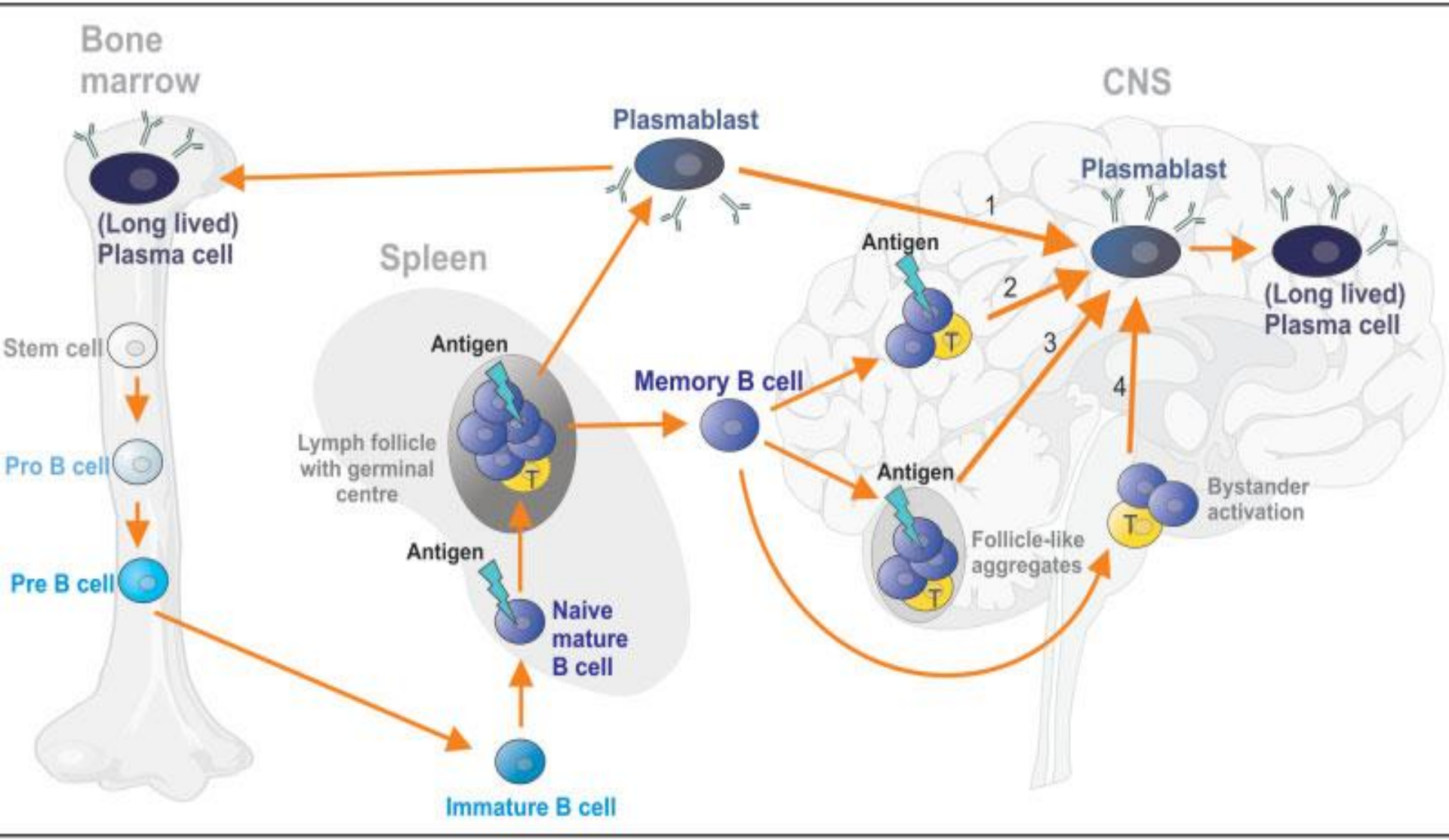
Lesion Formation: Macrophages Destroy Myelin



Courtesy Bruce Trapp. Frohman EM, et al. *N Engl J Med.* 2006;354(9):942-955.

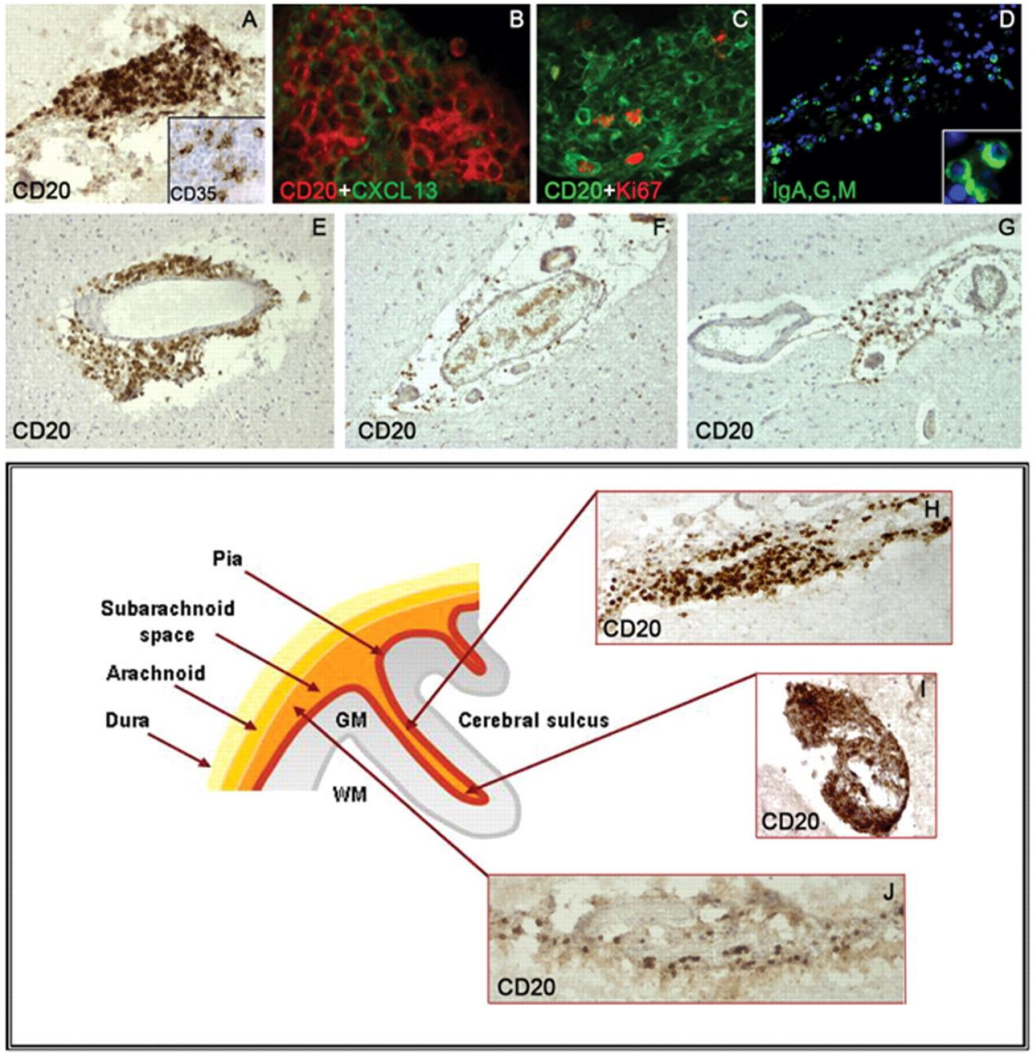
Helper T cell differentiation





Meinl et al2006

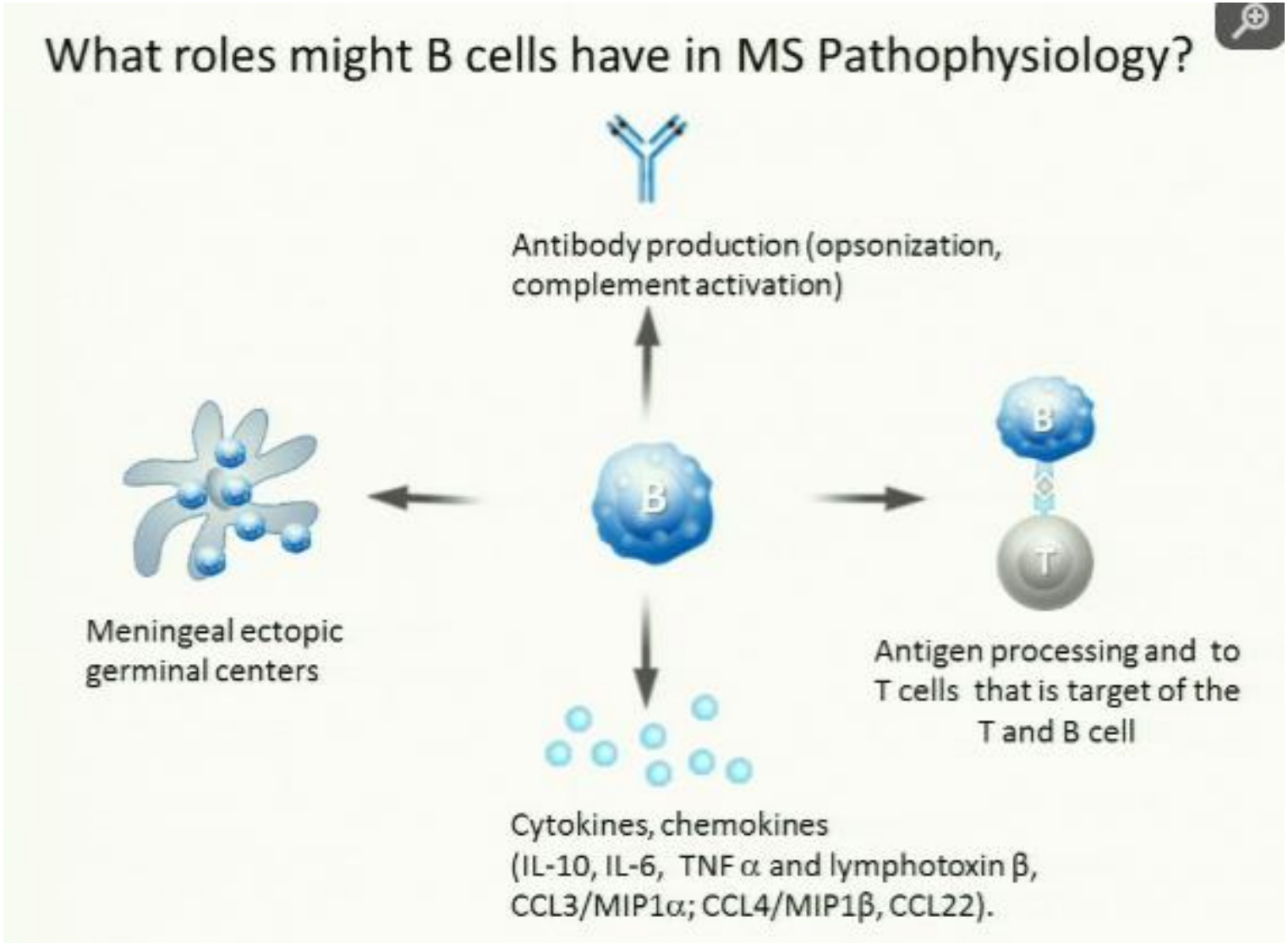
Characterization of ectopic B-cell follicles and inflammatory cell infiltrates in post-mortem brain tissue from cases with SPMS and PPMS



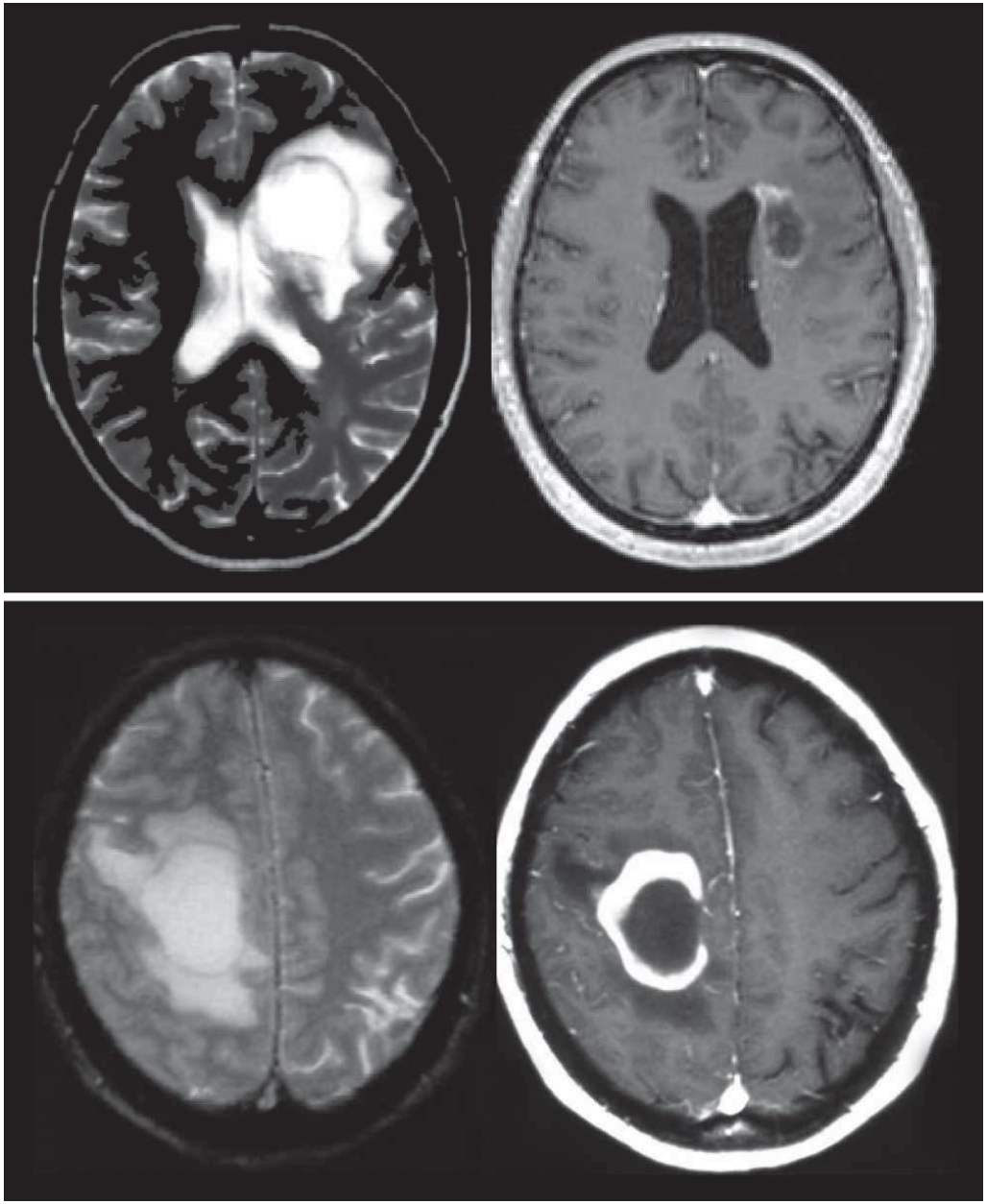
Magliozzi, R. et al. Brain 2007 130:1089-1104; doi:10.1093/brain/awm038

Copyright restrictions may apply.

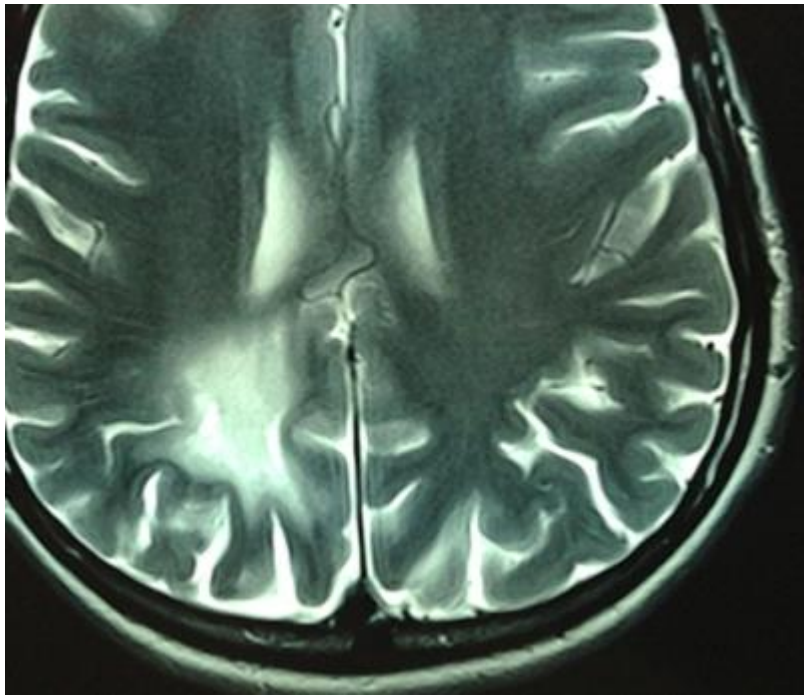
BRAIN A JOURNAL OF NEUROLOGY

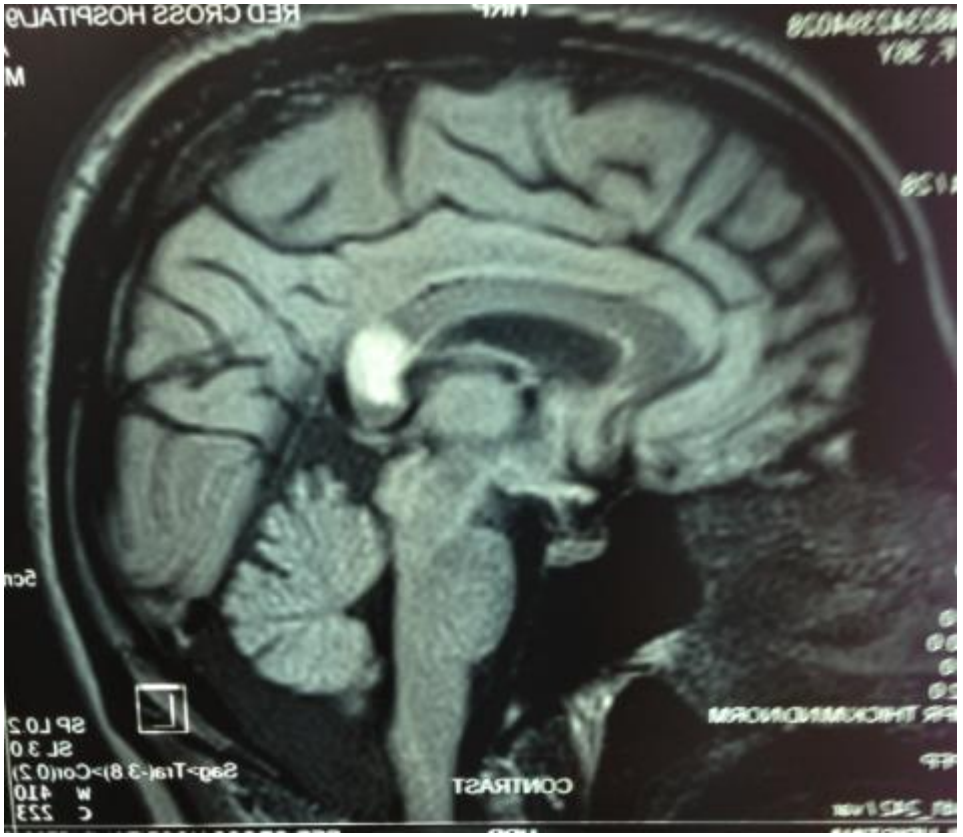

What roles might B cells have in MS Pathophysiology?
Antibody production (opsonization, complement activation)
B
Meningeal ectopic germinal centers
B
T
Antigen processing and to T cells that is target of the T and B cell
Cytokines, chemokines
(IL-10, IL-6, TNF α and lymphotoxin β, CCL3/MIP1α; CCL4/MIP1β, CCL22).

CrossA 2013

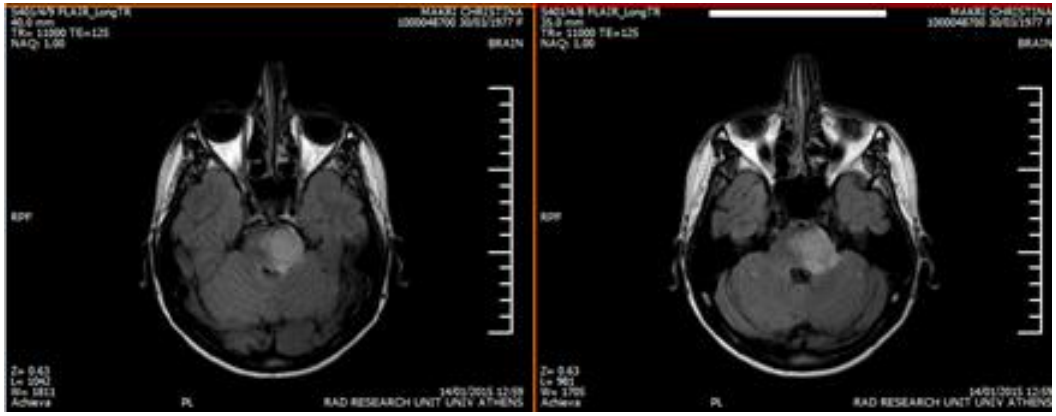


Bruck etal 2008





Pt M39 years old, tumefactive ms


BRAIN
RAD RESEARCH UNIT UNIV ATHENS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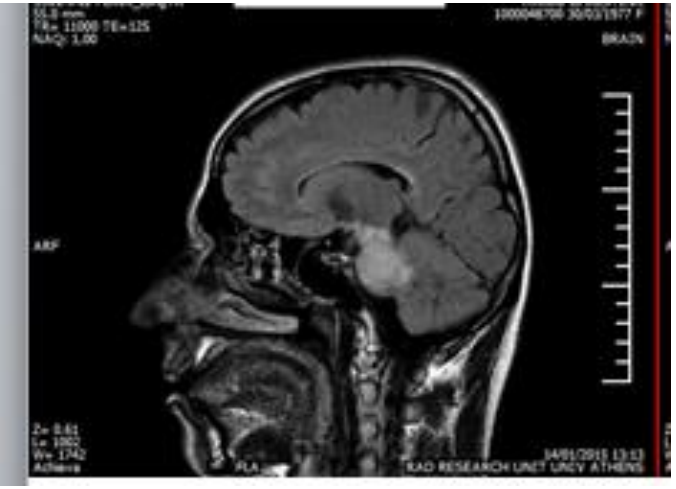
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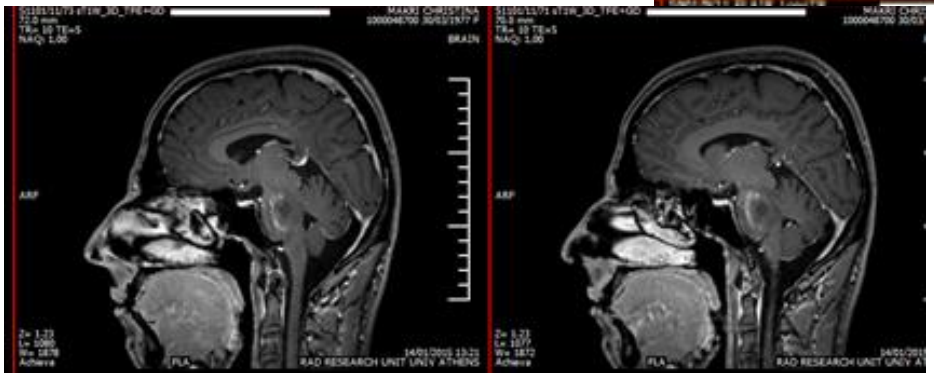
BRAIN
RAD RESEARCH UNIT UNIV ATHENS


BRAIN
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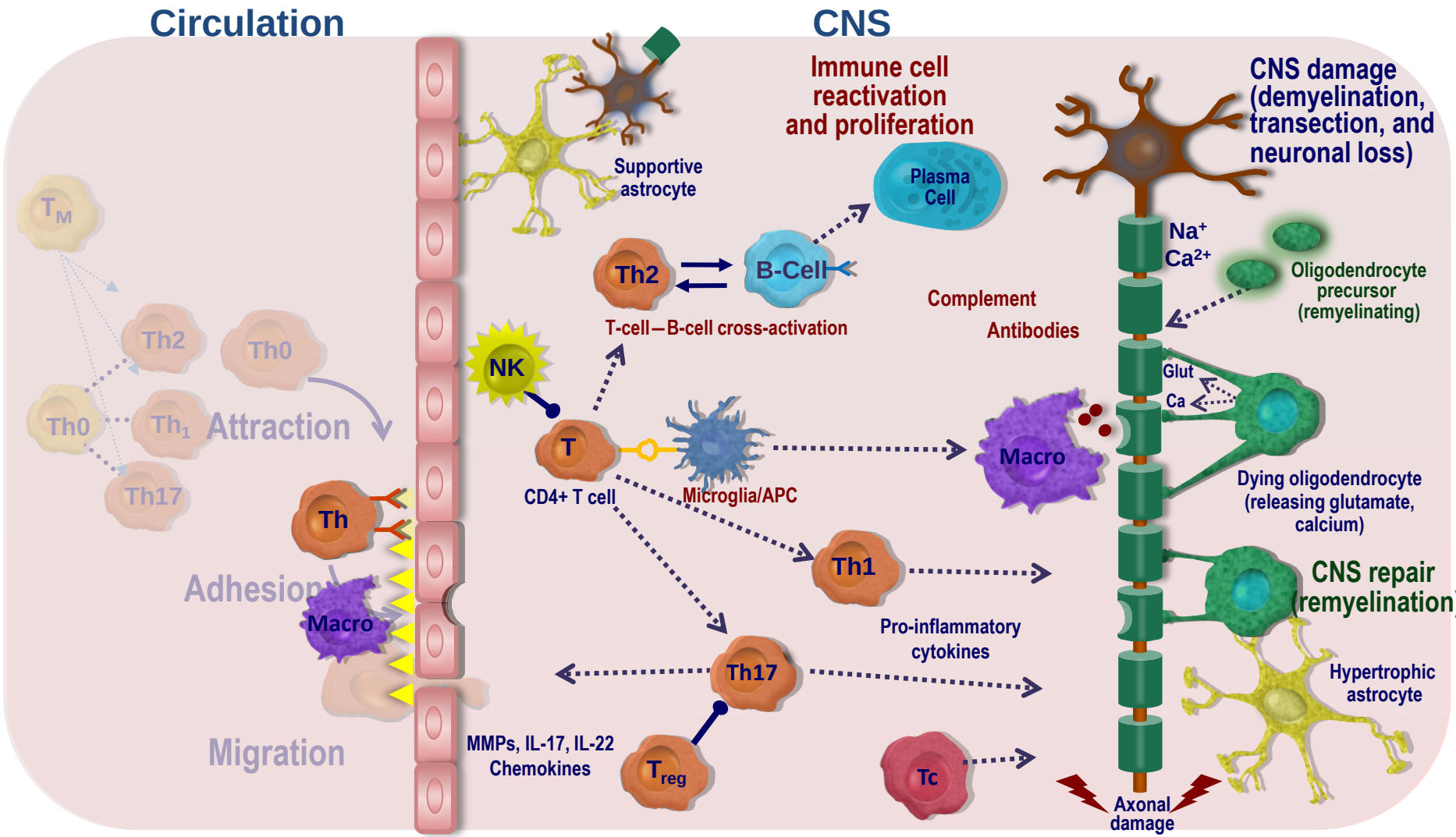
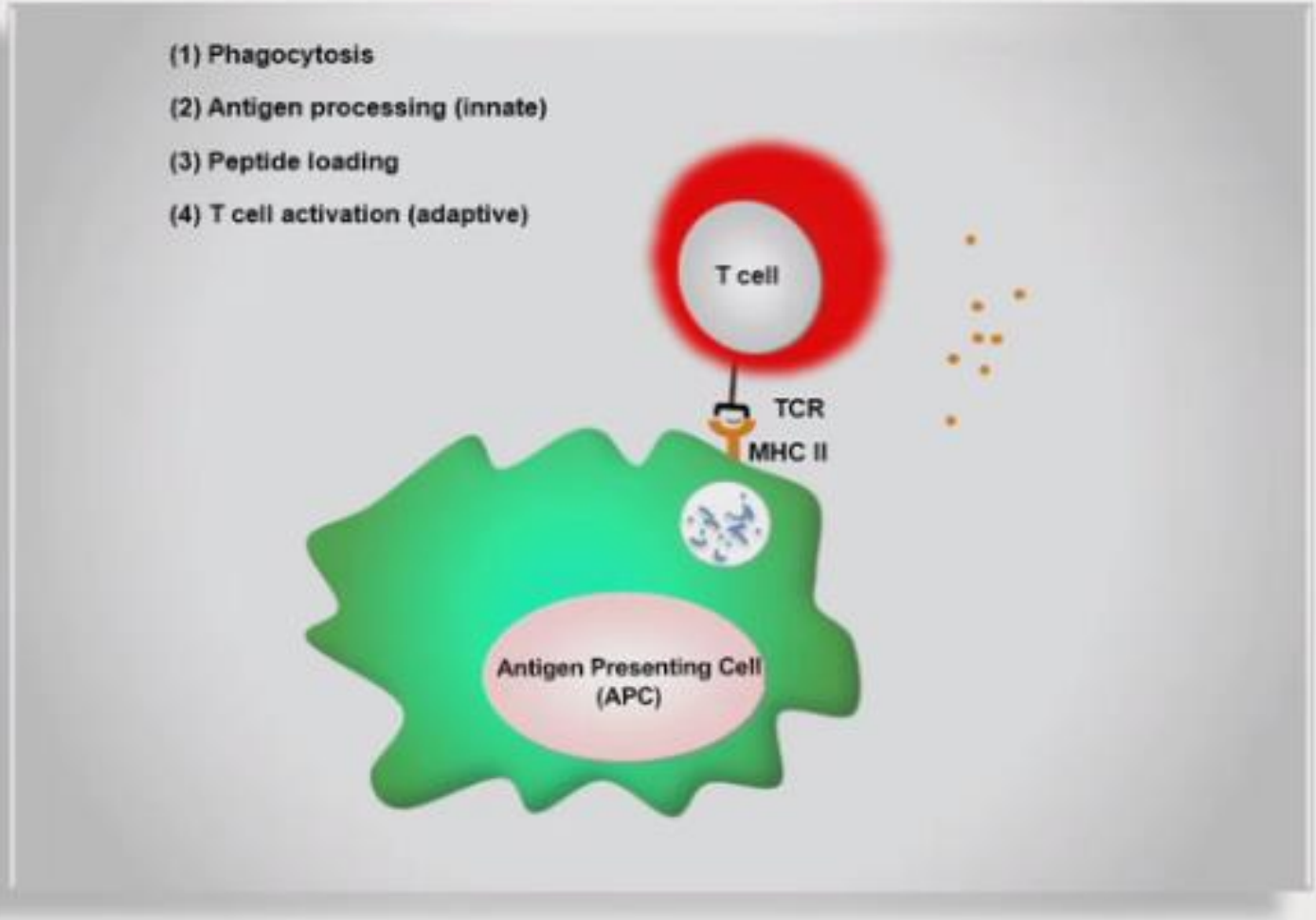
Inflammation Leads to Demyelination and Axonal Loss



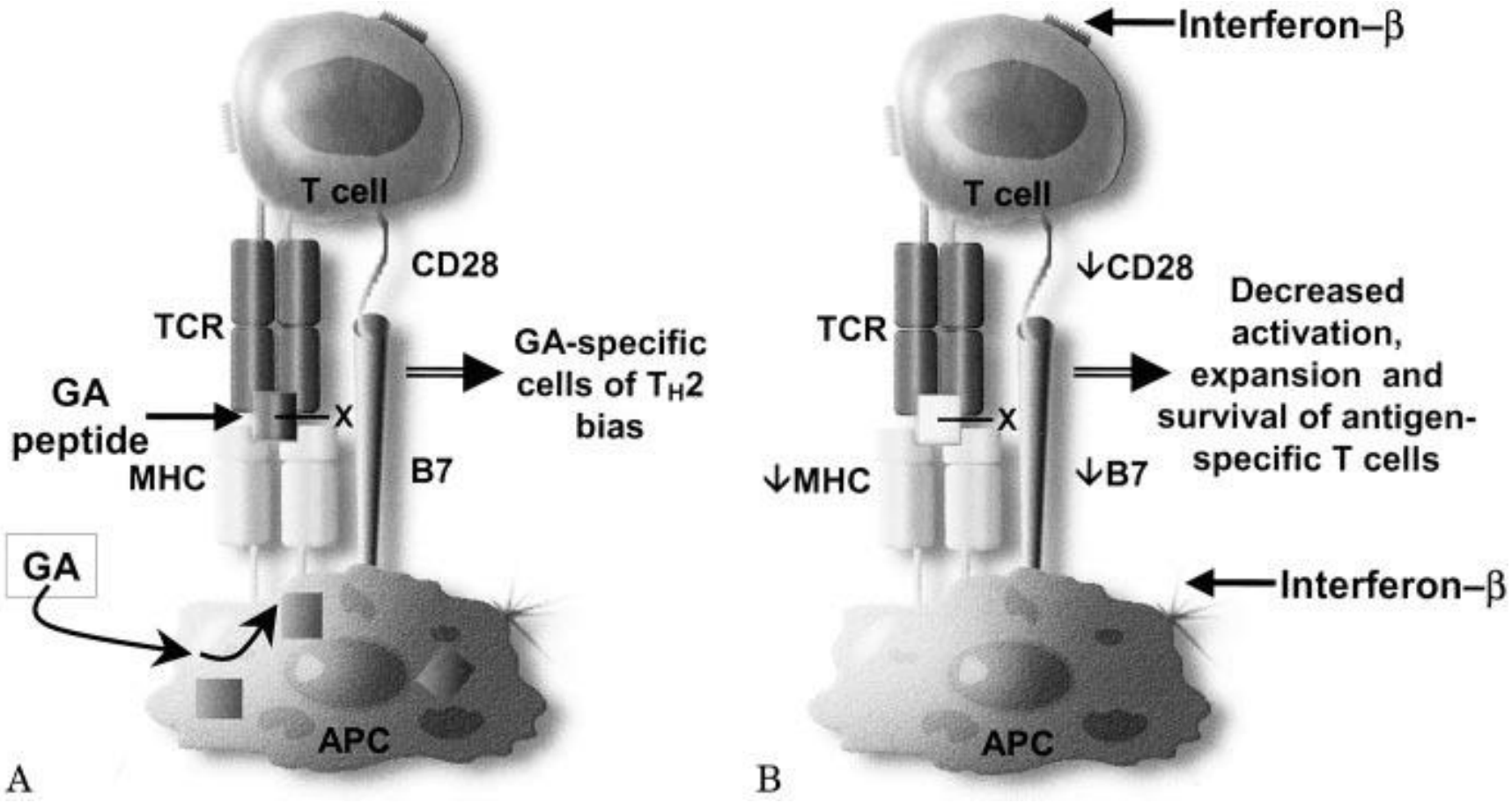
Alvarez J, et al. *Biochem Biophys Acta.* 2011;1812(2):252–264; Aminoff MJ, et al, eds. *Handbook of Clinical Neurology*. Amsterdam, The Netherlands: Elsevier BV; 2013. Barnes MP, Good CD, eds. *Neurological Rehabilitation*; vol 10 (3rd series); Frohman EM, et al. *N Engl J Med.* 2006;354(9):942-955; Frohman TC, et al, Eds. *Multiple Sclerosis for the Physician Assistant : a Practical Primer*. http://www.nationalmssociety.org Published 2011. Accessed January 23, 2014; Lopez-Diego RS, Weiner HL. *Nat Rev Drug Discov.* 2008;7(11):909-925; Murphy K, et al, eds. *Janeway's Immunobiology*. 8th ed. New York, NY: Garland Science; 2012; Wiendl H, Kieseier BC. *Expert Opin Investig Drugs*. 2003;12(4):689-712; Yong VW. *Neurology.* 2002;59(6):802-808;

TRIMOLECULAR COMPLEX

MHC class II-restricted antigen presentation
(connects innate and adaptive immunity)



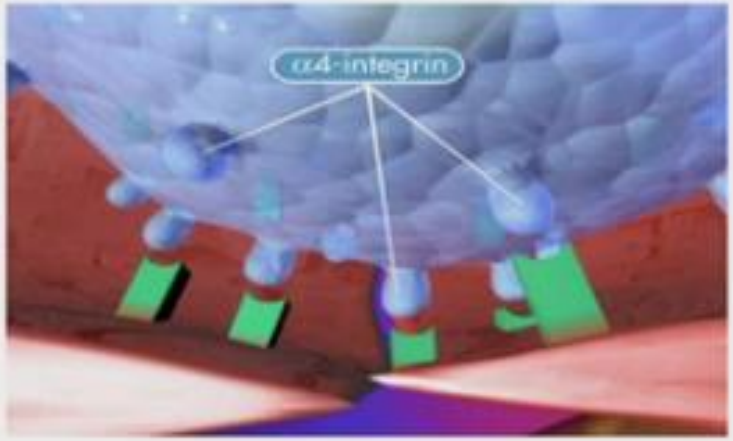
Ifn-b and GA differences
Yo et al 2002



MIGRATION

Role of α4-Integrins

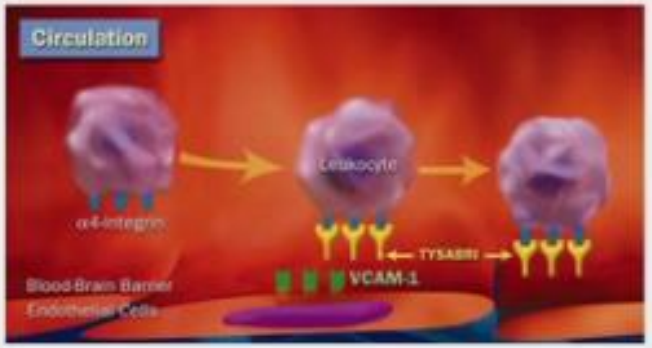
- Adhesion molecules expressed by all leukocytes except neutrophils
- Mediators of cell adhesion and transendothelial migration through the BBB
- Have been shown to modulate some immune cell activity



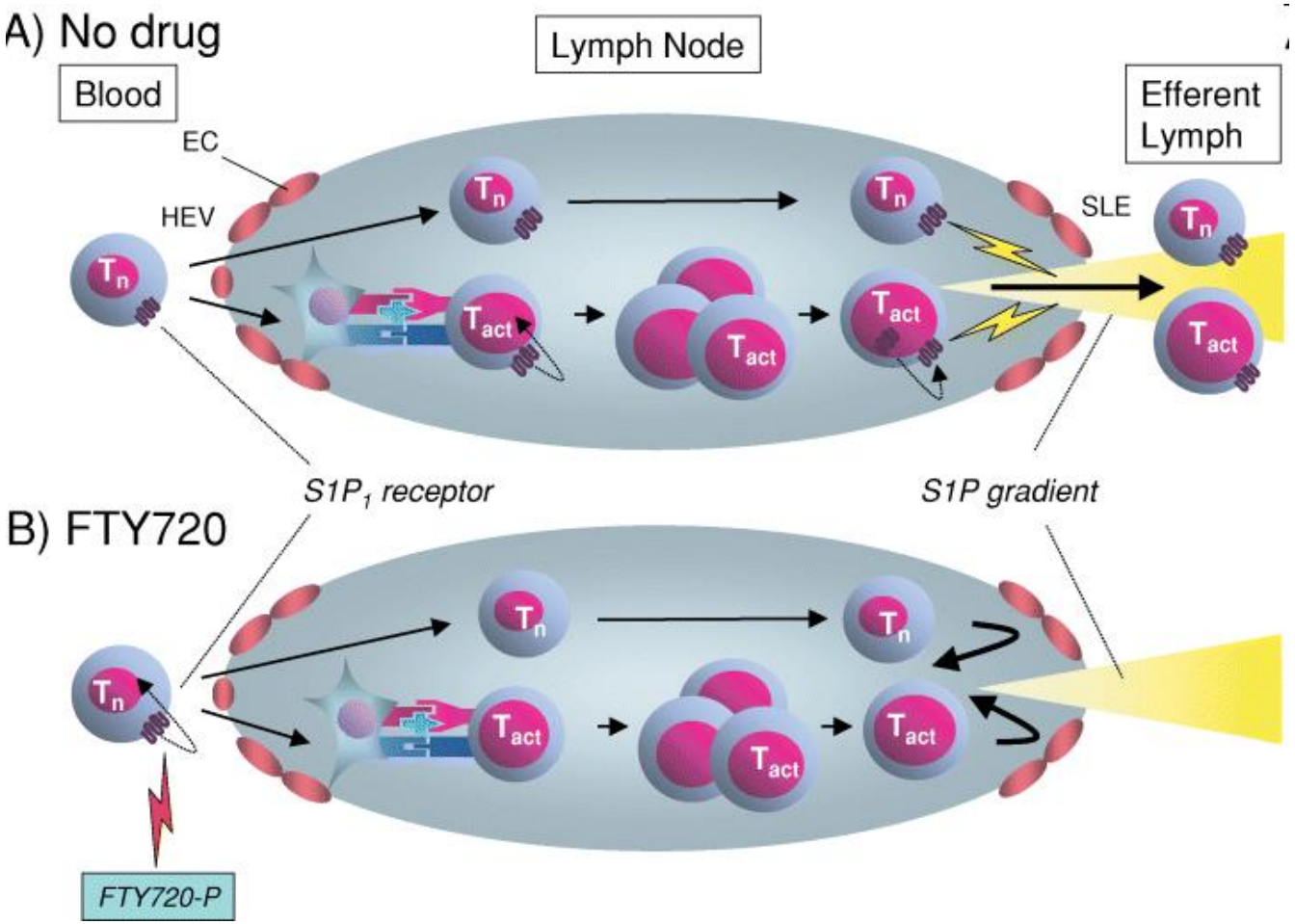
von Andrian UH, et al. *N Engl J Med*. 2003;348:68-72.

Natalizumab: Mechanism of Action

- Natalizumab binds to α4-integrin
- Prevents leukocyte transmigration into the CNS
  - Prevents α4-integrin–mediated leukocyte binding to endothelial VCAM-1, thus disrupting rolling and stopping phases of the recruitment process
- May prevent further recruitment and inflammatory responses in the CNS
  - Binds to α4-integrin ligand(s) such as osteopontin and alternatively spliced fibronectin Connecting Segment -1

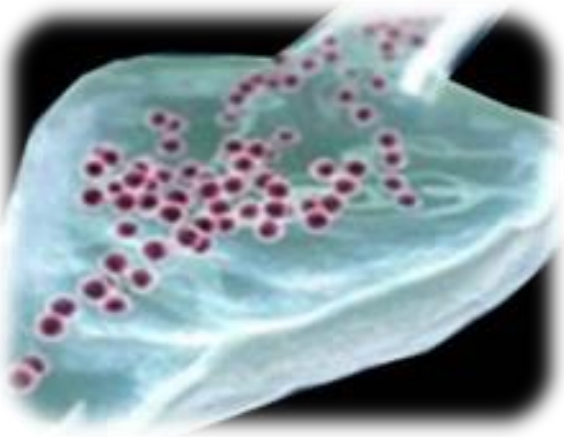


Egress from SLO

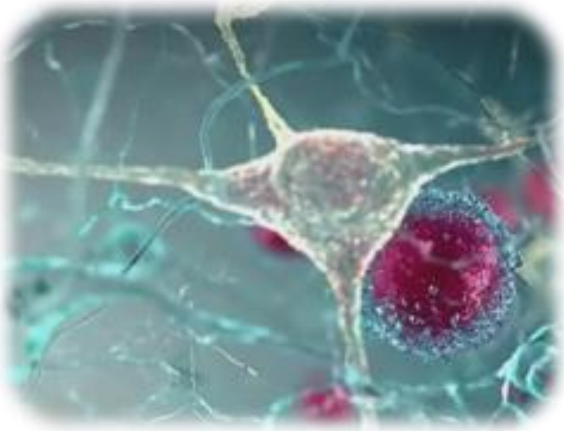


Fingolimod has a targeted mechanism of action, modulating S1P receptors peripherally and centrally

- Peripheral
  - fingolimod reversibly and selectively prevents lymphocyte egress from lymph nodes, as well as the recirculation of a subset of T and B lymphocytes through the lymph nodes.[1-3] However, a subset of T cells important for immune surveillance are unaffected[4,5]
  - fingolimod reduces infiltration of autoreactive cells into the CNS where they are involved in inflammation and tissue damage[6-9]



- Central
  - fingolimod crosses the BBB into the CNS and S1P receptors are expressed on neural cells[6-9]
  - animal model data suggest that fingolimod may limit demyelination and restore the function of neural cells[6,8,9]

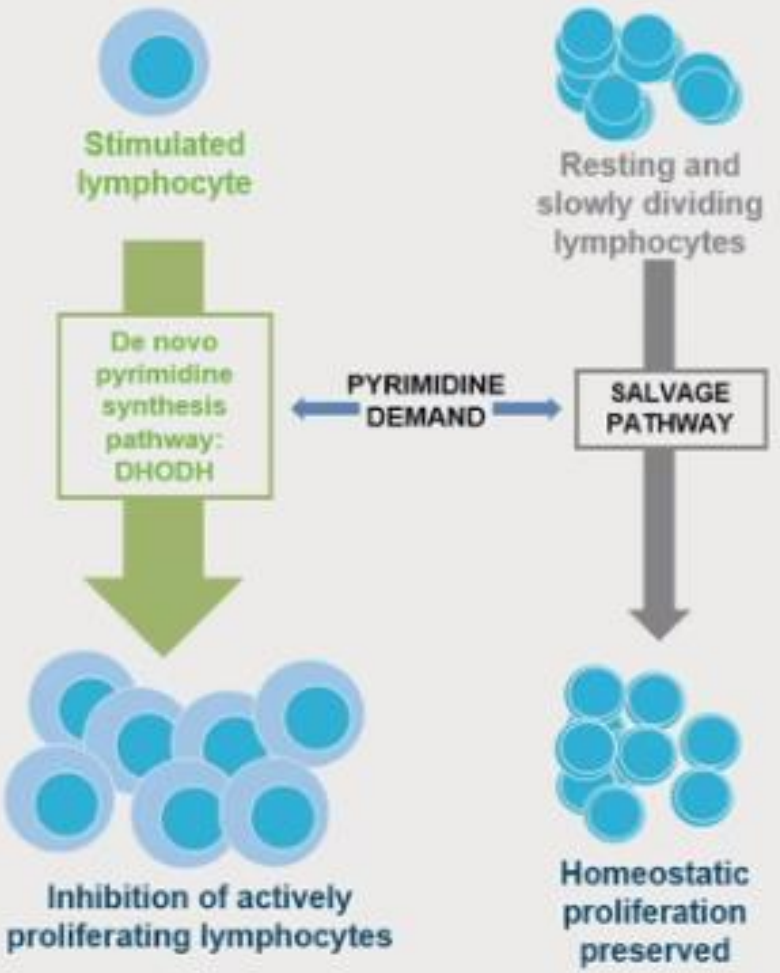


1. Brinkmann V *et al. J Biol Chem* 2002; 2. Matloubian M *et al. Nature* 2004; 3. Brinkmann V. *Br J Pharmacol* 2009;
4. Mehling M *et al. Neurology* 2008; 5. Gilenya® Prescribing Information; 6. Chun J & Hartung HP. *Clin Neuropharmacol* 2010;
7. Mehling M *et al. Neurology* 2010; 8. Aktas O *et al. Nature Reviews* 2010; 9. Brinkmann V *et al*. *Nat Rev Drug Discov* 2010

T CELL

Teriflunomide: Targeting Activated Lymphocyte Proliferation

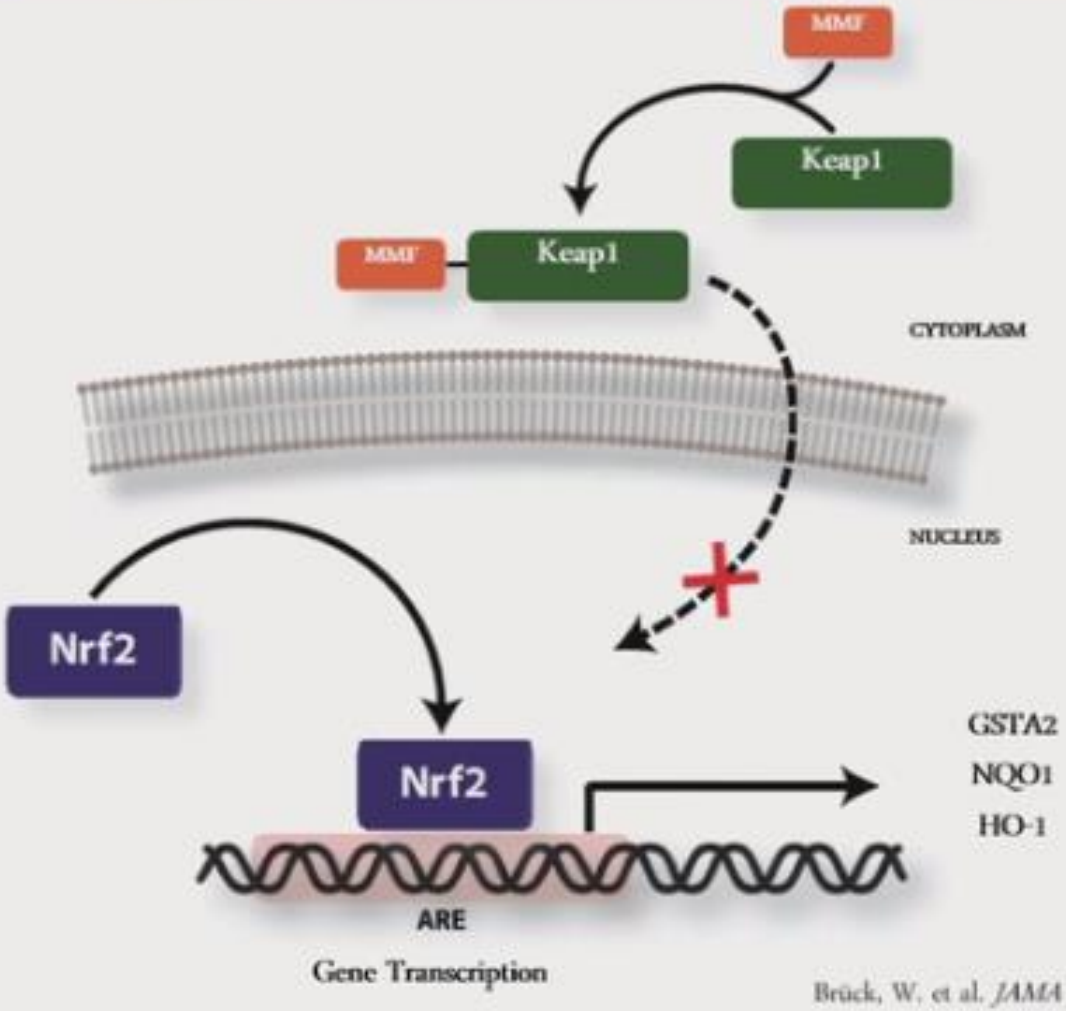
- Teriflunomide selectively and reversibly inhibits mitochondrial dihydro-orotate dehydrogenase (DHODH), impairing the proliferation of activated lymphocytes while sparing resting and slowly dividing cells*[1,2]
- The pyrimidine salvage pathway is not affected by teriflunomide[1]



* The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood

1.Gold R & Wolinsky J. Acta Neurol Scand 2011;124:75–84;
2. Warnke C et al. Neuropsychiatr Dis Treat 2009;5:333–40.

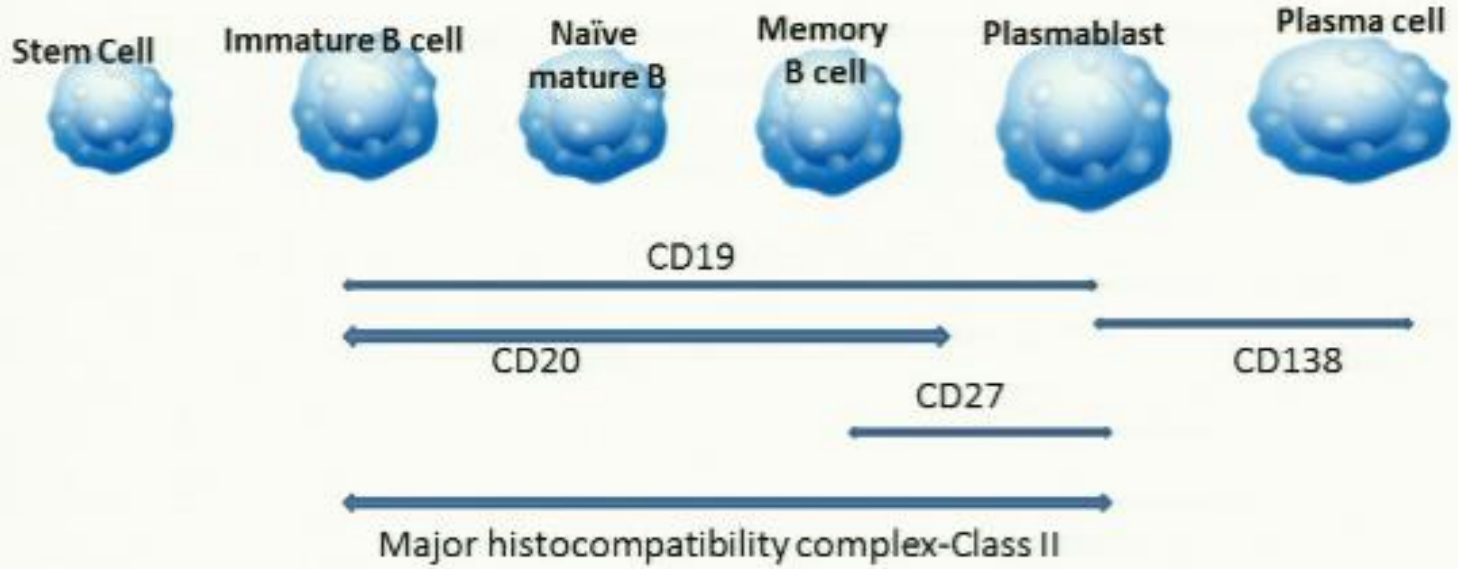
DMF and its Metabolite, MMF, "Inhibit the Inhibitor"



Brück, W. et al. *JAMA Neurol* 2013

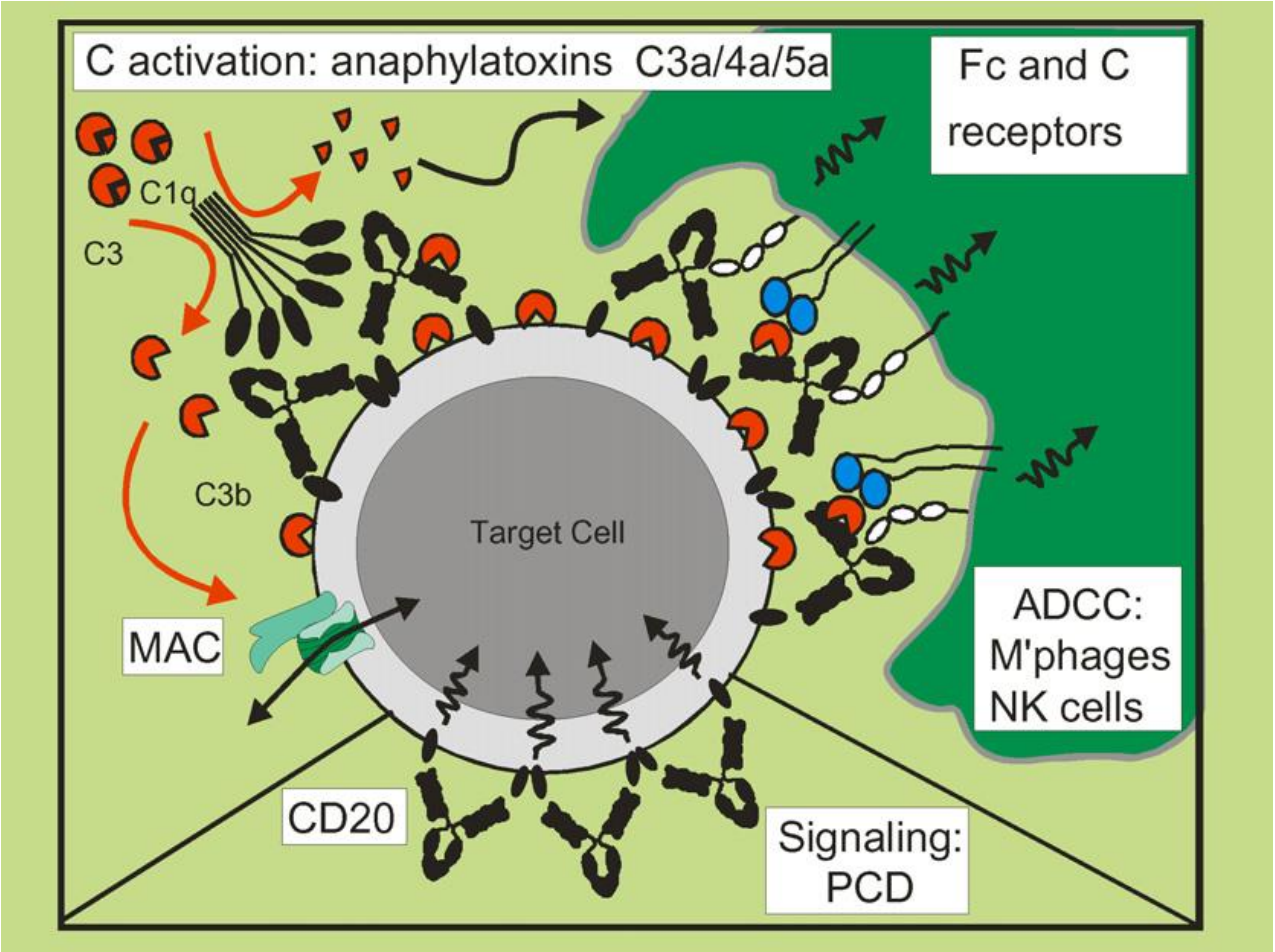
CELL DEPLETION

Surface markers during B cell ontogeny



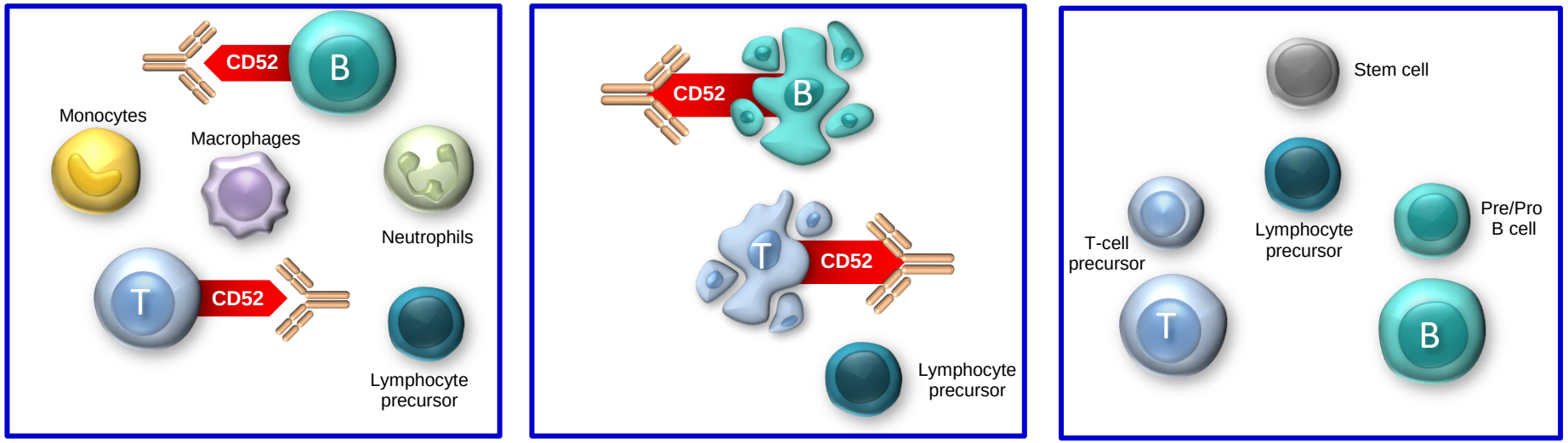
Based on Mei HE, et al. Rationale of anti-CD19 immunotherapy: an option to target autoreactive plasma cells in autoimmunity. *Arthritis Research & Therapy* 2012, 14(Suppl 5):S1.

Rituximab :mechanism of action



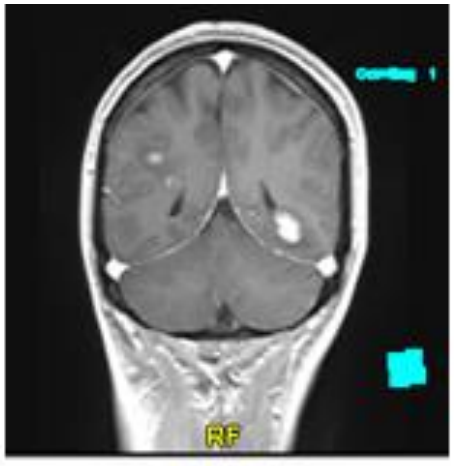
Alemtuzumab and Multiple Sclerosis: Mechanism of Action and Summary of Safety and Efficacy

Selection → Depletion → Repopulation



- **High efficacy in drug-naive patients *and* also useful as rescue therapy in drug resistant relapsing-remitting multiple sclerosis**
  - **No *net* benefit in progressive disease despite suppression of new lesions**
- **Unexpected adverse effects profile**
  - **Acute cytokine release syndrome**
  - **Low risk of opportunistic infection**
  - **Secondary thyroid autoimmunity**
- **Evidence for (post-inflammatory) neuroprotection**
- **Potential for enhancing endogenous remyelination**


ID: 1017493
9/2/2016
22:55:22
HFS
4/7/1996, 029Y
St: 22101
Se: 103
Im: 17
5 cm
L
P
F
R
A
H
TR: 20
TE: 4.92
Inj. with i.v. contrast
PFP
*tf3d1_ns
Ep: 5
L = 116
W = 264
0 256 240 0
RF
RF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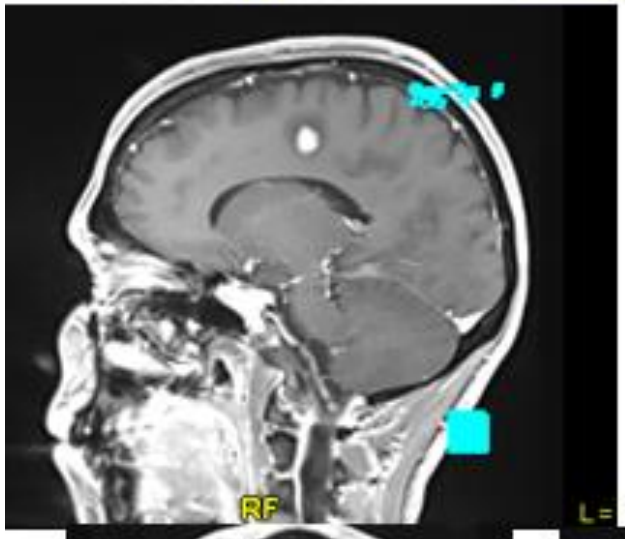
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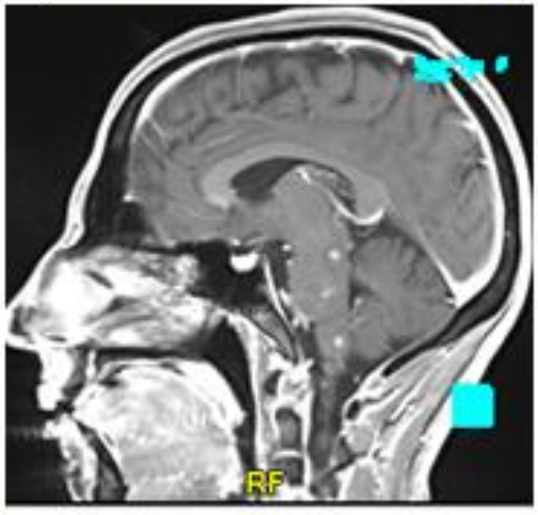
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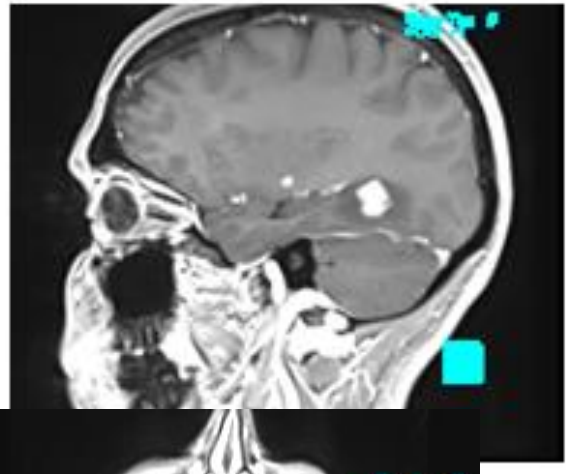
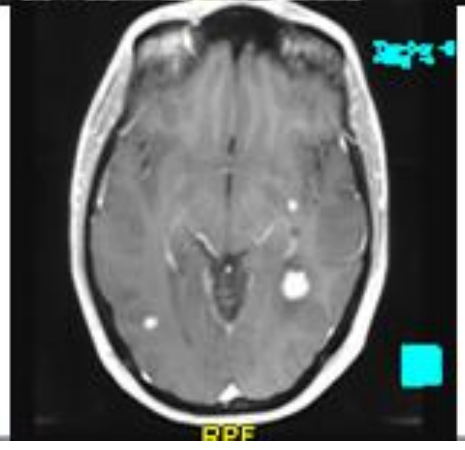
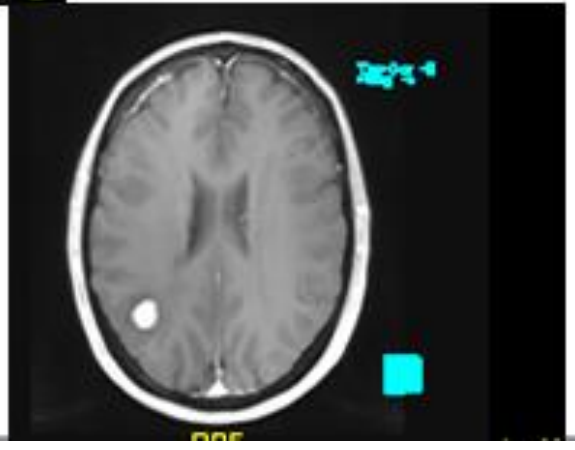
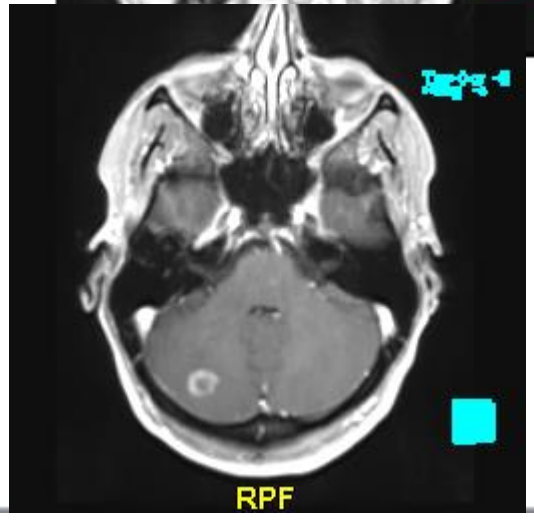
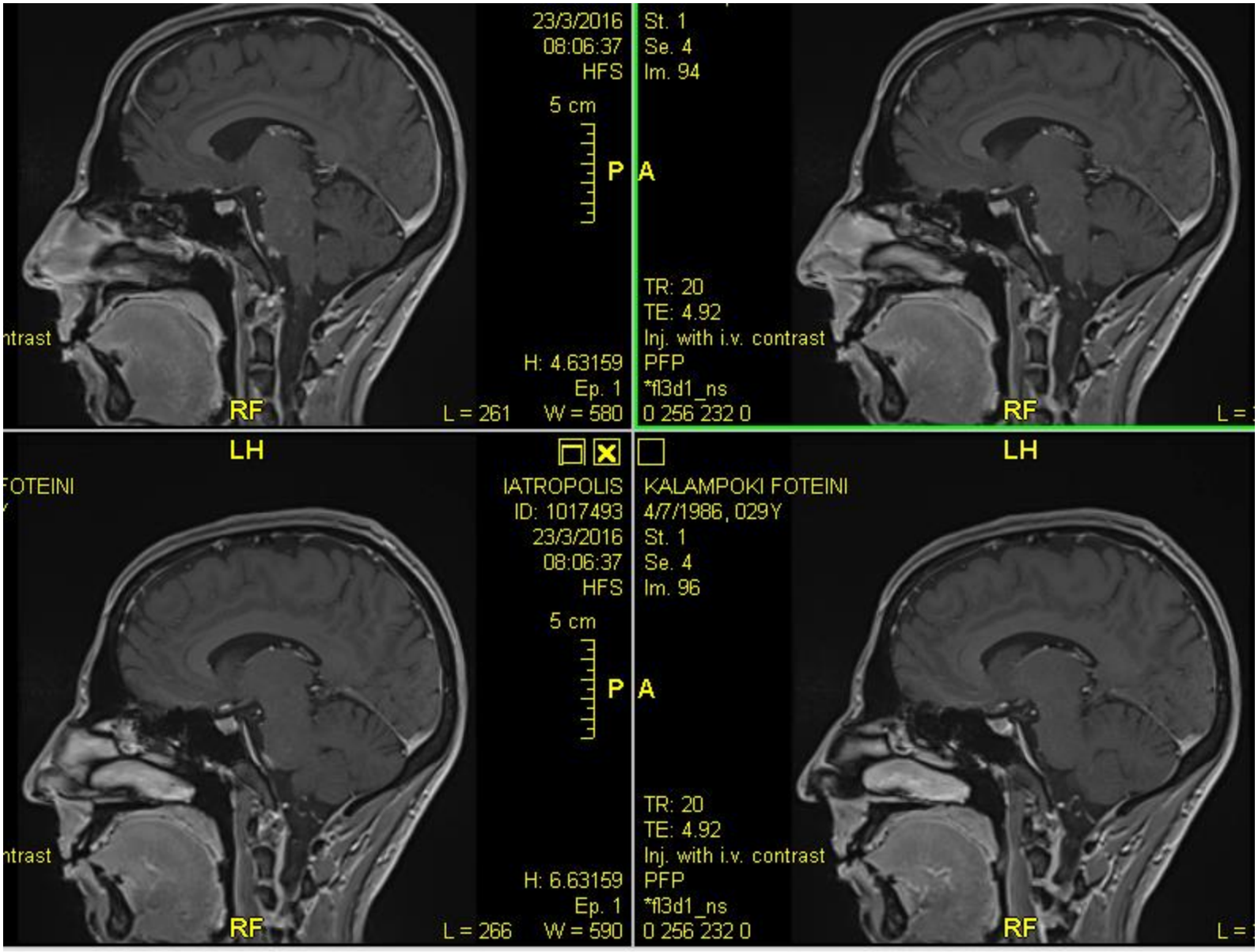



RPF

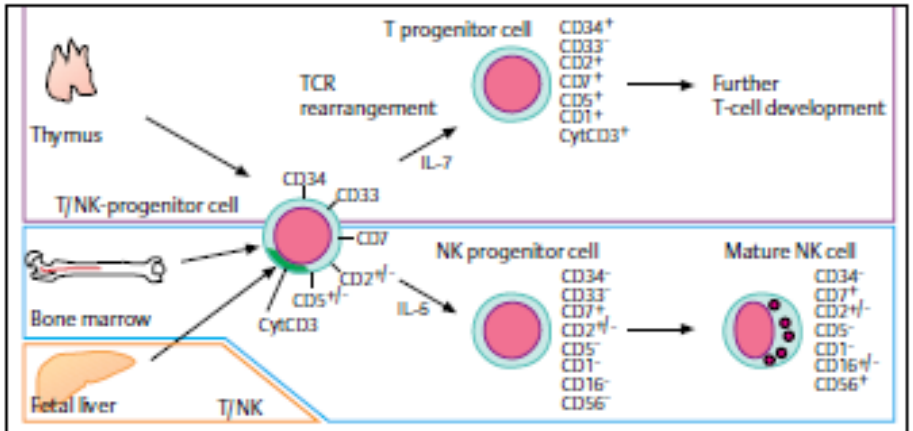



RPF

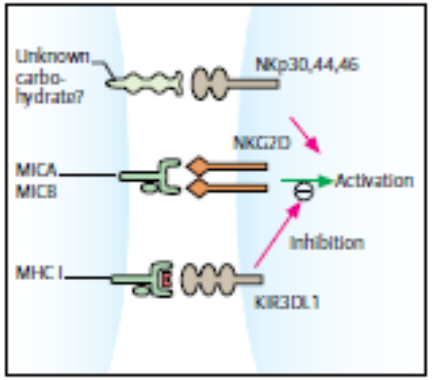
After alemtuzumab


23/3/2016
08:06:37
HFS
5 cm
P
ntrast
H: 4.63159
Ep. 1
RF
L = 261
W = 580
St. 1
Se. 4
Im. 94
A
TR: 20
TE: 4.92
Inj. with i.v. contrast
PFP
*fl3d1_ns
0 256 232 0
RF
LH
FOTEINI
IATROPOLIS
ID: 1017493
23/3/2016
08:06:37
HFS
5 cm
P
ntrast
H: 6.63159
Ep. 1
RF
L = 266
W = 590
KALAMPOKI FOTEINI
4/7/1986, 029Y
St. 1
Se. 4
Im. 96
A
TR: 20
TE: 4.92
Inj. with i.v. contrast
PFP
*fl3d1_ns
0 256 232 0
RF
LH

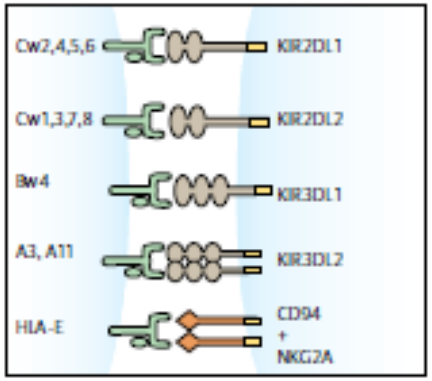
NK cells



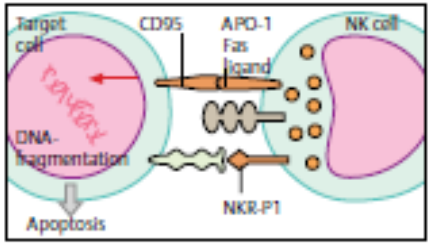
A. Development of NK cells



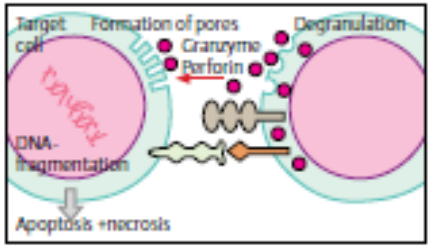
B. Target recognition by NK cells



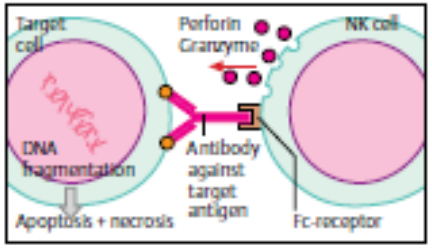
C. Inhibitory receptors of NK cells



1. Nonsecretory lysis

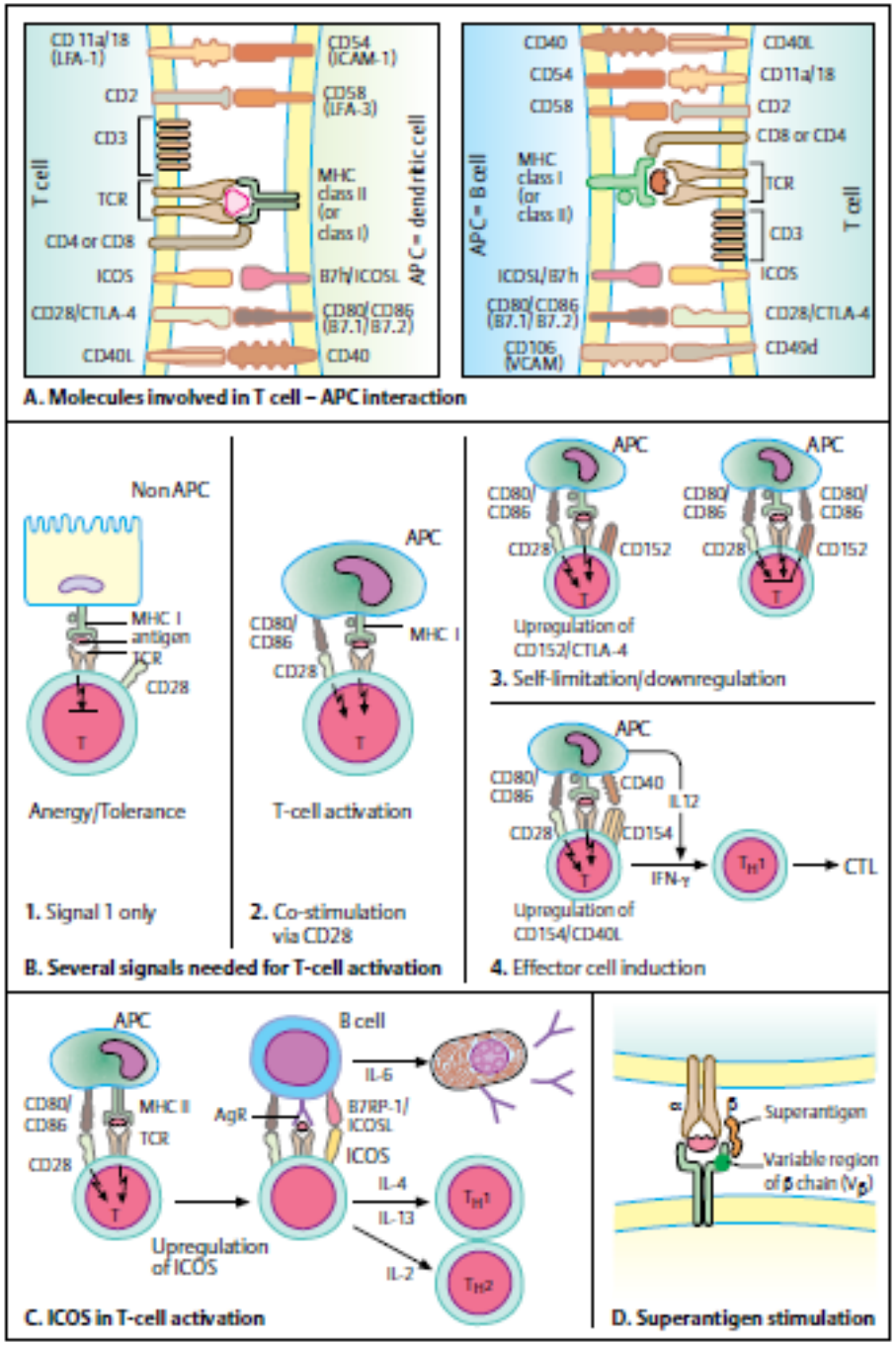


2. Secretory lysis



3. ADCC (antibody-dependent cellular cytotoxicity)

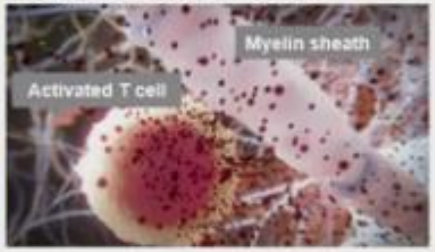
D. Cytolytic mechanisms of NK cells


CD 11a/18 (LFA-1)
CD2
CD3
TCR
CD4 or CD8
ICOS
CD28/CTLA-4
CD40L
T cell
CD54 (ICAM-1)
CD58 (LFA-3)
MHC class II (or class I)
B7h/ICOSL
CD80/CD86 (B7.1/B7.2)
CD40
APC = dendritic cell
A. Molecules involved in T cell – APC interaction
CD40
CD54
CD58
MHC class I (or class II)
ICOSL/B7h
CD80/CD86 (B7.1/B7.2)
CD106 (VCAM)
APC = B cell
CD40L
CD11a/18
CD2
CD8 or CD4
TCR
CD3
ICOS
CD28/CTLA-4
CD49d
T cell
Non APC
MHC I antigen
TCR
CD28
Anergy/Tolerance
1. Signal 1 only
APC
CD80/CD86
MHC I
CD28
T-cell activation
2. Co-stimulation via CD28
APC
CD80/CD86
CD28
CD152
Upregulation of CD152/CTLA-4
3. Self-limitation/downregulation
APC
CD80/CD86
CD40
IL12
CD28
CD154
IFN-γ
T_H1
CTL
Upregulation of CD154/CD40L
4. Effector cell induction
B. Several signals needed for T-cell activation
APC
CD80/CD86
MHC II
TCR
CD28
B cell
AgR
IL-6
B7RP-1/ICOSL
ICOS
IL-4
IL-13
IL-2
T_H1
T_H2
Upregulation of ICOS
C. ICOS in T-cell activation
α
β
Superantigen
Variable region of β chain (V_β)
D. Superantigen stimulation

Activated T cells and CD56^{bright} NK cells are functionally modulated by IL-2 through distinct IL-2 receptors

High-affinity IL-2R

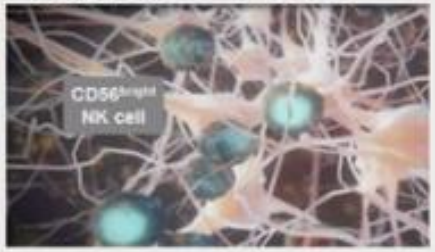
On activated T cells



- IL-2 signalling induces expansion and differentiation of activated T cells[1]
  - Anti-CD25 antibody binds the α chain (CD25) and blocks IL-2 association with the high-affinity IL-2R[1,2]

Intermediate-affinity IL-2R

On CD56^{bright} NK cells



- IL-2 signalling induces expansion and activation of CD56^{bright} NK cells[3]
  - Anti-CD25 antibody permits IL-2 signalling through the intermediate-affinity IL-2R[2,4]

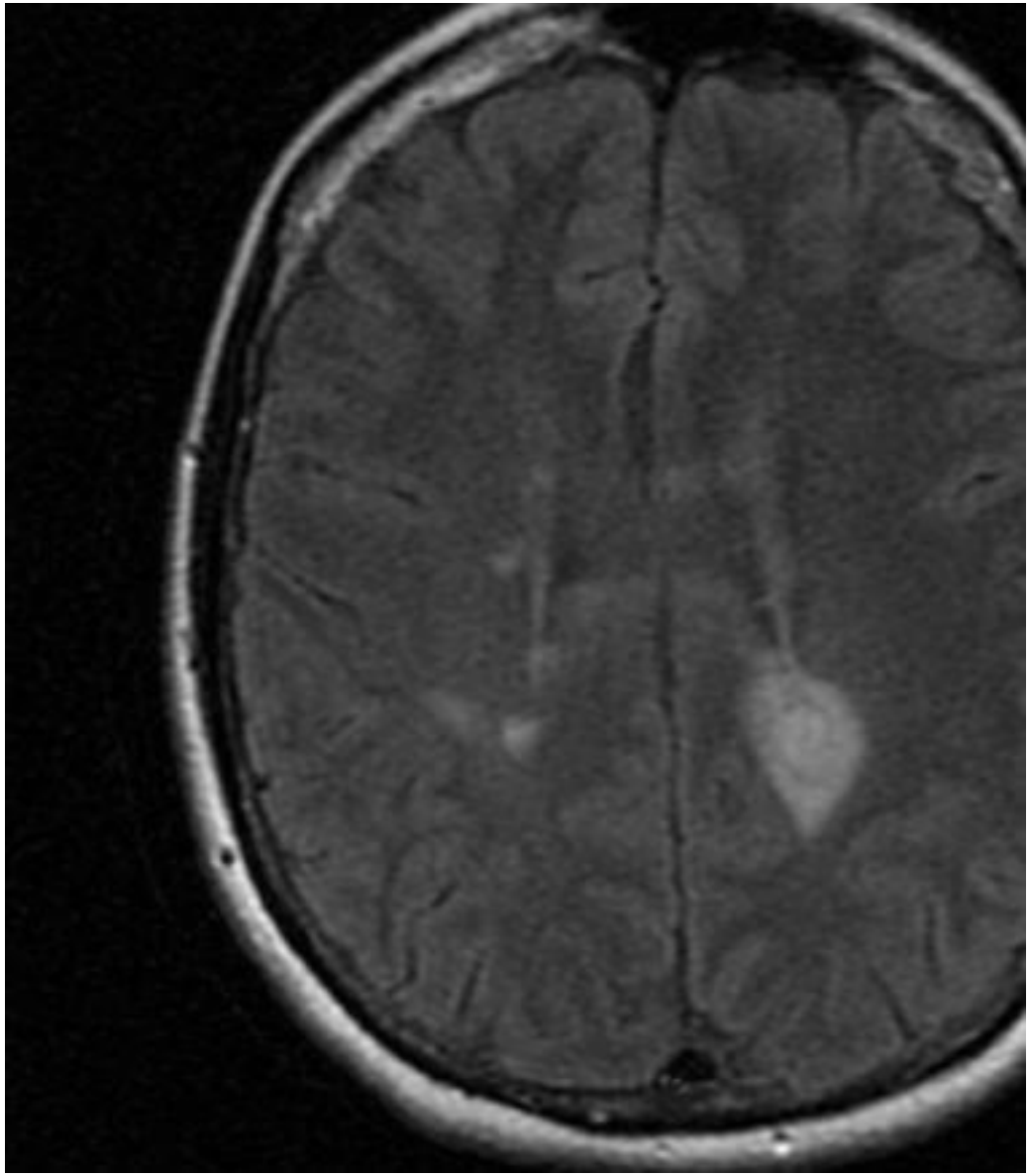
1. Bielekova B. *Neurotherapeutics*. 2013;10:55-67; 2. Amaravadi L et al. Presented at AAN; Washington, USA; 2015:P1.149;
3. Wiendl H et al. *Nat Rev Neurol*. 2013;9:394-404; 4. Pfender N et al. *Exp Neurol*. 2014;262:44-51.

Antibody targets in nervous system

- Central and Peripheral Myelin [MS andPN]
- Ranvier nodes [MN with MMCB]
- Neuromuscular junction [MG]
- Neuron [Paraneoplastic syndromes, autoimmune encephalopathy]
- Astrocytes [NMO]
- Oligodendrocyte

Ι. Αυτοαντισώματα κατά γλοιοκυττάρων

- **Anti-AQP4 (αστροκύτταρα)**
- **Anti-MOG (ολιγοδενδροκύτταρα)**



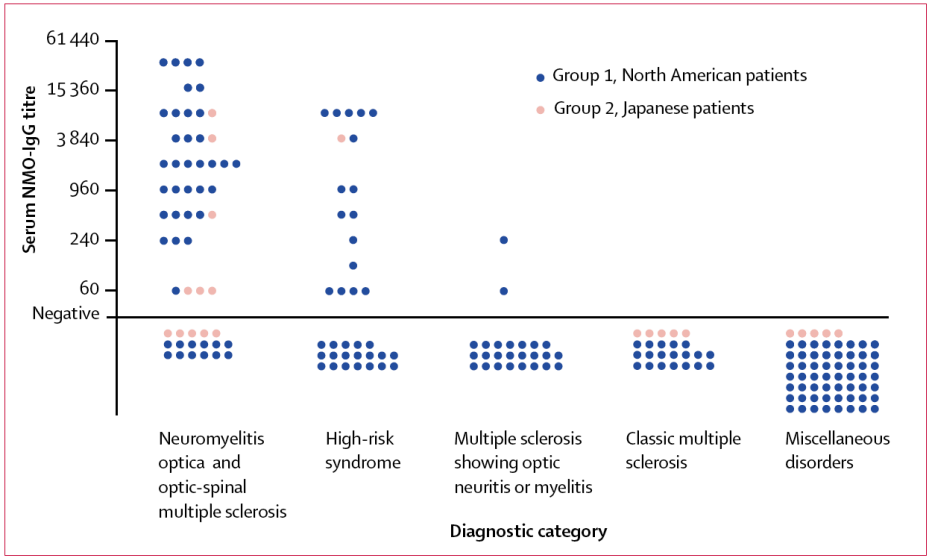
KD female

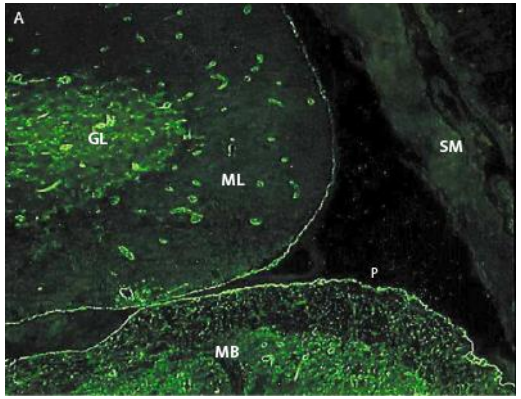
NMO IMUNOLOGY

- ANTIGEN
- Aqp4,molecular studies,tissue distribution, CNS topografy
- IMMUNE EFECTORS
- Immunoglobulins,complement
- IMMUNE ACTIVATION
- T and B-cells ,B cell epitopes,peripheral activation
- LESSION MECHANISM

Αντι-AQP4 ως ειδικός βιοδείκτης στην NMO

2004: NMO-IgG

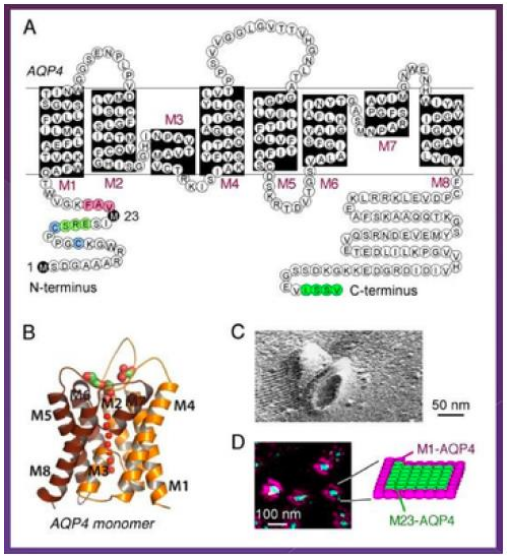


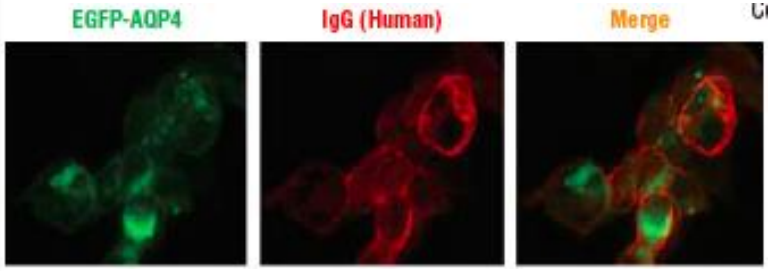


NMO-IgG στο ~50% των NMO

Lennon et al; 2004 Lancet

2005: Αντι-AQP4

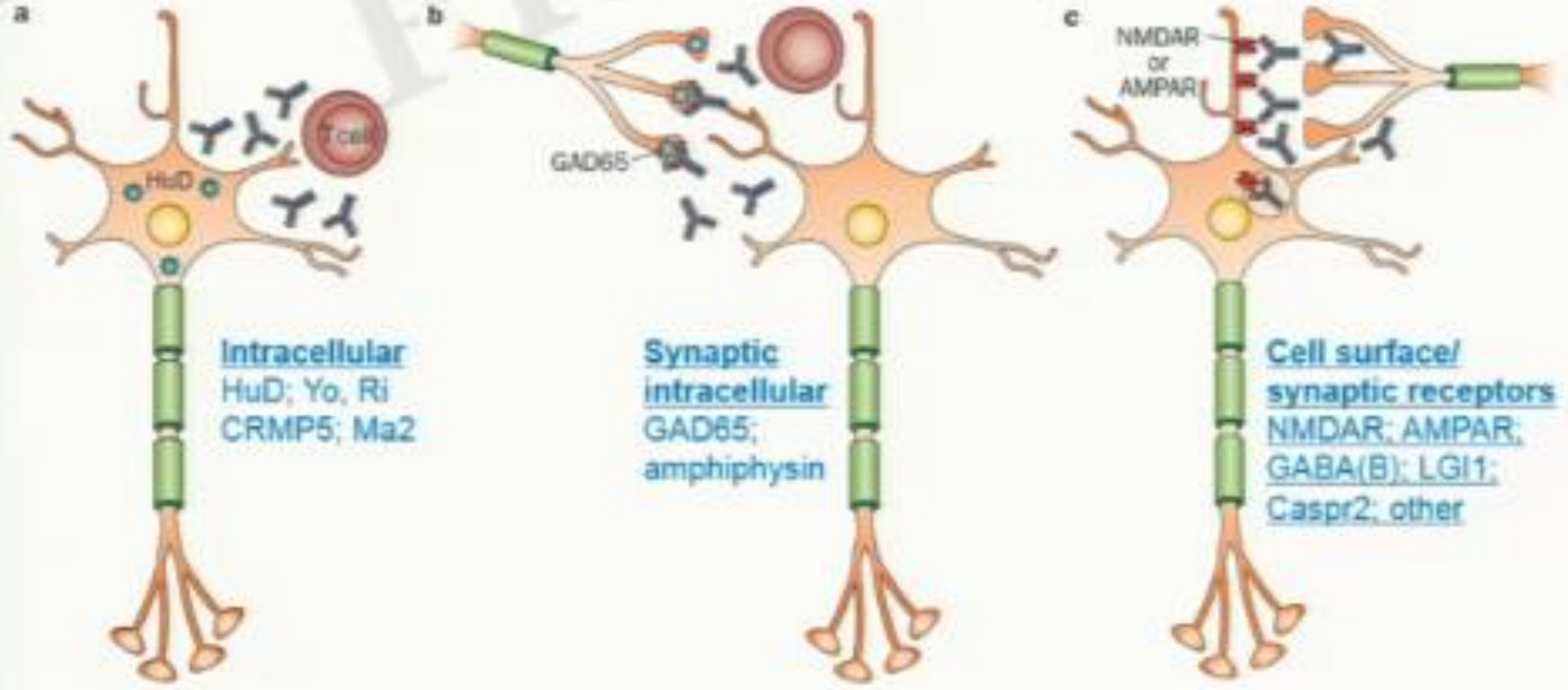




Anti-AQP4 στο 55-80% NMOsd

Waters et al, 2012 Neurology

ANTOBODIES AND AUTOIMMUNE ENCEPHALOPATHIES [THE ANTI-NMDR]



Intracellular
HuD; Yo, Ri
CRMP5; Ma2

- Encephalomyelitis
- Cerebellar degeneration
- Sensory ataxia
- Chorea
- Hypokinesia, rigidity
- Opsoclonus

Synaptic intracellular
GAD65; amphiphysin

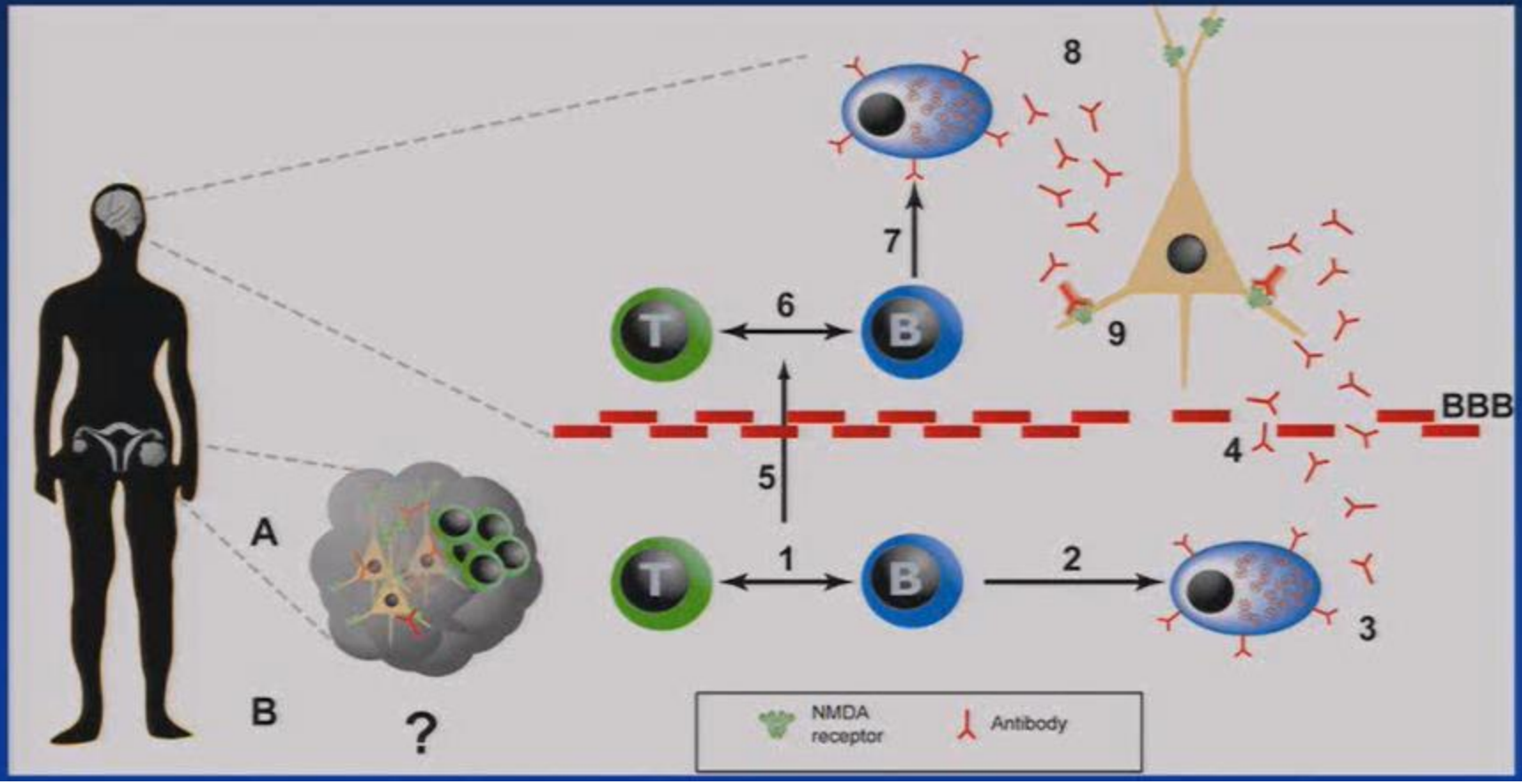
- Spectrum of Stiff-person syndrome,
- Limbic encephalitis,
- Seizures

Cell surface/ synaptic receptors
NMDAR; AMPAR; GABA(B); LGI1; Caspr2; other

- Psychosis
- Limbic encephalitis
- Dyskinesias
- Seizures
- Level of consciousness,
- Autonomic instability
- Sleep dysfunction

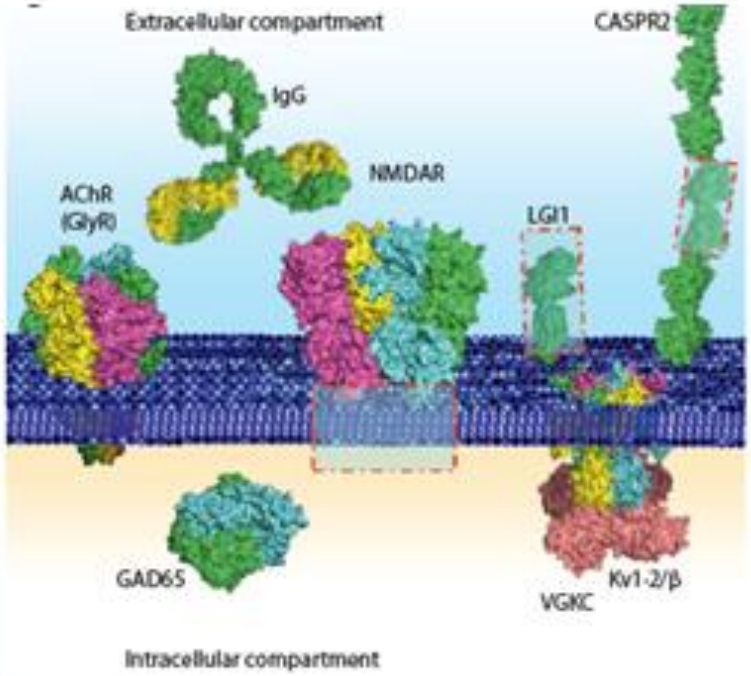
Lancaster and Dalmau, Nat Review Neurol 2012;8:380-390

NMDAR antibody synthesis and effects in the CNS

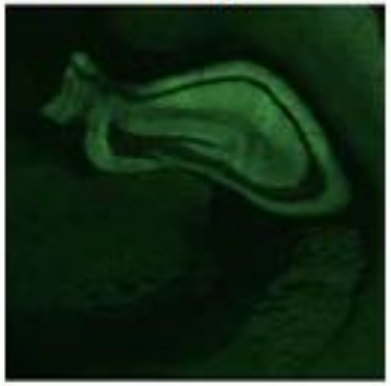


2. Αυτοαντισώματα κατά εξωκυτταρικών αντιγόνων νευρικών κυττάρων

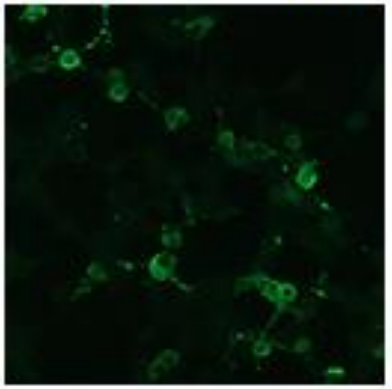
- Θεωρούνται παθογόνα
- Μόνο μερικές φορές σχετίζονται με όγκους
- Μερικές φορές παράγονται μετά από φλεγμονή, όπως μετά από HSV εγκεφαλίτιδα



Ανοσοφθορισμός σε ιππόκαμπο

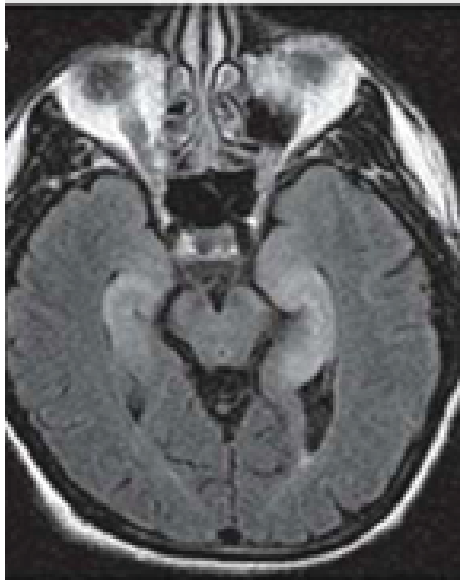


Κυτταρικός ανοσοφθορισμός (CBA)



Πρόσφατα προτεινόμενα κριτήρια για τη διάγνωση αυτοάνοσης εγκεφαλίτιδας χωρίς τη χρήση αντισωμάτων

- **Υποξεία επιδείνωση κλινικής εικόνας* <3 μήνες**
- **Αμφοτερόπλευρες βλάβες στον ιππόκαμπο στην MRI**
- **Παθολογικό ΕΝΥ ή ΗΕΓ**
- **Αποκλεισμός άλλης διάγνωσης**



*Ανοϊκή συνδρομή, επιληπτικές κρίσεις, ψυχικές διαταραχές

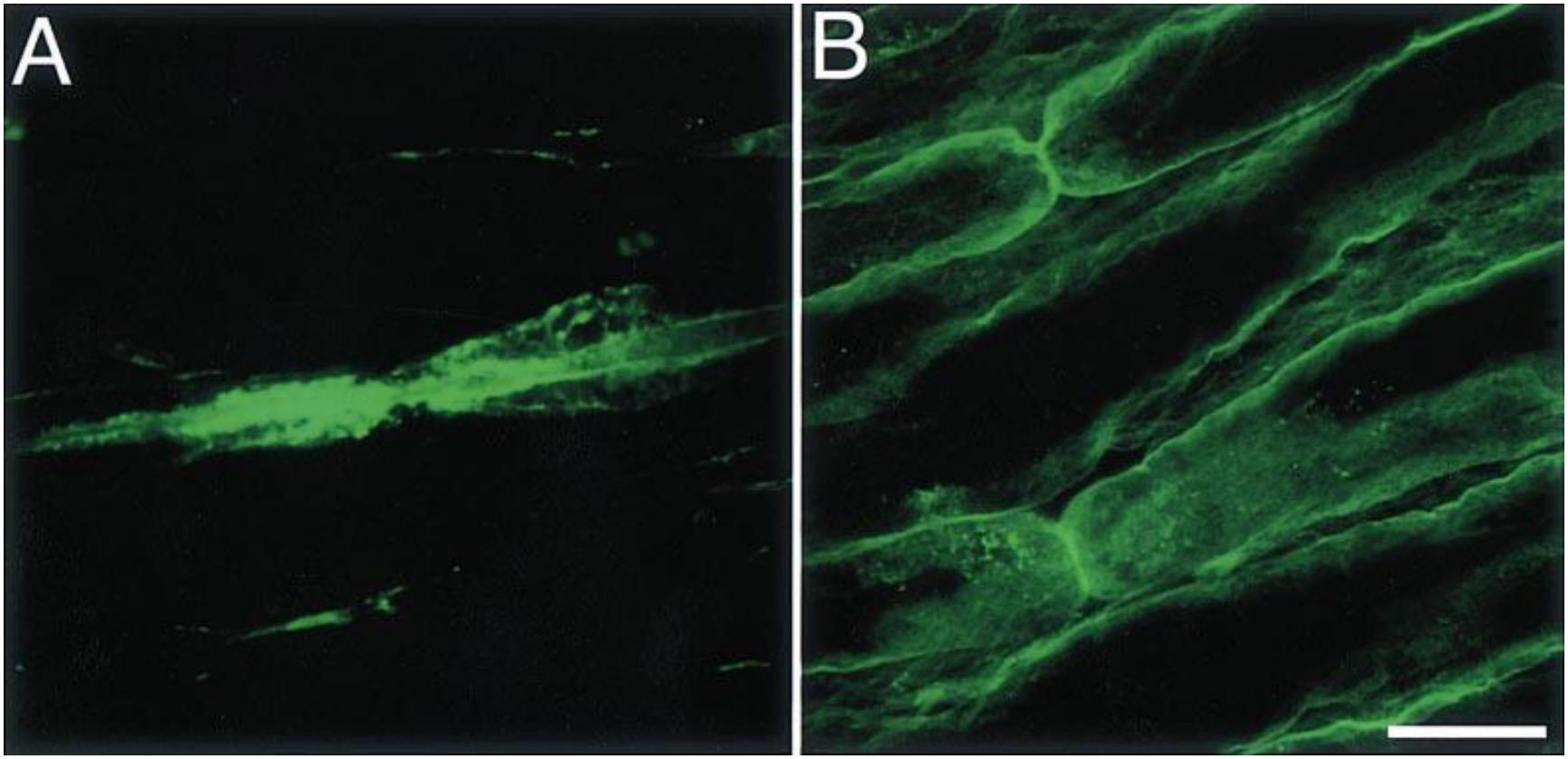
Graus et al 2016, Lancet Neurology

Antibody targets in nervous system

- Central and Peripheral Myelin [MS andPN]
- Ranvier nodes [MN with MMCB]
- Neuromuscular junction [MG]
- Neuron [Paraneoplastic syndromes, autoimmune encephalopathy]
- Astrocytes [NMO]
- Oligodendrocyte

Peripheral neuropathy

- Autoantibodies against
- gagliosides[GM1,GM2,GD1a,GD1b,GT1a,GQ1b cerebroside[Galc,SGPG, SGLPG Sulfatide]
- Proteins [MAG, OMgp,P0,PMP22 ,P2]
- Proteins- gagliosides cross reactivities
- T- cell indepented reactions


A
B

- Topographical distribution of antigen determines the clinical syndrome
- GM1 mainly localised in Ranvier nodes
- Clinical syndrome Motor neuropathy

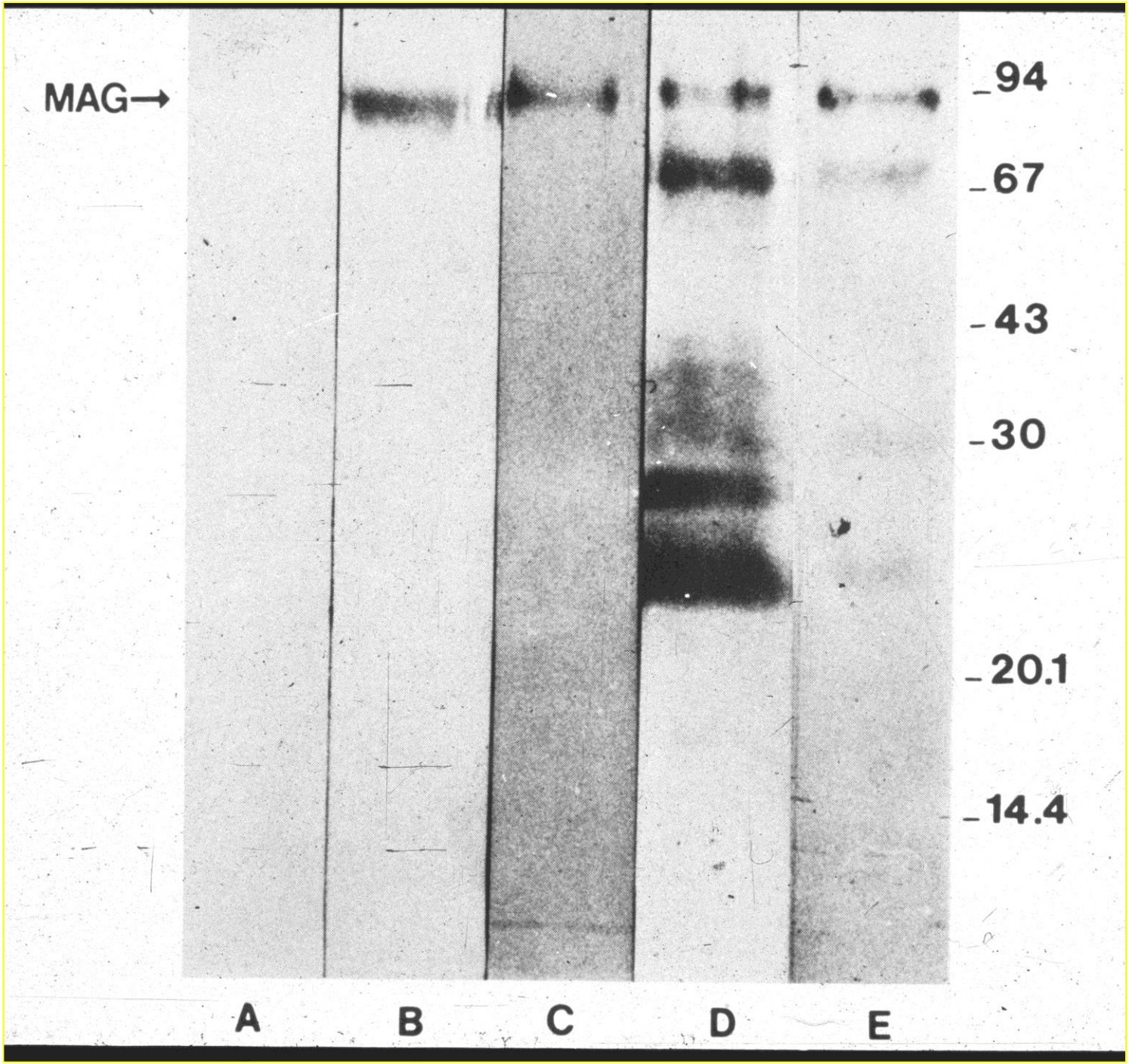
with multifocal conduction block

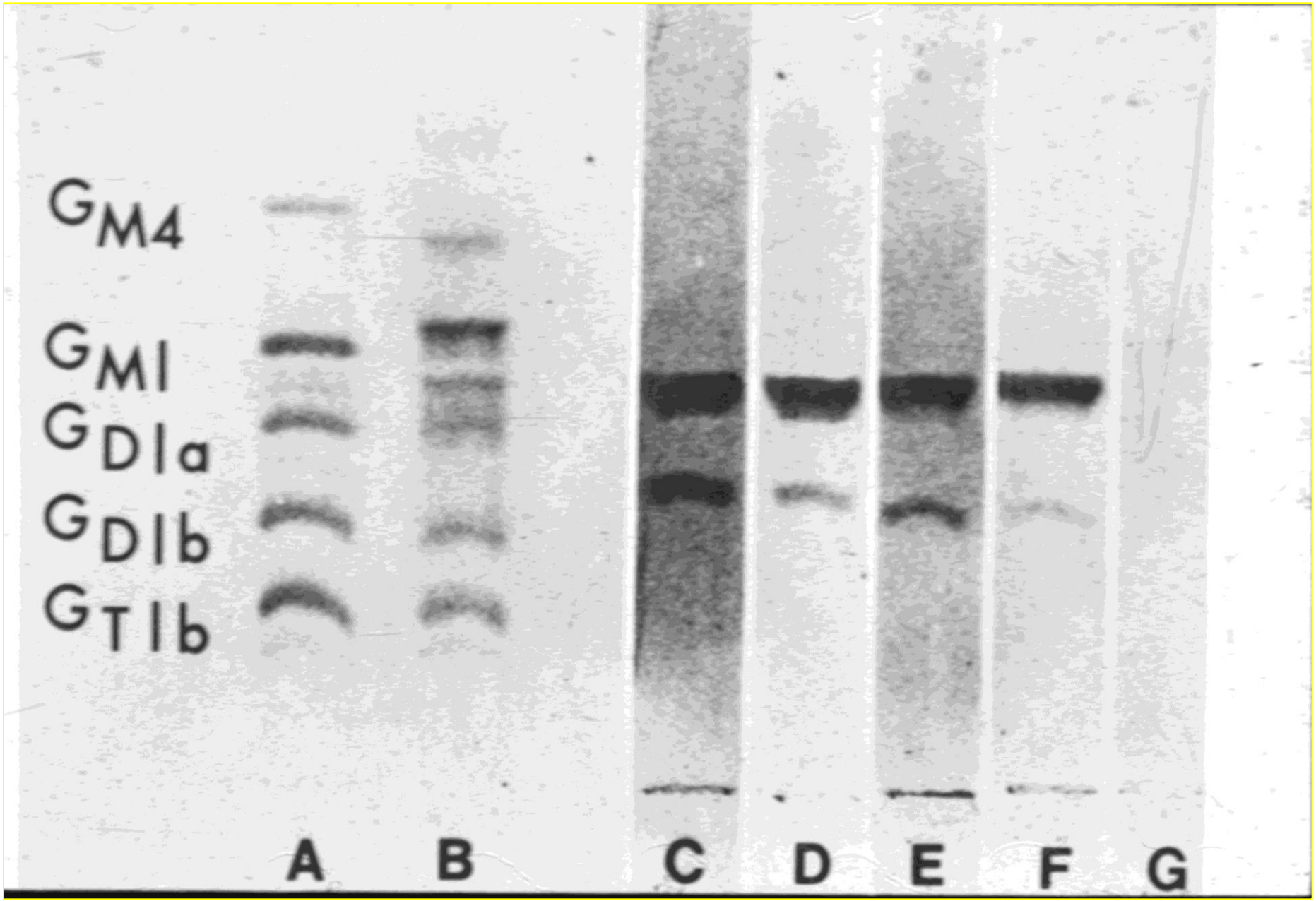
Anti-GM1 titers increased more than 1 6400

Target AG	Immunoglobulin Class	Clinical Syndrome
GM1	IgM	M.N withMMCB
GM1	IgG	axonal GBS

- Neuropathy pathogenesis
- 1.specificity of immunoglobulin
- 2.immunoglobulin class
- 3.other coexisting factors asVEGF in POEMS

ANTI-MAG NEUROPATHY

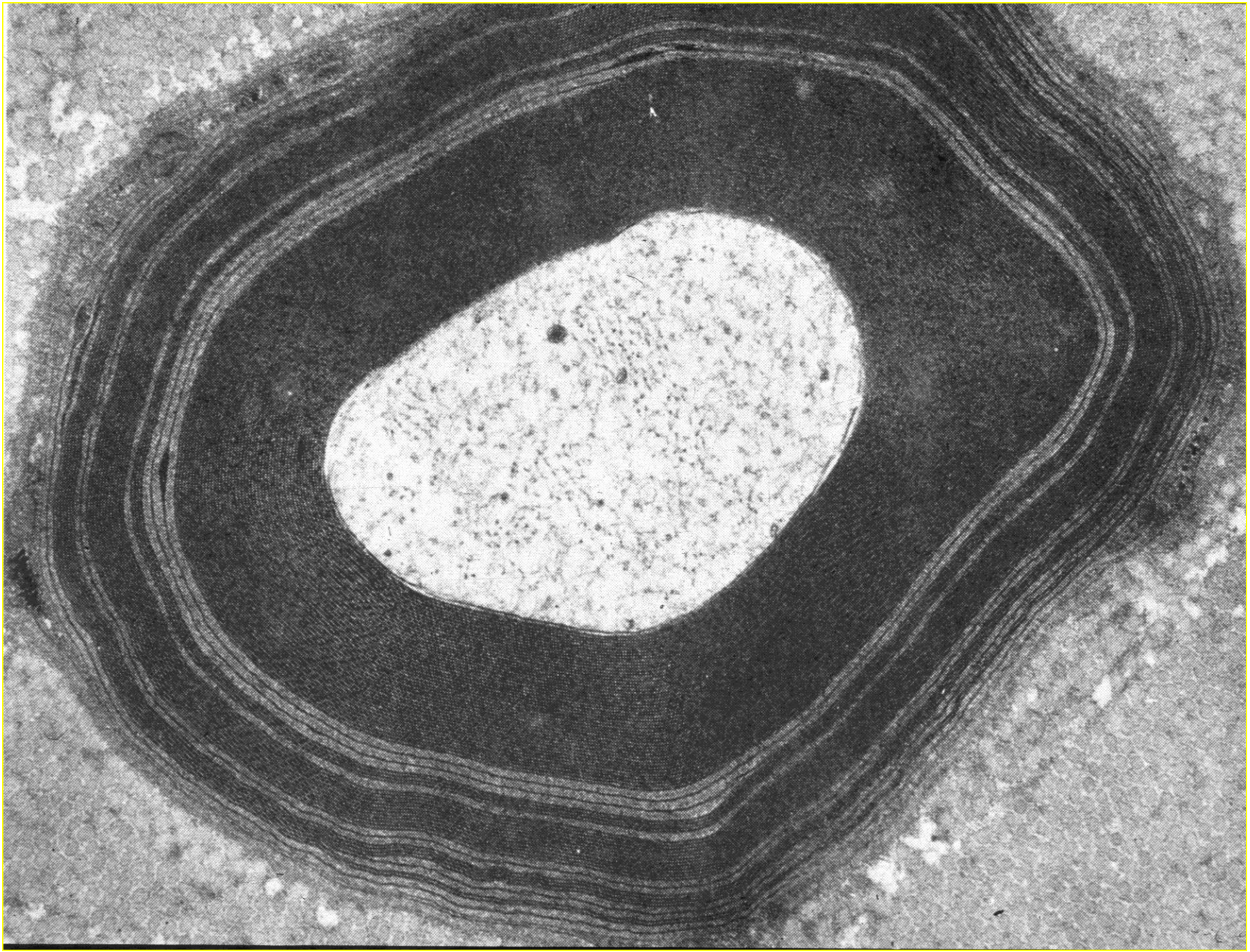

MAG→
94
67
43
30
20.1
14.4
A
B
C
D
E


GM4
GM1
GDIa
GDIb
GTIb
A
B
C
D
E
F
G

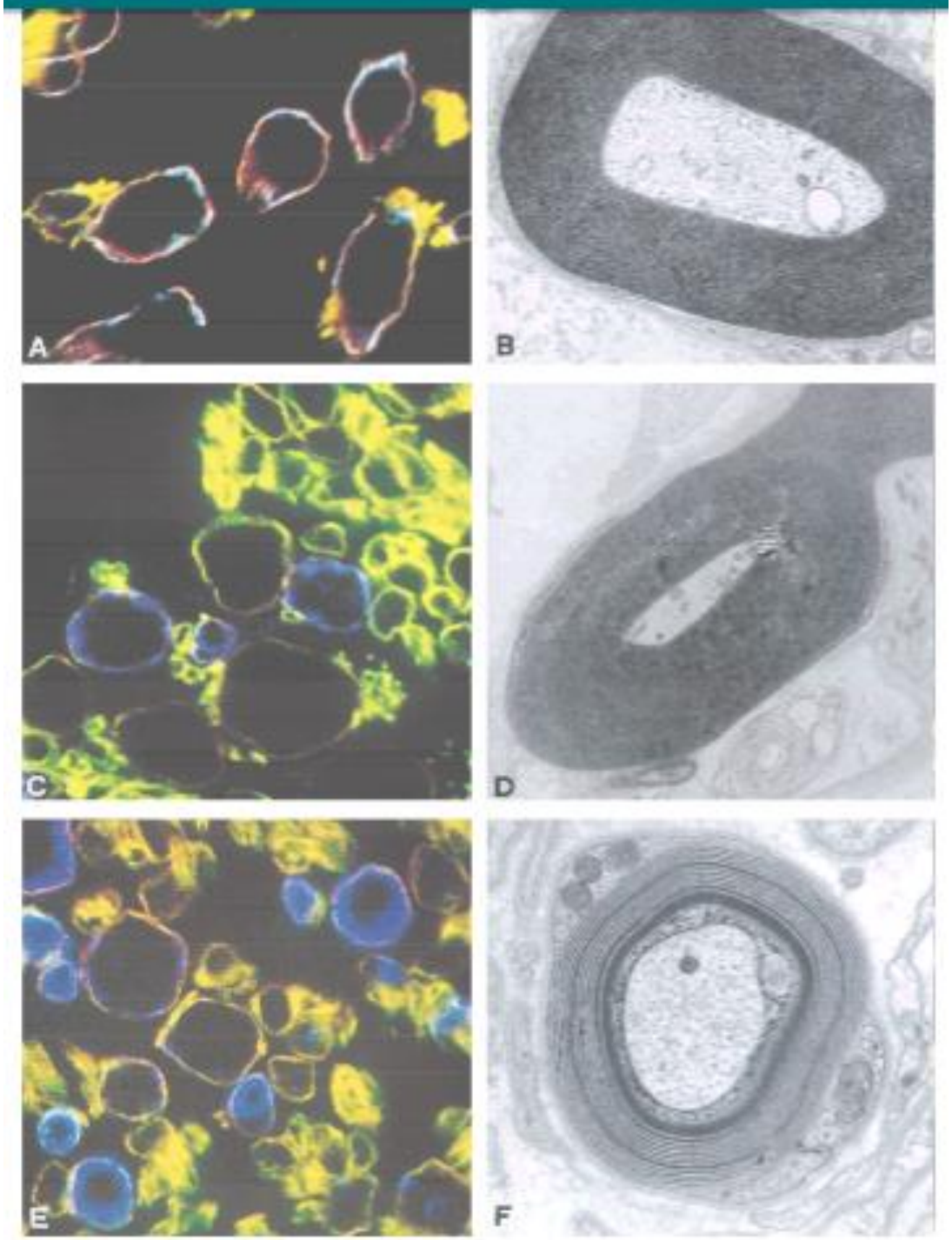
Cross-reactivities

MAG	SGPG
Po	SGLPG
Pm-22	

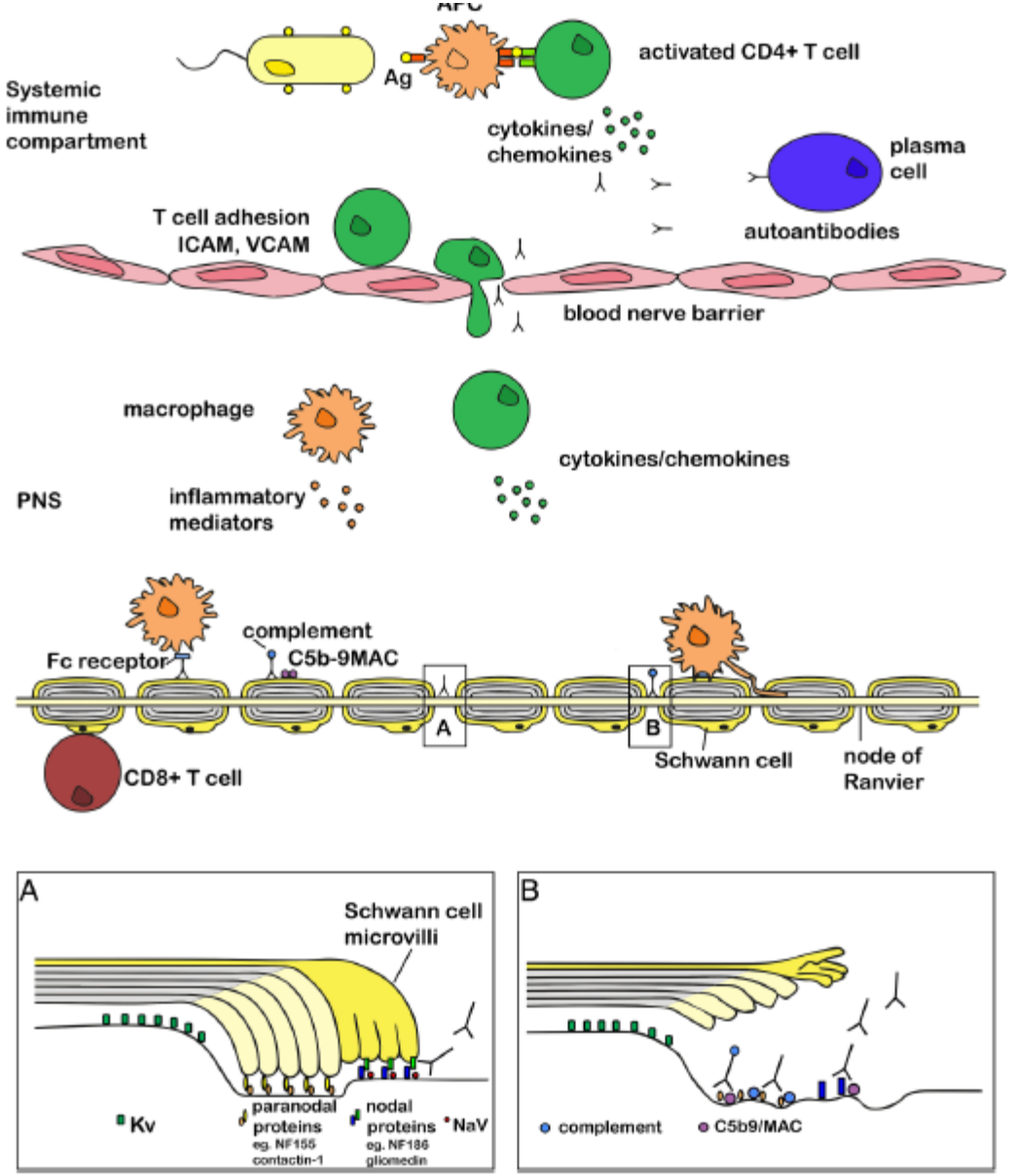
Common carboydrate epitope: HNK-1



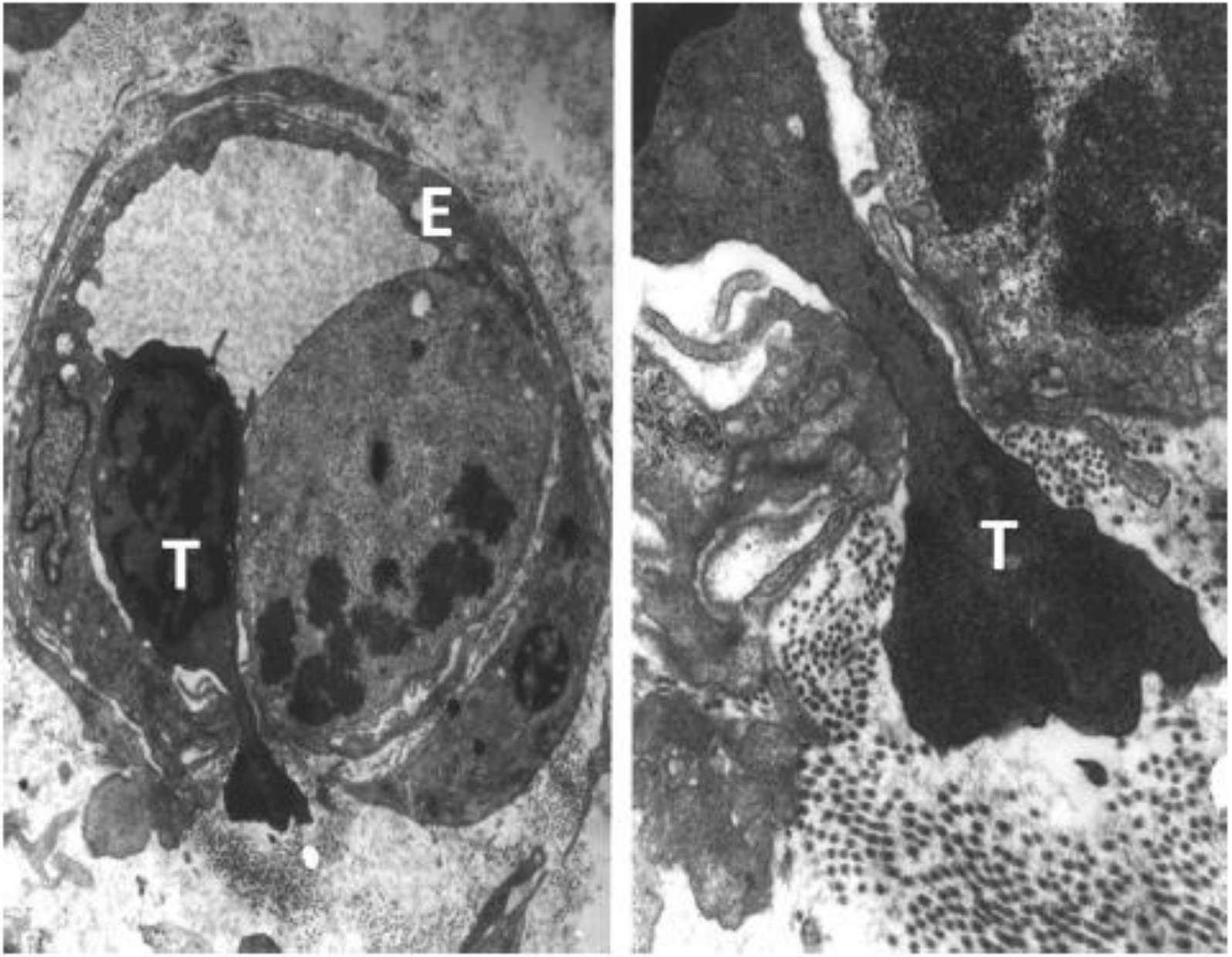
RITZ …STECK
1999



Anti-MAG antibodies


Systemic
immune
compartment
Ag
activated CD4+ T cell
cytokines/
chemokines
plasma
cell
autoantibodies
T cell adhesion
ICAM, VCAM
blood nerve barrier
macrophage
cytokines/chemokines
PNS
inflammatory
mediators
complement
Fc receptor
C5b-9MAC
A
B
Schwann cell
node of
Ranvier
CD8+ T cell
A
Schwann cell
microvilli
Kv
paranodal
proteins
eg. NF155
contactin-1
nodal
proteins
eg. NF186
gliomedin
NaV
B
complement
C5b9/MAC

Polard 2011


E
T
T