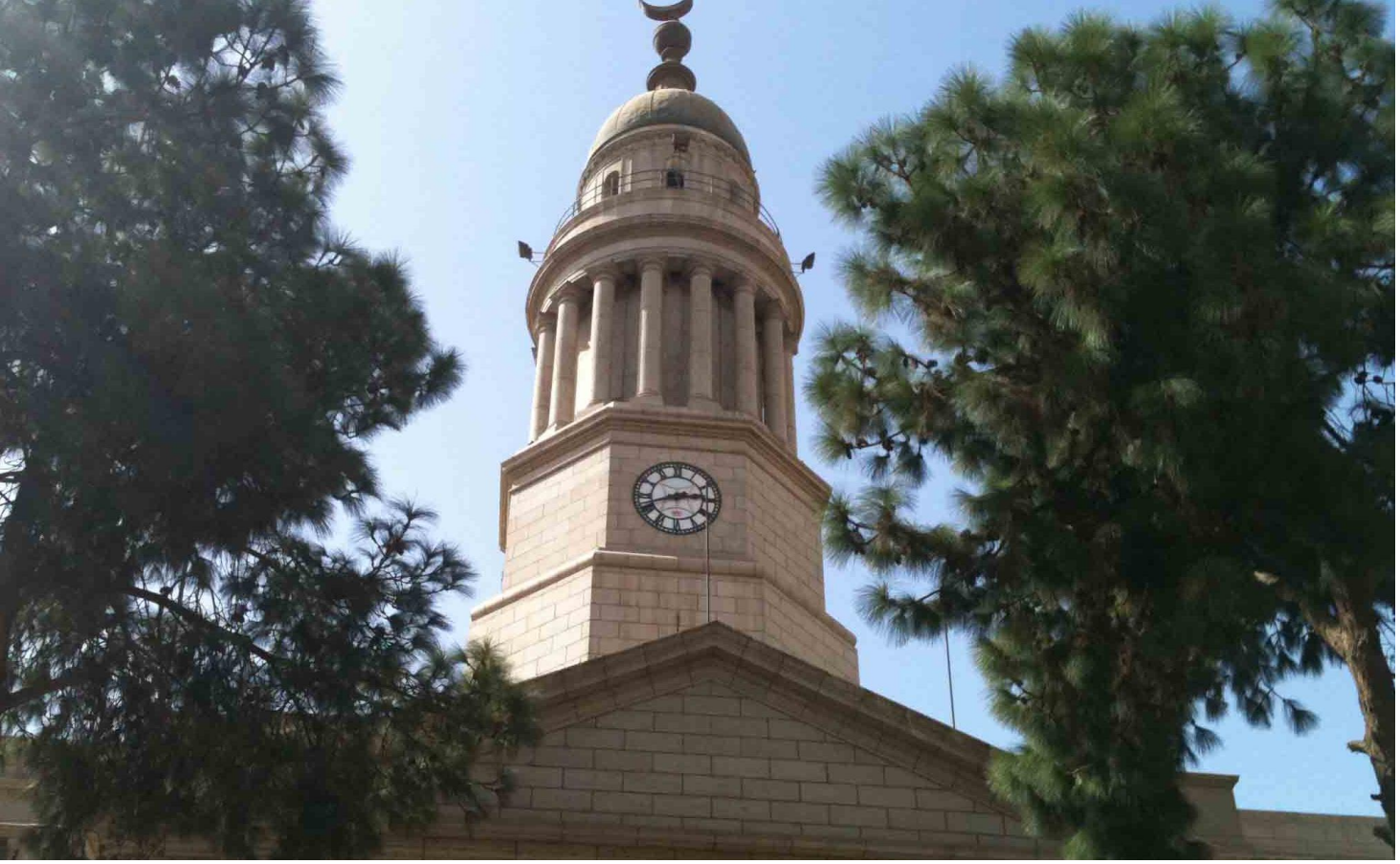


Practical Issues in Multiple Sclerosis

Amr Hassan MD,FEBN

Associate professor of Neurology

Cairo University

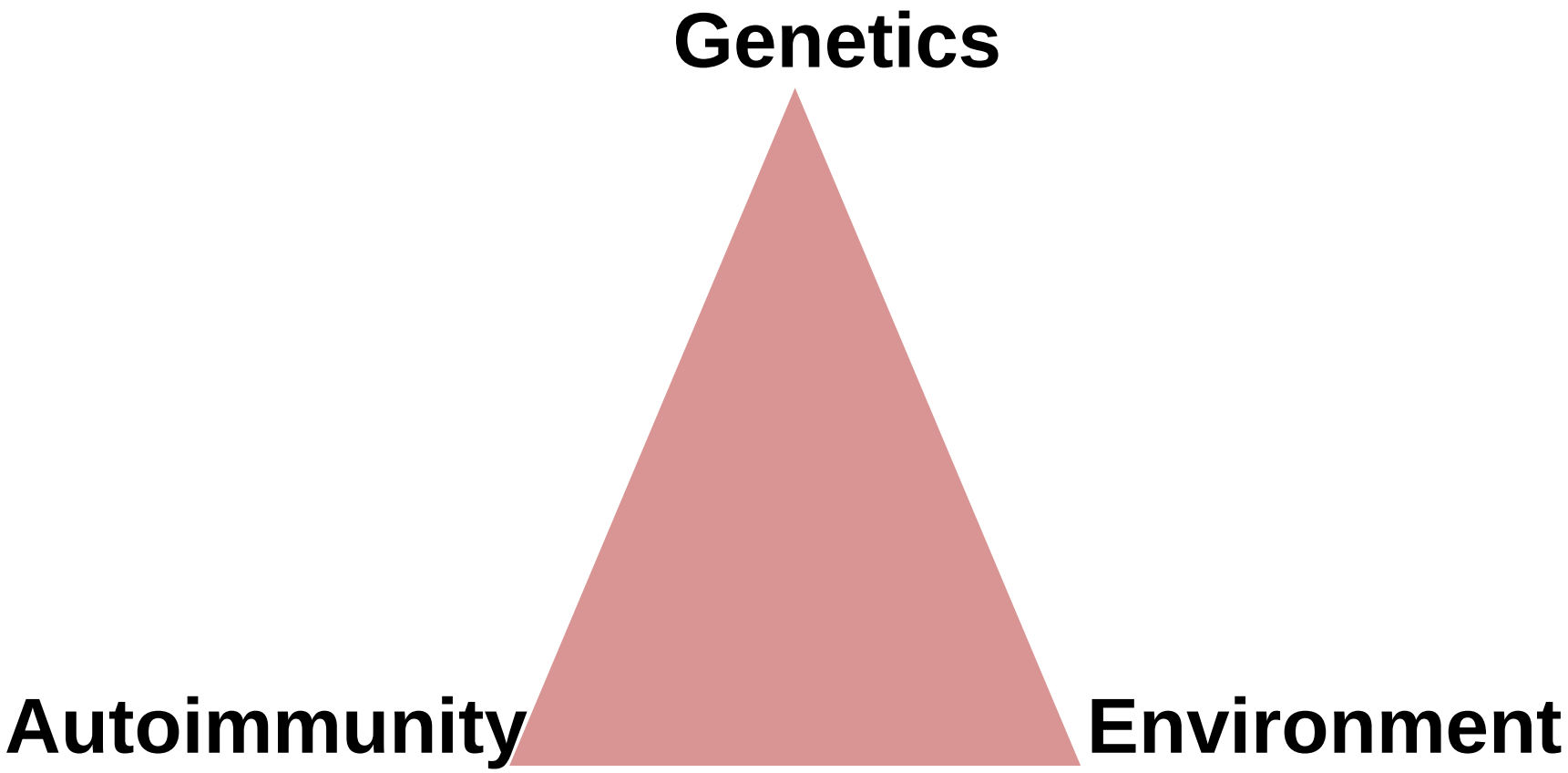
2017

AGENDA

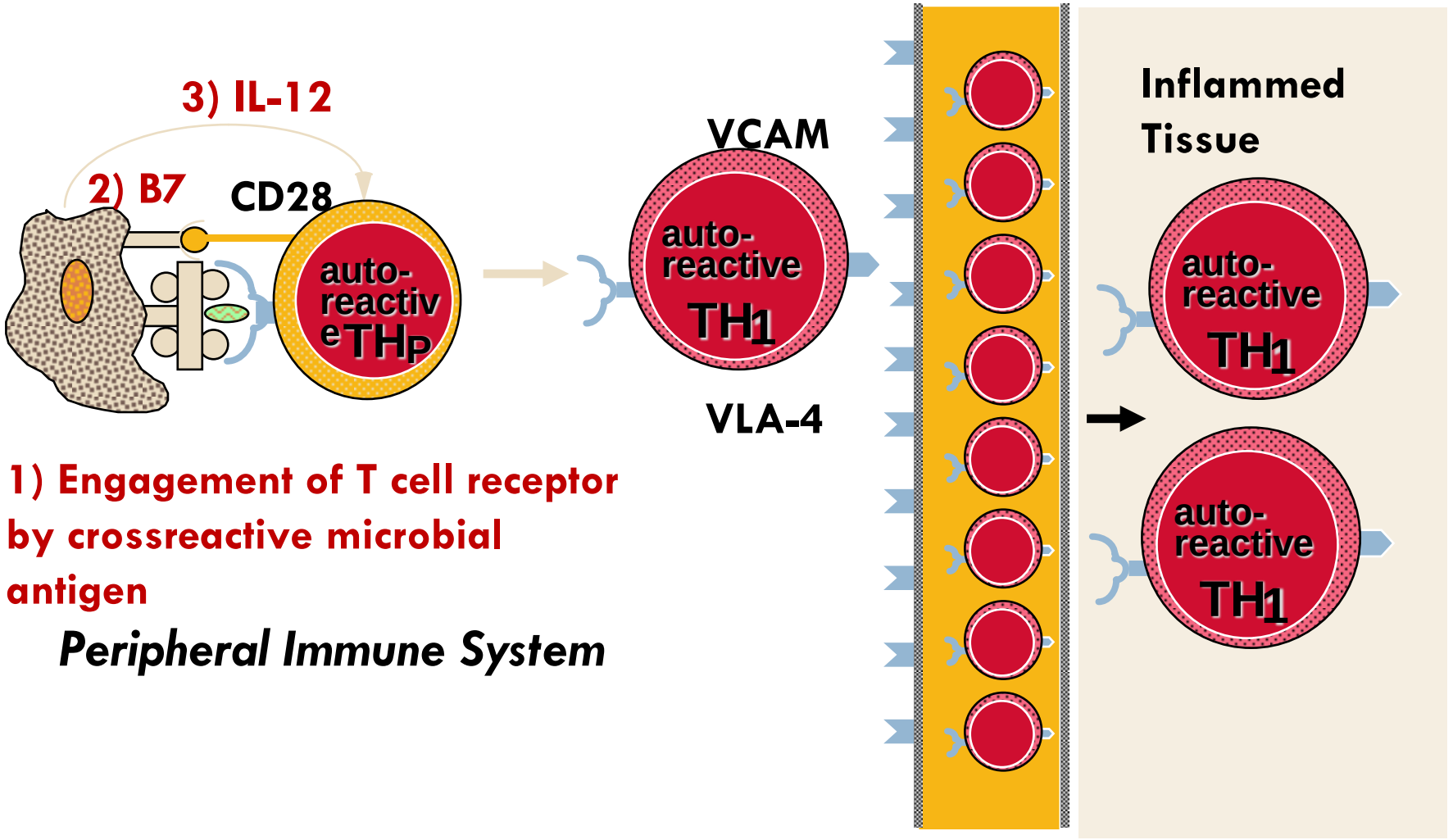
- Immunopathogenesis
- Diagnosis
- Biomarkers
- Treatment options
- Optimization of treatment

Immunopathogenesis

Pathogenesis of M.S.



Immunopathogenesis of M.S.



1) Engagement of T cell receptor by crossreactive microbial antigen

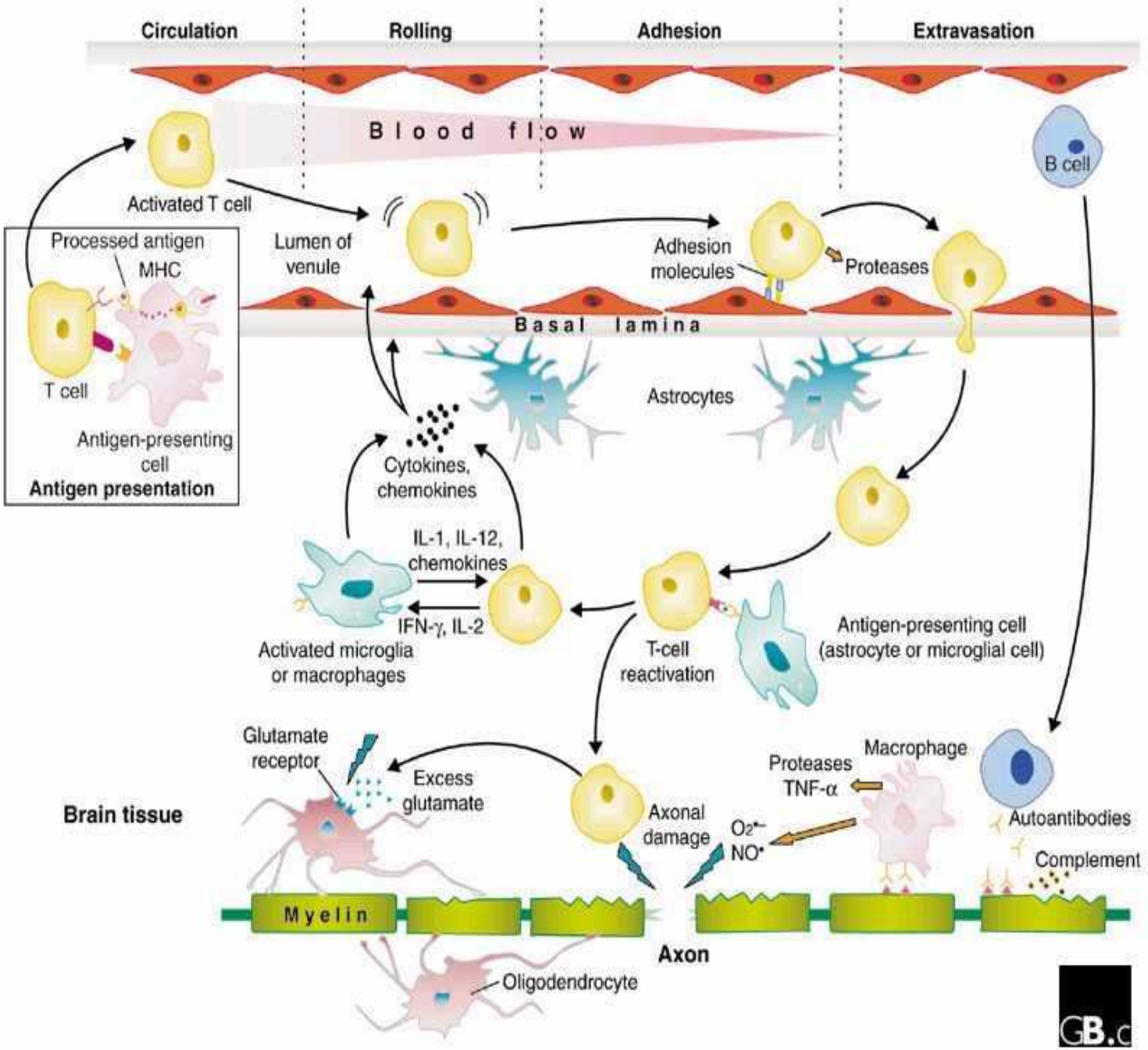
Peripheral Immune System

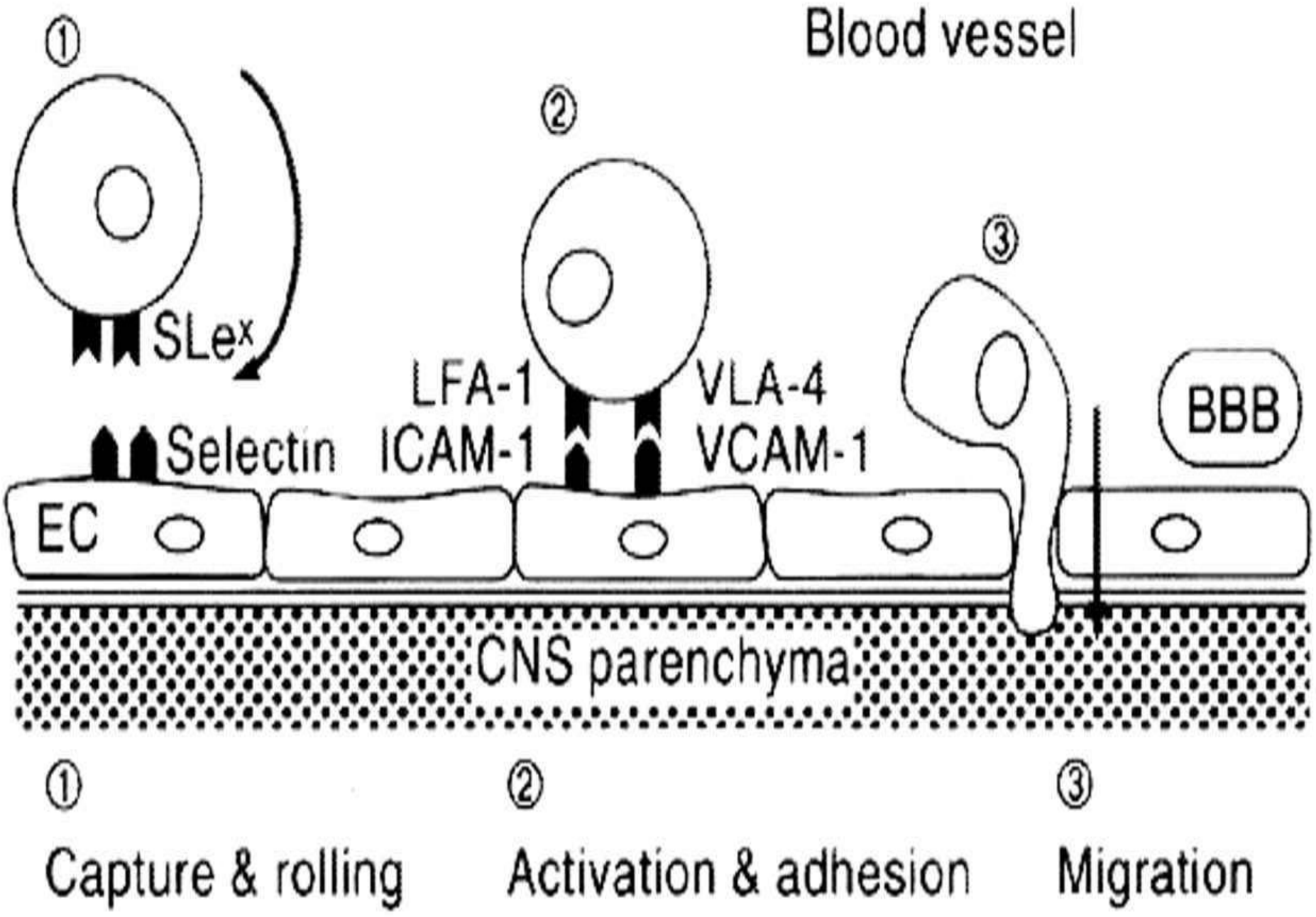
B.B.B.

Chemokines

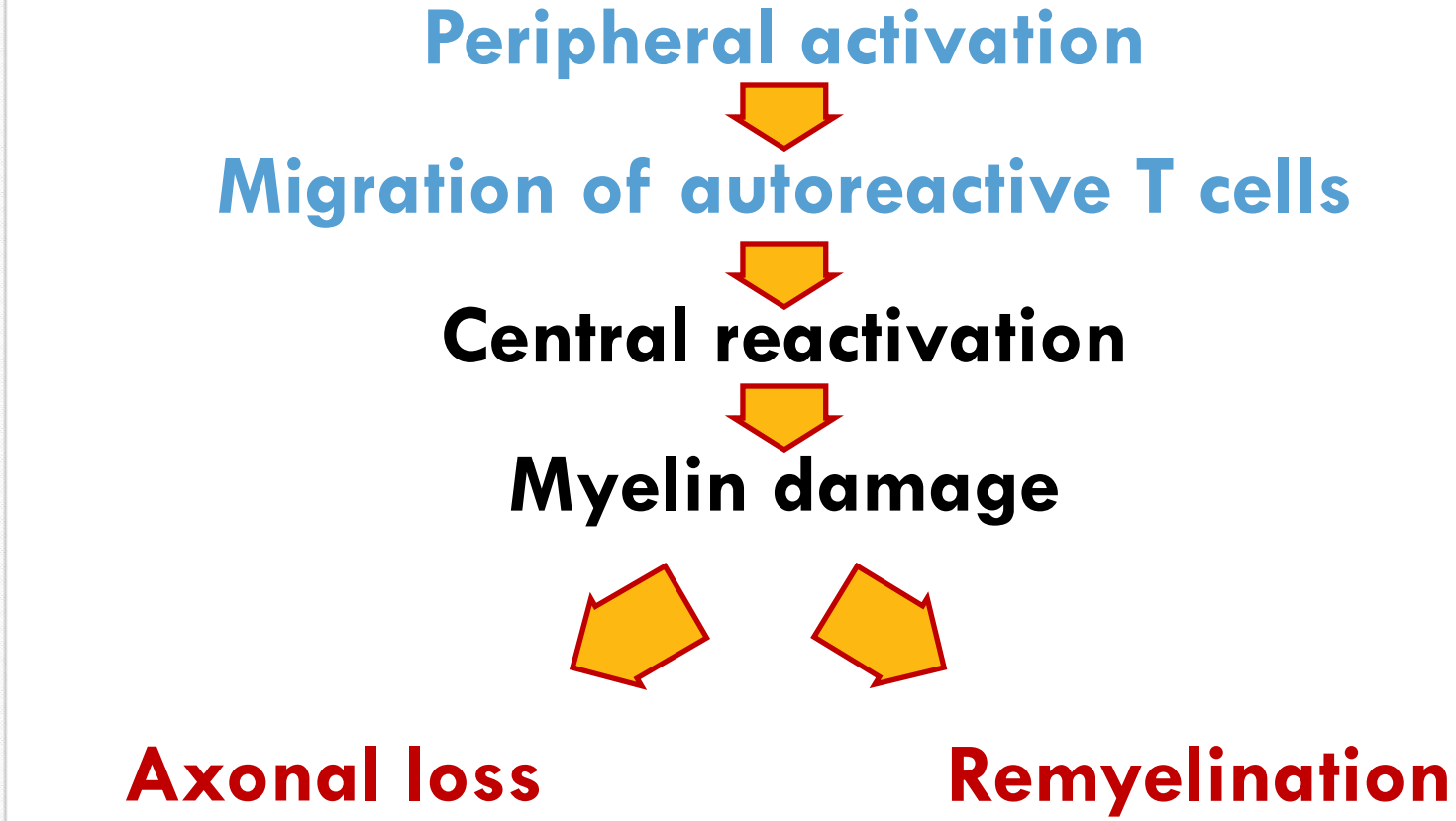
Matrix Metallproteinase

Adhesion Molecules

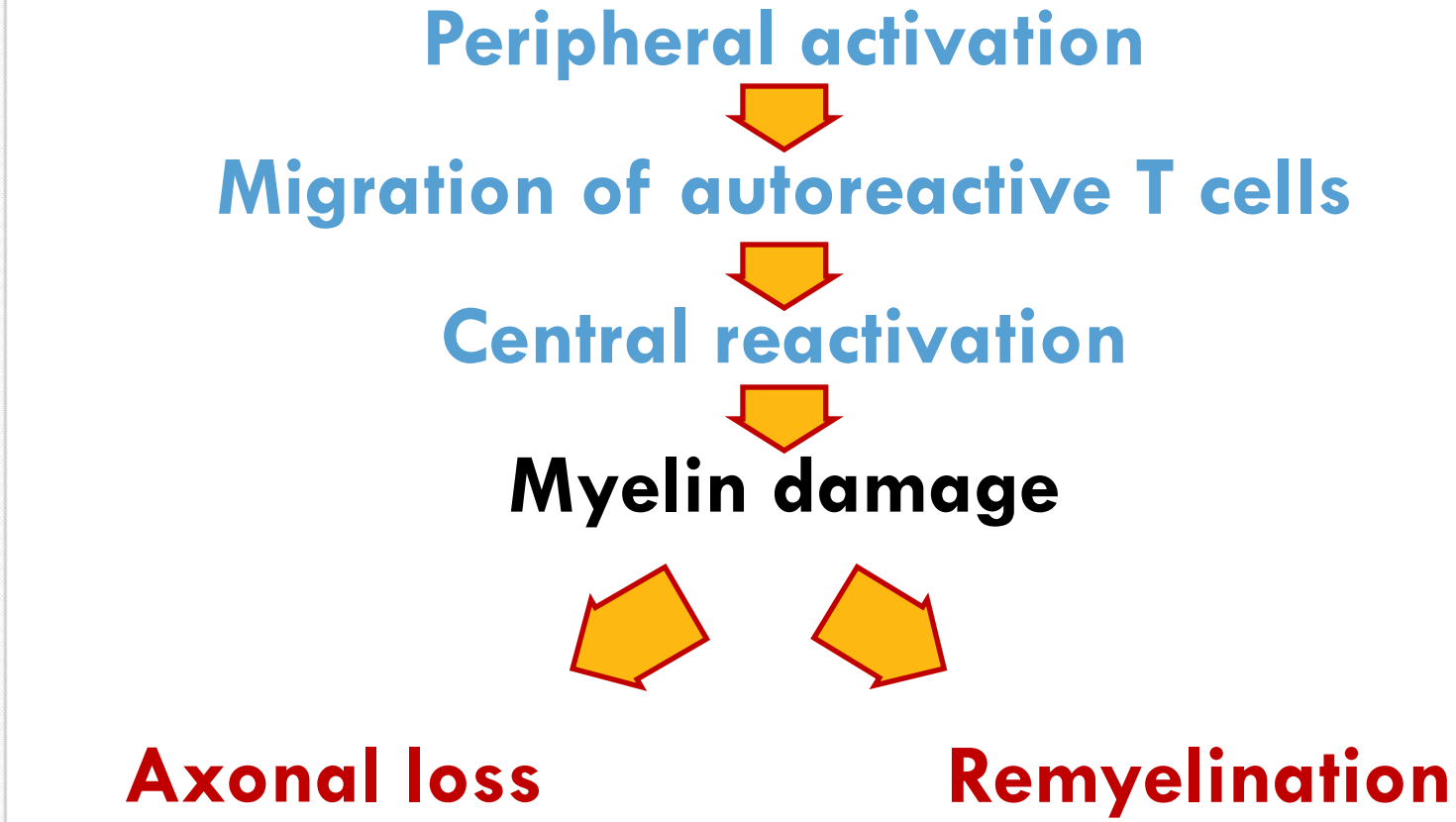

Circulation
Rolling
Adhesion
Extravasation
Blood flow
B cell
Activated T cell
Processed antigen
MHC
T cell
Antigen-presenting cell
Antigen presentation
Lumen of venule
Adhesion molecules
Proteases
Basal lamina
Astrocytes
Cytokines, chemokines
IL-1, IL-12, chemokines
IFN-γ, IL-2
Activated microglia or macrophages
T-cell reactivation
Antigen-presenting cell (astrocyte or microglial cell)
Glutamate receptor
Excess glutamate
Brain tissue
Axonal damage
Proteases
TNF-α
Macrophage
O2•−
NO•
Autoantibodies
Complement
Myelin
Axon
Oligodendrocyte


Blood vessel
①
②
③
SLex
Selectin
LFA-1
ICAM-1
VLA-4
VCAM-1
BBB
EC
CNS parenchyma
①
Capture & rolling
②
Activation & adhesion
③
Migration

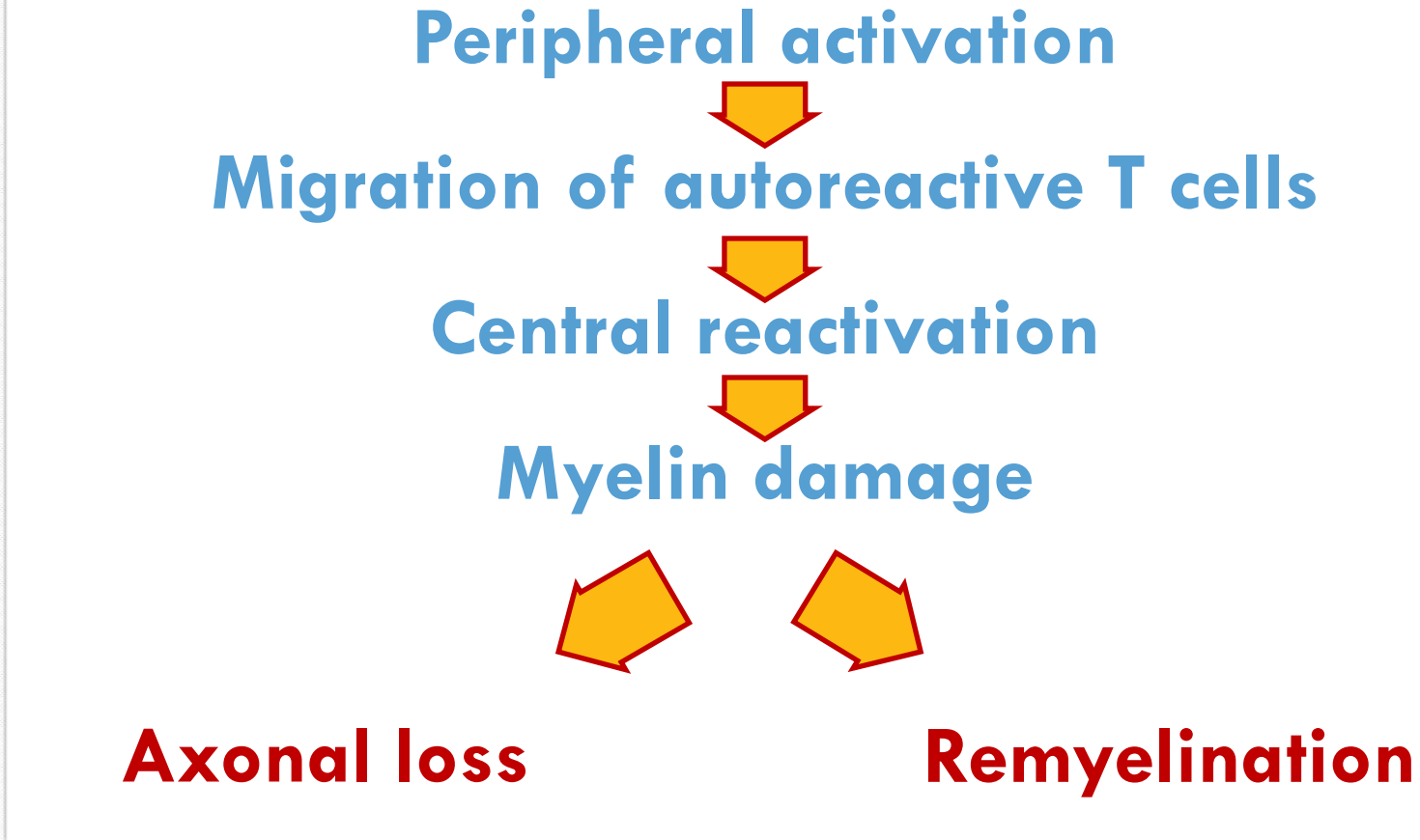
Immunopathogenesis of M.S.



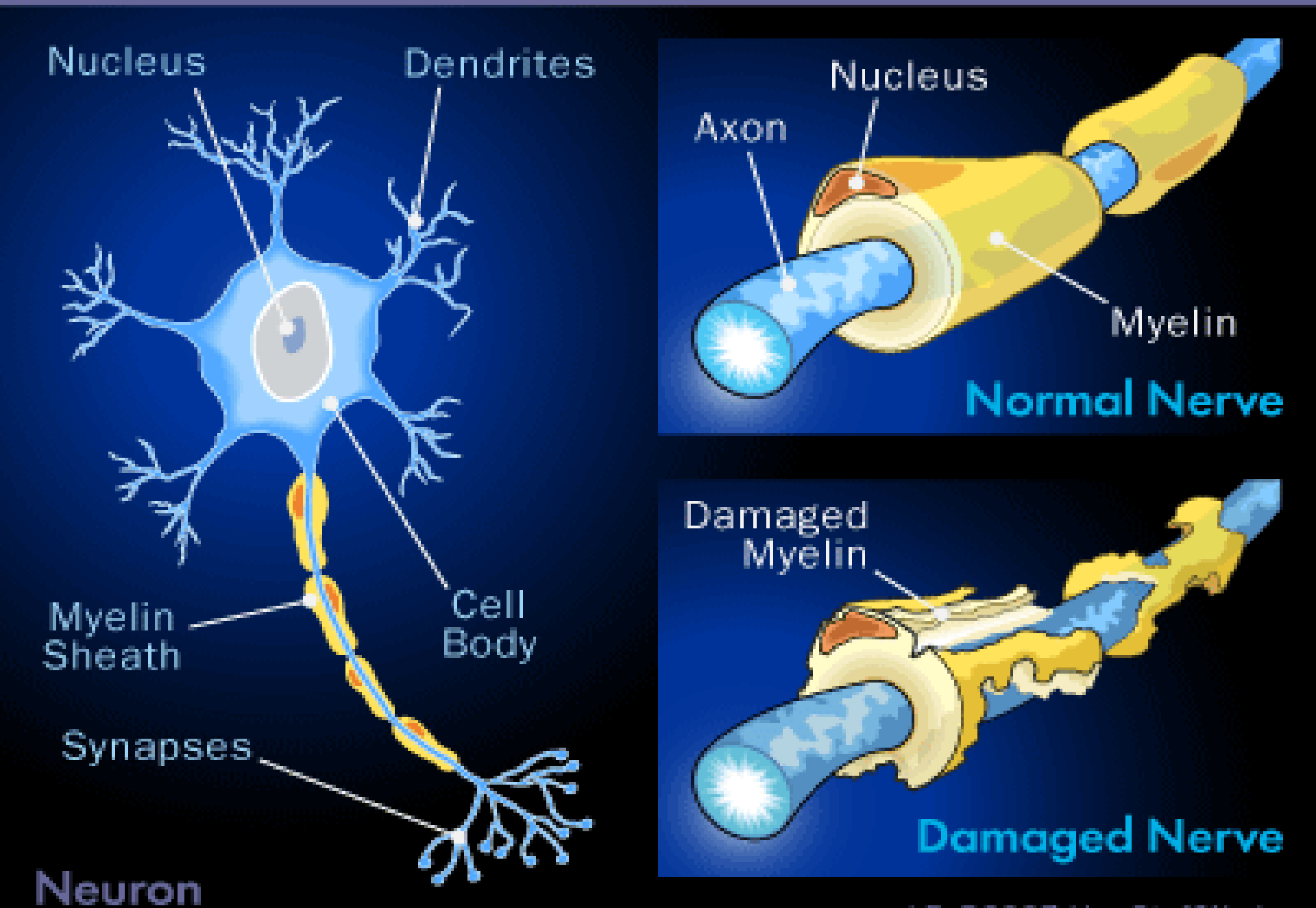
Immunopathogenesis of M.S.



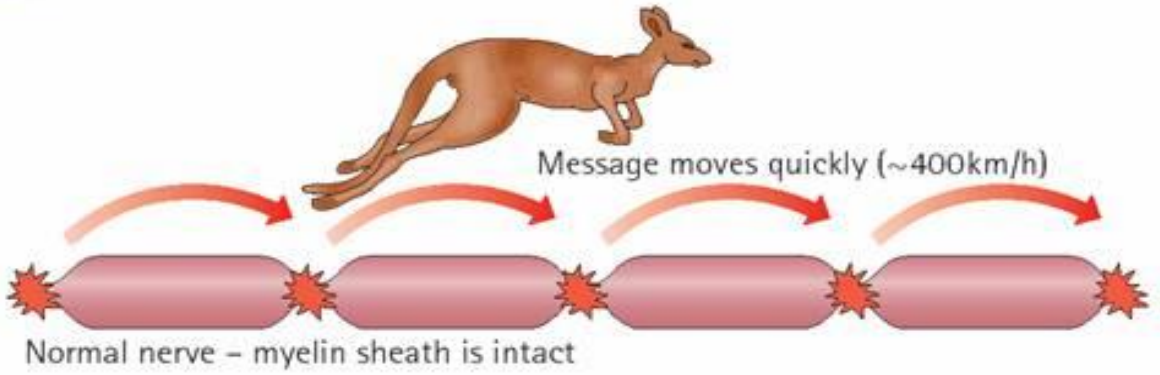
Immunopathogenesis of M.S.

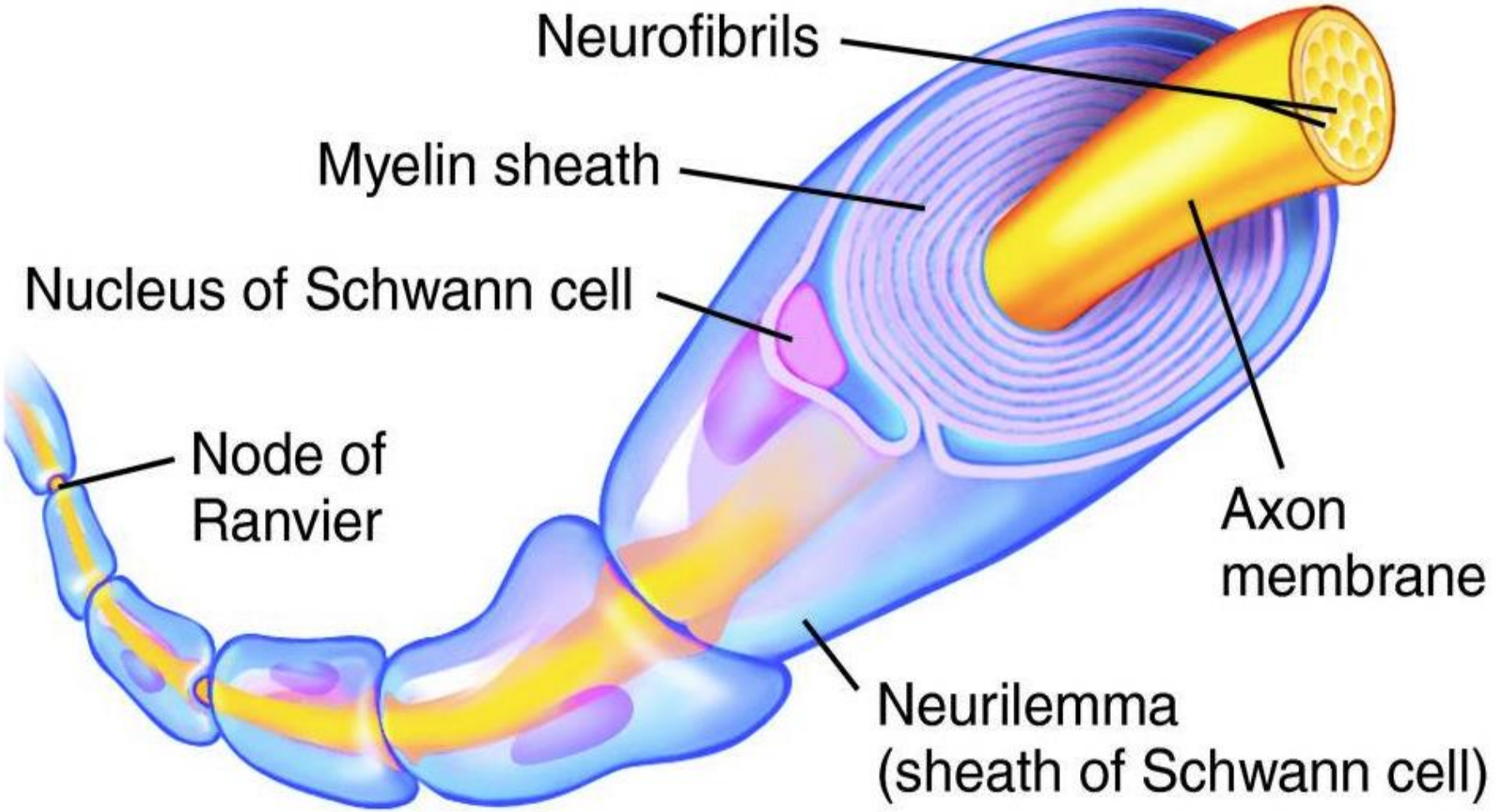


How Multiple Sclerosis Works Demyelinization



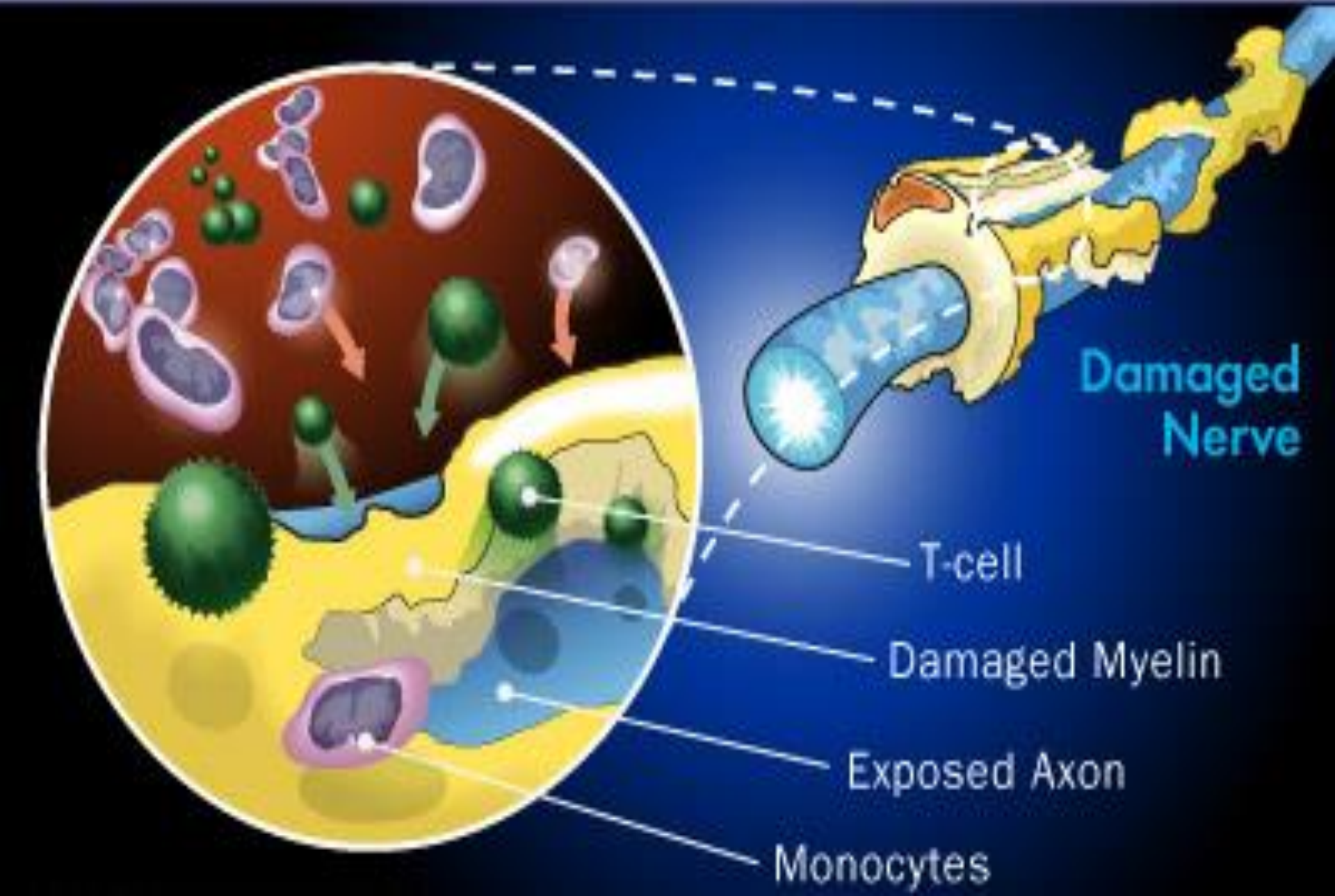
Myelin

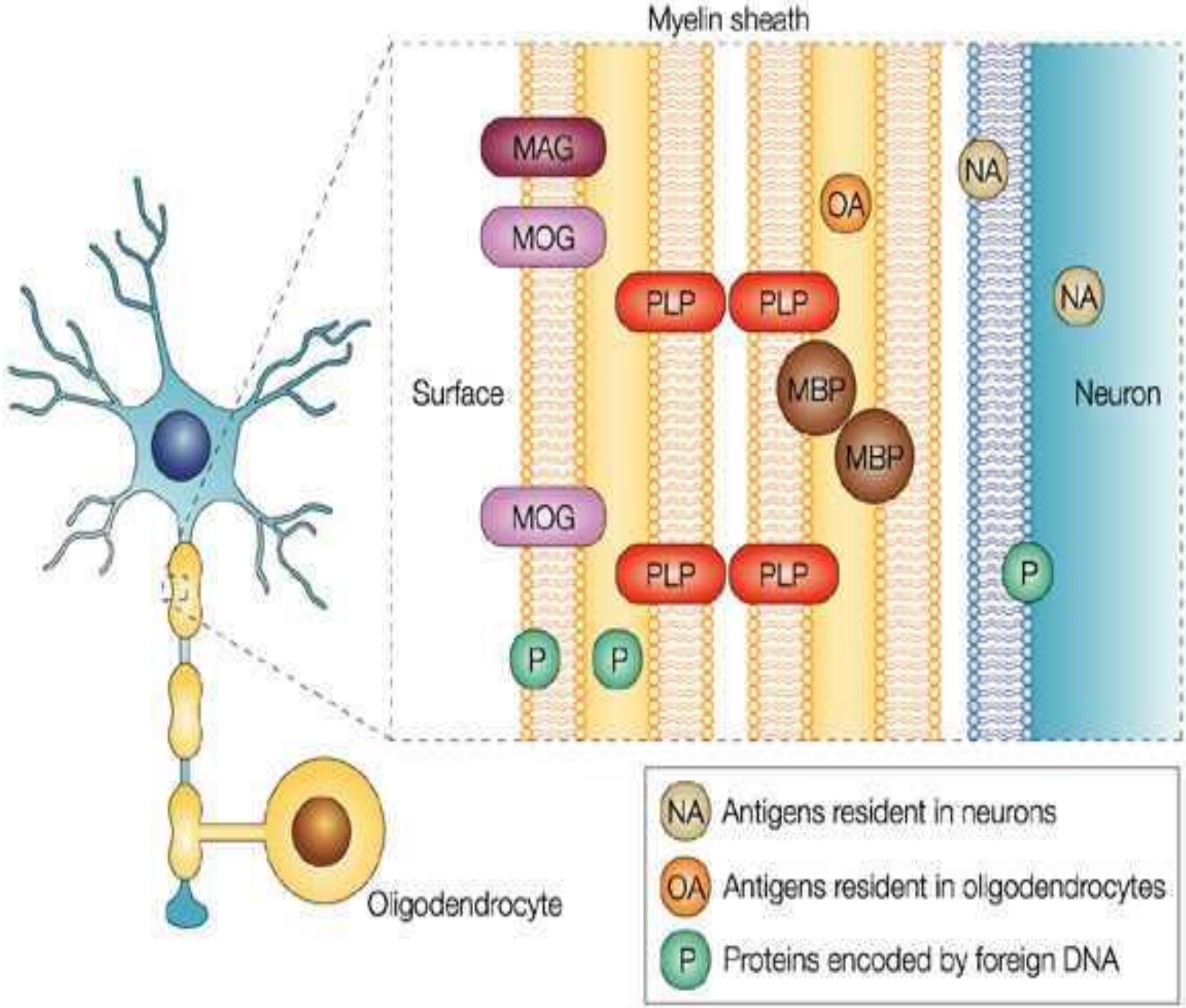

Message moves quickly (~400km/h)
Normal nerve – myelin sheath is intact


Neurofibrils
Myelin sheath
Nucleus of Schwann cell
Node of Ranvier
Axon membrane
Neurilemma (sheath of Schwann cell)

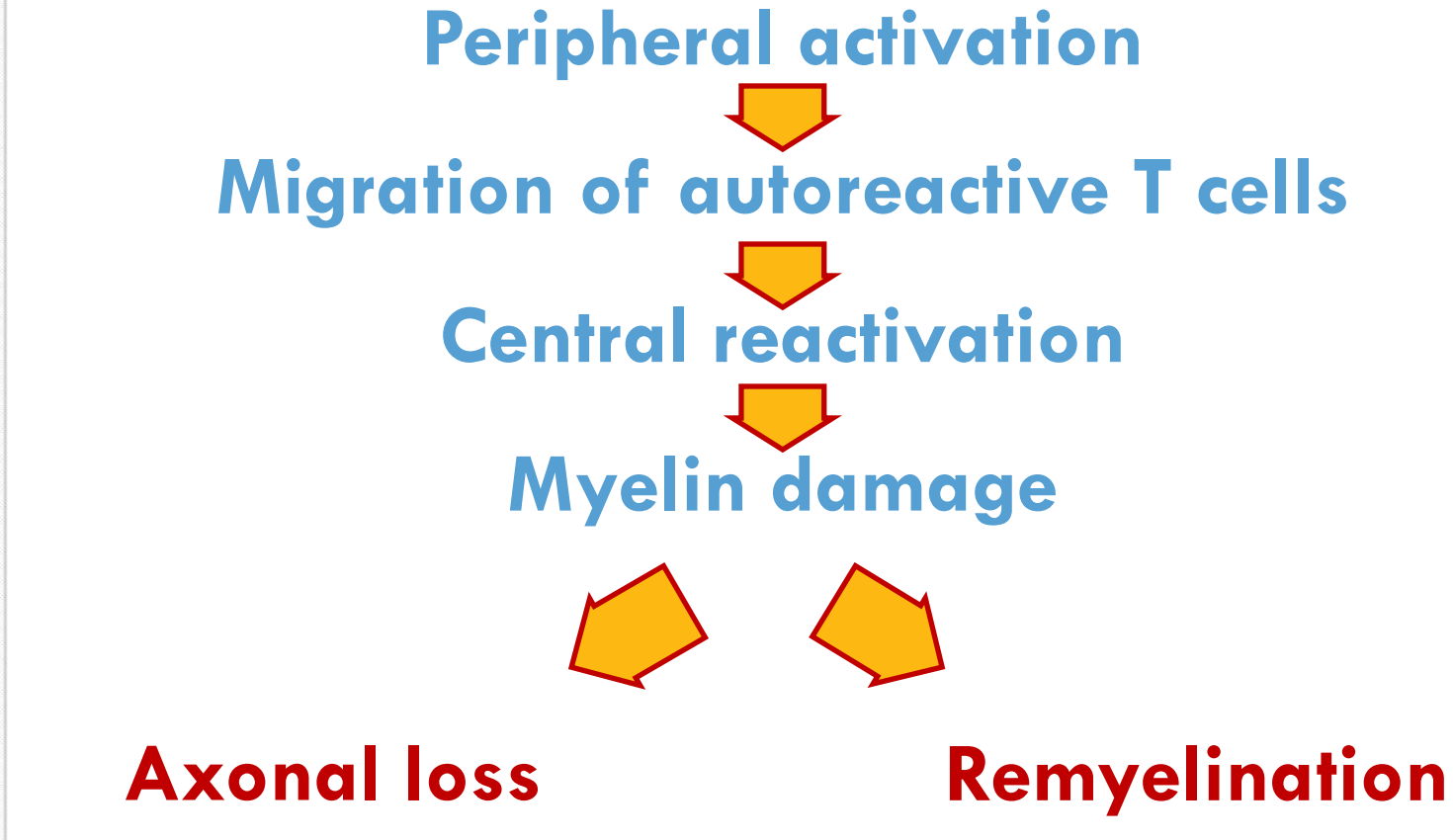
Myelin

How Multiple Sclerosis Works T-Cells and Monocytes

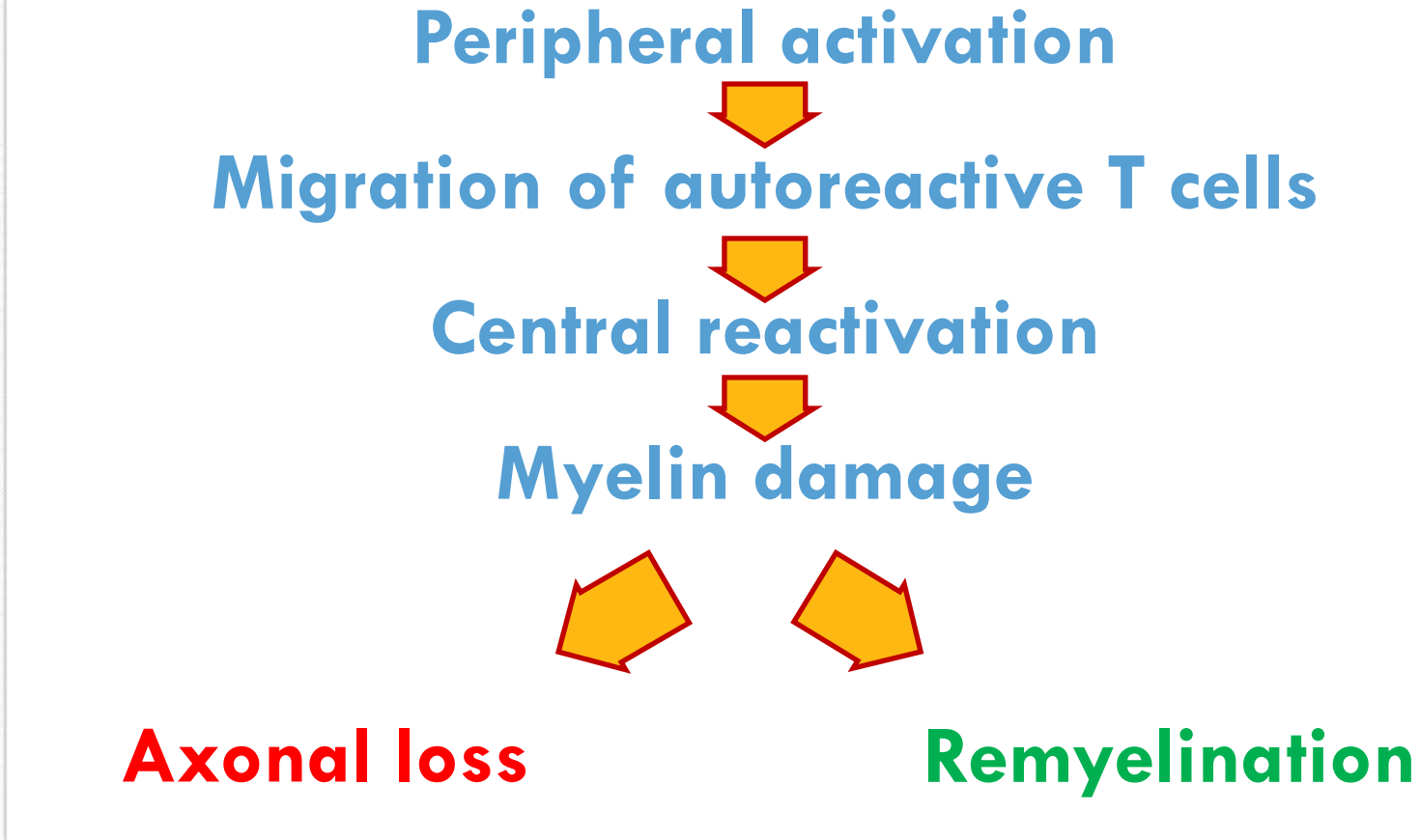



Myelin sheath
MAG
MOG
PLP
PLP
OA
NA
NA
MBP
MBP
Surface
Neuron
MOG
PLP
PLP
P
P
P
Oligodendrocyte
NA Antigens resident in neurons
OA Antigens resident in oligodendrocytes
P Proteins encoded by foreign DNA

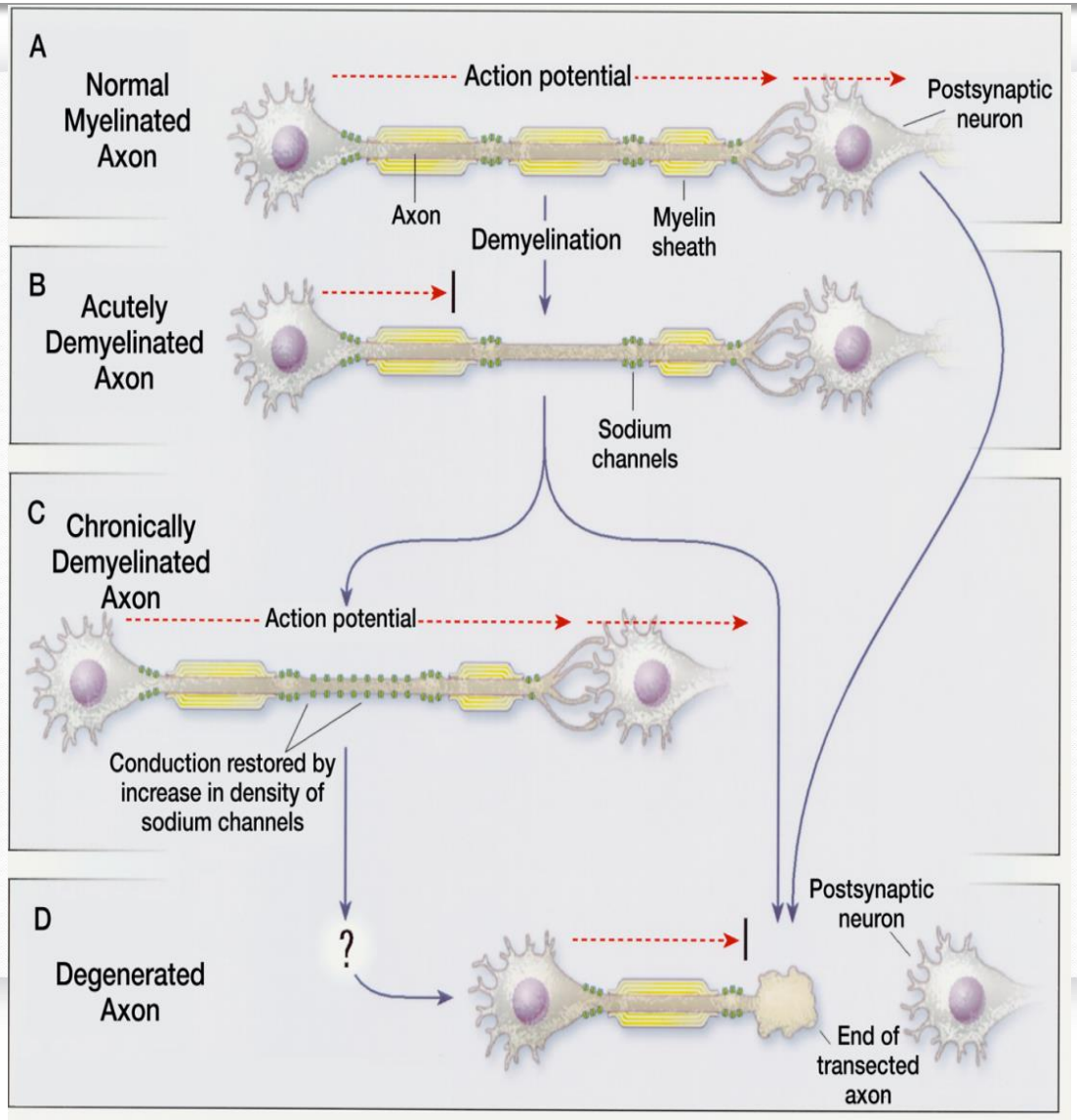
Immunopathogenesis of M.S.

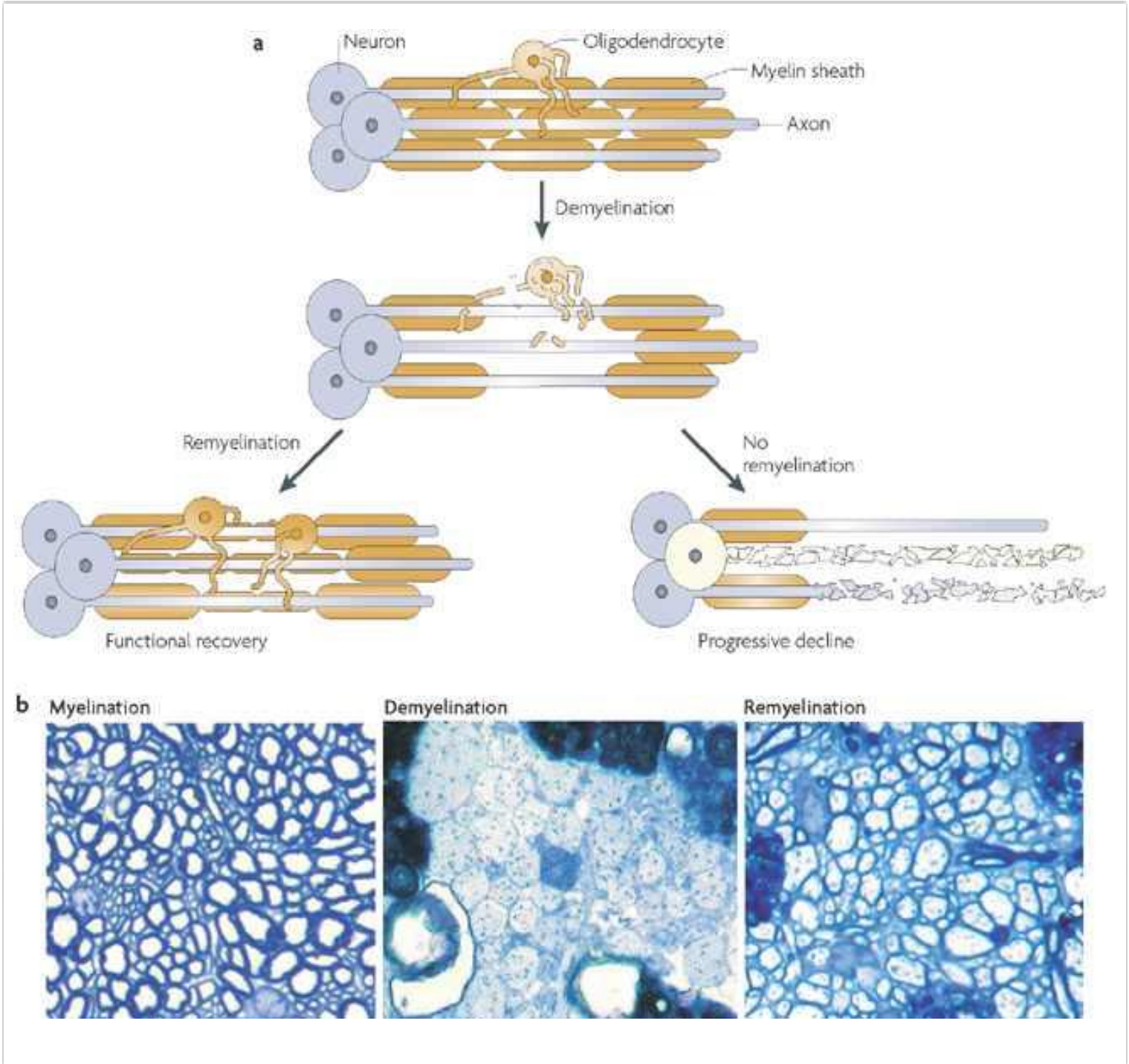


Immunopathogenesis of M.S.

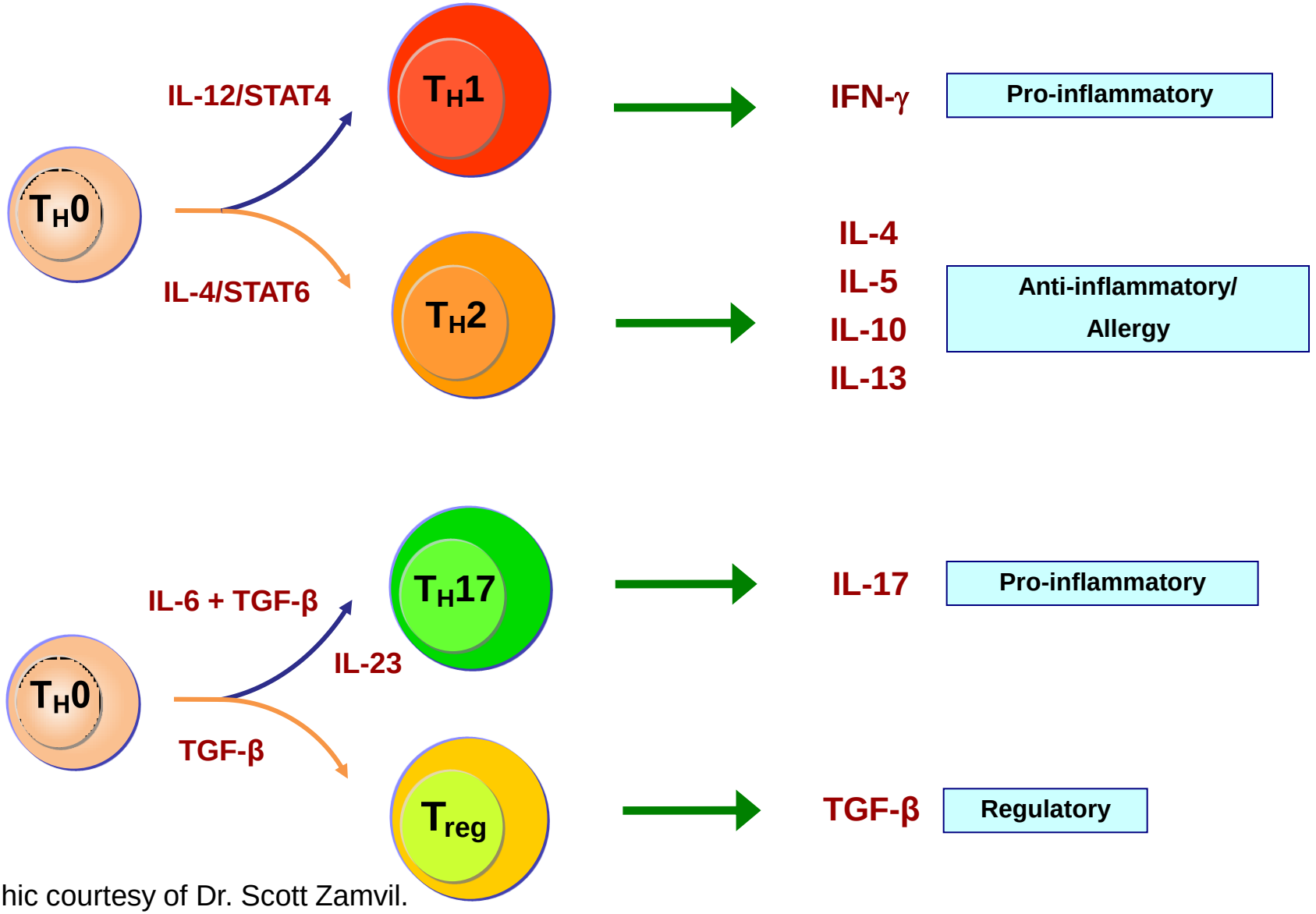


More Than a Demyelinating Disease




a
Neuron
Oligodendrocyte
Myelin sheath
Axon
Demyelination
Remyelination
No remyelination
Functional recovery
Progressive decline
b
Myelination
Demyelination
Remyelination

Helper T-Cell Differentiation



Graphic courtesy of Dr. Scott Zamvil.

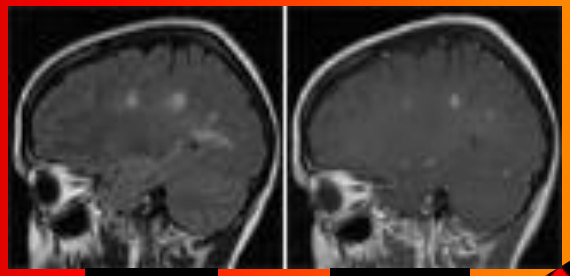
More Than a Demyelinating Disease

INFLAMMATORY ACTIVITY

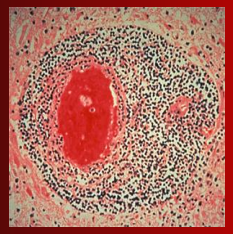
Relapses

cMRI WMLs

Rx effect



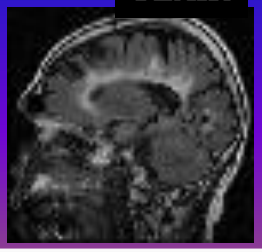
FLAIR T1 Gd+



Poor Rx effect

No New WMLs

PROGRESSION

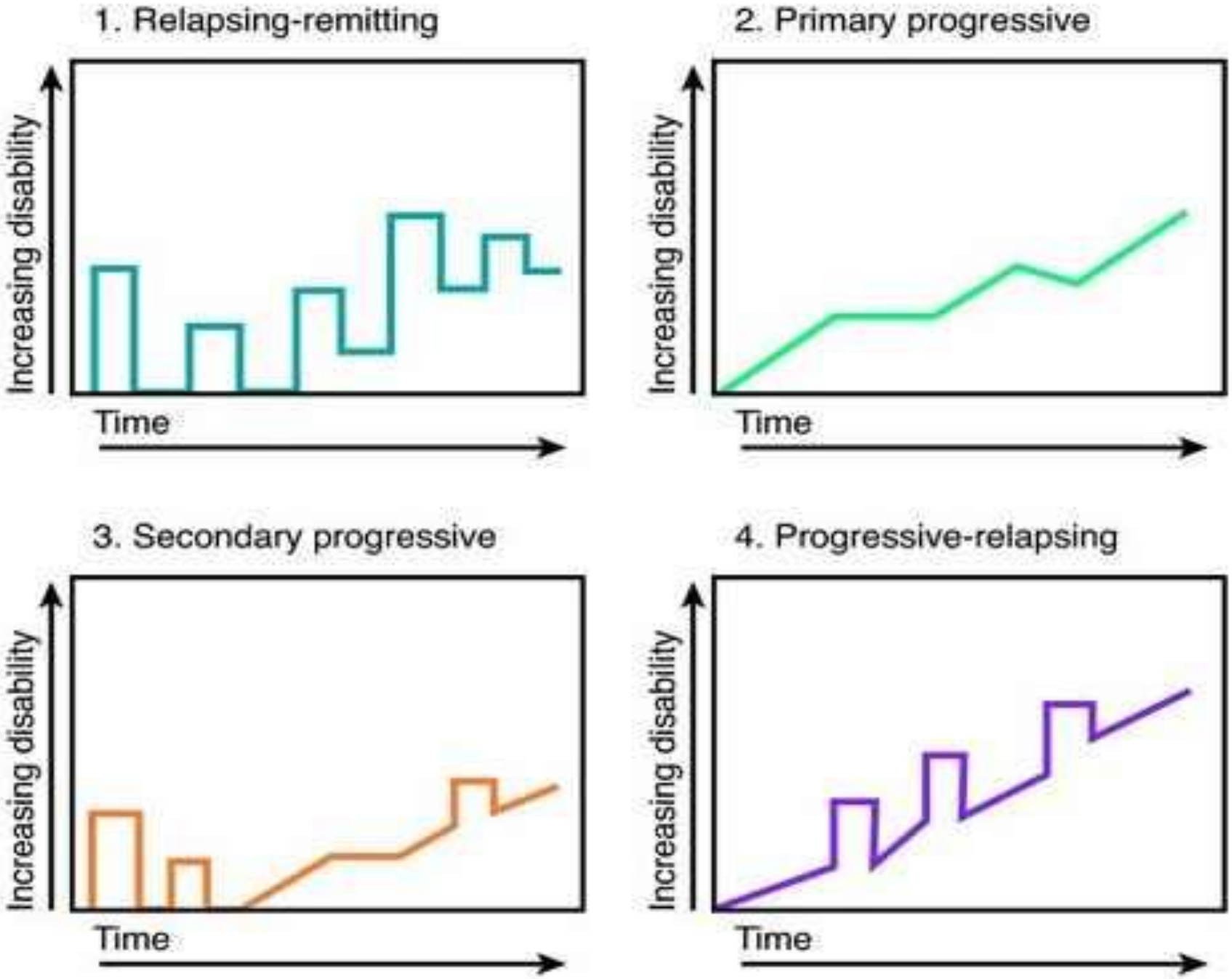


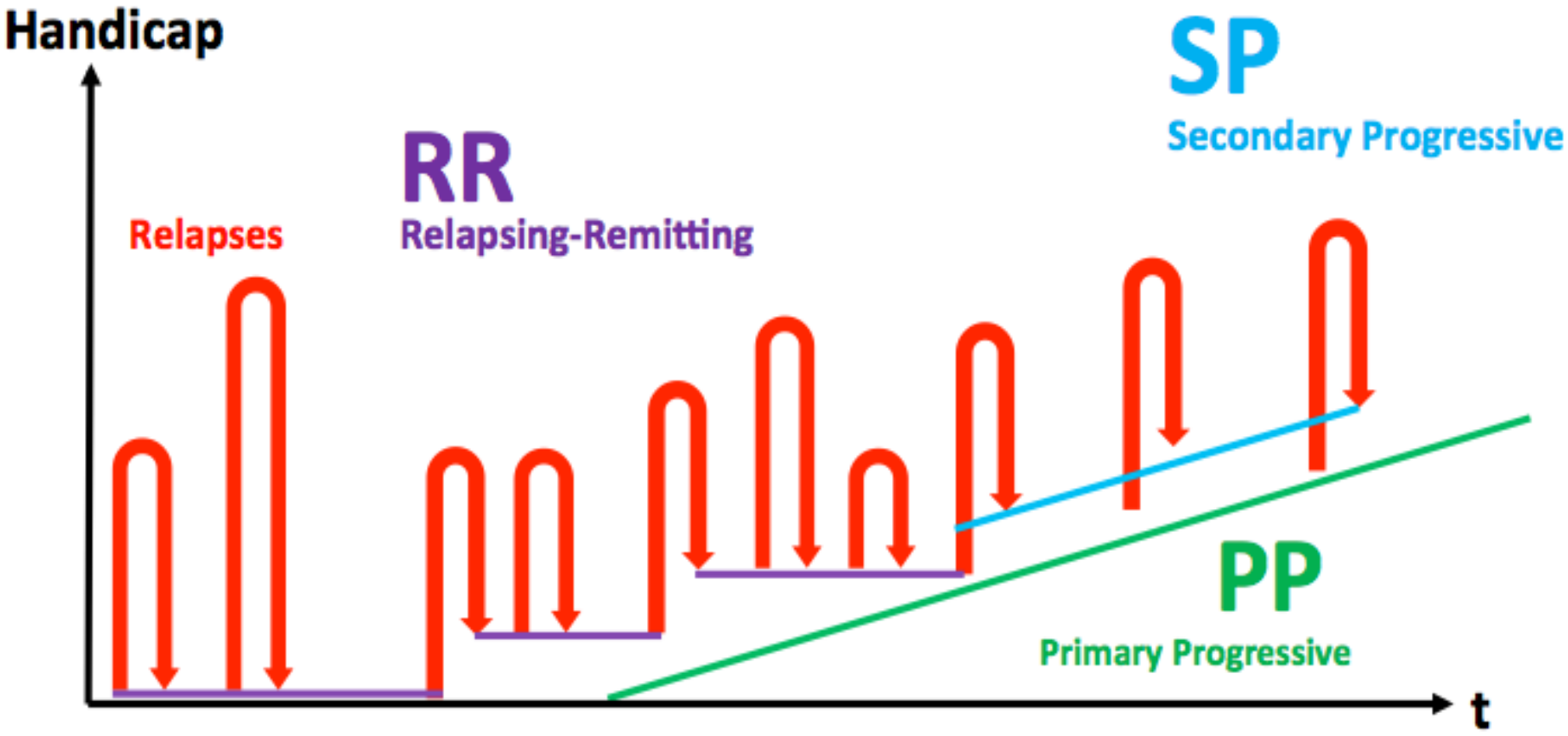
NEURODEGENERATION

Inflammation and Neurodegeneration in MS

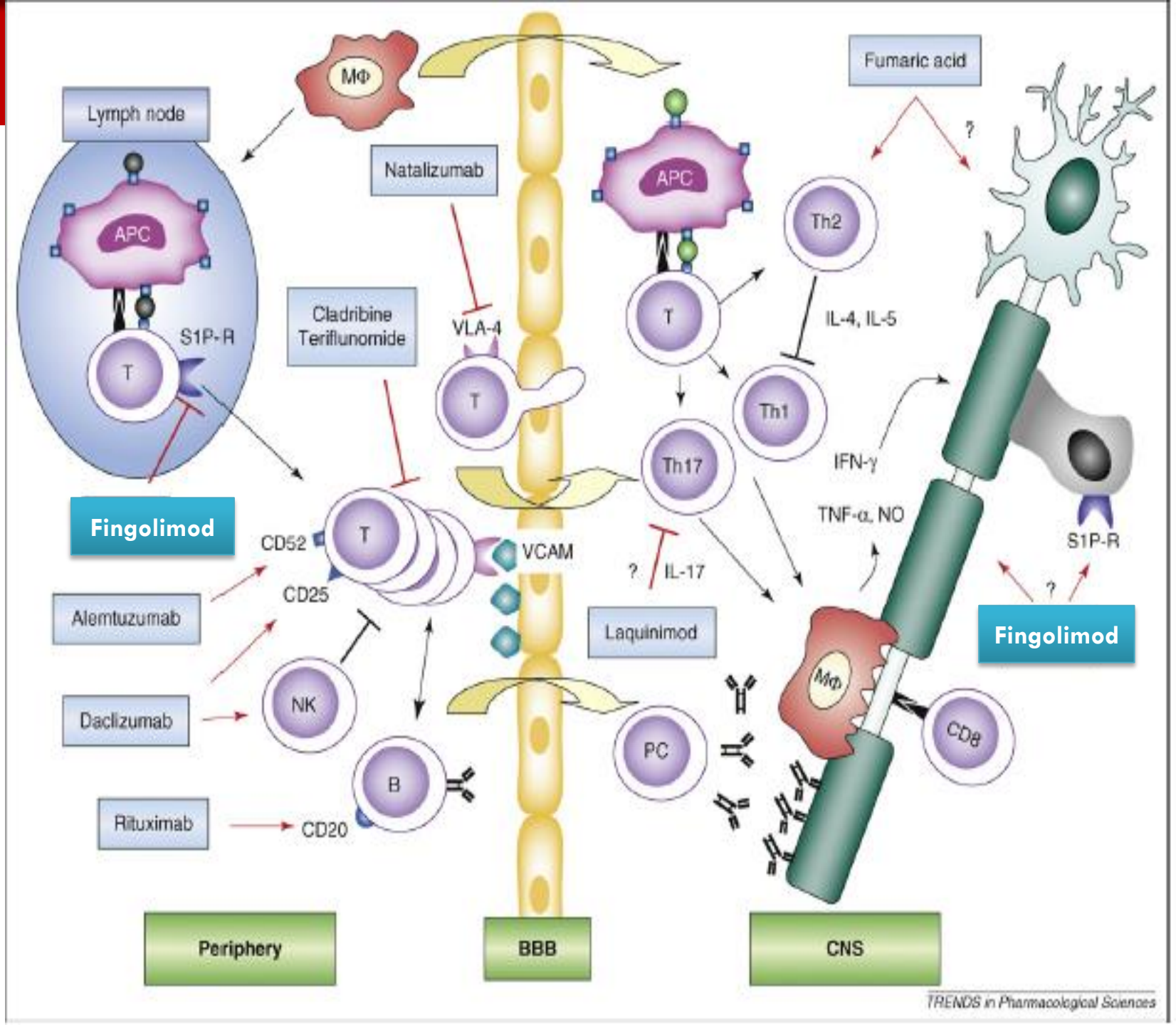
Disease Stage	Dominant Component	Main Clinical Outcome	MRI
Early	INFLAMMATION Edema Demyelination (axonal loss, brain atrophy)	Relapses	Gd enhancement
Late	NEURODEGENERATION Severe axonal injury Permanent tissue loss	Disability	Black Holes Gd enhancement Brain Atrophy

Filippi et al., EJN 2001, 8:291-297


1. Relapsing-remitting
Increasing disability
Time
2. Primary progressive
Increasing disability
Time
3. Secondary progressive
Increasing disability
Time
4. Progressive-relapsing
Increasing disability
Time

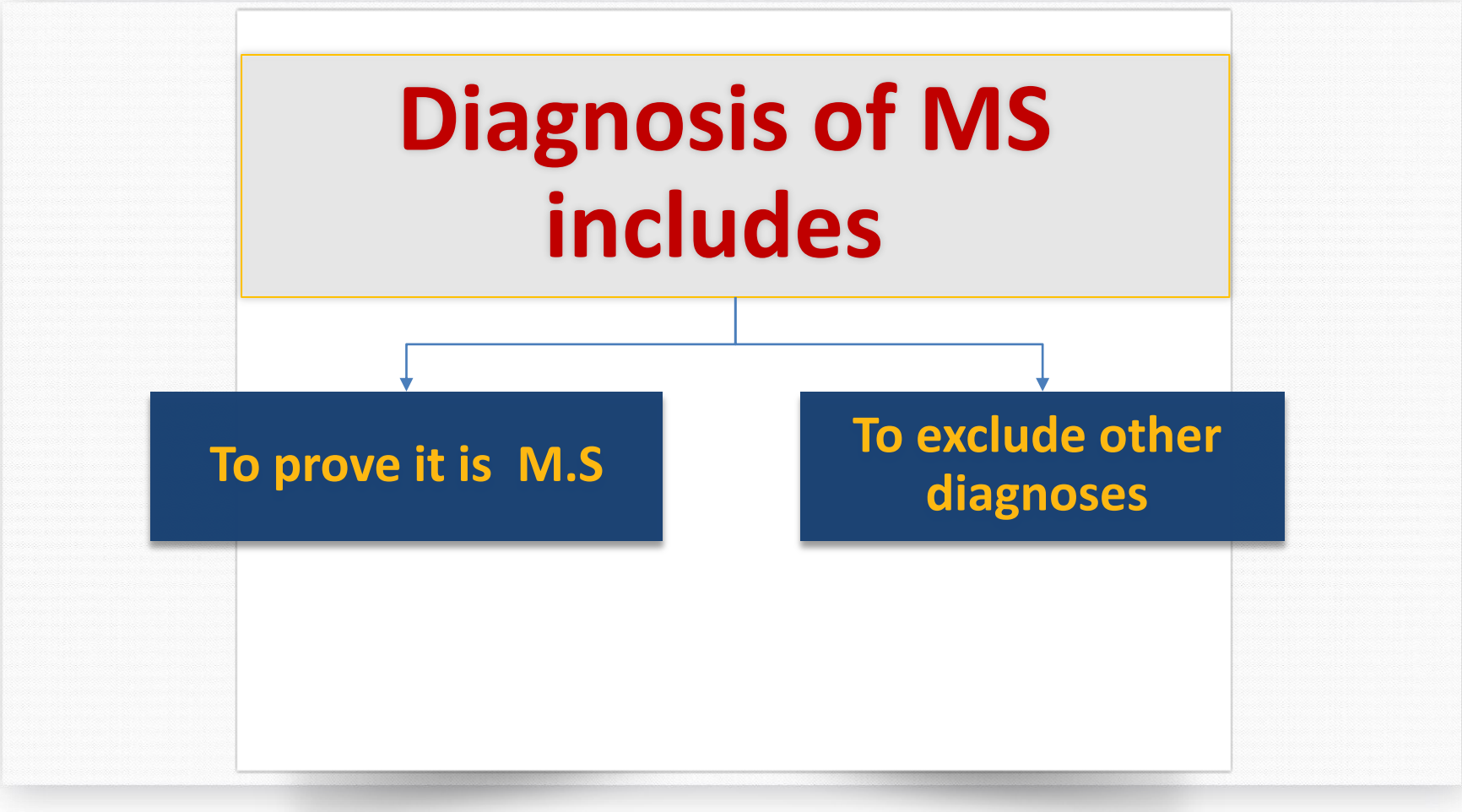


SEP	Predominant pathological mechanism	Accumulation of disability
RR	inflammation	stepwise
SP/PP	neurodegeneration	progressive

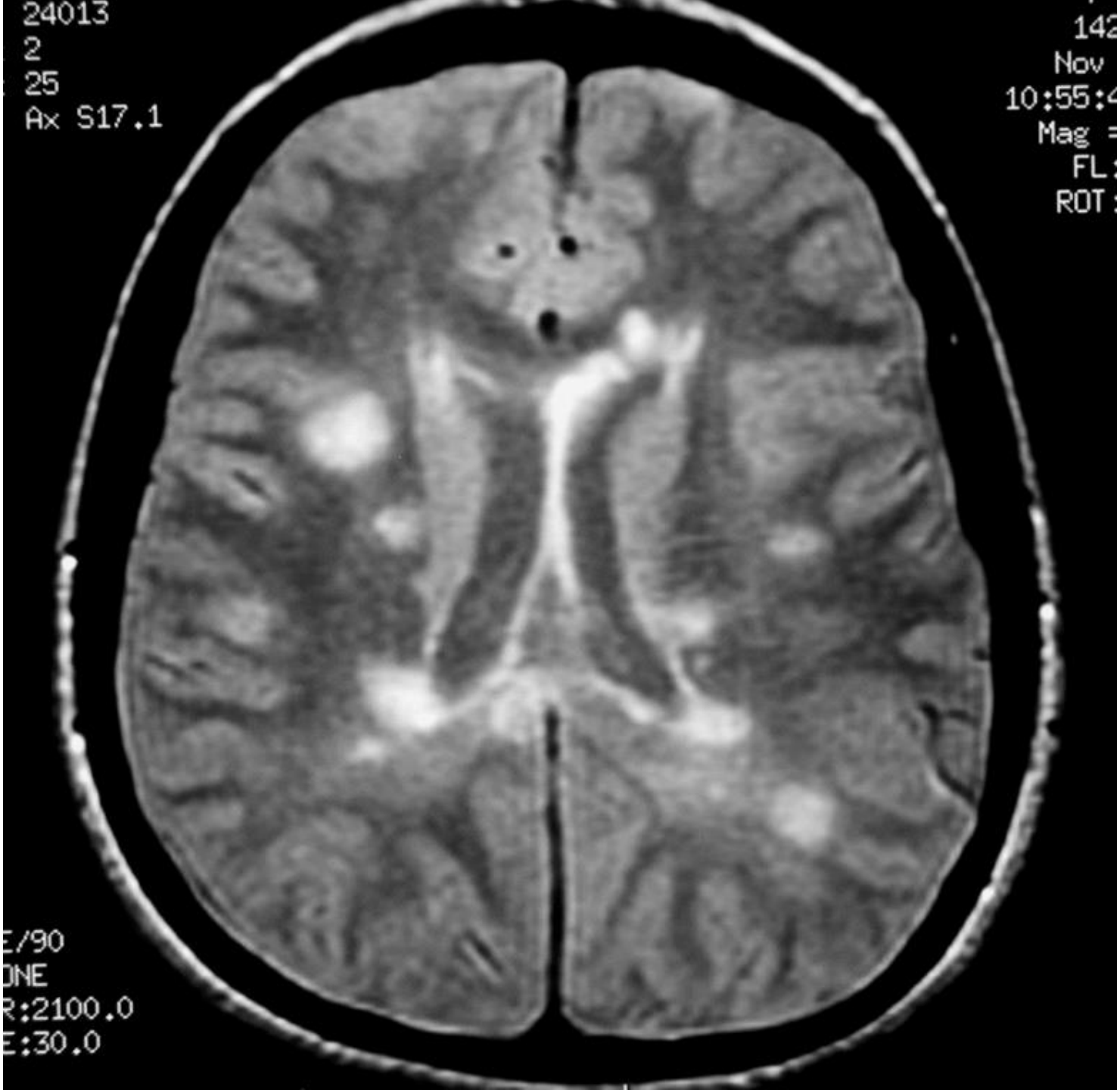

Lymph node
MΦ
APC
S1P-R
T
Fingolimod
Natalizumab
Cladribine
Teriflunomide
VLA-4
T
CD52
CD25
T
VCAM
Alemtuzumab
Daclizumab
NK
B
Rituximab
CD20
APC
T
Th2
IL-4, IL-5
Th1
Th17
? IL-17
Laquinimod
PC
Fumaric acid
?
IFN-γ
TNF-α, NO
S1P-R
?
Fingolimod
MΦ
CD8
Periphery
BBB
CNS
TRENDS in Pharmacological Sciences

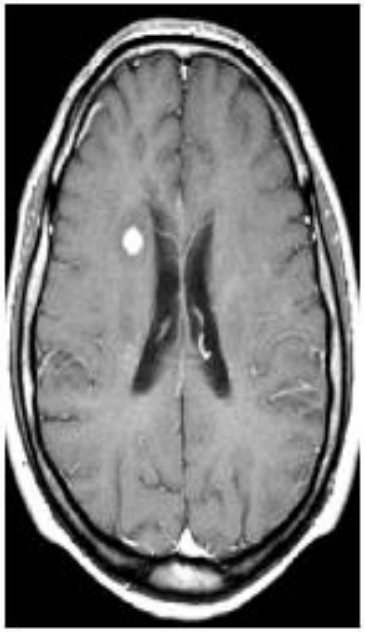
Diagnosis

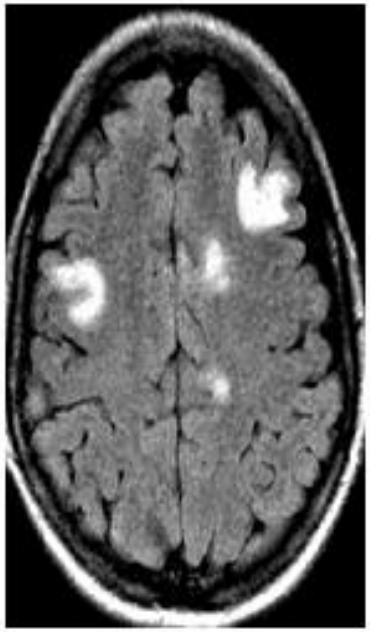
Multiple Sclerosis Diagnosis

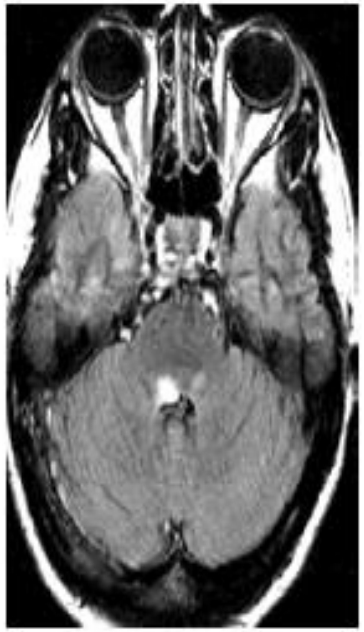


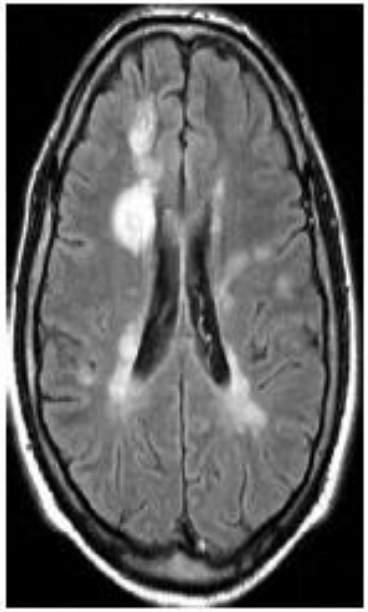
PRESENTING SYMPTOMS IN MS	Total %
SENSORY LOSS IN LIMBS	30.7
VISUAL LOSS	15.9
MOTOR WEAKNESS	14.2
DIPLOPIA	6.8
GAIT DISTURBANCE	4.8
INCOORDINATION	2.9
SENSORY LOSS-FACE	2.8
LHERMITTE'S	1.8
VERTIGO	1.7
BLADDER SYMPTOMS	1
AUTE TRANSVERSE MYELOPATHY	0.7
PAIN	0.5
OTHERS	2.5
POLYSYMPTOMATIC	13.7


24013
2
25
Ax S17.1
142
Nov
10:55:4
Mag
FL
ROT
E/90
ONE
R:2100.0
E:30.0



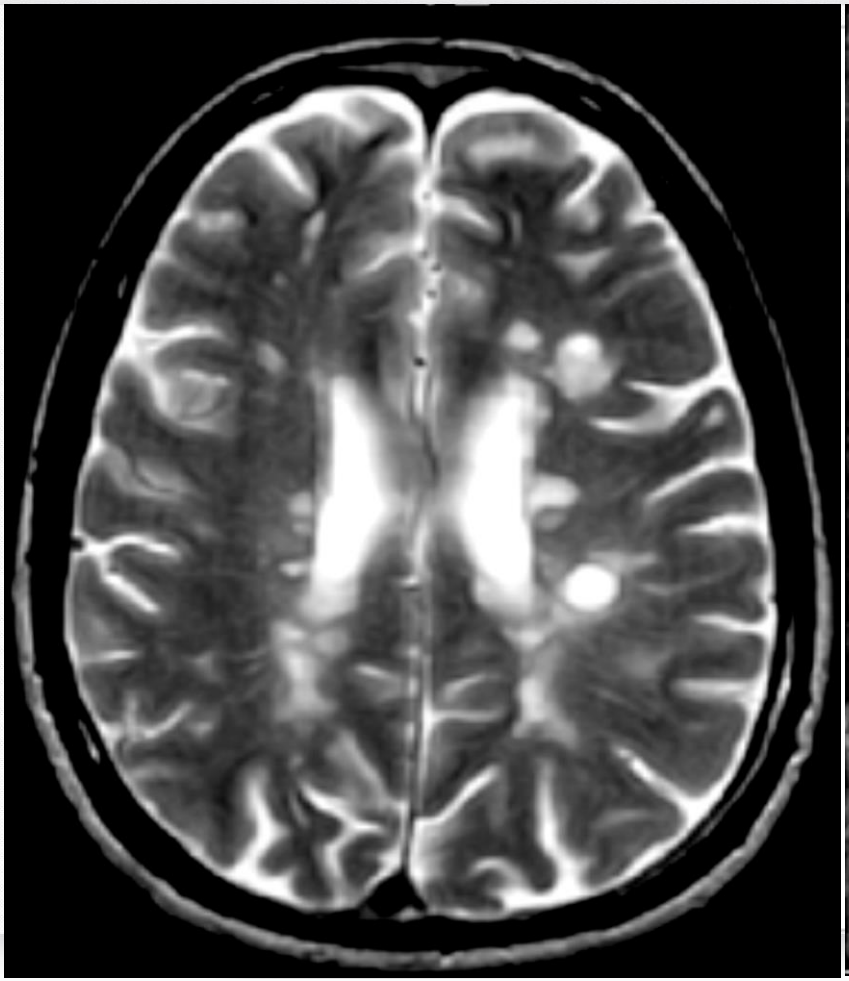


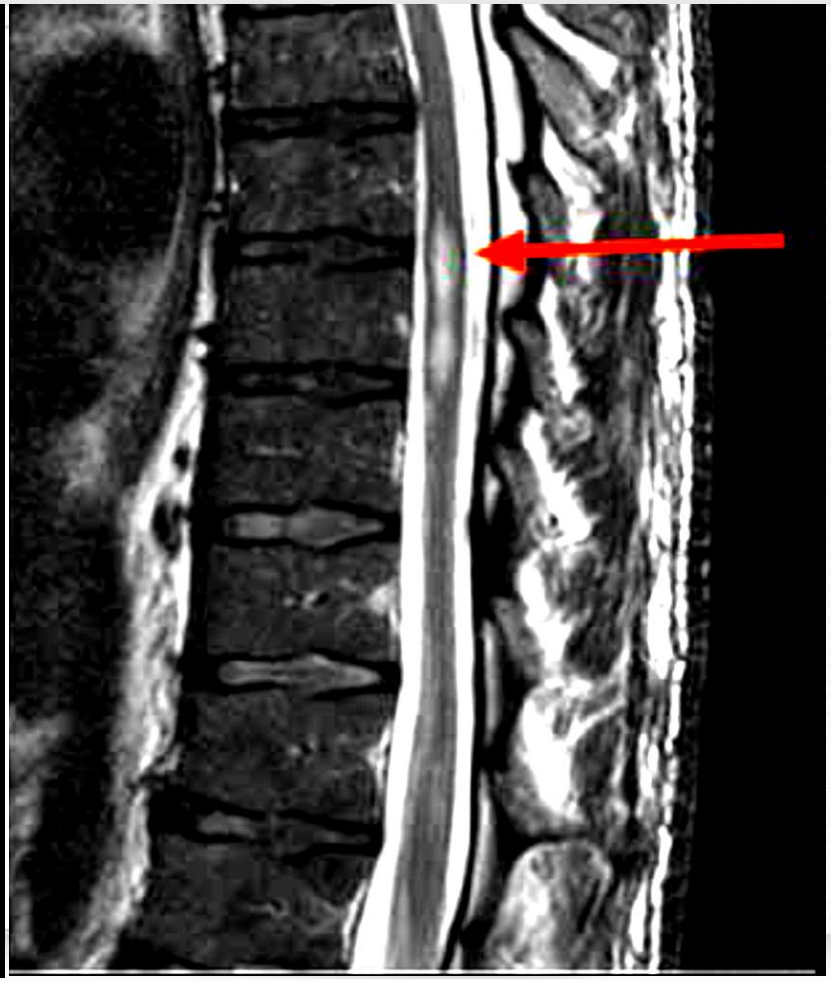


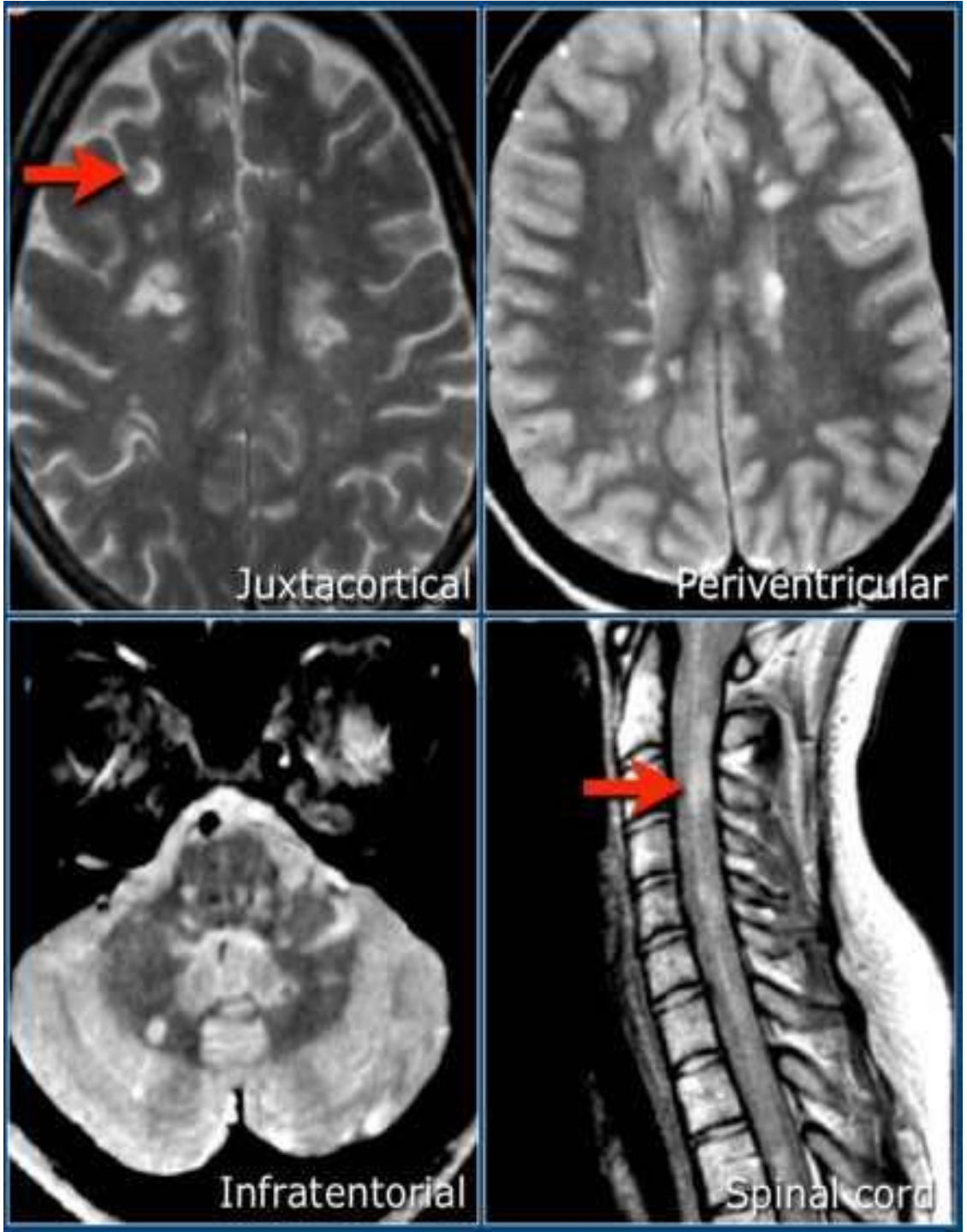


Gd juxta infra 3 PV Cem

Magnetic resonance imaging
T2 weighted images showing plaques






Juxtacortical
Periventricular
Infratentorial
Spinal cord

Mc Donald criteria for MS

ATTACKS	LESIONS	ADDITIONAL CRITERIA FOR DIAGNOSIS MS
2 or more	**2 or more**	**None.** Clinical evidence alone will suffice
2 or more	**1 lesion**	**Dissemination in space on MR** (or await further clinical attack implicating a different CNS site)
1 attack	**2 lesions**	**Dissemination in time on MR** (or await further clinical attack implicating a different CNS site)
1 attack	**1 lesion**	**Dissemination in space *and* time** (or await further clinical attack implicating a different CNS site)
0 attack progression from onset		One year of disease progression (retrospective or prospective) **AND** at least 2 out of 3 criteria: • Dissemination in space in the brain • Dissemination in space in the spinal cord based on 2 or more T2 lesions • Positive CSF

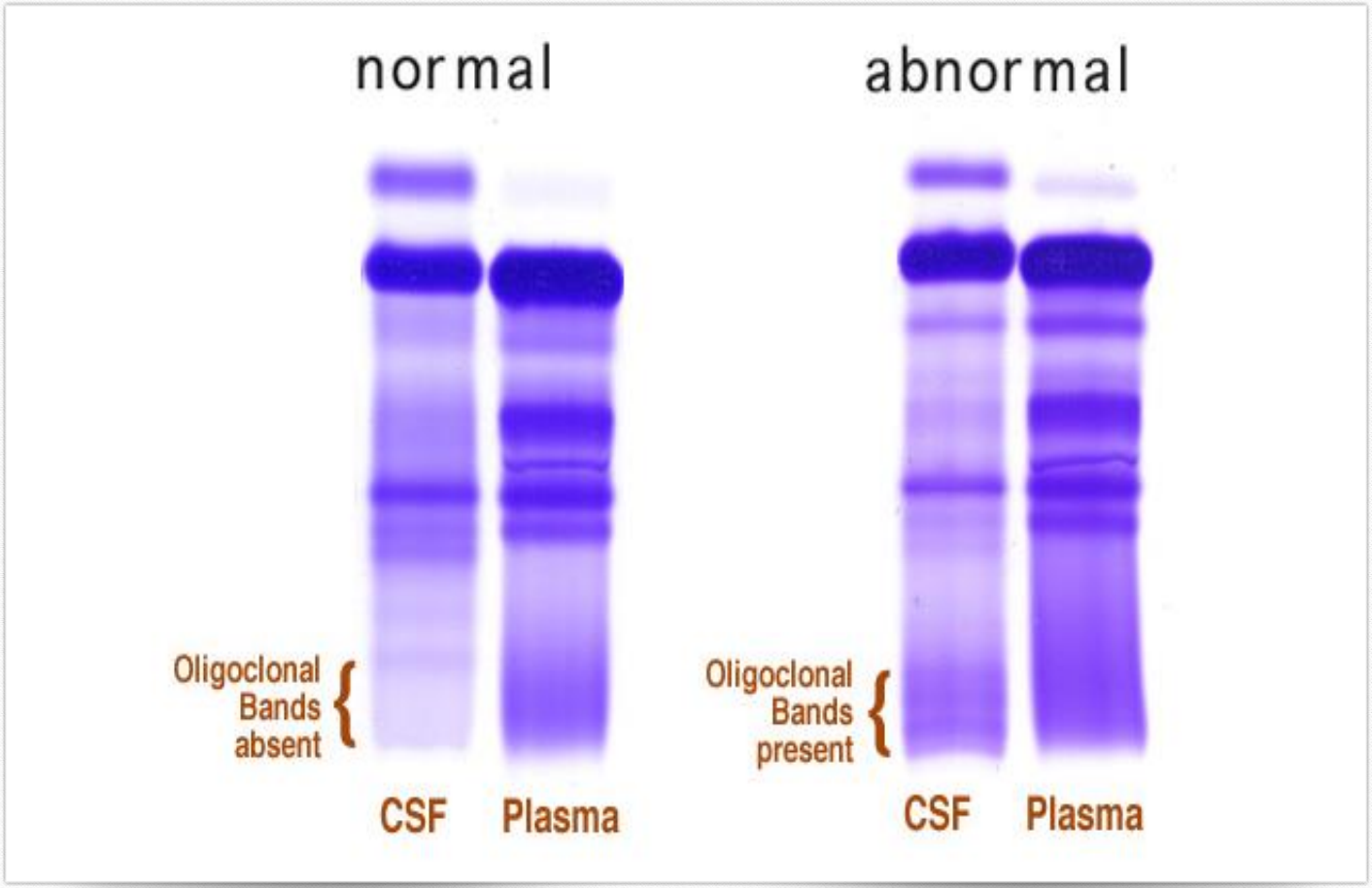
CSF examination

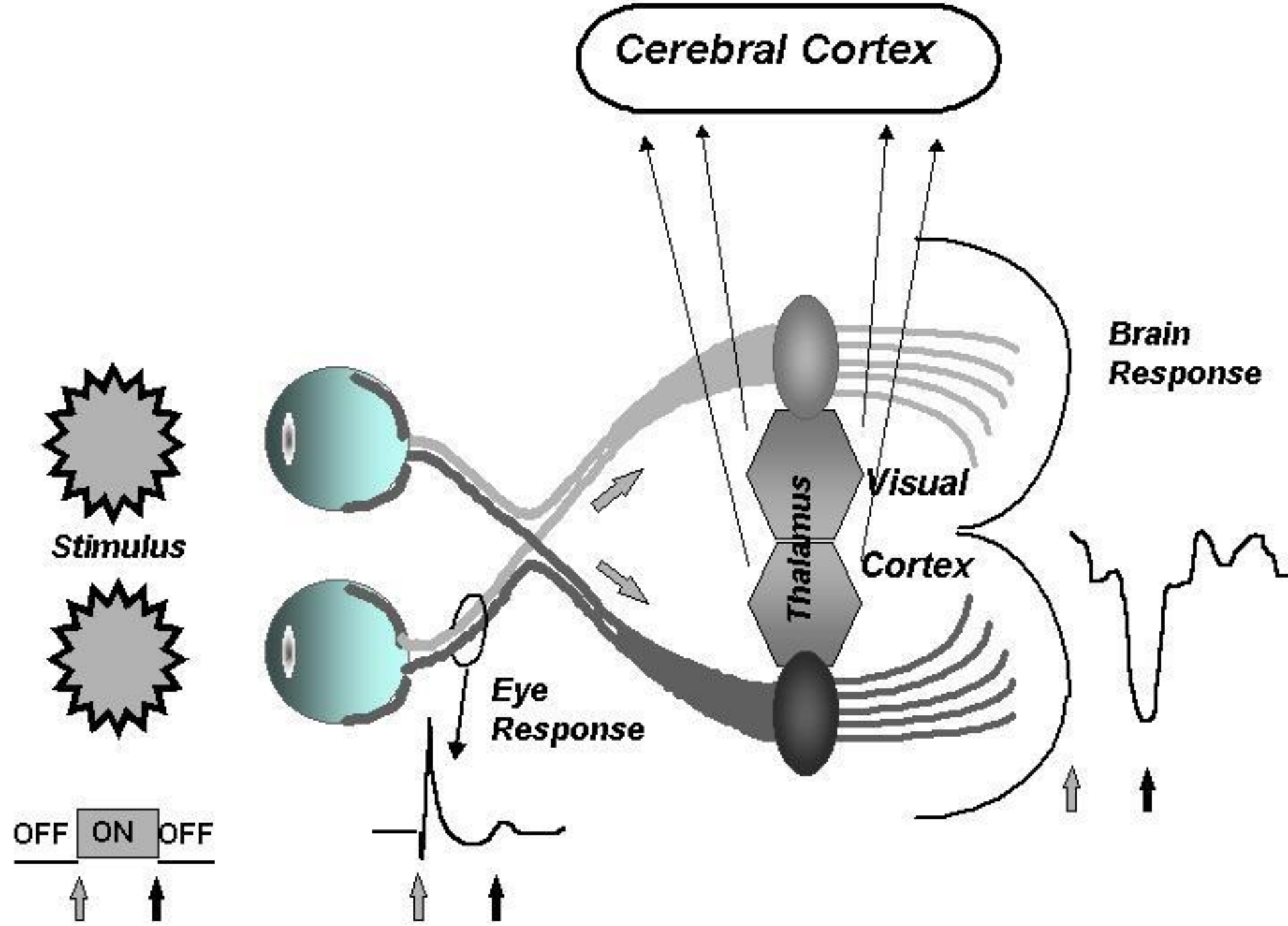
IgG index:

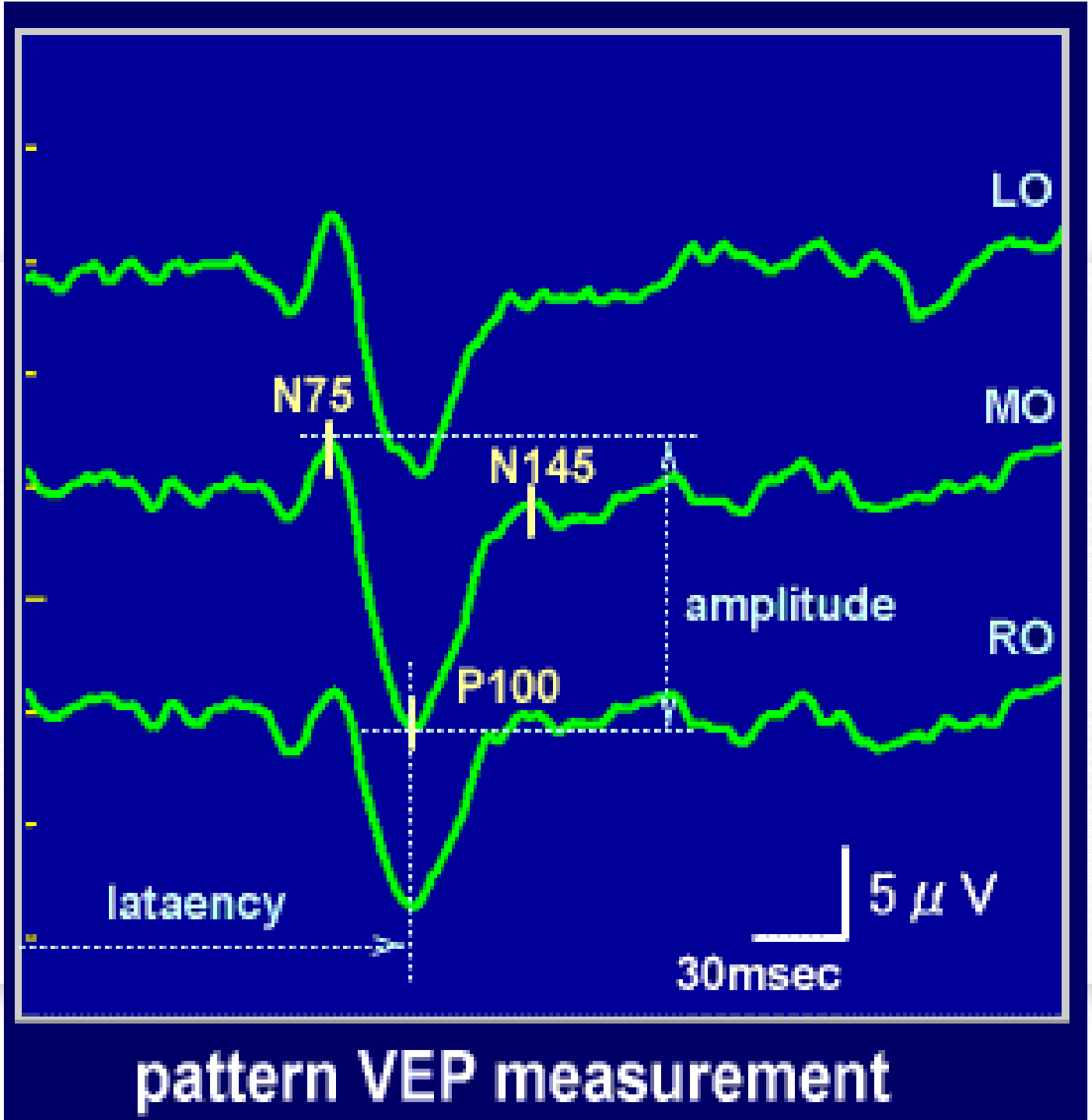
- $[IgG_{CSF}/albumin_{CSF}]/[IgG_{serum}/albumin_{serum}]$

MS patients elevated IgG index (>1.7). (normal is <0.77)

Oligoclonal Bands in CSF

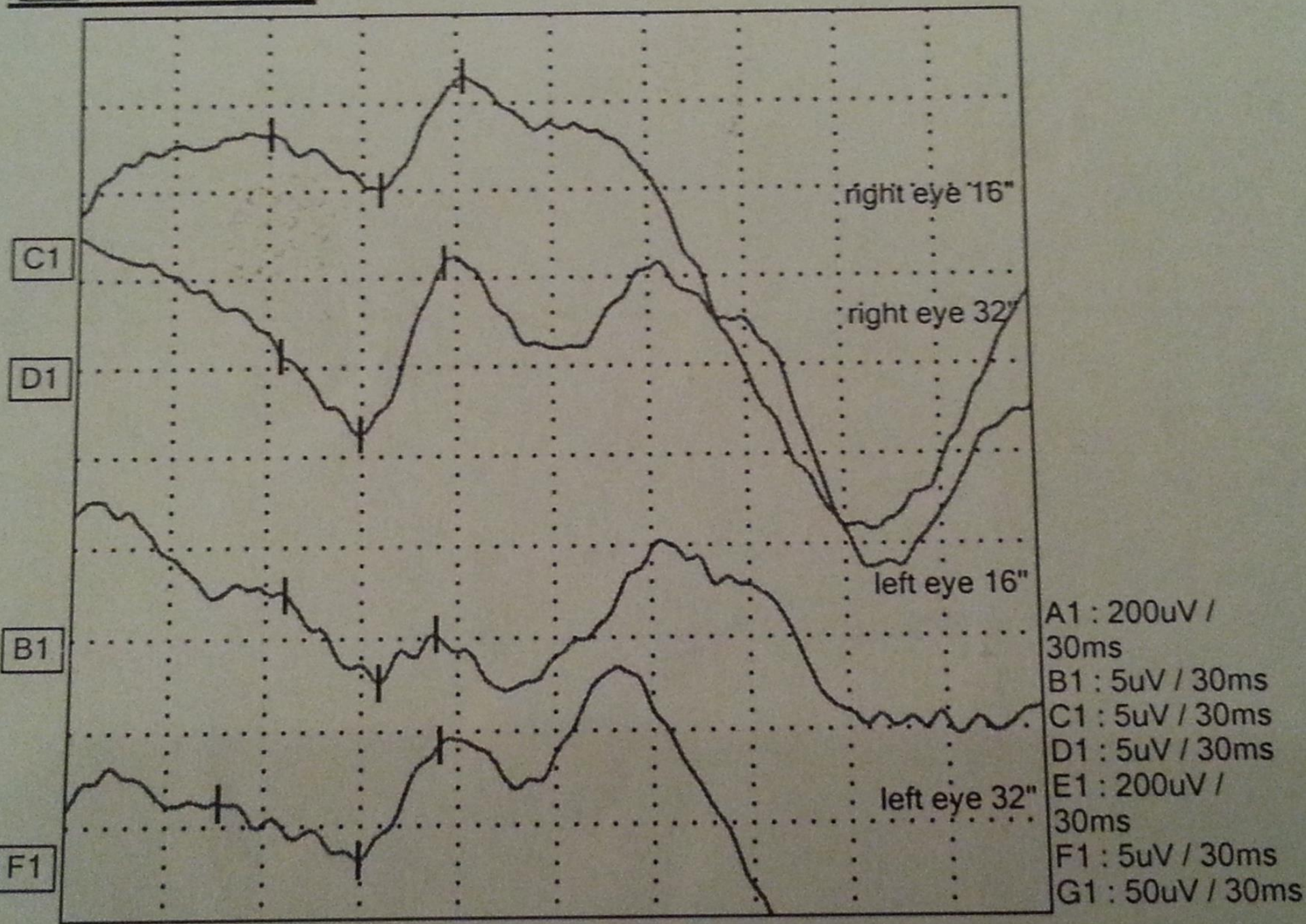



Cerebral Cortex
Brain
Response
Thalamus
Visual
Cortex
Stimulus
Eye
Response
OFF
ON
OFF

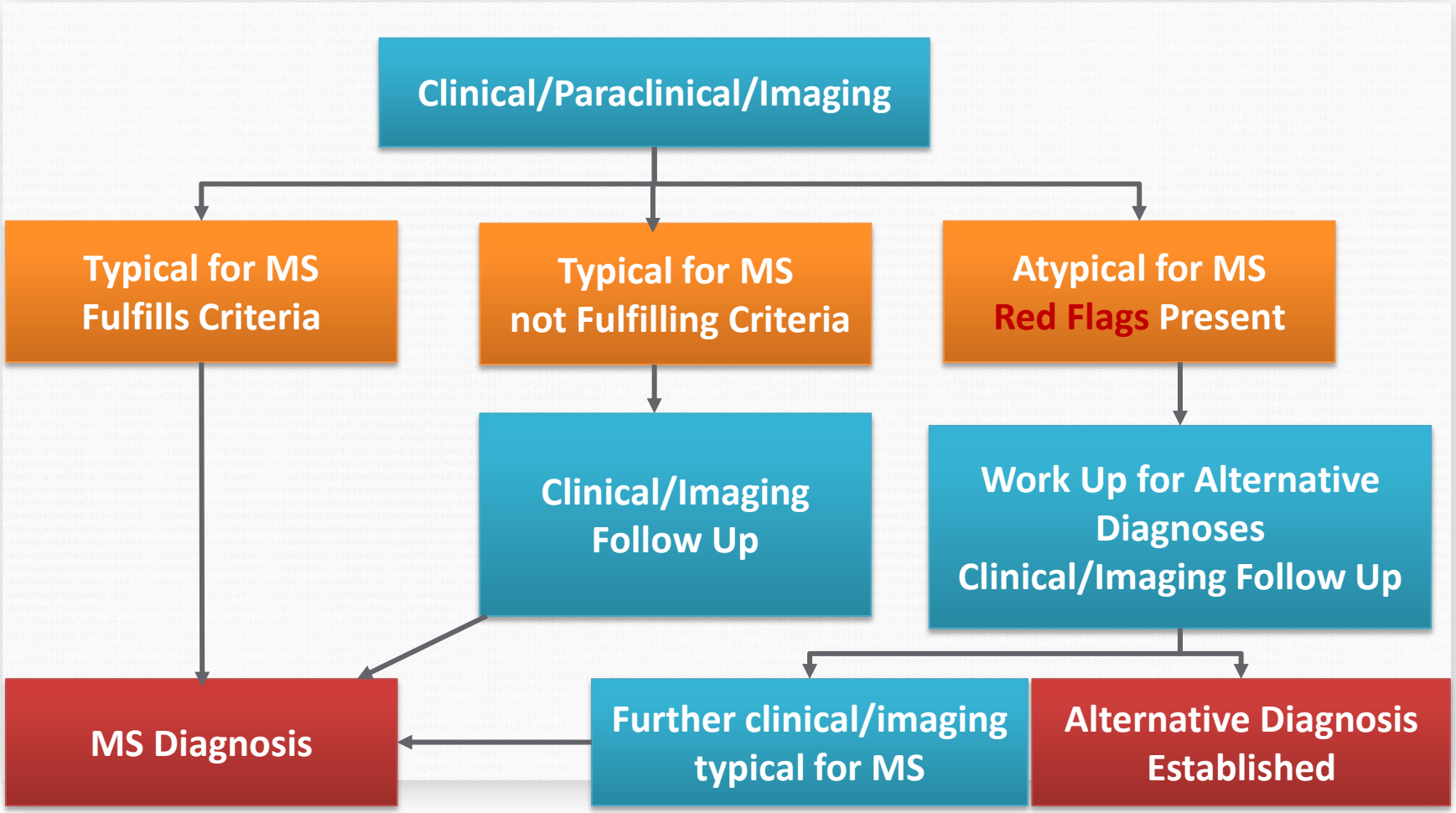


pattern VEP measurement

Pattern-VEP

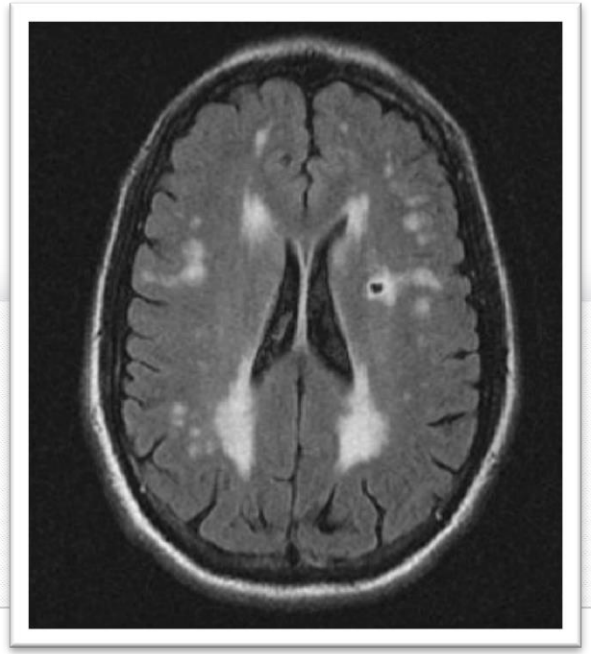

right eye 16"
right eye 32"
left eye 16"
left eye 32"
C1
D1
B1
F1
A1 : 200uV / 30ms
B1 : 5uV / 30ms
C1 : 5uV / 30ms
D1 : 5uV / 30ms
E1 : 200uV / 30ms
F1 : 5uV / 30ms
G1 : 50uV / 30ms

Mental map for diagnosis of MS



Clinical Red Flags

Laboratory Red Flags

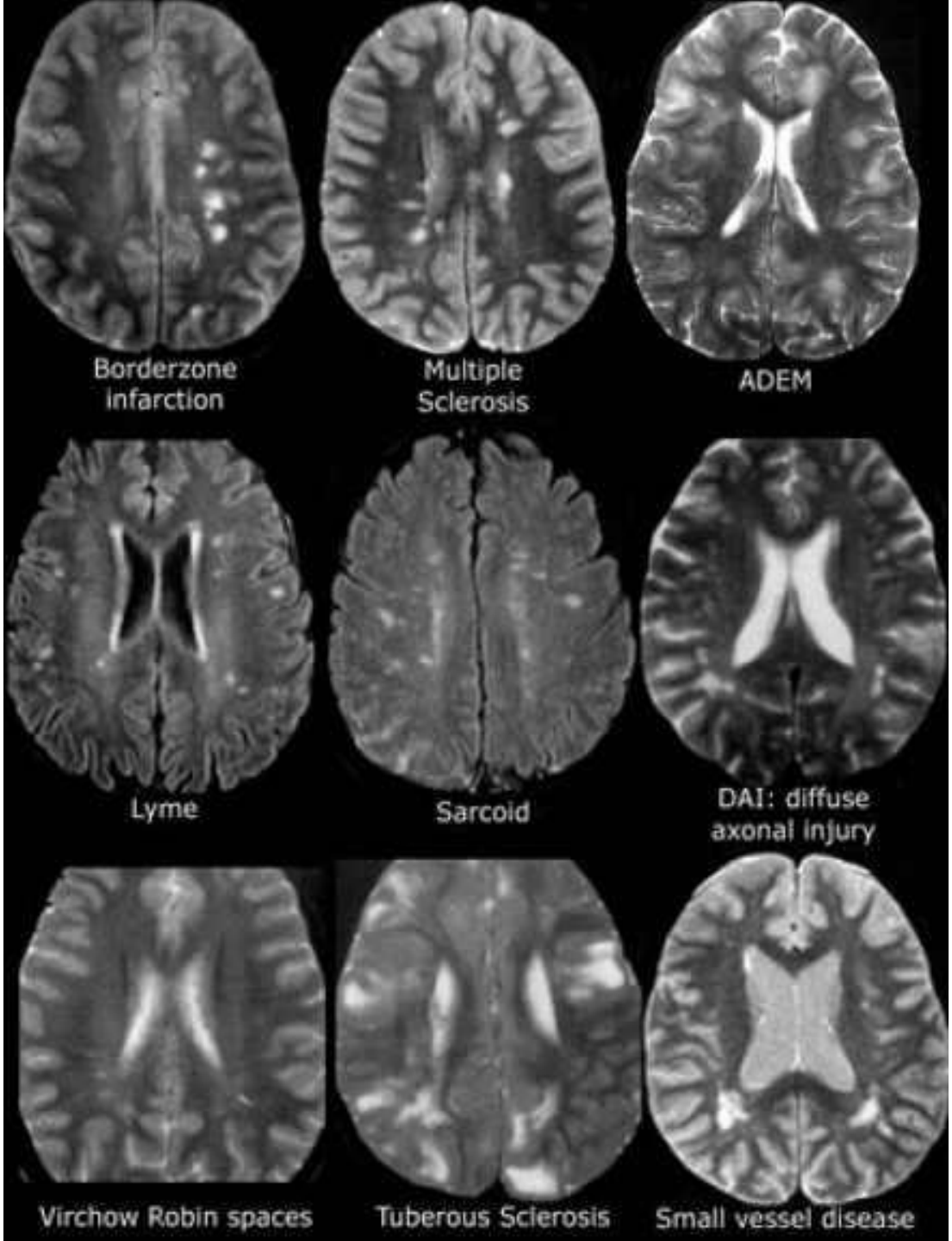


Imaging Red Flags

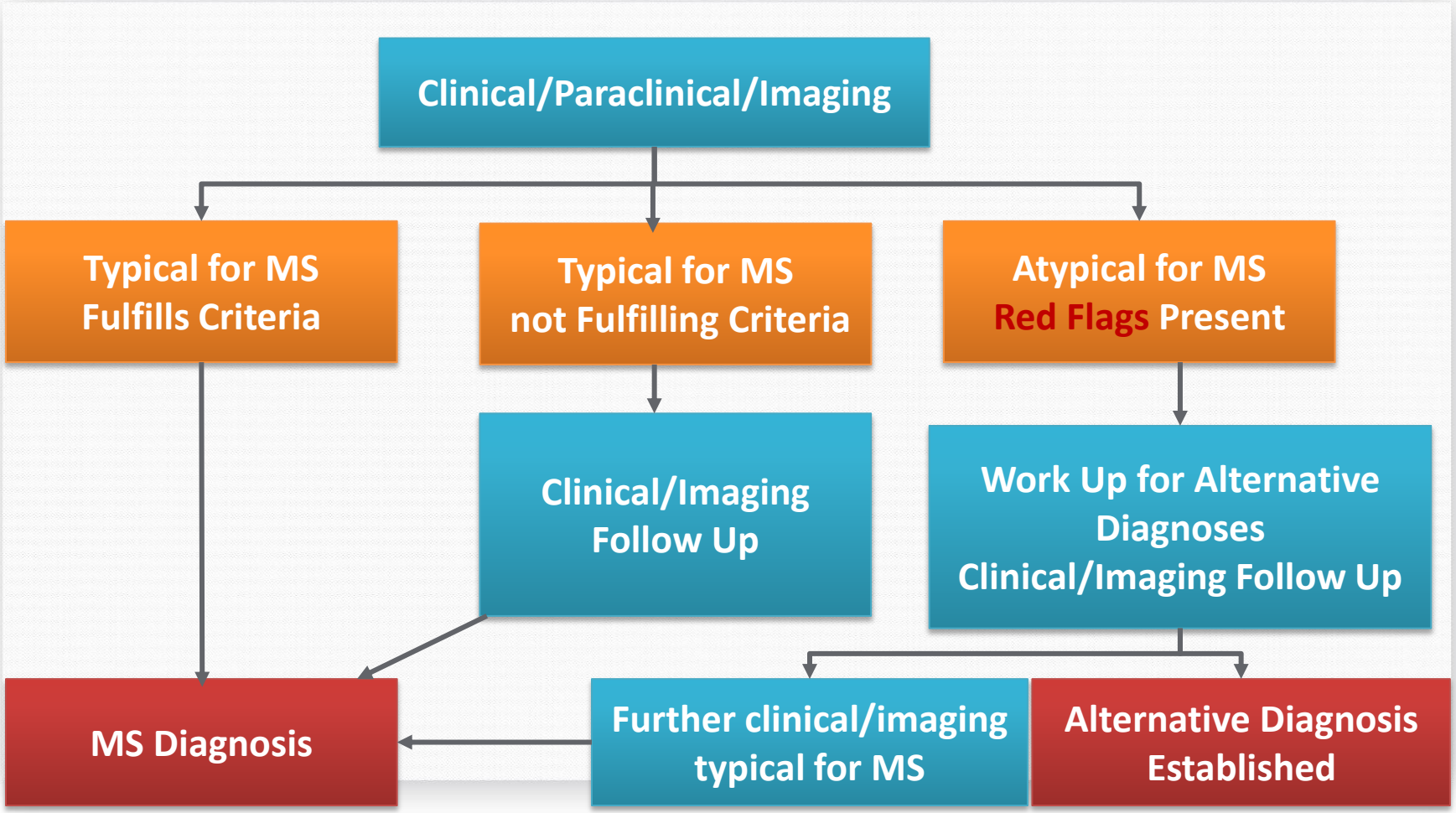
Famous Dictum

"The most common reason for falsely attributing a patient's symptoms to multiple sclerosis is faulty interpretation of the magnetic resonance imaging."

Loren A. Rolak
2007


Borderzone infarction
Multiple Sclerosis
ADEM
Lyme
Sarcoid
DAI: diffuse axonal injury
Virchow Robin spaces
Tuberous Sclerosis
Small vessel disease

Mental map for diagnosis of MS



Biomarkers

BIOMARKERS

GENETIC/IMMUNOGENETIC:

- Biomarkers specified via genomics and immunogenetic techniques.

LABORATORY:

- All other biomarkers that can be measured in body fluids.

IMAGING:

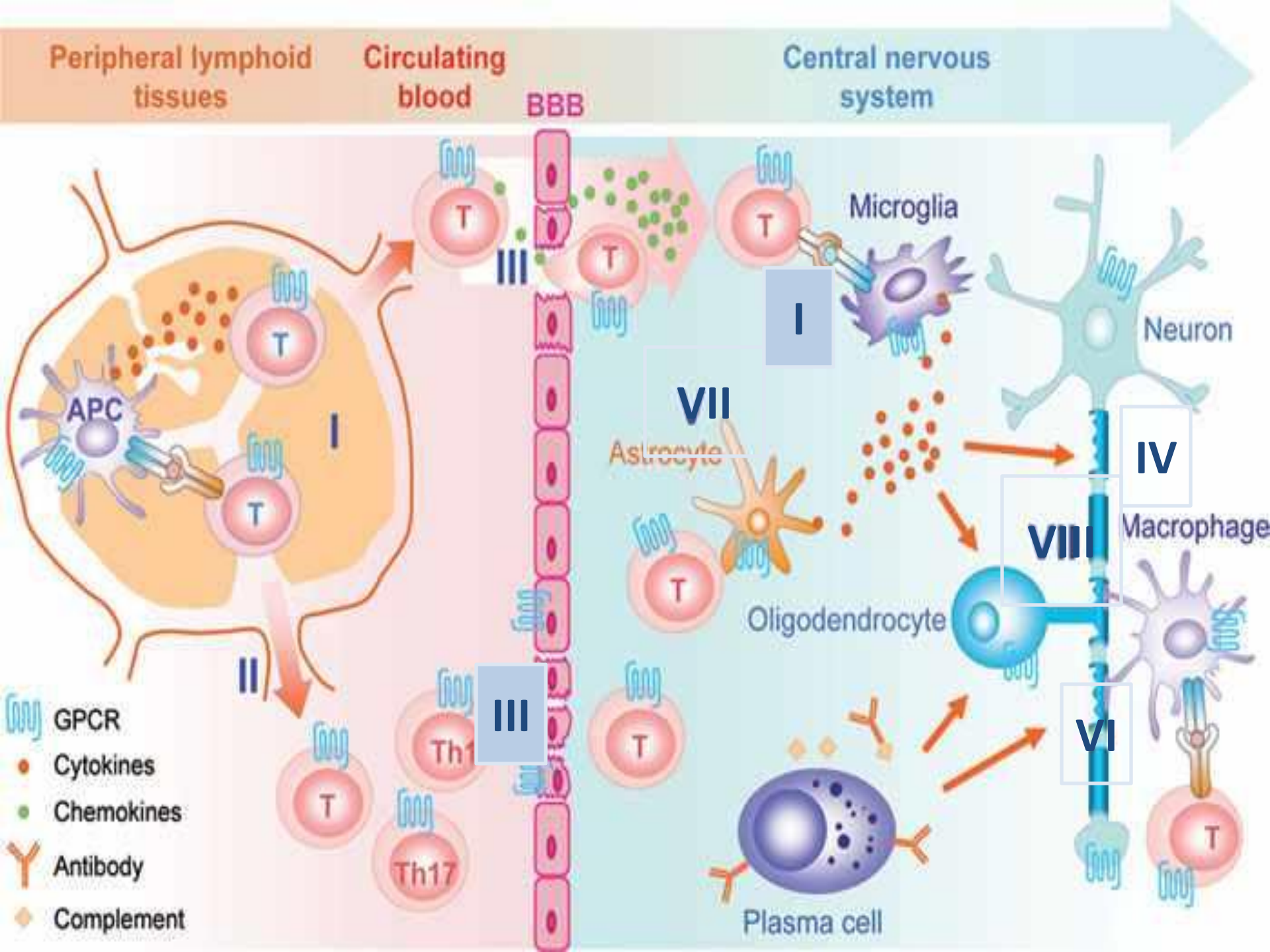
- Biomarkers provided by imaging techniques.

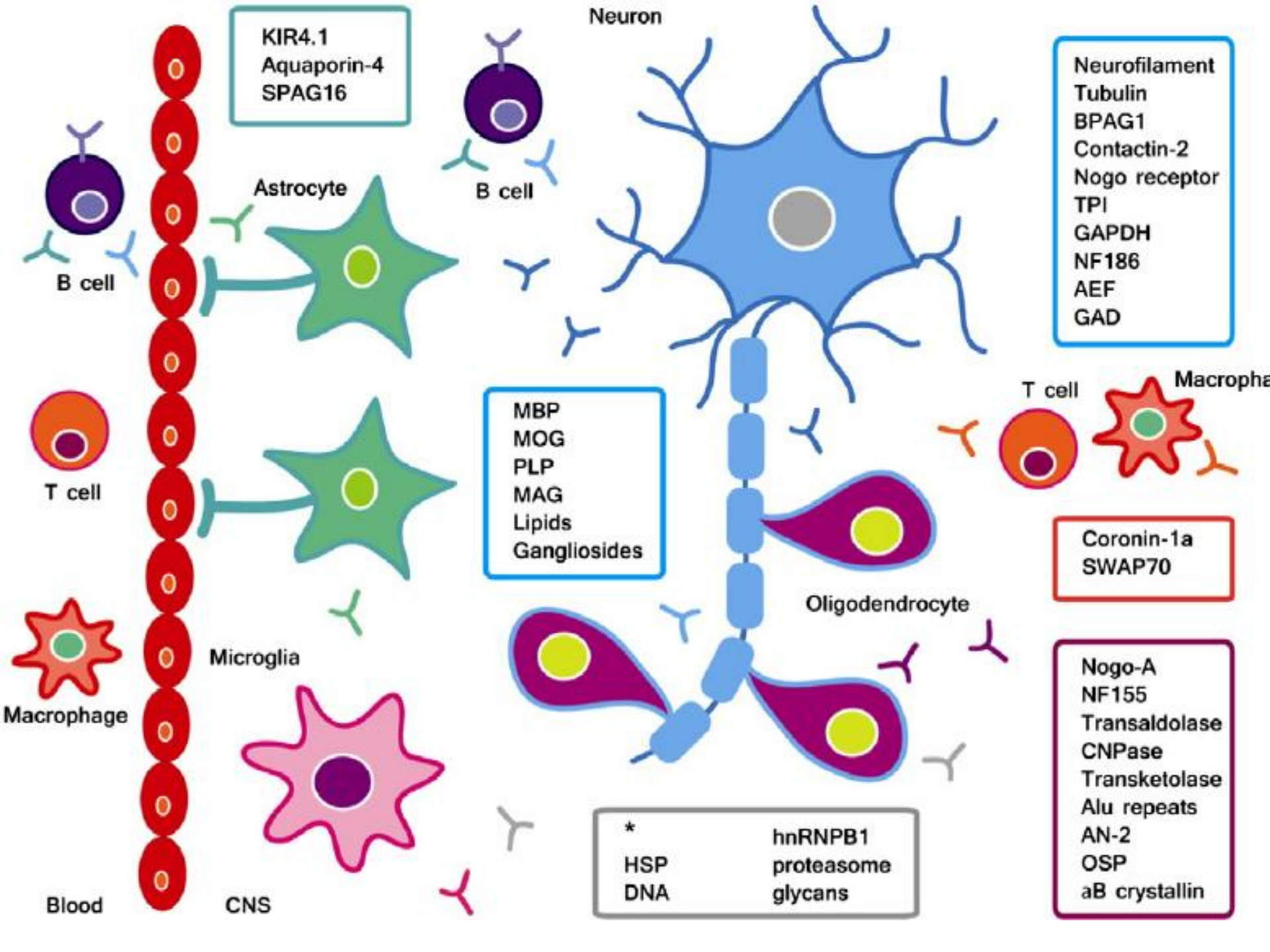
BIOMARKERS

B. LABORATORY BIOMARKERS

B. Laboratory Biomarkers

I. Biomarkers of Immunological Activation
II. Biomarkers of Neuroprotection
III. Biomarkers of BBB disruption
IV. Biomarkers of demyelination
V. Biomarkers of Oxidative Stress
VI. Biomarkers of Axonal Damage
VII. Biomarkers of Glial Activation Dysfunction
VIII. Biomarkers of Remyelination Repair
IX. Biomarkers of Therapeutic Response
X. Prognostic Biomarkers
XI. Emering biomarkers


Peripheral lymphoid tissues
Circulating blood
BBB
Central nervous system
APC
T
I
II
III
Th1
Th17
Microglia
Neuron
VII
Astrocyte
IV
VIII
Macrophage
Oligodendrocyte
VI
Plasma cell
GPCR
Cytokines
Chemokines
Antibody
Complement


KIR4.1
Aquaporin-4
SPAG16
Neuron
Neurofilament
Tubulin
BPAG1
Contactin-2
Nogo receptor
TPI
GAPDH
NF186
AEF
GAD
B cell
Astrocyte
B cell
T cell
MBP
MOG
PLP
MAG
Lipids
Gangliosides
T cell
Macropha
Coronin-1a
SWAP70
Oligodendrocyte
Microglia
Macrophage
Nogo-A
NF155
Transaldolase
CNPase
Transketolase
Alu repeats
AN-2
OSP
aB crystallin
*
HSP
DNA
hnRNPB1
proteasome
glycans
Blood
CNS

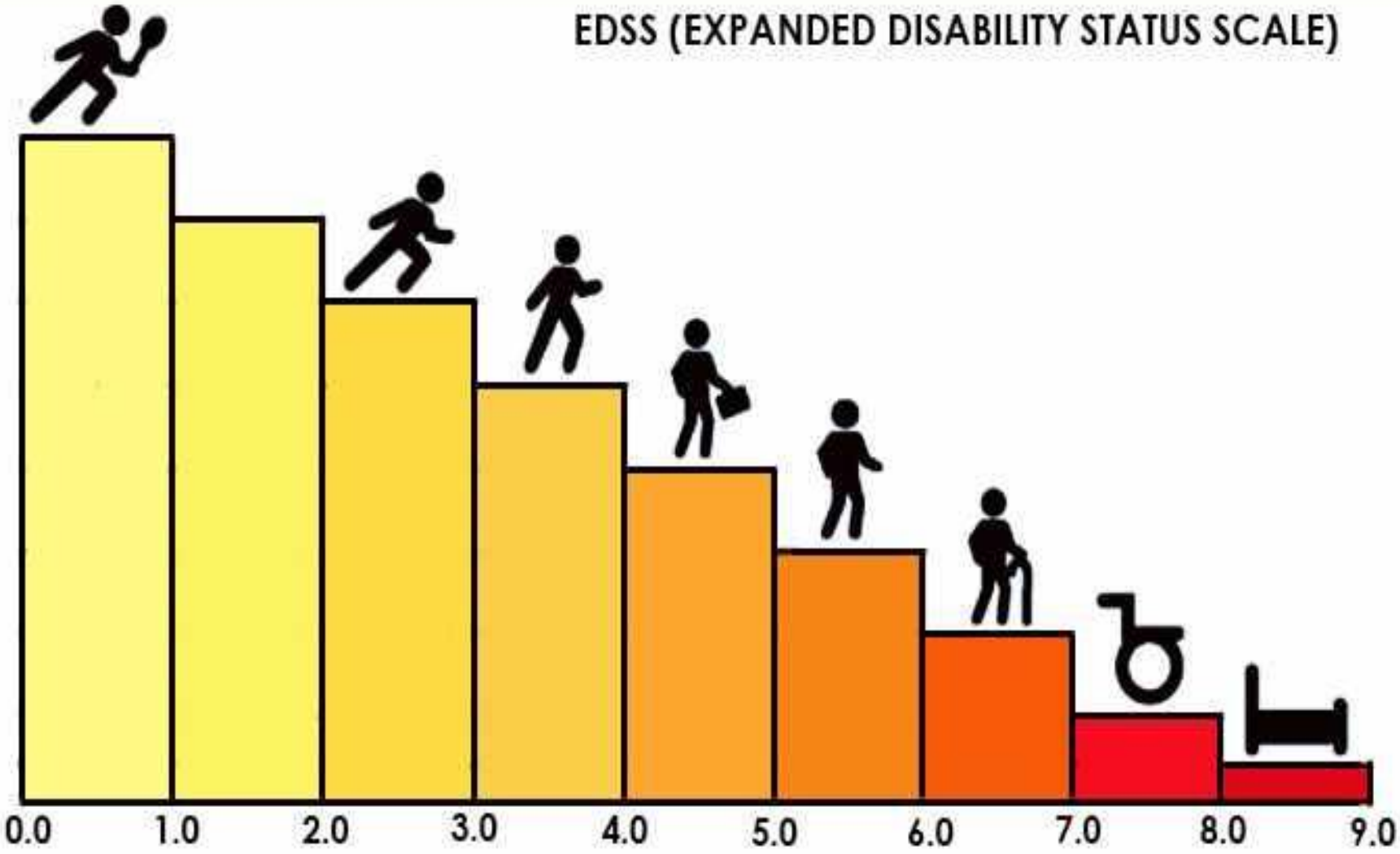
BIOMARKERS

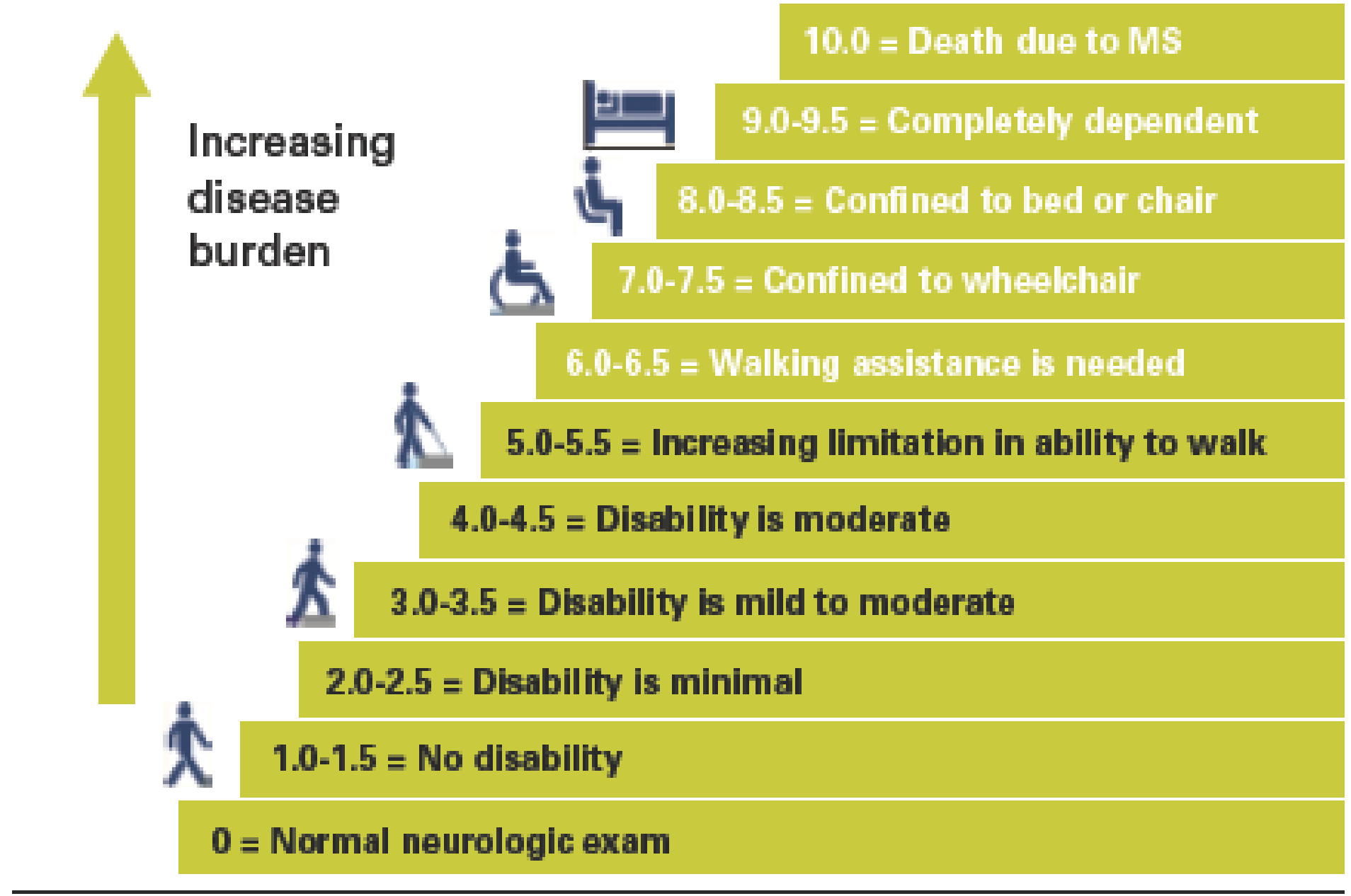
CLINICAL

OCB

MRI

EDSS (EXPANDED DISABILITY STATUS SCALE)

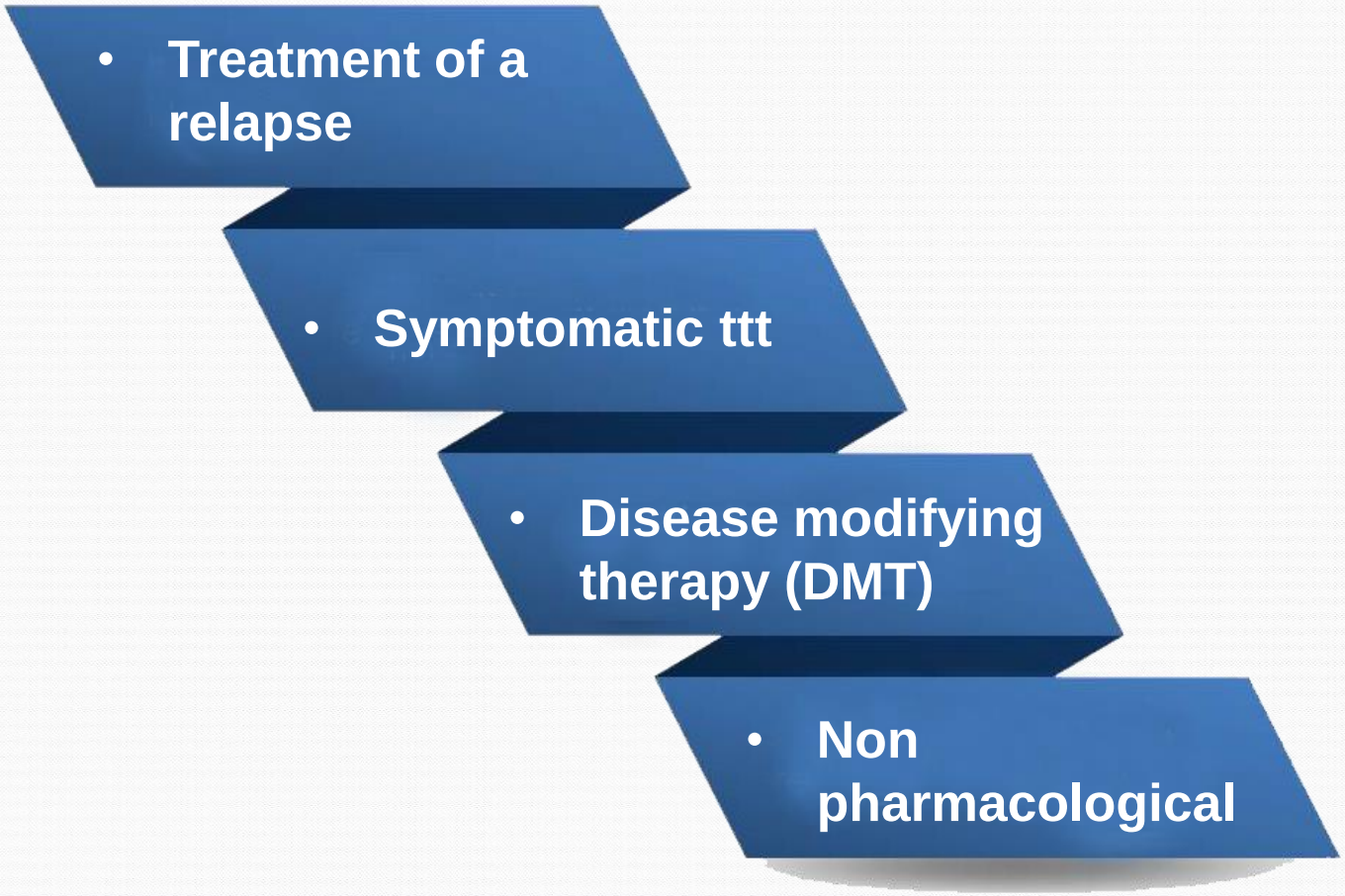




EDSS indicates Expanded Disability Status Scale; MS, multiple sclerosis.

Treatment options

Relapsing remitting multiple sclerosis (R.R.M.S.)



Relapse

Definition of a relapse

- Worsening of present symptoms or appearance of new symptoms
- At least 24 h
- 1 month from last attack.
- Not during steroid withdrawal or infection.
- ↑ EDSS ≥ 0.5

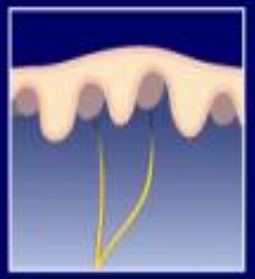
Symptomatic ttt

Fatigue

Mood problems

Pain

Sensory problems

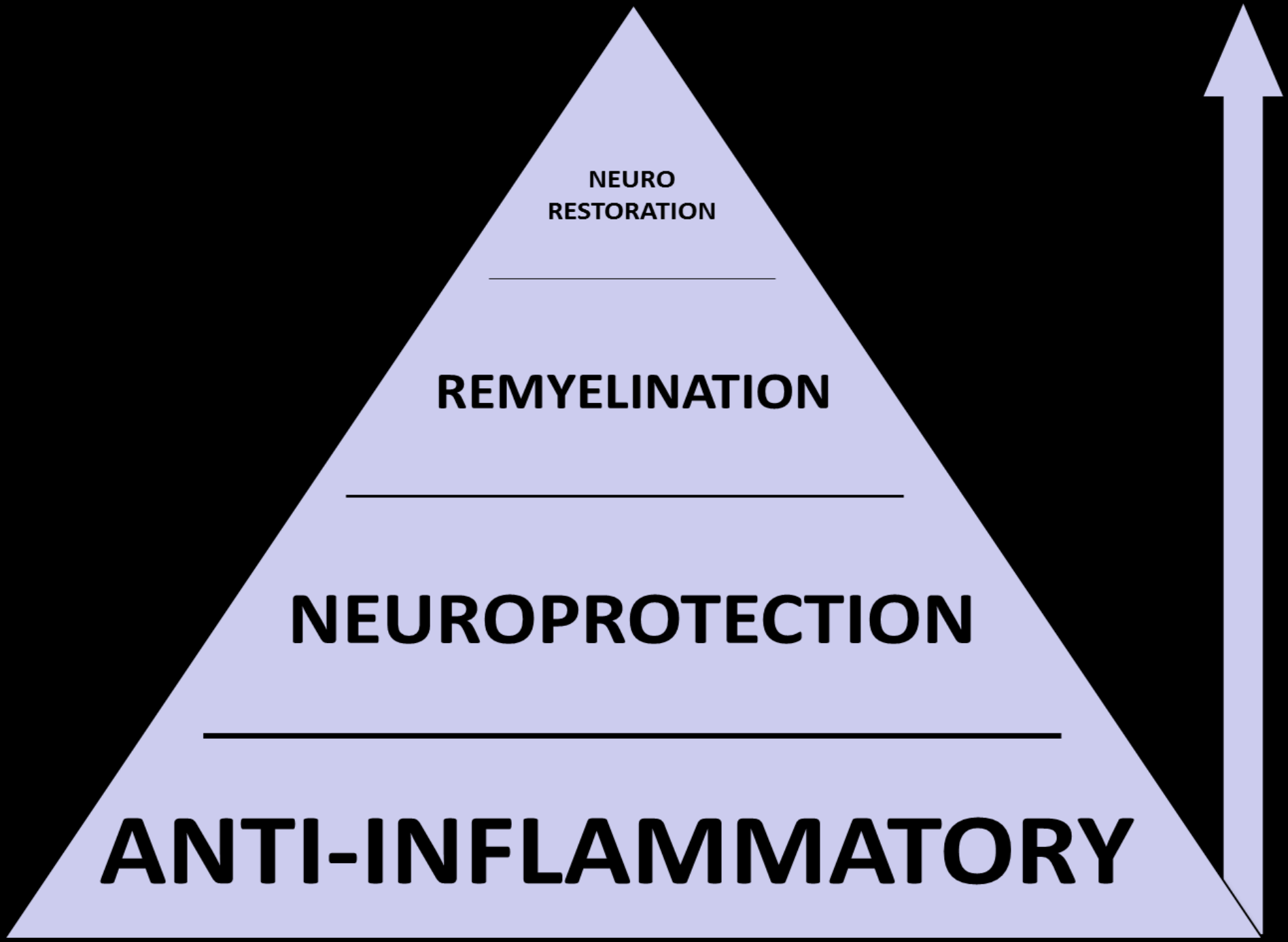


Genitosphincteral problems

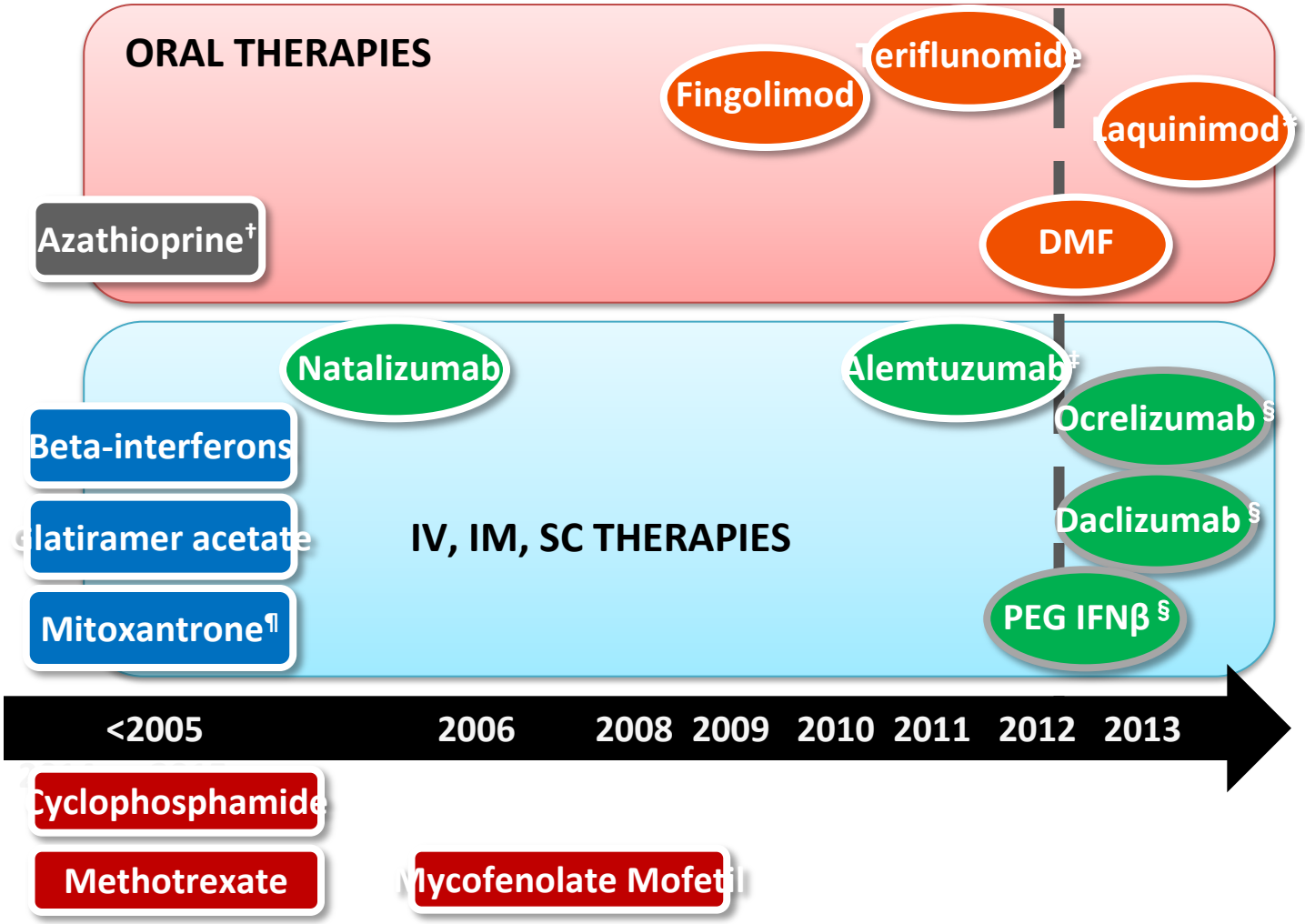
Tremor

Spasticity

Treatment optimization

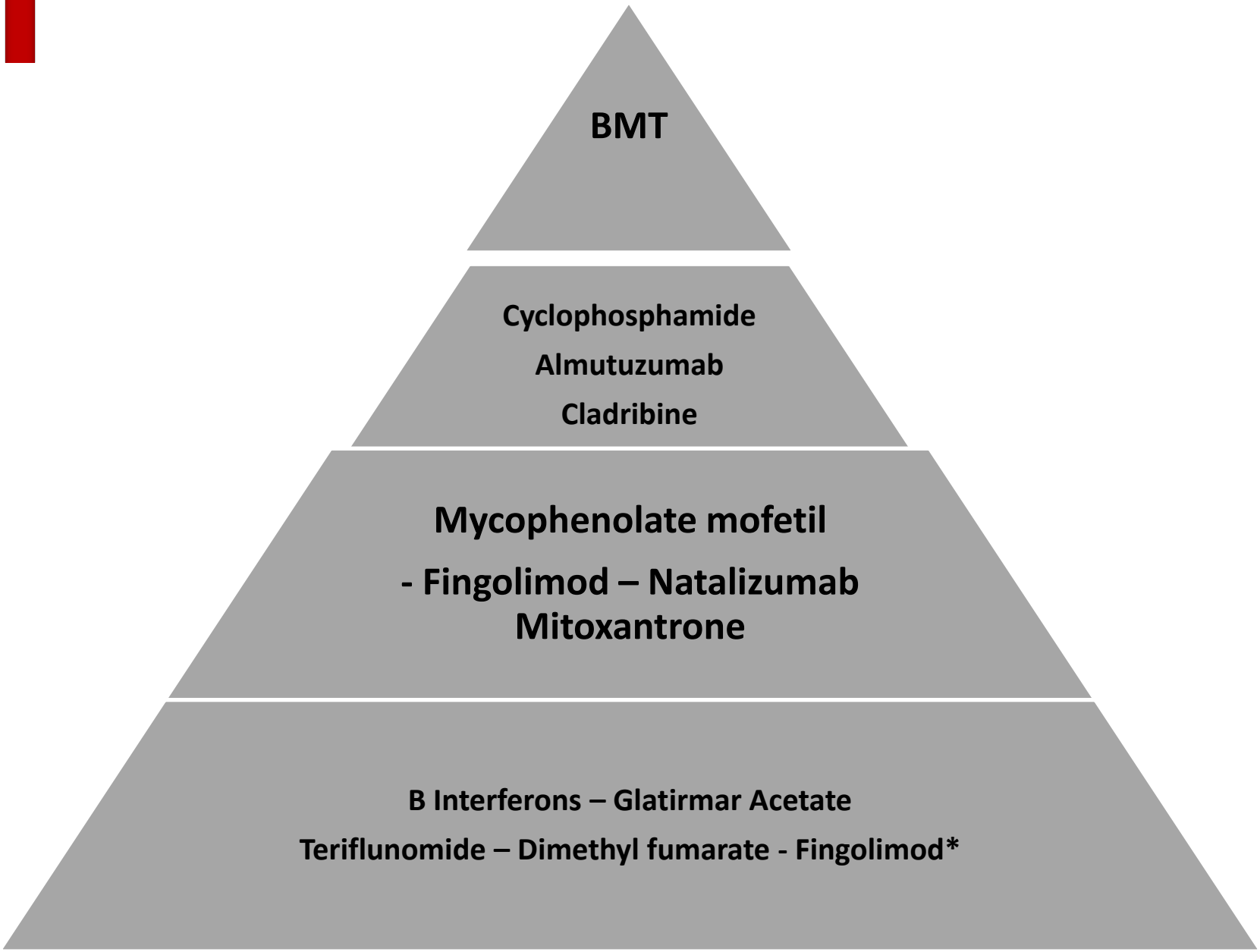

NEURO
RESTORATION
REMYELINATION
NEUROPROTECTION
ANTI-INFLAMMATORY

Current and future MS therapies



Product labelling (including indications, safety information and monitoring requirements) may vary by country; for more detailed information, refer to your local prescribing information for recommendations and contraindications for each DMT

Dates are approximate as approval dates vary between different countries; for drugs beyond 2014, approval dates are estimated, based on current regulatory status. *Not yet approved by the FDA; negative opinion adopted by CHMP in January 2014, opinion being re-examined as of 21 February 2014. †Not currently approved by the EMA or FDA. ‡Approved by the EMA, rejected by the FDA in December 2013. §Not yet approved by FDA or EMA. ¶Not currently

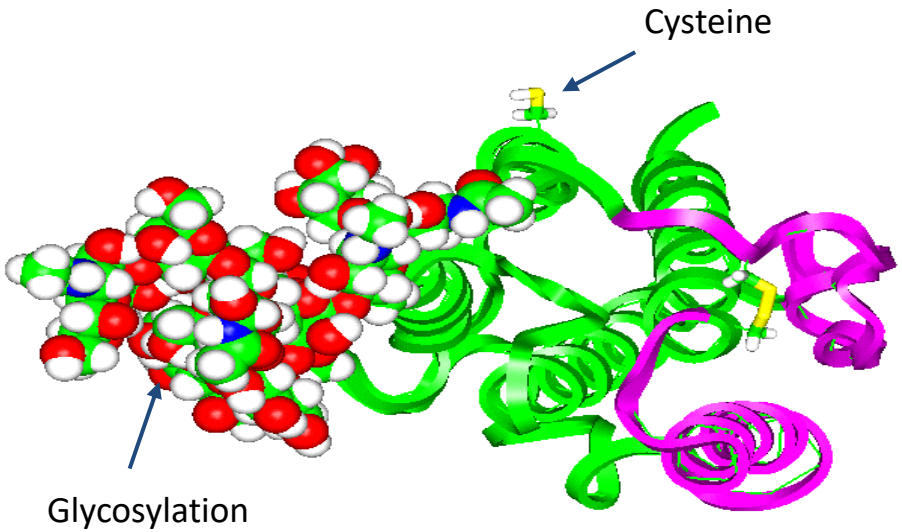

BMT
Cyclophosphamide
Almutuzumab
Cladribine
Mycophenolate mofetil
- Fingolimod – Natalizumab
Mitoxantrone
B Interferons – Glatirmar Acetate
Teriflunomide – Dimethyl fumarate - Fingolimod*

Pivotal Studies

	Avonex	**Betaferon**	**Rebif**	**Copaxone**
CIS	CHAMPS	BENEFIT	ETOMS REFLEX	PRECISE
RRMS	MSCRG	IFNB MS Study Group *Neurology 1993/1995*	PRISMS	Johnson Trial *Neurology 1995*
SPMS	IMPACT	European SPMS Trial North American SPMS Trial	SPECTRIMS	

Structure and Source of IFNβ-1a and IFNβ-1b

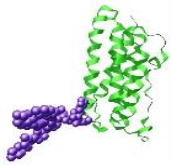
IFNβ-___



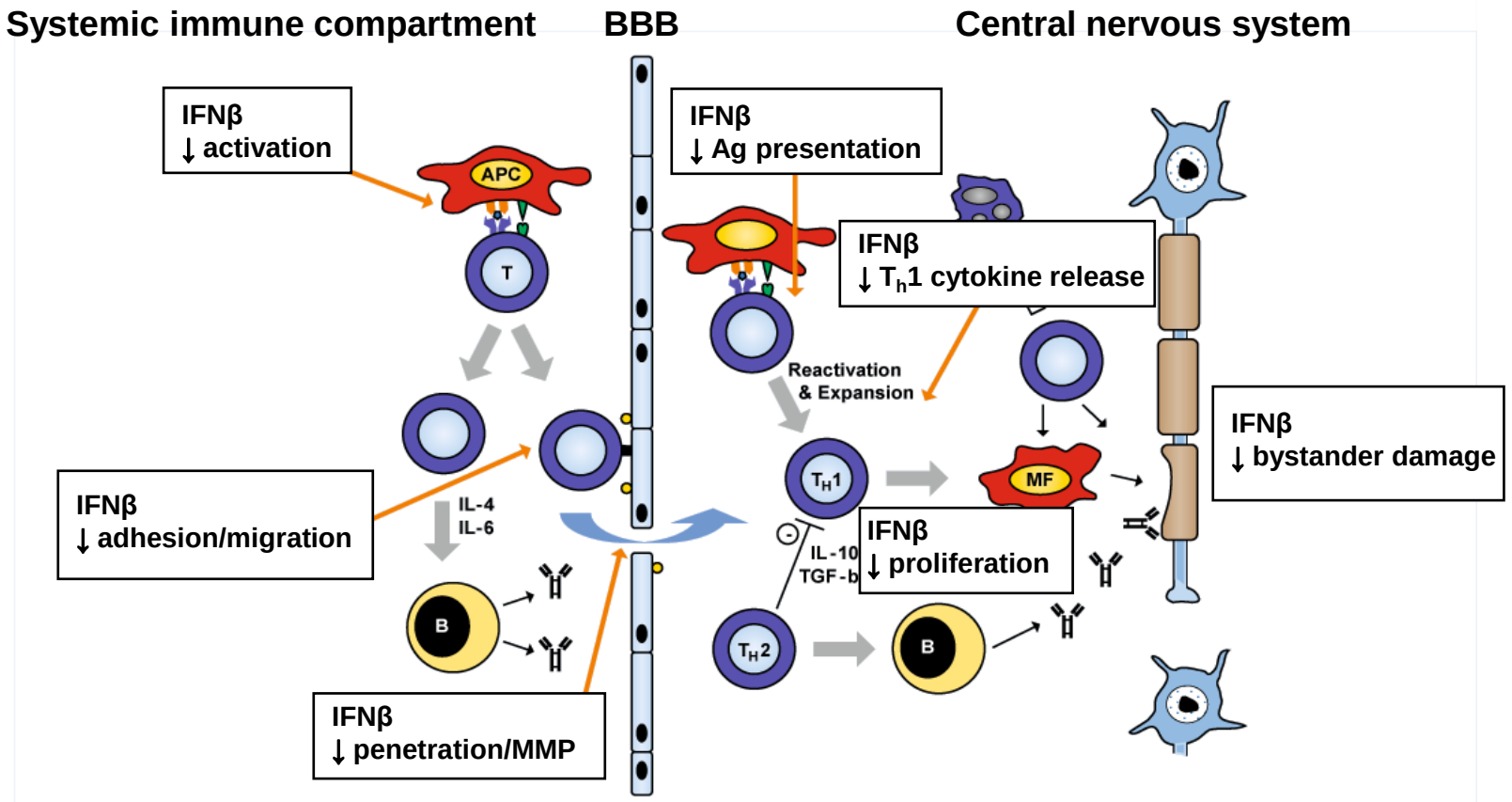
IFNβ-___

*Within same bioassay vs Standard NIH 531 (Study GF 8105) and Runkel L et al. *Pharm Res.* 1998;15:641-649.
CHO=Chinese hamster ovary.

Comparison of Interferonβ Products Used in MS

Type of IFN	Route	Dose	Schedule
Avonex (IFNβ-1a) 	Intra-muscular	30 μg	Once a week

Proposed IFNβ mechanism of action

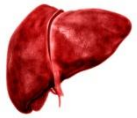
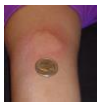


APC=antigen-presenting cell; T=T cell; IL=interleukin; B=B cell; MMP=matrix metalloproteinase; BBB=blood-brain barrier; Ag=antigen; T_H=T helper cell; TGF=transforming growth factor; MF=macrophage

Figure adapted from: Wiendl H et al. *Expert Opin Investig Drugs*. 2003;12:689-712

Side Effects of AVONEX, Betaseron, Rebif, and Copaxone in RRMS

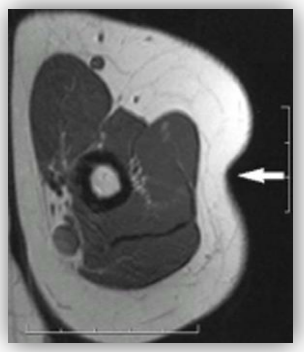


Side Effects	AVONEX	Betaseron	Rebif	Copaxone
FLS	√	√	√	
Depression	√	√	√	
Liver function	√	√	√	
ISR	minimal	√	√	√
Lipoatrophy				√
IPIR				√

√=mentioned in Warnings and Precautions section of prescribing information

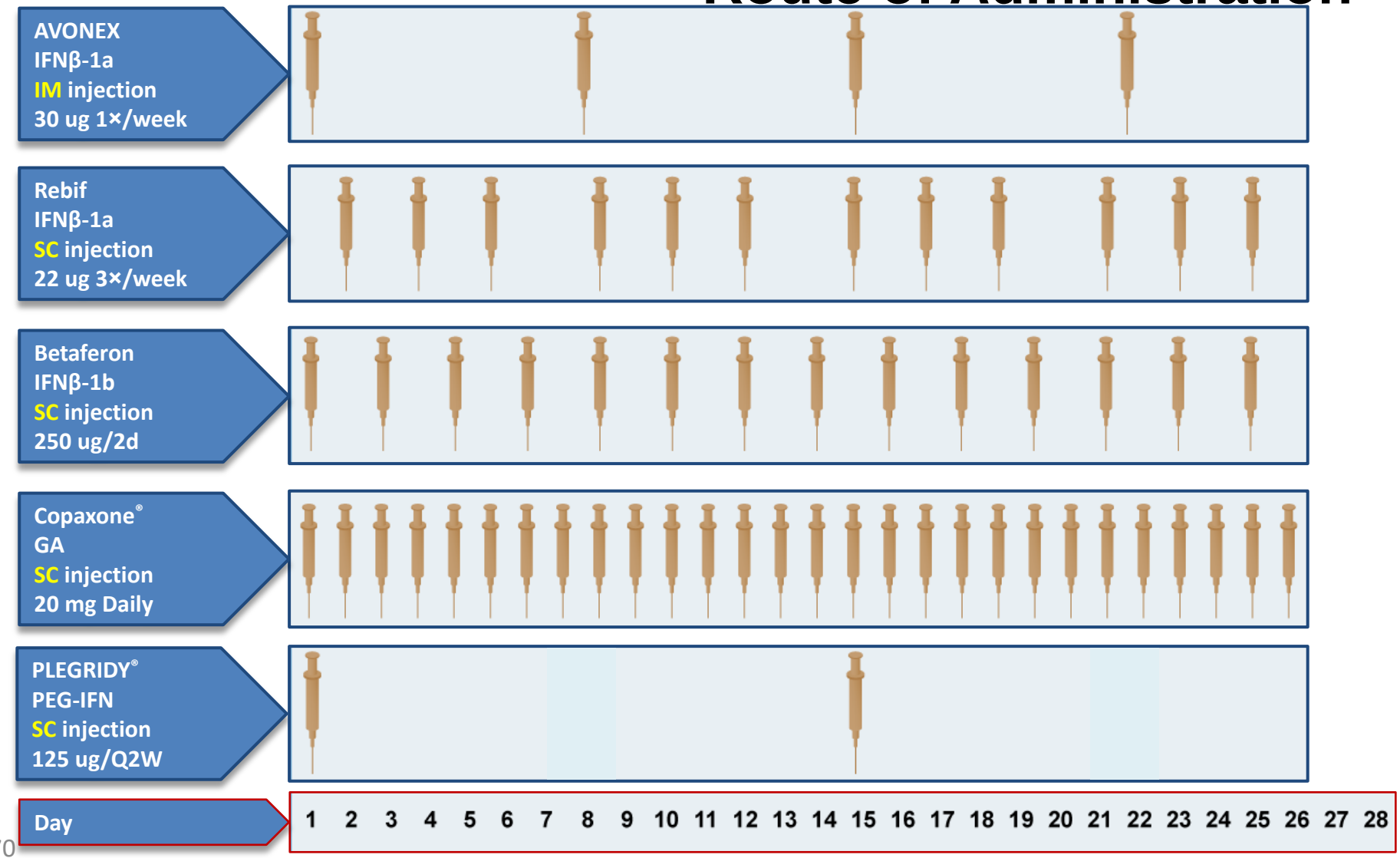
Lipoatrophy



MRI image of the thinning of subcutaneous fat distribution

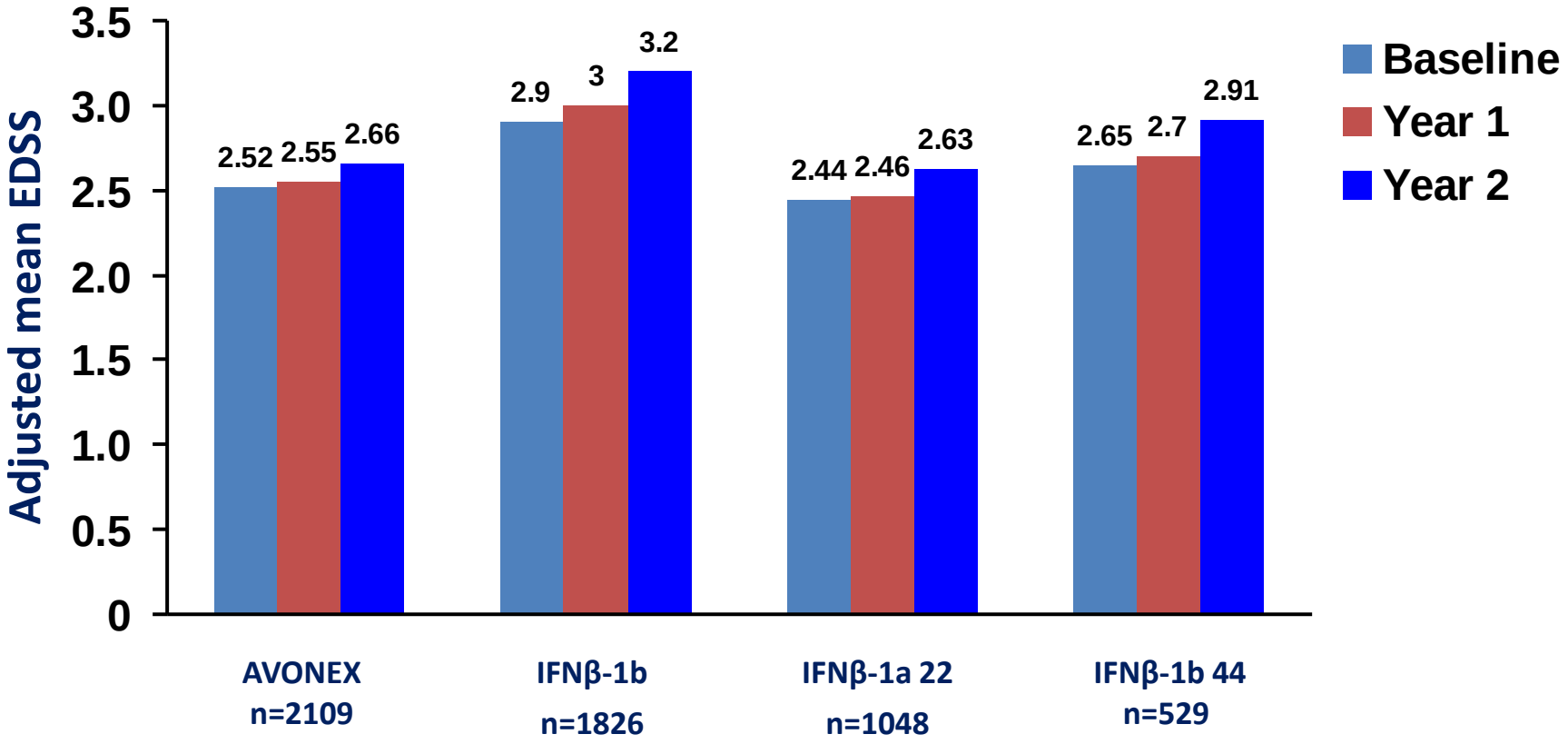
FLS=flu-like symptoms; ISR=injection site reaction; IPIR=immediate postinjection reaction, eg, chest pain and chest tightness (or 911 reaction).
AVONEX (IM IFNβ-1a) [prescribing information]. Cambridge, MA: Biogen Idec; 2012; Betaseron (SC IFNβ-1b) [prescribing information]. Emeryville, CA: Bayer Healthcare Pharmaceuticals; 2013; Rebif (SC IFNβ-1a) [summary of product characteristics]. Rockland, MA: EMD Serono; 2011; Copaxone (glatiramer acetate) [prescribing information]. Kansas City, MO: Teva Pharmaceuticals; 2009.

Treatments Differ in Frequency and Route of Administration



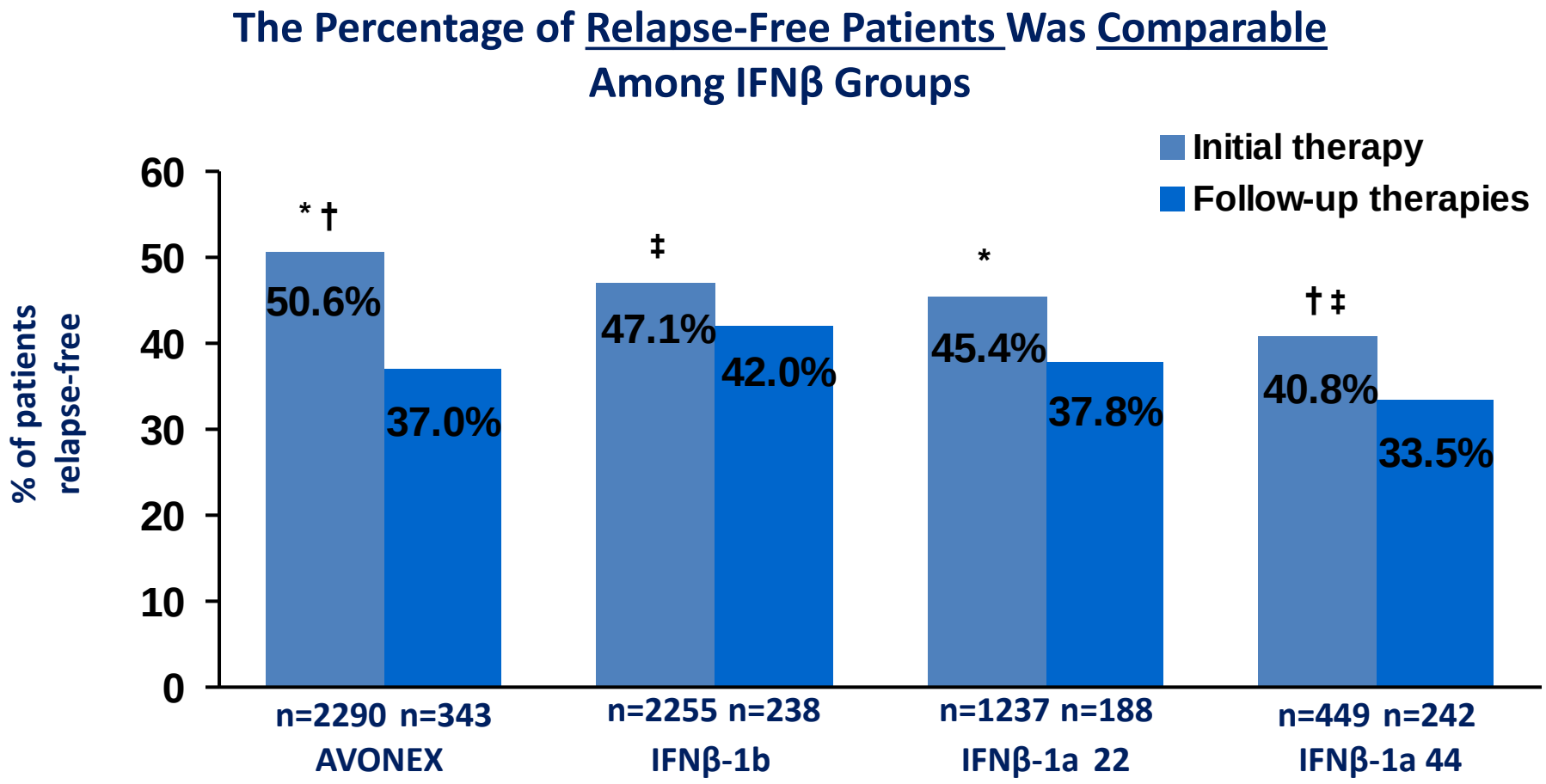
The Global QUASIMS Study: Disability Progression

Mean EDSS Was Comparable Among IFNβ Groups at Baseline and After 1 and 2 Years of Treatment



Limmroth et al. AAN, 2005. P05-123.

The Global QUASIMS Study: Relapse-Free Patients Over 2 Years

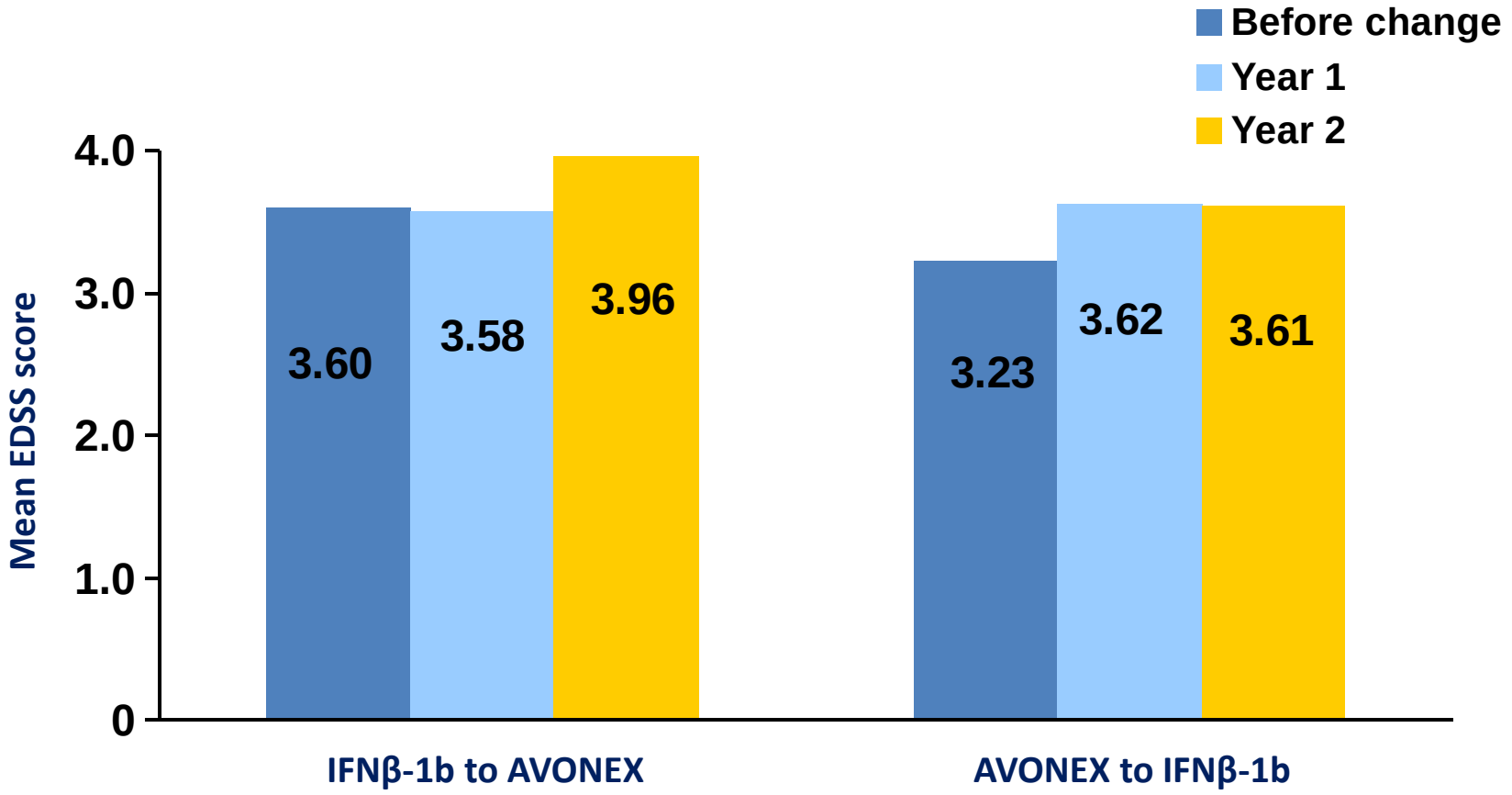


*AVONEX® vs IFNβ-1b 22, *P*=0.0017; †AVONEX® vs IFNβ-1a 44, *P*=0.0002; ‡IFNβ-1b vs IFNβ-1a 44, *P*=0.0061.

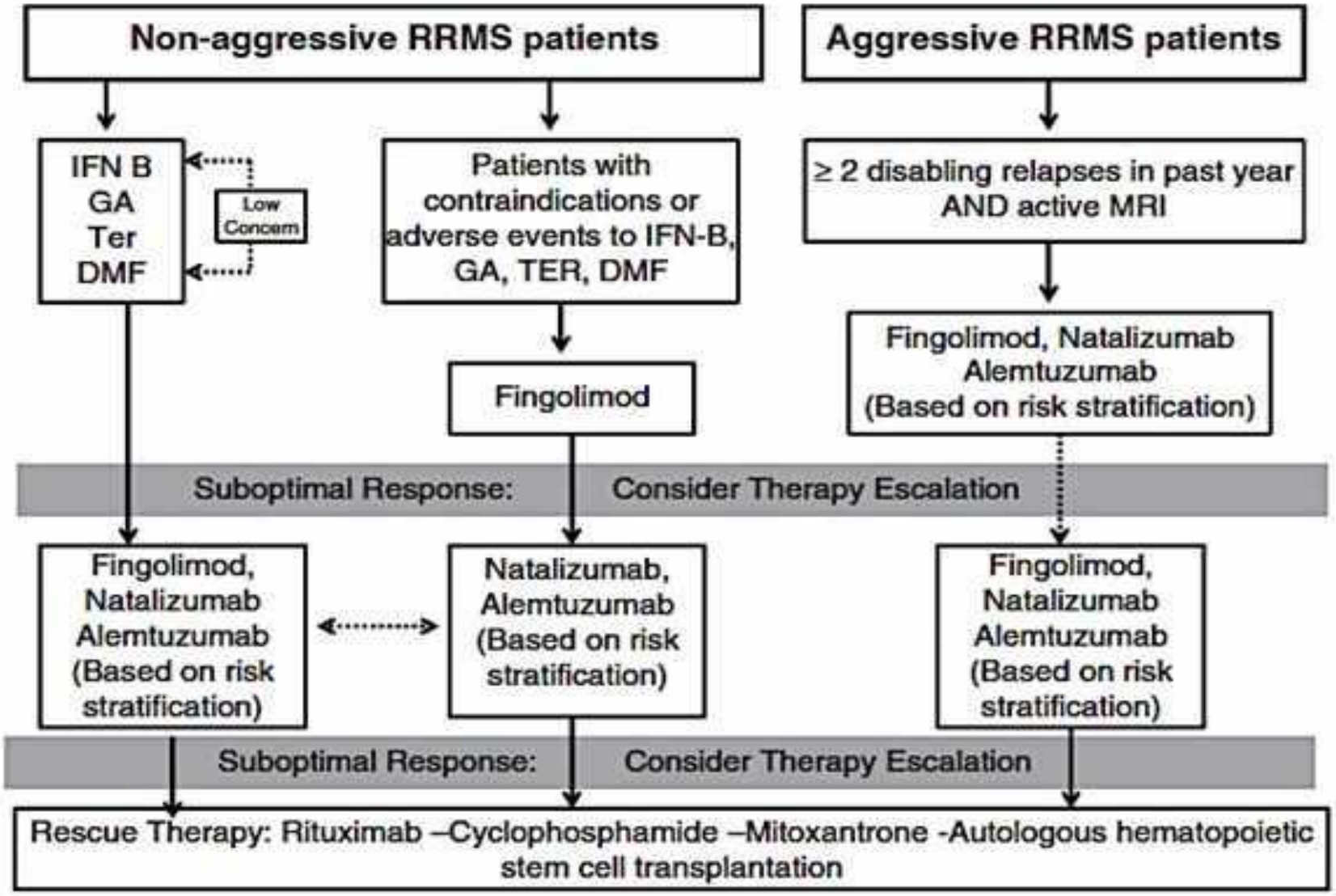
Limmroth et al. WCN, 2005. Abstract P529.

The Global QUASIMS Study: Change in the EDSS Score After Therapy Change

No Efficacy Benefit Is Seen When Switching From One IFNβ Product to Another



Limmroth et al. WCN, 2005.



IFN B, Interferon beta; GA, glatiramer acetate; Ter, teriflunomide; DMF, dimethyl fumarate.

Escalation: ⟶

Lateral switch: ⇢

Algorithm for the management of relapsing remitting multiple sclerosis.

AGENDA

- Immunopathogenesis
- Diagnosis
- Biomarkers
- Treatment options
- Optimization of treatment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THANK YOU