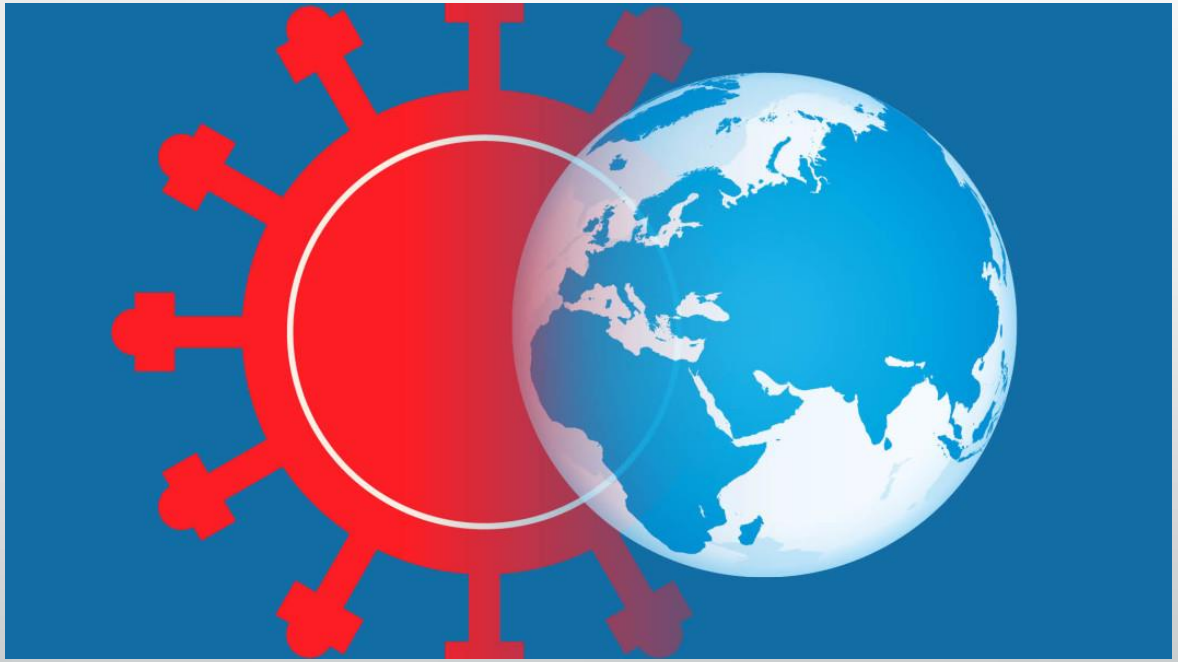
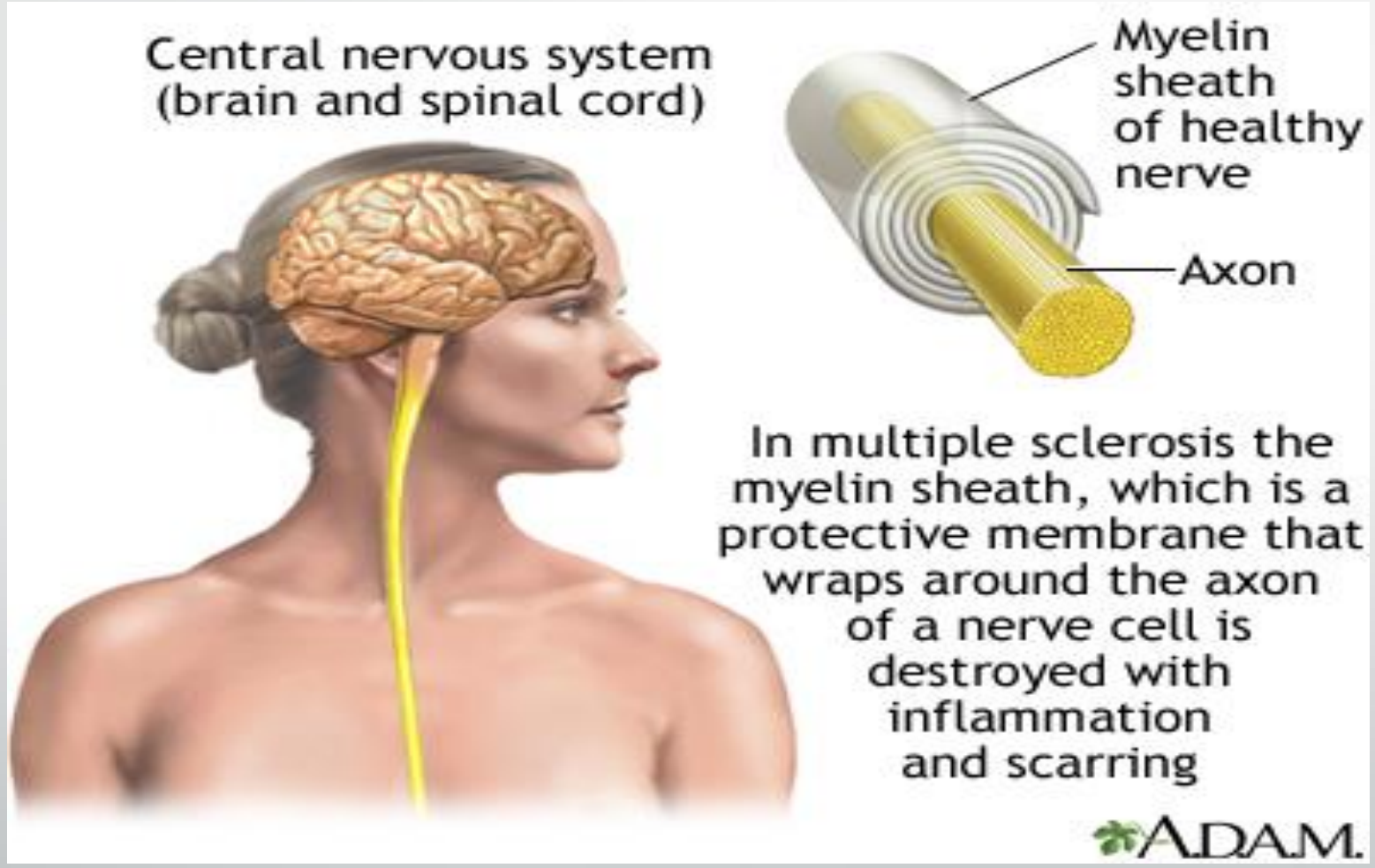
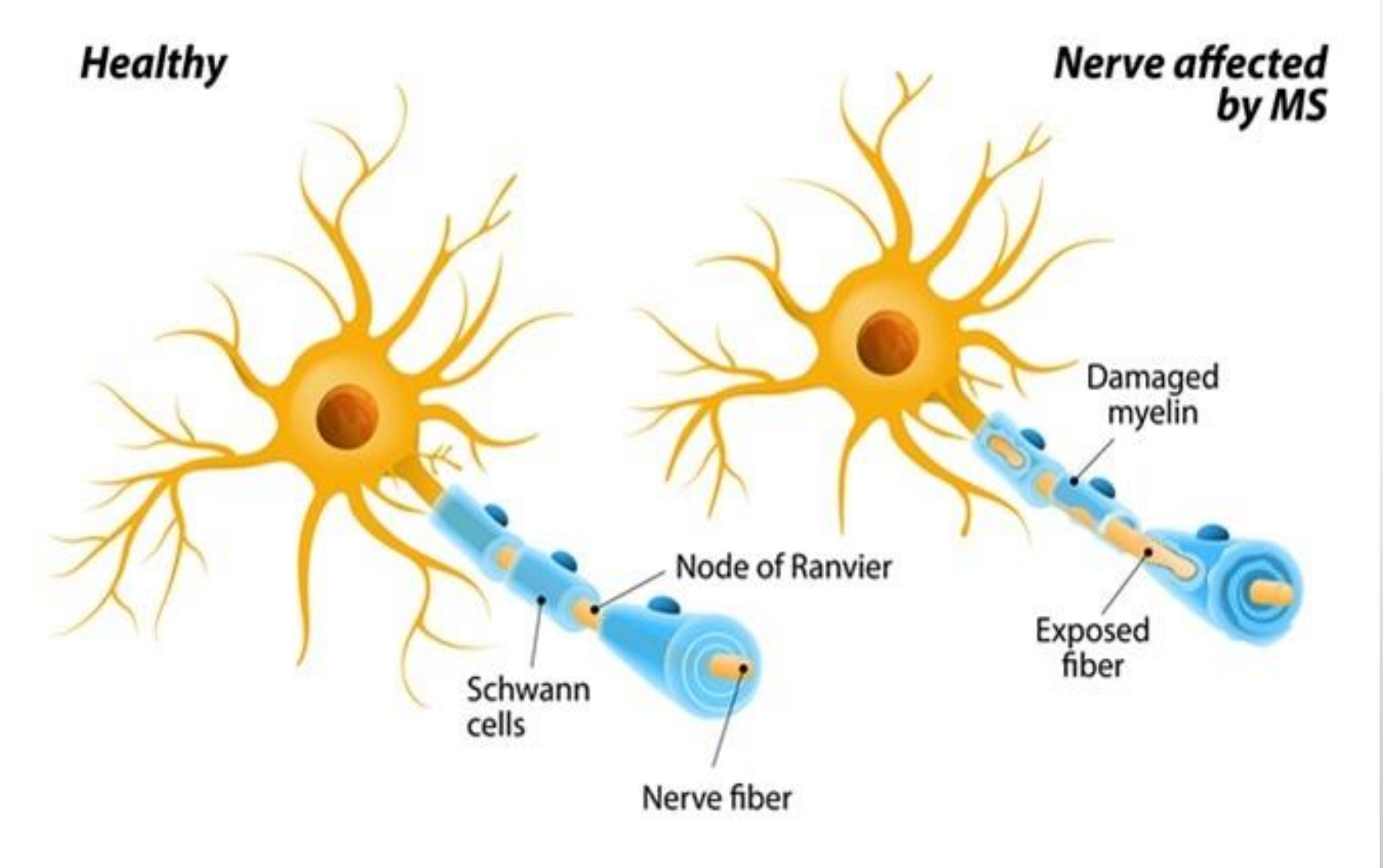
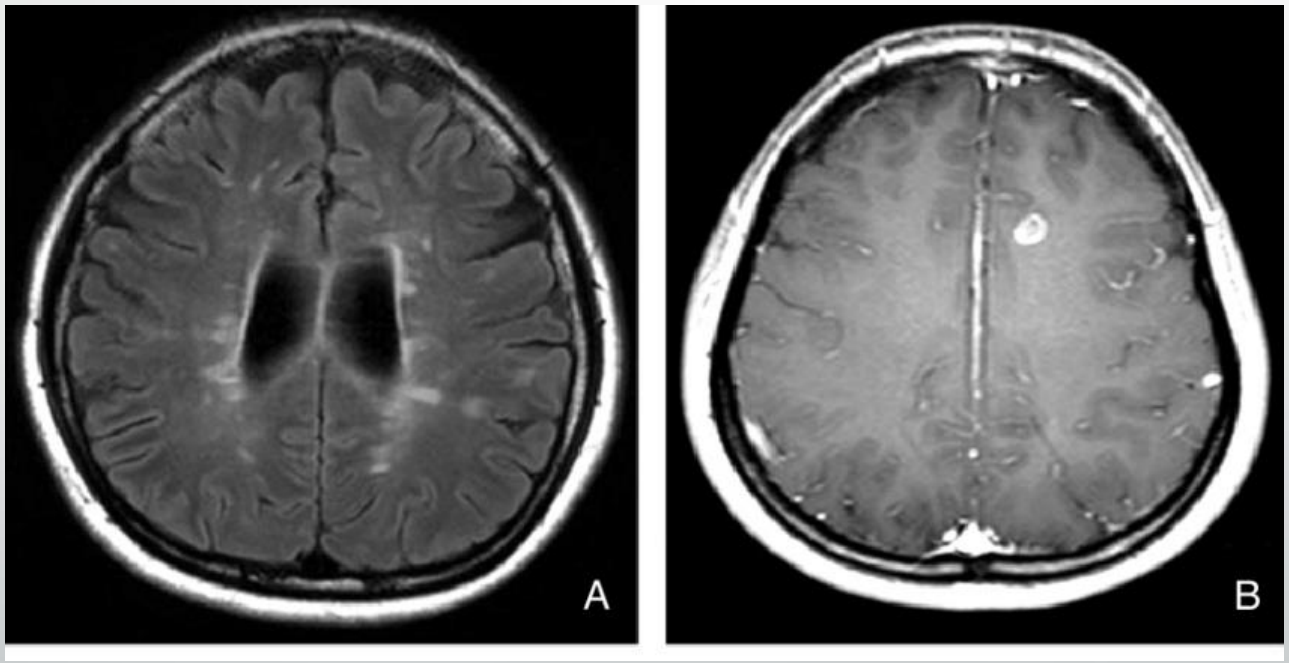
Autoimmune disease of CNS

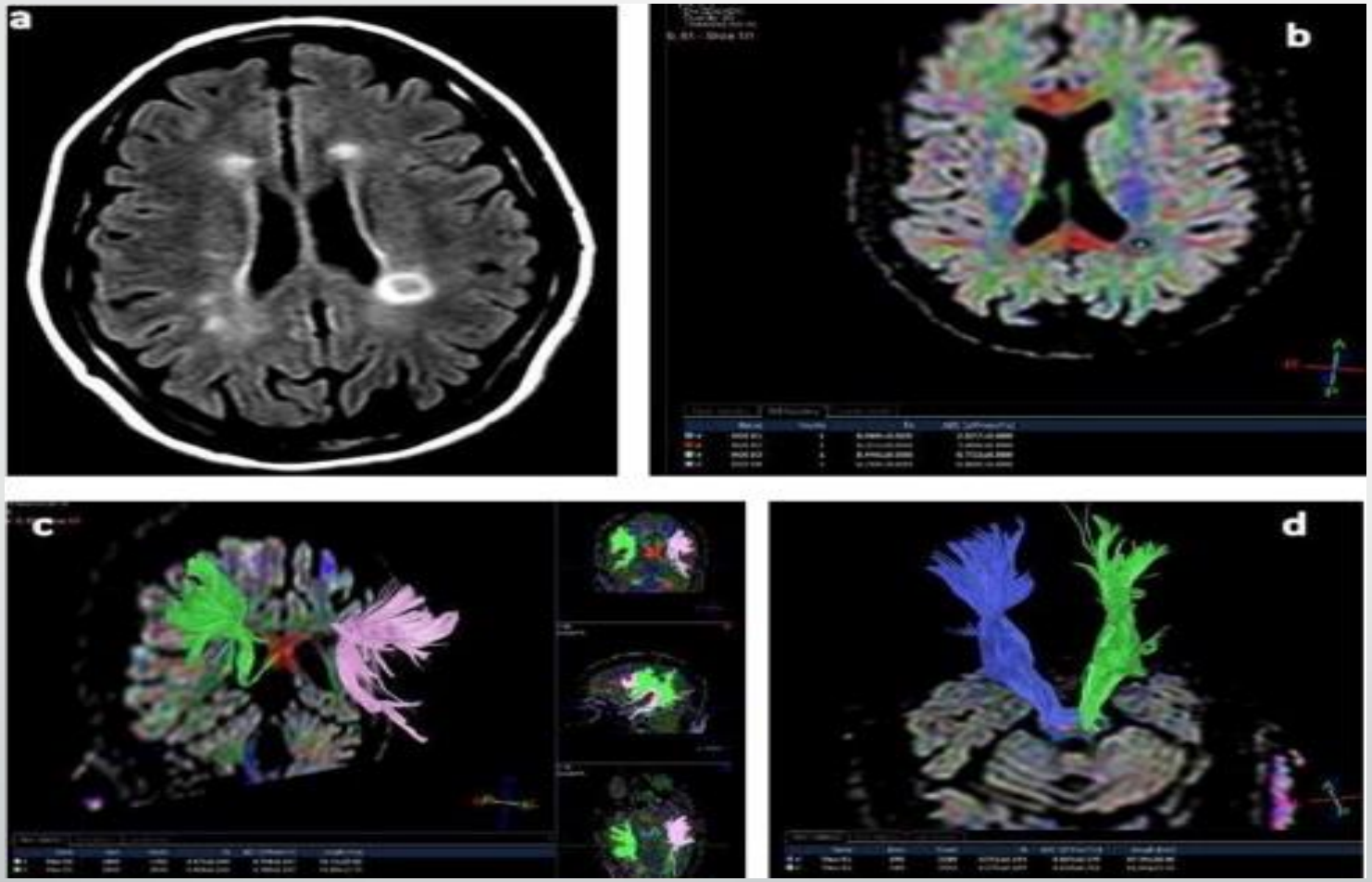
Abdorreza Naser Moghadasi



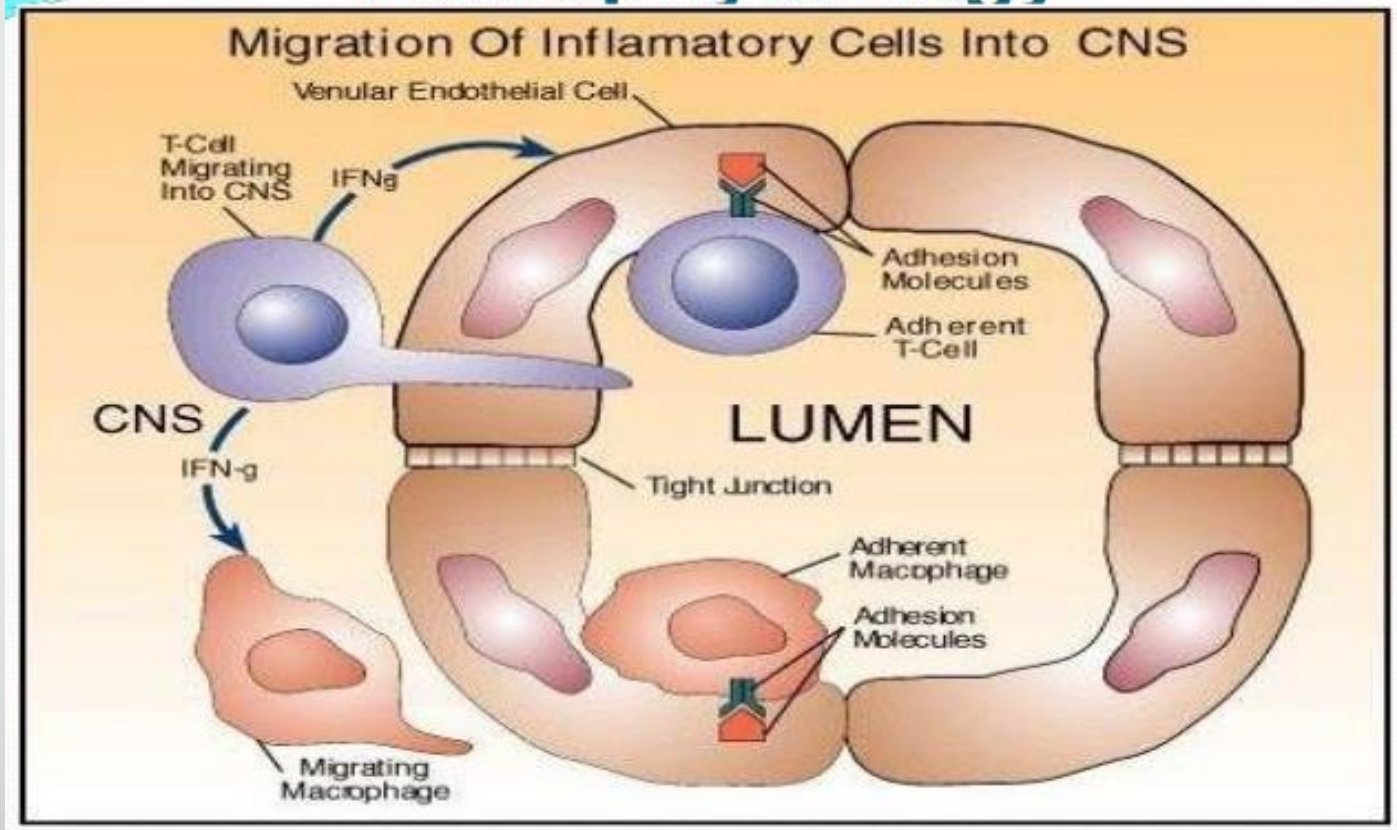

Central nervous system
(brain and spinal cord)
Myelin sheath of healthy nerve
Axon
In multiple sclerosis the myelin sheath, which is a protective membrane that wraps around the axon of a nerve cell is destroyed with inflammation and scarring
A.D.A.M.


Healthy
Nerve affected by MS
Damaged myelin
Node of Ranvier
Exposed fiber
Schwann cells
Nerve fiber

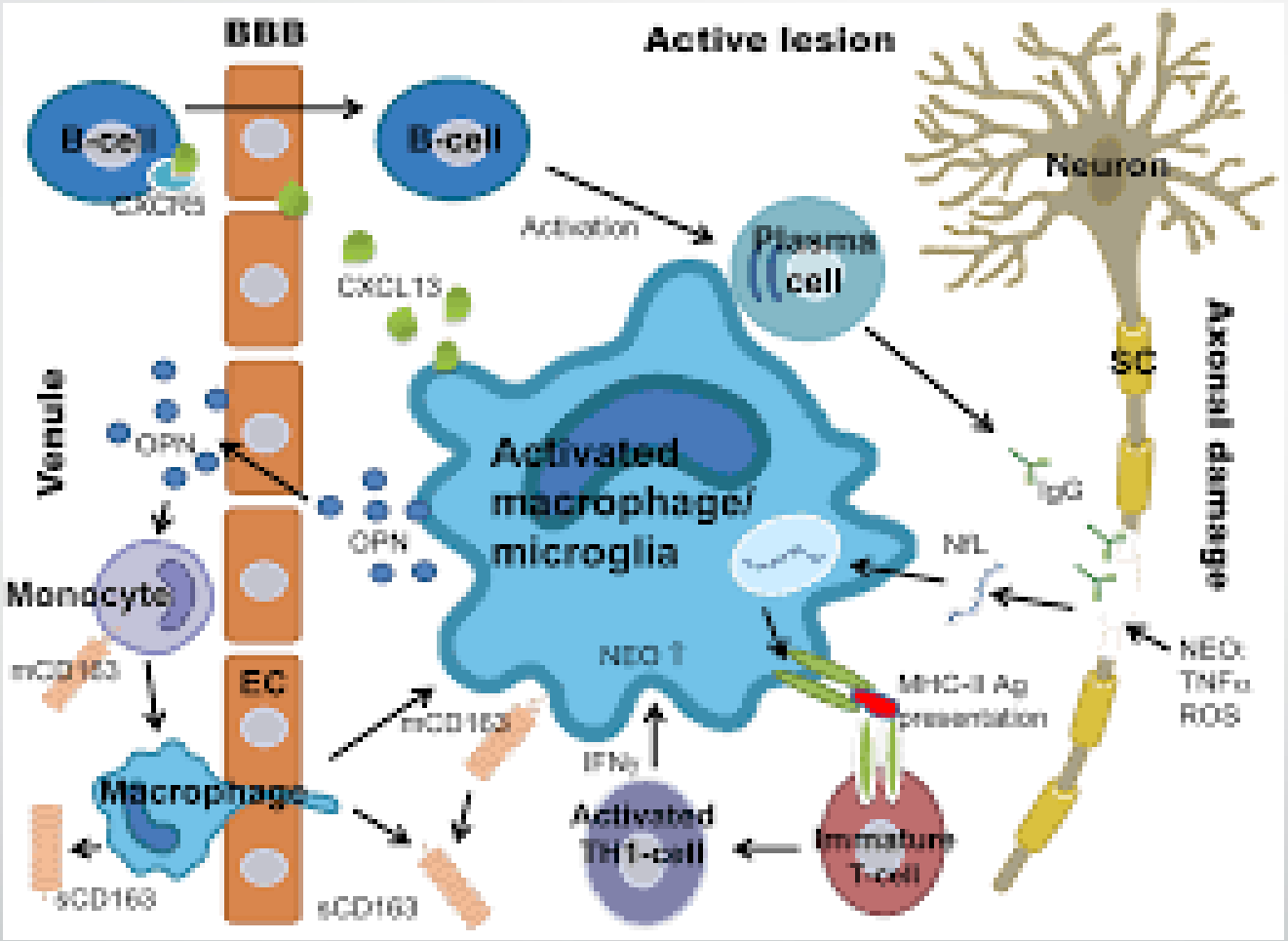

A
B

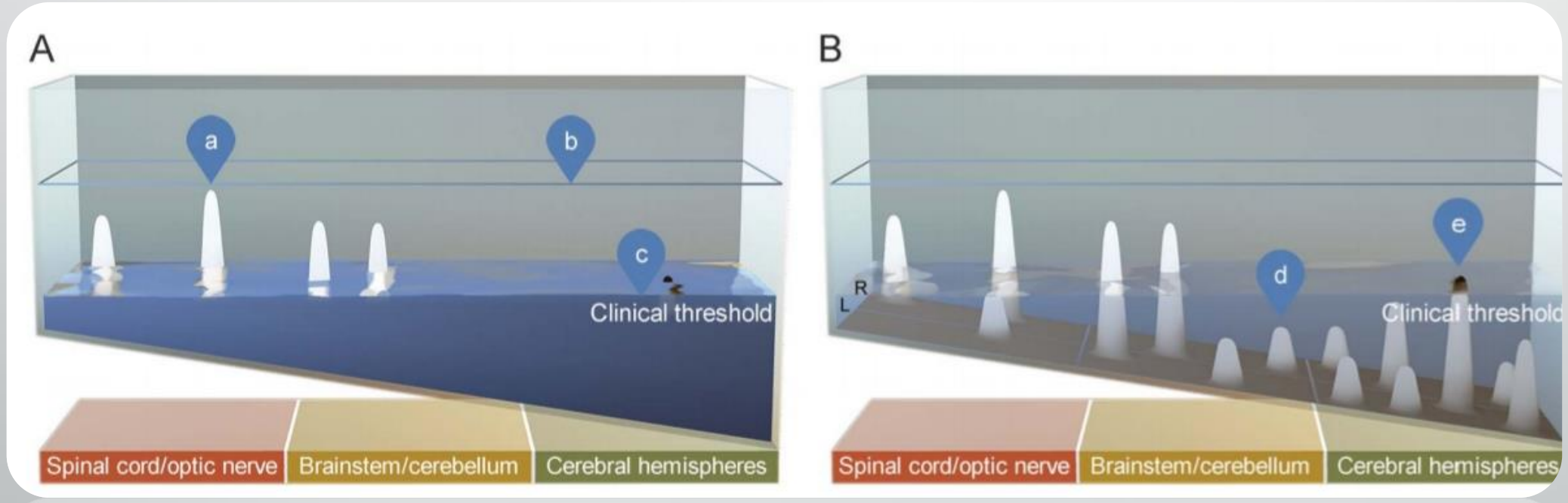

a
b
c
d

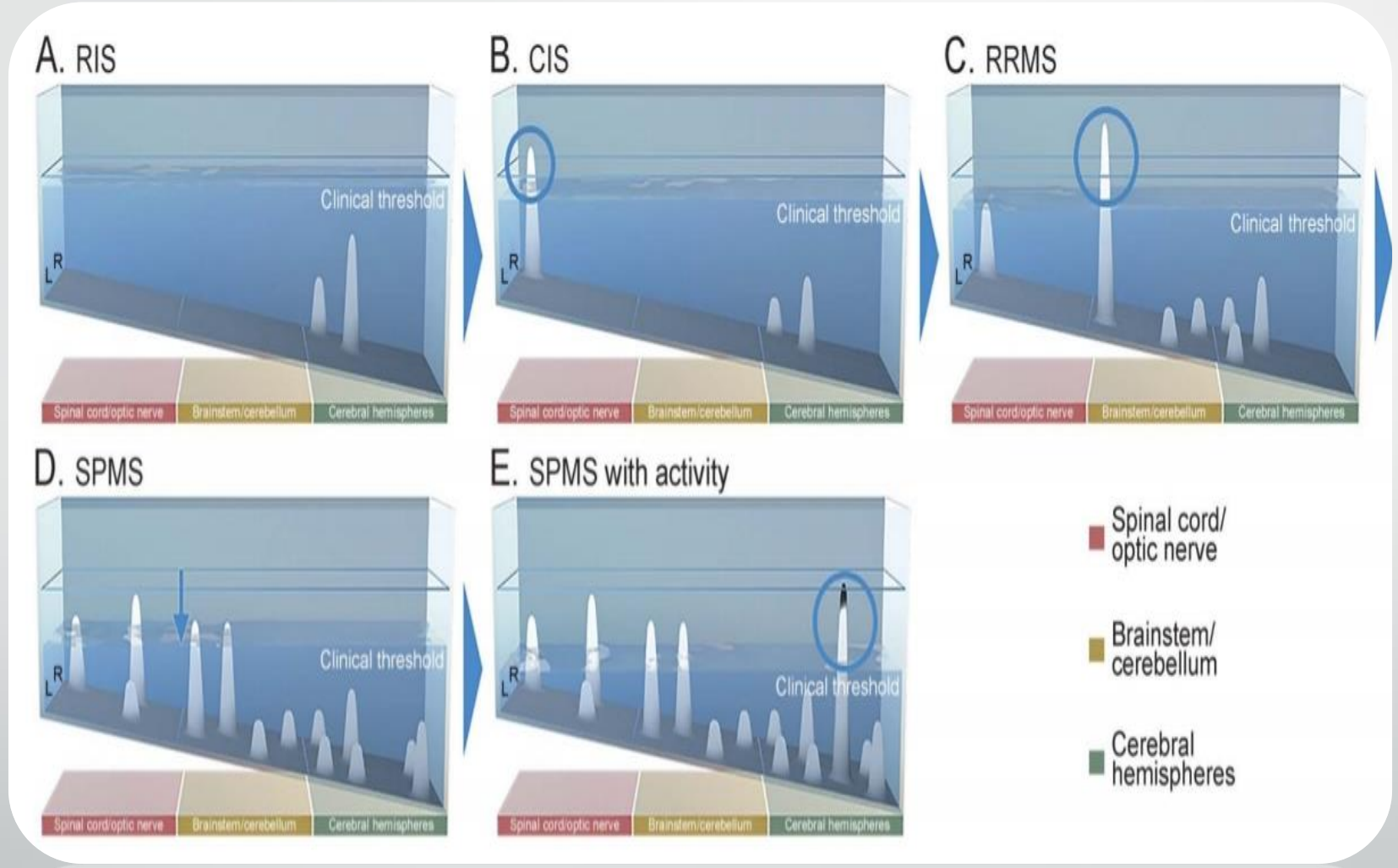
Pathophysiology



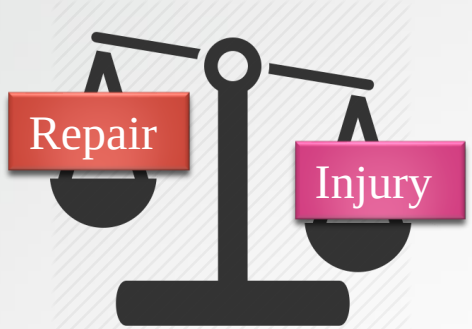
Possible Etiologic Mechanisms of Demyelination in CNS - Inflammation


BBB
Active lesion
B-cell
CXCR5
B-cell
Activation
Plasma cell
Neuron
CXCL13
SC
Axonal damage
Venule
OPN
OPN
Activated macrophage/ microglia
IgG
NfL
Monocyte
mCD163
NEO ↑
NEO
TNFα
ROS
EC
MHC-II Ag presentation
mCD163
IFNγ
Macrophage
Activated TH1-cell
Immature T-cell
sCD163
sCD163

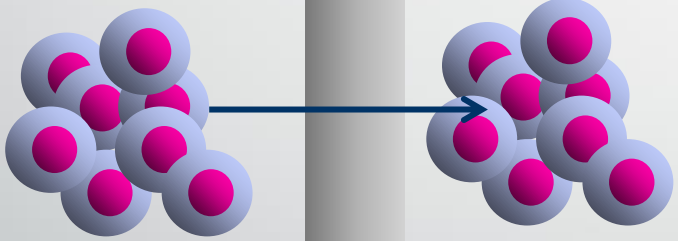

A
a
b
c
Clinical threshold
Spinal cord/optic nerve
Brainstem/cerebellum
Cerebral hemispheres
B
R
L
d
e
Clinical threshold
Spinal cord/optic nerve
Brainstem/cerebellum
Cerebral hemispheres


A. RIS
B. CIS
C. RRMS
D. SPMS
E. SPMS with activity
Clinical threshold
L
R
Spinal cord/optic nerve
Brainstem/cerebellum
Cerebral hemispheres
Spinal cord/ optic nerve
Brainstem/ cerebellum
Cerebral hemispheres

MS untreated



Blood/brain barrier



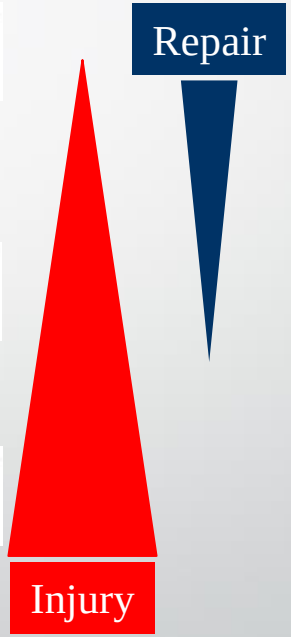
Circulating pathogenic lymphocytes

Central nervous system

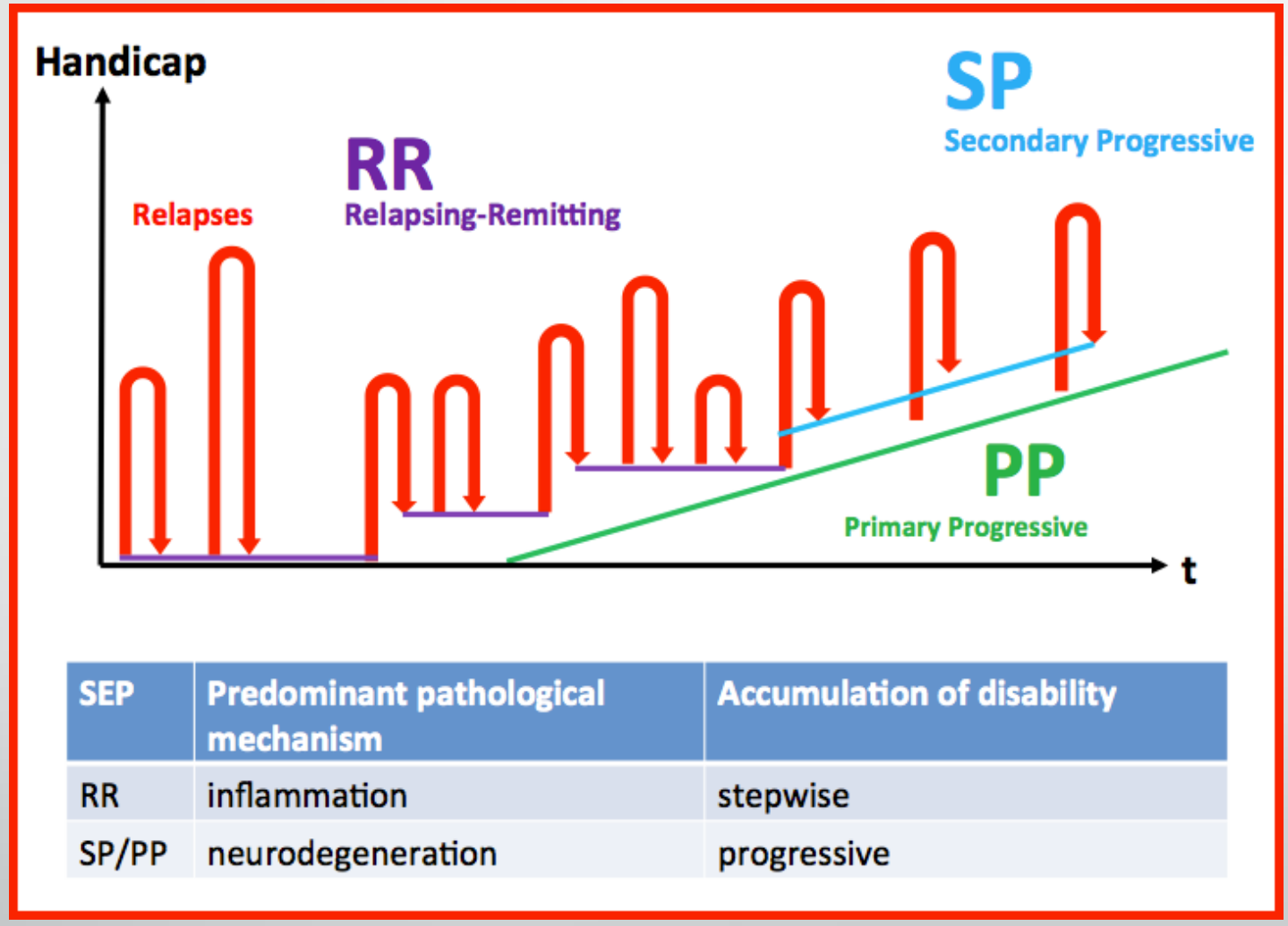
INFLAMMATION

Demyelination

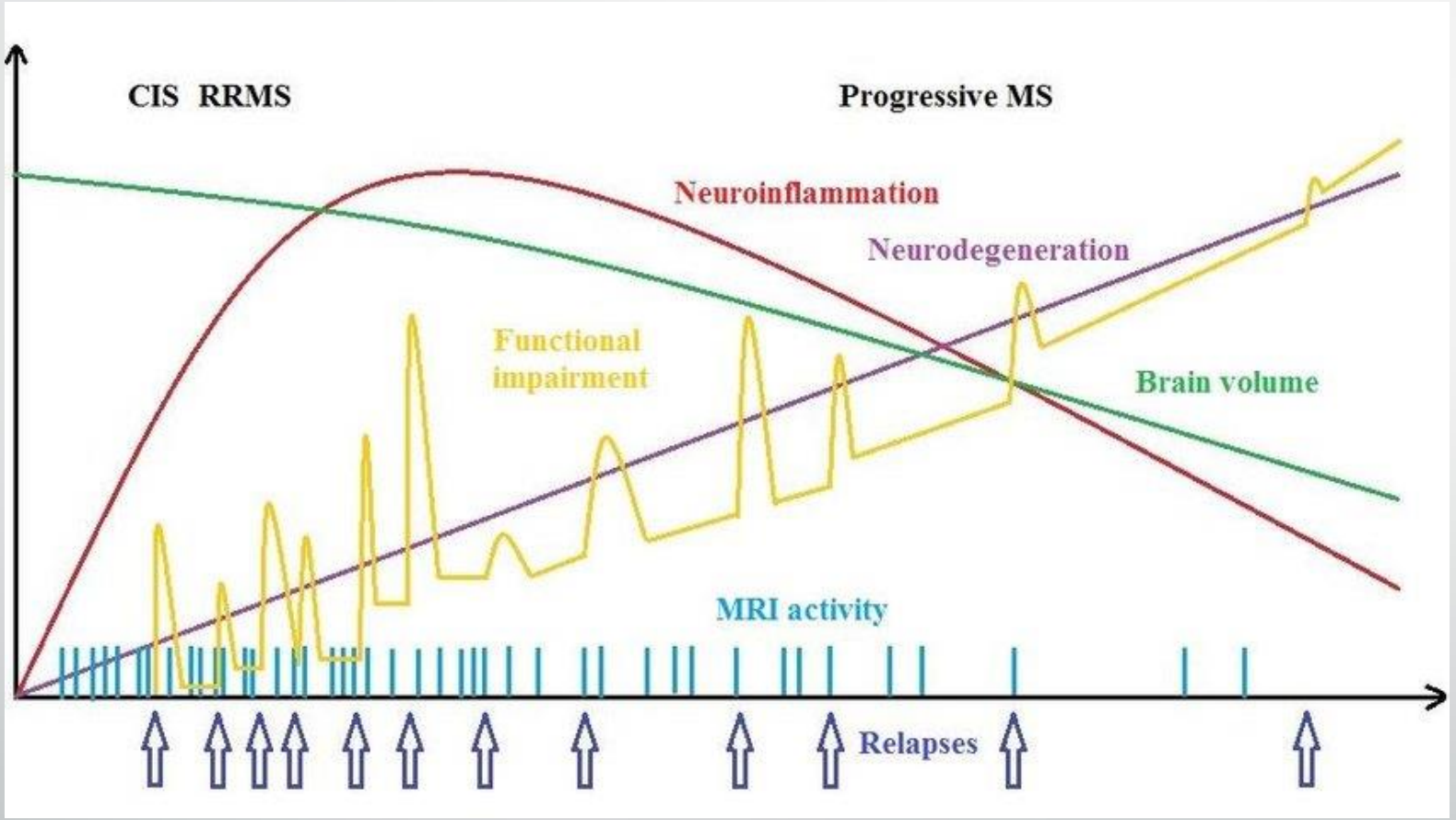
Neurodegeneration (axonal/neuronal loss, gliosis)



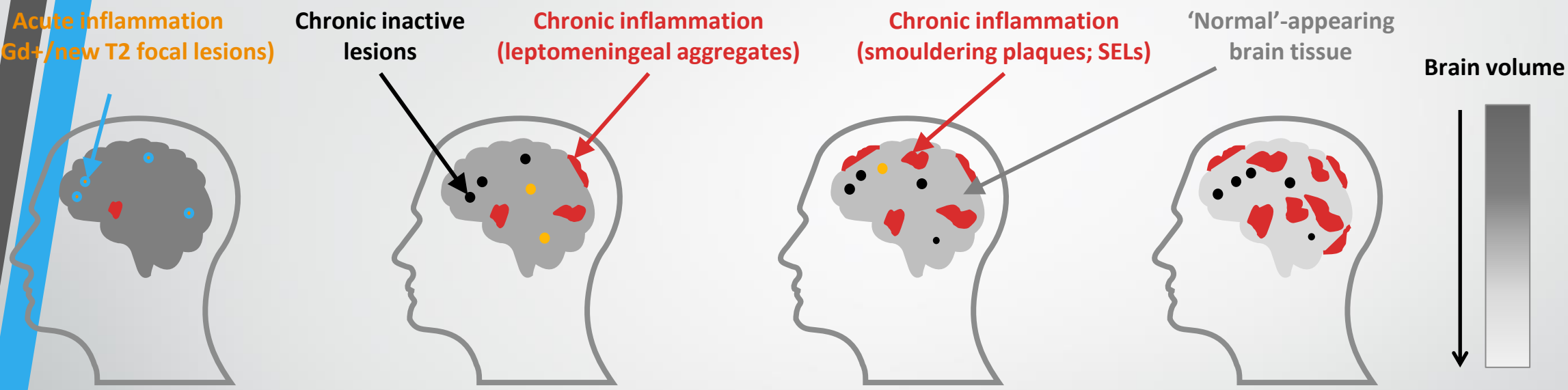
Therapies are needed that target both **inflammation** and **neurodegeneration**

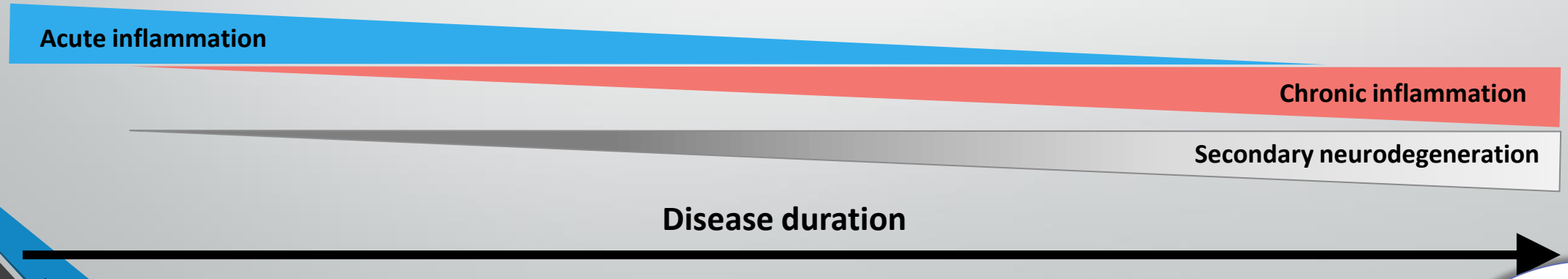


SEP	Predominant pathological mechanism	Accumulation of disability
RR	inflammation	stepwise
SP/PP	neurodegeneration	progressive


CIS RRMS
Progressive MS
Neuroinflammation
Neurodegeneration
Functional impairment
Brain volume
MRI activity
Relapses

Conceptualising acute and chronic disease activity



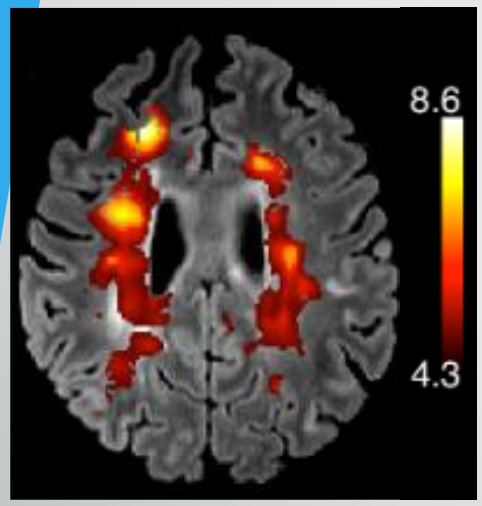


Gd+, gadolinium-enhancing;
SEL, slowly expanding/evolving lesion.

Rice CM, *et al. J Neurol Neurosurg Psychiatry* 2015;86:1100–6; Antel J, *et al. Acta Neuropathol.* 2012;123:627–38; Thompson AJ, *et al. Ann Neurol.* 1991;29:53–62; Frischer J, *et al. Ann Neurol.* 2015;78:710–21; Bramow S. *Brain* 2010;133:2983–98; Frischer JM. *Brain* 2009;132:1175–89; Schumacher A-M, *et al. Neur Im Open* 2017;1:E171–E181; Dal-Bianco A, *et al. Acta Neuropathol.* 2017;133:25–42; Absinta M, *et al. J Clin Invest.* 2016;126:2597–9.

What do these markers tell us about chronic inflammation and progression?

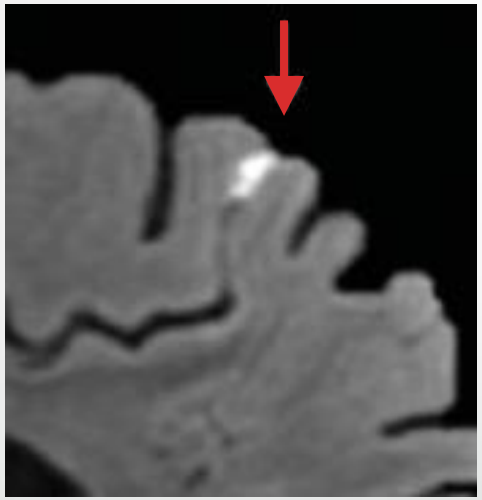
Microglial activation seen on TSPO PET binding[1,2]



Demonstrates chronic activity in NAWM and a high proportion of lesions

RMS ✓ PMS ✓

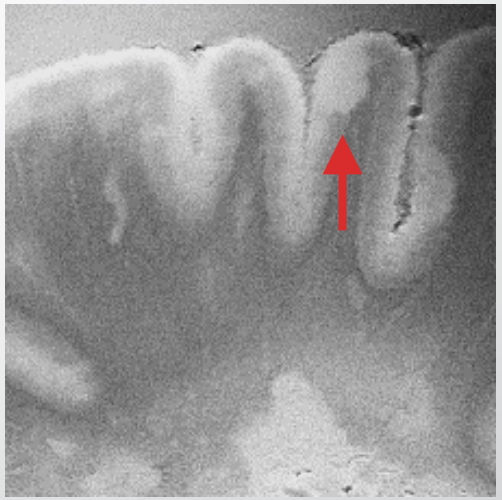
Leptomeningeal inflammation seen as contrast enhancement[3,4]



Correlates with clinical progression, and cortical demyelination and atrophy

RMS ✓ PMS ✓

Subtle grey matter pathology seen as lesions on 8T[5,6]



Cortical lesions correlate with clinical progression, and may be easily missed

RMS ✓ PMS ✓

NAWM, normal-appearing white matter; PMS, progressive MS; RMS, relapsing MS; SWI, susceptibility-weighted imaging; TSPO PET, translocator protein-18 kDa positron emission tomography.

1. Colasanti A, *et al. J Nucl Med.* 2014;55:1112–18; 2. Datta G, *et al. J Nucl Med.* 2017;58:1477–82; 3. Absinta M, *et al. Neurology* 2015;85:18–28; 4. Makshakov G, *et al. Neurol Res Int.* 2017;8652463; 5. Calabrese M, *et al. Brain* 2012;135:2952-61; 6. Image courtesy of Kottel W. Rammohan.

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Chronic inflammatory lesions demonstrate ongoing progressive damage

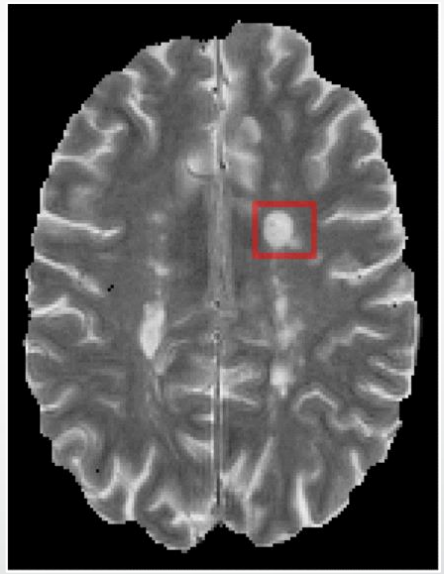
Slowly expanding iron rim lesions on SWI[1]

Baseline

Characteristic rim of iron-laden microglia and/or macrophages detected at the lesion edge indicating chronic inflammation[2]

RMS 53.4% **PPMS 66.7%**

Slowly evolving/expanding lesions on T2[3,4]



Baseline

SELs are T2 lesions (or areas within them) that undergo a local concentric and constant expansion that may reflect chronic inflammatory changes

RMS 68.2% **PPMS 71.9%**

PPMS, primary progressive MS; RMS, relapsing MS;
SEL, slowing evolving/expanding lesions; SWI, susceptibility weighted imaging.

1. Dal-Bianco A, *et al. Acta Neuropath* 2017;133:25–42; 2. Absinta M, *et al. JAMA Neurology* 2019;doi: 10.1001/jamaneurol.2019.2399; 3. Elliot C, *et al. Mult Scler J* 2018;doi.org/10.1177/1352458518814117; 4. Elliot C, *et al. Brain* 2019;142:2787–99.

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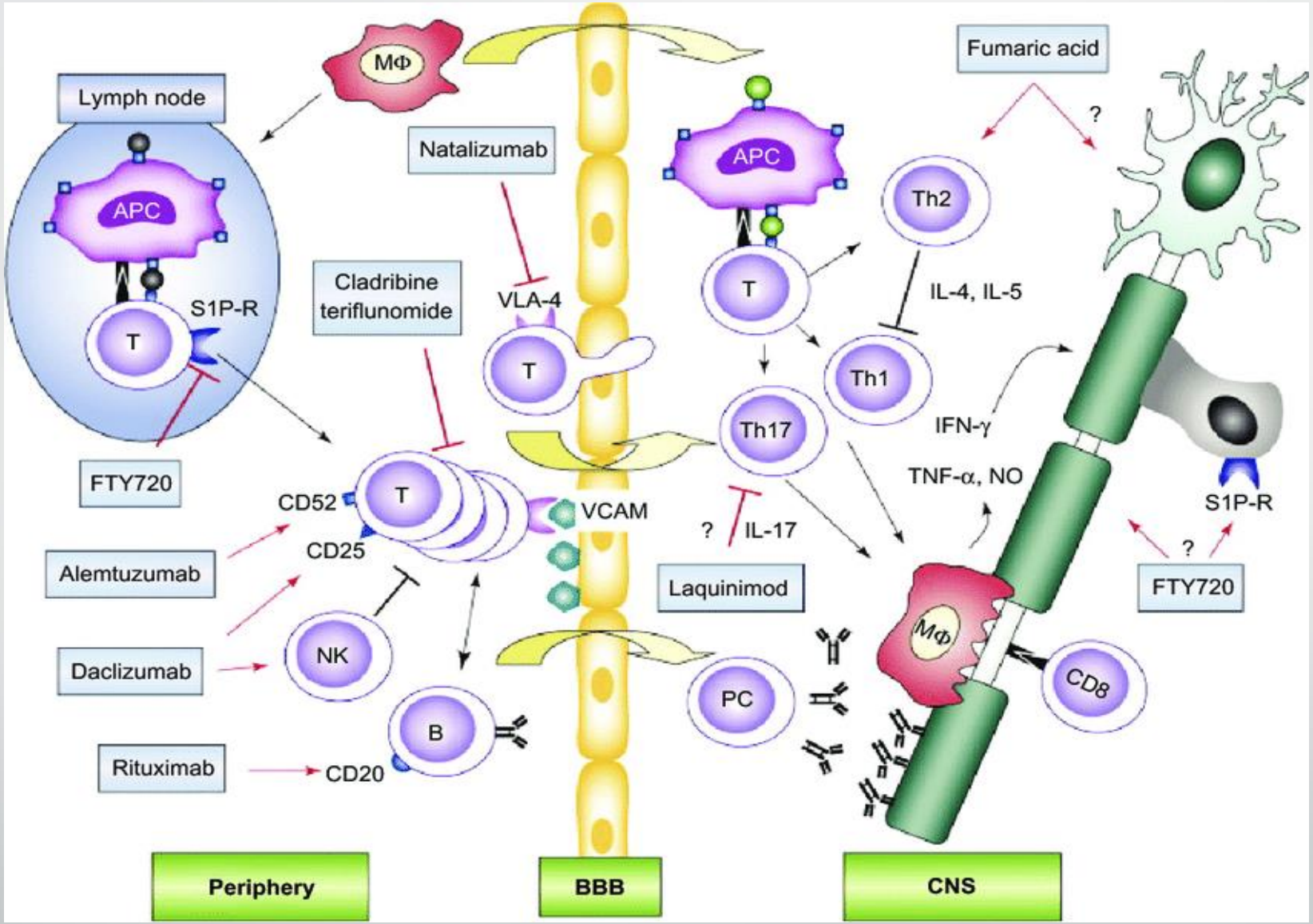
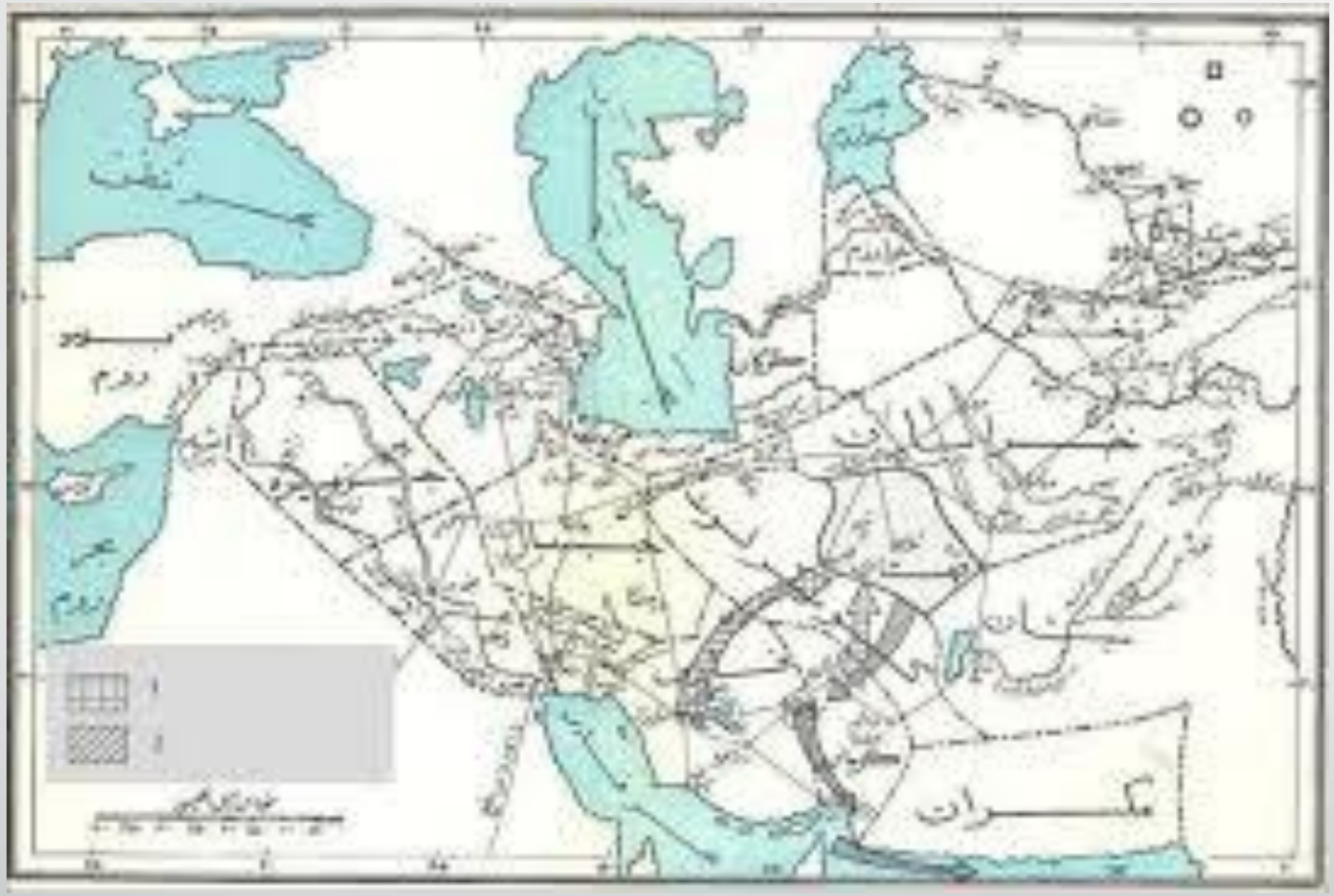

МΦ
Lymph node
APC
S1P-R
T
FTY720
Natalizumab
Cladribine
teriflunomide
VLA-4
T
CD52
CD25
T
VCAM
Alemtuzumab
Daclizumab
NK
B
Rituximab
CD20
APC
T
Th2
Th1
Th17
IL-4, IL-5
IFN-γ
TNF-α, NO
? IL-17
Laquinimod
PC
Fumaric acid
?
S1P-R
?
FTY720
МΦ
CD8
Periphery
BBB
CNS


مکران

Autoimmune Encephalitis is the broad name given to conditions in which the body's immune system attacks the brain. Infections can trigger the disease but the symptoms result from an overactive immune system.

Autoimmunity occurs when the body's immune system attacks healthy parts of the body. **Encephalitis** is inflammation in the brain caused by an immune response launched outside or inside the central nervous system

Autoimmune encephalitis covers a group of neurological disorders involving the production of antibodies to parts of the CNS, specifically to the receptors on the surface of nerve cells. The first recognized receptor antibody associated with a diagnosis of AE was in 2005 by Dr. Josep Dalmua. In AE antibodies attack and flag parts of the nerve cells as foreign, and an immune response is launched against parts of the nerve.

The inflammation disrupts the normal function of nerve cells and causes a spectrum of neuro-psychiatric symptoms. that are often not responsive to the typical medications for either the neurological symptoms (anti-seizure medications) or the psychiatric symptoms (anti-psychotic medications). Treatment usually requires medications that reduce inflammation and autoimmunity.