UPDATE ON MULTIPLE SCLEROSIS

FROM BENCH TO BEDSIDE

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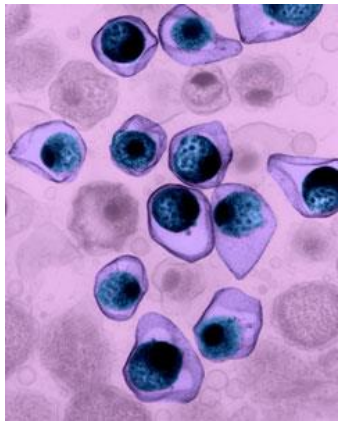
WHAT IS MS?

MS: The Disease

- >500,000 American victims, 2.3 million world wide.
- 80% of MS Patients develop MS between 16 and 45 yrs.
- Female to Male Risk Ratio 2.4:1
- Outcomes Untreated:
  - 50% require cane or more support for ambulation within 10 years of onset.
  - 30% will become wheelchair or bed bound
  - Average Life Span Decreased by <5 years.
- Health Related Costs: $35,000/Pt/Yr
  - Total Cost to US Economy: $9.4 Billion/Yr
- MS is leading cause of disability in young women and second leading cause of disability in young men in USA.

Potential Triggers for Multiple Sclerosis



Abnormal immunologic response → **MS**

Gilden DH. *Lancet Neurol*. 2005;4:195-202; Noseworthy JH, et al. *N Engl J Med*. 2000;343:938-952.

DIET AND MS

- Women with MS have lower levels of folate, magnesium, vitamin E, and other nutrients that may have important anti-inflammatory properties (AAN 2015)
- Adherence to the Mediterranean diet (MeDi) may prevent brain atrophy in old age (AAN 2015)
- Diet is sufficient to promote a significant improvement of those body regions were adipose tissue shows active pro-inflammatory properties (AAN 2015)
- Diet can reduce the burden of fatigue on the activities of daily living and in the self-care management of RRMS patients (AAN 2015)

Estimating Risk of MS

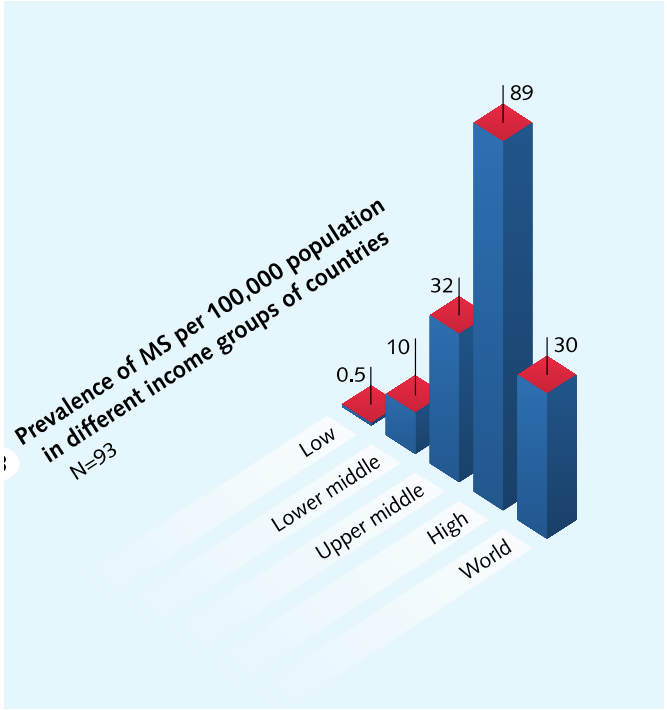
- Among white non-Hispanic individuals the lifetime risk of MS is about 1 in 400
- The risk tends to be lower in Hispanic, black and Asian populations. However Hispanics have higher risk of spinal cord disease (AAN 2015)
- The concordance rate of MS is fivefold higher in monozygotic twins (25%)
- Having a sibling with MS increases the risk of the disease 20-40 fold.12 new familial related genes!!! (AAN 2015)
- There is an increased incidence of MS worldwide (AAN 2015)
- During 1992-2013 period, the incidence rate in women increased from 1/100,000 (95%CI 0.8-1.6) to 4.9/100,000 (95%CI 4.1-5.4) (AAN 2015)

Viruses and MS

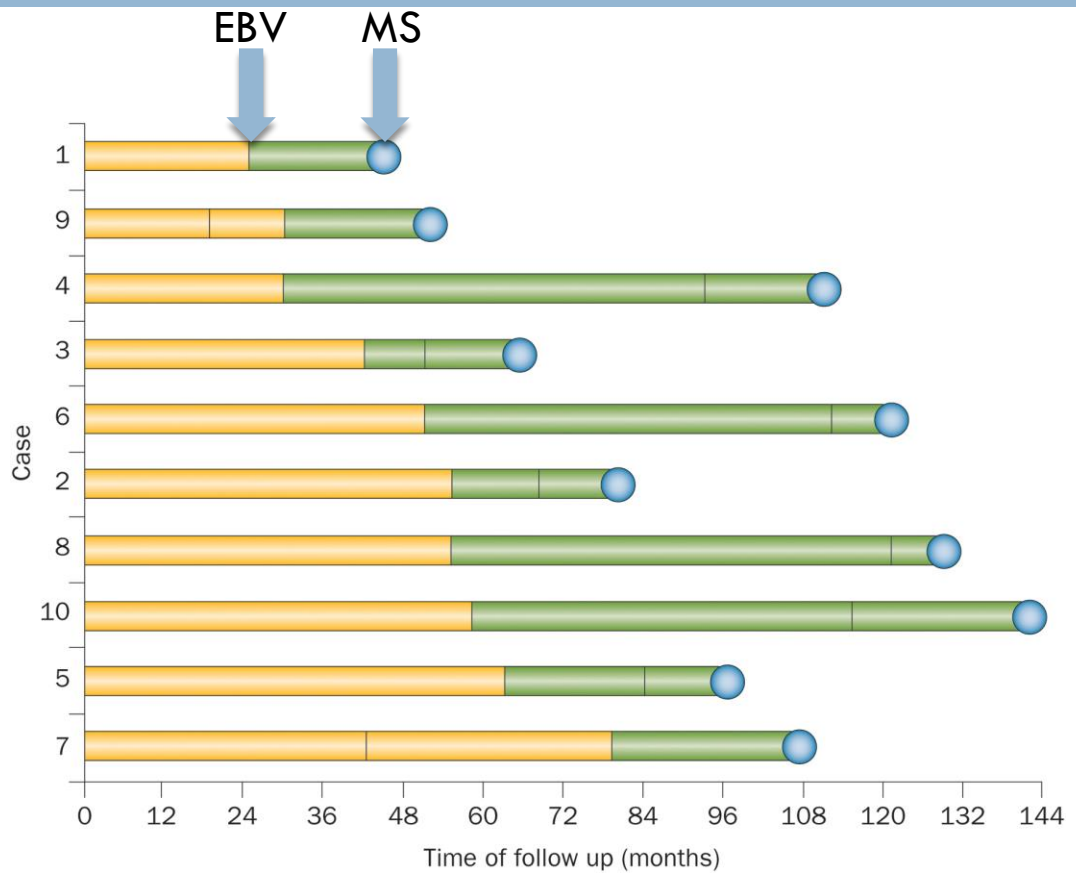
- EBV infection early in life is the rule in the tropics, in low-income populations and in Japan, whereas late EBV infection (Infectious mononucleosis) is more common in countries with higher socio-economical status.
- MS risk is 3-fold higher in

people with IM (older age at EBV factor for MS)

- EBV nuclear antigen (EBNA)

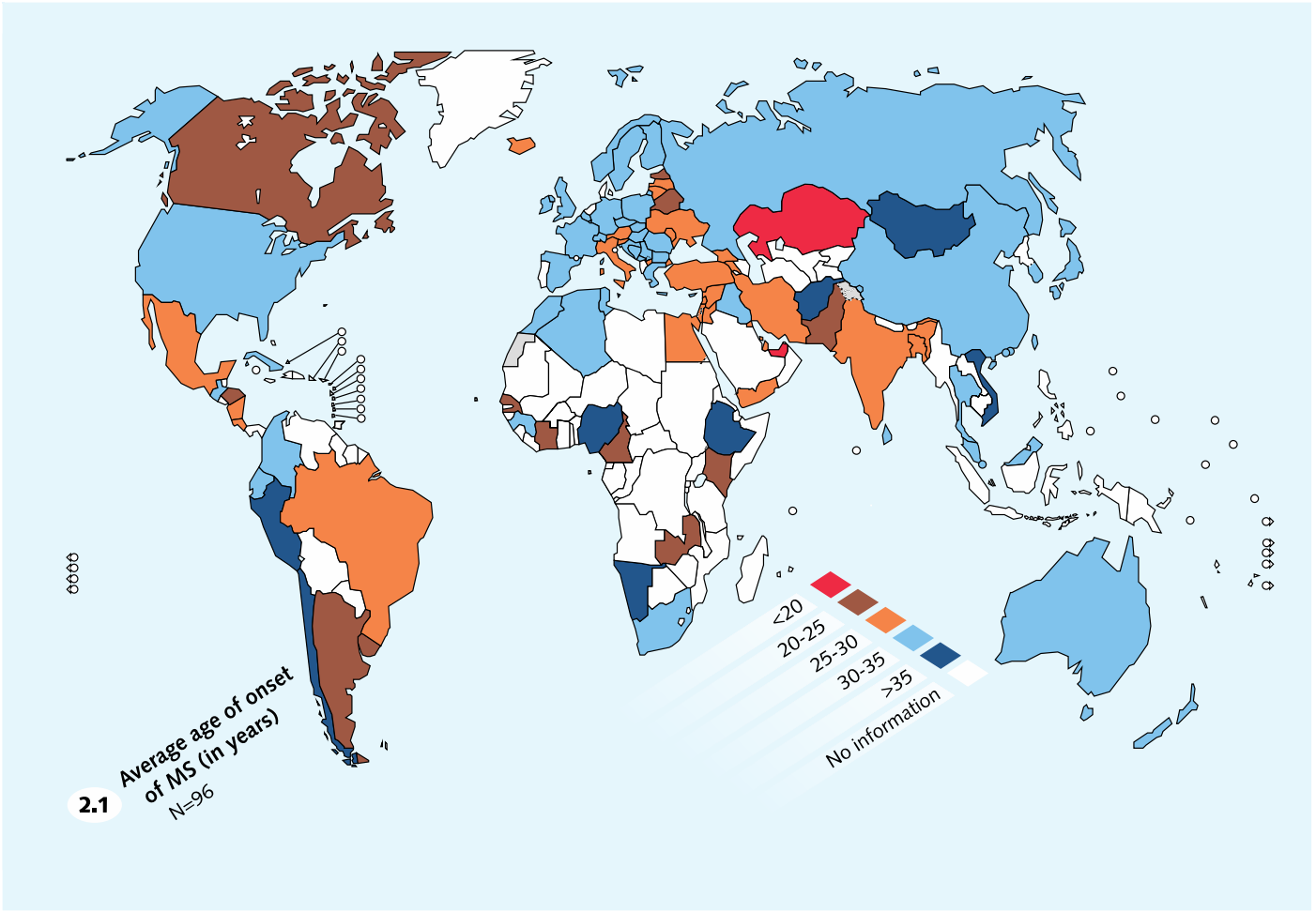


Relationship between time to EBV seroconversion and risk of MS



Ascherio, A. *et al.* (2012) The initiation and prevention of multiple sclerosis *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2012.198

Age of Onset and Geography



Parasites and MS

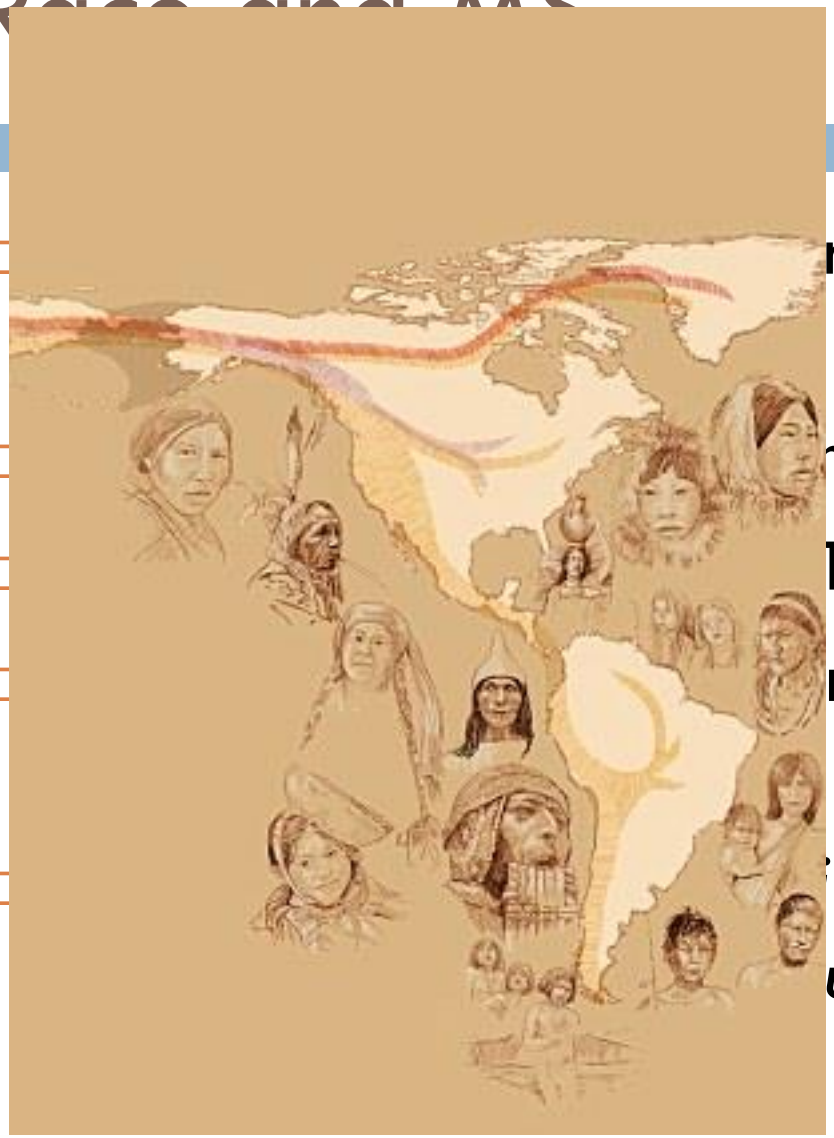
- Helminth-infected MS patients have lower disease activity compared with uninfected ones.
- Parasite regulation of host immunity is mediated, at least in part, by B reg cells producing high levels of IL-10 (AAN 2015)
- Negative association between an infection with the parasite *Toxoplasma gondii* and MS
- Toxoplasmosis infection could be considered as protective factor for the development and disease progression of MS (AAN 2015)

Genes and MS

- Over 110 MS susceptibility genes identified
- Strongest association HLA-DRB1*1501 allele
  - Present in 30% in high risk regions,
  - Increase 3-fold risk in heterozygous and 6-fold risk in homozygous individuals
- The effects of all alleles described in MS account for less than 50% estimates heritability of MS
- The contributions of genes in MS is likely driven by gene-gene interactions and HLA effect on immune-responses
- Rare variants of CYP27B1 increases the risk of MS

Beecham et al, Nature Genetics (2013) DOI: doi:10.1038/ng.2770; electronic publication 9/29/2013

Race and MS



- n, and Mestizos have the
- n Japan are Optico-Spinal
- 1 (and Not DR2)
- rn Europeans have the
- chura, S. stercholaris, H. umbricoides, T. cruzi

Jorge Correale. Helminth/Parasite Treatment of MS. Curr Treat Options Neurol (2014) 16:296

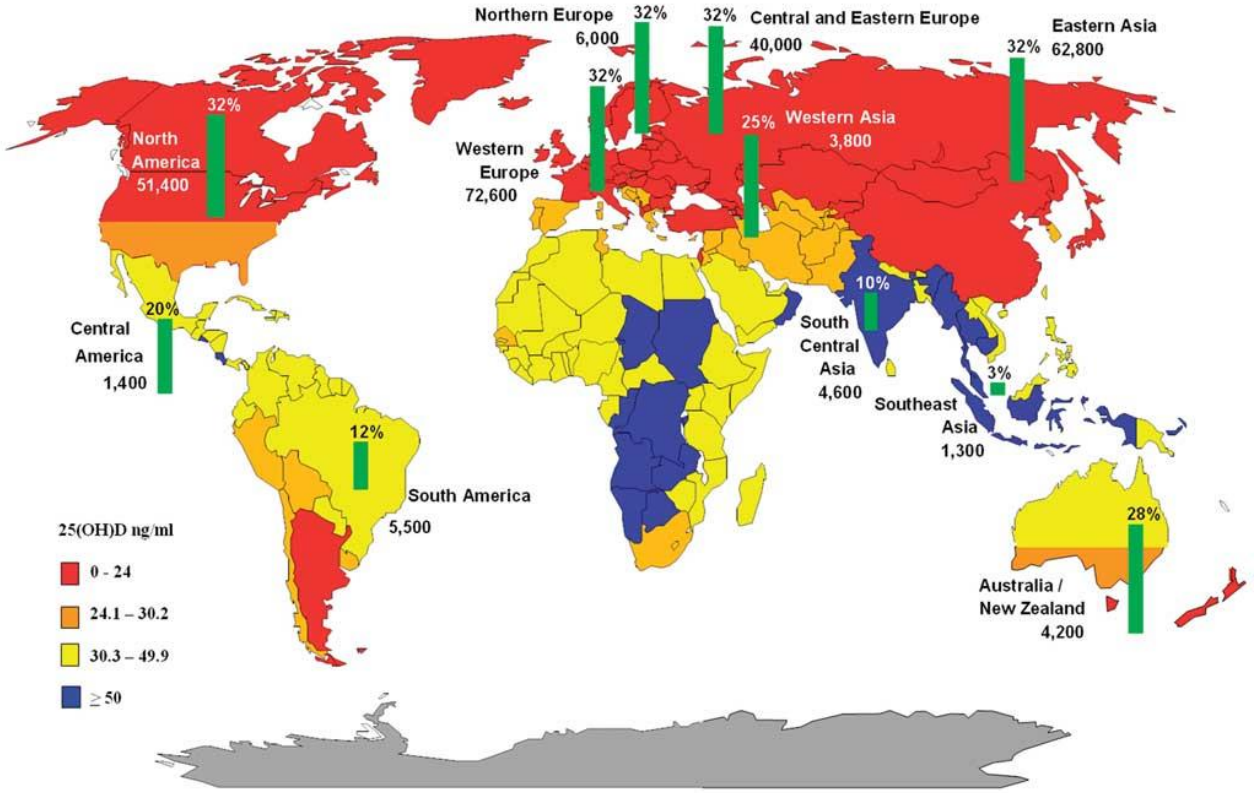
Geography and Migration

- Incidence of MS is lower between the tropics
- Incidence increase with increasing latitude in both hemispheres (Latitude gradient)
- A change in MS risk with migration was confirmed suggesting a 2-fold reduction in risk when moving from higher to lower latitudes
- Globally, the median estimated prevalence of MS is 30 per 100 000 (with a range of 0.1–140)
- Regionally, the median estimated prevalence of MS is greatest in US and Europe (140 per 100 000), followed by the Eastern Mediterranean (14.9), the Americas (8.3), the Western Pacific (5), South-East Asia (2.8) and Africa (0.3)

MS and Vitamin D Levels

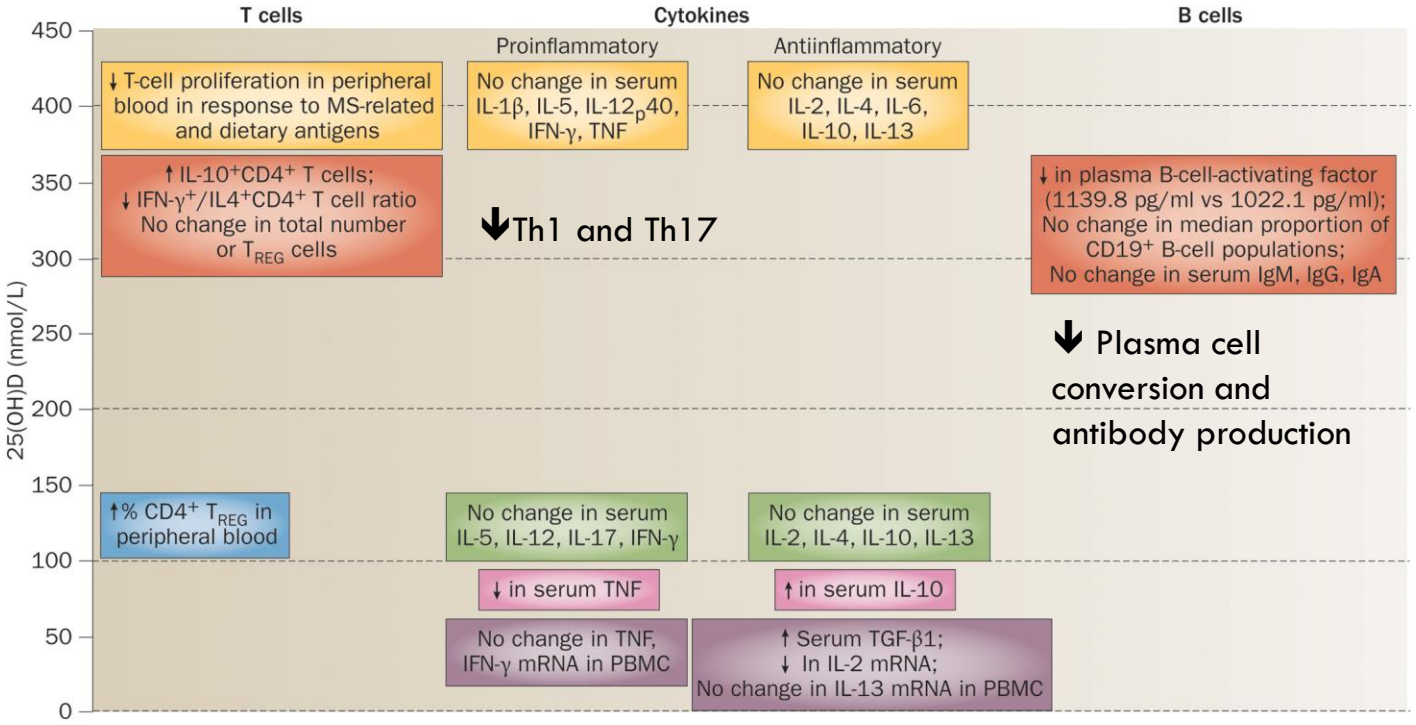
- High vitamin D associated with less severe EAE
- Low vitamin D levels, or intake, associated with higher risk of developing MS in Caucasians (AAN 2015)
- High vitamin D levels was associated with lower risk of developing MS (62%)
- Low vitamin D levels predict higher relapse rates and MRI lesion accumulation (AAN 2015)
- High level serum vitamin D in untreated MS patients is associated with expansion of ruminococcaceae in the gut. Ruminococcaceae are known to produce potent anti-inflammatory short chain fatty acid metabolites (AAN 2015)

Estimated Global Vitamin D levels



Estimated 25(OH)D serum levels (see legend) and projected percentage prevention of **colon cancer** cases (bars) with 2,000 IU/day of vitamin D_3 and 3-10 minutes daily of noon sunlight seasonally, when weather permits

Effects of vitamin D supplementation



Ascherio, A. *et al.* (2012) The initiation and prevention of multiple sclerosis *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2012.198

Salt and MS

- Salt has dramatically increased in Western diets, processed foods,
- Increased salt concentration boosts induction of CD4+ naïve >> T_H17 cells in mice and man
- Mice fed high-salt diet develop a more severe form of EAE, in line with augmented central nervous system infiltrating and peripherally induced antigen-specific T_H17 cells

Sodium chloride drives autoimmune disease by the induction of pathogenic T_H17 cells.
Kleinewietfeld et al. Nature Volume: 496, Pages: 518–522 Date published: (25 April 2013)

MS and Salt: Farez et al

ECTRIMS, Copenhagen, October, 2013

- 70 patients, RRMS
- Followed for 2 years
- Na+ intake measured in urine samples
- Clinical/MRI outcomes every 3 months
- vs a low salt intake
  - Medium salt intake had 2.75 x relapse rate
  - High salt intake (>4.8 g/day) had 3.95 x relapse rate; 3.4 x risk of developing a new MRI lesion; on average had 8 more lesions
- WHO recommends salt intake not exceed 2 g/day, but average is 4-4.8 g/day

Cigarette Smoking and MS

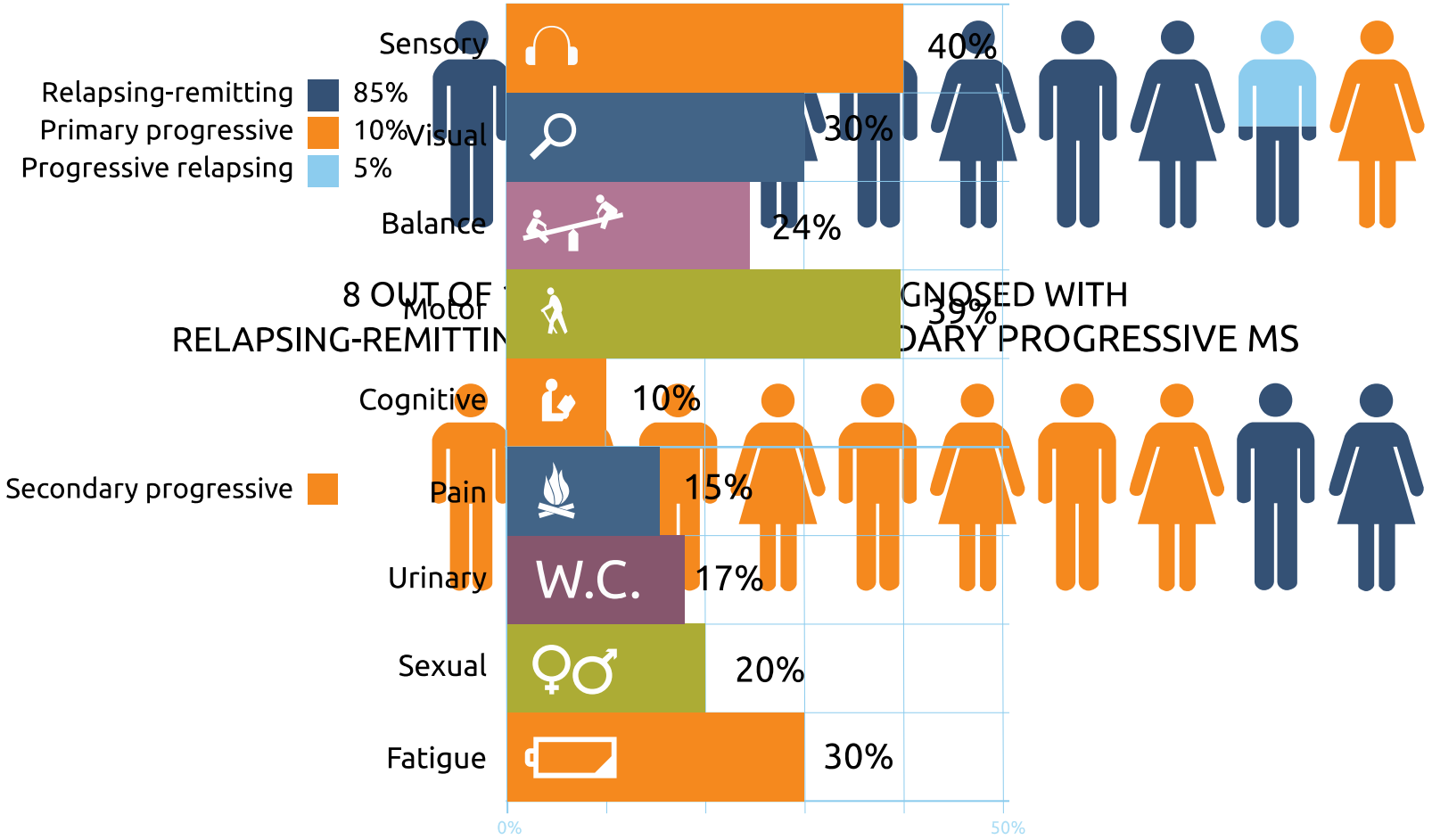
- Risk of MS in ever smokers is 50% higher
- Risk is directly associated with smoking duration and intensity
- Cigarette smoking is associate with worse clinical and MRI outcomes in MS patients
- Direct effect on demyelination, disruption of BBB, increased nitric oxide and metabolites, negative effects on remyelination and immune-modulation

Coffee and MS

- People who regularly drink at least four cups of coffee daily were one third less likely to develop MS than their peers who did not drink coffee
- The authors took other factors into consideration, such as smoking, vitamin D levels, and age (AAN 2015)

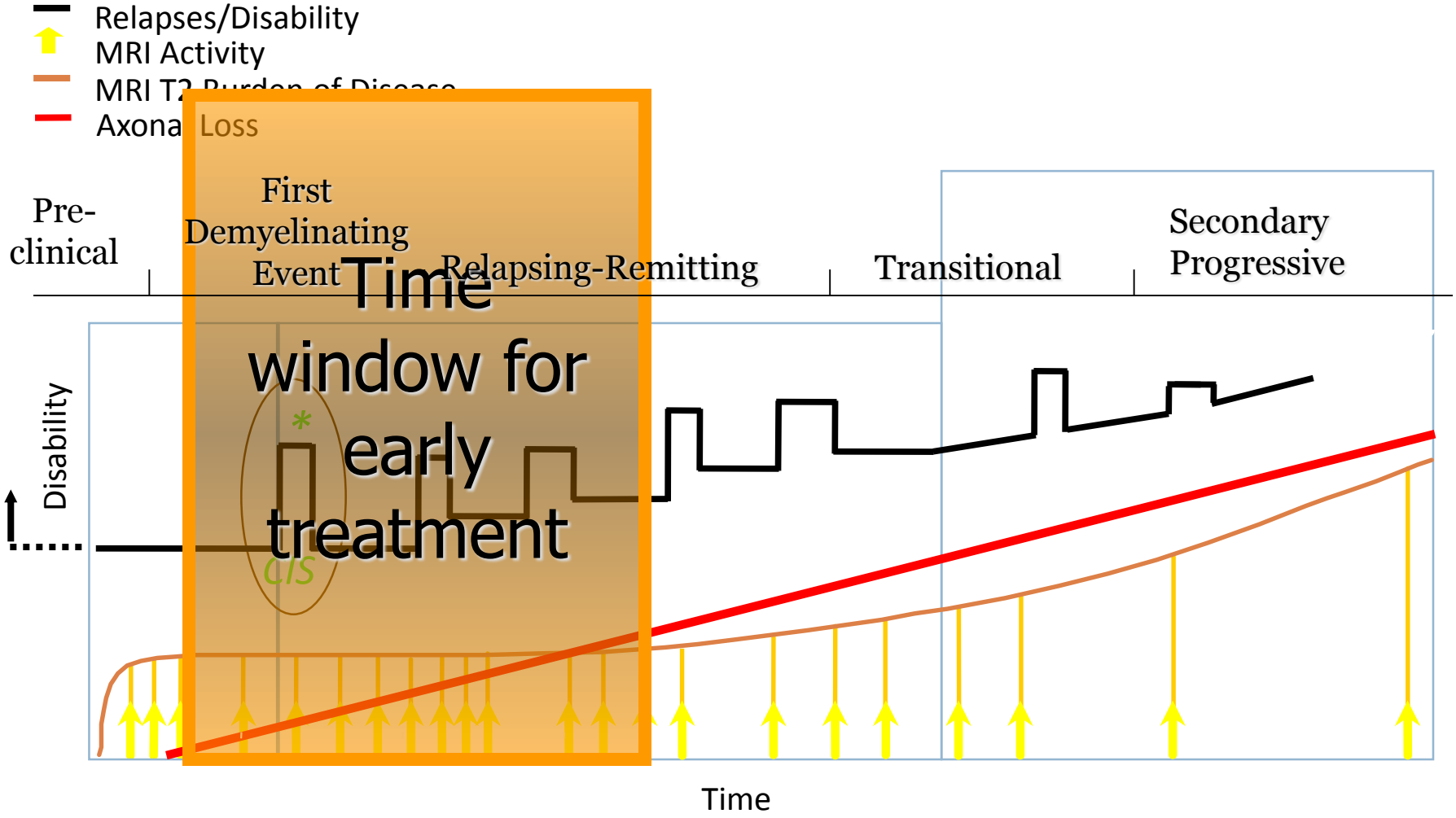
WHAT IS THE CLINICAL COURSE OF MS?

Natural History of MS
MS type distribution



Natural History of MS

Clinical and MRI Measures



Reprinted from Trapp BD, et al. *Neuroscientist.* 1999;5:48-57, with permission from Sage Publications.

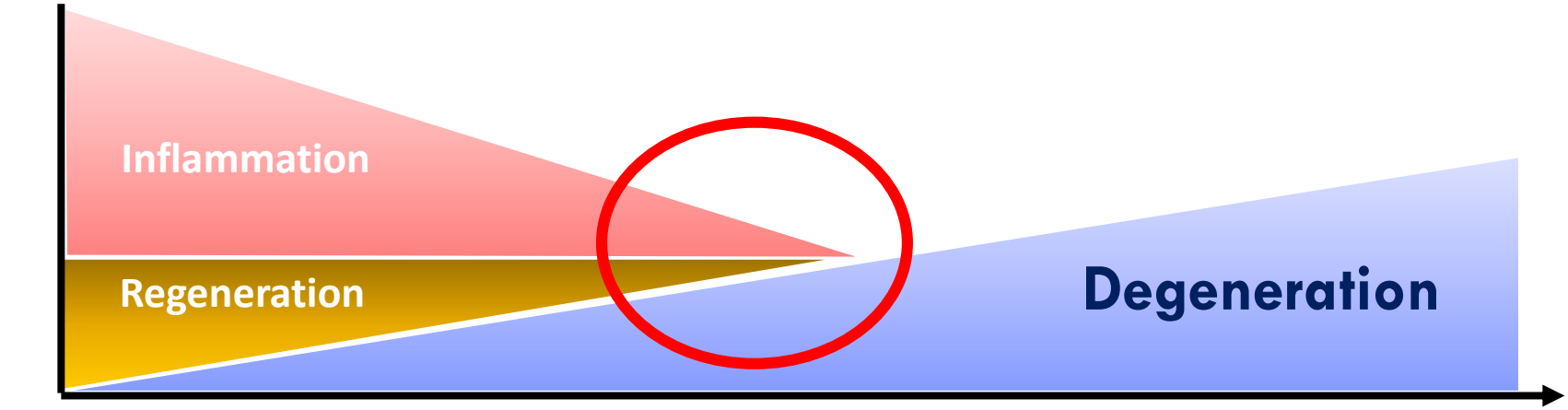
Diagnostic Criteria for MS: Application of MRI

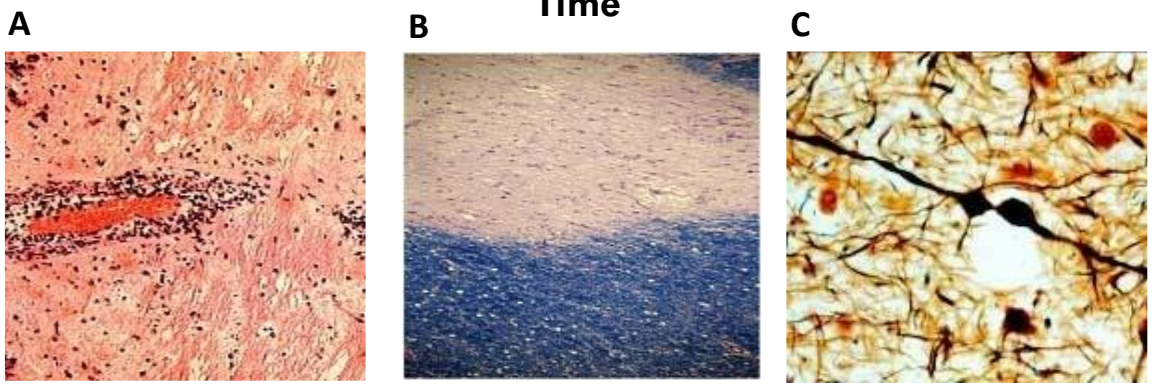
	McDonald 2001	McDonald 2005	MAGNIMS 2010 Proposal
Dissemination in Space (DIS; on either baseline or follow-up MRI)	**≥ 3 of:**	**≥ 3 of:**	**≥ 1 lesion in each of ≥ 2 characteristic locations**
	≥ 9 T2 lesions or ≥ 1 gadolinium-enhancing lesion	**≥ 9 T2 lesions or ≥ 1 gadolinium-enhancing lesion**	**Periventricular**
	≥ 3 periventricular lesions	**≥ 3 periventricular lesions**	**Juxtacortical**
	≥ 1 juxtacortical lesion	**≥ 1 juxtacortical lesion**	**Posterior fossa**
	≥ 1 posterior fossa lesion	**≥ 1 posterior fossa lesion**	**Spinal cord**
	1 cord lesion can replace 1 brain lesion	**Any number of lesions can be included in lesion count**	**All lesions in symptomatic regions excluded in brain stem and spinal cord syndromes**
Dissemination in Time (DIT)	**1) ≥ 1 gadolinium-enhancing lesion ≥ 3 months after CIS onset (if not related to CIS)**	**1) ≥ 1 gadolinium-enhancing lesion ≥ 3 months after CIS onset (if not related to CIS)**	**1) Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions *at any time***
	2) A new T2 lesion with reference to a prior scan obtained ≥ 3 months after CIS	**2) A new T2 lesion with reference to a prior scan obtained ≥ 30 days after CIS**	**2) A new T2 and/or gadolinium-enhancing lesion on follow-up MRI *irrespective of timing of baseline scan***

McDonald WI, et al. *Ann Neurol.* 2001;50:121–127.
Polman CH, et al. *Ann Neurol.* 2005;58:840–846.
Montalban X, et al. *Neurology*. 2010;74:427–434.

Immunopathogenesis of MS

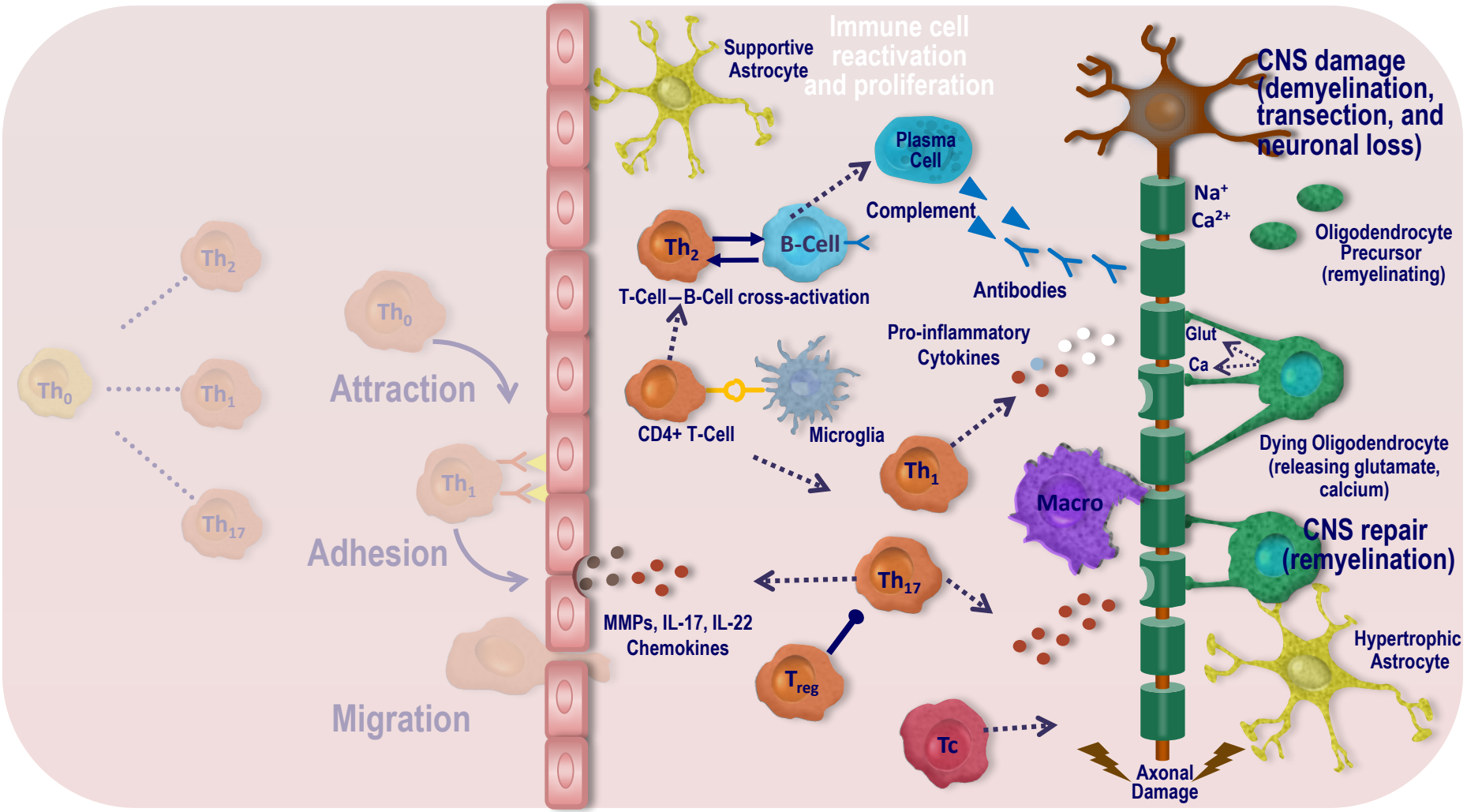
Inflammatory processes occurring <u>early</u> in MS lead to demyelination and axonal loss



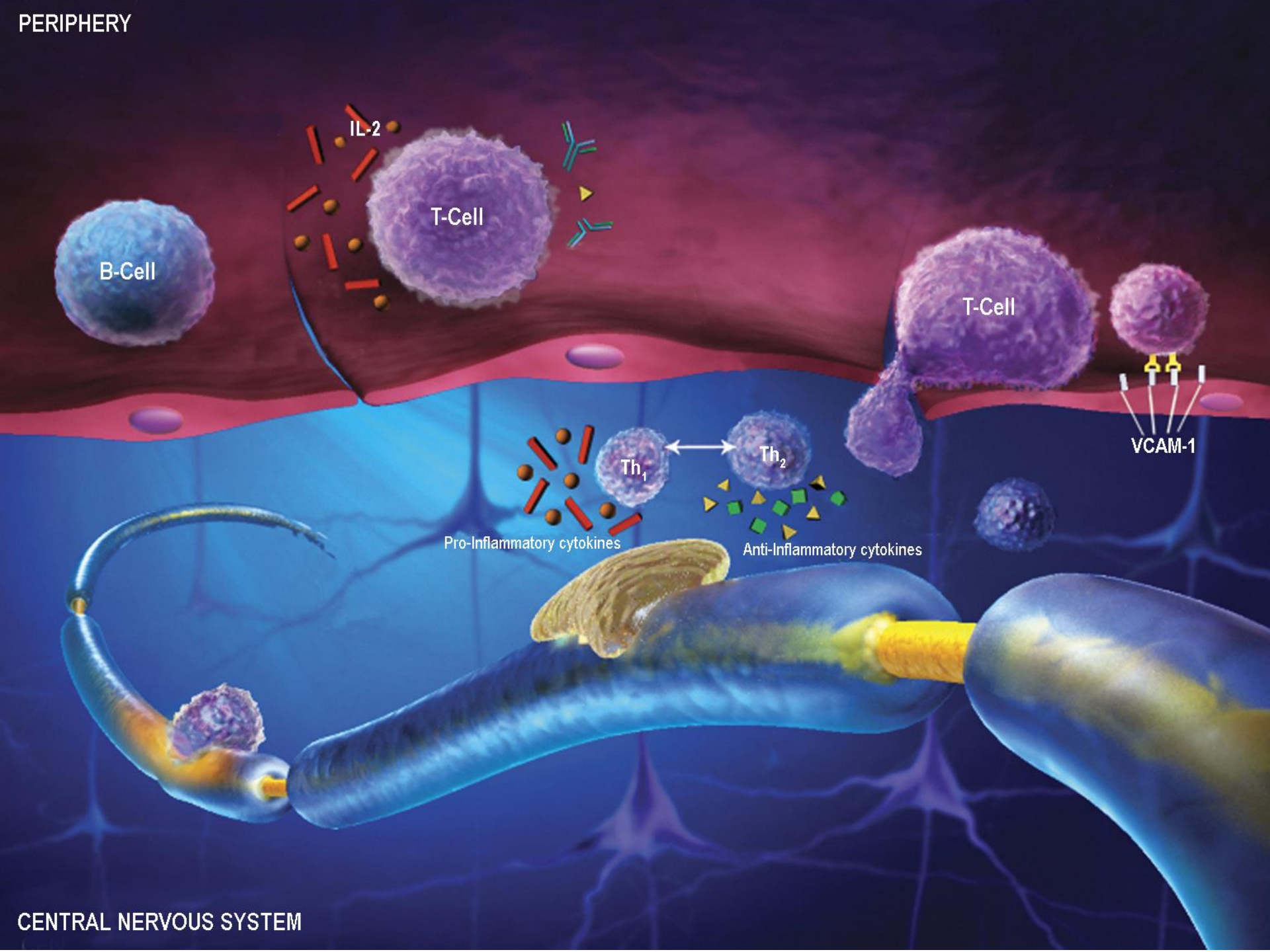


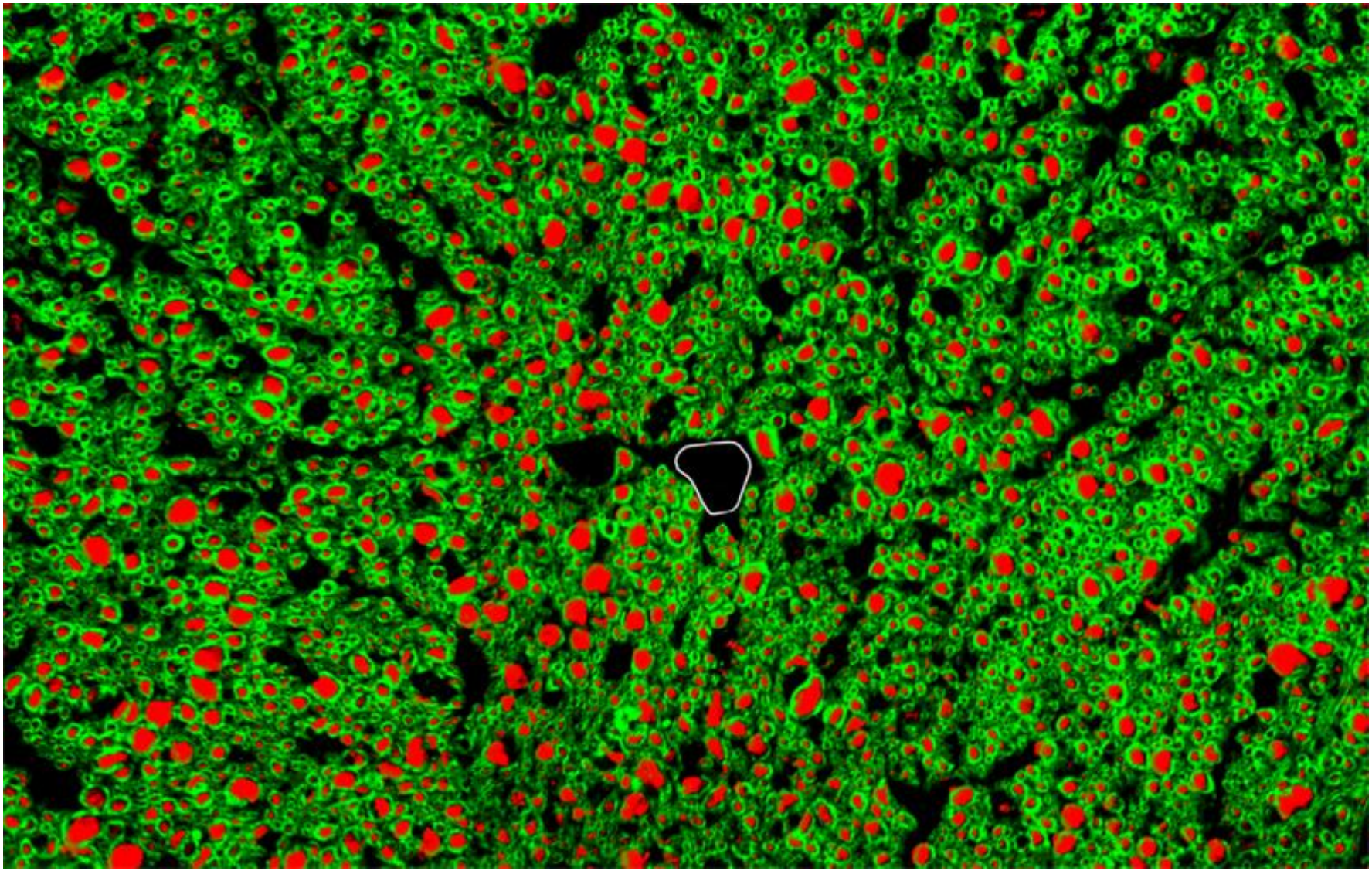
Kuhlmann T, et al. *Brain*. 2002;125:2202-2212; Paolilo A, et al. *J Neurol*. 2004;251:432-439.

Proposed Immunopathogenesis of MS

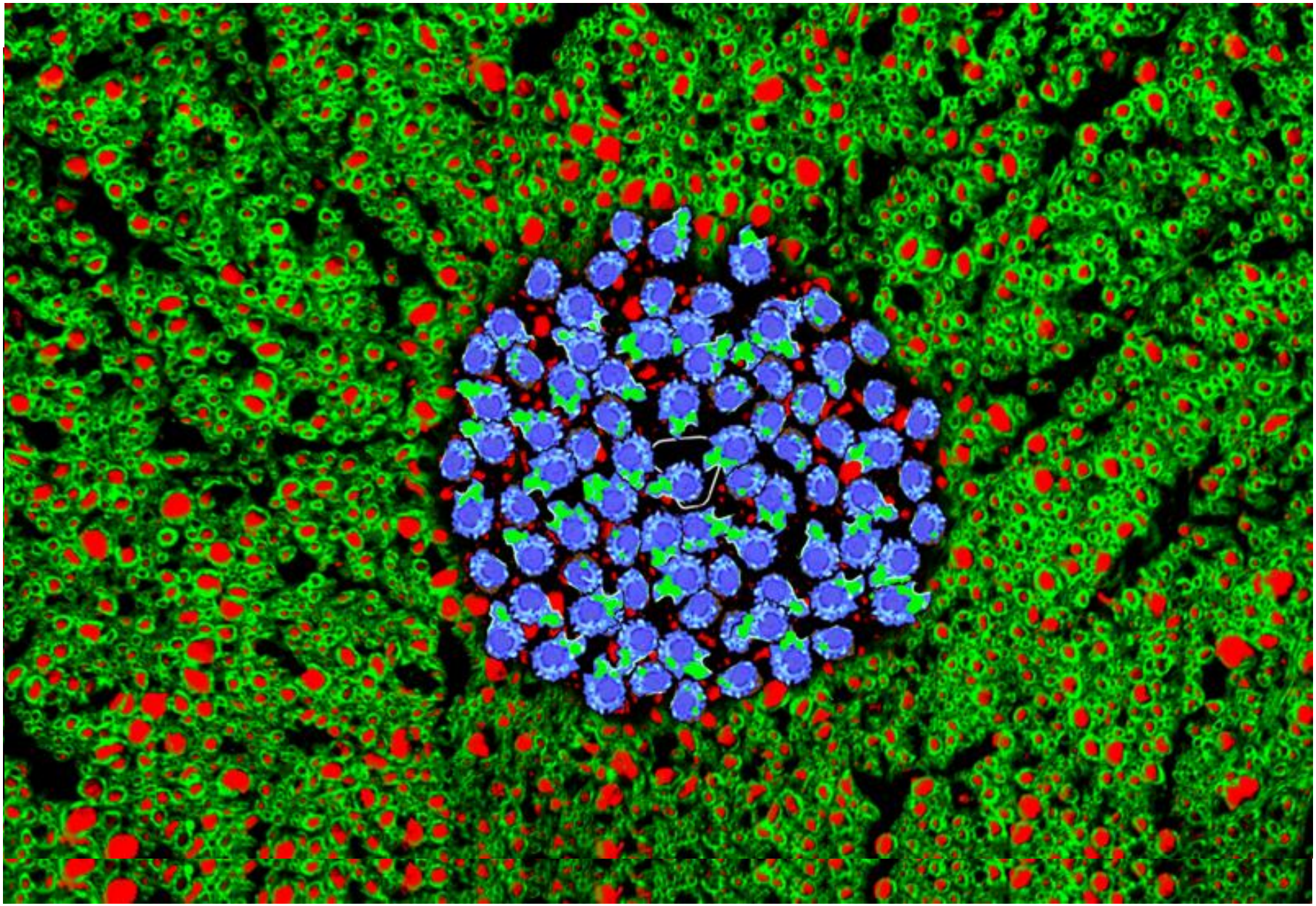


Adapted from Wiendl H, et al. *Expert Opin Investig Drugs*. 2003;12:689-712; Yong VW. *Neurology.* 2002;59:802-808; Frohman EM, et al. *N Engl J Med*. 2006;345:942-955; Lopez-Diego RS, et al. *Nat Rev Drug Discov.* 2008;7:909-925.


PERIPHERY
IL-2
T-Cell
B-Cell
T-Cell
VCAM-1
Th1
Th2
Pro-Inflammatory cytokines
Anti-Inflammatory cytokines
CENTRAL NERVOUS SYSTEM



Courtesy of Dr. Bruce Trapp, Cleveland Clinic



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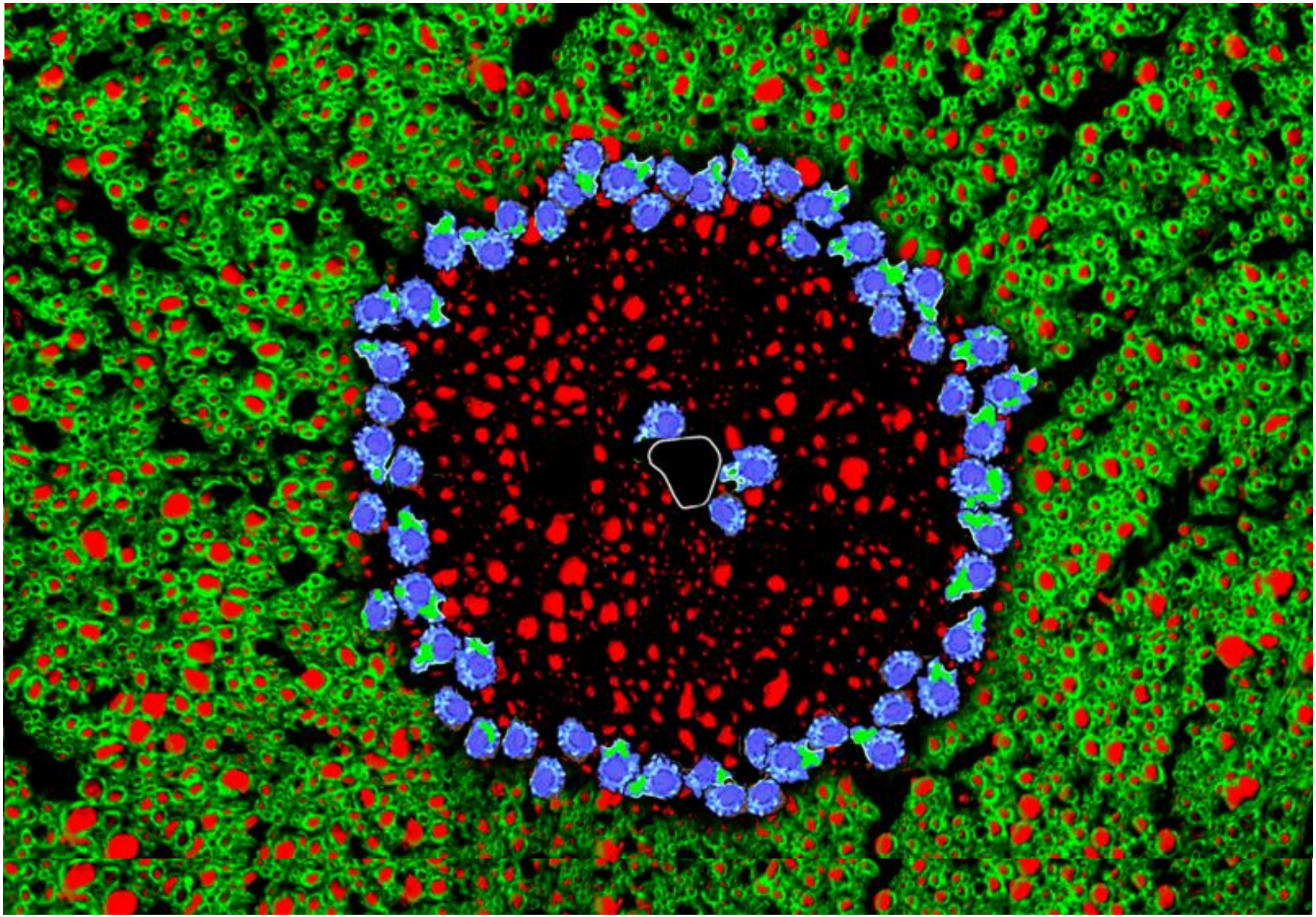
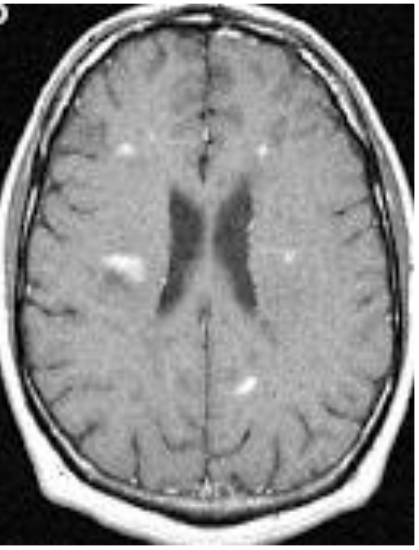


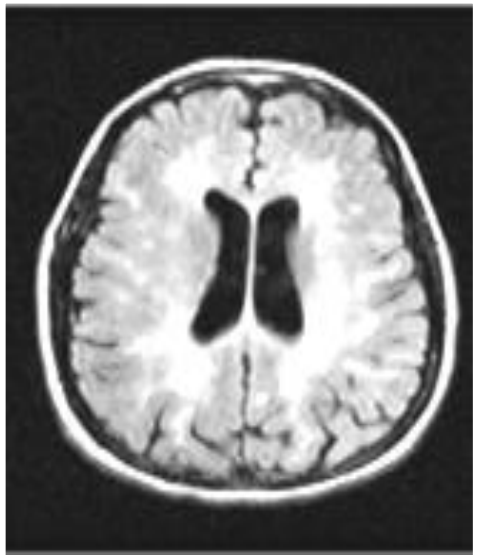
Courtesy of Dr. Bruce Trapp, Cleveland Clinic

Brain lesions over time

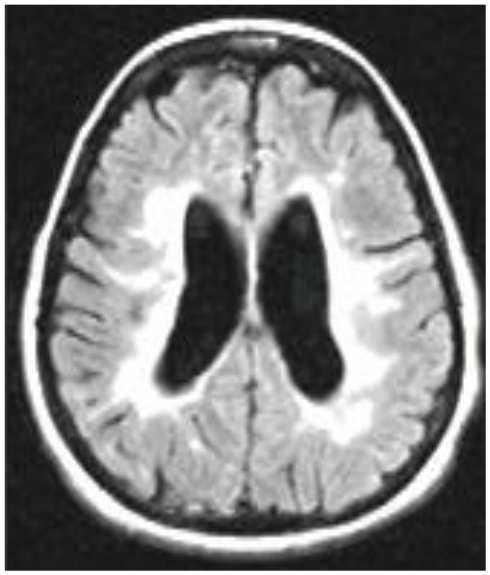
CIS

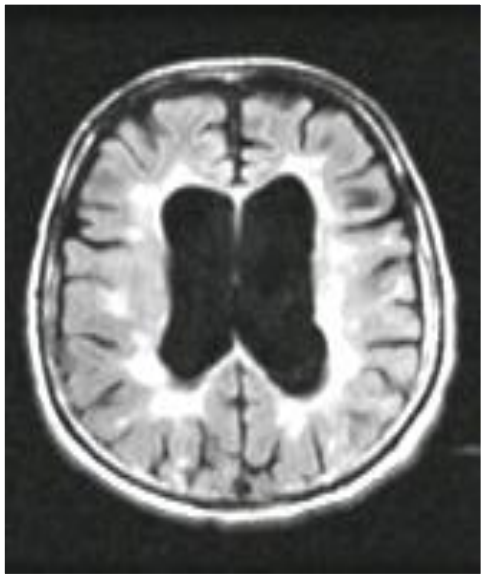


RRMS



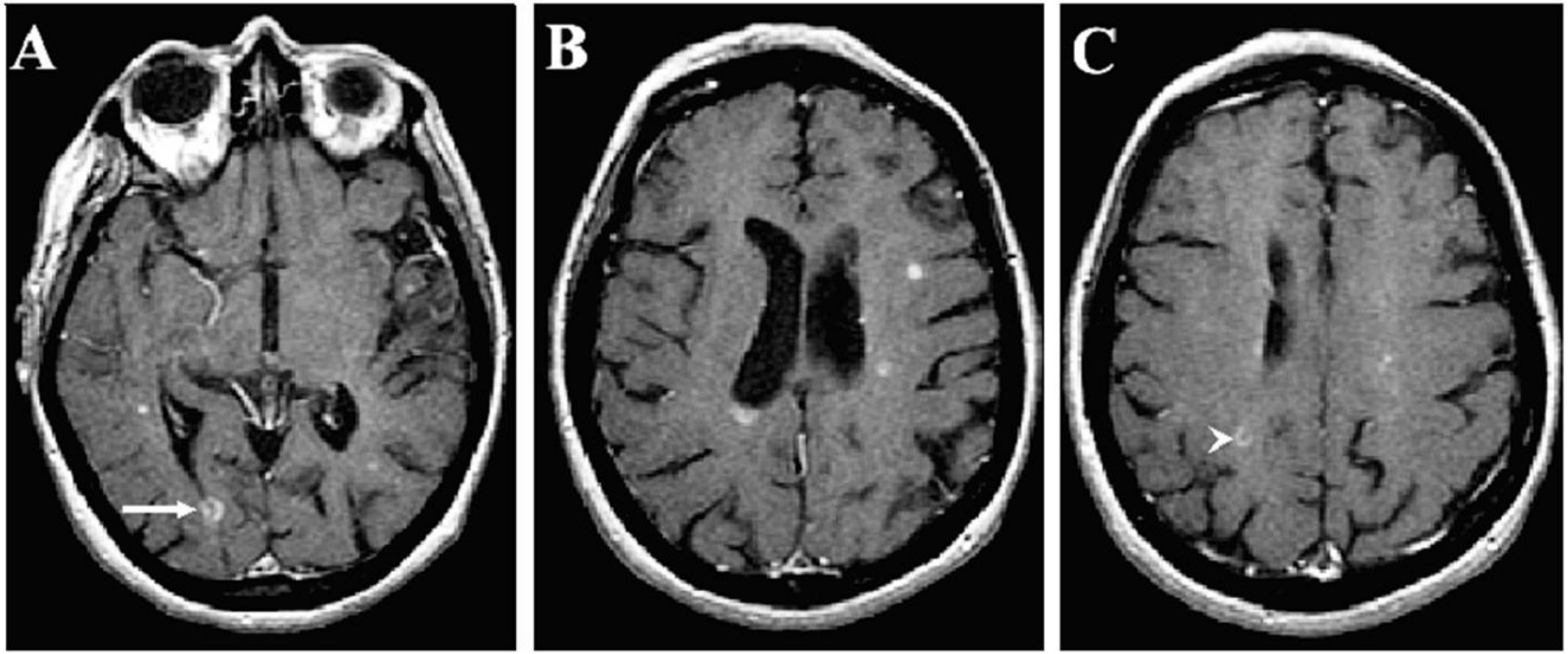
SPMS





Gadolinium enhancement

The Open Ring Sign



Active BBB disruption

Passage of inflammatory cells in to the CNS

5–10x more frequent than relapses

Predictive of relapses, but lessens in SPMS

Window 2-8 wk; mean 3 wk

Cortical lesions

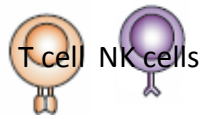
8T MRI

Kottil Rommohan et al.

WHAT ARE THE AVAILABLE THERAPIES IN MS?

Elevated CD56Bright

Daclizumab



CD 25

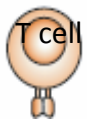
Non-specific immune modulation

Dimethylfumarate

Glatiramer Acetate

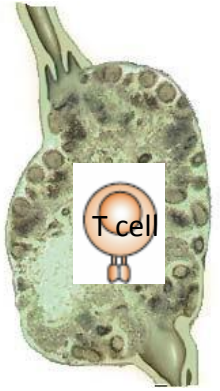
Interferons

Laquinimod



+ IL4, NT3, BDNF

- CD8, CD14 and NK cells



Immune sequestration

Fingolimod

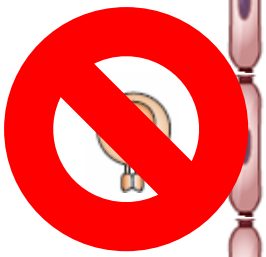
Lymphocyte targeted therapies

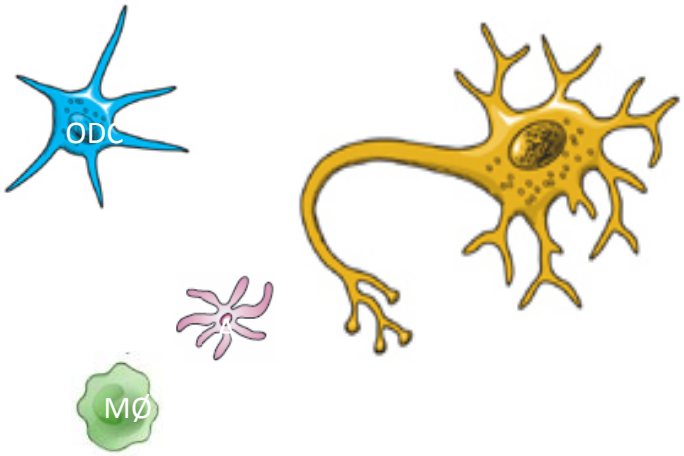
Cell proliferation

Teriflunomide

Leukocyte migration

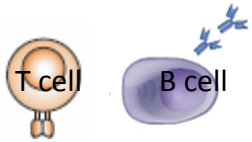
Natalizumab





Antibody dependent cell lysis

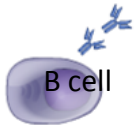
Alemtuzumab



CD 52

Rituximab

Ocrelizumab



CD 20

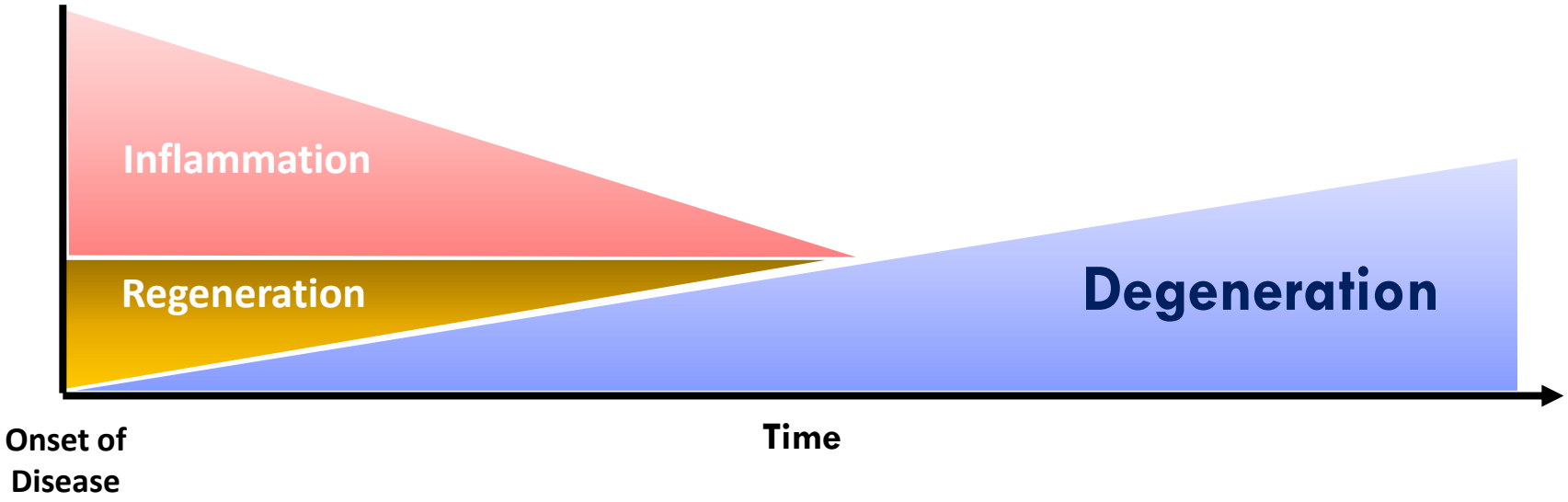
BBB

ODC: Oligodendrocytes; A: Astrocytes; MØ: Macrophages

Various definitions of suboptimal response to therapies used in clinical trials

Definition of suboptimal response	References
Two or more relapses in 24 months, Sustained disability (>1 EDSS) in 24 months	Lus R, et al. Azathioprine nd interferon beta 1° in RRMS patients. Eur Neurol 2004;51:15-20
One or more relapses in 18 months, Sustained disability (>1 EDSS) in 18 months	Bielekova et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in MS...Proc Natl Acad sci USA 2004;101:8705-08
One or more relapses in the last year, More than 1 Gd+ lesions in the last year	Coehn et al. Avonex combination trial in MS. Mult scler 2008;14:370-82
One or more relapses per year on treatment, Continued MRI activity Sustained disability (>1 EDSS) in 6 months	Carra et al. Therapeutic outcomes 3 years after switching of immunomodulatory therapies in RRMS in Argentina. Eut J Neurol 2008

Goal for Treatment of MS



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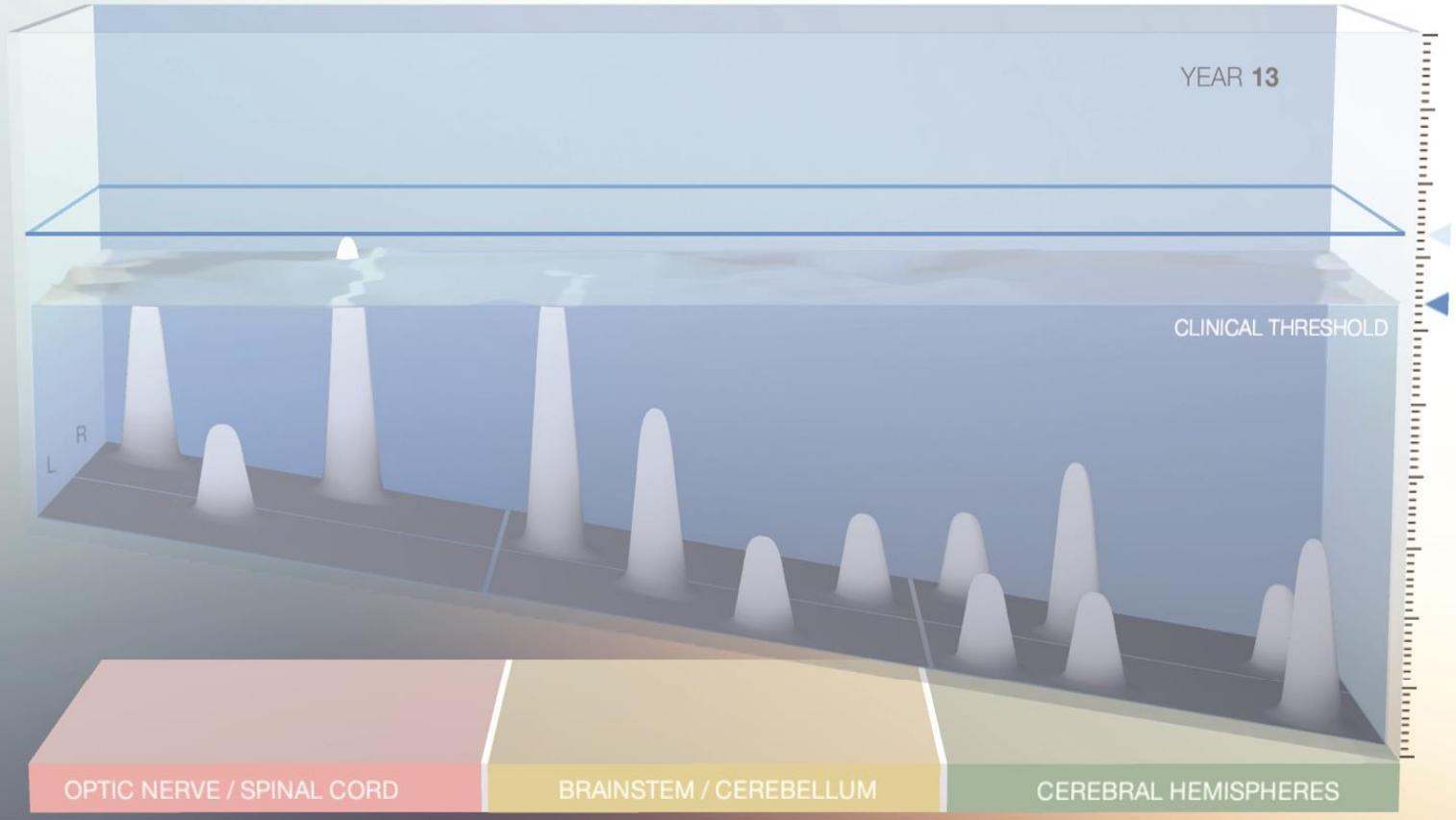
RELAPSING MS: CLASSIC PHENOTYPE



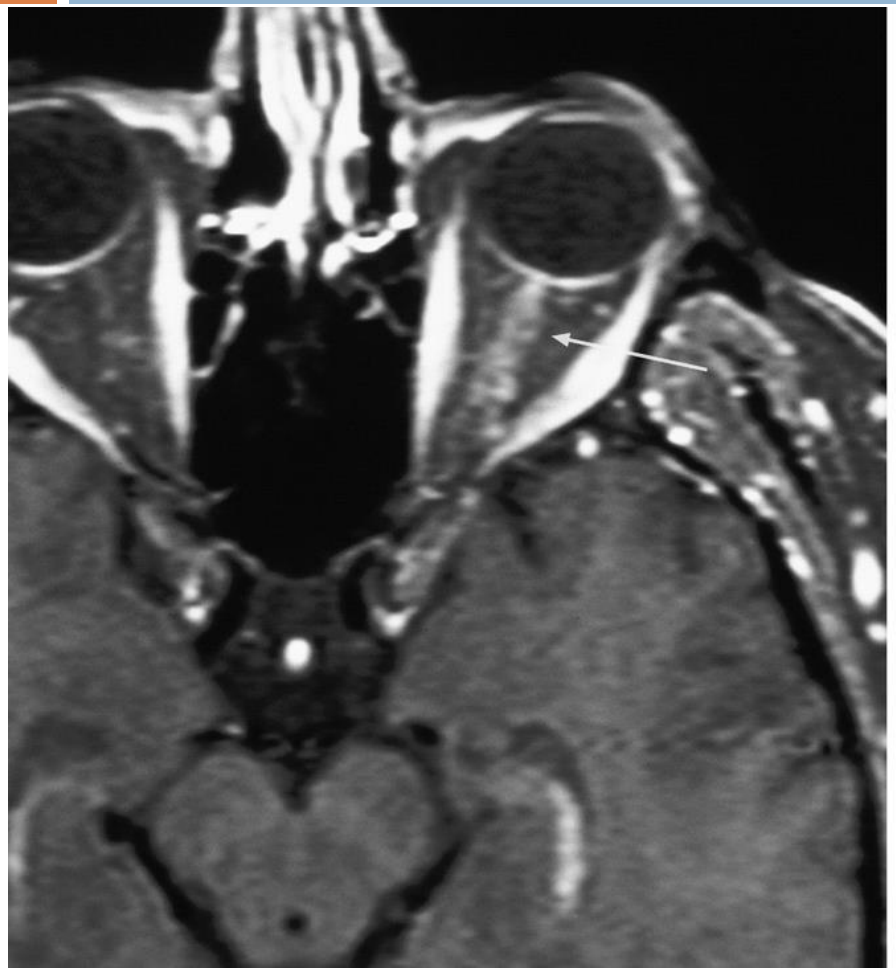
The second clinical relapse defines **clinically definite MS**—in this example, a brainstem attack. Additional lesions denote ongoing disease activity, ie, "floor effects."

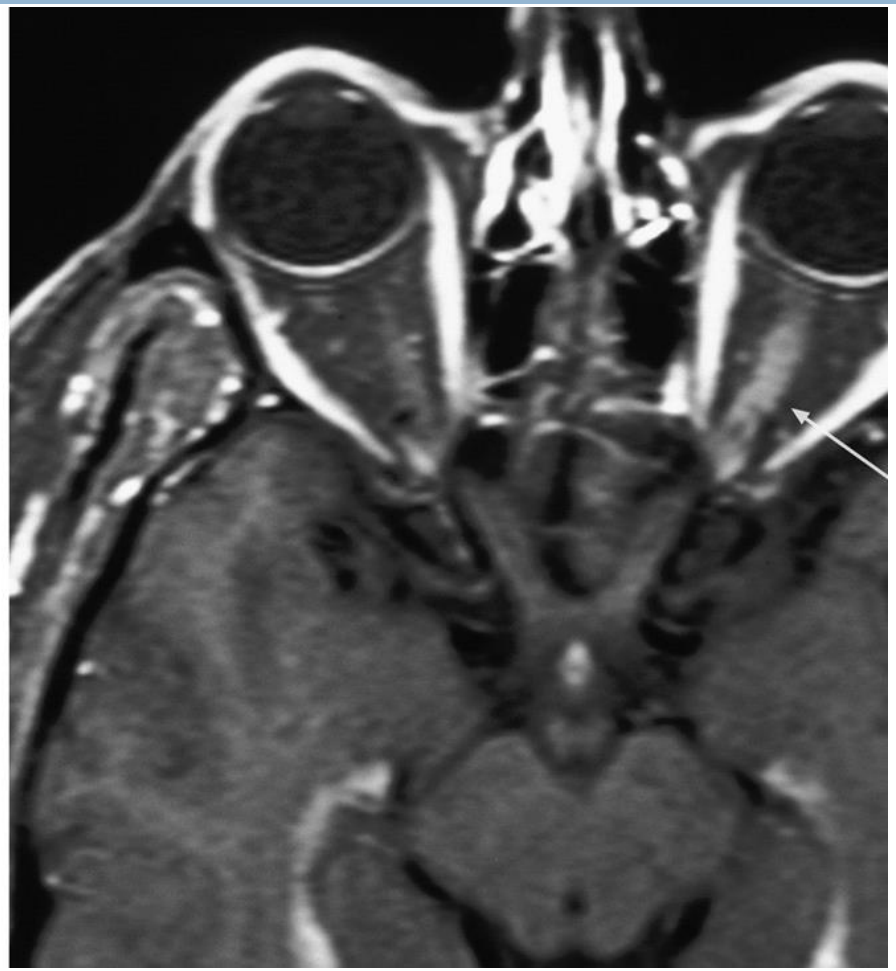
EDITOR

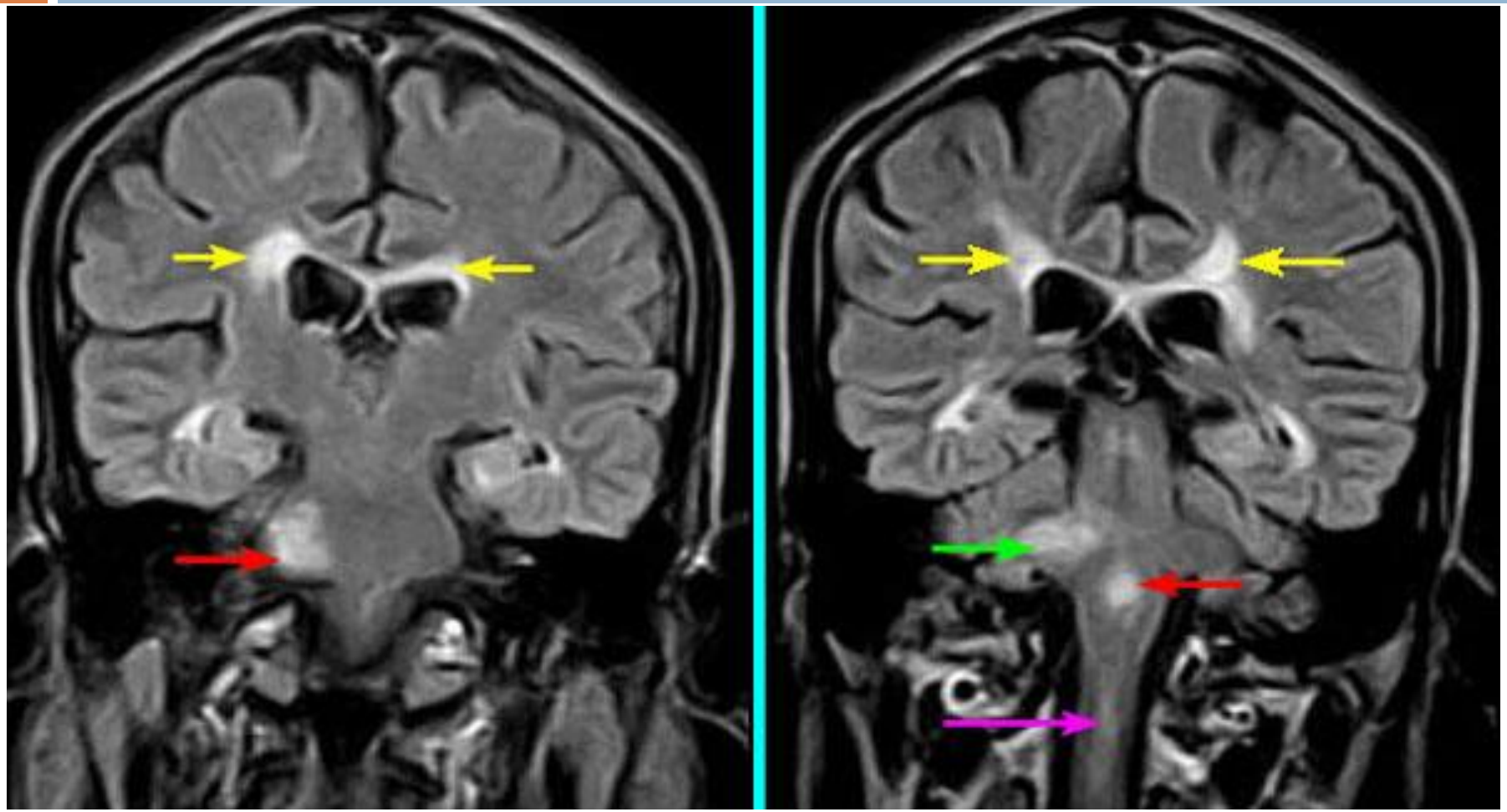
01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20

Case 1

- A 32 yo woman presents with blurry vision and pain with eye movement on the left eye for the last 2 weeks. On examination patient has decreased VA on the left.
- MRI brain demonstrates multiple T2 and FLAIR lesions located in the PV spaces and brainstem along with enhancement on the left optic nerve
- Spinal fluid analysis suggest the presence of inflammatory markers with elevated IgG index and 6 oligoclonal bands







Take Home Message

- MS is a chronic disease with different clinical presentation and levels of disability
- The immune system plays an important role in perpetuating the disease
- MRI is a Clinical Biomarker that can help us understand response to treatment as well as disease type
- "Individualized therapies" is the best approach to treating the disease