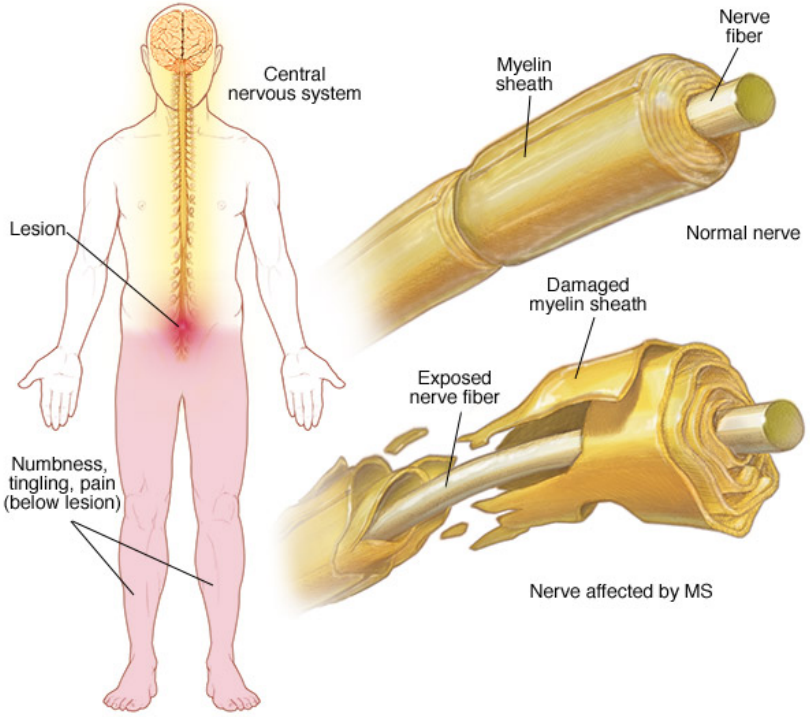
The importance of barriers in multiple sclerosis

Nathalie Schmitt
CNRS UMR 5164

Multiple sclerosis (MS)

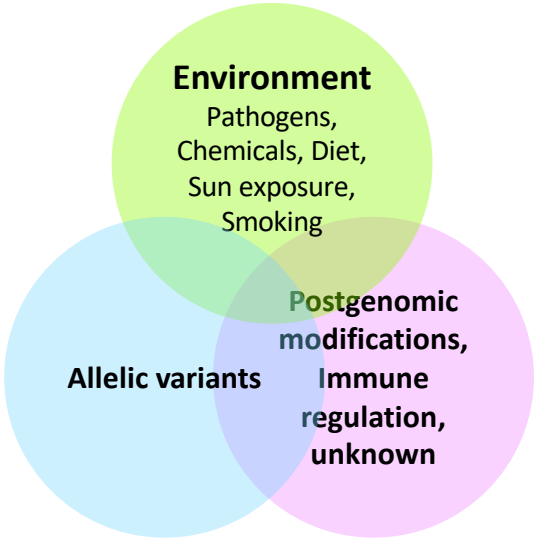
- A chronic auto-immune disease that damages the central nervous system
- Destruction of myelin and associated tissues
- Causes severe physical and cognitive disabilities
- > 2 million patients world-wide
- No treatments completely stop the progression of the disease



What causes multiple sclerosis?

Etiology of MS

- **Causes**: undetermined and multifactorial
- **Disease penetrance**: Stochastic events and environmental factors in genetically susceptible individuals
- **Genetic factors**: 30-40% risk to develop MS in concordant twins

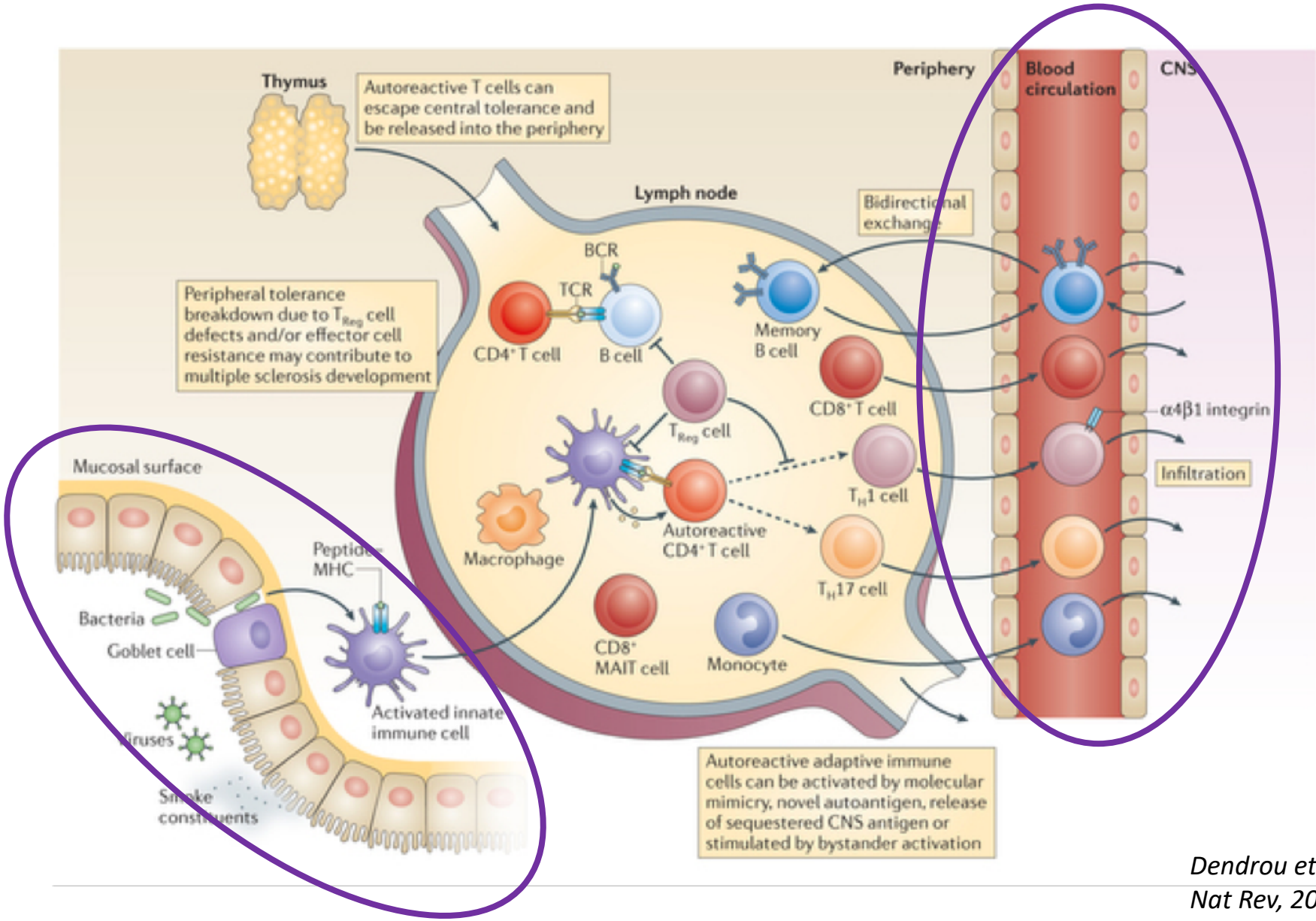


Immunological mechanistic of disease triggering:

- CNS extrinsic model:
  - Autoractive T cells activated at peripheral sites
  - Activated autoreactive T cells traffic to the CNS together with activated B cells and monocytes

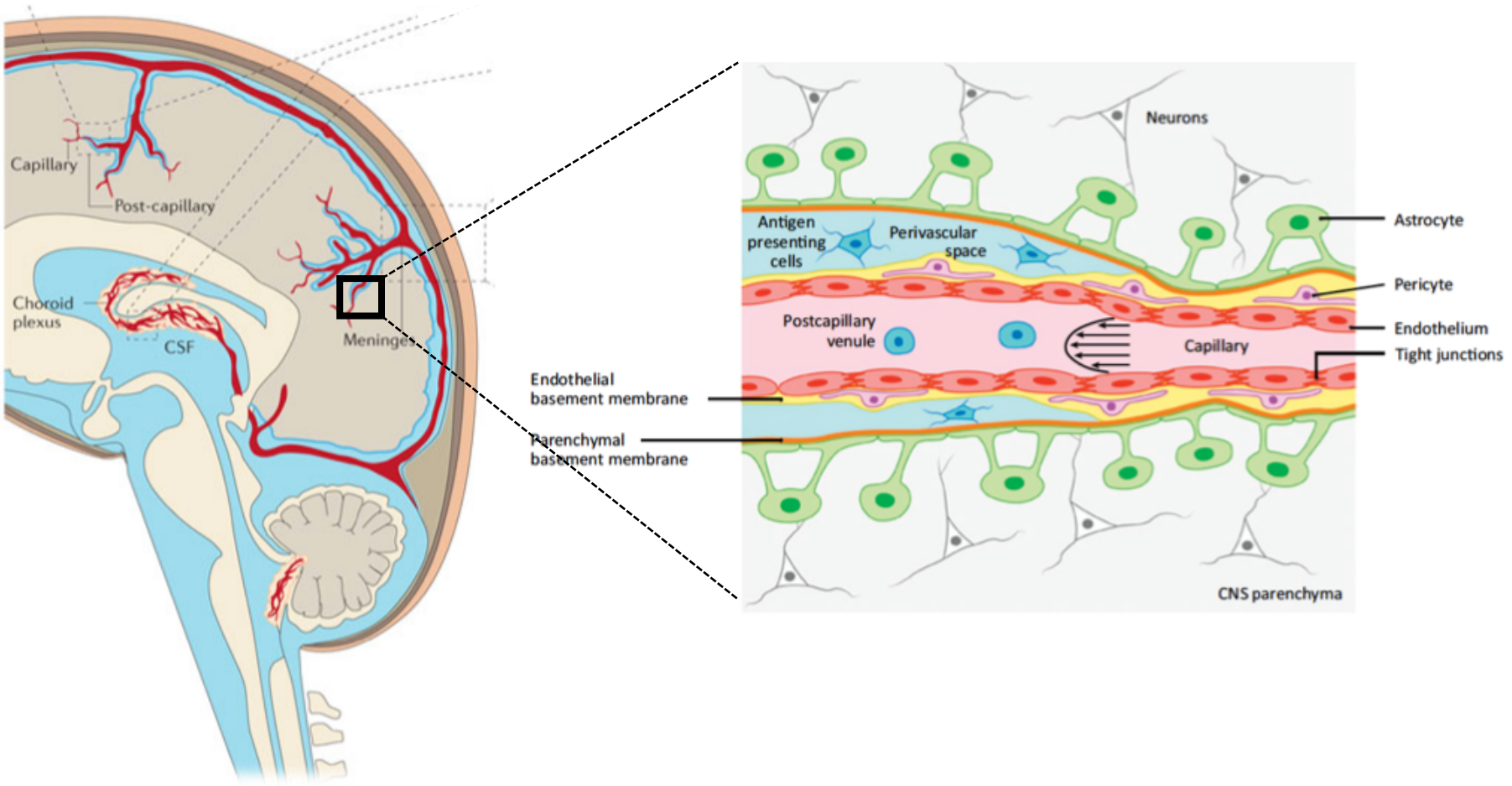
- CNS intrinsic model:
  - CNS intrinsic events trigger the disease development
  - Infiltration of autoreactive T cells as a secondary phenomenon

Immune system dysregulation outside of the central nervous system



Dendrou et al.
Nat Rev, 2015

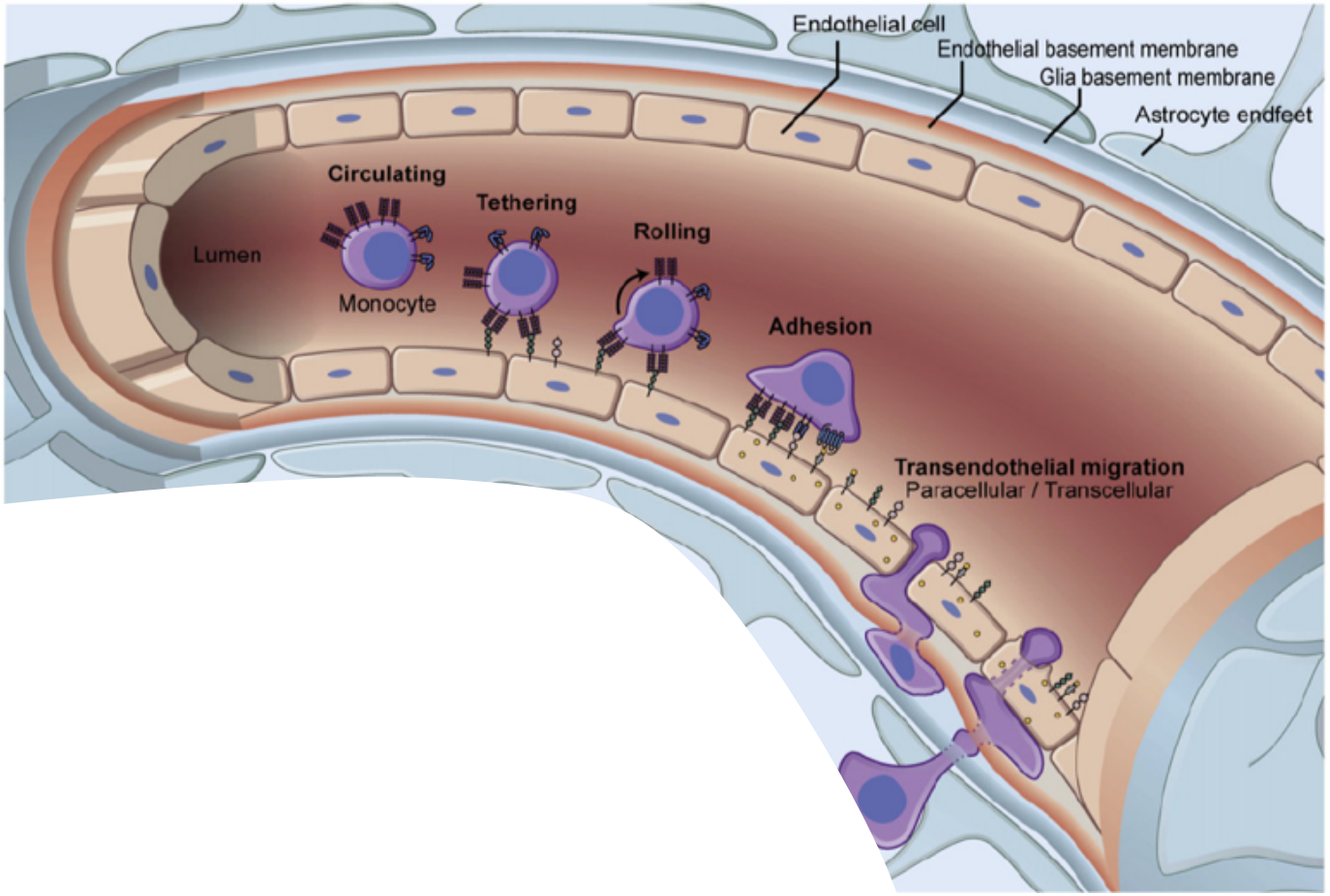
Neuroanatomy of the vascular blood–brain barrier (BBB)



Shechter et al, Nat rev, 2013

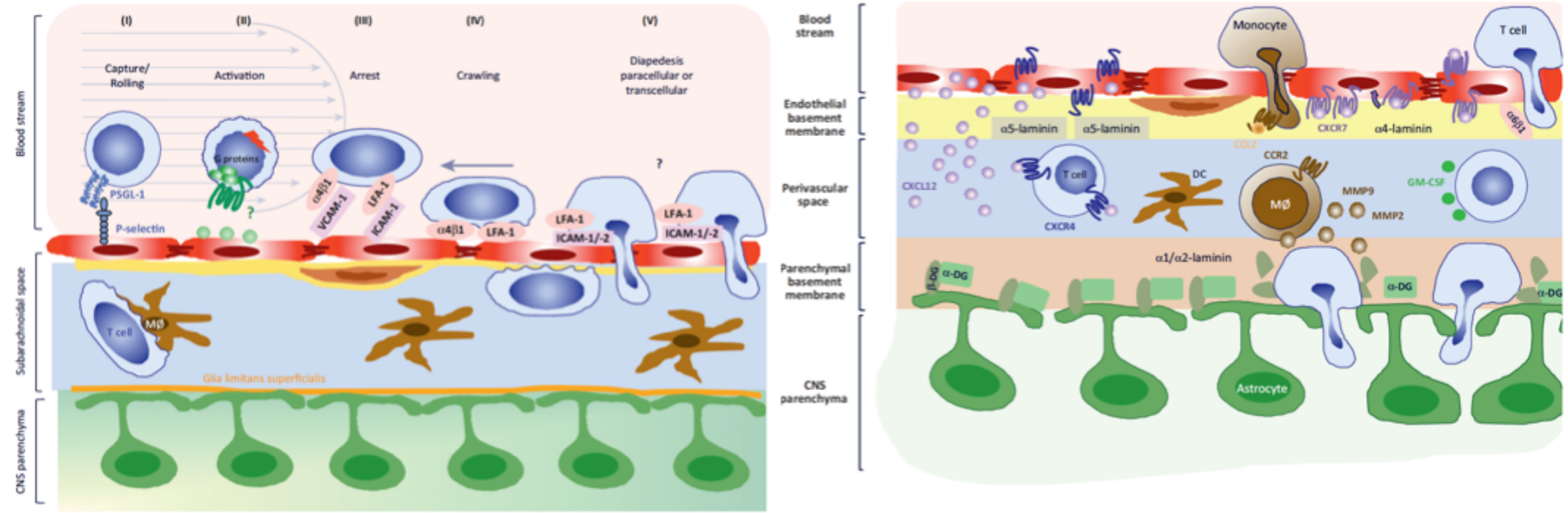
Engelhardt et al, Trends in immunology, 2012

The blood brain barrier (BBB): a protective barrier



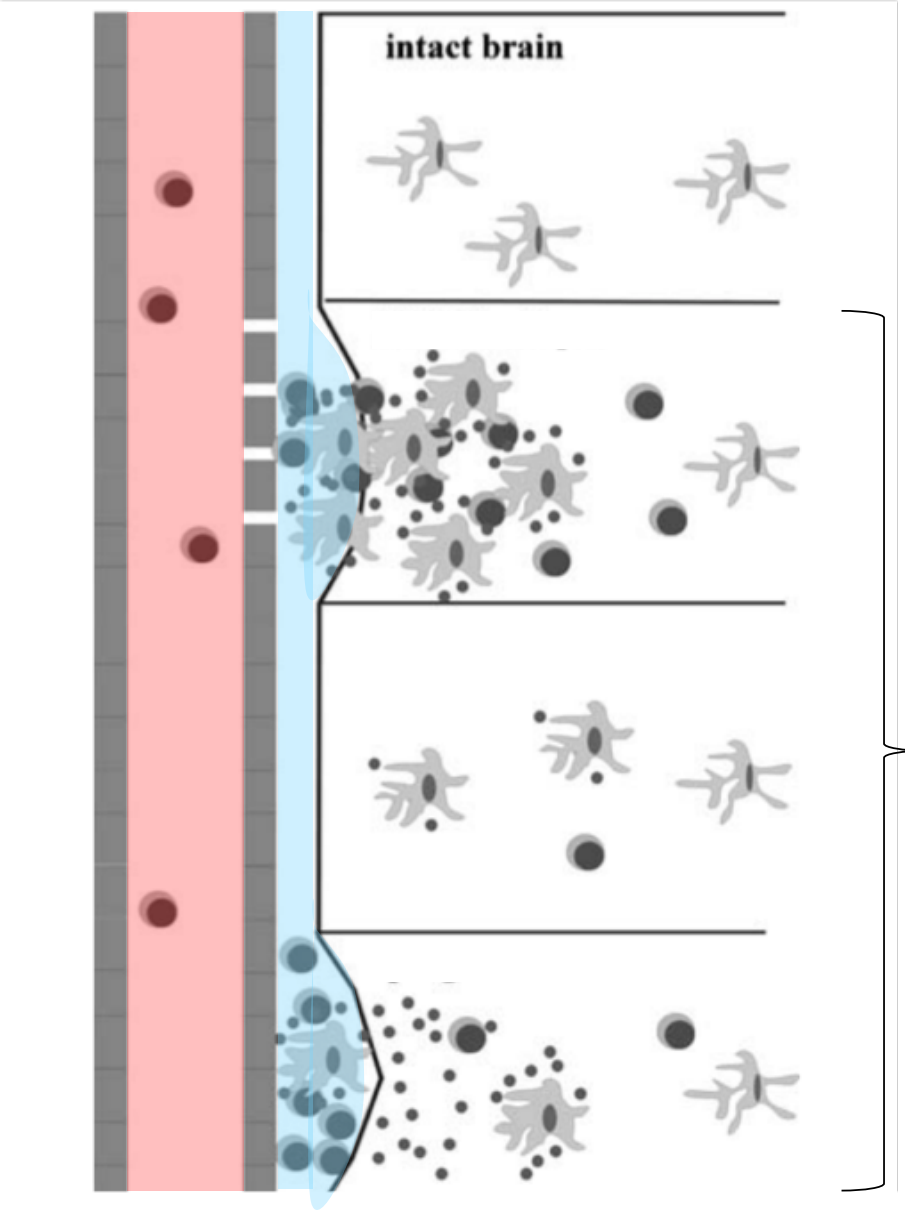
Pinheiro et al, Biochimica et Biophysica Acta, 2016

The blood brain barrier (BBB): a protective barrier



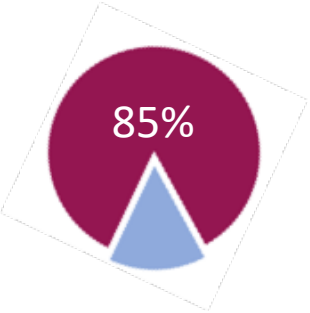
Engelhardt, Trends in Immunology, 2012

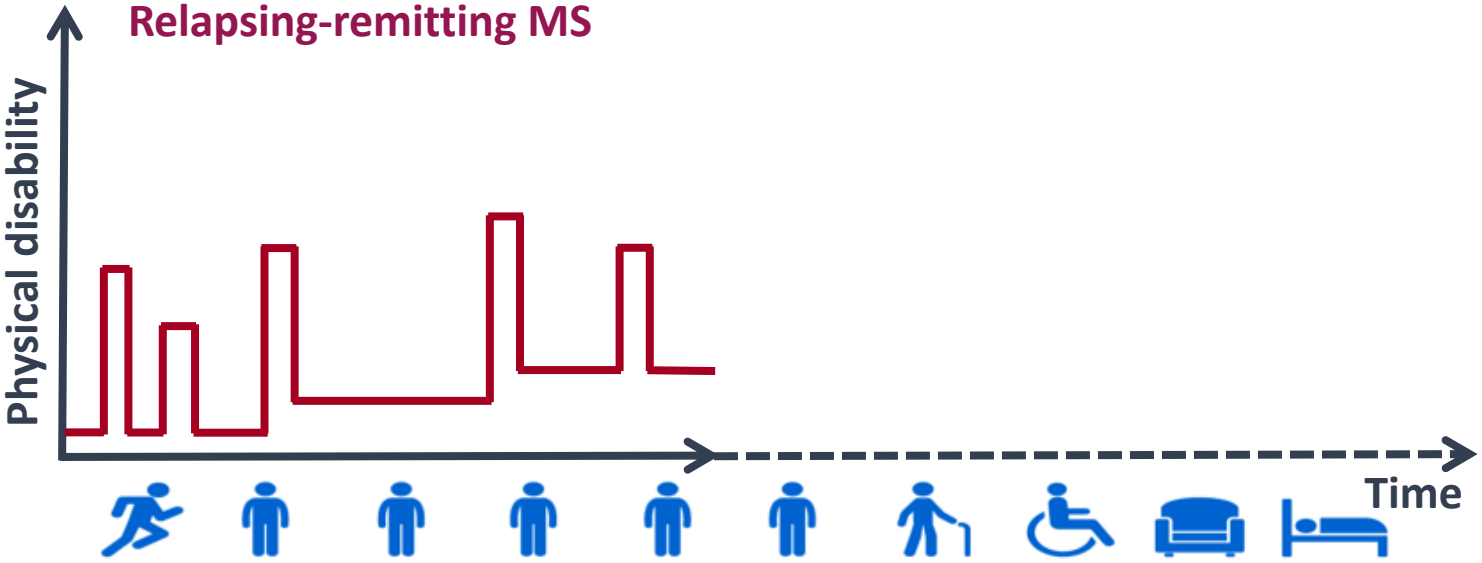
Alteration of BBB in multiple sclerosis



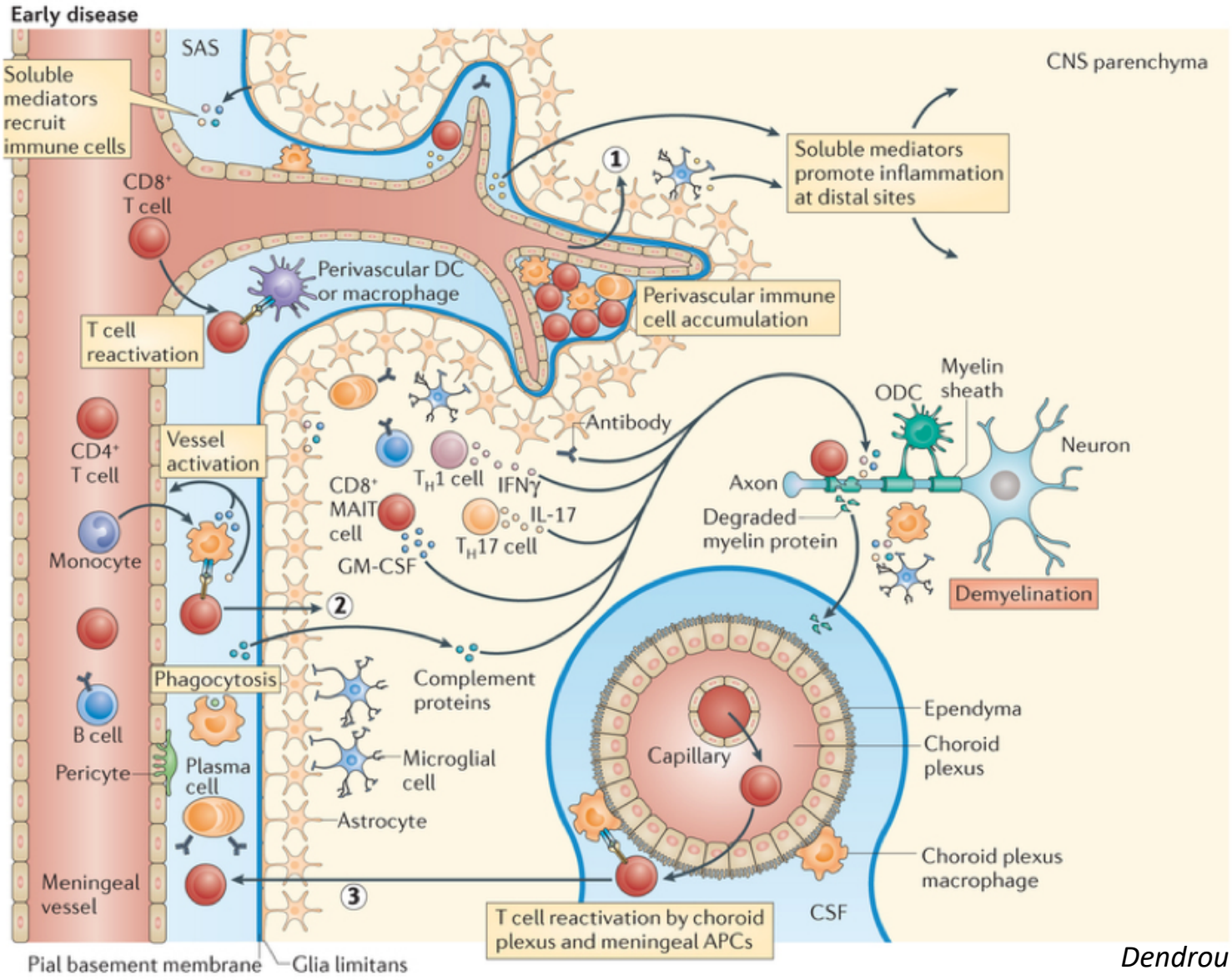
Bradl et al, Seminars in Immunopathology, 2009

Different clinical forms of MS



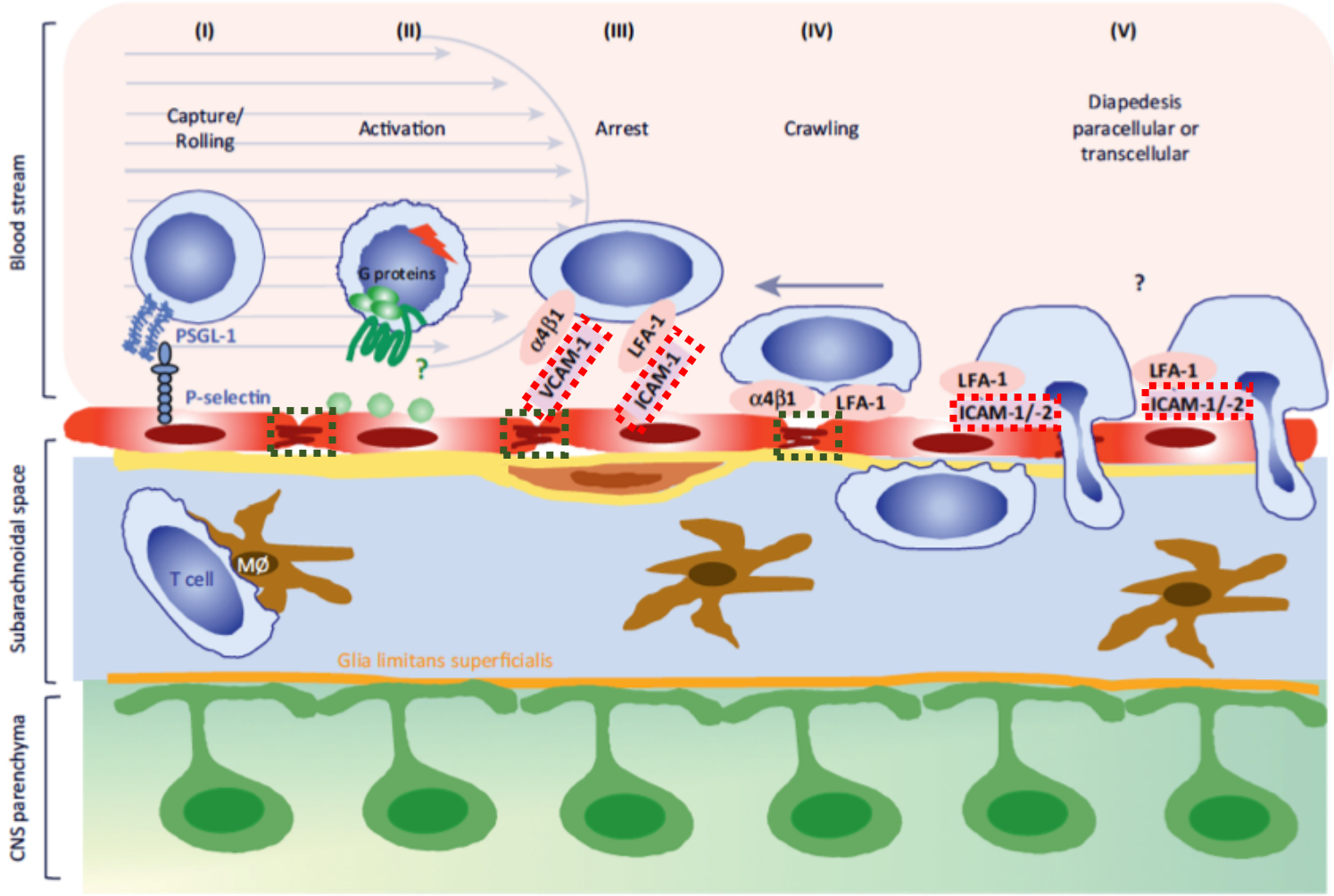


CNS inflammation in RRMS



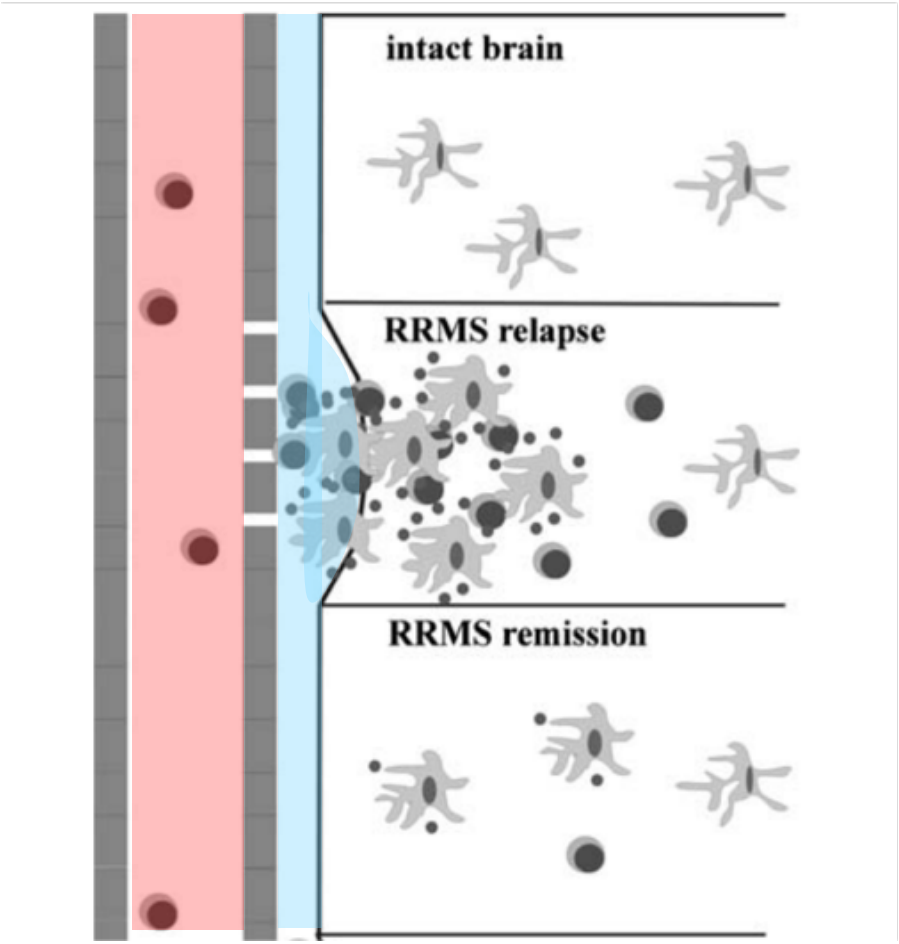
Dendrou et al. Nat Rev, 2015

Inflammation in the CNS leads to an upregulation of trafficking molecules on the BBB



Engelhardt et al, Trends immunol, 2012

Opened BBB in RRMS



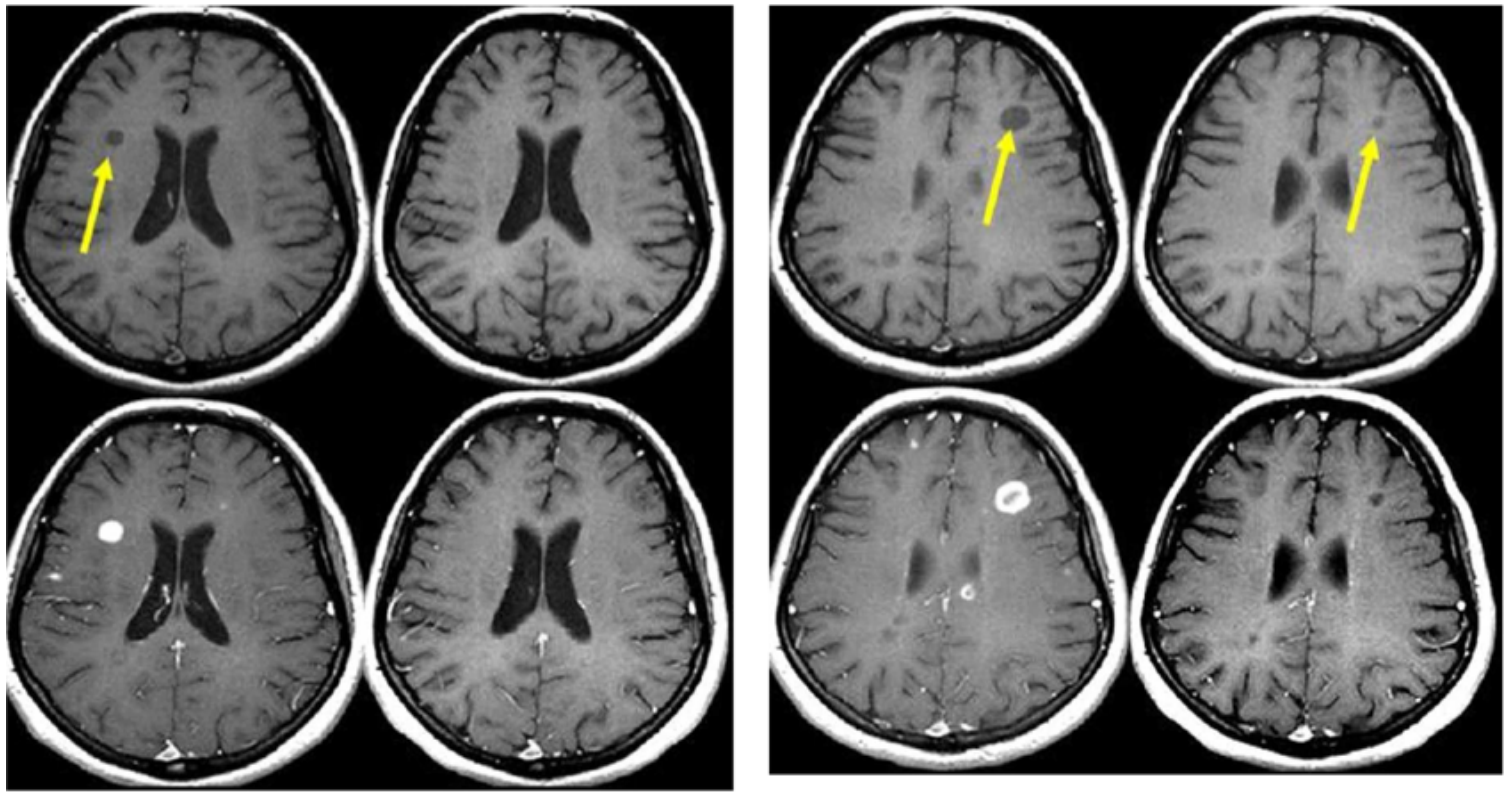
Bradl et al, Seminars in Immunopathology, 2009

Inflammatory activity in RRMS

RRMS patient #1

RRMS patient #2

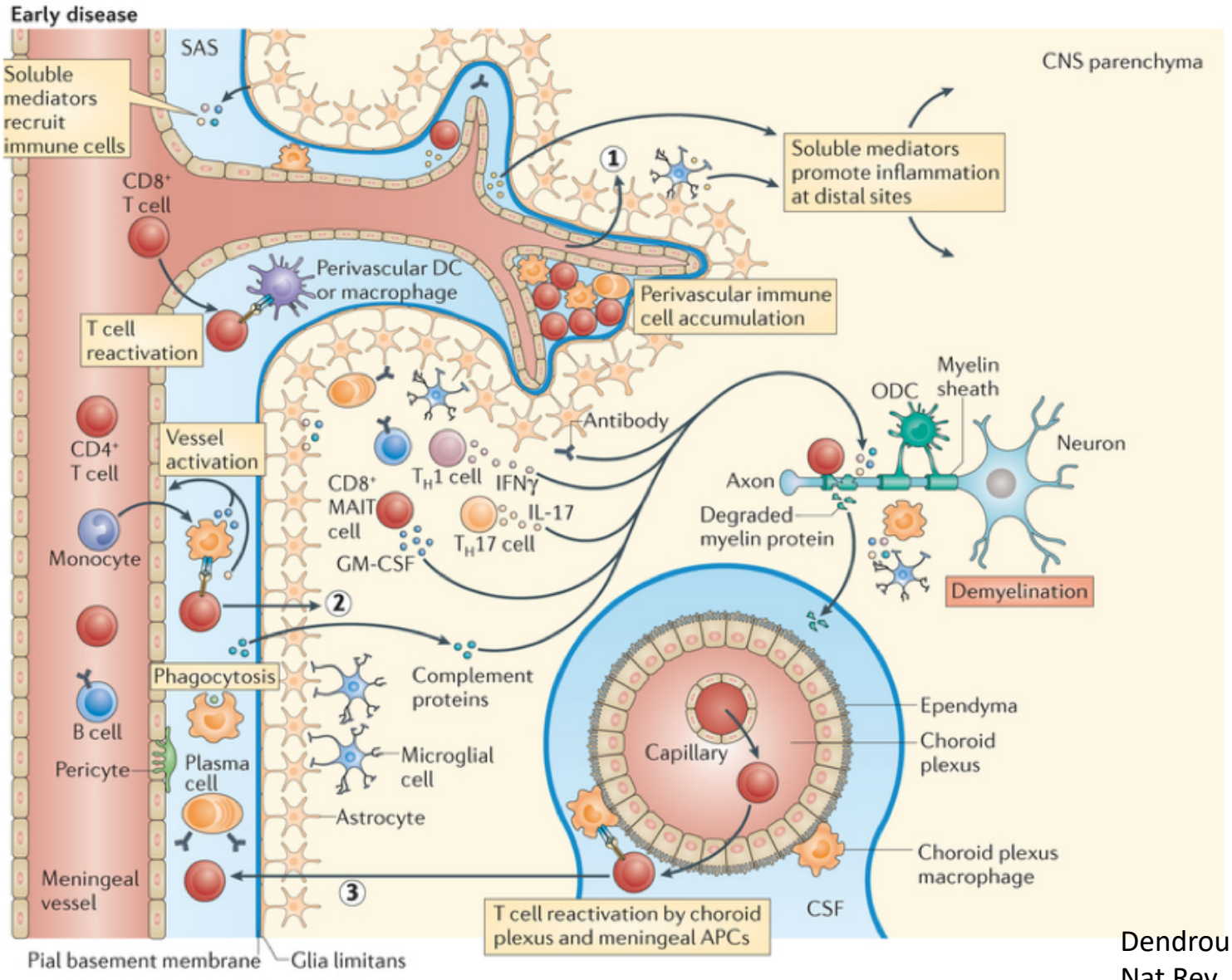
after gadolinium injection



T0 T0 + 1 year T0 T0 + 1 year

Rovira et al, Ther Adv Neurol Disord, 2013

What are the immune cells involved in RRMS phase?



Dendrou et al.
Nat Rev, 2015

Multiple Sclerosis: a CD4 T cell mediated disease

Human

- GWAS studies: association of CD4 T cell loci, including MHCII alleles, with disease susceptibility
- Activated myelin antigen specific CD4 T cells in MS patients
- Alteration of CD4 T cell subsets in MS patients (**Th17, Th1,** Treg)

Mouse model

- EAE induction: dependent on myelin-specific CD4 T cells (immunization with myelin Ag, transfer of activated T cells isolated from animal immunized w/ myelin Ag, myelin specific Tg TCR)
- Mice deficient in CD4 T cells are resistant to EAE induction, susceptibility restored by the transfer or induction of CD4+ T cells

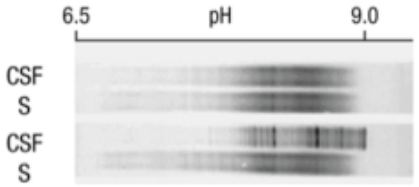
B cells in Multiple sclerosis (1960-2008)

1960

THE DIFFERENTIAL DIAGNOSIS OF NEUROLOGICAL DISEASES BY FRACTIONATING ELECTRO-PHORETICALLY THE CSF γ-GLOBULINS*

A. LOWENTHAL, M. VAN SANDE and D. KARCHER
(Translated from French by C. M. POSER)
Neurochemical Research Laboratory of the Neurological Department,
Institut Bunge, Berchem, Antwerp

(*Received* 15 *January* 1960)



Discovery of <u>intrathecally synthesized oligoclonal IgG bands</u> (OCB) in CSF of MS patients: indicates clonal expansion of B cells in the CSF

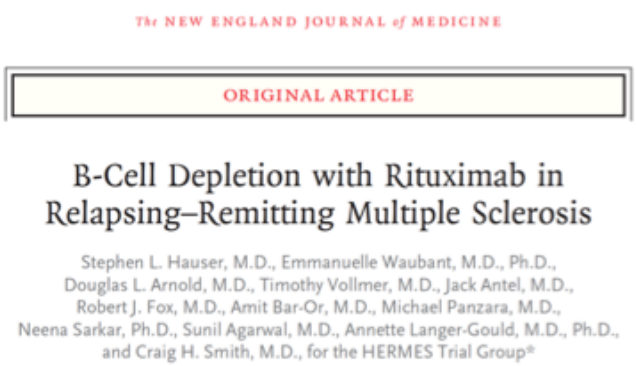
- Present in >90% of MS patients
- <u>BUT</u>: not specific of MS, undetermined antigen-specificity, unclear pathogenic role

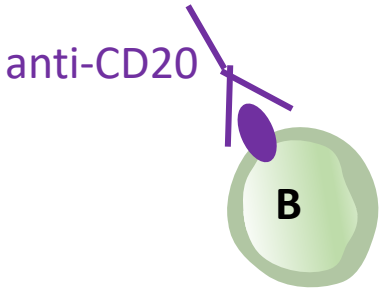
⇒ Indicates abnormal B cell activation within the CNS

⇒ Diagnostic criteria for MS

B cells in Multiple sclerosis (2008-.....)

2008

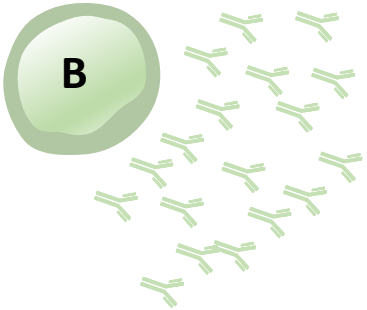




B cell depletion (CD20 antibody) reduces symptoms of RRMS

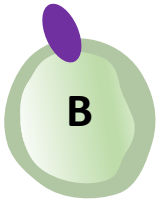
=> **Role of B cells in MS pathogenesis?**

Antibody dependent?



- No change in OCB

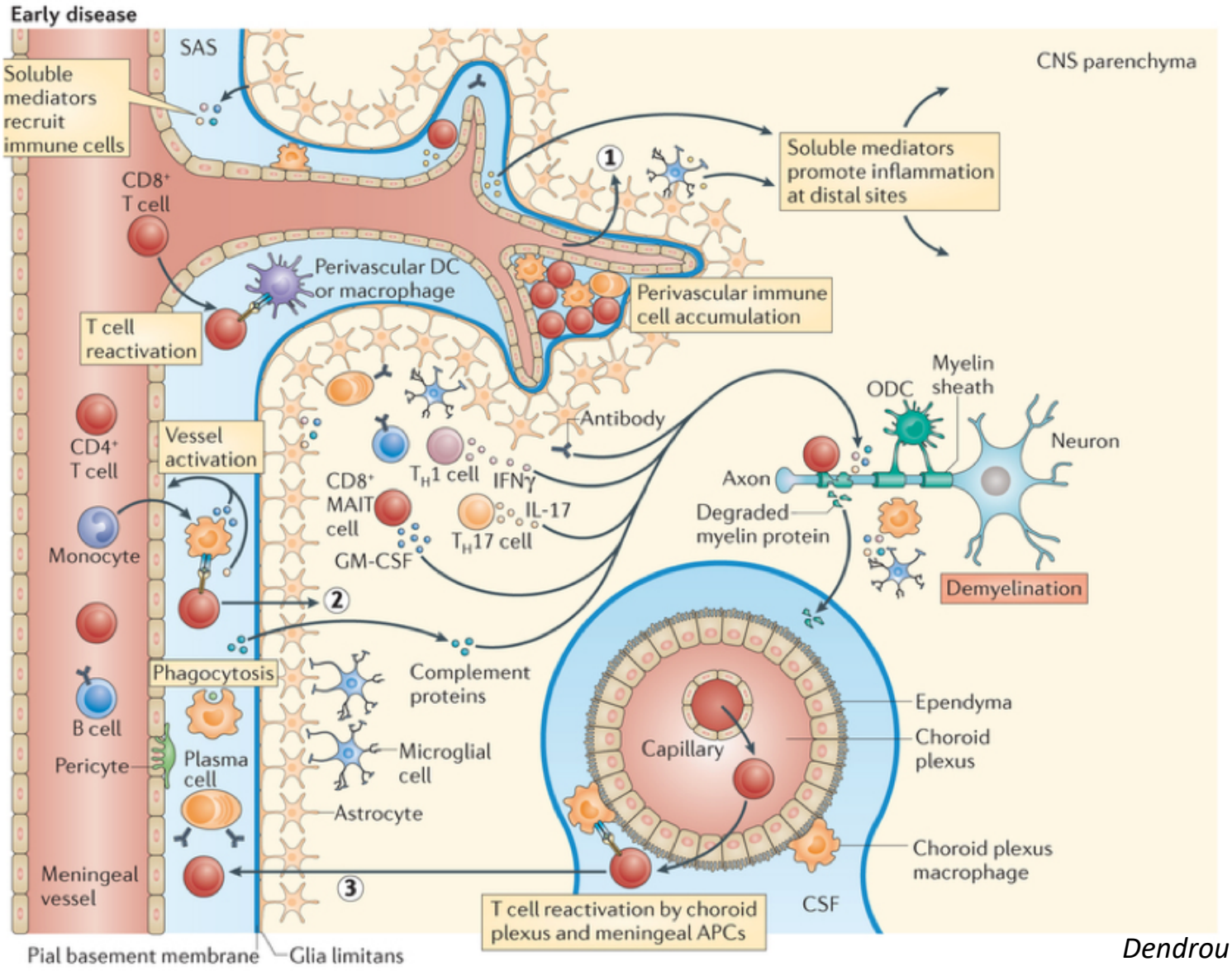
Antibody independent?



- APC
- Bystander effect
- Regulatory role

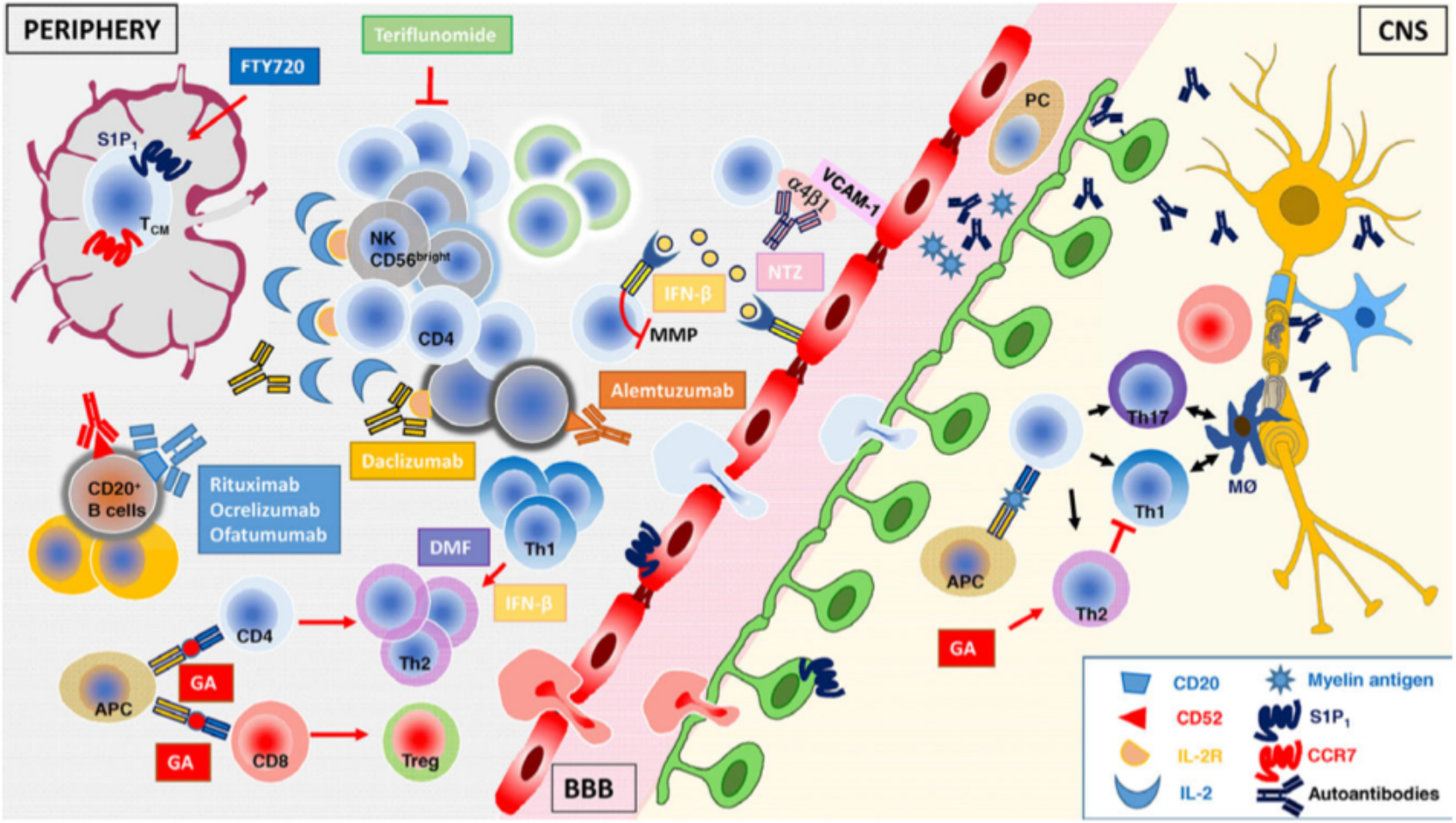
...

Plus other immune cell types….



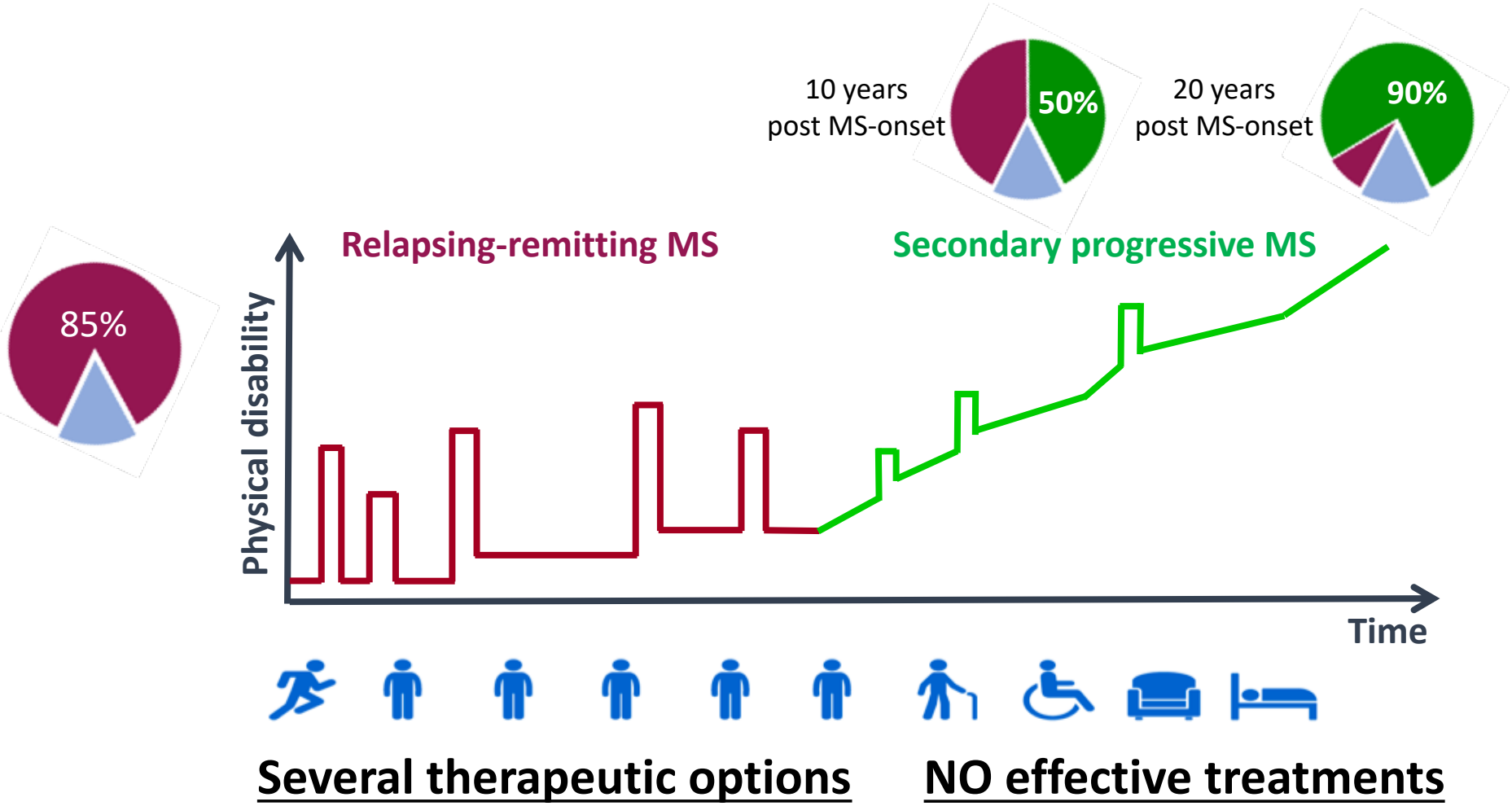
Dendrou et al. Nat Rev, 2015

Therapeutic approaches in RRMS



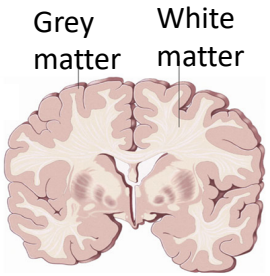
Martin et al, EJI, 2016

Secondary progressive Multiple Sclerosis (SPMS)

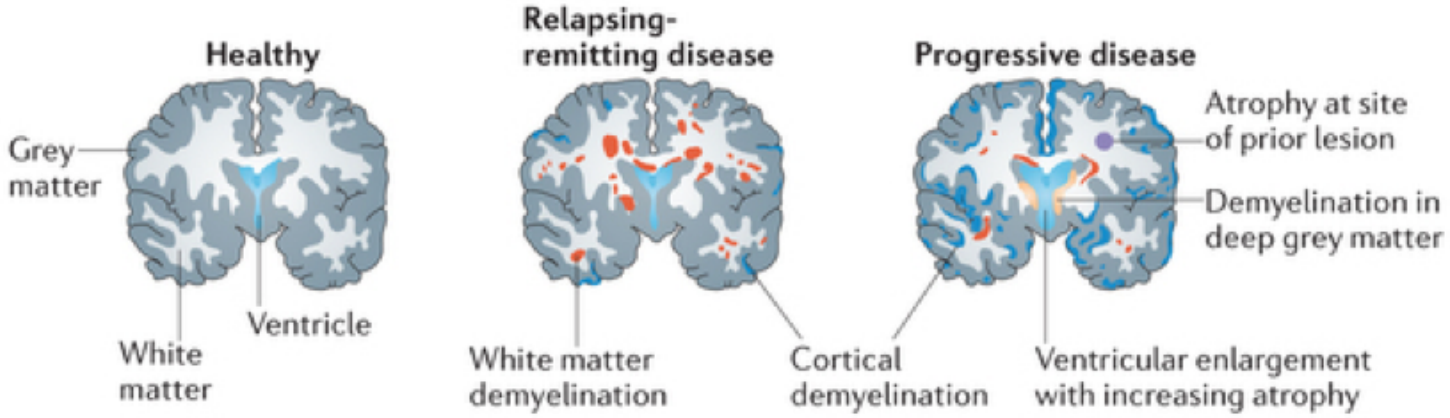


Recent paradigm shift in MS : Association of grey matter lesions with progression

Long believed to be
"white matter disease"

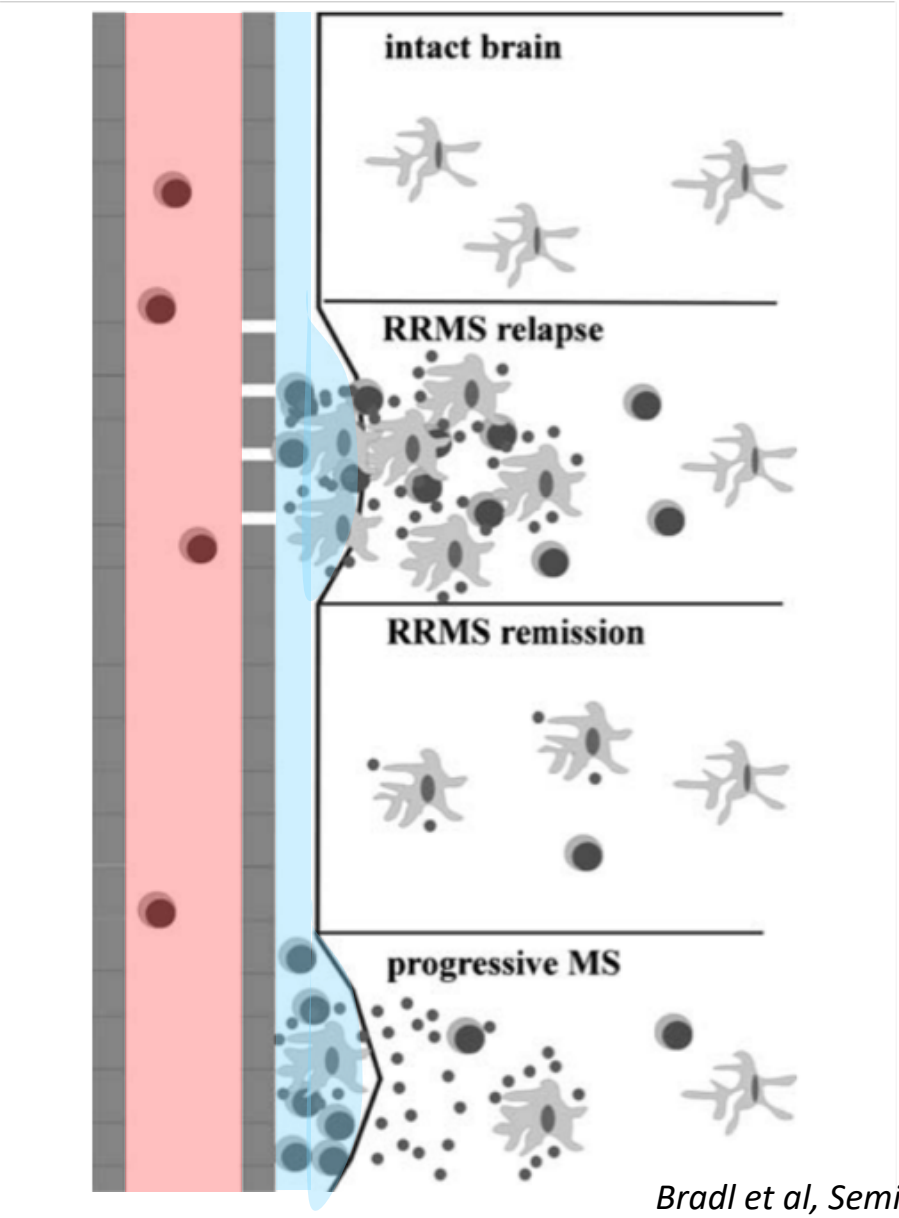


- Grey matter lesions are much more common than initially anticipated
- Grey matter lesions are associated with disease progression (Magliozzi et al. Brain 2007 ; Rudick et al. NEJM, 2009)



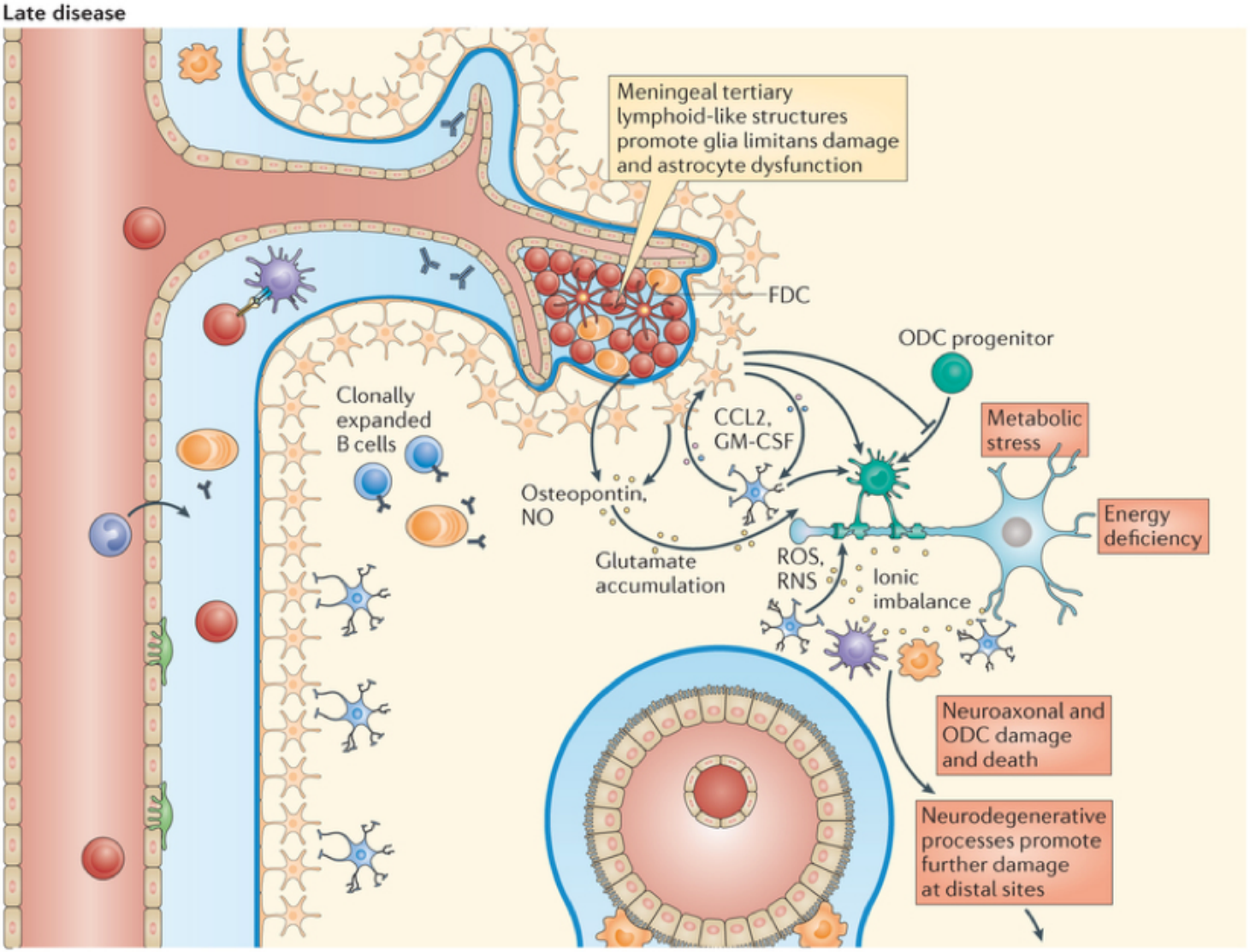
Dendrou et al. Nat Rev, 2015

SPMS:
meningeal inflammation behind a closed BBB

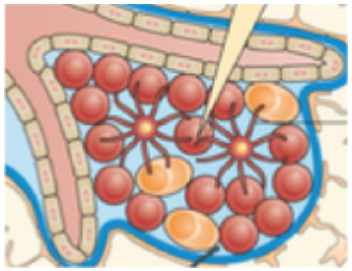


Bradl et al, Seminars in Immunopathology, 2009

Meningeal inflammation, lymphoid tissue formation and closed BBB in SPMS



Dendrou et al.
Nat Rev, 2015

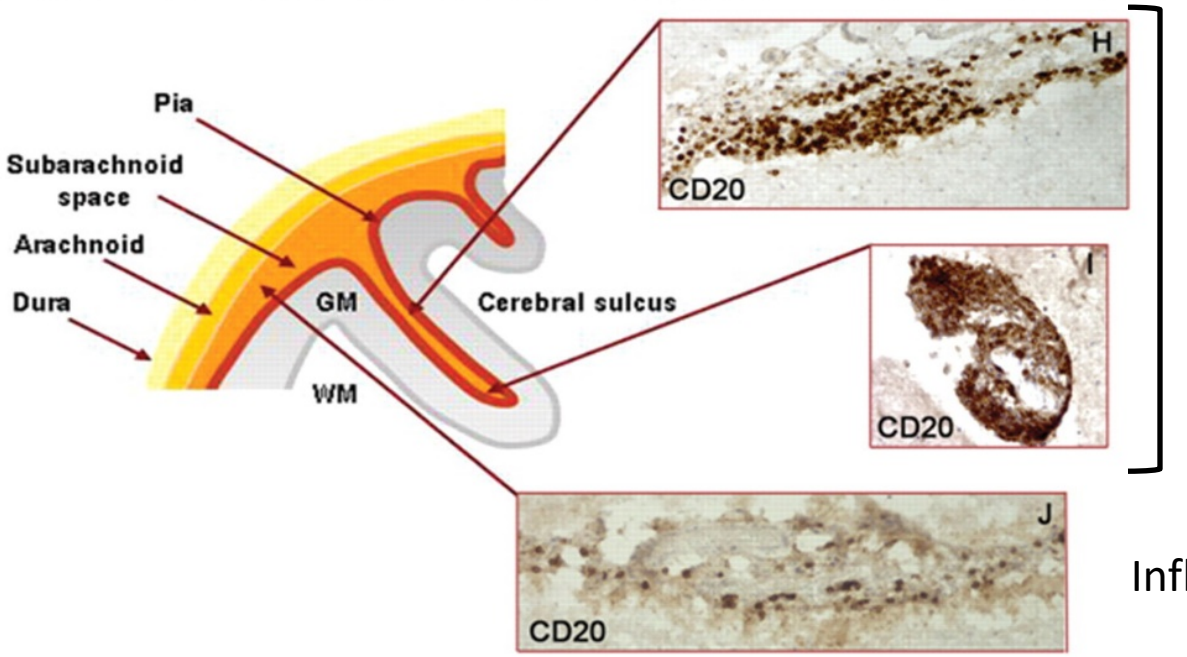


Ectopic GCs in SPMS

- Lymphoid like structure: antibody generation, affinity maturation, class switching, clonal expansion of B cells
- Present in 40-54% of SPMS patients
- Almost exclusively found adjacent to large subpial lesions
- Associated to an increased severity of pathological changes and clinical manifestations of the disease
- Gradient of neuronal loss suggesting that soluble factors diffusing from these structures have a pathogenic role

Calabrese et al, Nature Rev Neurosci, 2015

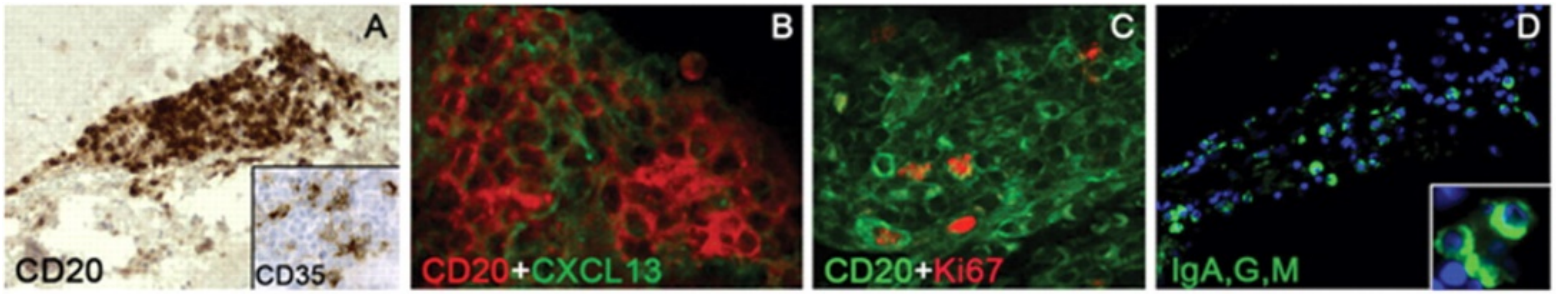
Meningeal B-cell follicle-like structures in SPMS patients



Ectopic germinal centers

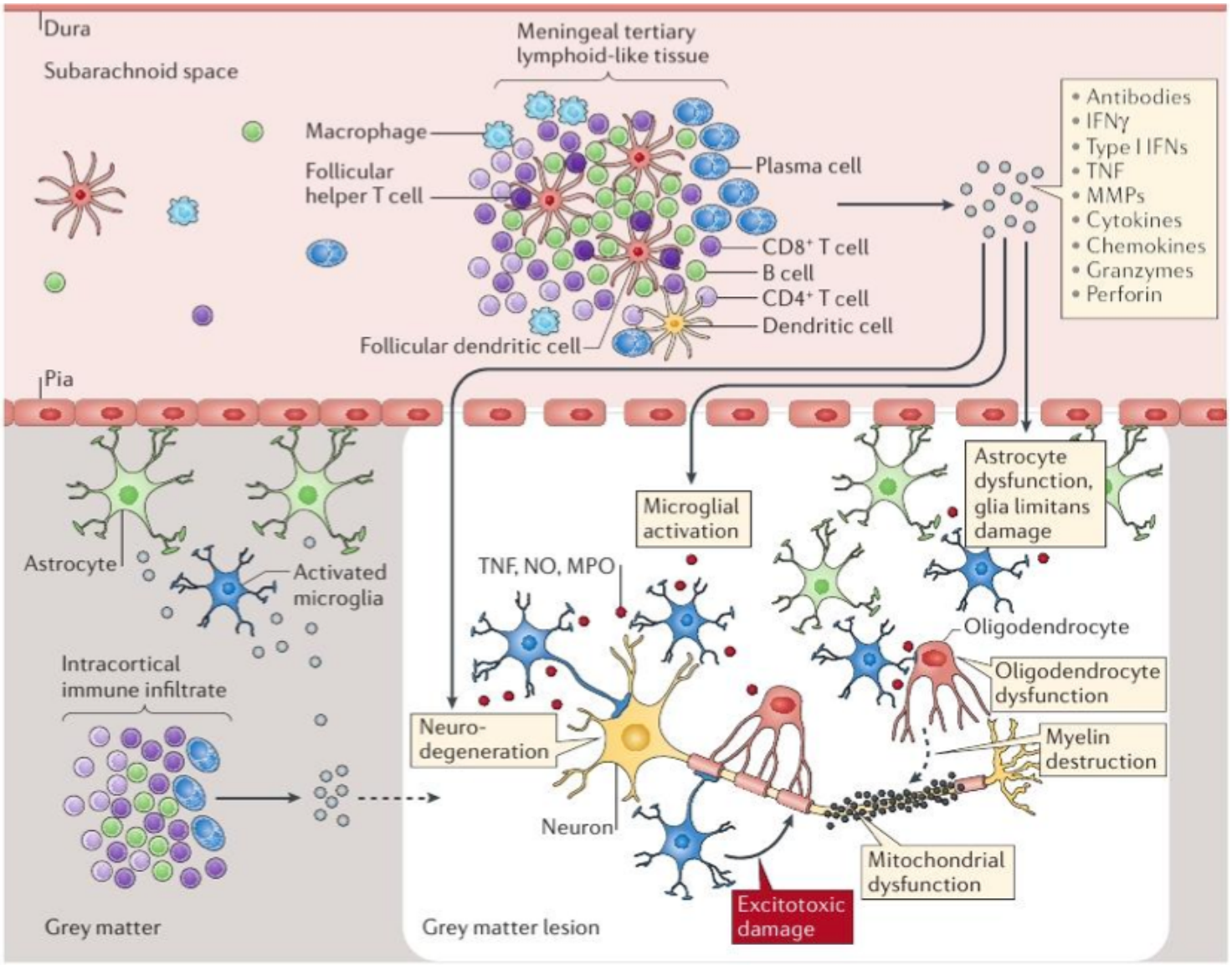
Inflammatory cell infiltrates

Ectopic Germinal Centers



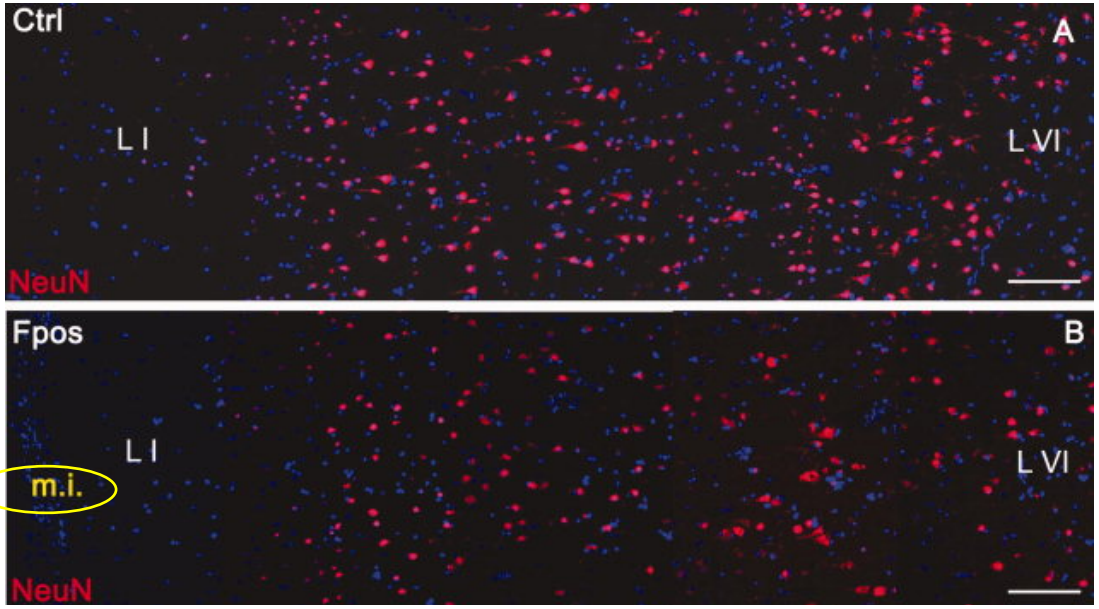
Magliozzi et al. Brain, 2007

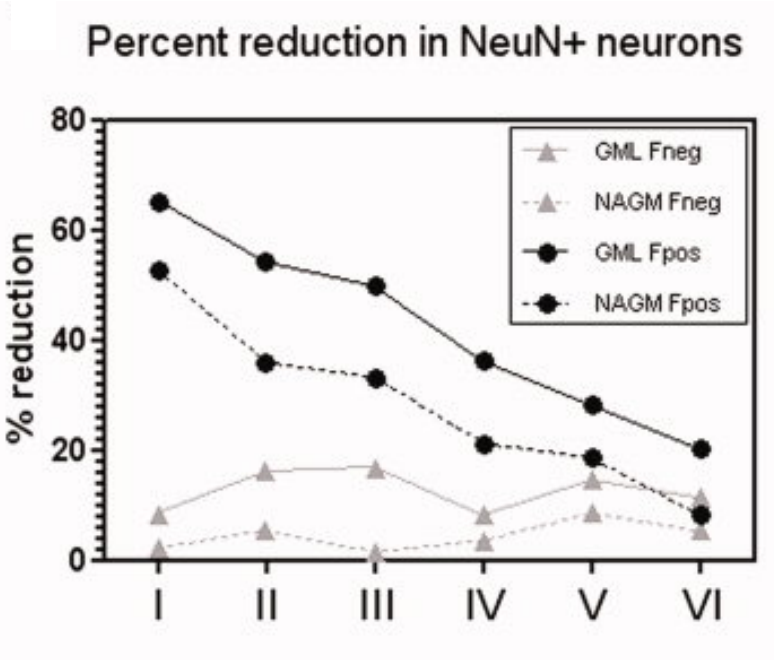
Immune-mediated mechanisms of subpial cortical demyelination in progressive multiple sclerosis



Calabrese et al. Nat rev neurosciences, 2015

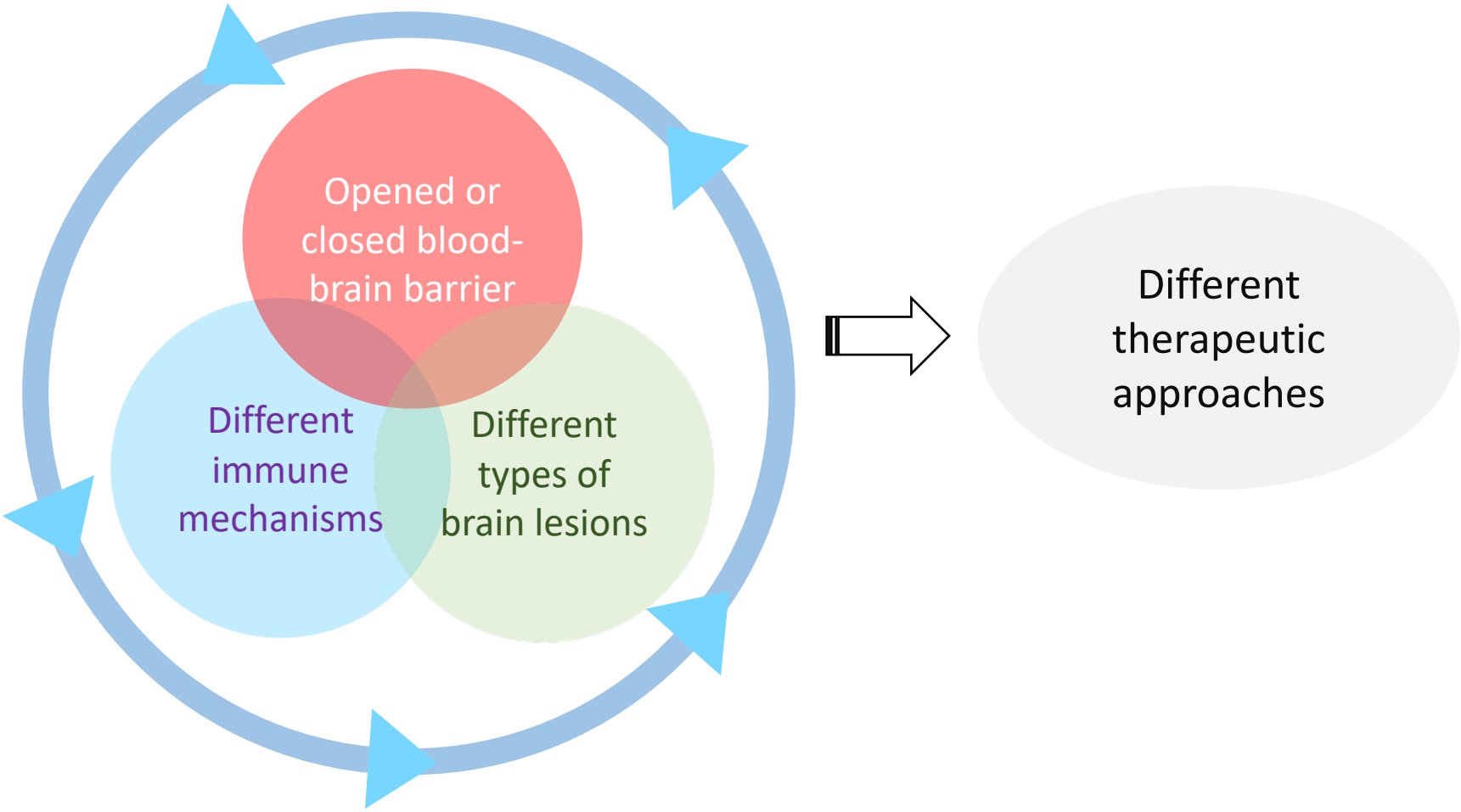
Gradient of neuronal loss in follicle positive SPMS patients



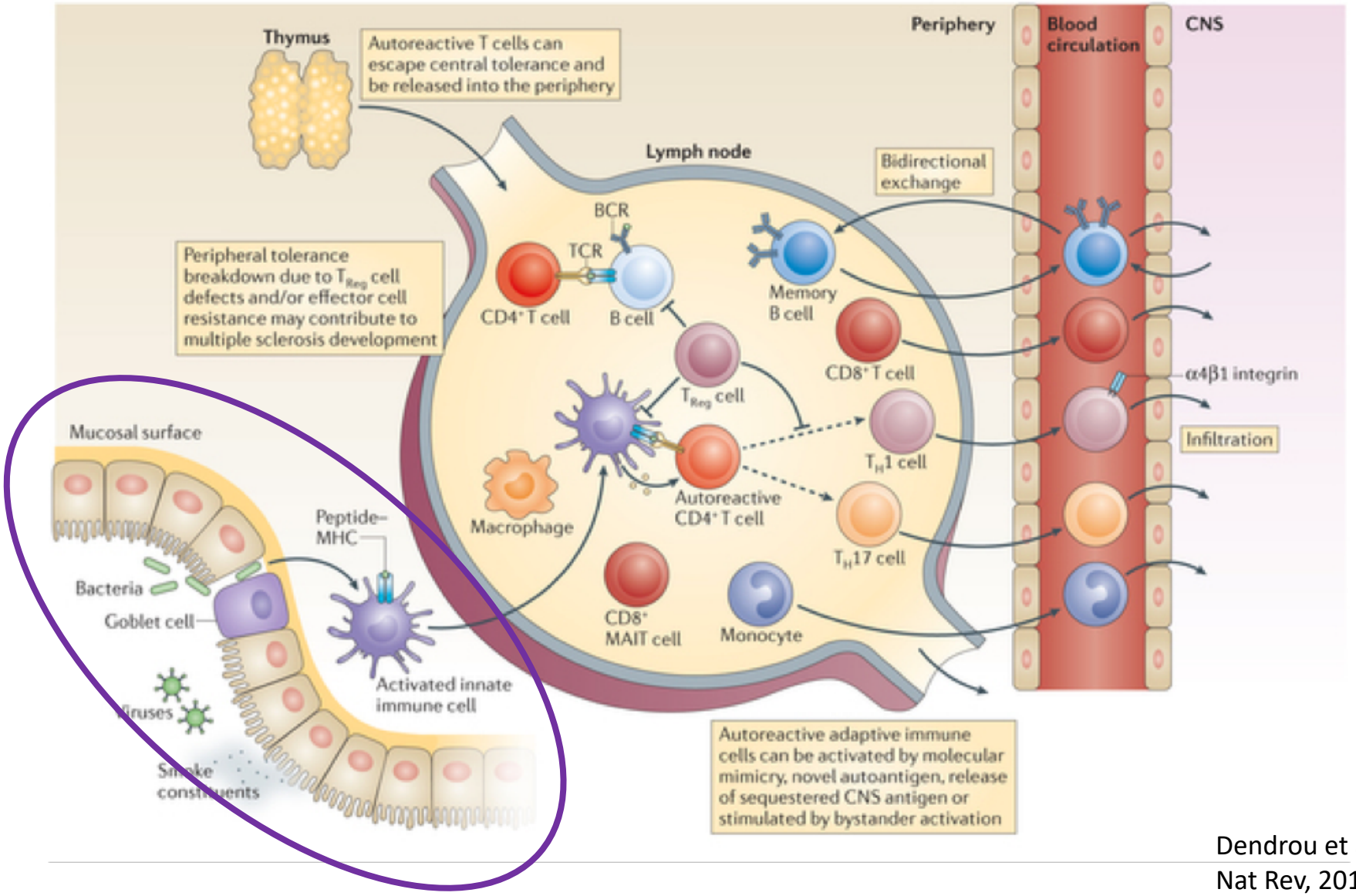


Magliozzi et al. Annals of Neurology, 2010

Different clinical forms of MS and…

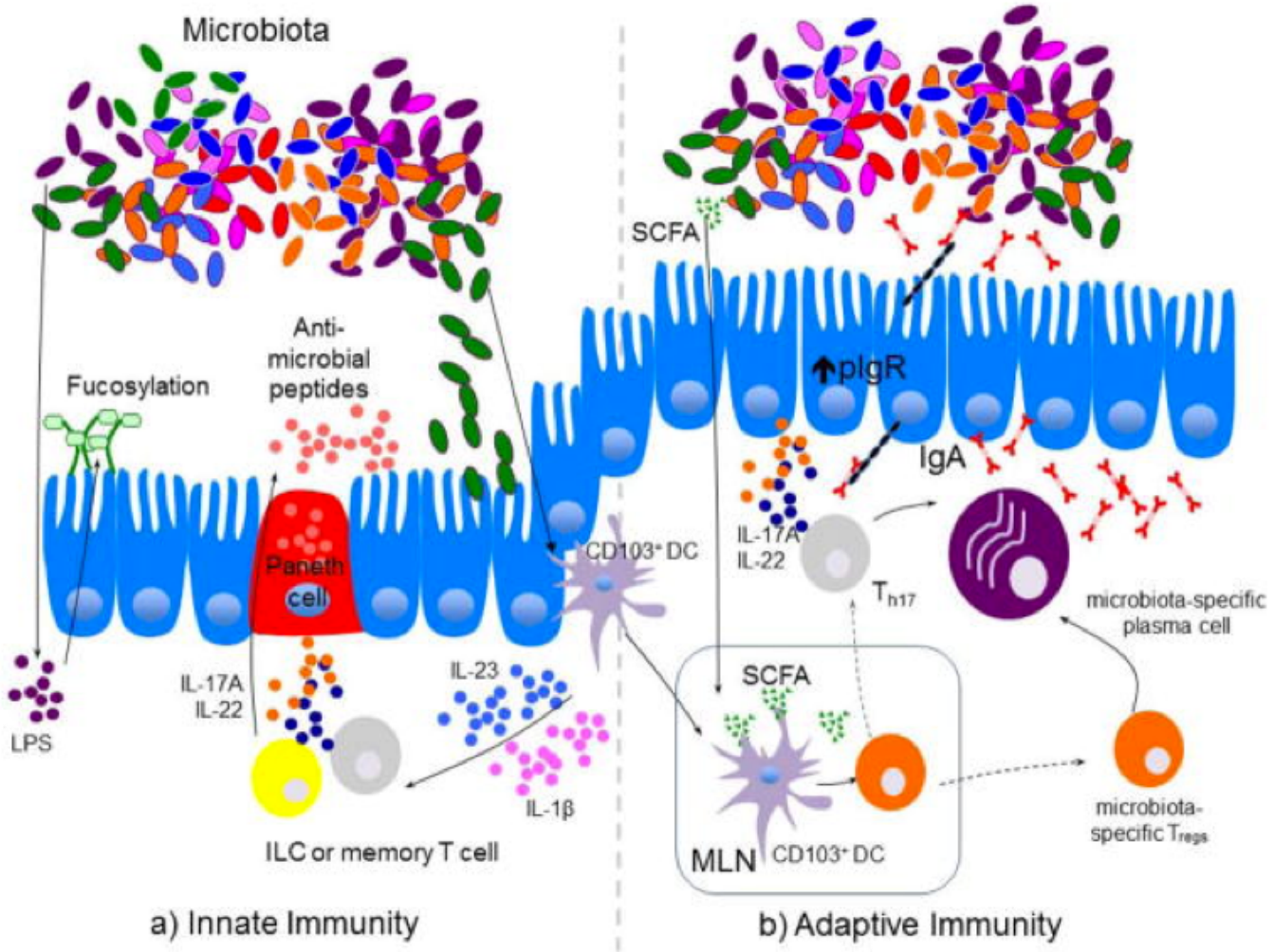


Intestinal barrier: another barrier of interest in Multiple Sclerosis?



Dendrou et al.
Nat Rev, 2015

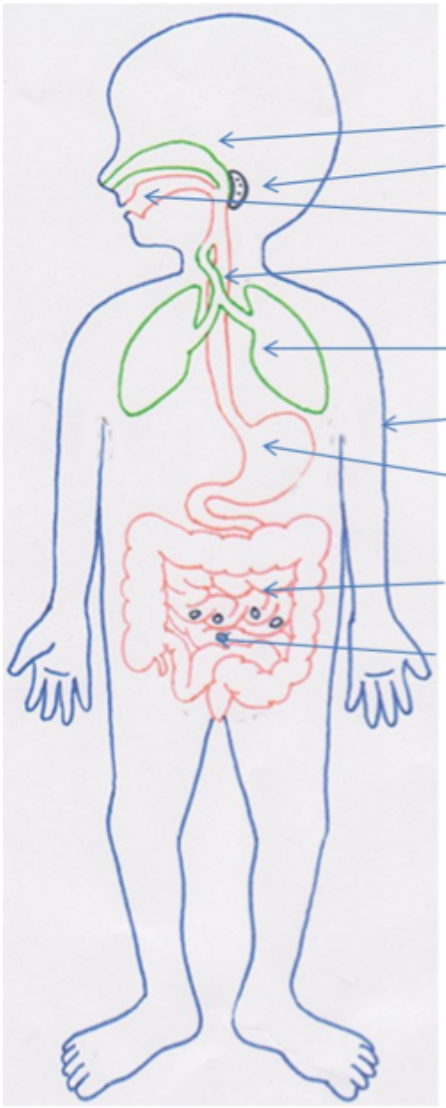
Microbiota, intestinal barrier and gut immune system



Hand et al,
Trends in Immunology, 2016

The mucosal layer represents the major immune interface with the environment

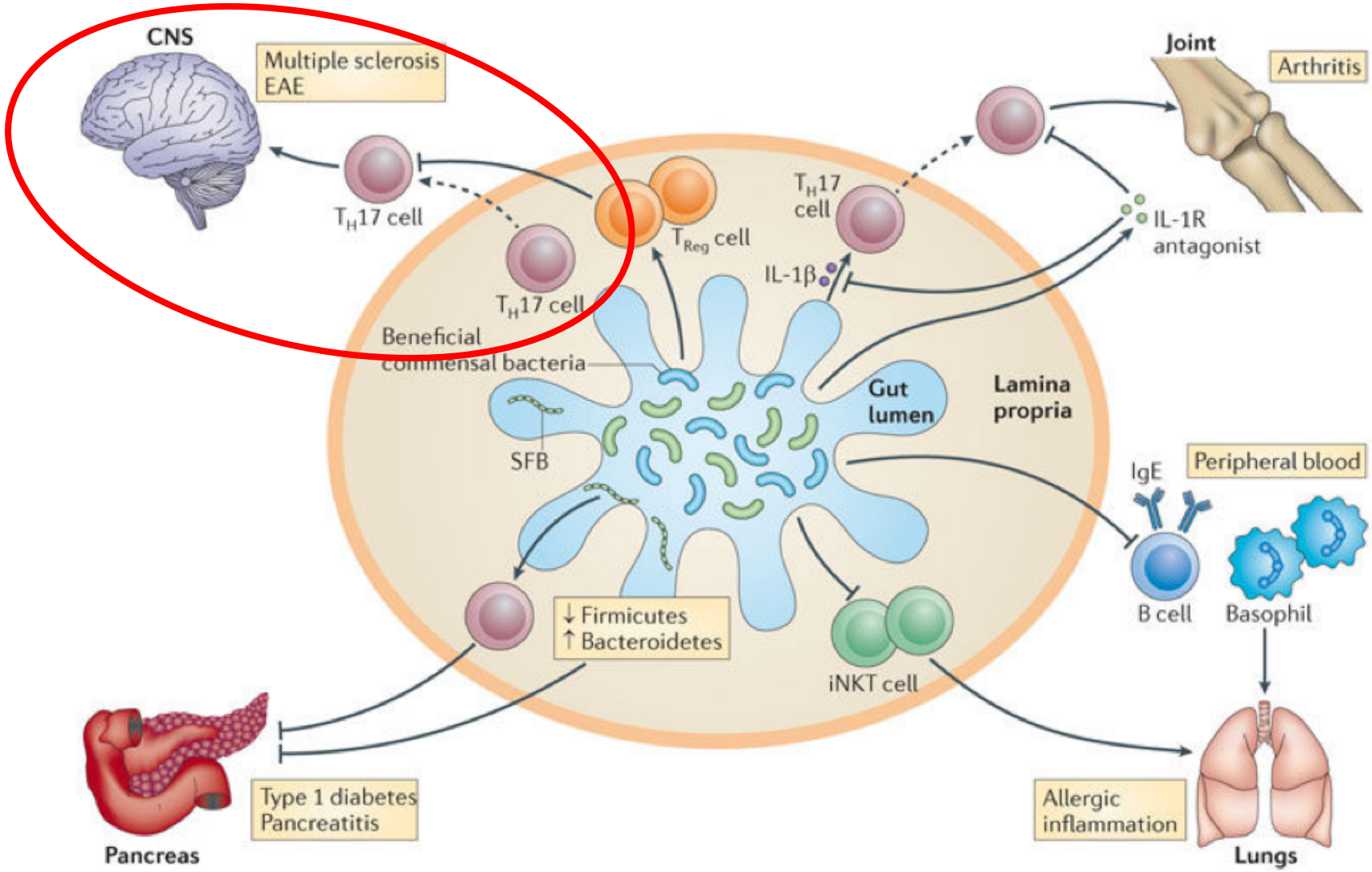
Environment
Pathogens,
Chemicals, Diet,
Sun exposure,
Smoking



=> largest mucosal surface

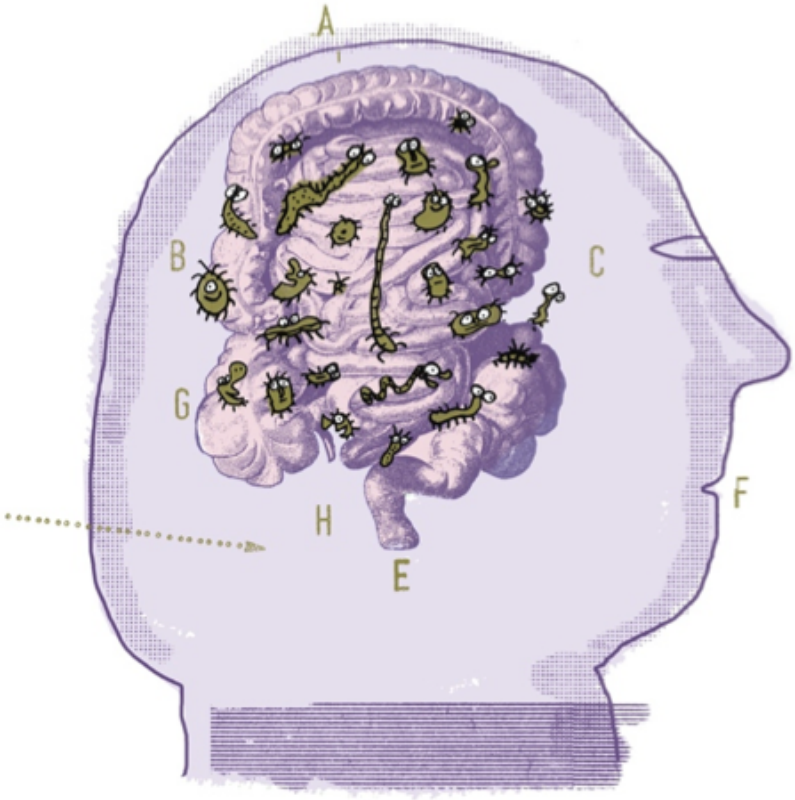
=> 70% of our immune cells reside in the GI tract

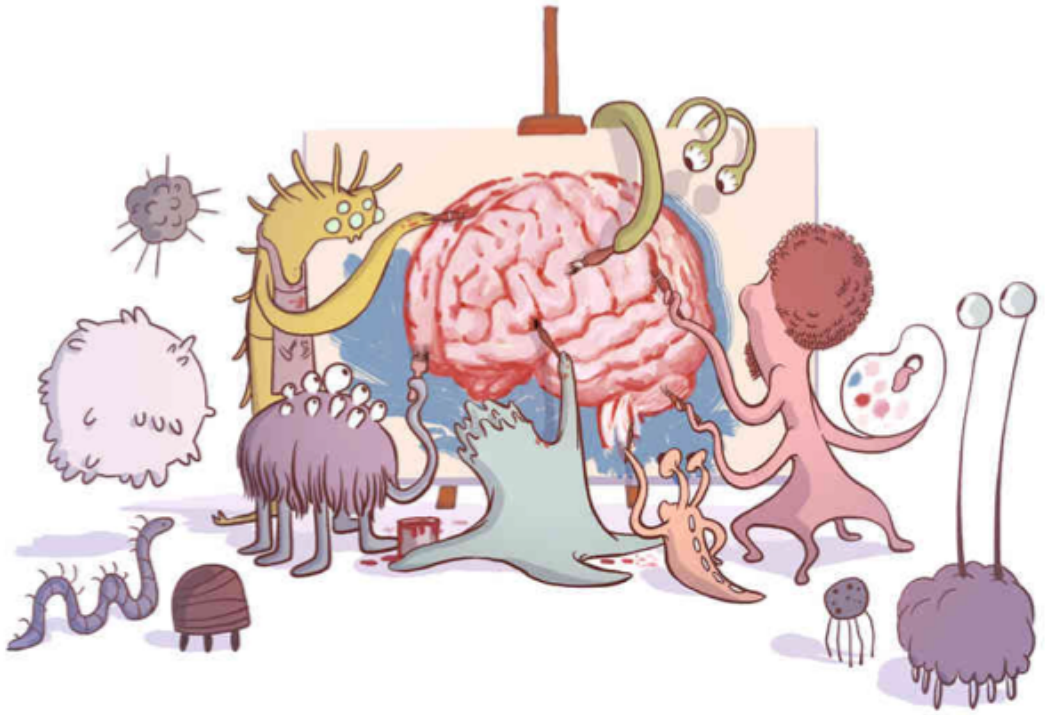
Role of the gut microbiota in autoimmune diseases



Kamada et al, Nat. Rev, 2013

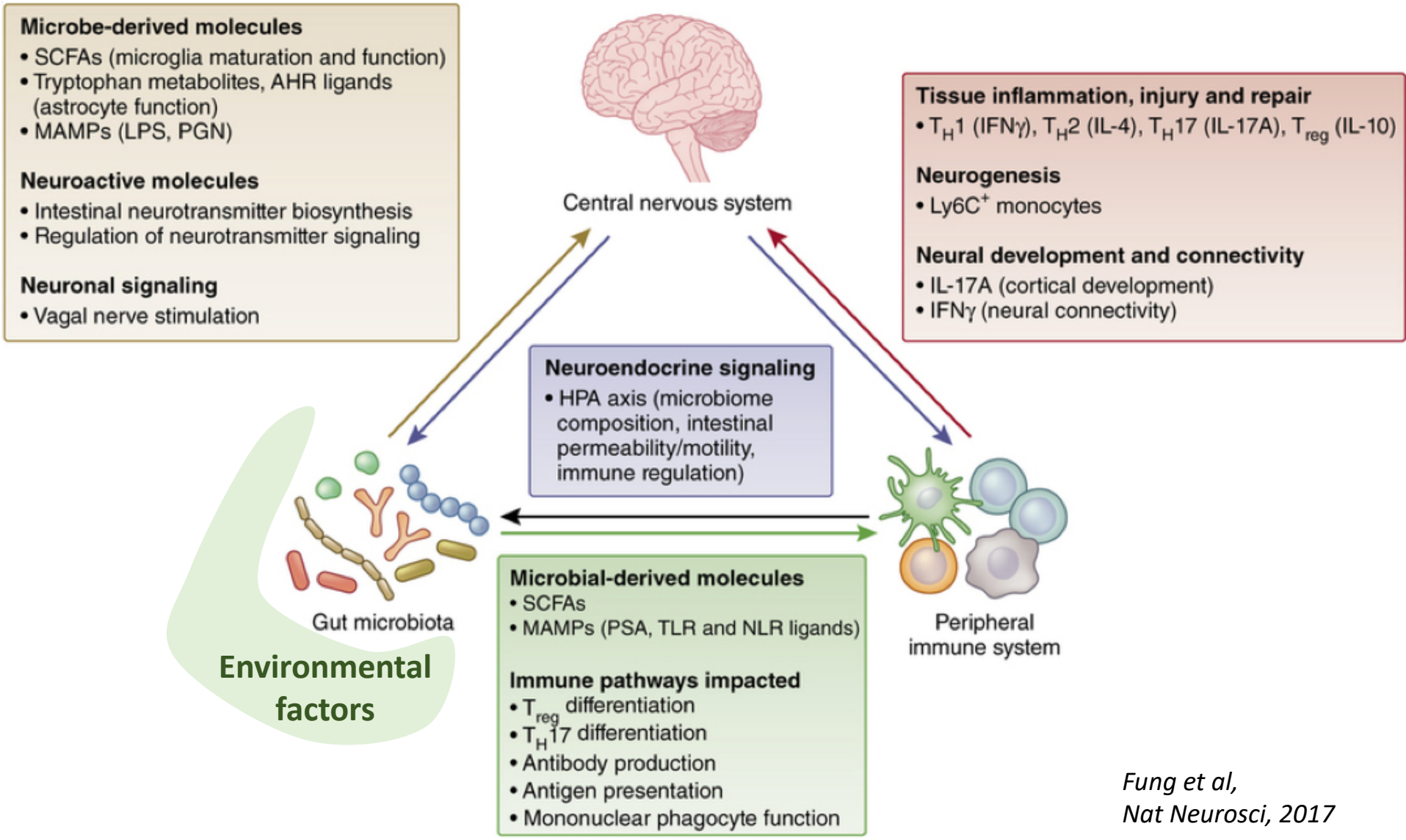
The microbiota-gut-brain axis





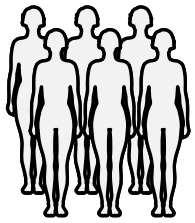
Smith, Nature, 2015

Crosstalk between the microbiota, immune system and CNS: Metabolic, endocrine, neural and immune pathways



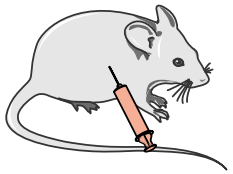
Fung et al,
Nat Neurosci, 2017

Gut microbiota and Multiple Sclerosis



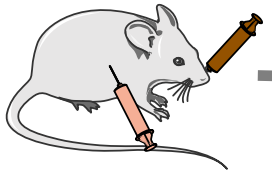
Dysbiosis in MS patients
Increased intestinal permeability
Differences in Firmicutes, Bacteroidetes and Proteobacteria

Germ-free



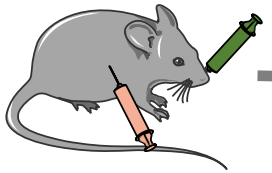
Attenuated EAE
↓ IFNg and IL-17 expression by CD4 T cells
↑ Treg
intestine and CNS

Germ-free
+ SFB (Segmentous filamentous bacteria)



Restored susceptibility to EAE
↑ IL-17+ CD4 T cells **intestine and CNS**

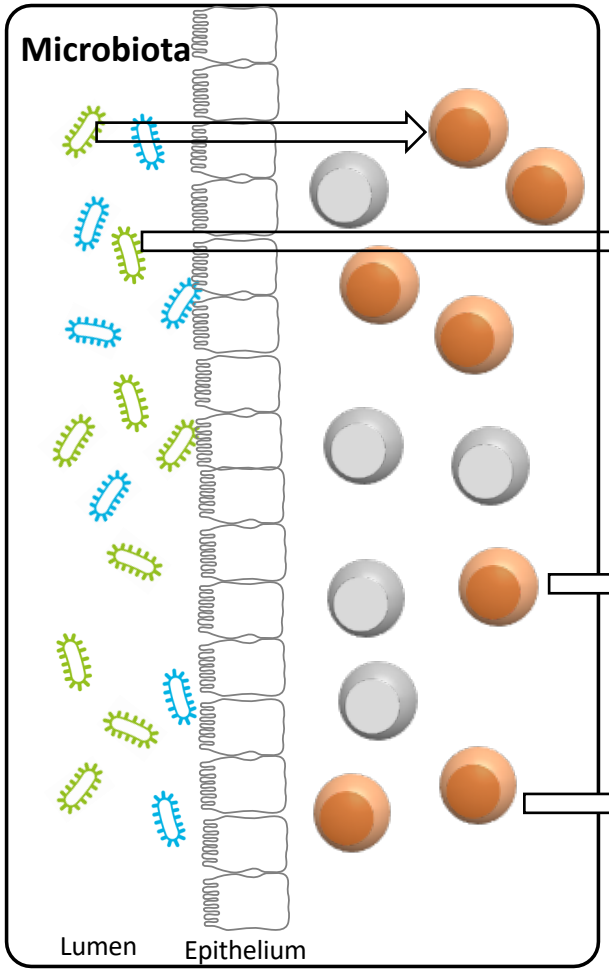
+ PSA
(Bacteroides fragilis)



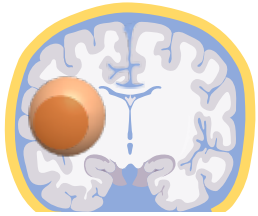
Attenuated EAE
↑ IL-10+ Treg

Lee et al, PNAS, 2011
Berer et al, Nature, 2011
Ochoa-Reparaz et al, Mucosal Immunol, 2010
Buscarinu et al, Neurotherapeutics, 2018
Fung et al, Nat Neurosci, 2017

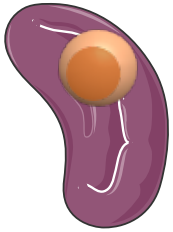
Migration of gut CD4 T cells to target organs in autoimmune disease



Gut immune system



<u>EAE</u>
Microbiota composition induces pathogenic CD4 T cells in the brain



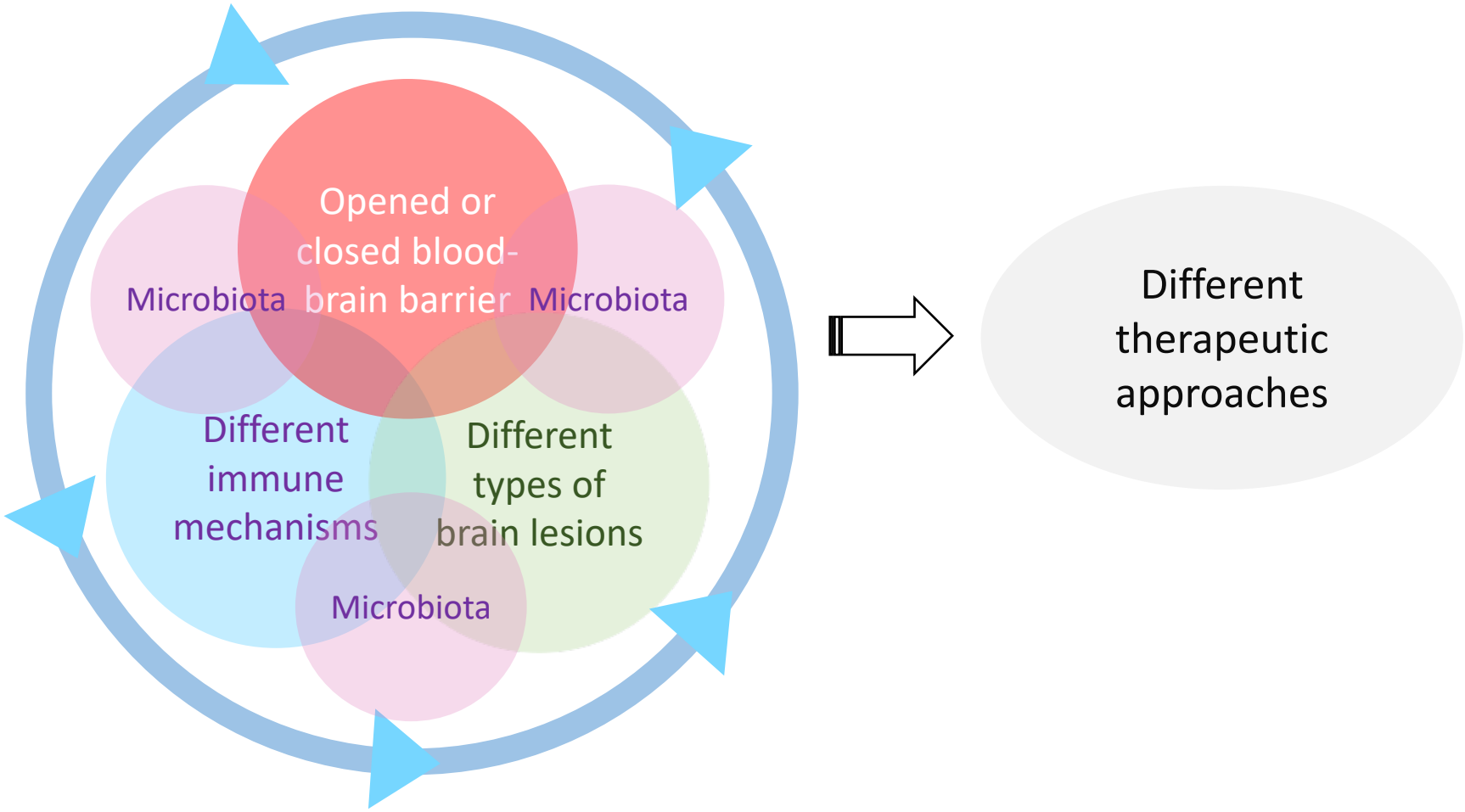
<u>Autoimmune arthritis</u>
Egress of Peyer's path TFh to systemic lymphoid tissues
=> Arthritis exacerbation

<u>Glomerulonephritis</u>
Intestinal Th17 migrate to inflamed kidney
=> Aggravation of the disease

Teng et al, Immunity, 2016
Krebs et al, Immunity, 2016

The international MS microbiome study

Gut microbiota in MS → Beneficial & harmful bacteria (animal model)

http://imsms.org

Different clinical forms of MS and…