SCLEROSE EN PLAQUES

Dominique DIVE
Neuroimmunologie
CHU – LIEGE

General Introduction

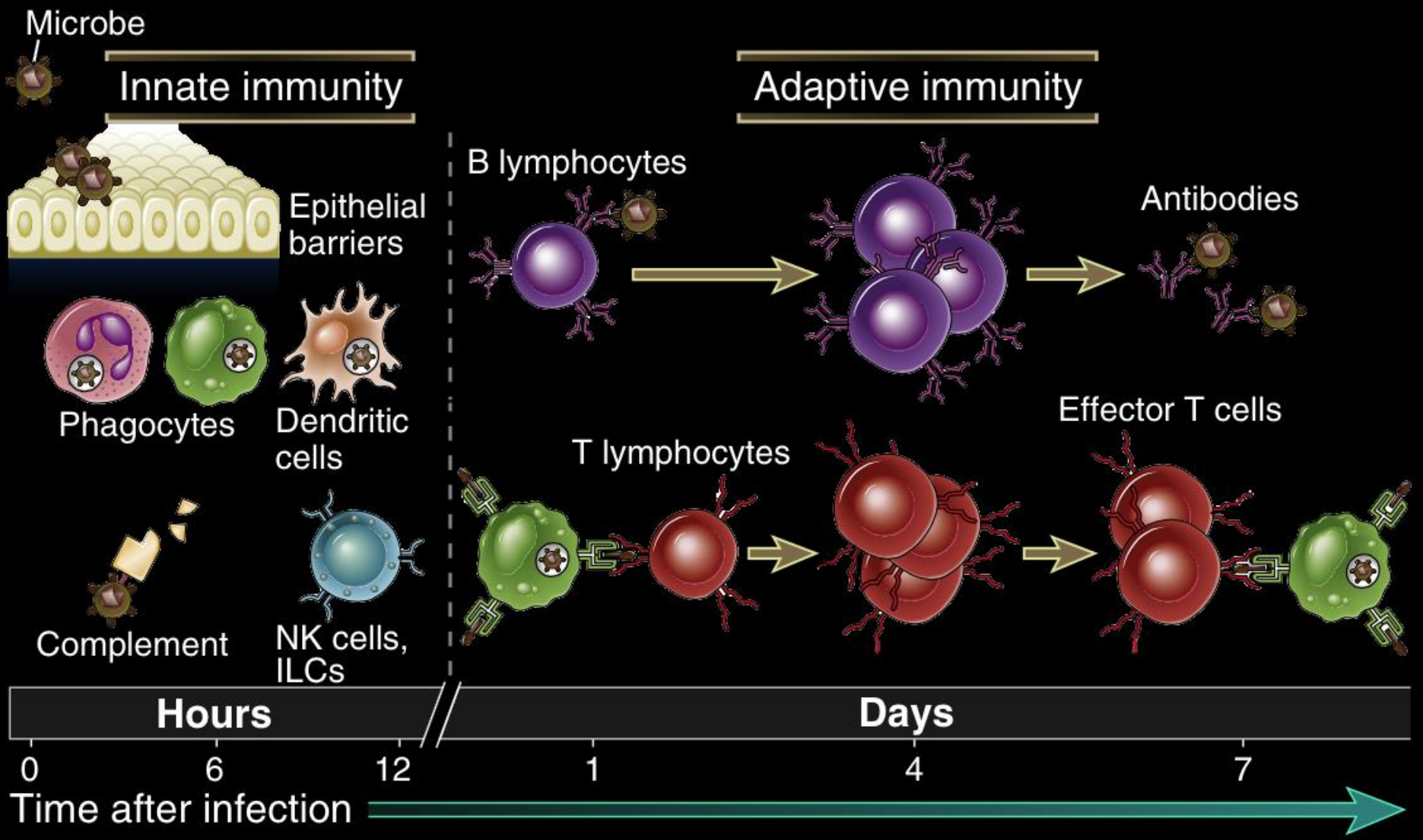
- MS is a CNS disease characterized by
  - multicentric inflammation
  - destruction of myelin
  - multifocal remyelination and gliosis
- MS is a white and grey matter disease

The name « Multiple Sclerosis » (Charcot, 1868)

Epidemiology – gene and environment

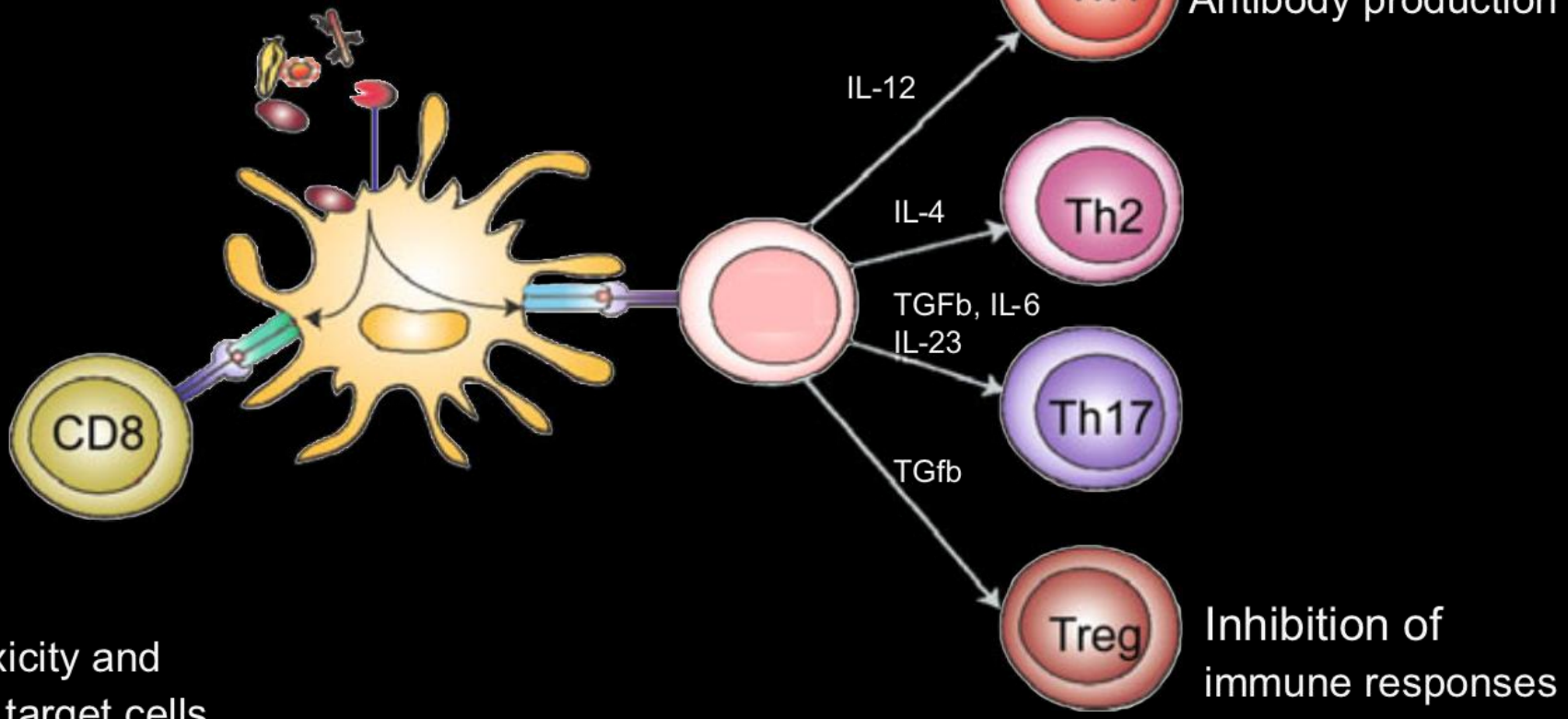
- An interval of several years exists between exposure of individuals at risk and the development of clinical symptoms.
- Environmental event(s) occur in childhood and onset is in young adult.
- Exposure may be delayed and the latency prior to development of clinical manifestations can be short or long.
- Wide spectrum both in the age at which susceptibility converts to disease and in the year of onset.

Innate and Adaptive Immunity



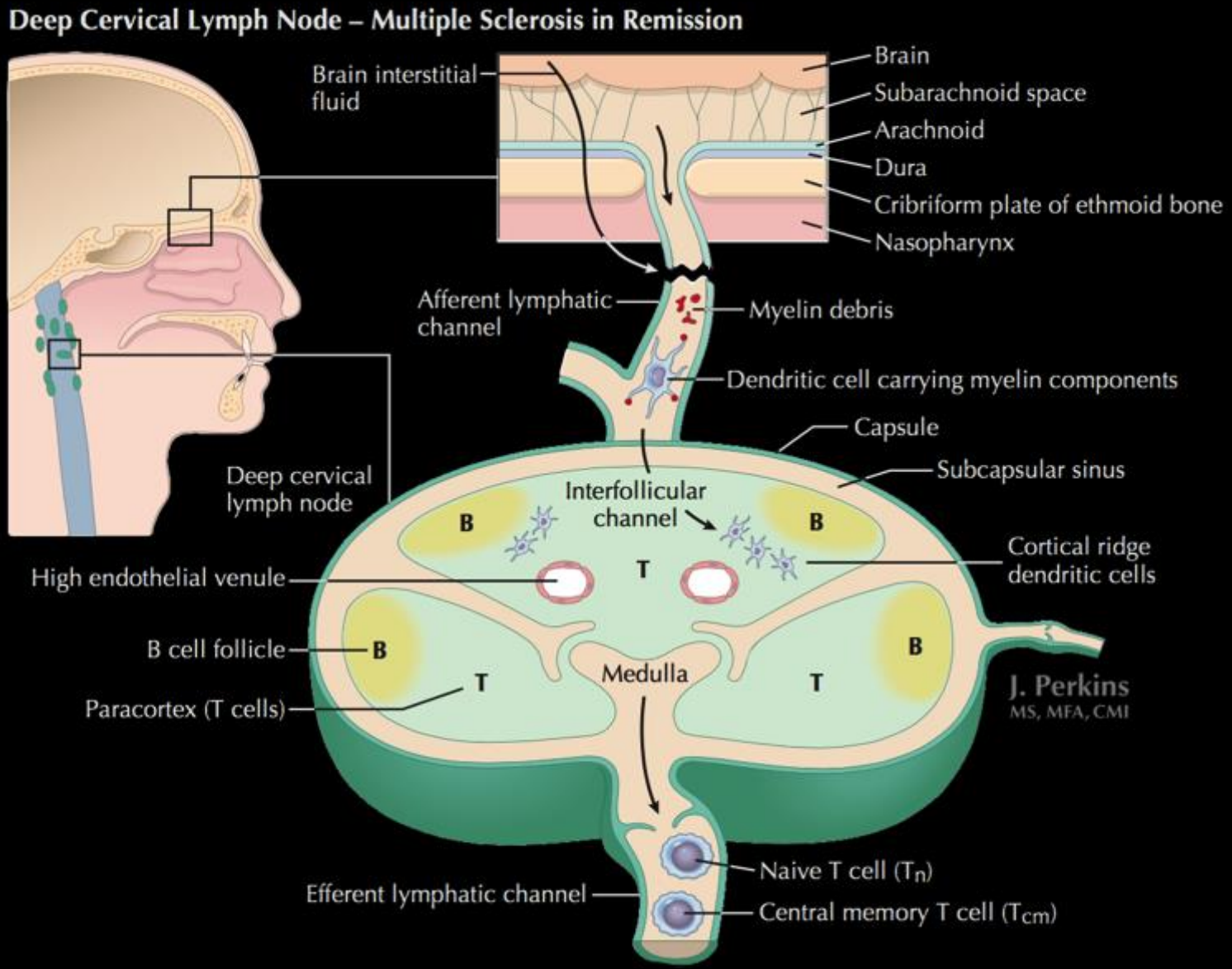
Abbas et al., CELLULAR AND MOLECULAR IMMUNOLOGY, 2015

Dendritic cells: crucial players in directing T cell responses

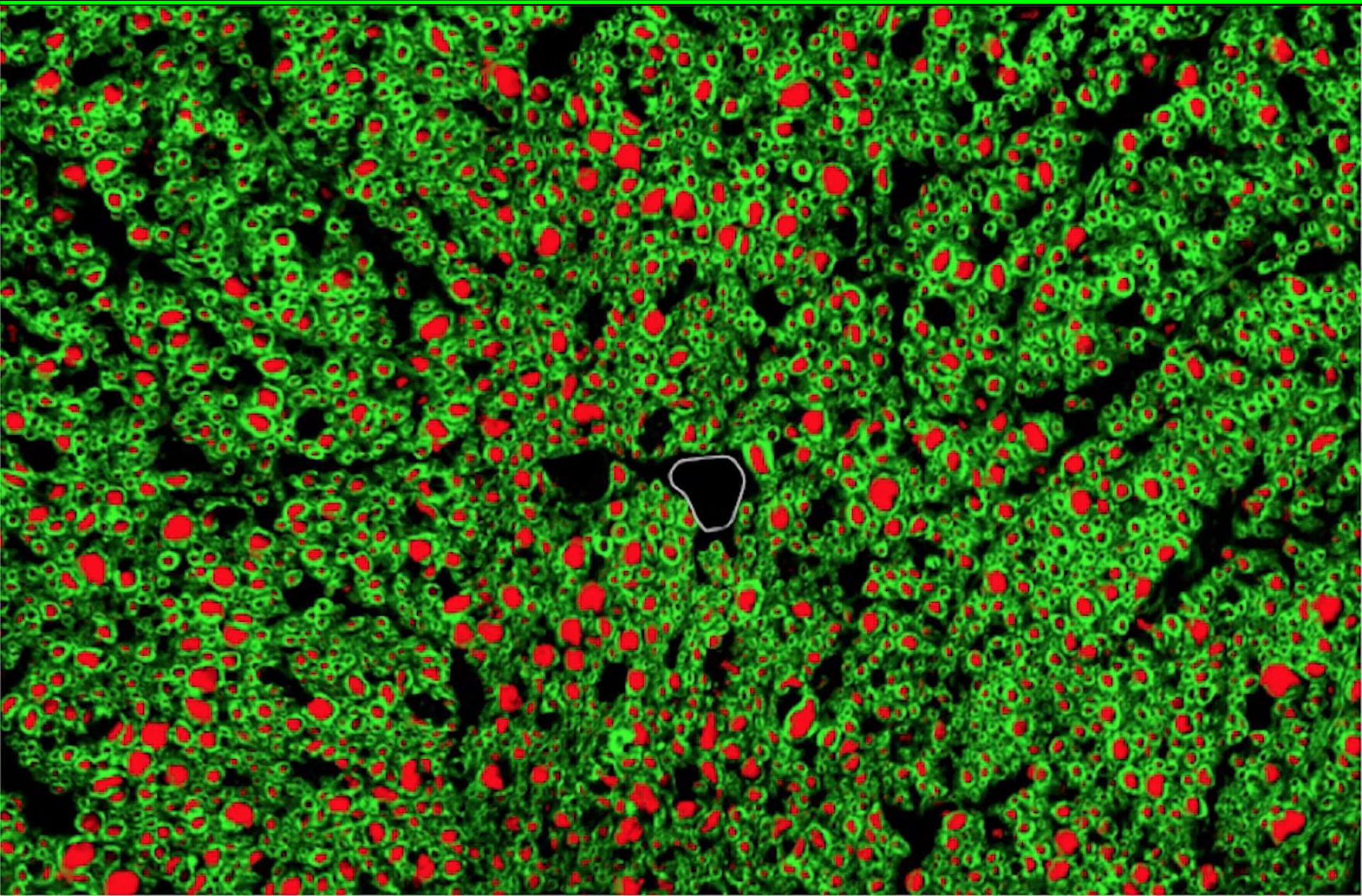


Koning N., et al., Multiple Sclerosis Immunology, 2013

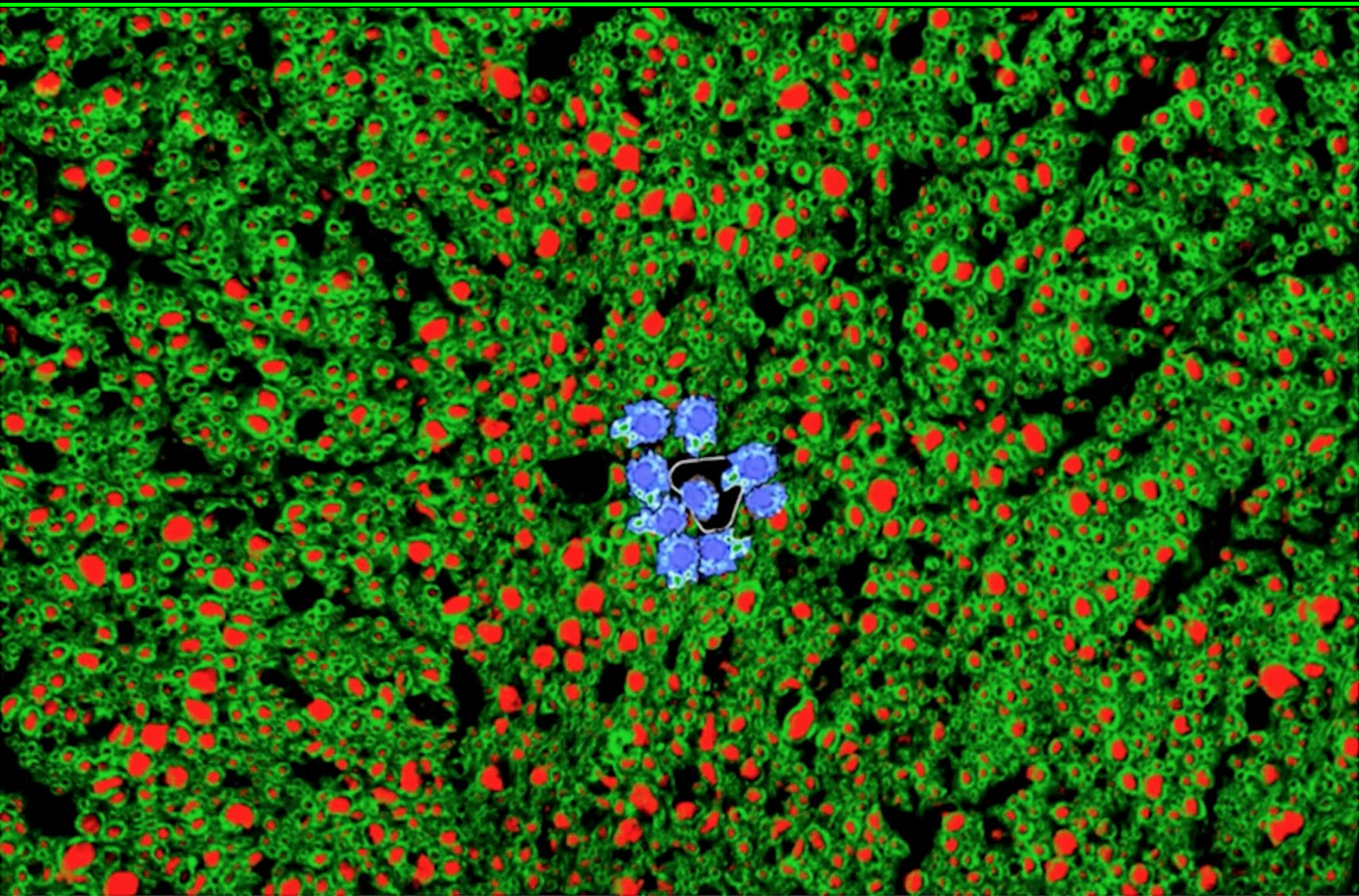
Inflammation and MS
Out-In and In-Out interplay



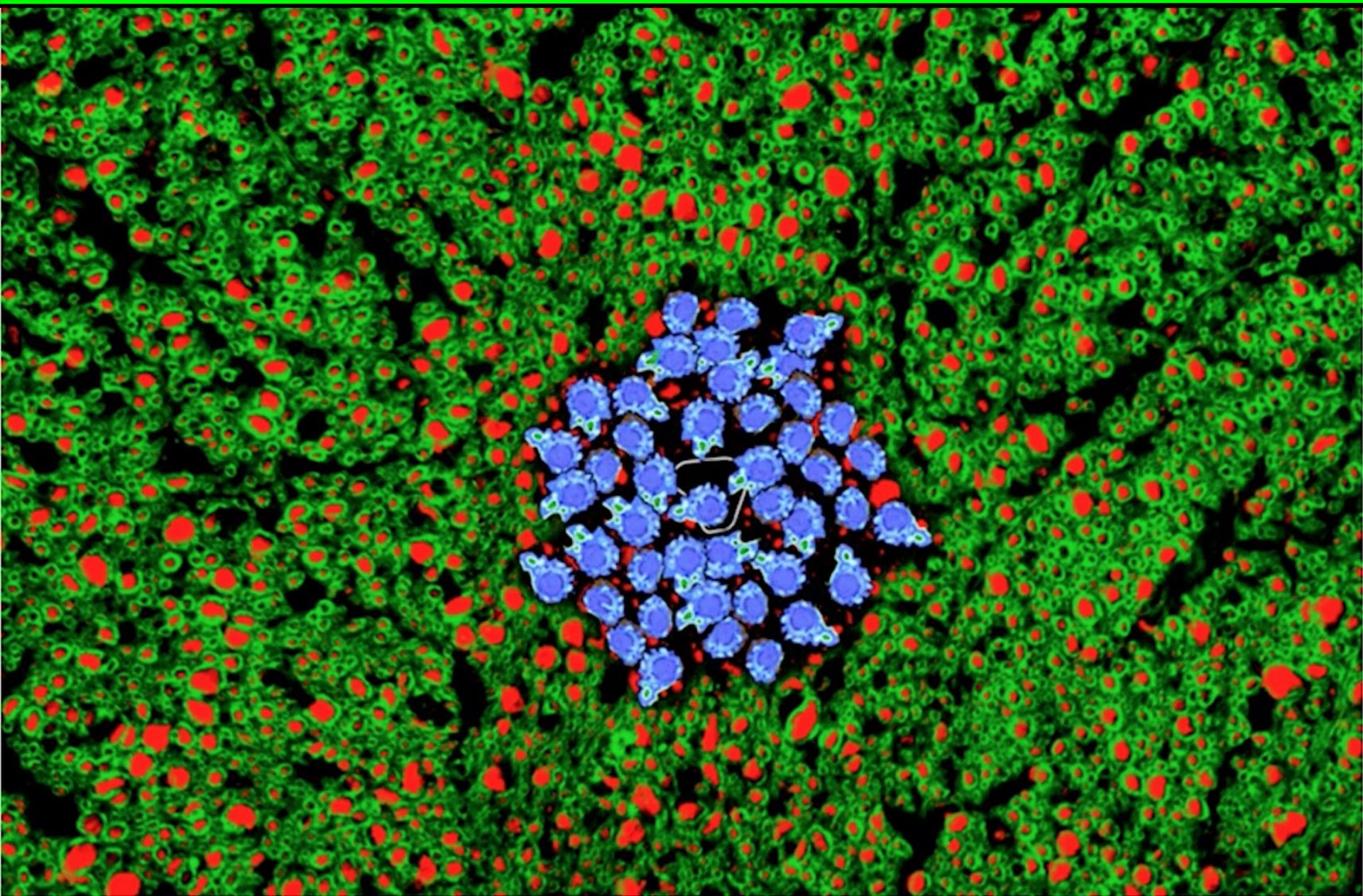
SEP – Neuropathologie



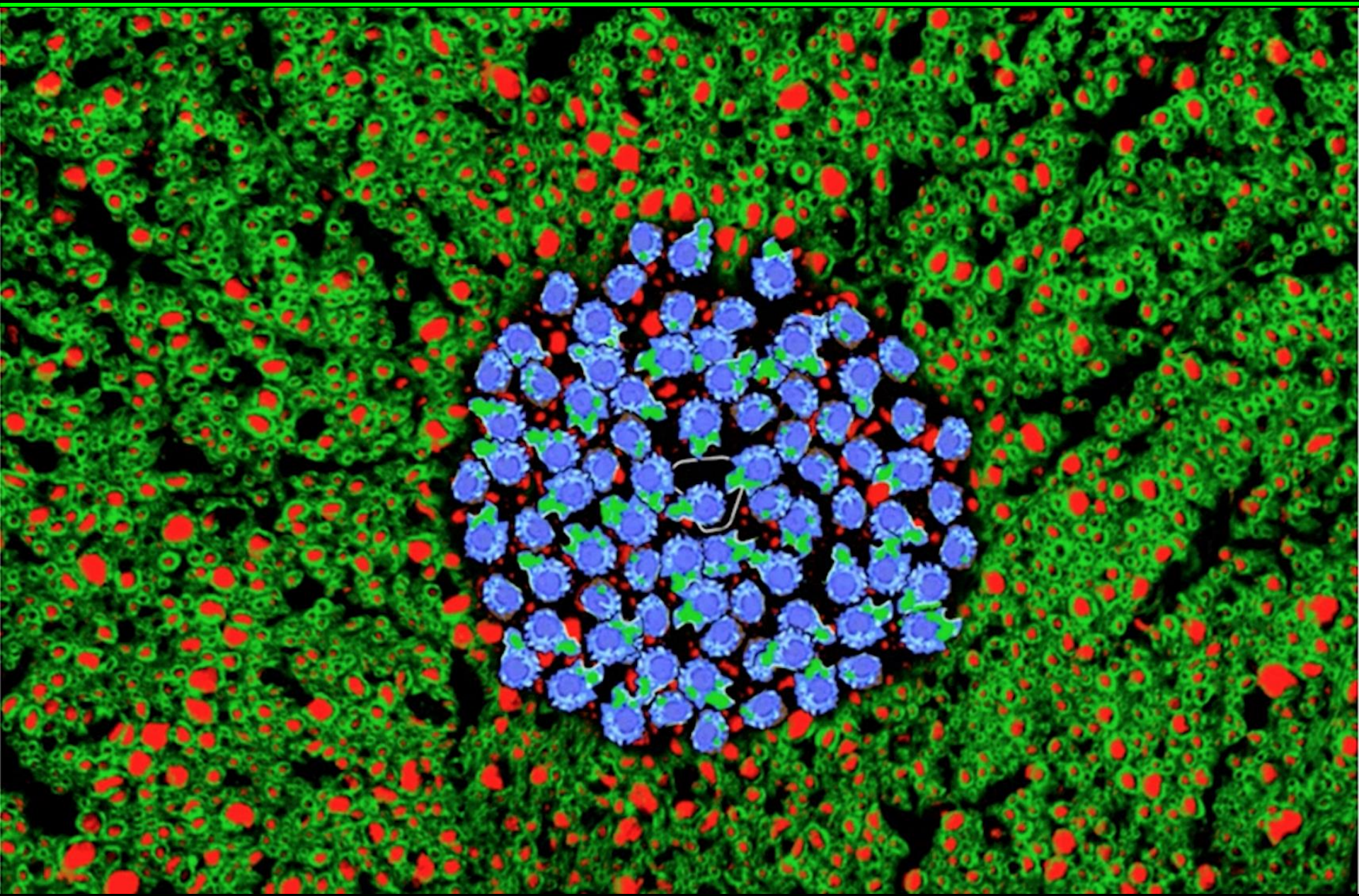
SEP – Neuropathologie



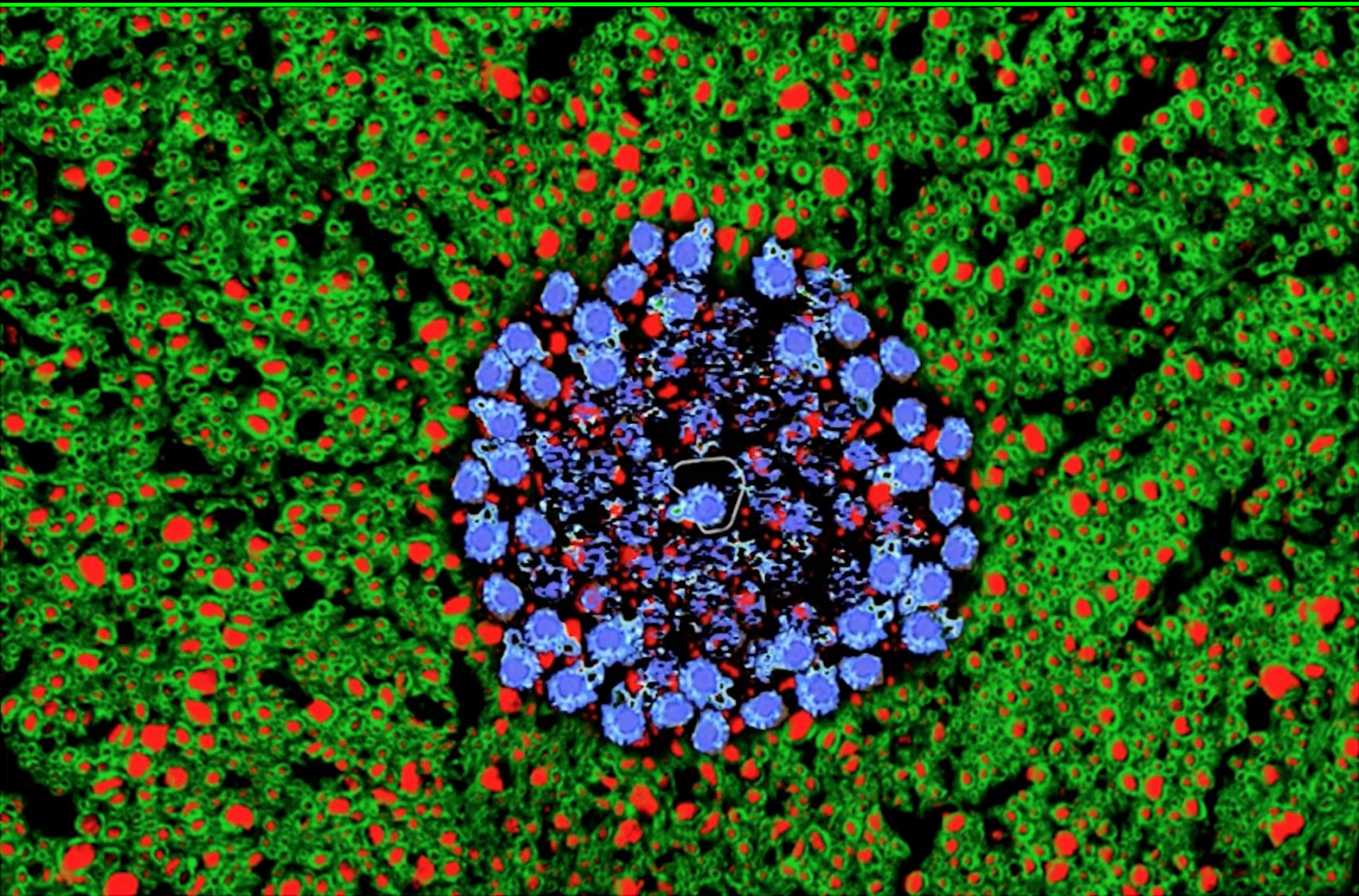
SEP – Neuropathologie



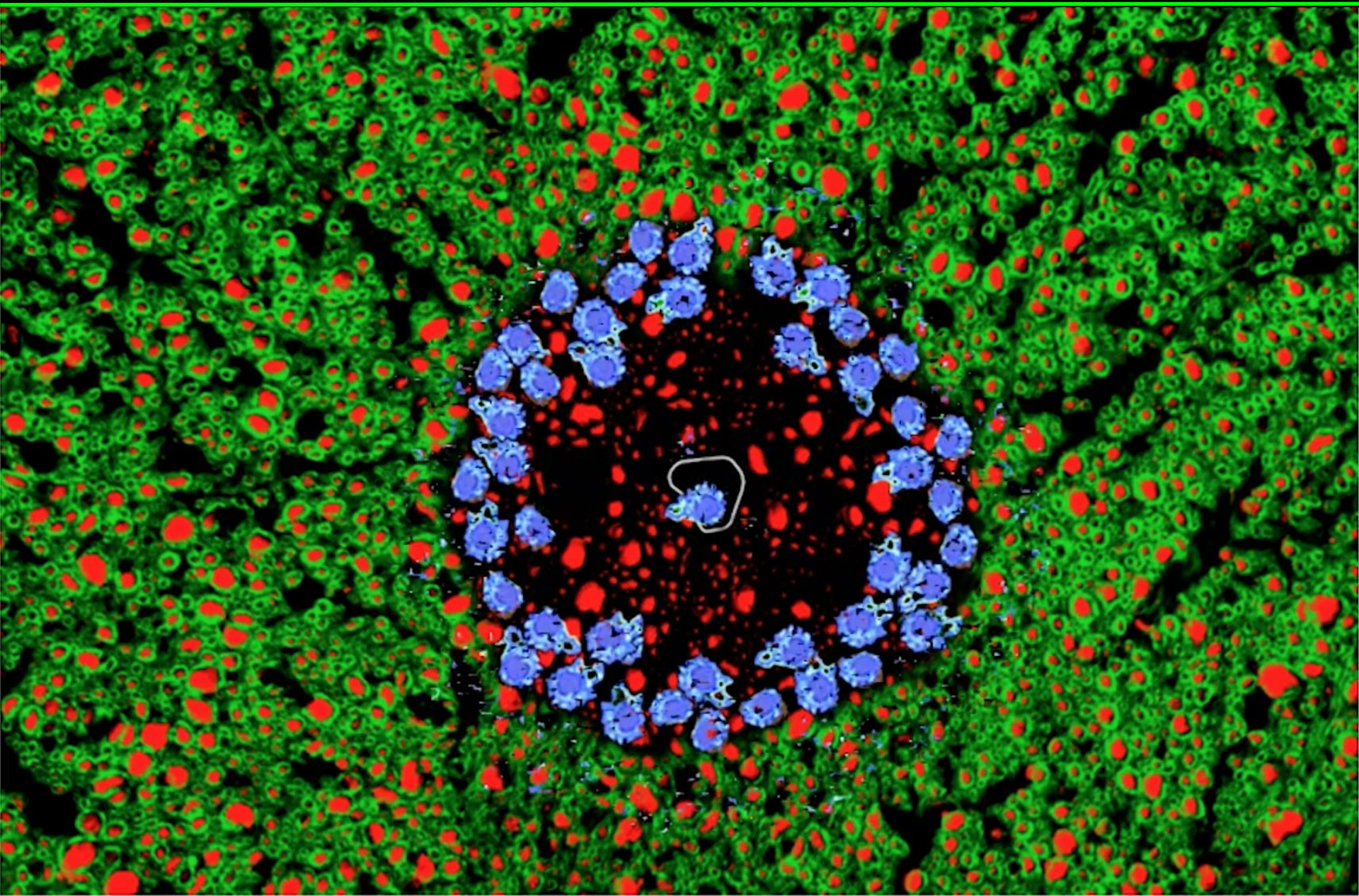
SEP – Neuropathologie



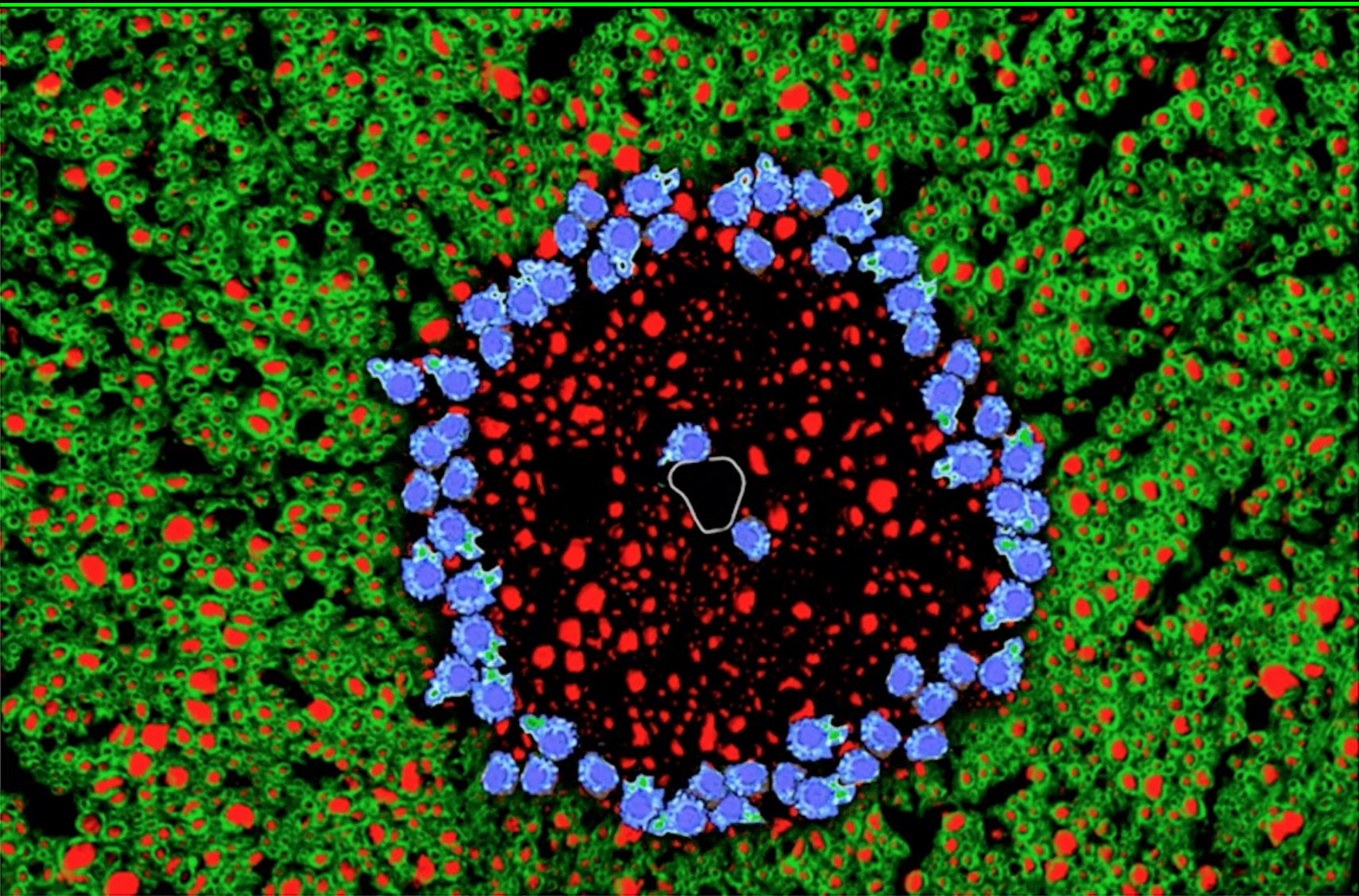
SEP – Neuropathologie



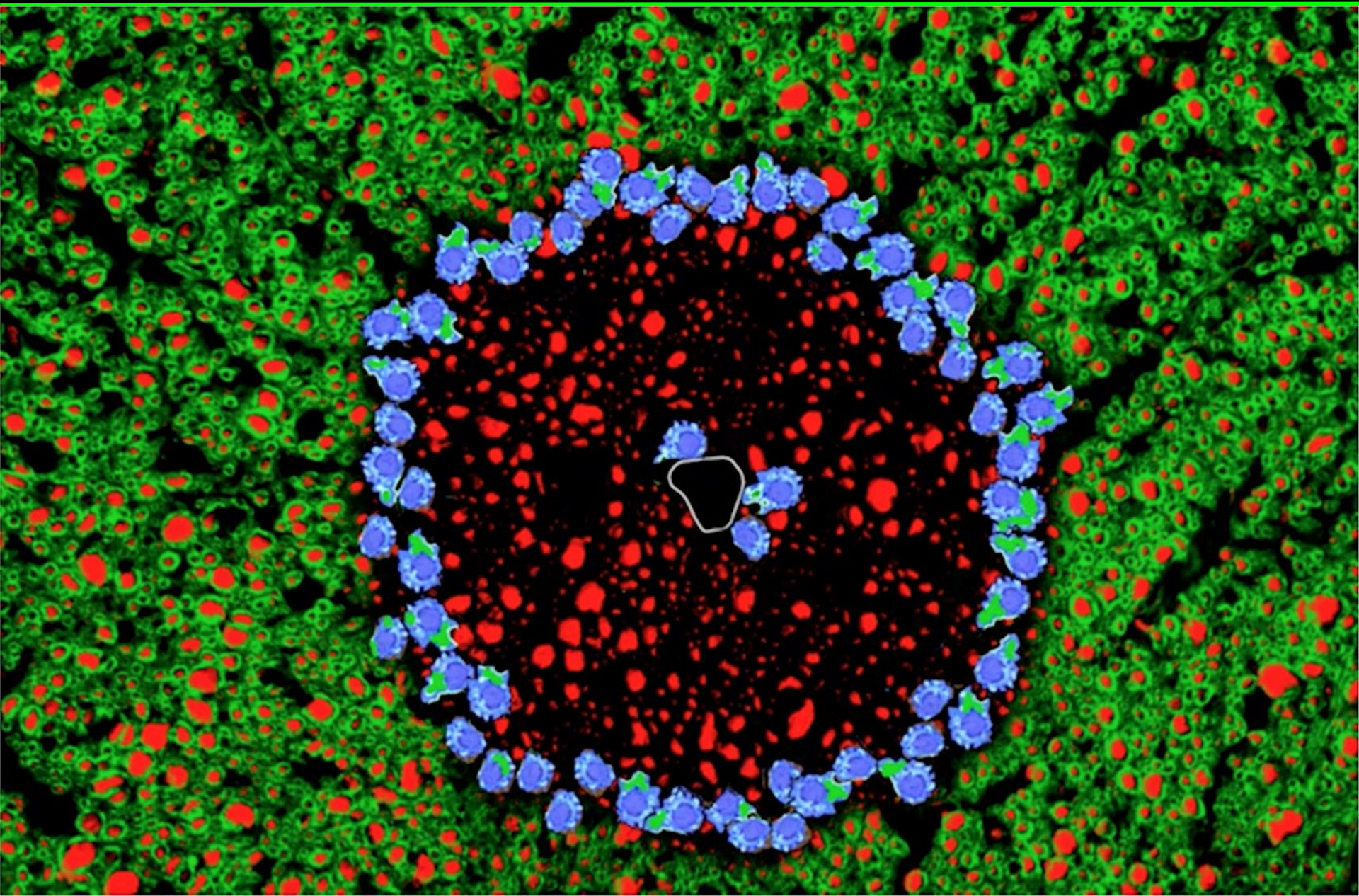
SEP – Neuropathologie



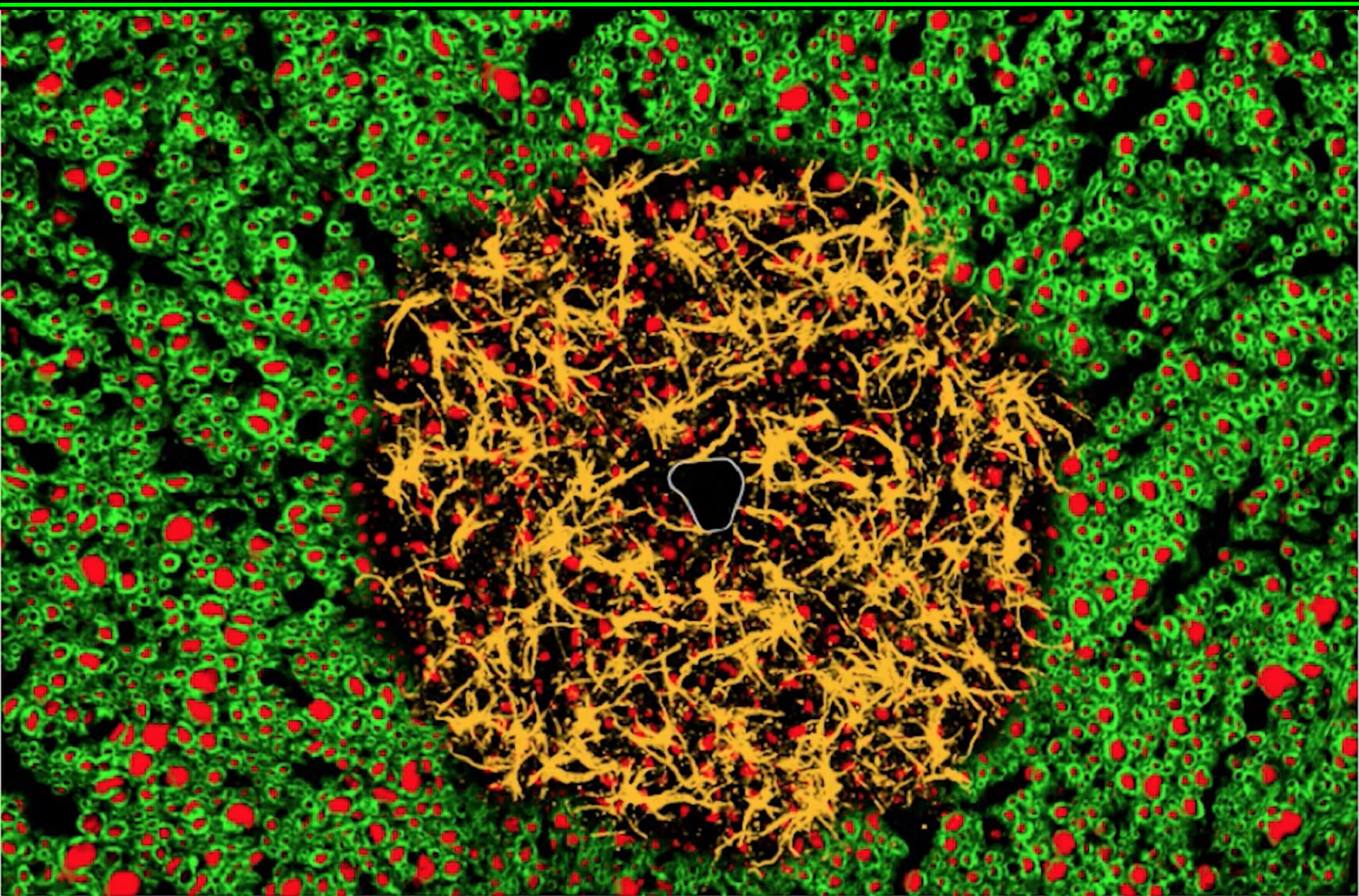
SEP – Neuropathologie



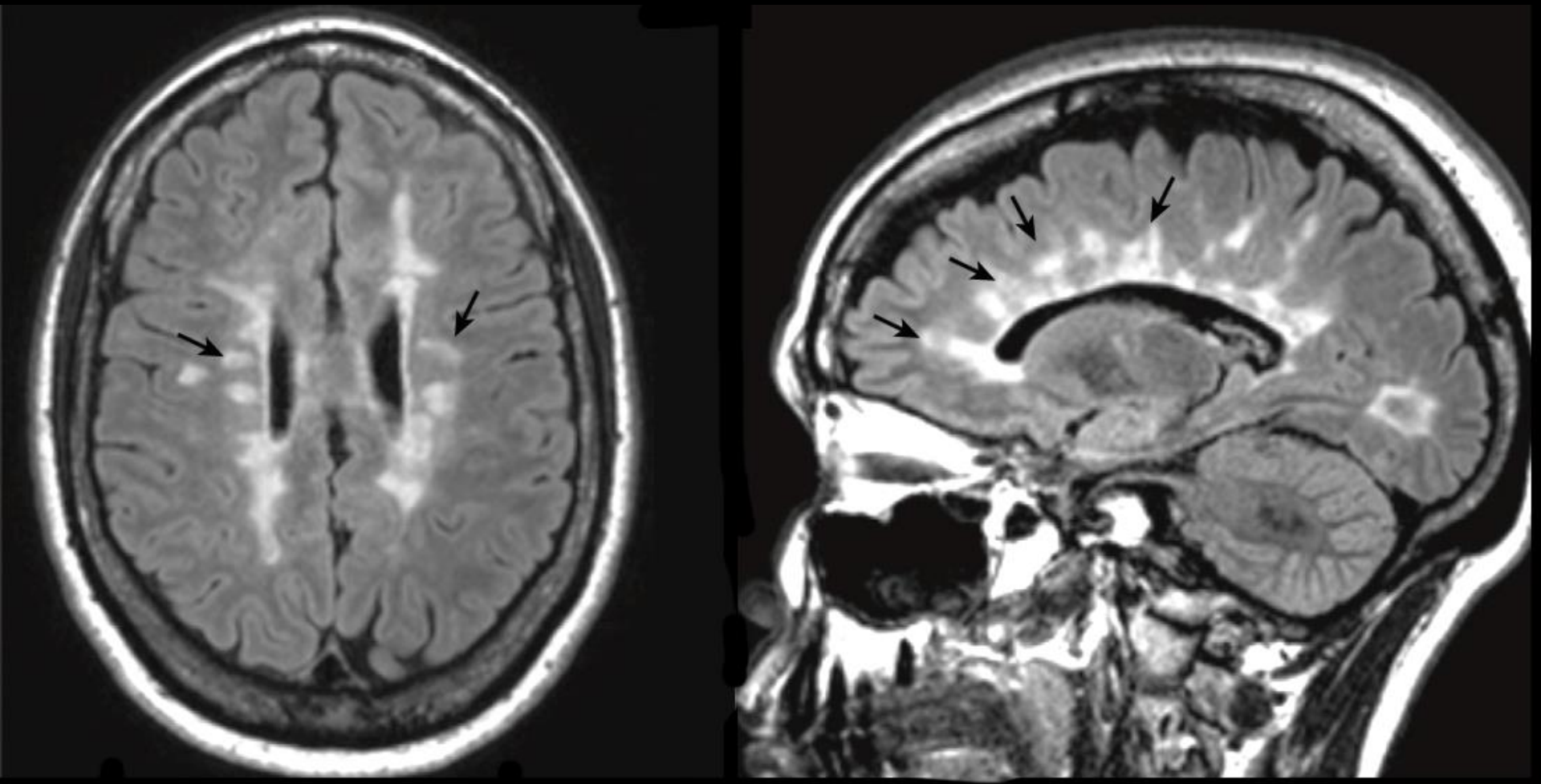
SEP – Neuropathologie



SEP – Neuropathologie

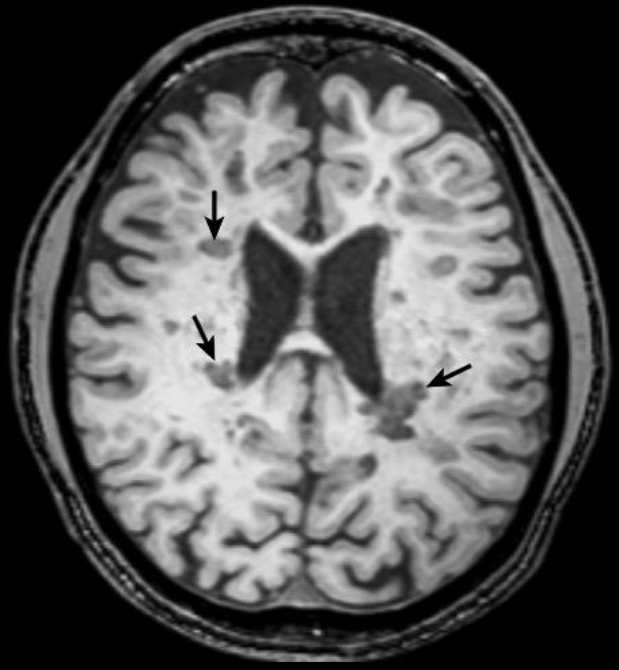


Diagnosis of MS - MRI



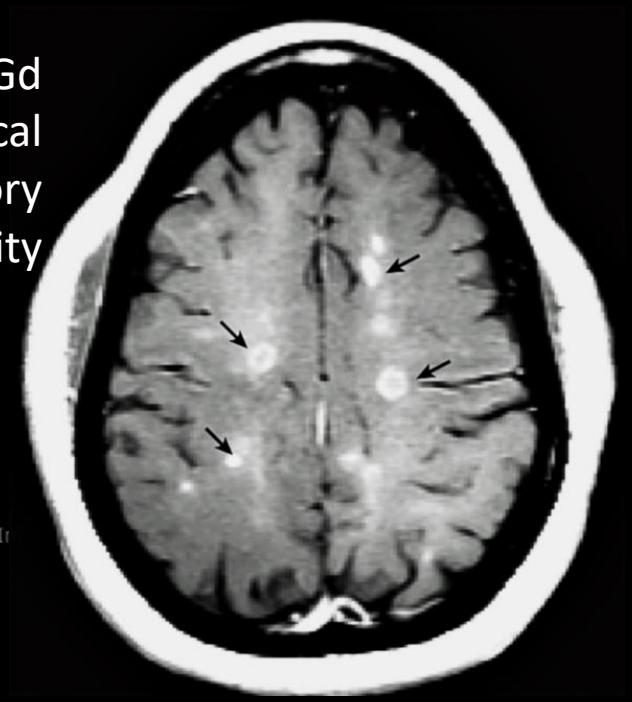
FLAIR hyperintensities and Dawson’s fingers

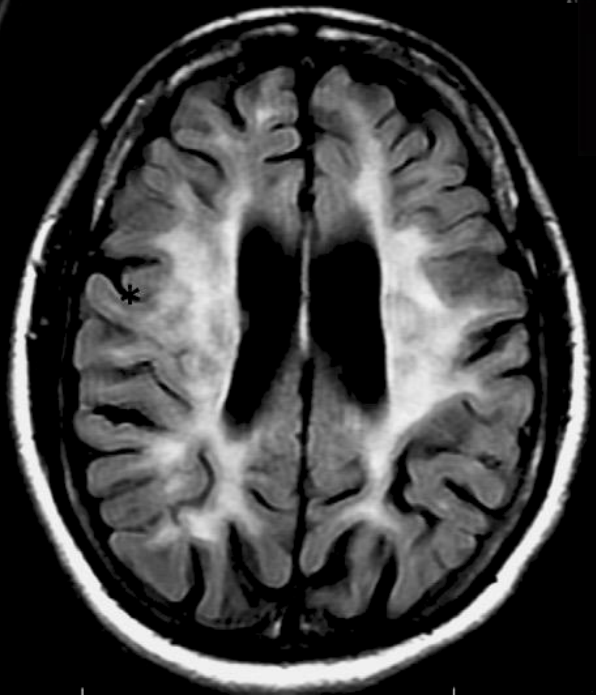
Diagnosis of MS - MRI



T1-Gd
Numerous black holes

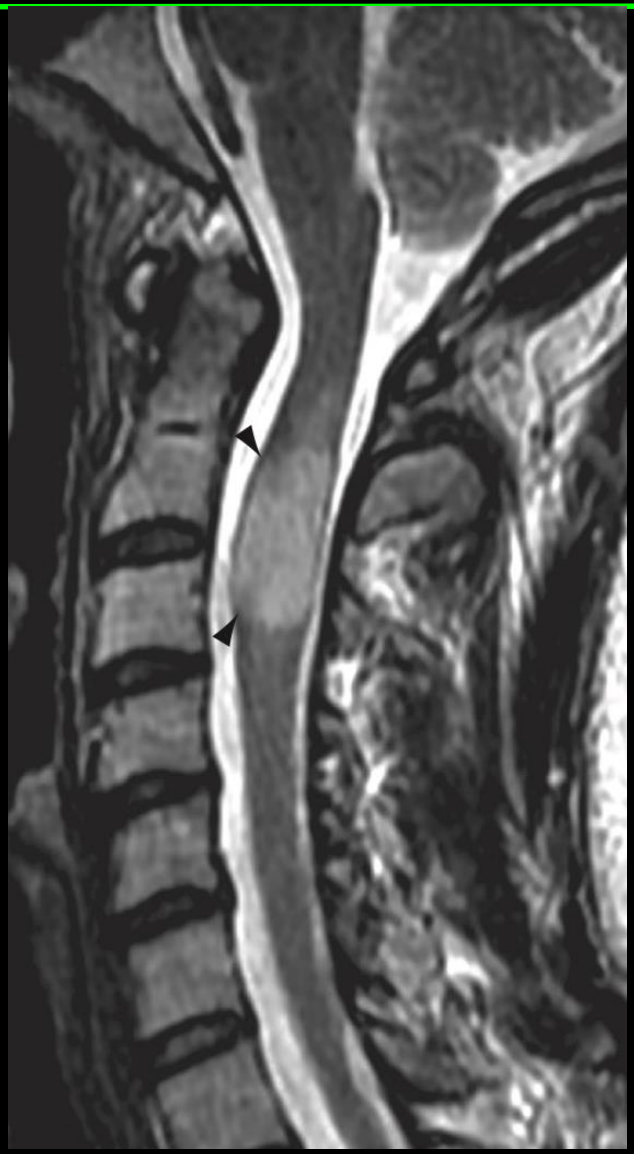
T1+Gd
High focal inflammatory activity



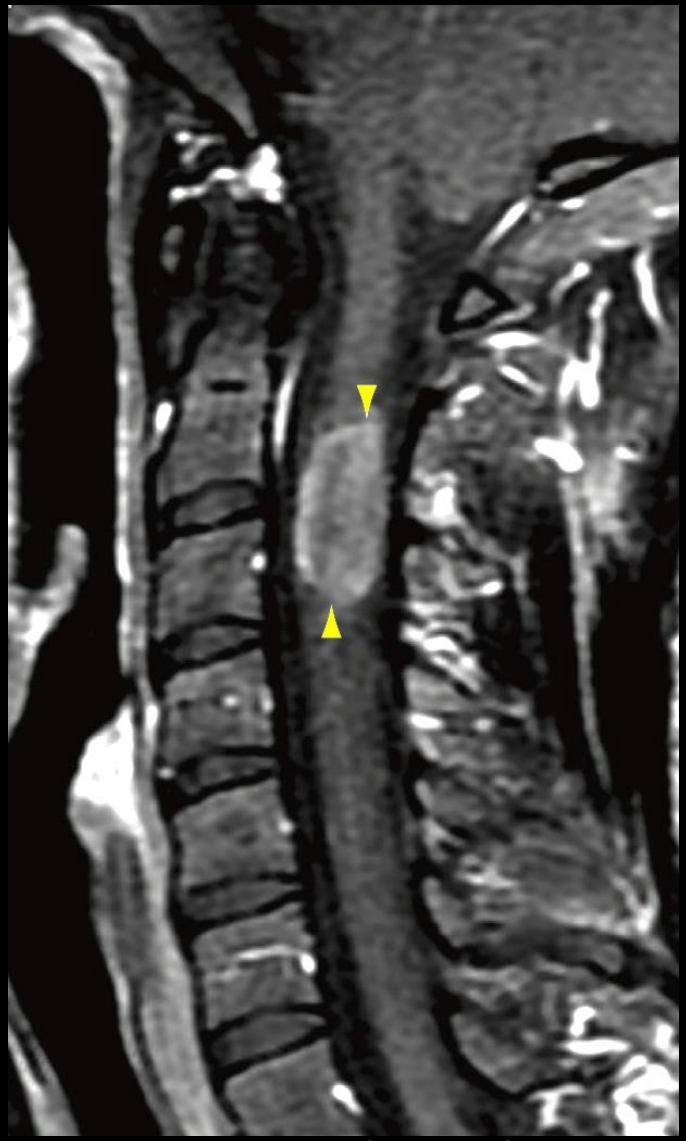


Chronic stage
FLAIR
Confluent hyperintensities
Atrophy

Diagnosis of MS - MRI



Sagittal T2 hypersignal



Sagittal T1+Gd
Large expansive lesion

MRI and MS Diagnosis

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Brenda Banwell, MD,[3] Michel Clanet, MD,[4] Jeffrey A. Cohen, MD,[5] Massimo Filippi, MD,[6] Kazuo Fujihara, MD,[7] Eva Havrdova, MD, PhD,[8] Michael Hutchinson, MD,[9] Ludwig Kappos, MD,[10] Fred D. Lublin, MD,[11] Xavier Montalban, MD,[12] Paul O'Connor, MD,[13] Magnhild Sandberg-Wollheim, MD, PhD,[14] Alan J. Thompson, MD,[15] Emmanuelle Waubant, MD, PhD,[16] Brian Weinshenker, MD,[17] and Jerry S. Wolinsky, MD[18]

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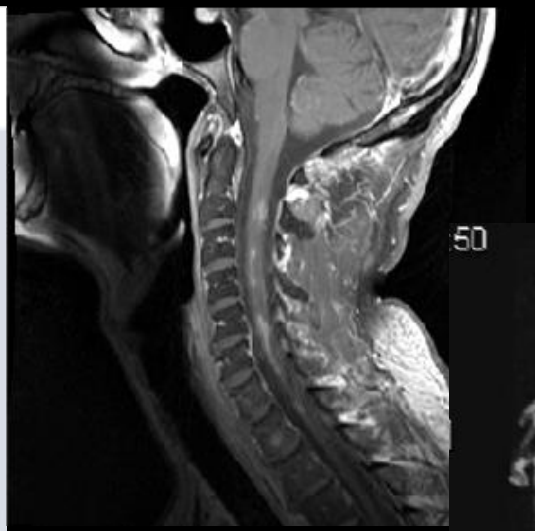
	Sensitivity	Specificity
McDonald 2001	47.1	91.1
McDonald 2005	60	87.8
McDonald 2010	71.8	87.6

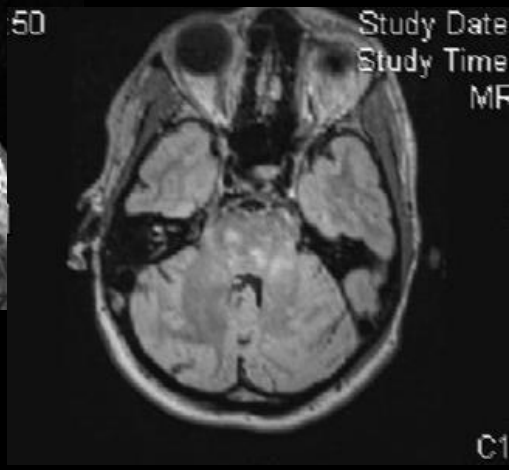
MS Criteria: Dissemination in Space

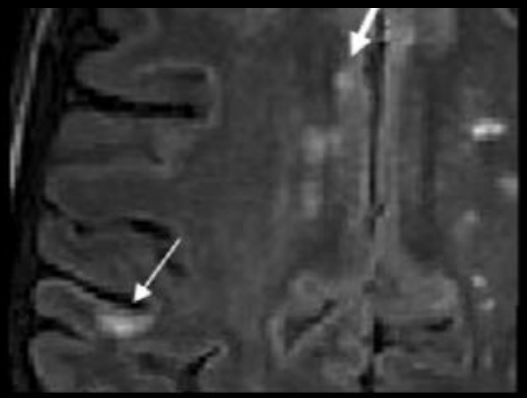
TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:
Periventricular
Juxtacortical
Infratentorial
Spinal cord[b]

Based on Swanton et al 2006, 2007.[22,27]
[a]Gadolinium enhancement of lesions is not required for DIS.
[b]If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.
MRI = magnetic resonance imaging; DIS = lesion dissemination in space; CNS = central nervous system.







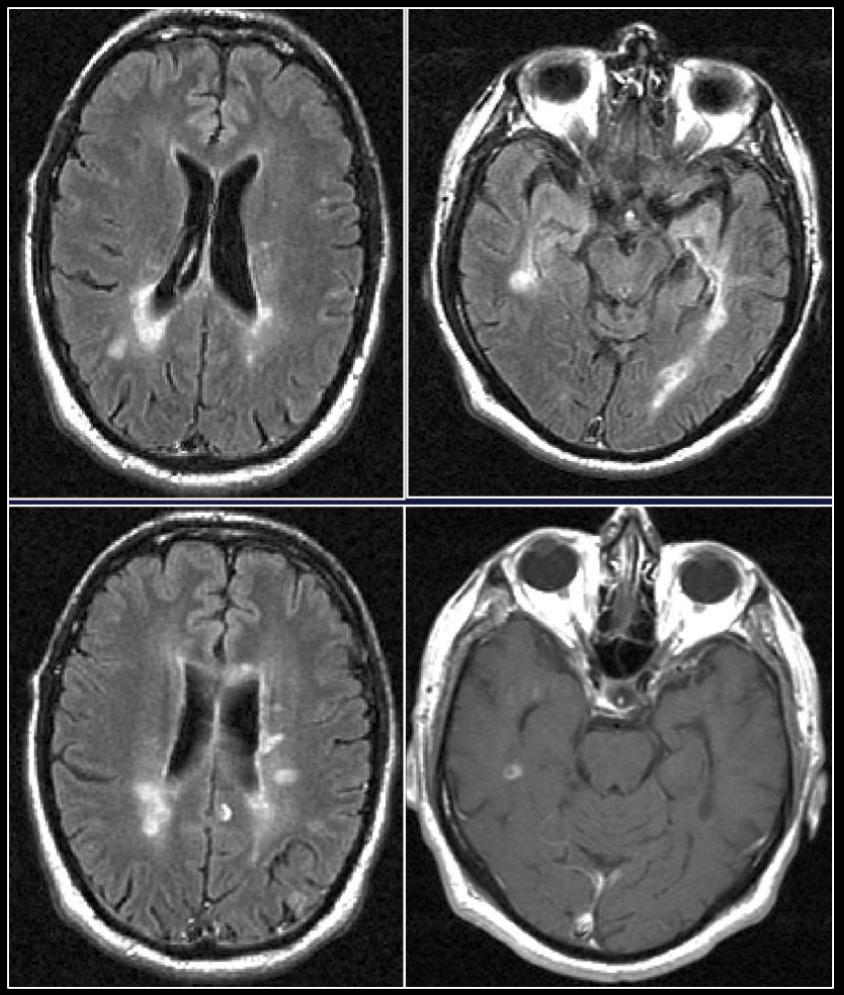
Polman et al., Ann Neurol, 2011

MS Criteria: Dissemination in Time

TABLE 2: 2010 McDonald MRI Criteria for Demonstration of DIT

DIT Can Be Demonstrated by:
1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Based on Montalban et al 2010.[24]
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.



Possible to have MS after only 1 episode of optic neuritis and 1 MRI!

Polman et al. Ann Neurol, 2011

MAGNIMS publication

MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines

*Massimo Filippi, Maria A Rocca, Olga Ciccarelli, Nicola De Stefano, Nikos Evangelou, Ludwig Kappos, Alex Rovira, Jaume Sastre-Garriga, Mar Tintorè, Jette L Frederiksen, Claudio Gasperini, Jacqueline Palace, Daniel S Reich, Brenda Banwell, Xavier Montalban, Frederik Barkhof, on behalf of the MAGNIMS Study Group**

Lancet Neurol 2016; 15: 292–303

Published Online
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http://dx.doi.org/10.1016/S1474-4422(15)00393-2

See Comment page 238

*MAGNIMS Steering Committee members are listed at the end of the paper

Panel 2: Recommended 2016 MAGNIMS MRI criteria to establish disease dissemination in space in multiple sclerosis

Dissemination in space can be shown by involvement* of at least two of five areas of the CNS as follows:

- Three or more periventricular lesions
- One or more infratentorial lesion
- One or more spinal cord lesion
- One or more optic nerve lesion
- One or more cortical or juxtacortical lesion†

*If a patient has a brainstem or spinal cord syndrome, or optic neuritis, the symptomatic lesion (or lesions) are not excluded from the criteria and contribute to the lesion count. †This combined terminology indicates the involvement of the white matter next to the cortex, the involvement of the cortex, or both, thereby expanding the term juxtacortical lesion.

Les nouveaux critères diagnostiques 2017

Ce qui a changé au niveau paraclinique

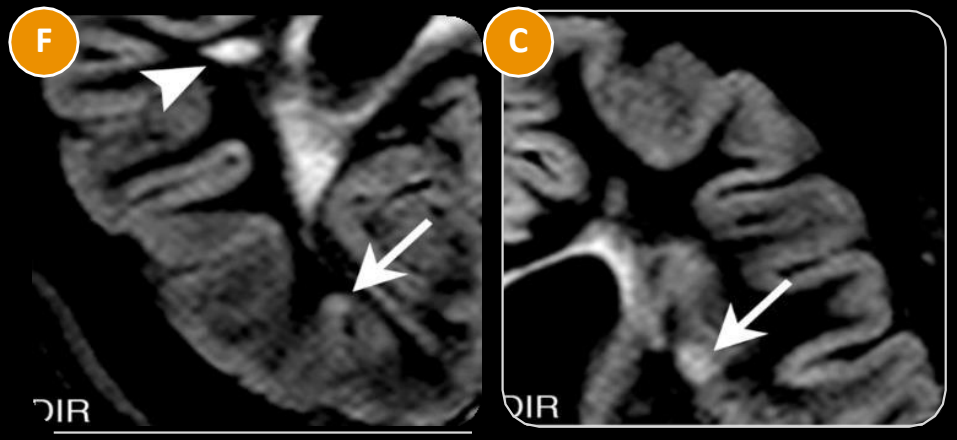
Dissémination dans l'espace :
deux des 4 atteintes focales suivantes

≥ 1 lésion périventriculaire

≥ 1 lésion infra tentorielle

≥ 1 lésion moelle épinière

≥ 1 cortical/juxtacortical lésion



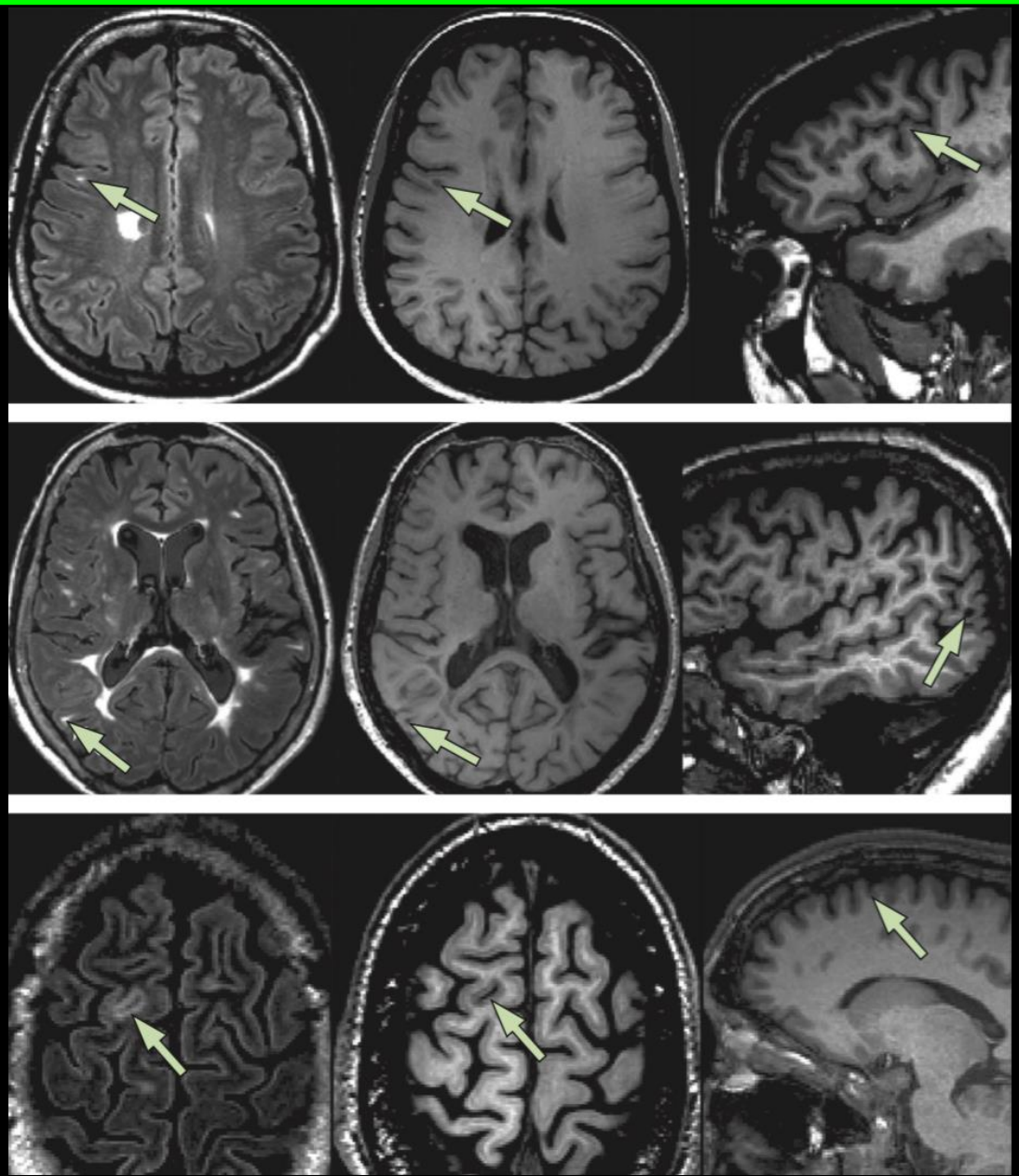
Dissémination dans le temps : trois cas de figure possibles

Si sur l'IRM de baseline, présence simultanée de lésions T2 et d'au moins **une lésion gado (symptomatique ou non)**

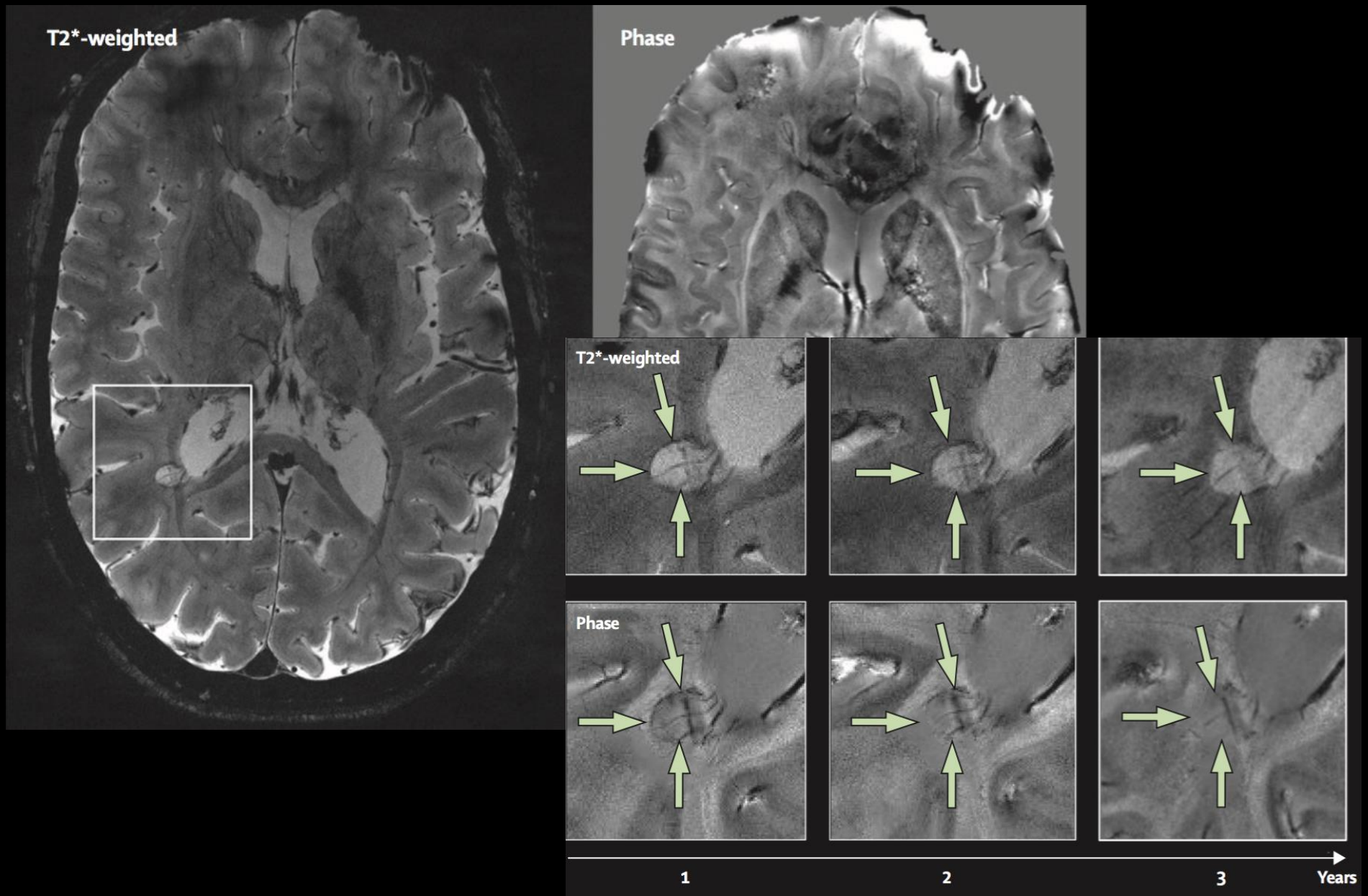
Si sur l'IRM de suivi, présence d'une nouvelle lésion T2 et/ou Gado positif quelque soit la date de sa réalisation

Si à l'examen du LCR : Présence de BOC

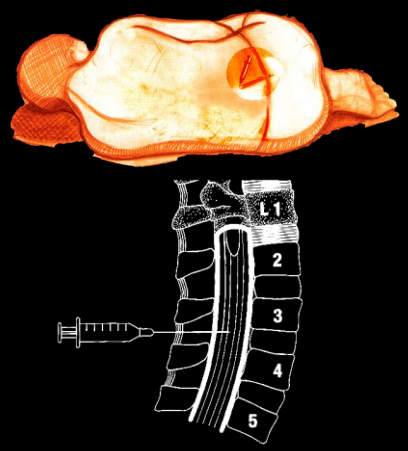
WM-Juxta-C and Cortical lesions



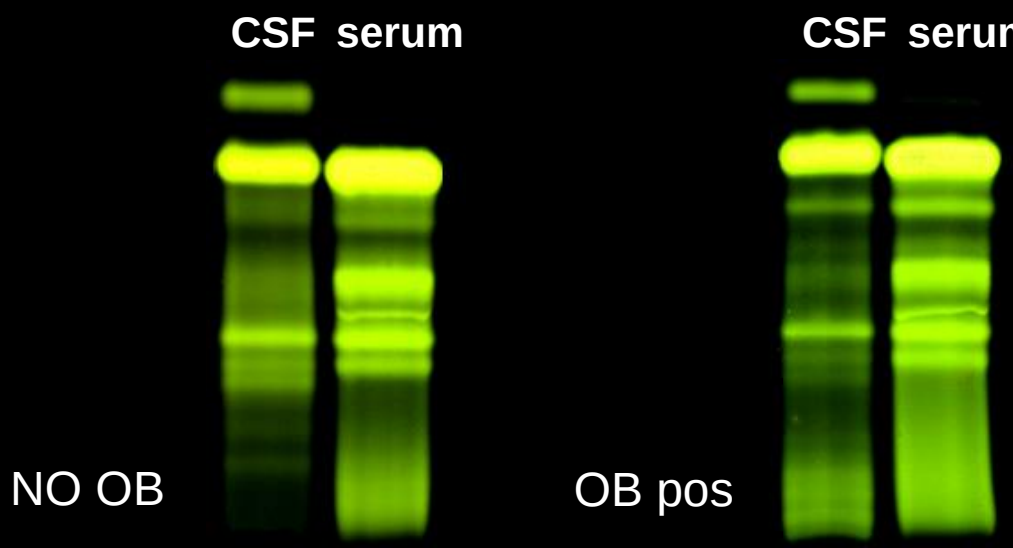
Ultra High Field MRI- 7 T



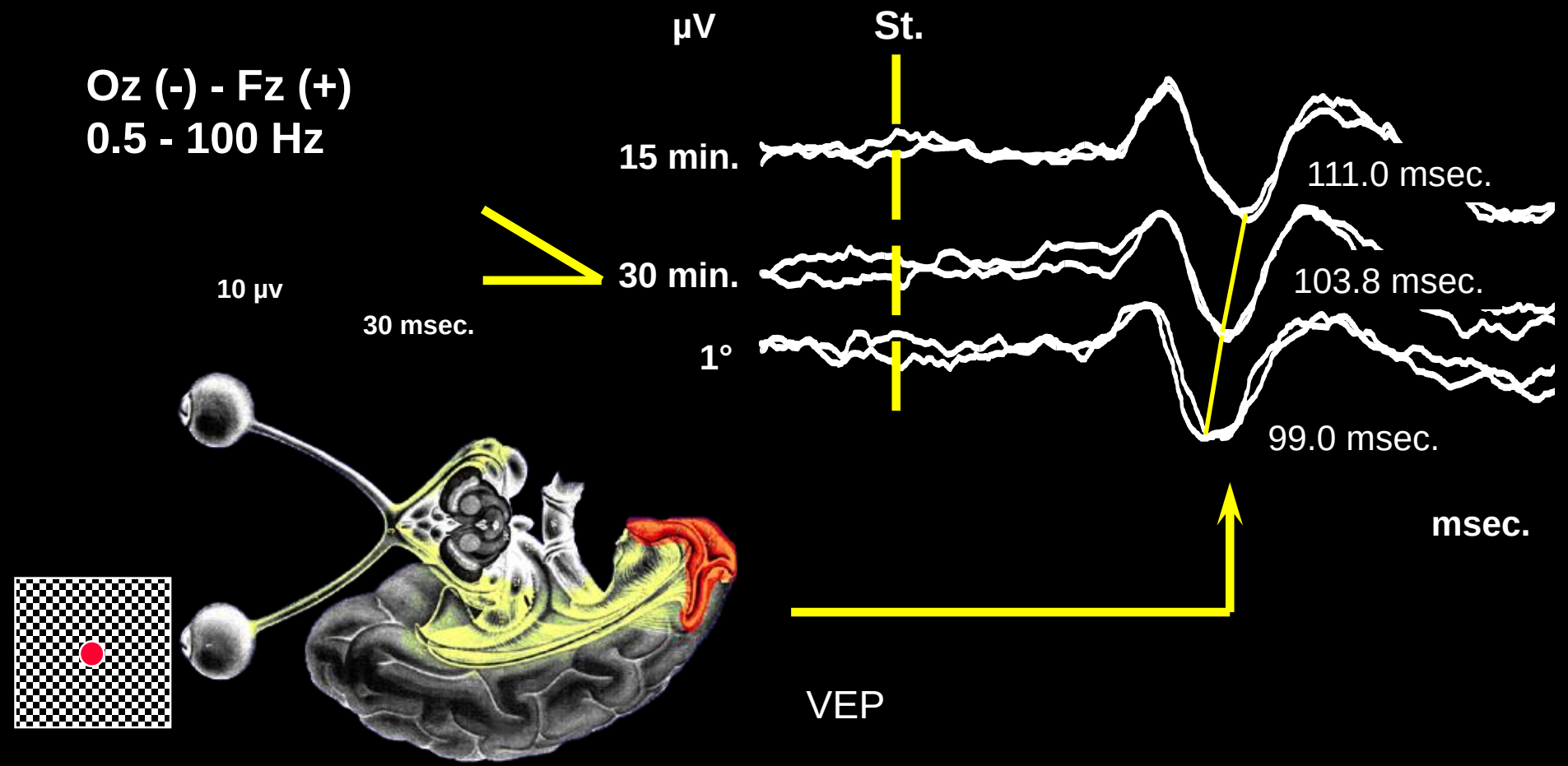
Diagnosis of MS - CSF



- CSF analysis
  - Recent criteria and pos/neg prognostic value after CIS
  - Oligoclonal bands and intrathecal IgG synthesis
  - Red flags and other diagnosis ruling out



MS diagnosis and follow-up - Neurophysiology



Les pièges…

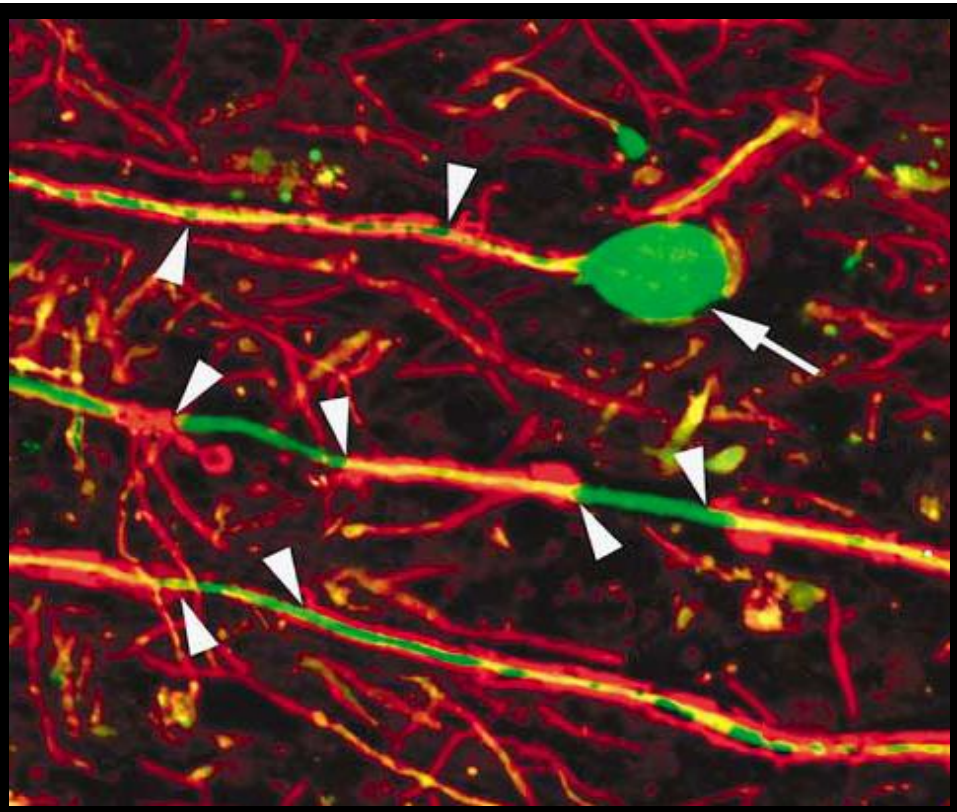
- Taches blanches n’est pas synonyme de :
  - Démyélinisation inflammatoire…
  - Maladie acquise…

Axonal pathology in MS

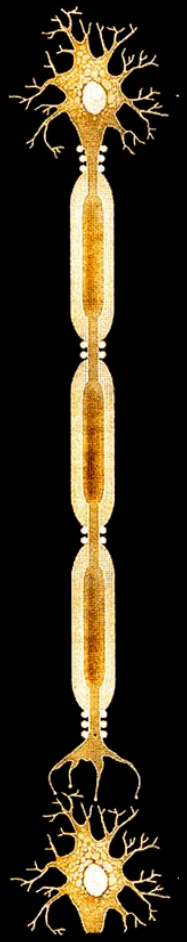
The New England Journal of Medicine

AXONAL TRANSECTION IN THE LESIONS OF MULTIPLE SCLEROSIS

Bruce D. Trapp, Ph.D., John Peterson, B.S., Richard M. Ransohoff, M.D., Richard Rudick, M.D., Sverre Mörk, M.D., Ph.D., and Lars Bö, M.D.



Progressive axonopathy



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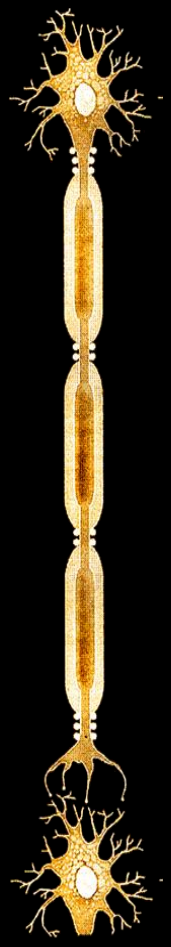
R.R.-M.S. axonopathy

1 : Normal

Progressive axonopathy



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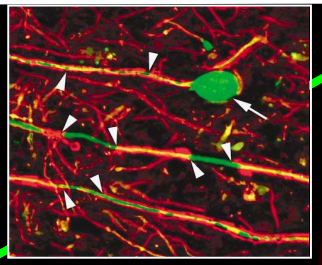
S.P.-M.S.
Non inflam. axonopathy

1 : Normal

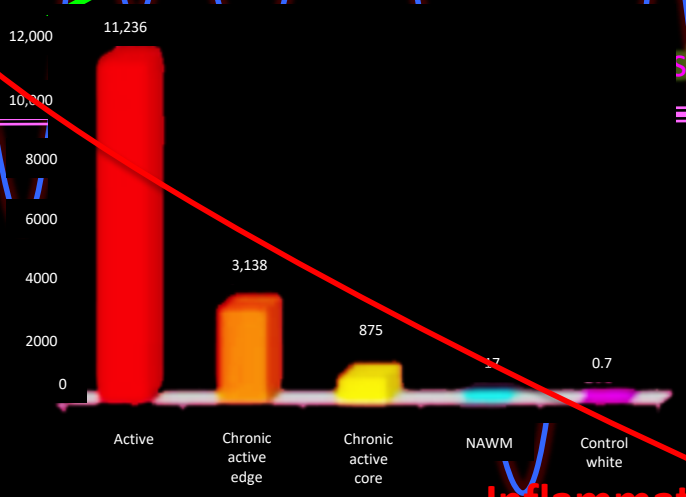
Pathological vs. Clinical Course

RIS | CIS | Relapsing - Remitting | Transitional | Secondary Progressive

First Clinical Attack



Axonal Loss



shold

Demyelination

Inflammation

Disease parameter

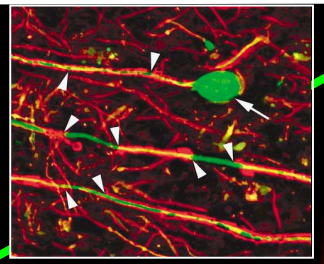
Time (Years)

Freedman M., AAN 2014

l vs. Clinical Course

New Diagnostic Criteria Have Changed the Definition of CIS

RIS | CIS | Relapsing - Remitting | Transitional | Secondary Progressive



Treatment depends on WHERE in the window you think the patient is when you are initiating treatment

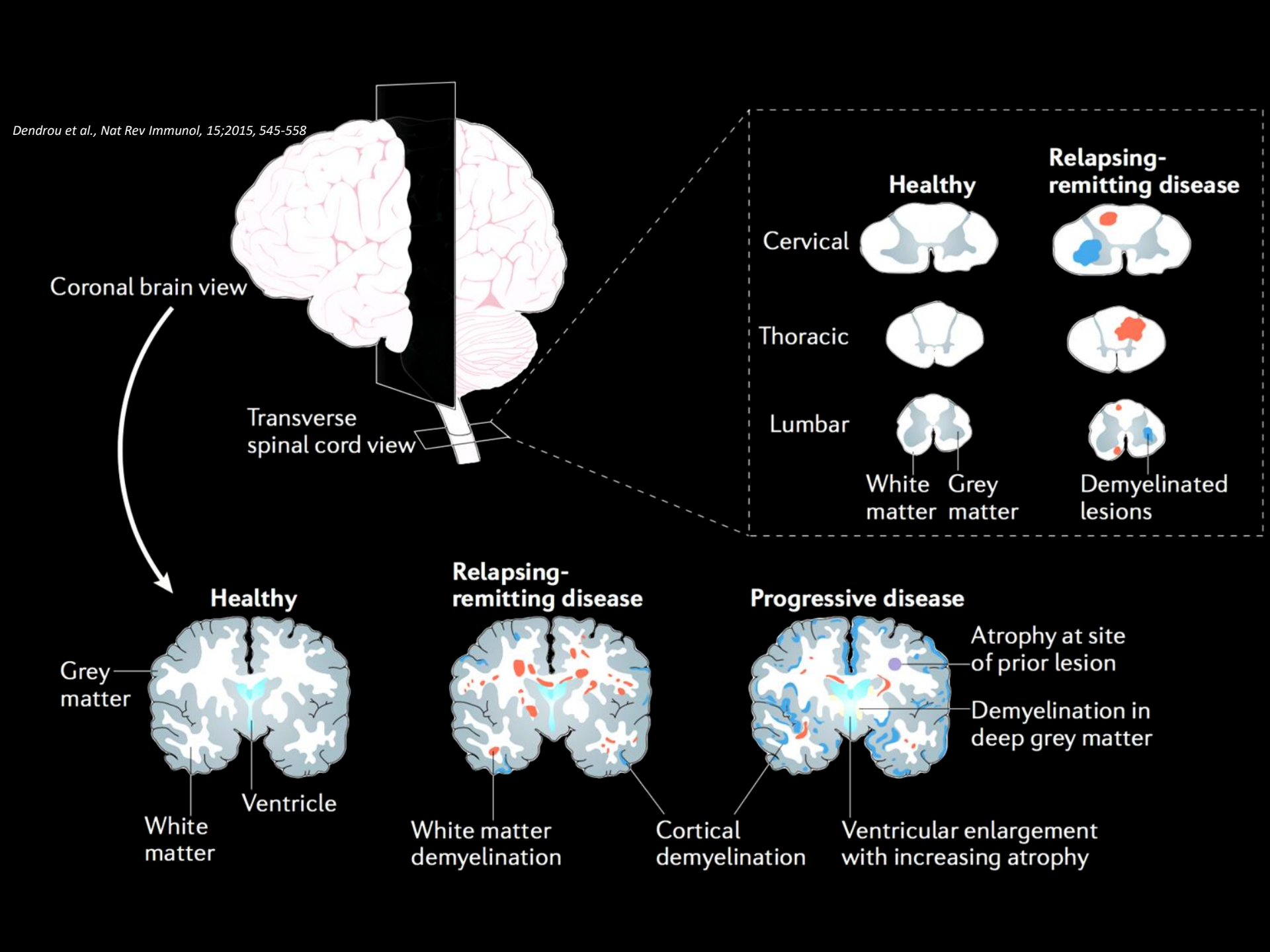
Time Window for Early Treatment

Inflammation

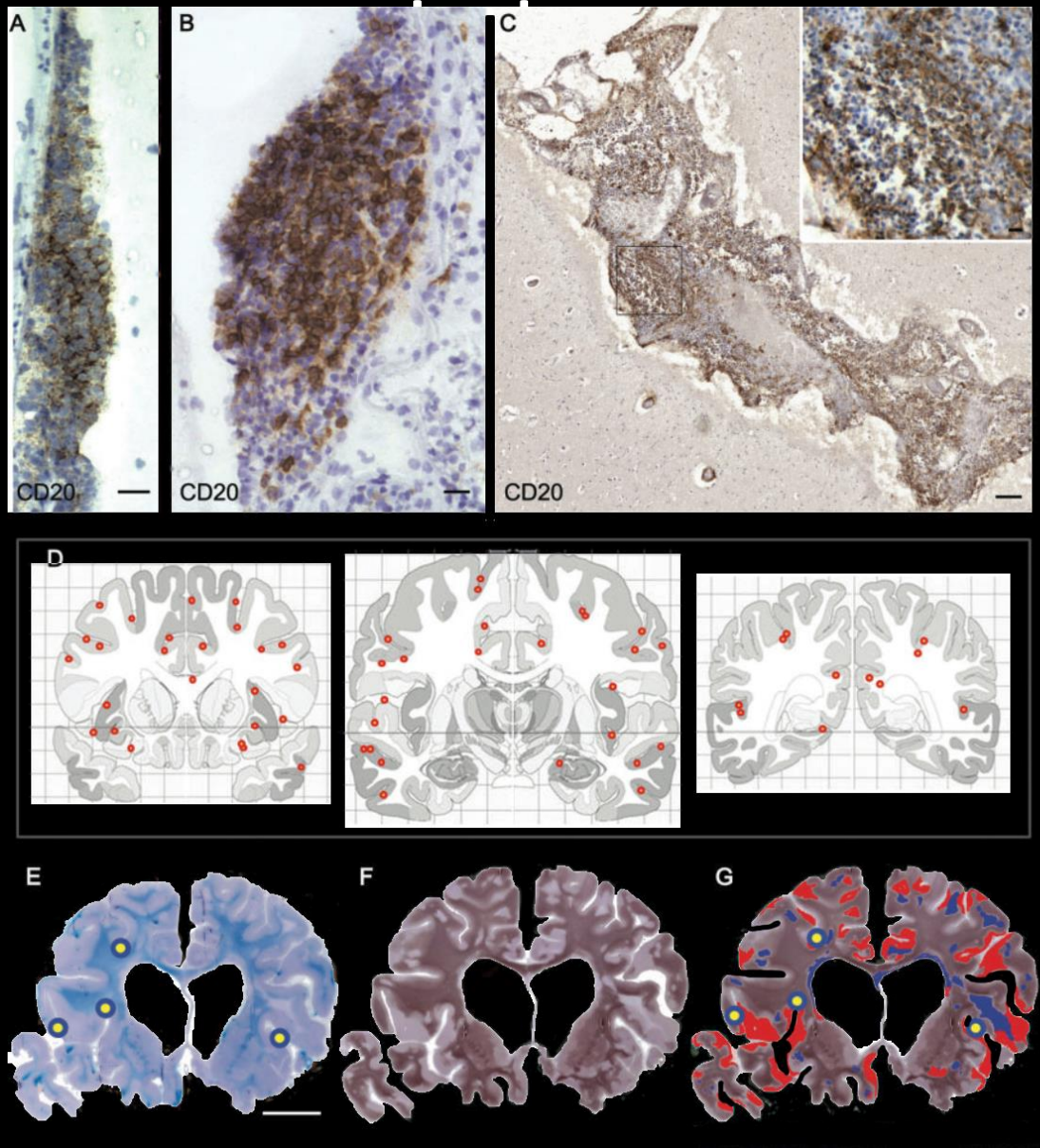
Disease parameter

Time (Years)

Freedman M., AAN 2014


Dendrou et al., Nat Rev Immunol, 15;2015, 545-558
Coronal brain view
Transverse spinal cord view
Healthy
Relapsing-remitting disease
Cervical
Thoracic
Lumbar
White matter
Grey matter
Demyelinated lesions
Healthy
Relapsing-remitting disease
Progressive disease
Grey matter
White matter
Ventricle
White matter demyelination
Cortical demyelination
Atrophy at site of prior lesion
Demyelination in deep grey matter
Ventricular enlargement with increasing atrophy

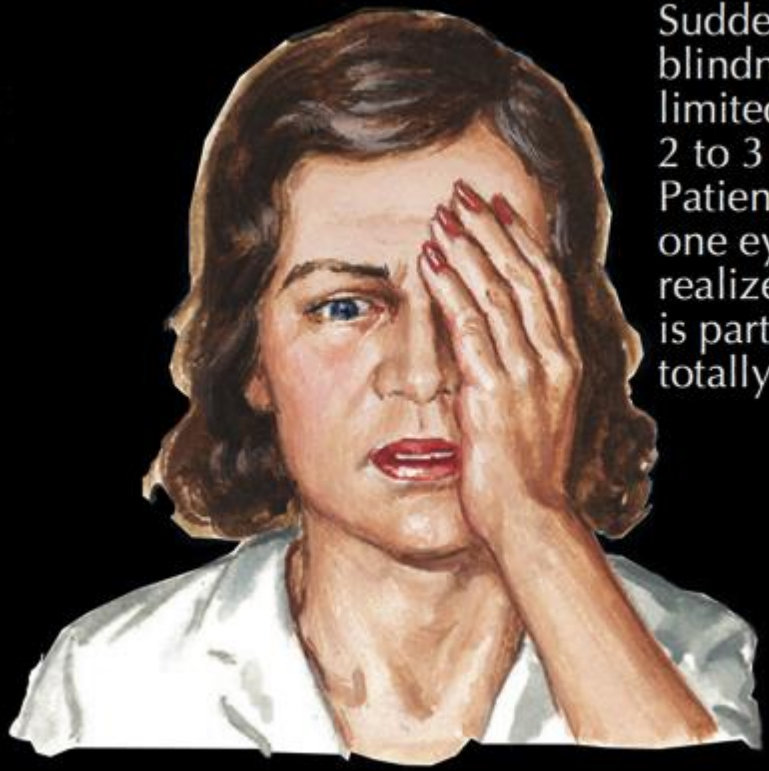
Meningeal B cells follicles and cortical



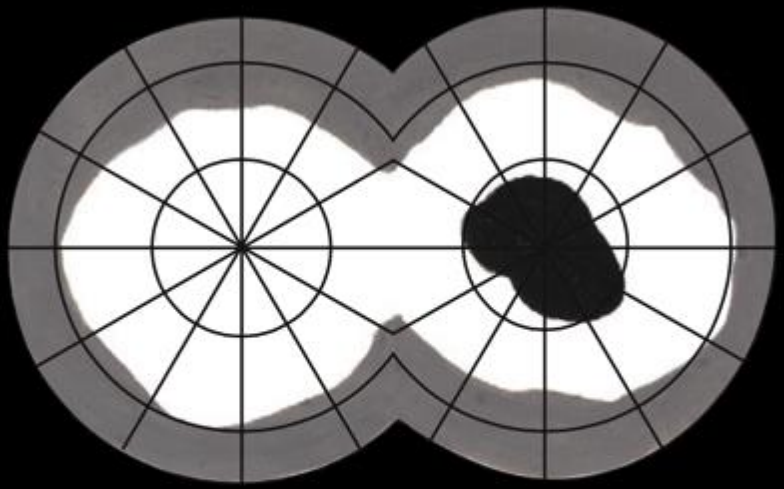
Howell O. et al., Brain 2011, 134

MS SYMPTOMS

Visual manifestations

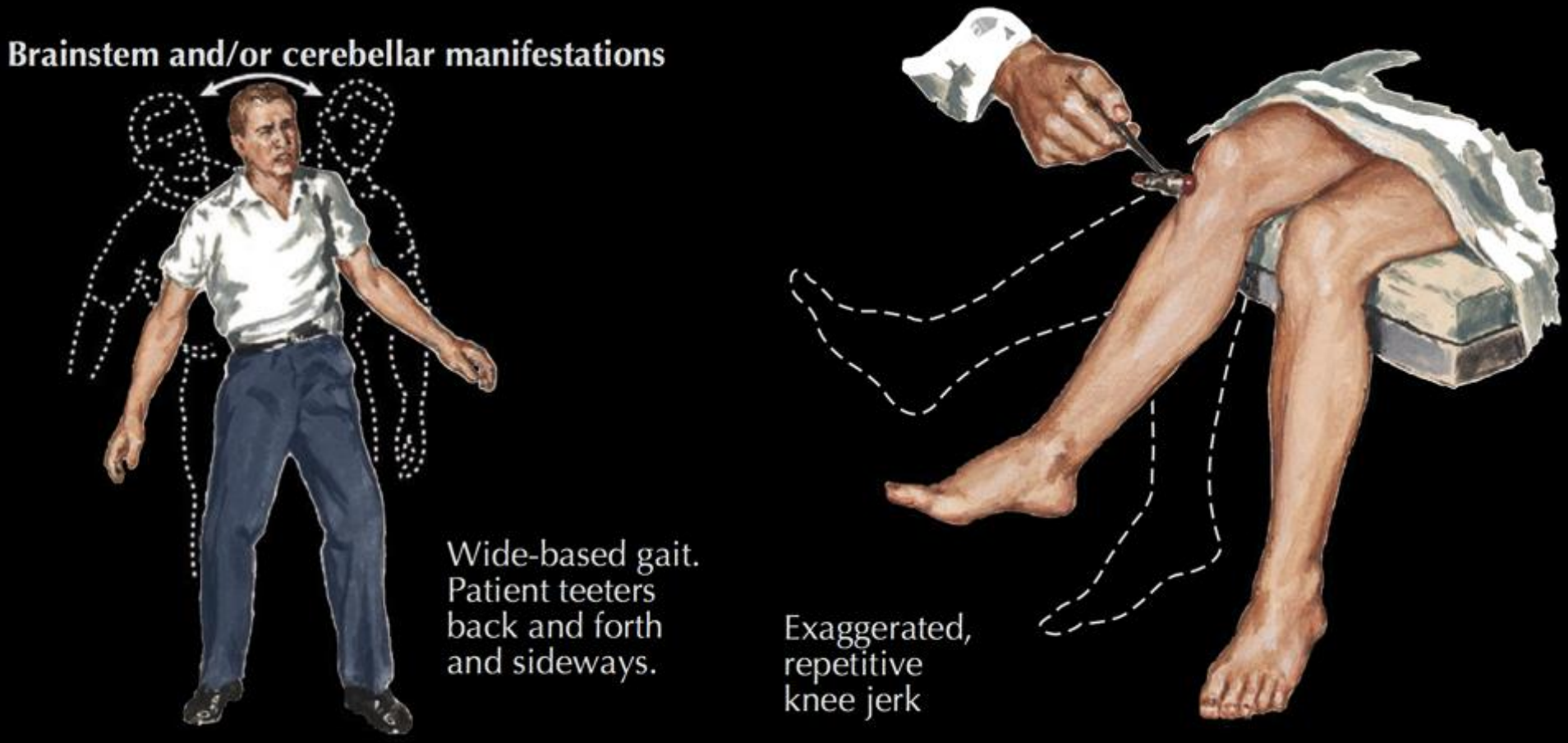


Sudden unilateral blindness, self-limited (usually 2 to 3 weeks). Patient covering one eye, suddenly realizes other eye is partially or totally blind.

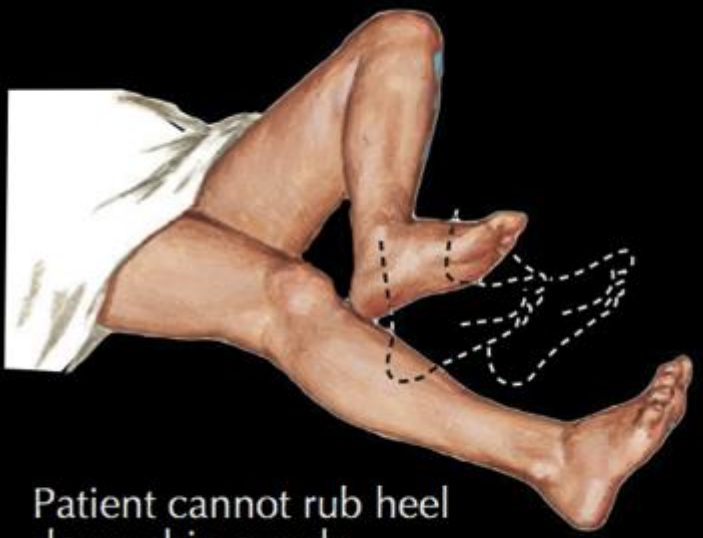


Visual fields reveal central scotoma due to acute retrobulbar neuritis

MS SYMPTOMS


Brainstem and/or cerebellar manifestations
Wide-based gait. Patient teeters back and forth and sideways.
Exaggerated, repetitive knee jerk

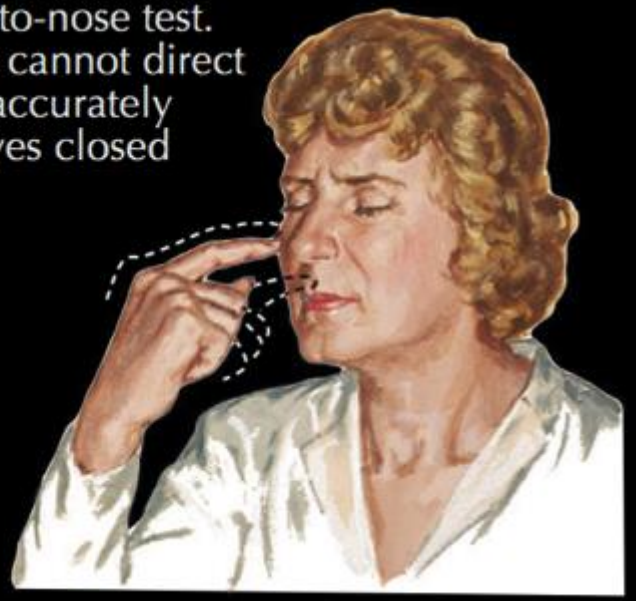
MS SYMPTOMS



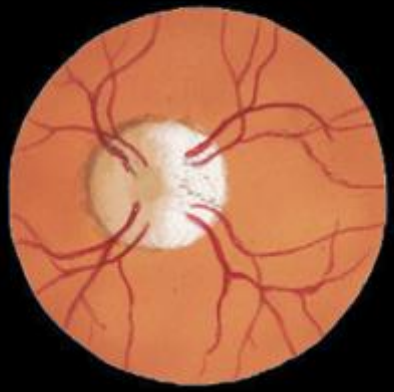
Patient cannot rub heel down shin evenly

Intention tremor. Hand unsteady on attempting to hold glass, write, etc.

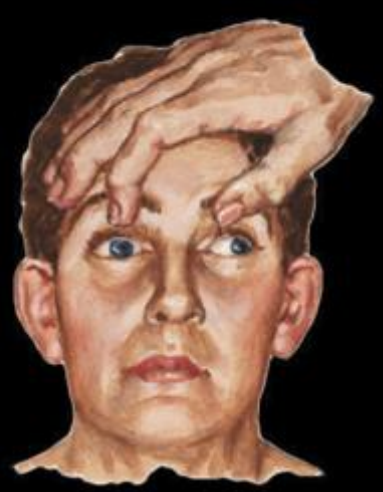
Finger-to-nose test. Patient cannot direct finger accurately with eyes closed



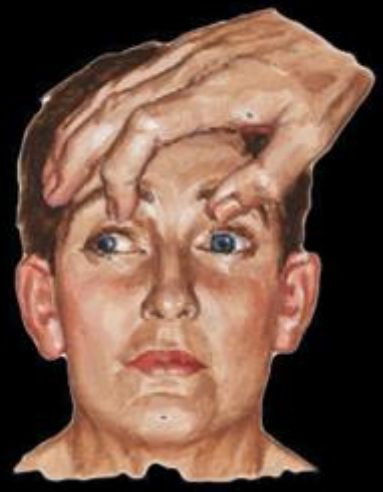
MS SYMPTOMS



Temporal pallor in optic disc, caused by delayed recovery of temporal side of optic (II) nerve



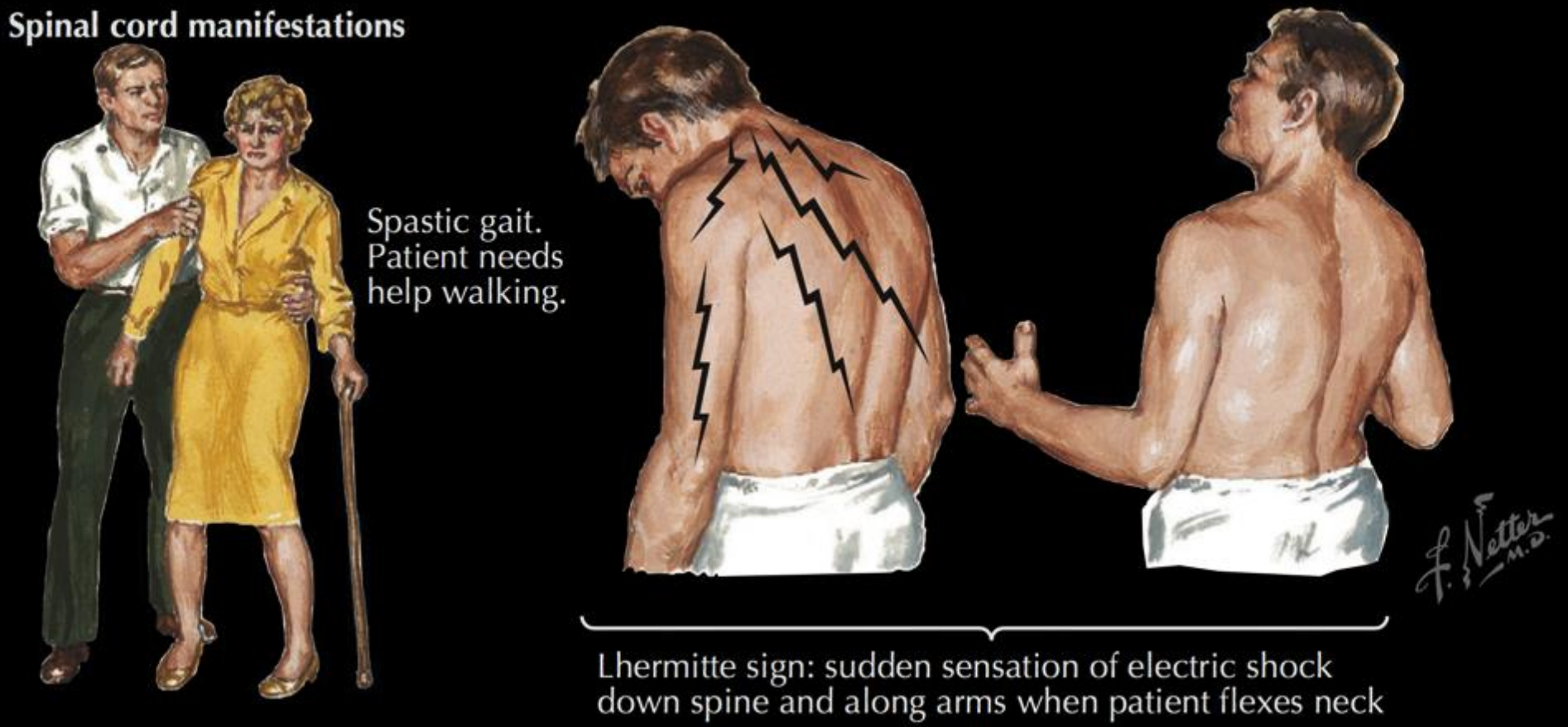
Eyes turned to left, right eye lags



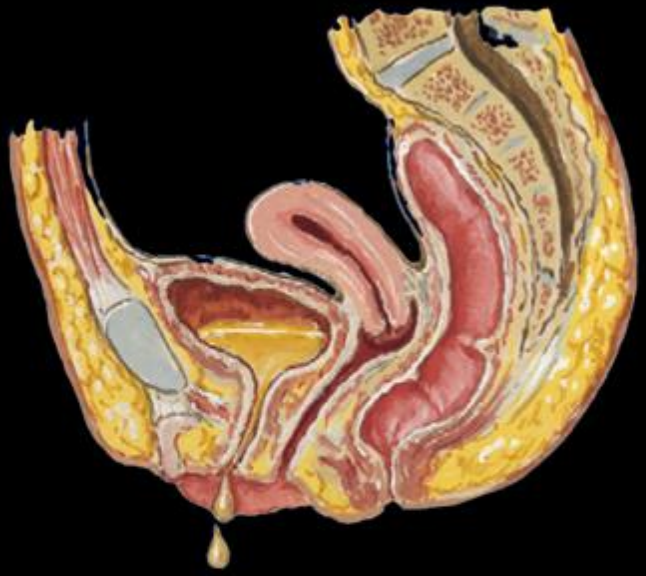
Eyes turned to right, left eye lags (to lesser degree)
Internuclear ophthalomoplegia

Convergence unimpaired

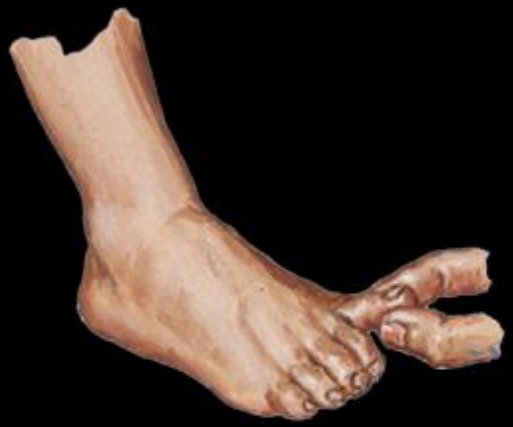
MS SYMPTOMS


Spinal cord manifestations
Spastic gait.
Patient needs
help walking.
F. Netter M.D.
Lhermitte sign: sudden sensation of electric shock
down spine and along arms when patient flexes neck

MS SYMPTOMS



Neurogenic bladder, with urinary urgency and dribbling



Loss of position sense

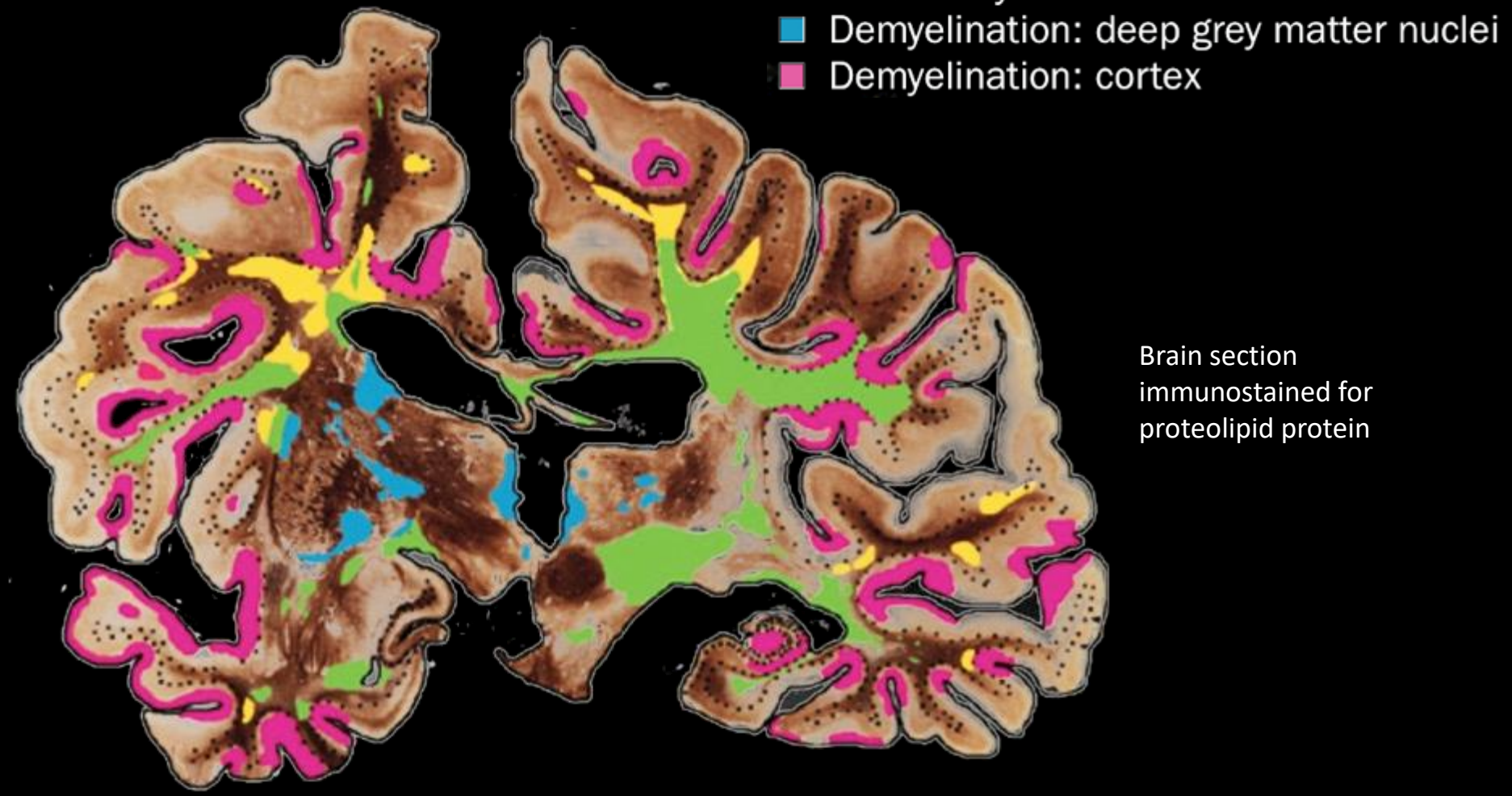
Paraplegia, partial or complete. Patient in wheelchair.

F. Netter M.D.

Progressive MS and compartmentalized inflammation

Progressive multiple sclerosis: pathology and pathogenesis

Hans Lassmann, Jack van Horssen and Don Mahad



Brain section immunostained for proteolipid protein

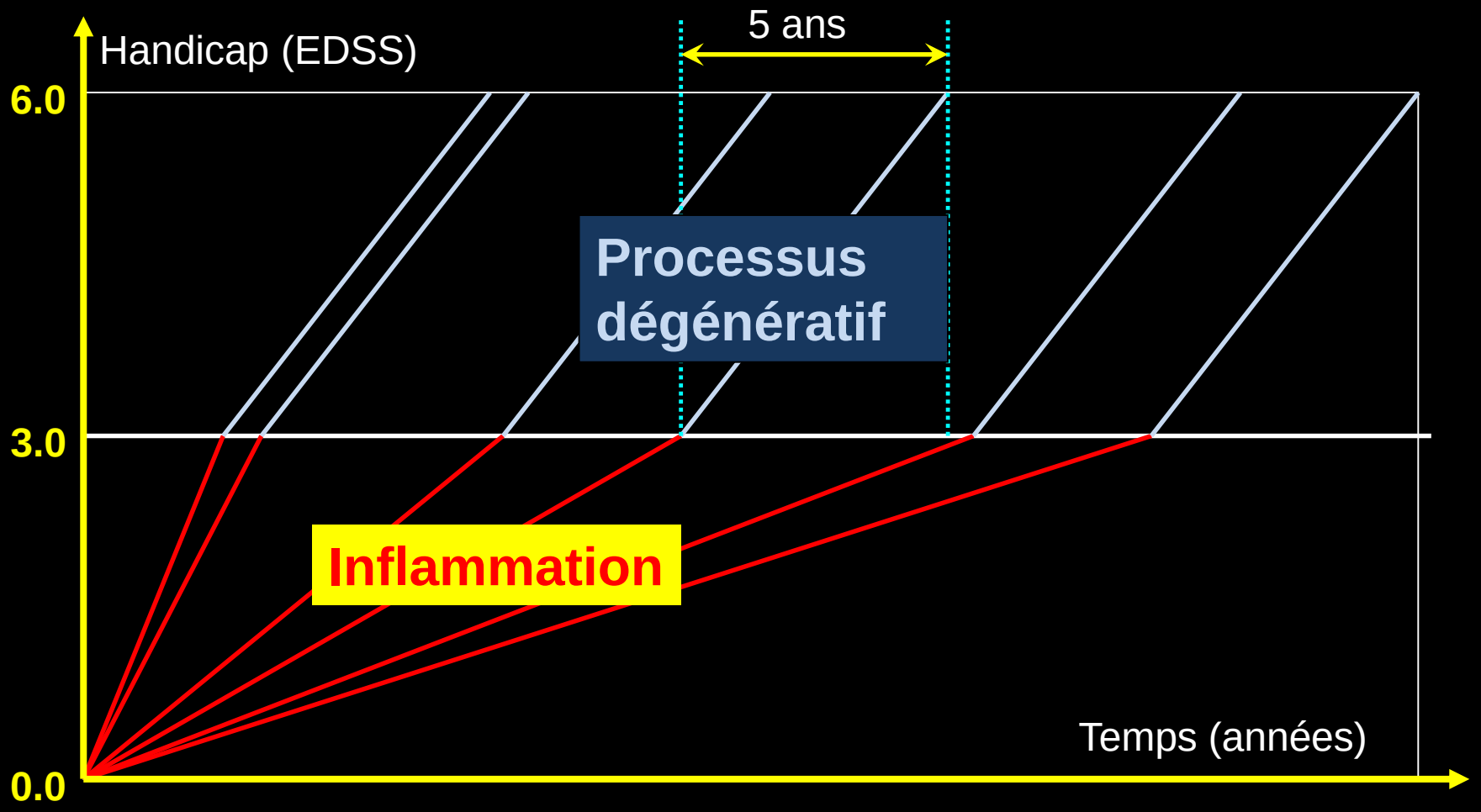
SEP : EDSS

0 : examen neurologique normal
1.0 : Aucune invalidité - signes minimes
2.0 : Invalidité minime
3.0 : Invalidité modérée - patient ambulatoire
4.0 : Invalidité relativement sévère - patient ambulatoire
5.0 : Marche sans aide ni repos - activités quotidiennes perturbées
6.0 : Assistance intermittente ou unilatérale constante
7.0 : Incapable de marcher plus de 5 mètres sans aide
8.0 : Alité ou en chaise - usage préservé des bras
9.0 : Patient alité - peut communiquer et manger

5.5

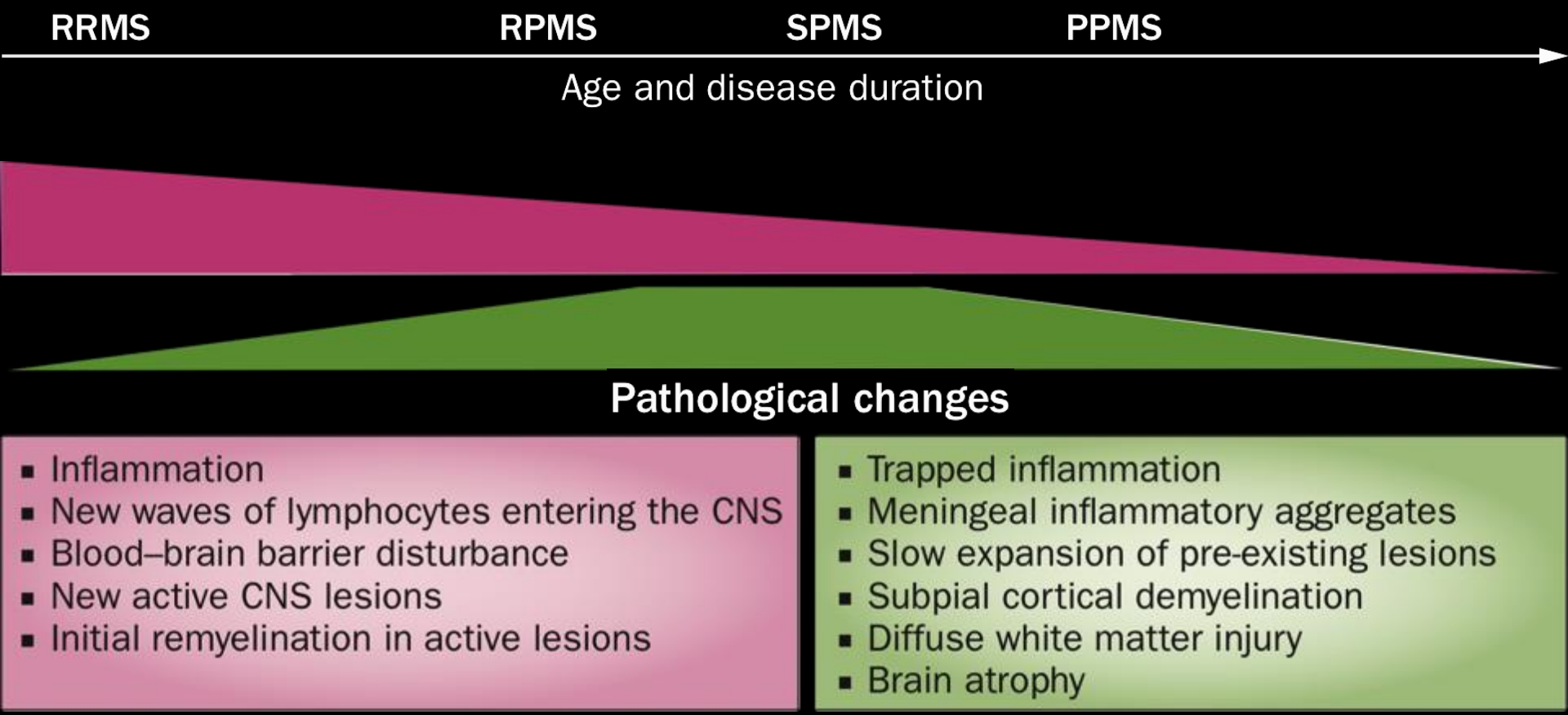
Kurtzke, 1983

Maladie en 2 étapes



Pathological Changes Throughout MS duration

Progressive multiple sclerosis: pathology and pathogenesis 2012



Disease Mechanisms Throughout MS duration

Progressive multiple sclerosis: pathology and pathogenesis 2012

Hans Lassmann, Jack van Horssen and Don Mahad

Disease mechanisms

- Oxidative injury
- Mitochondrial dysfunction
- Inflammation
- Microglia activation
- Oxidative burst
- Expression of NADPH oxidases
- iNOS expression

- Oxidative injury
- Mitochondrial dysfunction
- Mitochondrial DNA deletions
- Iron accumulation with ageing (oligodendrocytes, microglia, axons, neurons and astrocytes)

Controverse ECTRIMS 2017 Traiter les RIS ?

- C LEBRUN **(Contre)** :

  → **Argument principal :** Nous n'avons pas d'études épidémiologiques permettant d'affirmer que les contextes RIS et CIS soient superposables en terme d'histoire naturelle et de menaces. Il importe donc de mener d'abord des études complémentaires et notamment thérapeutiques (actuellement en cours au US et en Europe)

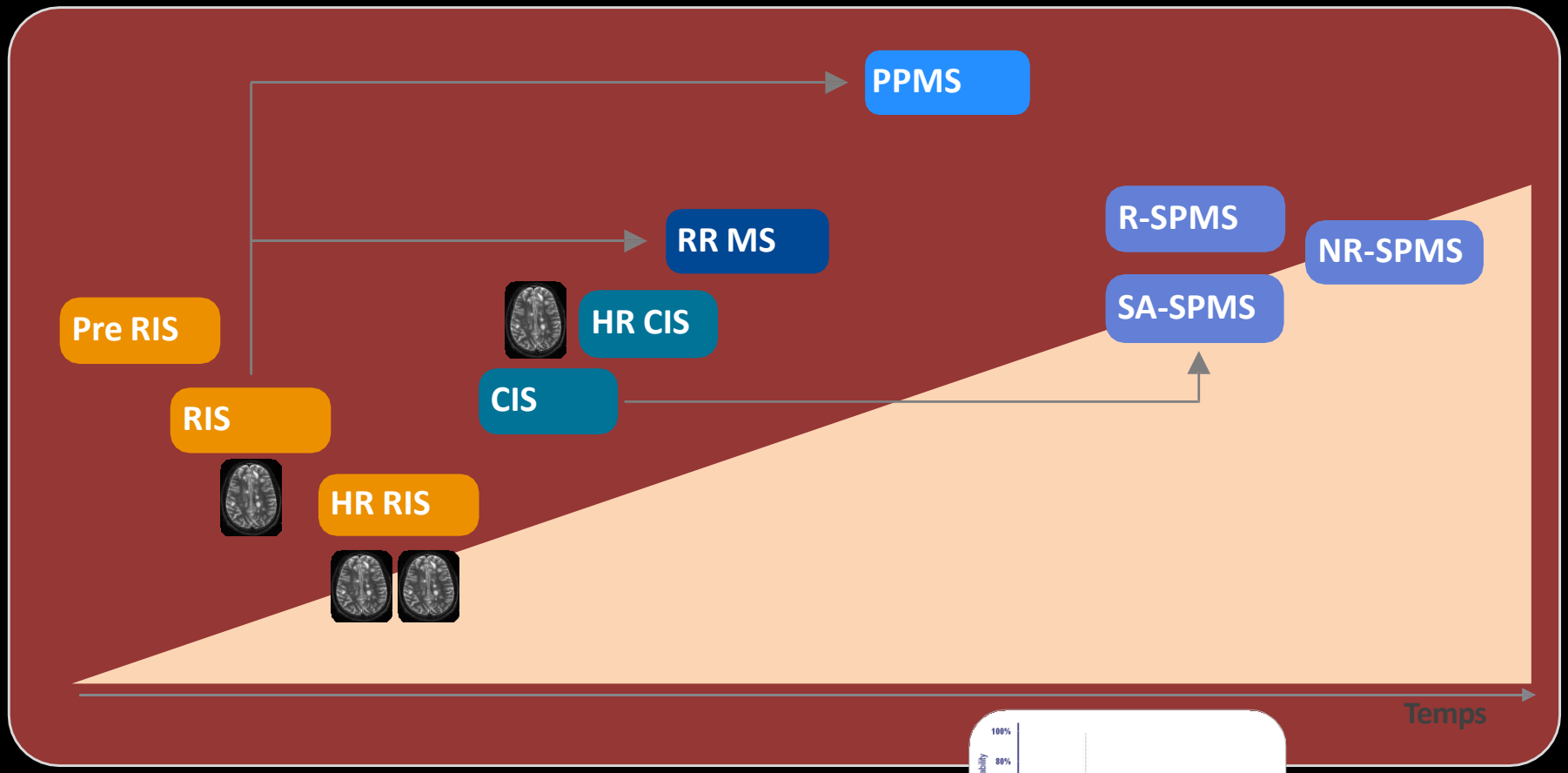
- DT OKUDA **(Pour)** :

  → **Argument principal :** L'imagerie et l'examen du LCR permettent d'identifier avec quasi certitude la présence d'une maladie inflammatoire chronique accumulant des lésions inflammatoires du SNC qui doivent être combattus

- O. KANTARCI **(Le médiateur)** :

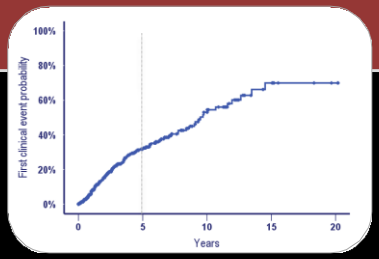
  → S'il n'y avait pas le coût des traitements chroniques, la controverse serait moins vive.. Les RIS identifiés comme à haut risque méritent dès à présent notre attention. Il faudra que les études en cours soient menées à leur terme pour lever cette controverse.

Le spectre des maladies inflammatoires démyélinisantes



34% de conversion à 5ans

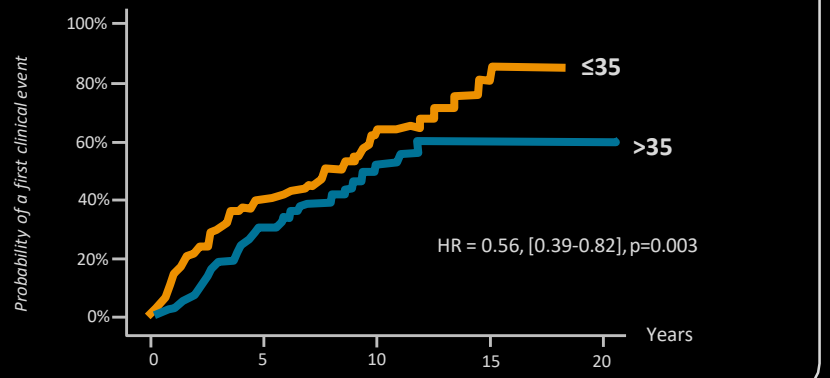
Okuda et al, et al, PLOS, 2014



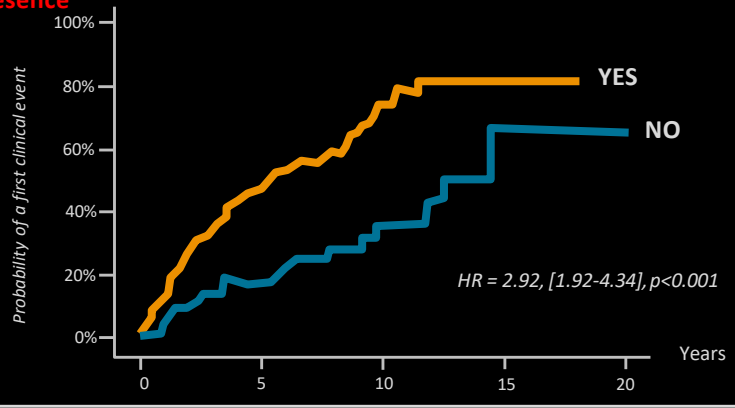
Les facteurs de risque de conversion

Les RIS à haut risques (HR RIS)

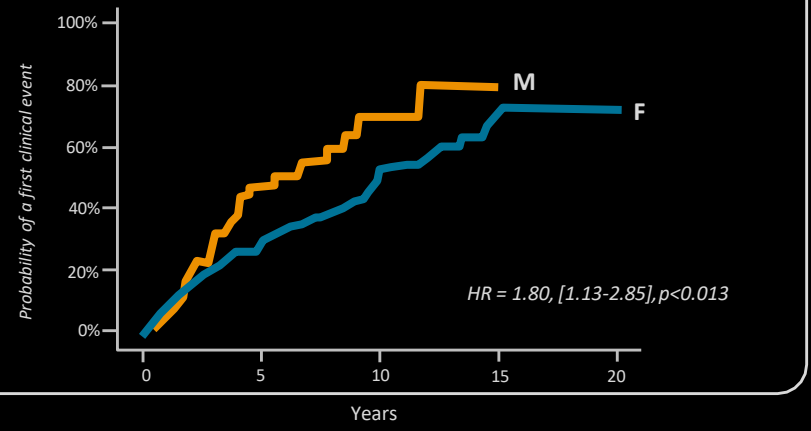
Age at RIS MRI



Spinal cord lesions presence



Sex



Age < 35, sexe masculin, lésions de moelle épinière sont des critères péjoratifs

Caractéristiques des patients ayant converti							
RIS converti	N	F (%)	Age	Délai (a)	LCR+ (%)	médullaire IRM + (%)	Gad + (%)
RR	153	79	37.1	2.3	65	68	43
PP	14	43	43.8	3.7	83	83	6

Okuda et al, et al, AAN, 2013 - Kantarci et al, ECTRIMS, 2013

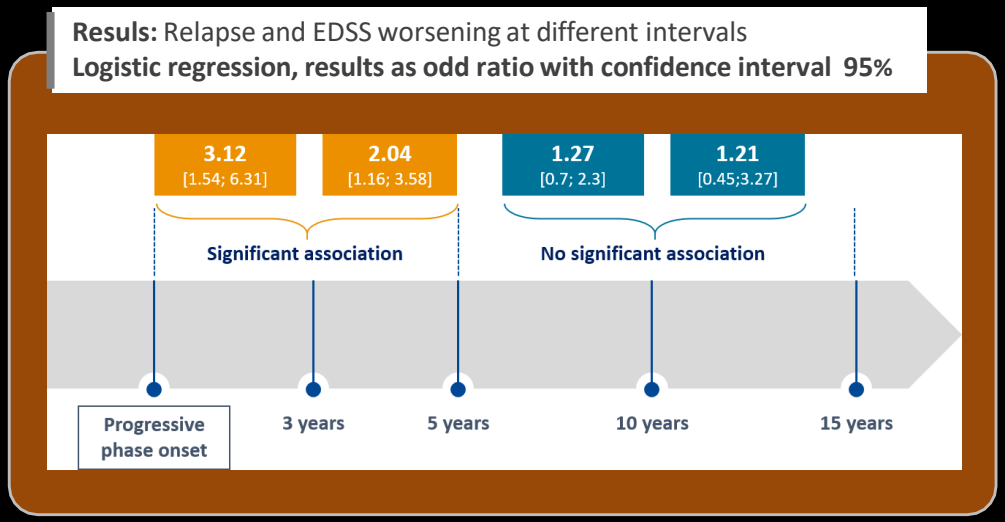
Les poussées dans les formes secondairement progressives

La place de l'âge et leur lien avec la progression des handicaps

- **Objectifs**
  Préciser la fréquence des poussées , les facteurs prédictifs de leur survenue, leur place dans la progression du handicap à la phase progressive de la maladie.

- **Méthode**
  506 patients de la cohorte EDMUS Rennes ayant une forme secondairement progressive ont été suivis pour une durée moyenne de 24 ans après le début de la phase progressive. 35% ont des poussées pendant la phase progressive (24% dans les 5 premières années après le début de la progression).

- **Résultats**
  Le seul facteur prédictif de poussée à la phase progressive est **l'âge**.
  Les poussées n'influencent pas globalement le temps entre le début de la progression et le passage à un EDSS 6, mais **influencent l'aggravation des handicaps au cours des 5 1ères années après début de la phase progressive pas au-delà.**



A. Ahrweiller, ECTRIMS 2017, communication 108

Quel impact à long terme des traitements de fond sur l'évolution des patients vers la forme secondairement progressive ?

- Patients sélectionnés de MS Base (240 traites par immunomodulateurs (INF ou GA), 109 par Fingolimod, Natalizumab 93, Alemtuzumab 44) comparés à des non traités … suivi moyen 9 ans
- Harmonisation clinique des patients (score de propension)
- Résultats
  - → Le temps de passage à une forme secondairement progressive était significativement allongé chez les patients traités par immunomodulateurs, fingolimod, natalizumab ou natalizumab comparé aux patients non traités.
  - → Le temps de passage à une forme secondairement progressive était significativement allongée chez les patients traités par des traitements dits "très actifs" comparé aux immunomodulateurs injectables
  - → L'effet bénéfique des traitements était supérieur si ceux-ci étaient débutés dans les 5 premières années

JWL Brown, ECTRIMS 2017, communication 128

Marqueurs en imagerie prédictifs du risque de passage en forme secondairement progressive

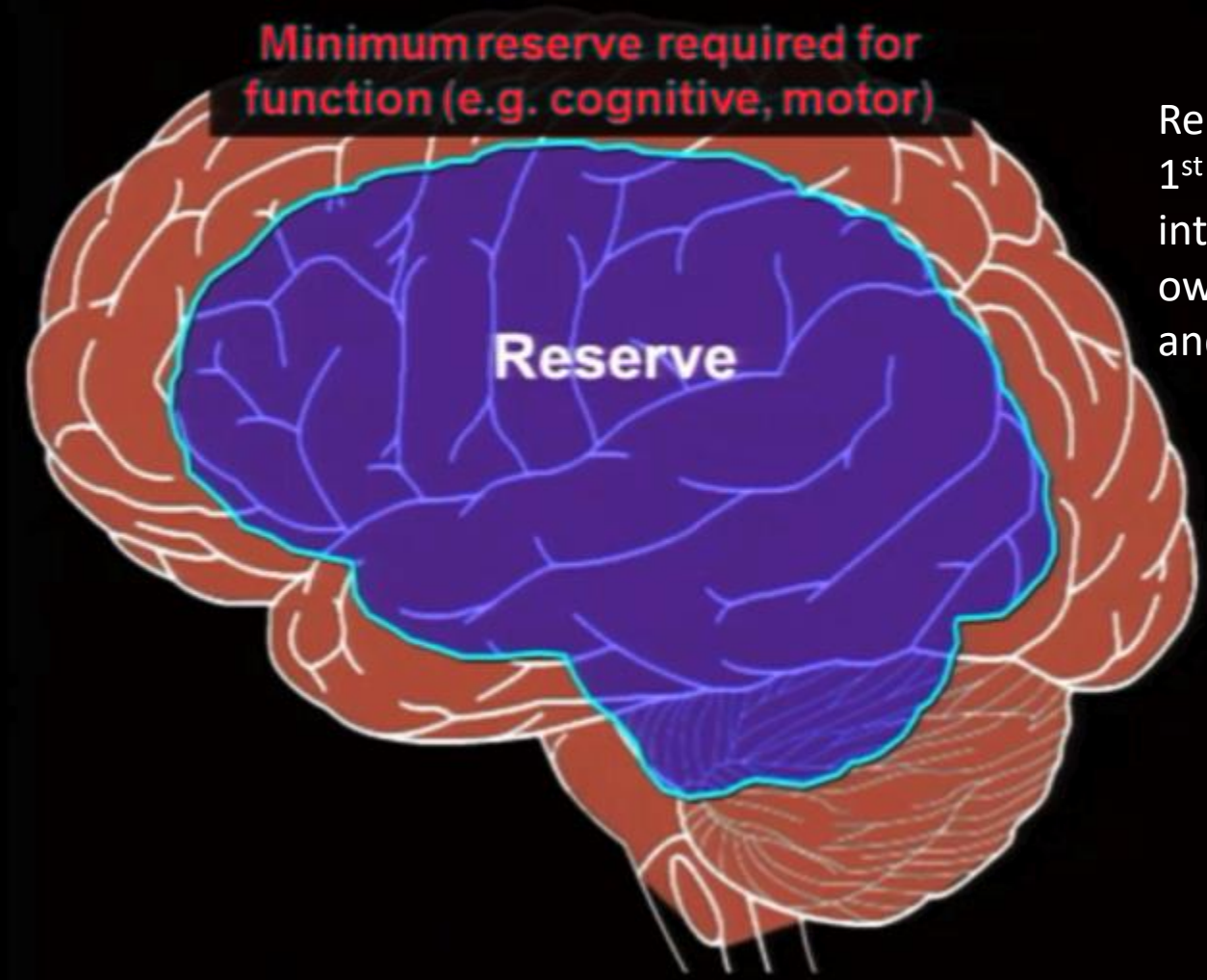
- Population et méthodes
  - → 164 patients ont eu une IRM médullaire et cérébrale au stade CIS, 136 à 1 an, 121 à 3 ans et ont été suivis cliniquement 15 ans
  - → À 15 ans de suivi, 25 patients (15% environ) ont eu une évolution secondairement progressive, 94 patients étaient en forme rémittente, 45 patients étaient toujours au stade CIS

- Les lésions médullaires et infra-tentorielles sont fortement prédictives de SEP secondairement progressive
  - → A 1 an, si lésions gadolinium sur la moelle , le "odds ratio (OR)" est=2,3, de nouvelles lésions T2 (OR=5.7) et de lésions infra tentorielles (OR = 7)
  - → A 3 ans, si nouvelles lésions médullaires (OR= 3,8), nouvelles lésions infra tentorielles (OR= 3,3)
  - → Chez les patients qui n'ont ni nouvelle lésion médullaire , ni lésions infra-tentorielles à 3 ans, le risque d'être SPMS est de 0,9% *vs* 53% chez ceux qui ces deux marqueurs positifs

L'accumulation de lésions dans des zones éloquentes pourrait représenter un des mécanismes puissants conduisant la la SPMS !

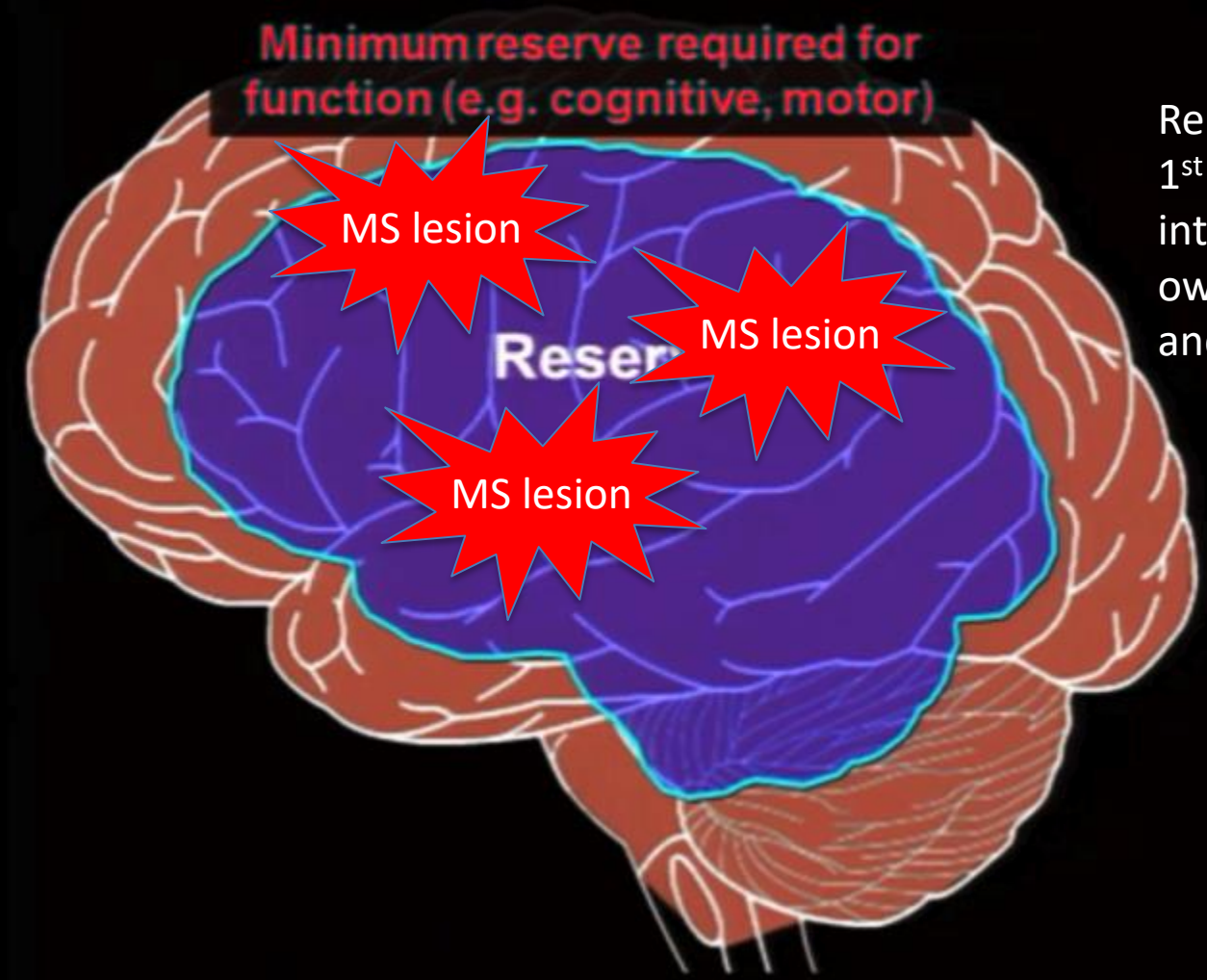
WJ Brownlee, ECTRIMS 2017, communication 101

Early MS disease Activity Depletes Functional "Reserve"



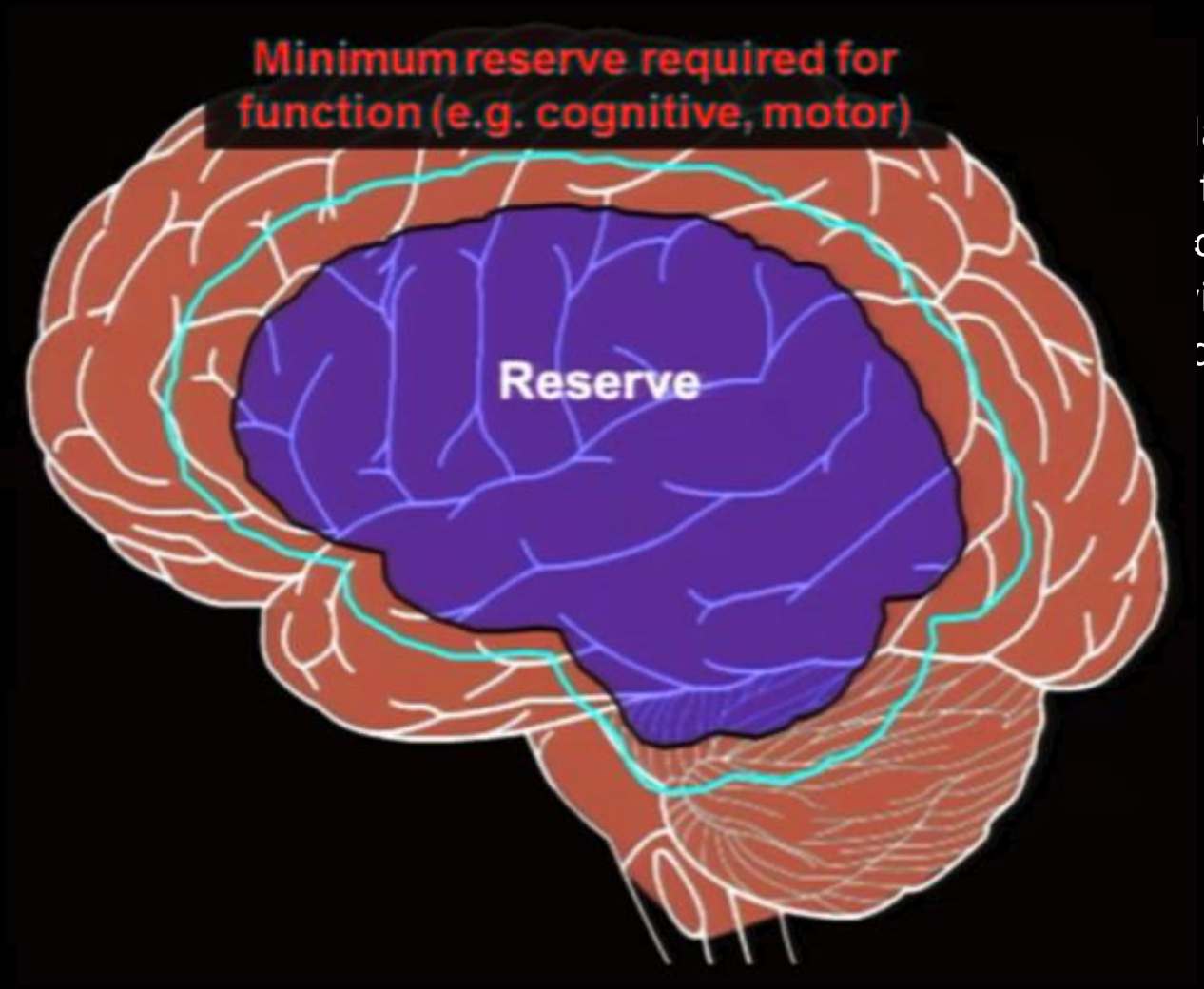
Relapses & MRI activity in the 1st few years may not translate into immediate disability owing to neuronal plasticity and redundancy

Early MS disease Activity Depletes Functional "Reserve"



Relapses & MRI activity in the 1st few years may not translate into immediate disability owing to neuronal plasticity and redundancy

Early MS disease Activity Depletes Functional "Reserve"



apses & MRI activity in the
few years may not translate
o immediate disability
ing to neuronal plasticity
d redundancy

Interféron beta et mortalité dans la SEP

La question du bénéfice à long terme des traitements de la SEP reste une question ouverte..
L'influence sur la portalité en est un marqueur puissant.

- **Méthode**
  - → A partir d'une cohorte de Vancouver et Rennes de 7009 patients Sur un suivi median 12 ans, 30% de ce temps ont été exposé à l'INF, 11% à l'acétate de glatiramer, 12% à d'autres IS. 649 patients sont décédés (âge médian 60 ans). l'association déces/INF a été comparée à une population contrôle de 20 patients non traités.

Association between all-cause deaths and IFNβ exposure

	CANADA Cases : 569	FRANCE Cases : 80	COMBINED Cases : 649
IFNβ (≥180 days)	0.67 (0.50 - 0.90)	0.67 (0.35 - 1.28)	0.68 (0.52 – 0.89)
Cumulative exposure			
IFNβ ≥3 years	0.95 (0.67 - 1.36)	1.11 (0.52 - 2.40)	1.00 (0.73 - 1.38)
IFNβ > 3 years	0.46 (0.30 - 0.70)	0.37 (0.15 - 0.95)	0.44 (0.30 - 0.66)

- **Résultats**
  - → Le risque de décès est de 32% moindre chez ceux traités par INF et plus particulièrement chez ceux qui ont reçu INF> 3ans (OR: 0,44)

La prescription d'interféron a été associée dans les deux centres à un risque diminué de mortalité sur une période d'observation de 18 ans

E Kingwell, ECTRIMS 2017, communication 218

Traitement de la poussée

- Authentification de la poussée
  - Pièges multiples
  - Fièvre et facteurs confondants
  - Accentuation d'un signe déficitaire ou nouveau signe
  - Symptômes spécifiques (Lhermitte)
- Corticoïdes
  - Haute dose – courte période
    - Méthylprednisolone 1000 mg / j
      - 3 à 5 jours
      - IV ou per os

Traitement de la poussée

- Traitements associés
  - Protection gastrique (IPP ou Ranitidine)
  - Calcium 1250 mg/j – 2 mois
  - Vitamine D : D-cure 1 amp/sem – 2 mois
  - Benzodiazépine si nécessaire
- Surveillance étroite
  - Glycémie
  - Rythme cardiaque
  - Comportement et sommeil

Traitements “de fond”

- Syndrome cliniquement isolé (SCI)
  - 1er événement
  - Pas de dissémination temporelle
  - Traitements de première ligne
  - Facteurs pronostiques
    - Charge lésionnelle FLAIR
    - Nombre de lésions IRM
  - Grande importance du suivi

Traitements “de fond”

- Sclérose en plaques (MacDonald 2010)
  - Hiérarchie des traitements
    - 1ère ligne
      - Injectables (Interférons β – Copolymère)
      - Voie orale (Tériflunomide, DMF)
    - 2ème ligne
      - Voie orale (Fingolimod)
      - Voie IV
        - » Natalizumab
        - » Alemtuzumab
    - « Secours »
      - Cytostatiques (Mitoxantrone, Cyclophosphamide)
      - Greffe de moelle osseuse
    - En développement
      - Ocrelizumab, Daclizumab, Cladribine, Siponimod, anti-Lingo, Ofatumumab, etc.

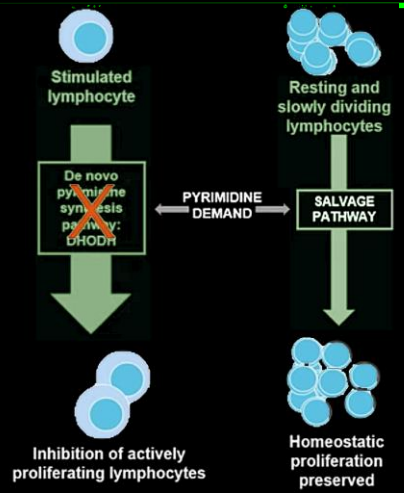
Injectables 1ère ligne

- Interféron-β1b (Betaferon°)
  - s/c – 1 j / 2
- Interféron-β1a
  - IM 1 x / sem (Avonex°)
  - s/c 3 x / sem (Rebif° 22 & 44 µg)
  - s/c 1 x / 15 j (Plegridy°)
- Association de petits acides aminés
  - s/c
  - 1 x / j – Copaxone° 20 mg
  - 3 x / sem – Copaxone° 40 mg

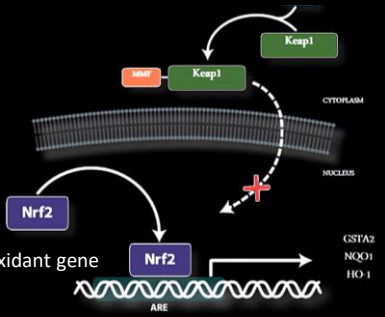
- Effet partiel sur la fréquence des poussées (court terme)
- Effet partiel sur la progression du déficit (long terme)

Voie orale - 1ère ligne

- AUBAGIO (Teriflunomide)
  - 1 prise par jour
  - Surveillance
    - Hémogramme et tests hépatiques (6 premiers mois++ puis 1x / 3 mois)
    - PA
    - Acide folique si cheveux plus fins et troubles digestifs



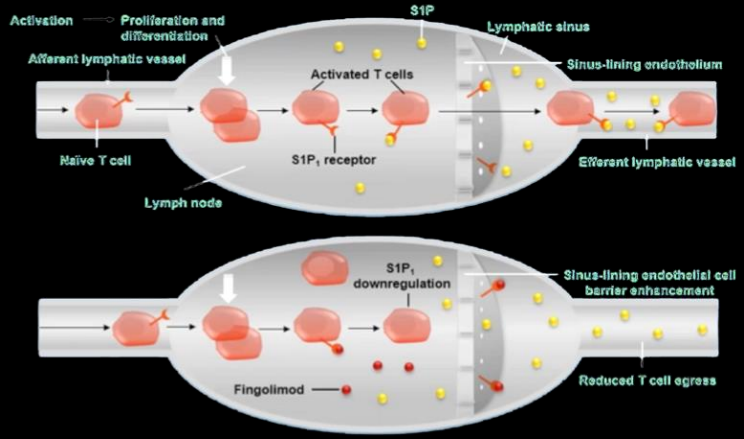
- TECFIDERA (Dimethyl-fumarate)
  - 2 prises par jour (120 puis 240 mg 2x/j)
  - Surveillance
    - Lymphocytose (âge) et tests hépatiques
    - Flushs et troubles digestifs



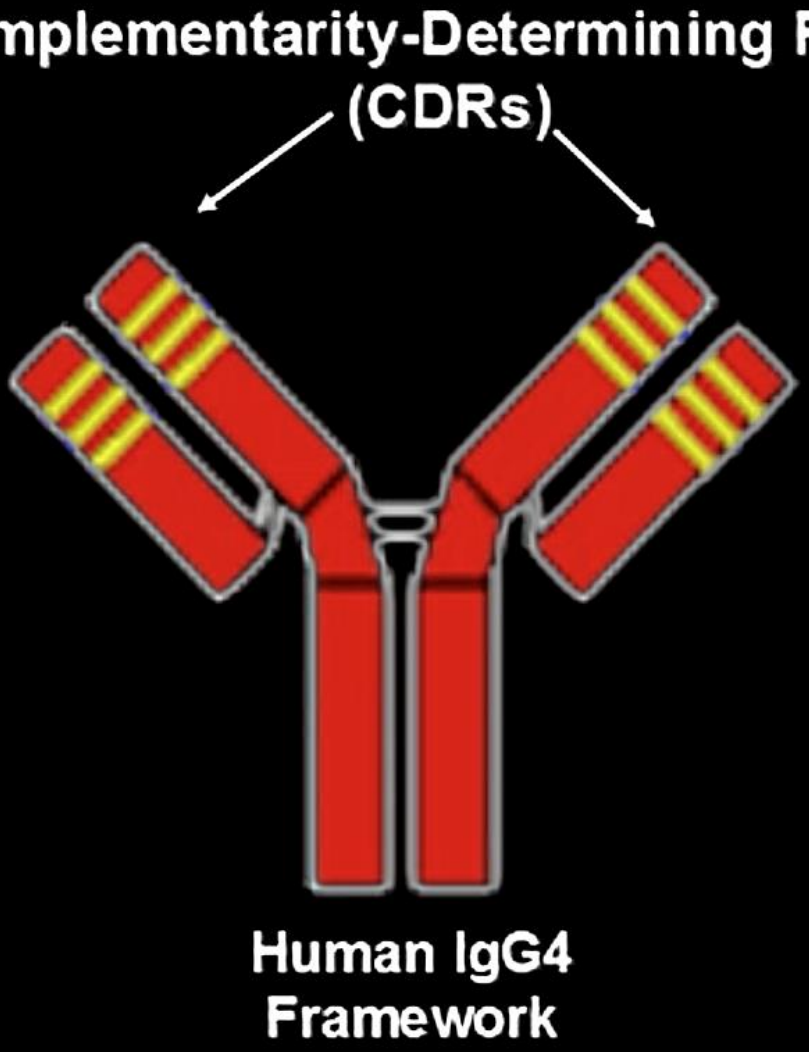
Nrf2 induces antioxidant gene transcription

2ème ligne – GILENYA (Fingolimod)

- Voie orale
- 1 x par jour
- Délivrance hospitalière uniquement
- Status HVZ avant traitement
- Surveillance
  - ECG et rythme cardiaque – 6 premières heures
  - Ex. ophtalmologique à 3 mois (œdème papillaire)
  - Lymphocytose (300-900 / mm^3)
  - Tests hépatiques
  - Infections virales
  - Pas de vaccins vivants

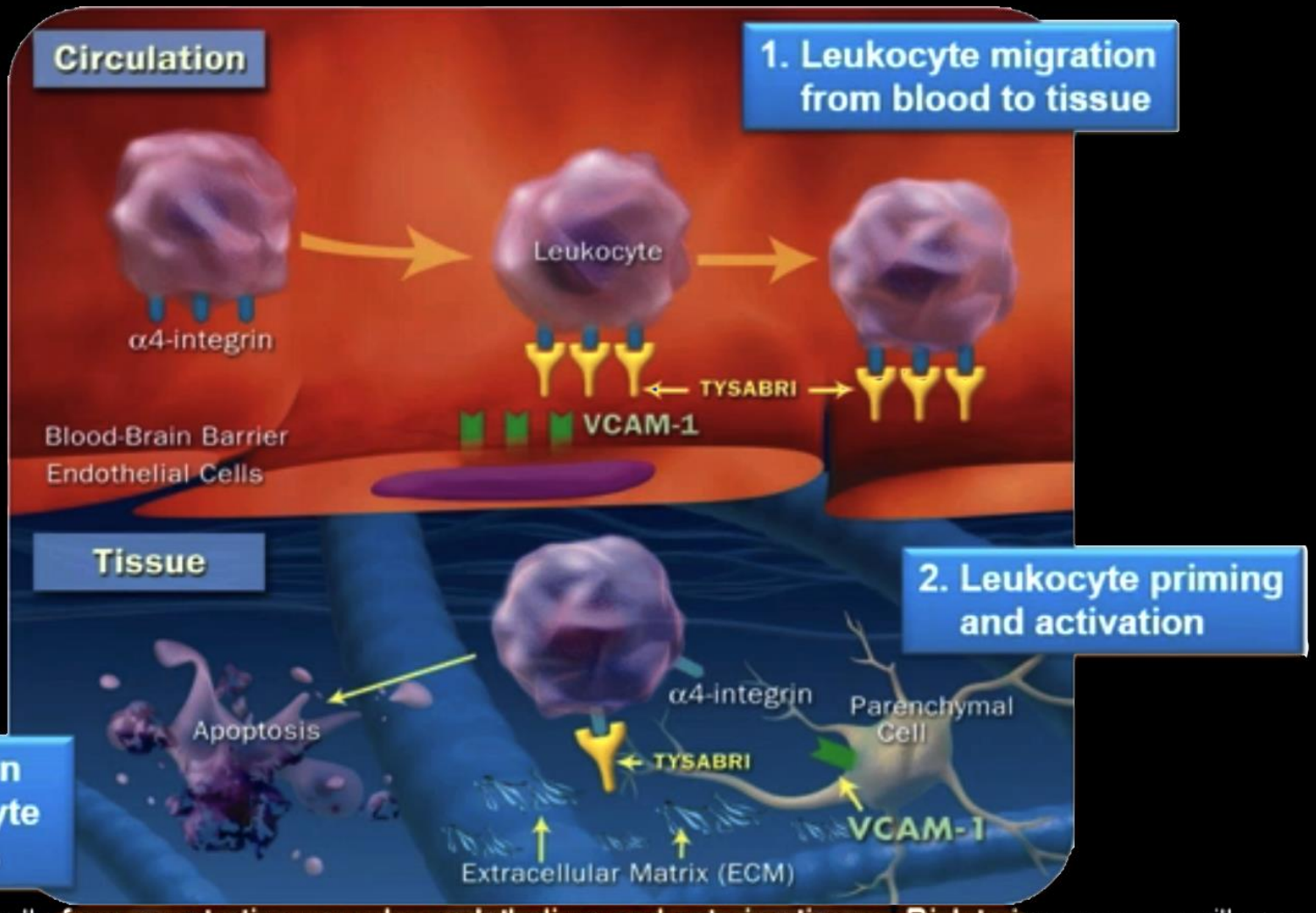


Natalizumab



- CDR grafted from murine antibody
- Human IgG_4 framework
- Retains full potency

Tysabri Mechanism of Action



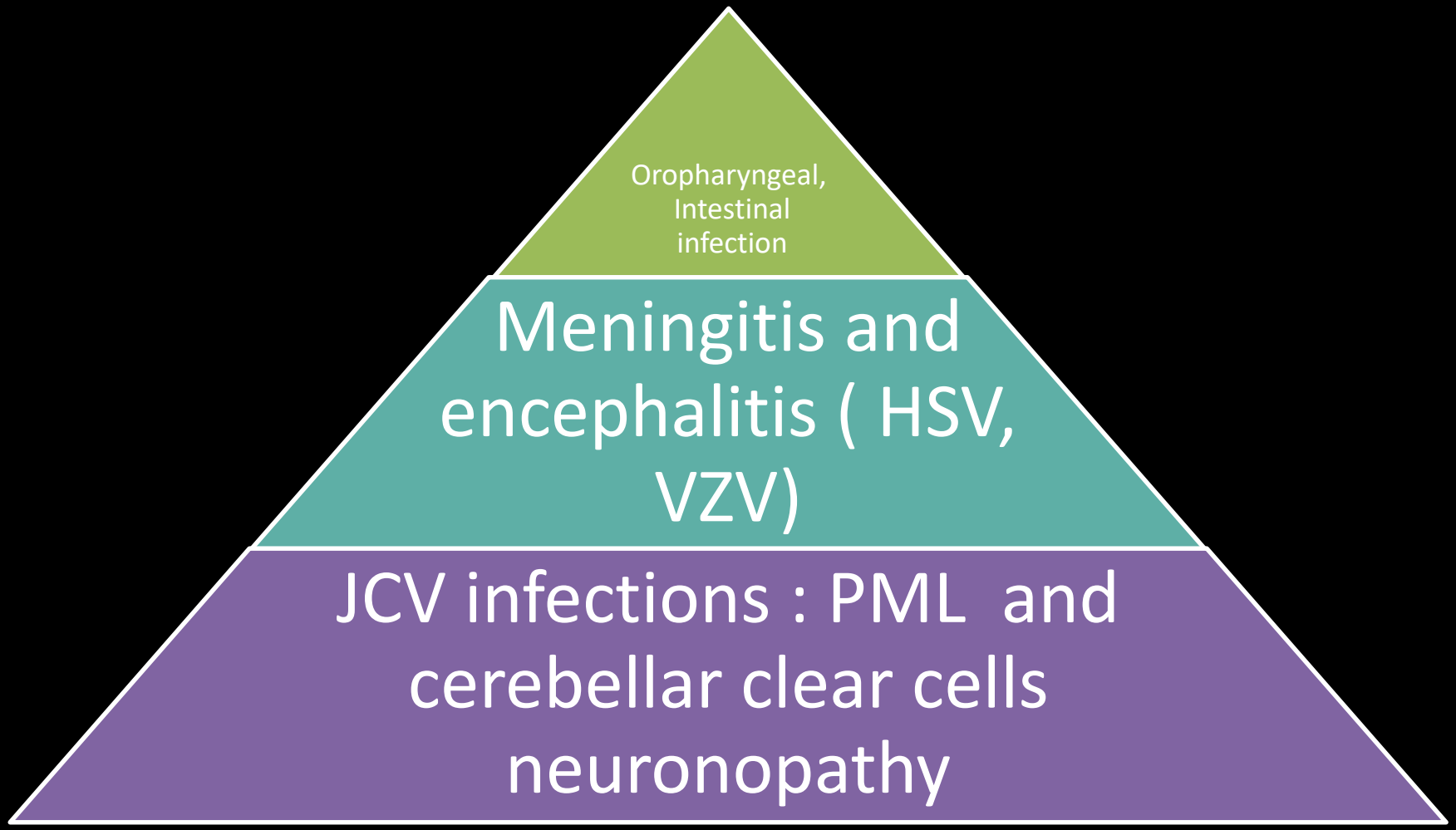
Tysabri inhibits cells from penetrating vascular endothelium and entering tissue. Risk to immune surveillance.

Cannella B. et al. *Ann Neurol.* 1995;37:424-435; TYSABRI® (natalizumab) US Prescribing Information; Yednock TA, et al. *Nature.* 1992;356

Natalizumab – Tysabri°

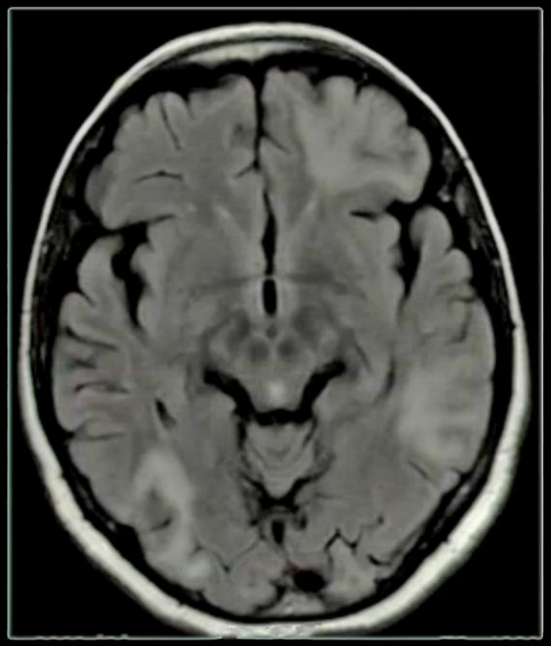
- Voie IV
- 300 mg 1 x / mois
- Surveillance :
  - Hémogramme et tests hépatiques
  - Selon sérologie JC virus
    - JC V négatif : risque de LEMP < 1/10000
    - JC V positif : risque de LEMP 1-5/100 si traitement > 2 ans
      - » Surveillance IRM +++
- Tolérance :
  - Réactions immédiates et risque allergique

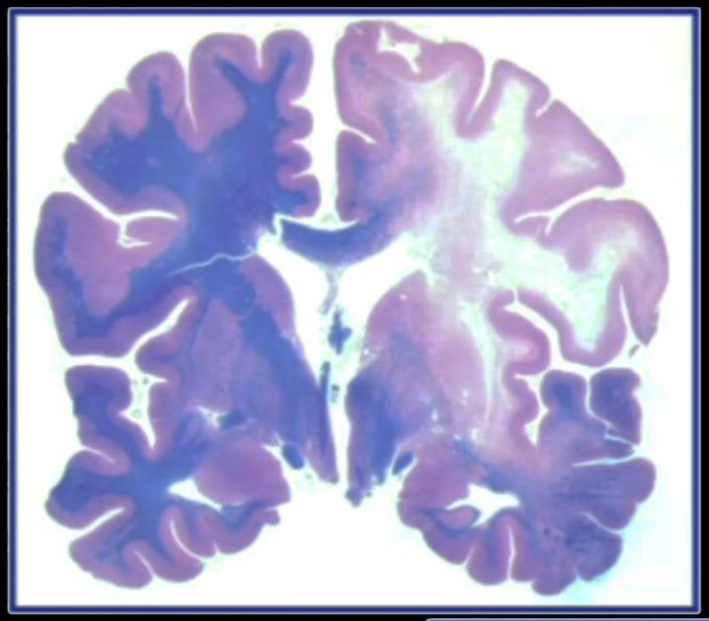
Natalizumab et infections

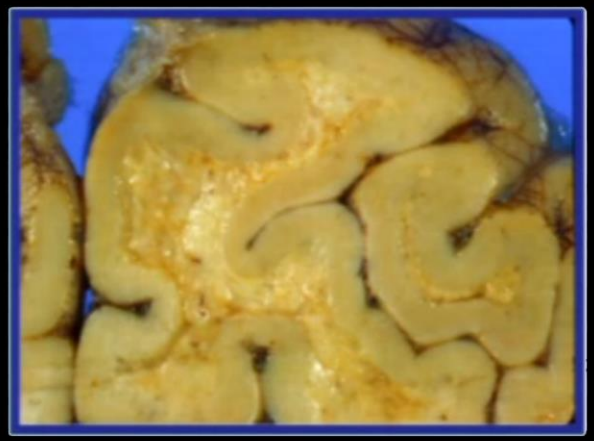


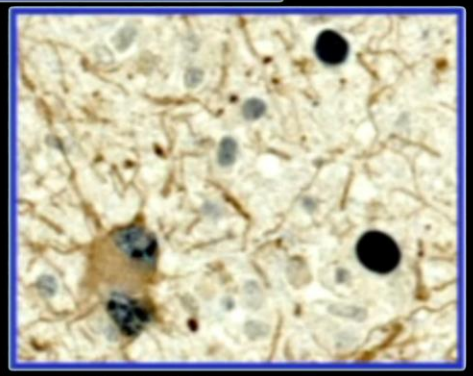
Tysabri° et LEMP

Progressive Multifocal Leukoencephalopathy







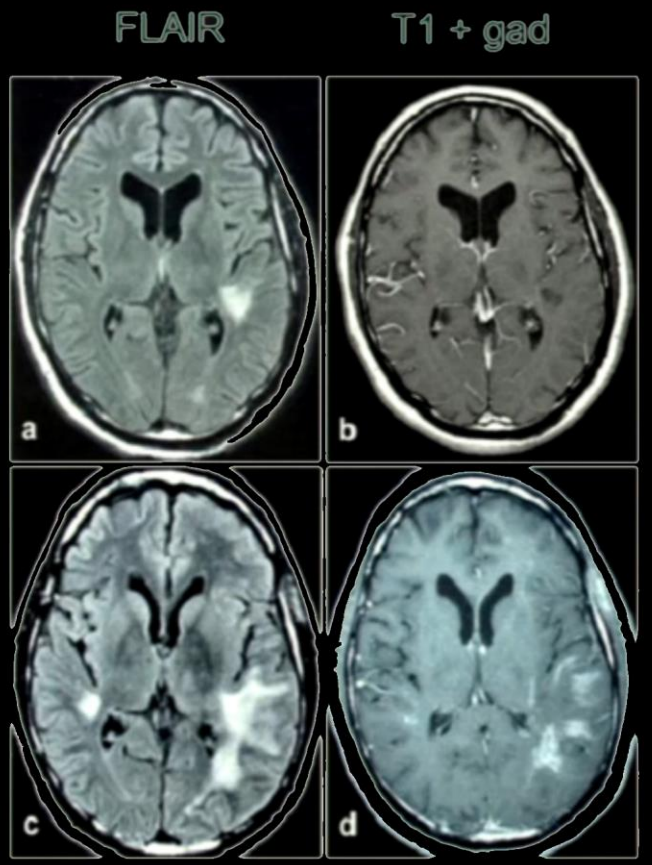


RUSH UNIVERSITY MEDICAL CENTER

Syndrome de Reconstitution Immune - IRIS

PML/IRIS

- immune reconstitution inflammatory syndrome (IRIS)
- abrupt worsening of neurological function in the setting of immune recovery, *different* than the natural progression of PML
- paradoxical development of an inflammatory form of PML
- Common in HIV-PML patients treated with cART



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Alemtuzumab

A humanized IgG1 monoclonal antibody (mAb) specific for CD52 expressed on T cells, B cells and monocytes/macrophages. Leads to rapid cell depletion. Used in treatment of B cell chronic lymphocytic leukemia.

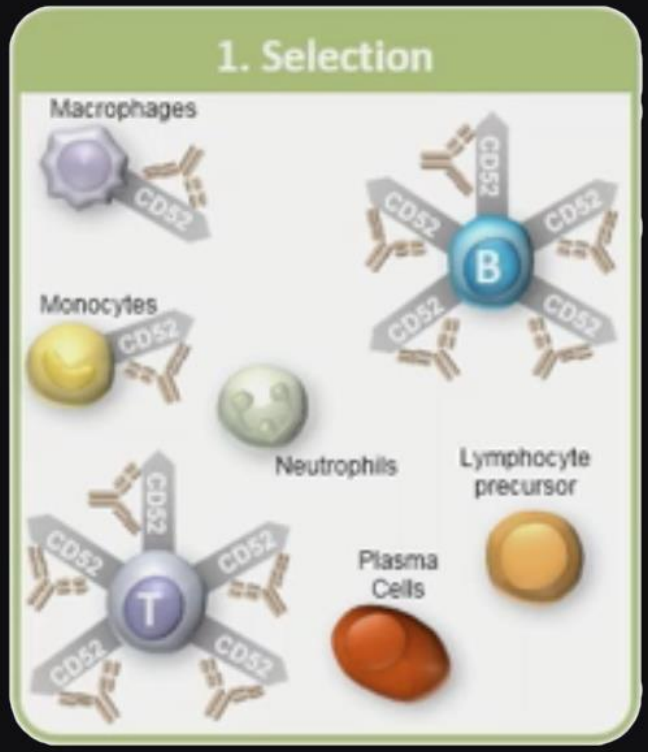
Alemtuzumab effectively reduced RR in comparison to subcutaneous IFN-β 1a in phase III trials (Cohen, J.A., et al. *Lancet Neurol*. 2012; Coles, A.J., et al. *Lancet Neurol*. 2012).

Depletion of lymphocytes poses risk of immune suppression. Some data indicate alemtuzumab promotes immune modulation (e.g. transient increase in Treg cells).

Alemtuzumab treatment is associated with autoimmune conditions, including idiopathic thrombocytopenic purpura, thryoiditis and antiglomerular basement membrane disease (Goodpasture's Syndrome.

Alemtuzumab Proposed Mechanism of Action in MS : CD52 Targeting

- The mechanism by which alemtuzumab exerts its therapeutic effects in MS is presumed to involve binding to CD52[1]
- CD52 is a cell surface antigen present on T and B lymphocytes, and on natural killer cells, monocytes, and macrophages[1]

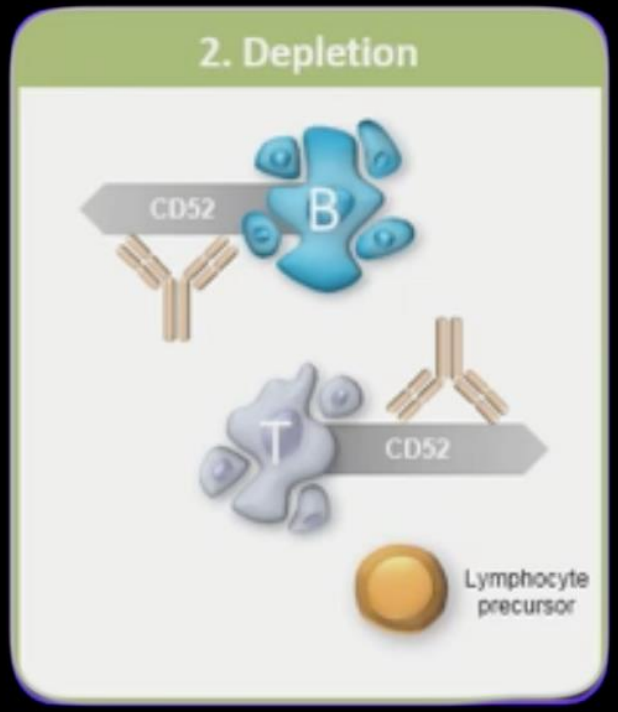


The mechanism by which alemtuzumab exerts its therapeutic effects in MS is unknown

Hu Y et al. *Immunology* 2009;128;260-70; 3. Coles AJ et al. *Lancet* 2012;380:1829-39.

Alemtuzumab Proposed Mechanism of Action in MS : Lymphocyte Depletion

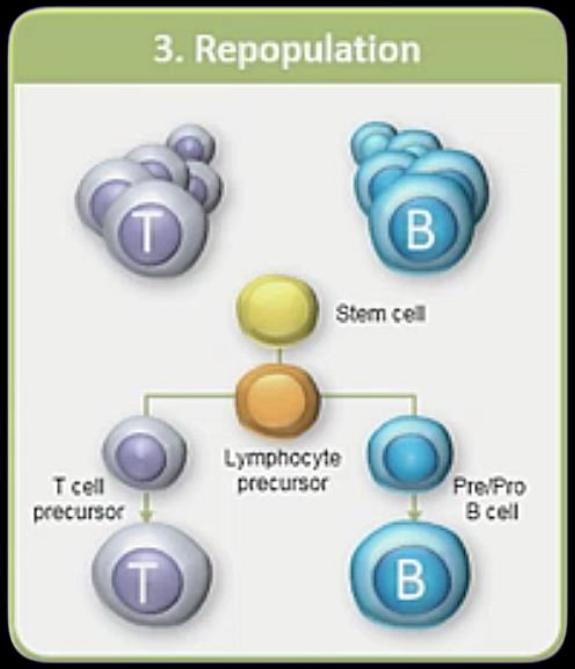
- Following cell surface binding to T and B lymphocytes, alemtuzumab results in lymphocyte depletion via antibody-dependent cellular cytolysis and complement-mediated lysis[1]



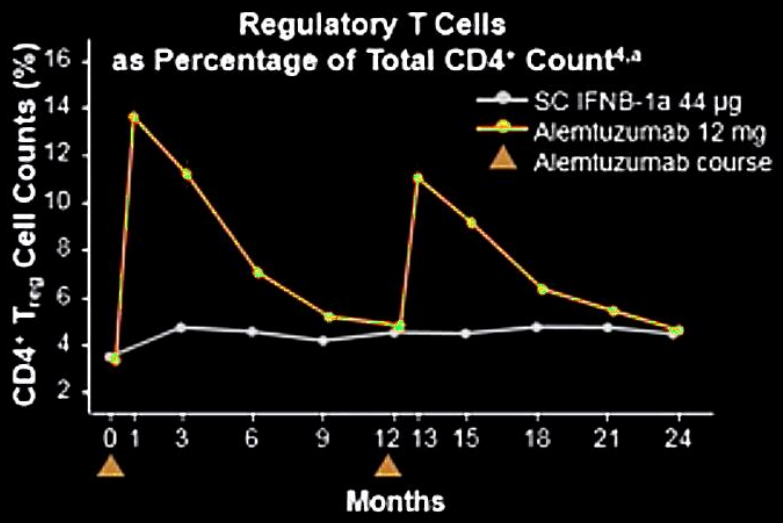
The mechanism by which alemtuzumab exerts its therapeutic effects in MS is unknown

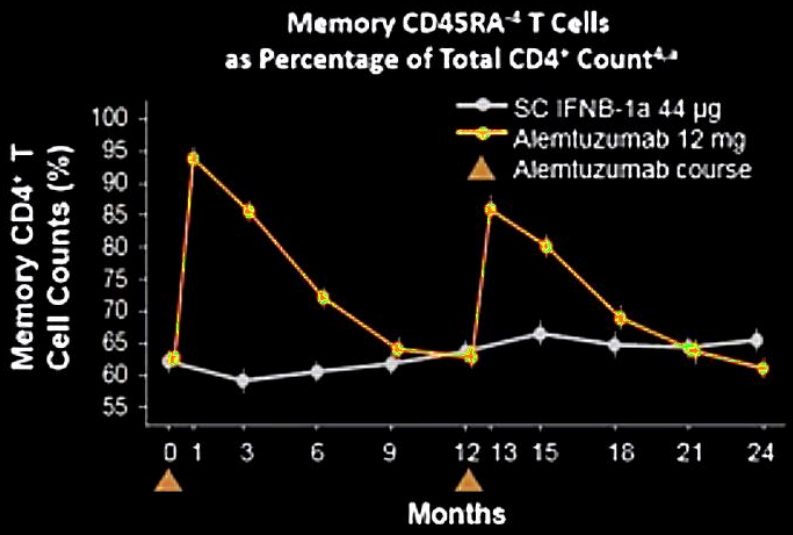
Hu Y et al. *Immunology* 2009;128:260-70. 3 Turner MJ et al. *J Neuroimmunol* 2013;261:29-36. 4. Kovarova I et al. ENS 2012, P341.

Alemtuzumab Proposed Mechanism of Action in MS : Repopulation of Immune Cells



The mechanism by which alemtuzumab exerts its therapeutic effects in MS is unknown





[a] Alemtuzumab was administered at Months 0 and 12.

SC IFNB-1a=subcutaneous interferon beta-1a; Treg=regulatory T cell

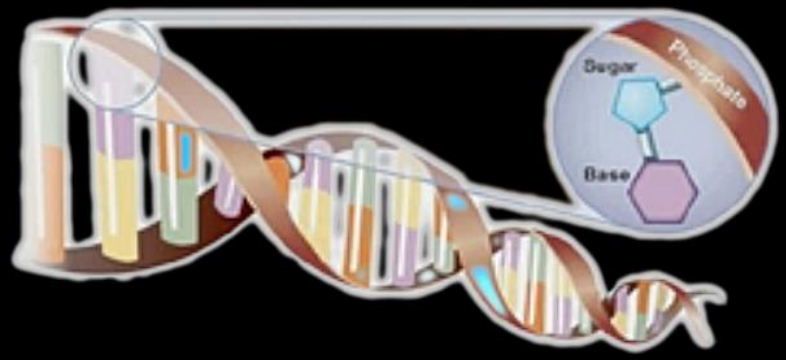
1. Hu Y et al. *Immunology* 2009;128;260-70; 2.Turner MJ et al. *J Neuroimmunol* 2013;261:29-36; 3. Cox AL et al. *Eur J Immunol* 2005;35:3332-42; 4. Hartung HP et al. ECTRIMS 2012, P935;

Alemtuzumab – Lemtrada°

- Voie IV
- 12 mg en 4 à 6 heures / j
  - 5 jours année 1
  - 3 jours année 2
  - Cycles complémentaires si nécessaire (30%)
- Surveillance++
  - Biologie (hémogramme, urines, TSH)
    - 1 x / mois pendant 4 ans
- Risques :
  - Auto-immunité secondaire
    - » Thyroïdite (Basedow – rôle du tabac)
    - » PTI monophasique
    - » Glomérulopathie

Anti-neoplastic (DNA-targeting) Agents

Mitoxantrone (Novantrone®)



An anthracenedione

Related to the anthracycline, Adriamycin (Daunorubicin)

Approved in 2000 for progressive MS (i.e. secondary progressive, progressive relapsing or worsening relapsing MS)

Binds DNA, inhibits topoisomerase II. Nonspecifically reduces B and T cells.

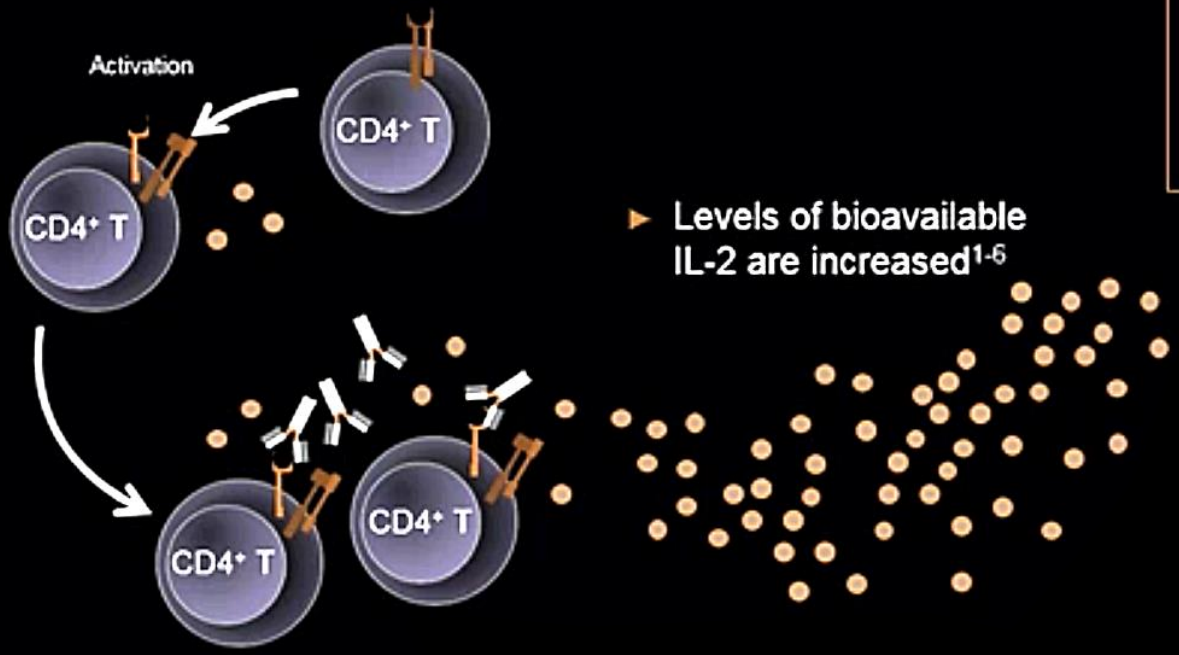
Like the anthracyclines, mitoxantrone is associated with cardiac toxicity and long-term risk of secondary acute promyelocytic leukemia (aPL) (t(15;17) translocation). In 2000, estimated risk of aPL for treatment in MS (1/401 or appx 0.25%). In 2010, risk estimate for aPL (1/123 or appx 0.81%) (Marriott, JL, *et al. Neurology* 74:1463-1470).

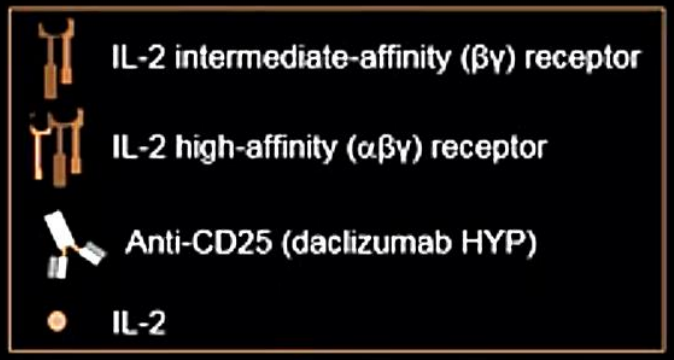
Cyclophosphamide

Alkylating agent used in progressive MS. Also, risk of secondary malignancy.

CD25 blockade induces a shift of IL-2 signalling from activated T-cells to CD56^{bright} NK cells

- Activation of T cells induces expression of IL-2 high-affinity receptor and production of IL-2[1-5]





- Levels of bioavailable IL-2 are increased[1-6]

- CD25 blockade prevents IL-2 consumption by activated T cells and increases IL-2 production (via inhibition of negative feedback)[1-5]

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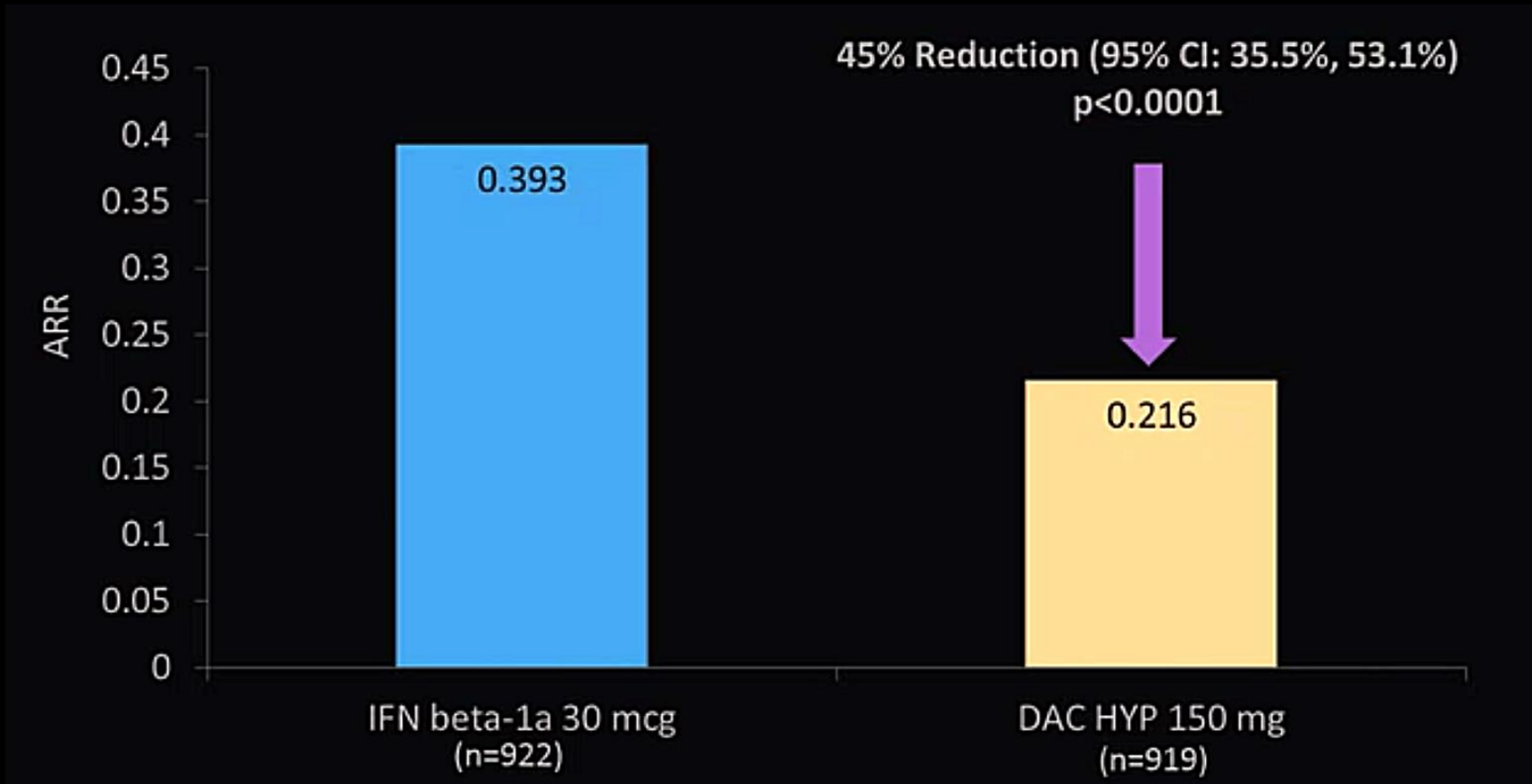
Annualized Relapse Rate (ARR)



Estimated from a negative binomial regression model adjusted for baseline relapse rate, history of prior IFN beta use, baseline EDSS (≤2.5 vs > 2.5) and baseline age (≤35 vs >35). Patients were censored at the earliest of the following events: 1) start of alternative MS medication, 2) 180 days post treatment discontinuation or 3) end of treatment period. CI, confidence interval.

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DECIDE: Safety and Tolerability of DAC HYP[1-3]

- Safety findings consistent with known safety profile of DAC HYP:
  - Higher incidence of serious AEs and discontinuation (excluding relapse) in DAC HYP vs IFN
  - Increased rates of infections, cutaneous events, and elevated liver transaminases
  - No evidence of increased risk of malignancies
- Most common cutaneous AEs (>3%) were rash (DAC HYP 7%; IFN beta-1a 3%) and eczema (DAC HYP 4%; IFN beta-1a 1%)
- Cutaneous AEs leading to treatment discontinuation (≥ 3 patients) were rash, dermatitis and urticaria

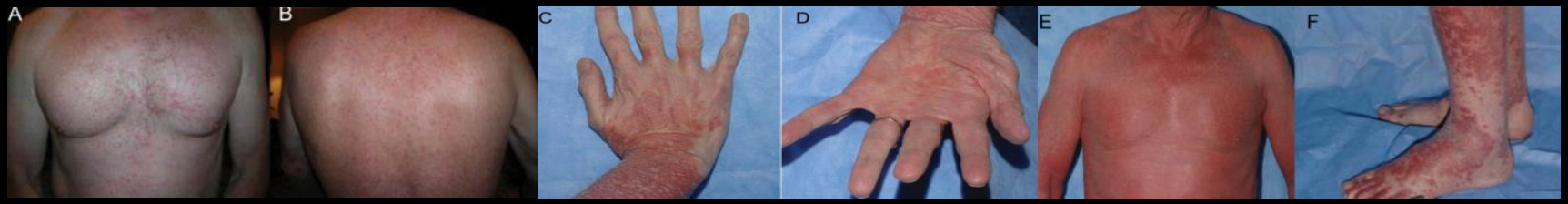
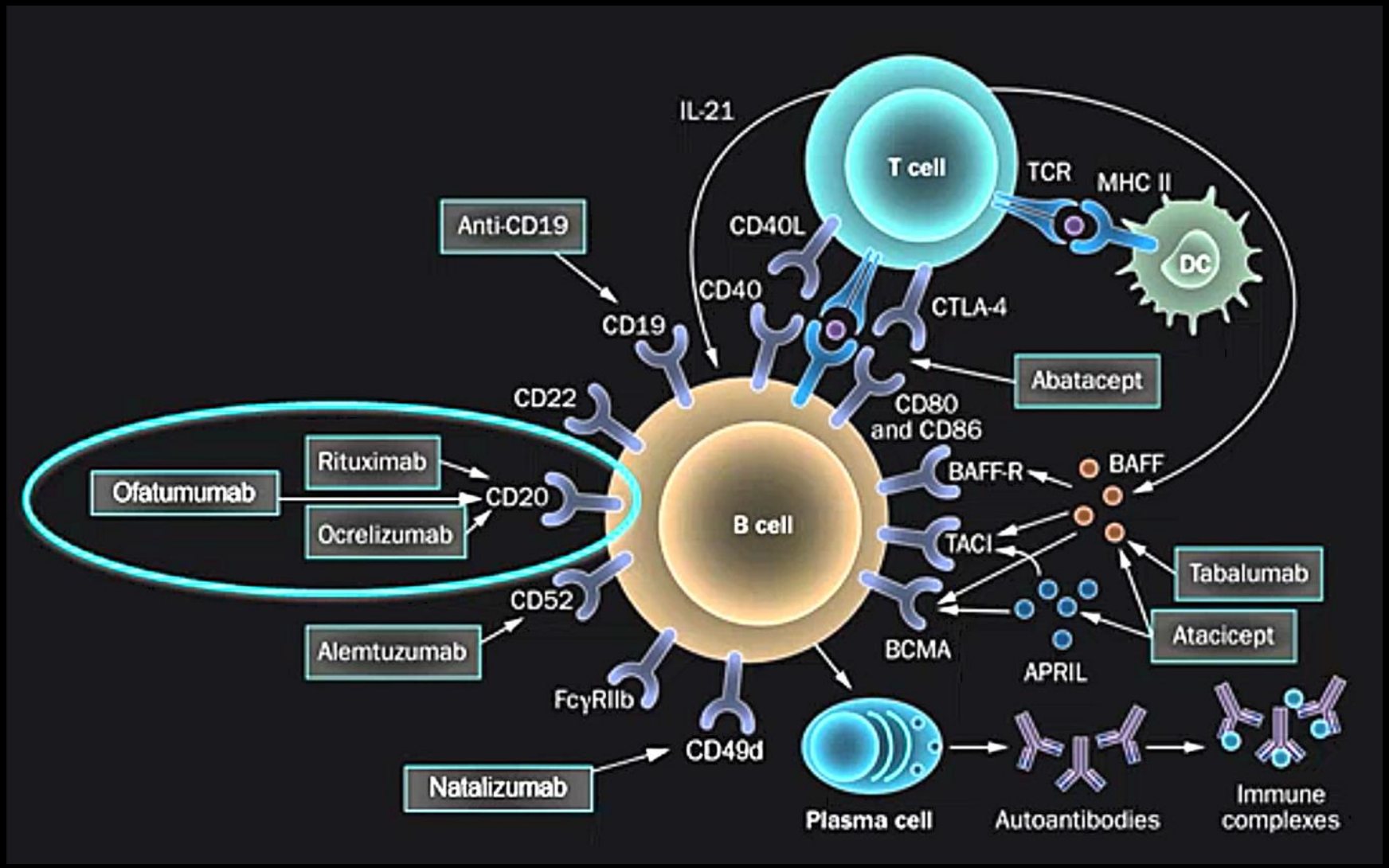


Figure adapted from Oh J et al Neurology. 2014 18;82(11):984-8.

AE, adverse event; DAC HYP, daclizumab high-yield process; IFN, interferon

1. Selmaj K et al. Poster (P094) presented at the Joint ACTRIMS-ECTRIMS Meeting; Boston, MA; September 11, 2014; 2. Kappos L, et al. Free Communication FC1.1 presented at the Joint ACTRIMS-ECTRIMS Meeting; Boston, MA; September 12, 2014; 3. Kappos L, et al. N Engl J Med. 2015 ; 373(15):1418-1428.

Potentially therapeutic monoclonal antibodies targeting B cells



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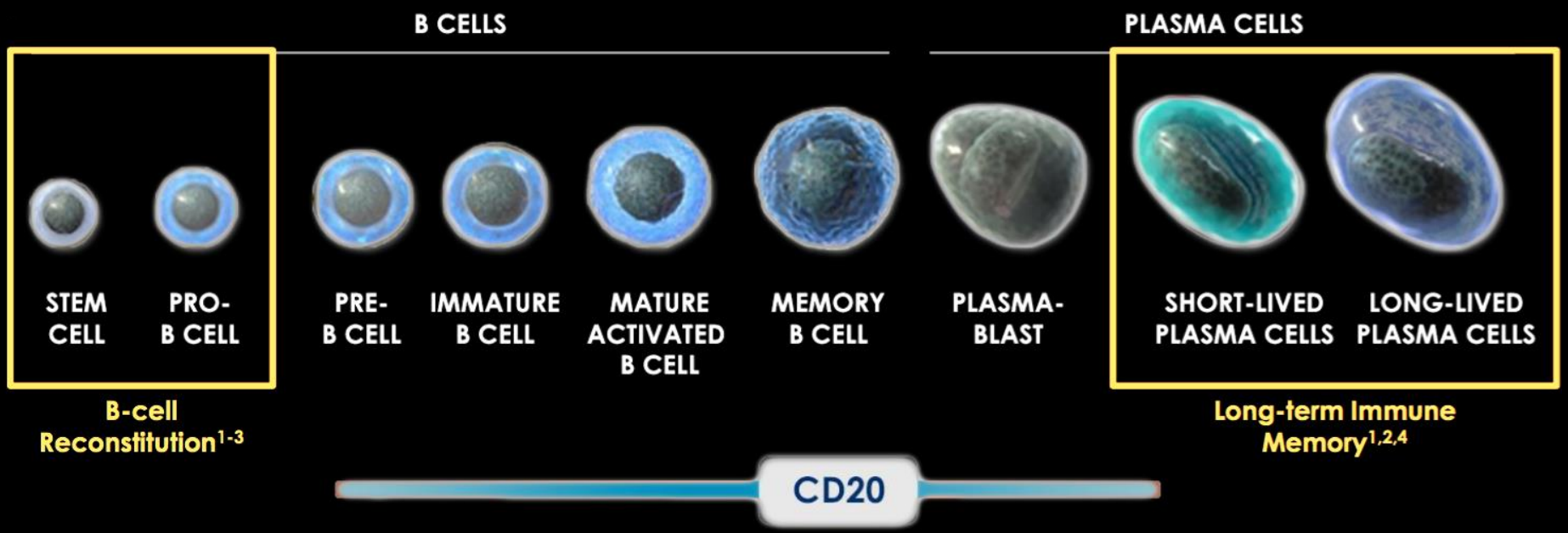
Targeting CD20+ B cells may preserve B-cell reconstitution and long-term immune memory



Ocrelizumab is a humanised monoclonal antibody that selectively depletes CD20+ B cells

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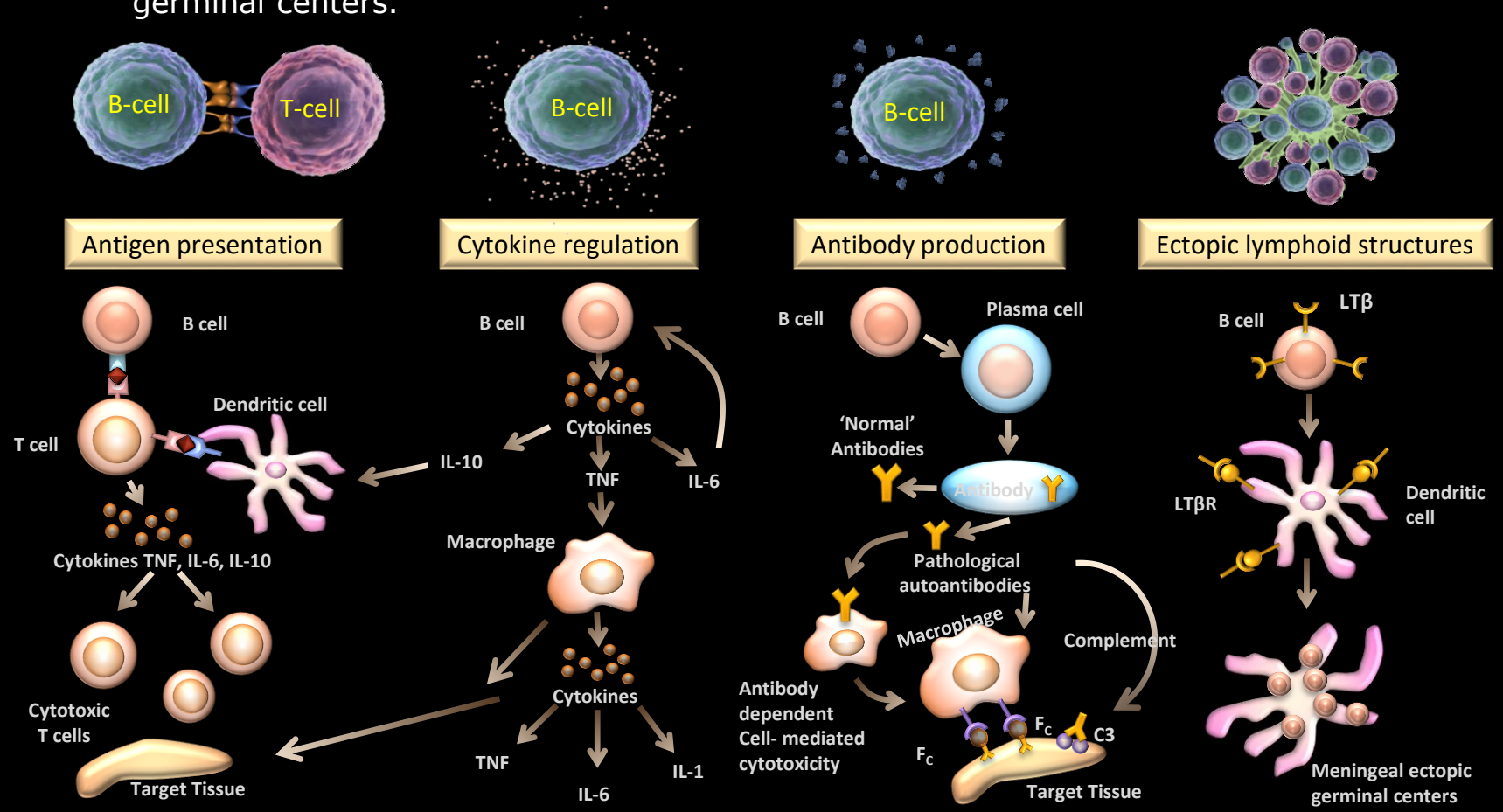
Role of B-cell in Multiple Sclerosis

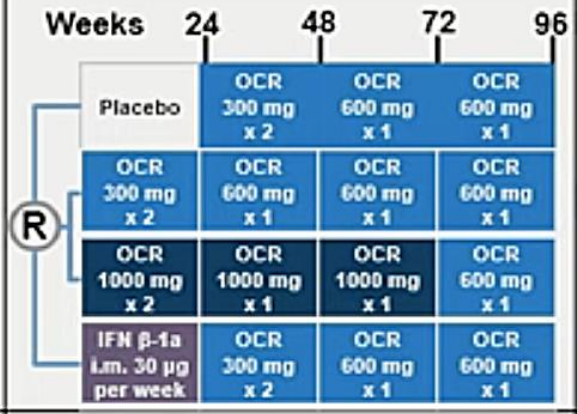
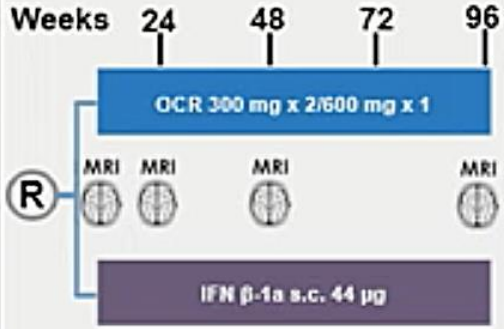
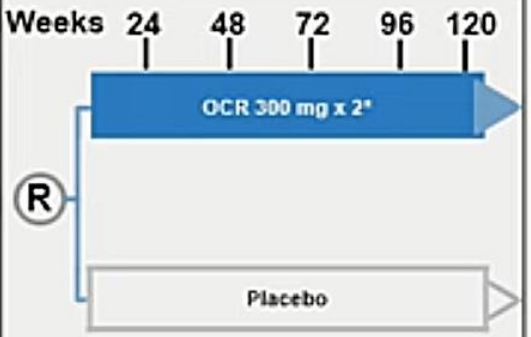
- B cells play a key role in pathophysiology of MS and has four main functions: acts as antigen-presenting cells, responsible for production of proinflammatory cytokines, acts as precursors of antibody-secreting plasma cells, and formation and maintenance of ectopic germinal centers.



1. Barun B et al. Clin Immunol. 2012 Jan;142(1):31-37.
2. Image adapted from Dalakas et al., Nat Clin Pract Neurol 2008;4:557-67

ADCC, antibody-dependent cellular cytotoxicity; APCs, antigen-presenting cells; CDC, complement dependent cytotoxicity; CNS, central nervous system; mAb, monoclonal antibody; MS, multiple sclerosis; OCB, oligoclonal band

In Phase II and III trials, Ocrelizumab has been studied in 2608 patients with MS

	Phase II Study[1]	OPERA I/II[2]	ORATORIO[3]
Patients	N = 220	N = 821 / N = 835	N = 732
Patient Population	RRMS, age 18-55 years, ≥2 relapses within last 3 years, ≥1 relapse in last year, EDSS=1.0–6.0	RMS, age 18-55 years, ≥2 clinical relapse within last 2 years, or 1 clinical relapse in last year, EDSS=0.0–5.5	PPMS, age 18-55 years, EDSS=3.0–6.5, diagnosis of PPMS
Treatment Arms			
Primary Endpoint	Total number of Gd-enhancing lesions at weeks 12, 16, 20, and 24	ARR at 96 weeks	Time to onset of CDP, sustained for ≥12 weeks
Key Secondary Endpoint	ARR by week 24	Time to onset of CDP for ≥12 weeks	Time to onset of CDP, sustained for ≥24 weeks

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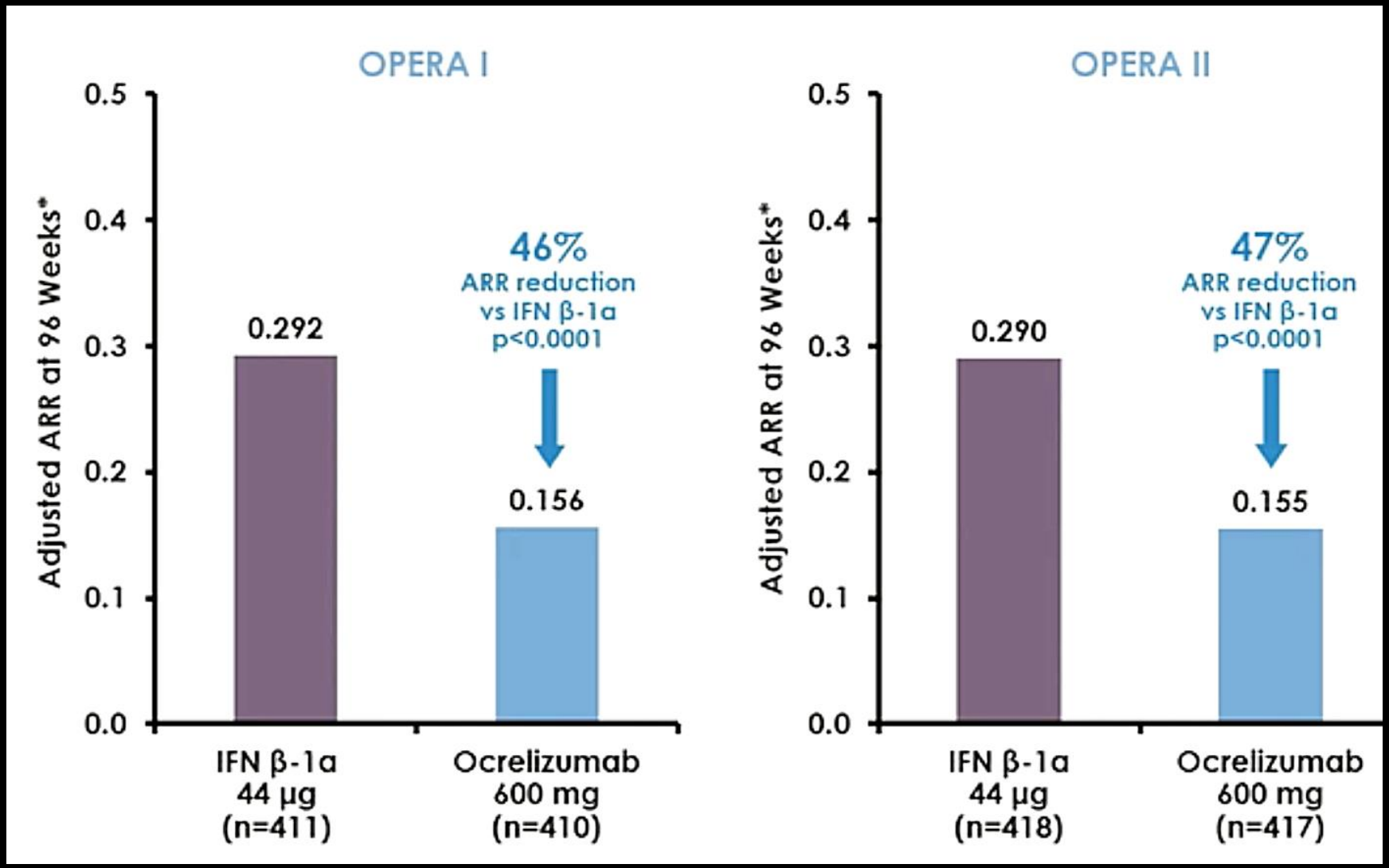
Annualized Relapse Rate (ARR)
Primary Endpoint



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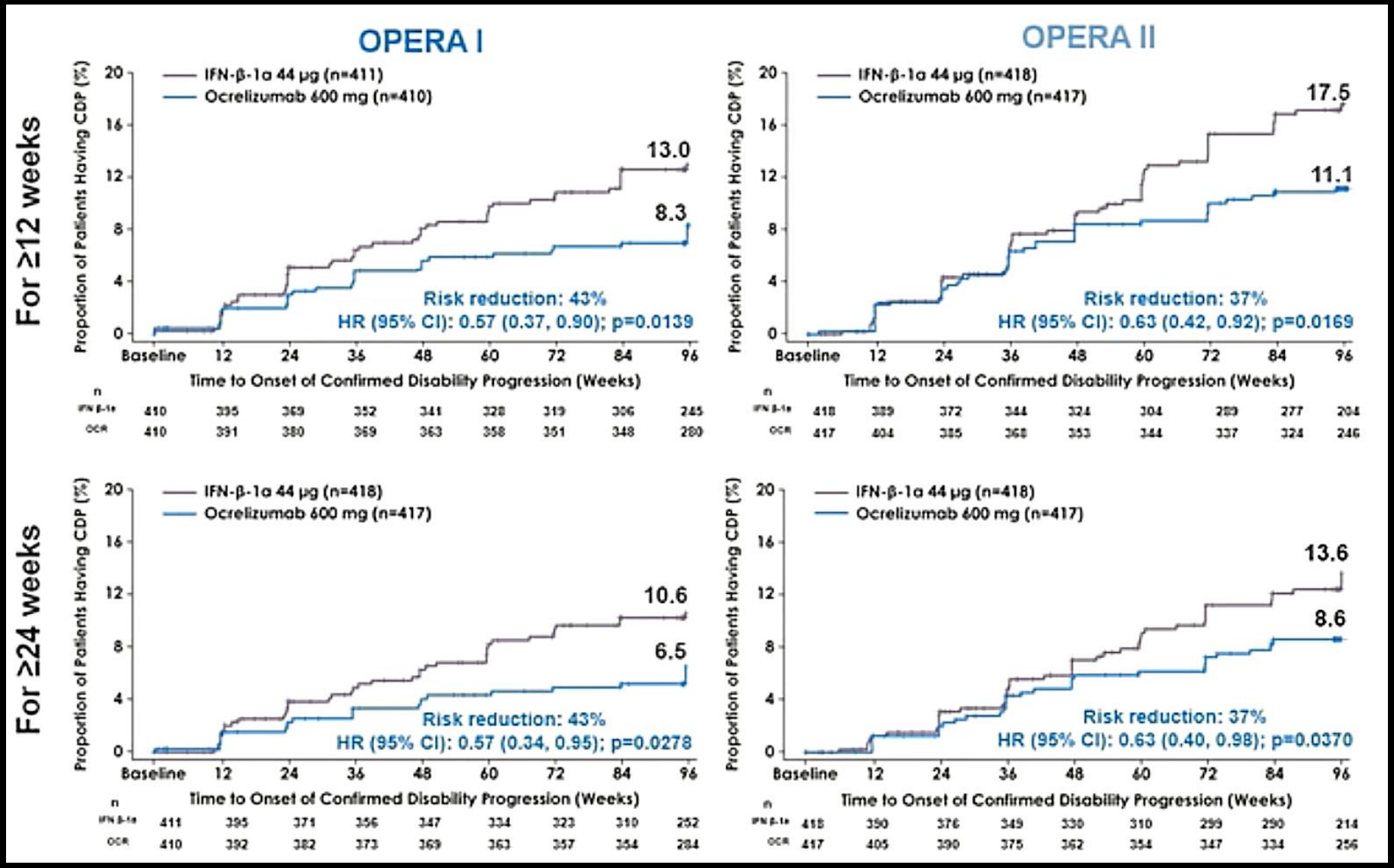
Confirmed Disability Progression at 12 and 24 weeks



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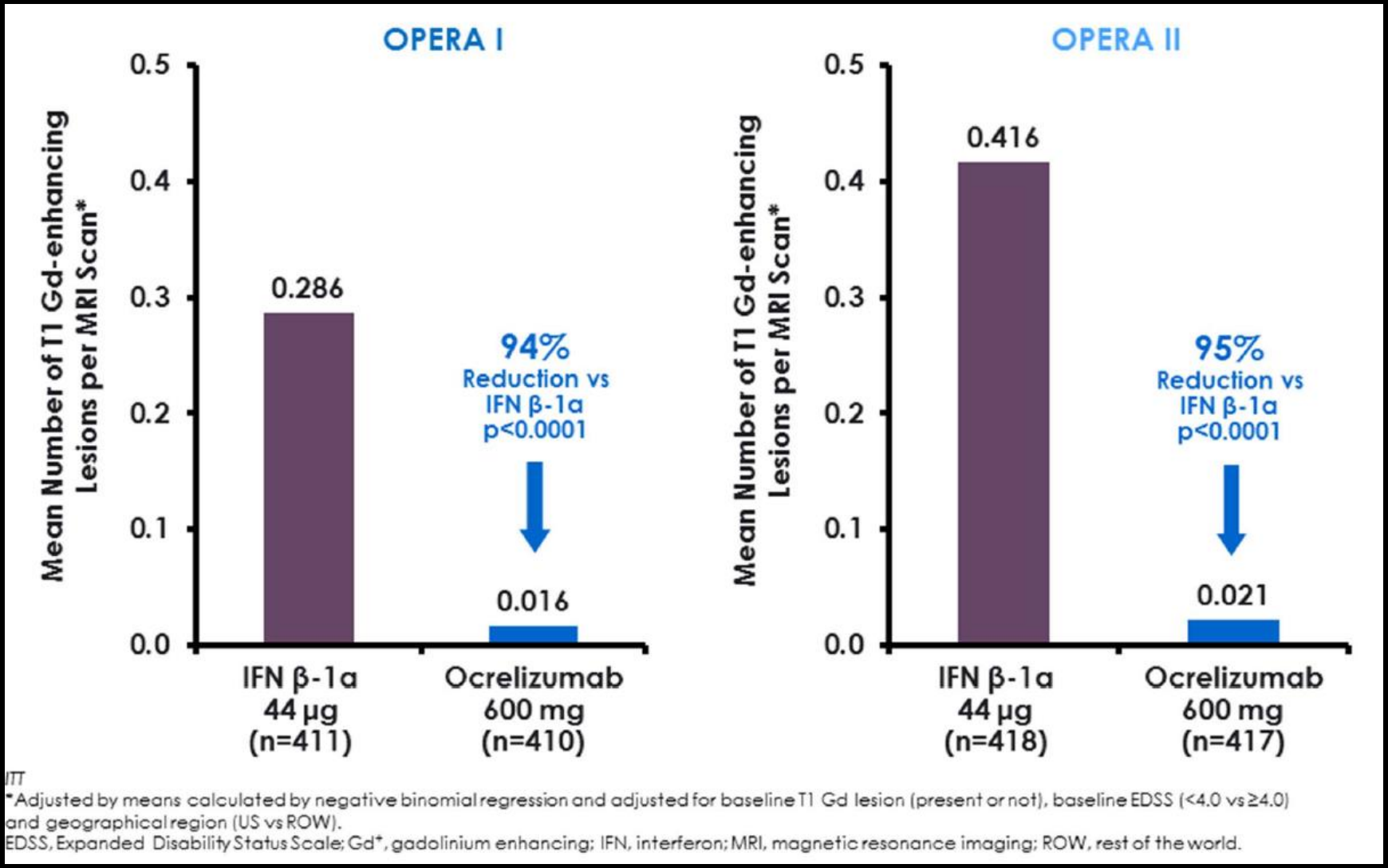
Reduction in number of T1 Gd$^+$ lesions compared with IFN β-1a



ITT

*Adjusted by means calculated by negative binomial regression and adjusted for baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW).

EDSS, Expanded Disability Status Scale; Gd$^+$, gadolinium enhancing; IFN, interferon; MRI, magnetic resonance imaging; ROW, rest of the world.

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Adverse Events over 96 weeks

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n (%)	IFN β-1a 44 µg (n=826)	Ocrelizumab 600 mg (n=825)
Total number of patients with ≥1 AE	**688 (83.3)**	**687 (83.3)**
Total number of patients with ≥1 AE occurring at a frequency ≥5% in either arm	**539 (65.3)**	**544 (65.9)**
Injury, Poisoning and Procedural Complications	**155 (18.8)**	**333 (40.4)**
Infusion-related reaction	80 (9.7)	283 (34.3)
General Disorders and Administration-site Conditions	**396 (47.9)**	**173 (21.0)**
Influenza-like illness	177 (21.4)	38 (4.6)
Injection-site erythema	127 (15.4)	1 (0.1)
Fatigue	64 (7.7)	64 (7.8)
Injection-site reaction	45 (5.4)	2 (0.2)
Infections and Infestations	**433 (52.4)**	**482 (58.4)**
Upper respiratory tract infection	87 (10.5)	125 (15.2)
Nasopharyngitis	84 (10.2)	122 (14.8)
Urinary tract infection	100 (12.1)	96 (11.6)
Sinusitis	45 (5.4)	46 (5.6)
Bronchitis	29 (3.5)	42 (5.1)
Nervous System Disorders	**252 (30.5)**	**224 (27.2)**
Headache	124 (15.0)	93 (11.3)
Psychiatric Disorders	**144 (17.4)**	**149 (18.1)**
Depression	54 (6.5)	64 (7.8)
Insomnia	38 (4.6)	46 (5.6)
Musculoskeletal and Connective Tissue Disorders	**207 (25.1)**	**204 (24.7)**
Back pain	37 (4.5)	53 (6.4)
Arthralgia	51 (6.2)	46 (5.6)

Table includes only pooled AEs occurring in ≥5% of patients in at least one treatment group and the corresponding system organ classes.
AE, adverse event; IFN, interferon.

ORATORIO – PP MS

	Placebo n=244	Ocrelizumab 600 mg n=488
Age, yr, mean (SD)	44.4 (8.3)	44.7 (7.9)
Female, n (%)	124 (50.8)	237 (48.6)
Time since symptom onset, yr, mean (SD)	6.1 (3.6)	6.7 (4.0)
Time since diagnosis, yr, mean (SD)	2.8 (3.3)	2.9 (3.2)
MS disease-modifying treatment naive, n (%)	214 (87.7)	433 (88.7)
EDSS, mean (SD)	4.7 (1.2)	4.7 (1.2)
MRI		
Patients with Gd^+ lesions, n (%)	60 (24.7)	133 (27.5)
Number of Gd^+ T1 lesions, mean (SD)	0.6 (1.6)	1.2 (5.1)
T2 lesion volume, cm^3, mean (SD)	10.9 (13.0)	12.7 (15.1)
Normalised brain volume, cm^3, mean (SD)	1469.9 (88.7)	1462.9 (83.9)

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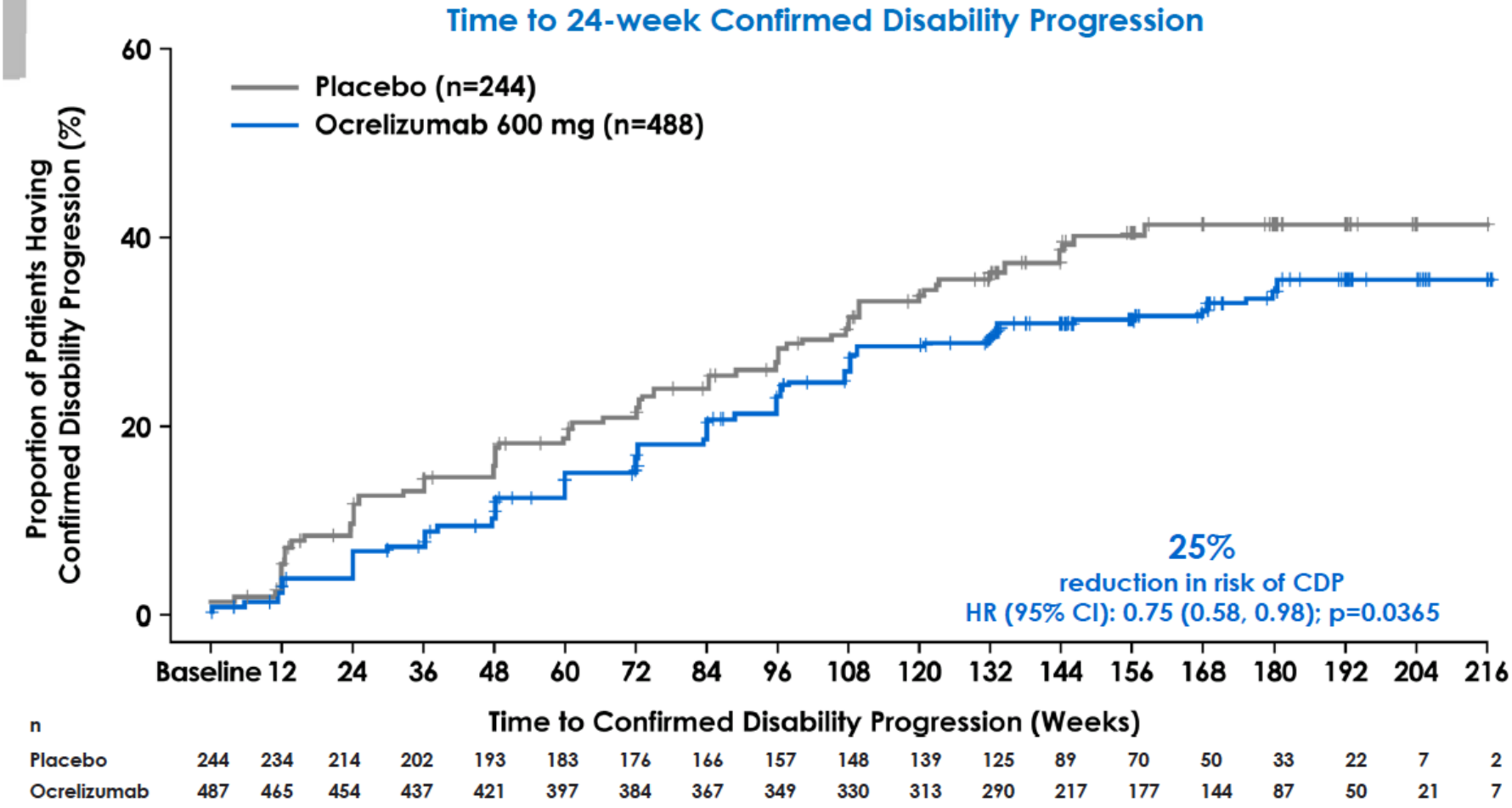
ORATORIO: Significant reduction in 24-week CDP



n																		
Placebo	244	234	214	202	193	183	176	166	157	148	139	125	89	70	50	33	22	7	2
Ocrelizumab	487	465	454	437	421	397	384	367	349	330	313	290	217	177	144	87	50	21	7

Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age.
Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression.
CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intent to treat.

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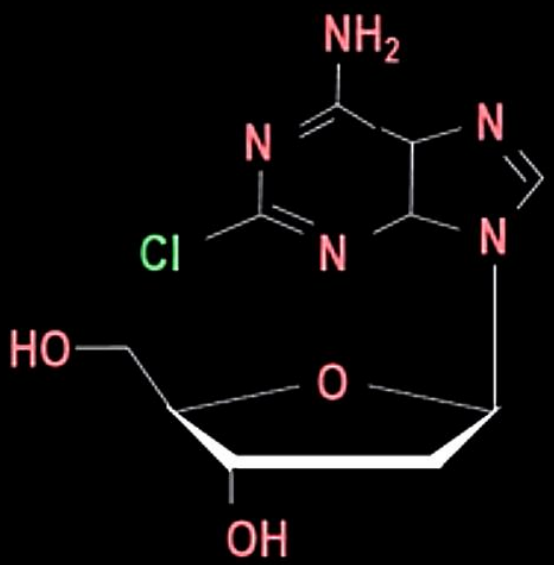
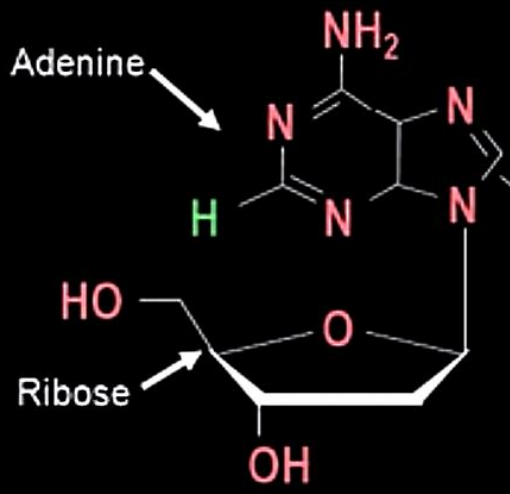
Cladribine: an analog of deoxyadenosine

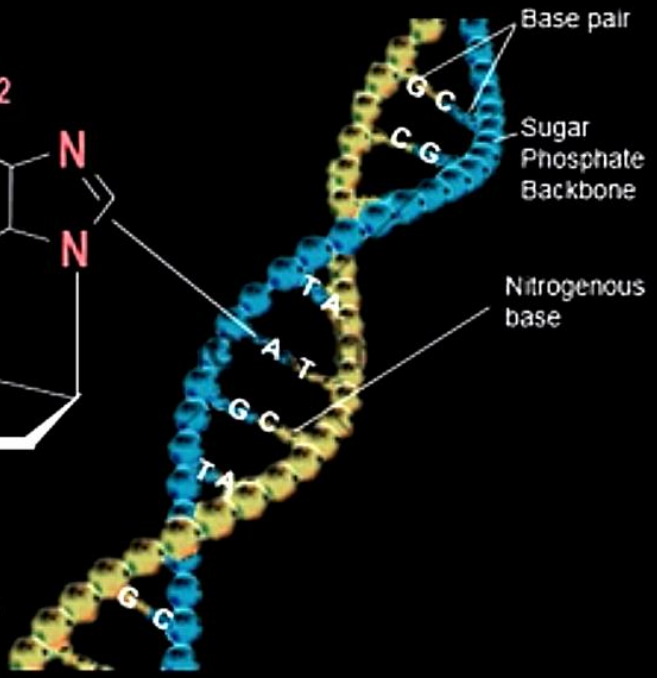
- Cladribine is an analog of deoxyadenosine, one of the building blocks of DNA, that differs from the naturally occurring nucleoside, deoxyadenosine by a chlorine substitution for hydrogen[1,2]
- Cladribine is resistant to deamination by the enzyme adenosine deaminase (ADA) by virtue of its structural design[1,2]



2-chlorodeoxyadenosine (cladribine)



Deoxyadenosine

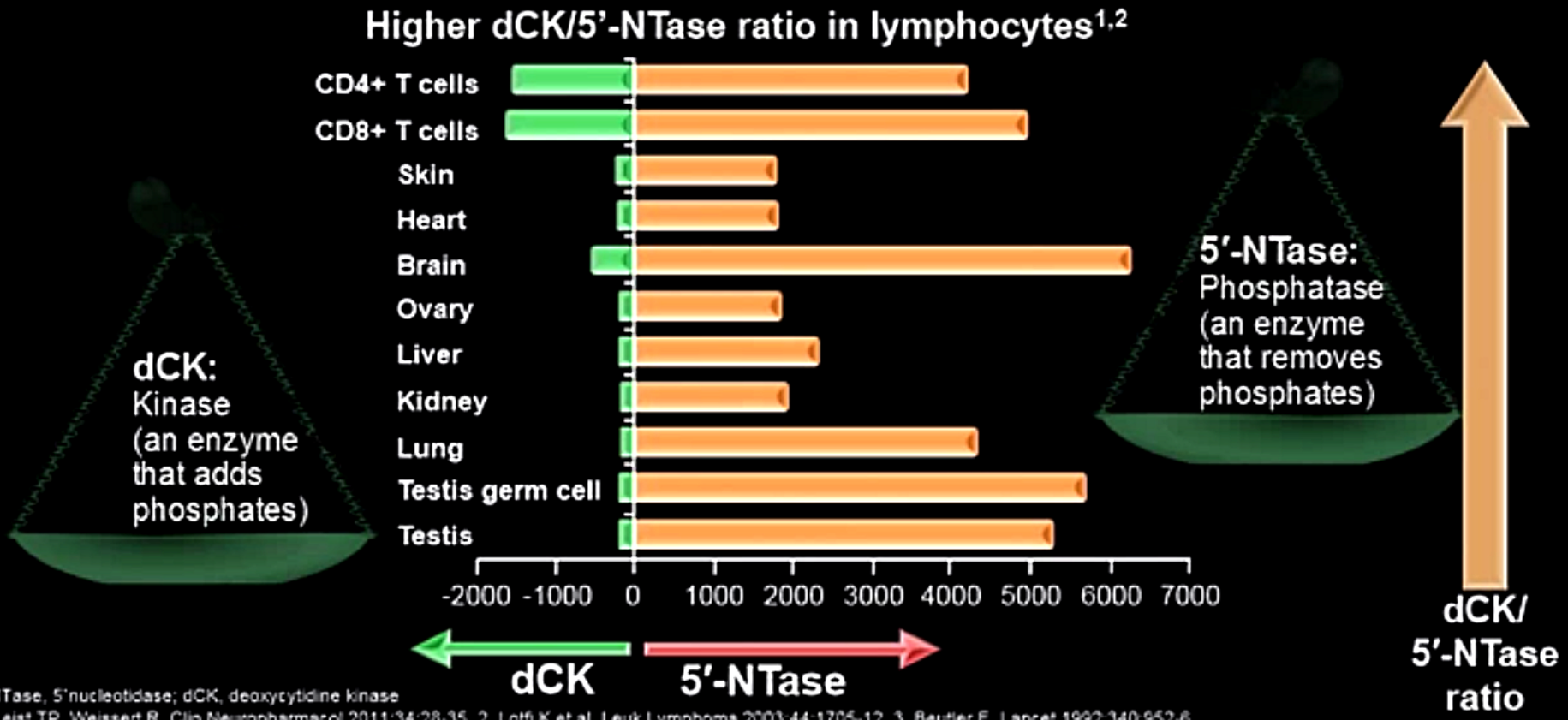


The exact mechanism of action of cladribine is unknown

1. Carson DA et al. Proc Natl Acad Sci USA 1980;77:6865-9. 2. Beutler E. Lancet 1992;340:952-6

Activated cladribine accumulates preferentially in lymphocytes vs other cells, based on kinase-to-phosphatase levels

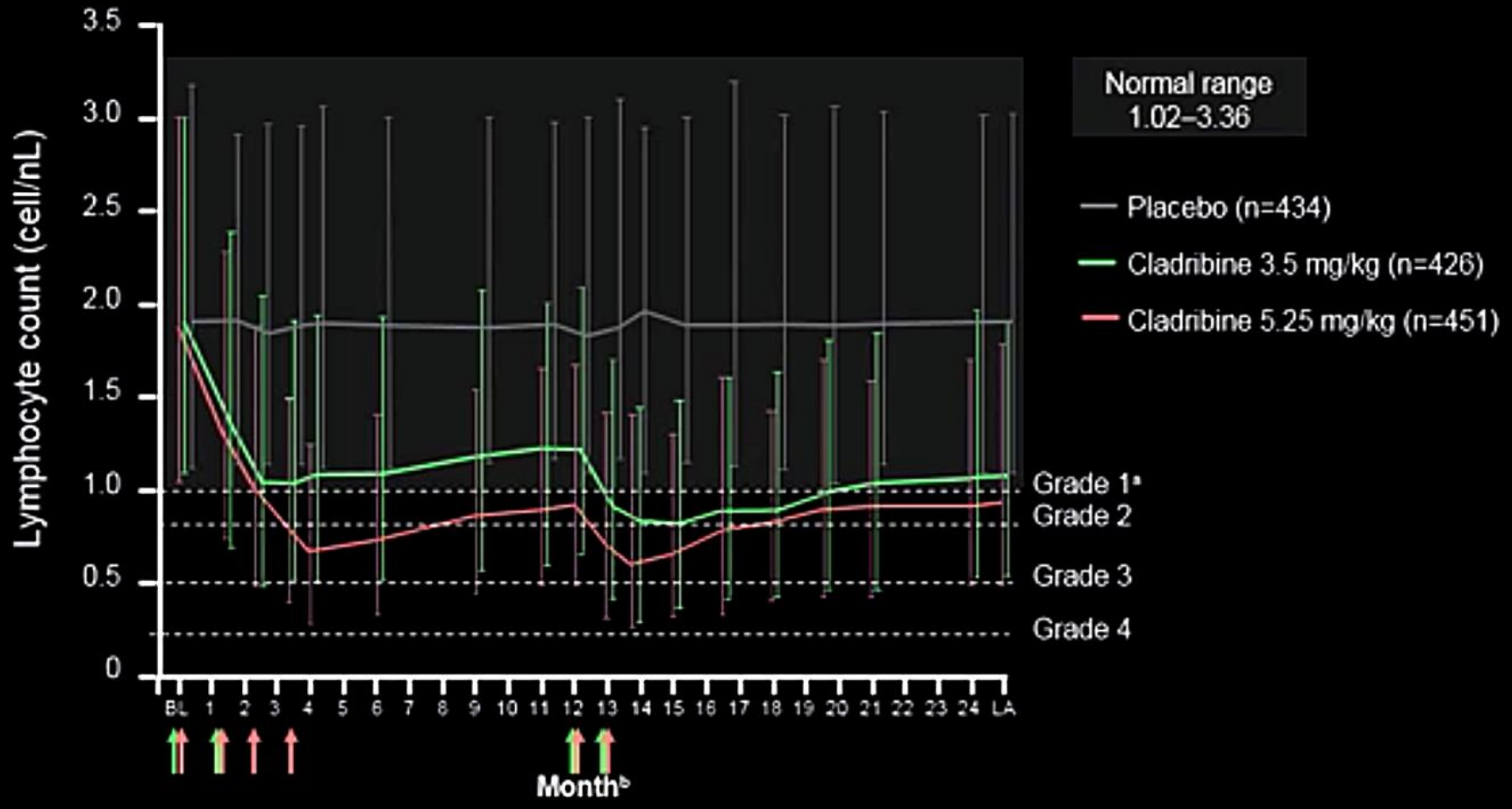
Cells other than lymphocytes have an enzymatic rescue mechanism: higher levels of 5′-NTase – this may prevent activated cladribine from accumulating and causing DNA damage[1,2]



5-NTase, 5`nucleotidase; dCK, deoxycytidine kinase

1. Leist TP, Weissert R. Clin Neuropharmacol 2011;34:28-35. 2. Lotfi K et al. Leuk Lymphoma 2003;44:1705-12. 3. Beutler E. Lancet 1992;340:952-6. 4. Kawasaki H et al. Blood 1993;81:597-601

Cladribine leads to specific, discontinuous reductions in lymphocytes



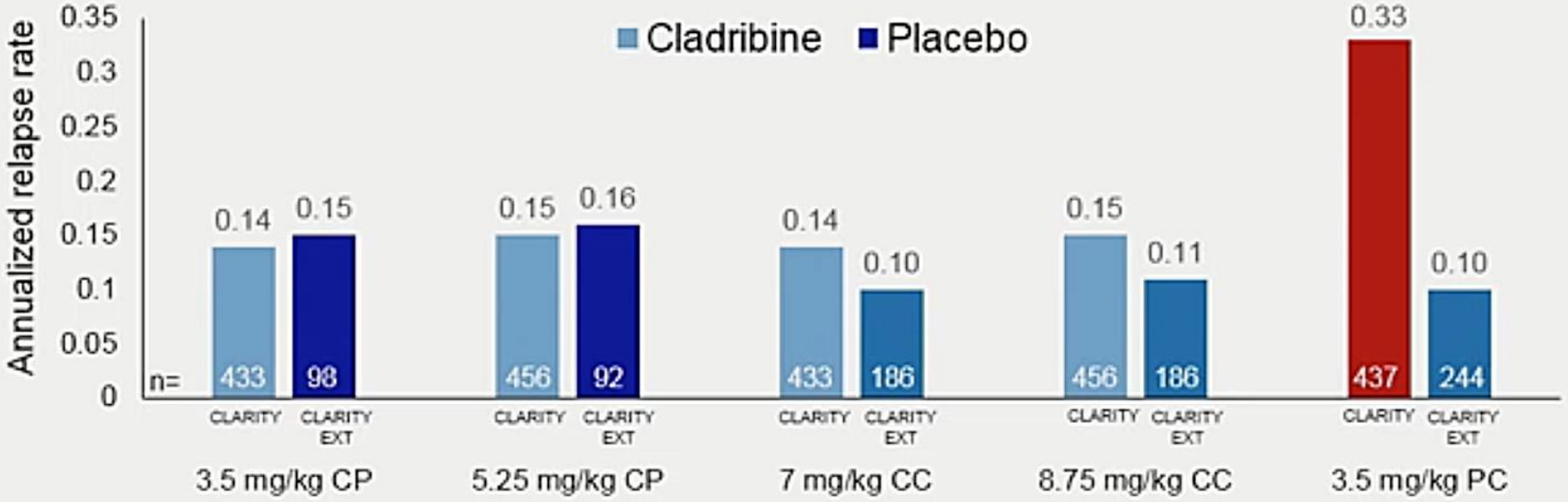
Arrows indicate administration of Cladribine Tablets. In patients receiving cladribine 3.5 mg/kg, the median lymphocyte count recovered to levels above the lower limit of normal (Grade 1 lymphopenia) and no patient had severe lymphopenia (Grades 3 or 4) at 2 years.

[a]Reductions in absolute lymphocyte counts (lymphopenia) were graded according to the Common Terminology Criteria for Adverse Events: 1, <lower limit of normal–800/mm^3; 2, <800–500/mm^3; 3, <500–200/mm^3; 4, <200/mm^3. [b]Please note that lymphocyte count data were not available for all patients at every observation. BL, baseline; LA, last assessment.

Soelberg-Sørensen P et al. ECTRIMS 2011 [P917] Giovannoni G et al. N Engl J Med 2010;362:416-26 (Suppl)

CLARITY EXT demonstrates the durable efficacy of Cladribine on relapses and reconfirms the efficacy outcomes of CLARITY

CLARITY/
CLARITY EXT

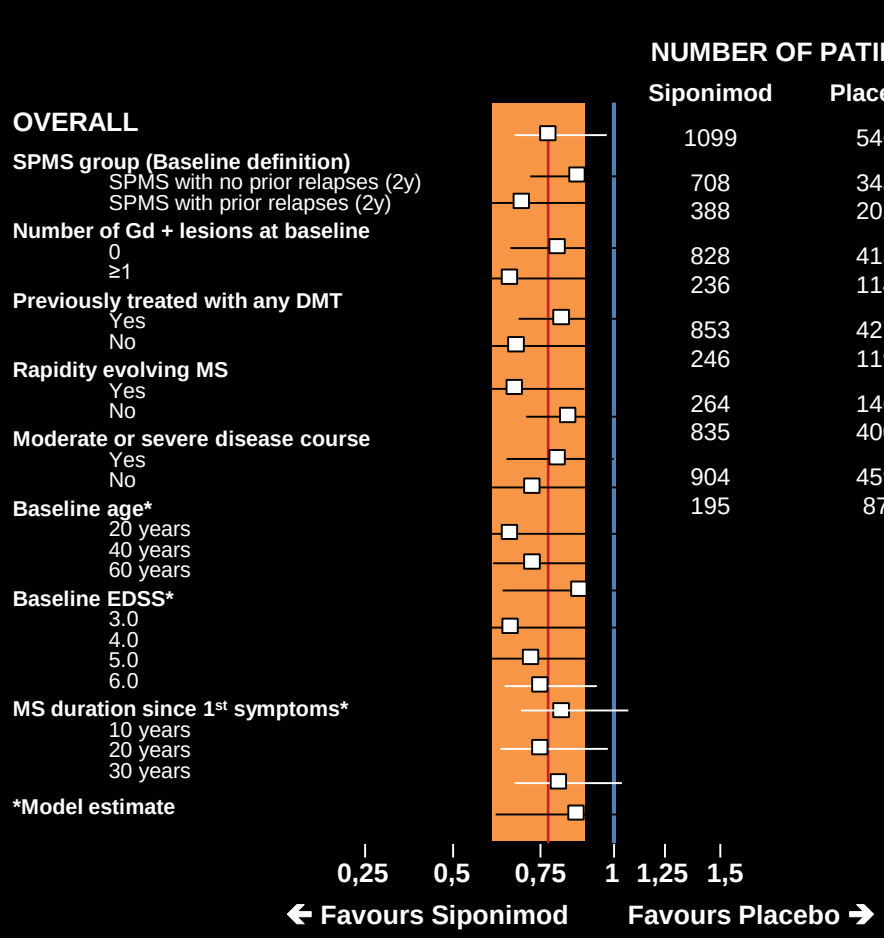


The similar ARRs seen in CLARITY and CLARITY EXT suggest that treatment with Cladribine leads to a durable effect on ARR for up to 4 years. In addition, within-treatment group analysis of the 3.5 mg/kg PC group (n=244) demonstrated that switching to cladribine treatment in Years 3 and 4 led to a significant reduction in ARR in patients previously treated with placebo in Years 1 and 2 (ARR fell from 0.25 to 0.10; $p<0.001$)[a]

CP=cladribine (3.5 mg/kg) in CLARITY, placebo in CLARITY EXT; PC=placebo in CLARITY, cladribine (3.5 mg/kg) in CLARITY EXT; CC=cladribine (3.5 or 5.25 mg/kg) in CLARITY, cladribine (3.5 mg/kg only) in CLARITY EXT. For each group, cladribine dose refers to cumulative dose over 4 years in CLARITY EXT. [a]p-values for within-group comparisons were based on the two-sided Wilcoxon signed–rank test (see slide notes for more details).

Giovannoni G et al. N Engl J Med 2010;362:416-26. Giovannoni G et al. AAN 2013 [P07.119]

Siponimod in SPMS: Subgroup Analysis for Time to 3-month Confirmed Disability Progression



Kappos L, et al. Presented at ECTRIMS 2016; Presentation O250.

Treatment Initiation

Induction

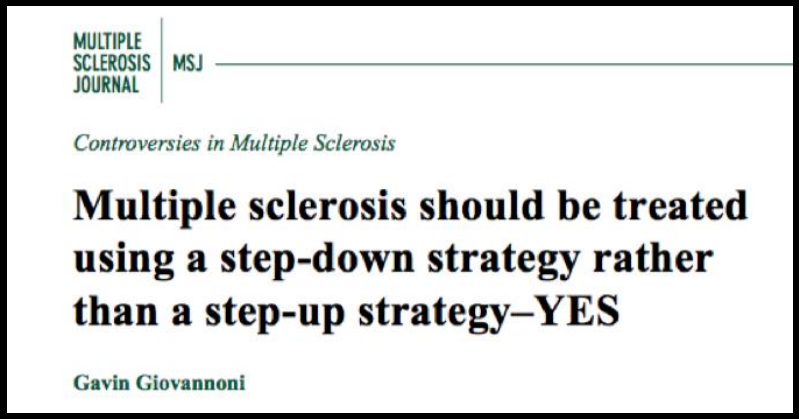
- Start with a 2nd or higher tier agent
- Obtain a treatment "response" for a given period of time
- Revert back to a 1st line treatment to maintain efficacy and minimize toxicity

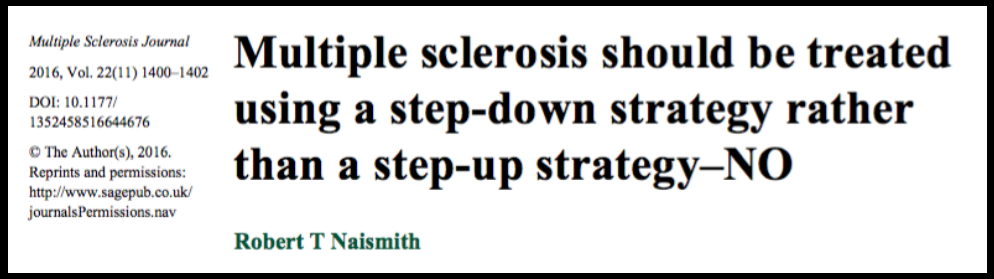
vs

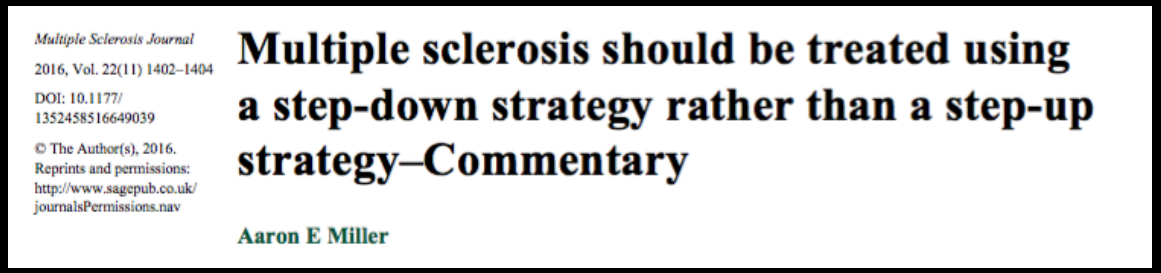
Escalation

- Start with a 1st line agent
- If sub-optimal response, move to a 2nd tier agent
- Monitor treatment "response"
- Move to a 3rd tier or higher agent

Actual Controversy







Multiple Sclerosis Journal, 22(11), Oct 2016

Inertie Thérapeutique !

Theme 1: better outcomes: the enemy is therapeutic inertia: a warning *(Saposnik et al., Canada & Spain)*

Therapeutic inertia: *failure to escalate therapy with evident disease activity in a patient on a DMT*

The biggest enemy to better outcomes in MS:

In 96 Spanish neurologists (67% MS experts; 50% academic)

: 7/10 had evidence of therapeutic inertia

predictors of therapeutic inertia were:

a) low tolerance to uncertainty
b) aversion to ambiguity
c) lower volume of patients seen / week

9

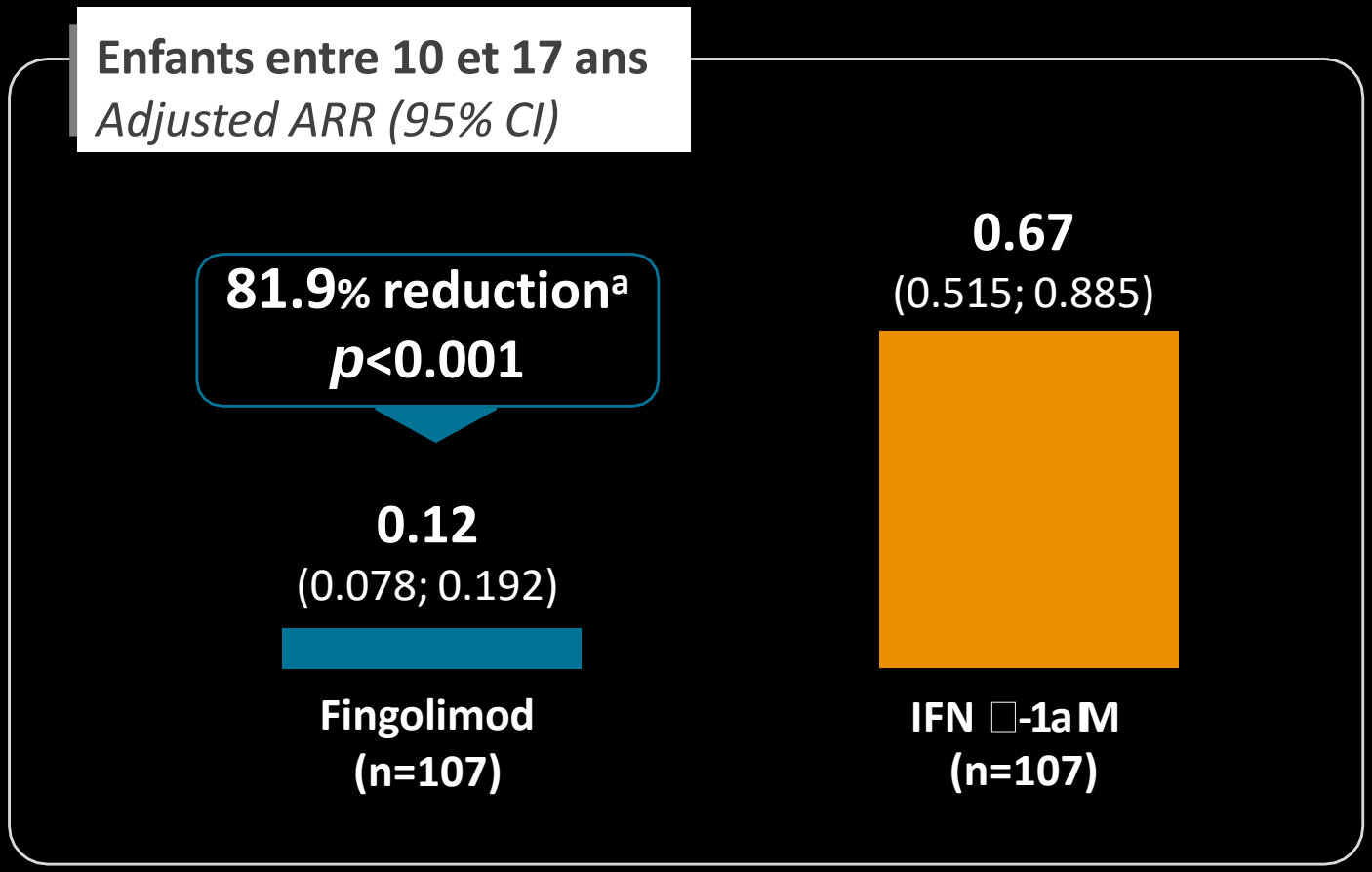
M. HUTCHINSON, ECTRIMS 2016

Le Traitement de la SEP c'est aussi…

- Prise en charge rééducative
  - Evaluation des besoins et du déficit
  - Entraînement physique et à l'effort
  - Stratégies de compensation
  - Rééducation
    - Motrice
    - Sensitive
    - Coordination

Etude PARAGIGMS de phase 3

en double aveugle et double placebo durant 2 ans comparant l'efficacité du Fingolimod à l'interféron 1a IM une fois par semaine chez l'enfant

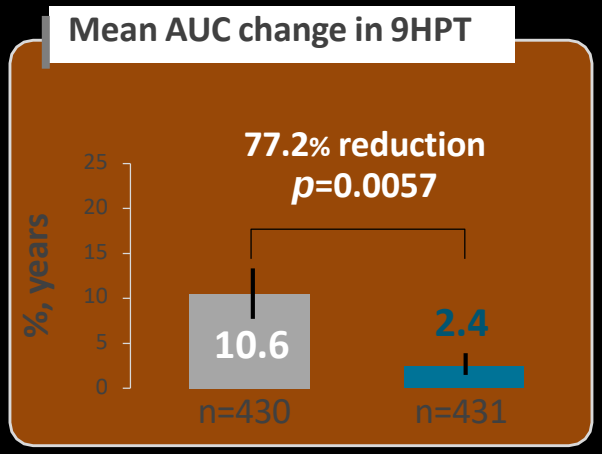


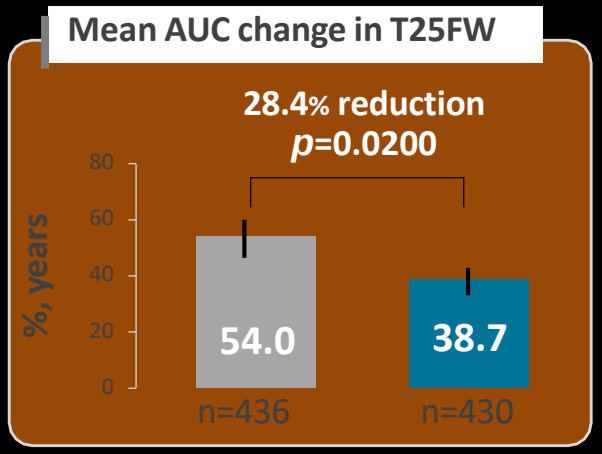
Résultat post Hoc de l'étude de phase 3 ASCEND dans la SEP secondairement progressive

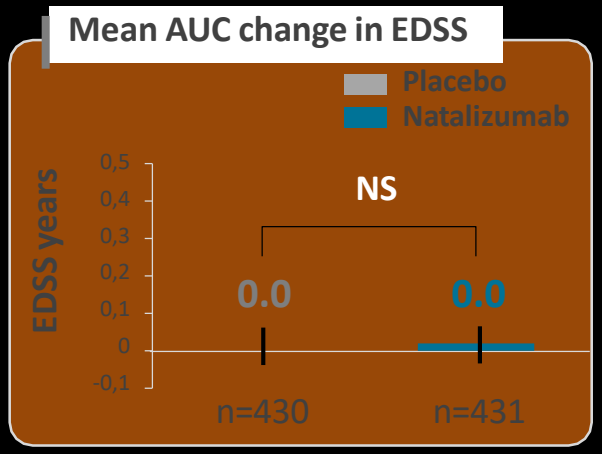
Efficacité du Natalizumab sur le risque de progression du handicap des membres supérieurs

AUC change in 9HPT, T25FW, and EDSS

- Over 2 years, natalizumab was associated with significantly less disability worsening from baseline relative to placebo as assessed by T25FW and 9HPT, but not EDSS
- Natalizumab-treated patients had a negative median AUC for 9HPT







Efficacité plus modérée sur la marche

Recommandations ECTRIMS-EAN

ECTRIMS-EAN Clinical Practice Guideline on Pharmacological Management of MS

X. Montalban[1], R. Gold[2], A.J. Thompson[3], S. Otero-Romero[1,4], M.P. Amato[5], D. Chandraratna[6], M. Clanet[7], G. Comi[8], T. Derfuss[9], F. Fazekas[10], H. P. Hartung[11], E. Havrdova[12], B. Hemmer[13], L. Kappos[14], R. Liblau[15], C. Lubetzki[16], E. Marcus[17], D. H. Miller[18], T. Olsson[19], S. Pilling[17], K. Selmaj[20], A. Siva[21], P. S. Sorensen[22], M.P. Sormani[23], C. Thalheim[24], H. Wiendl[25], F. Zipp[26]

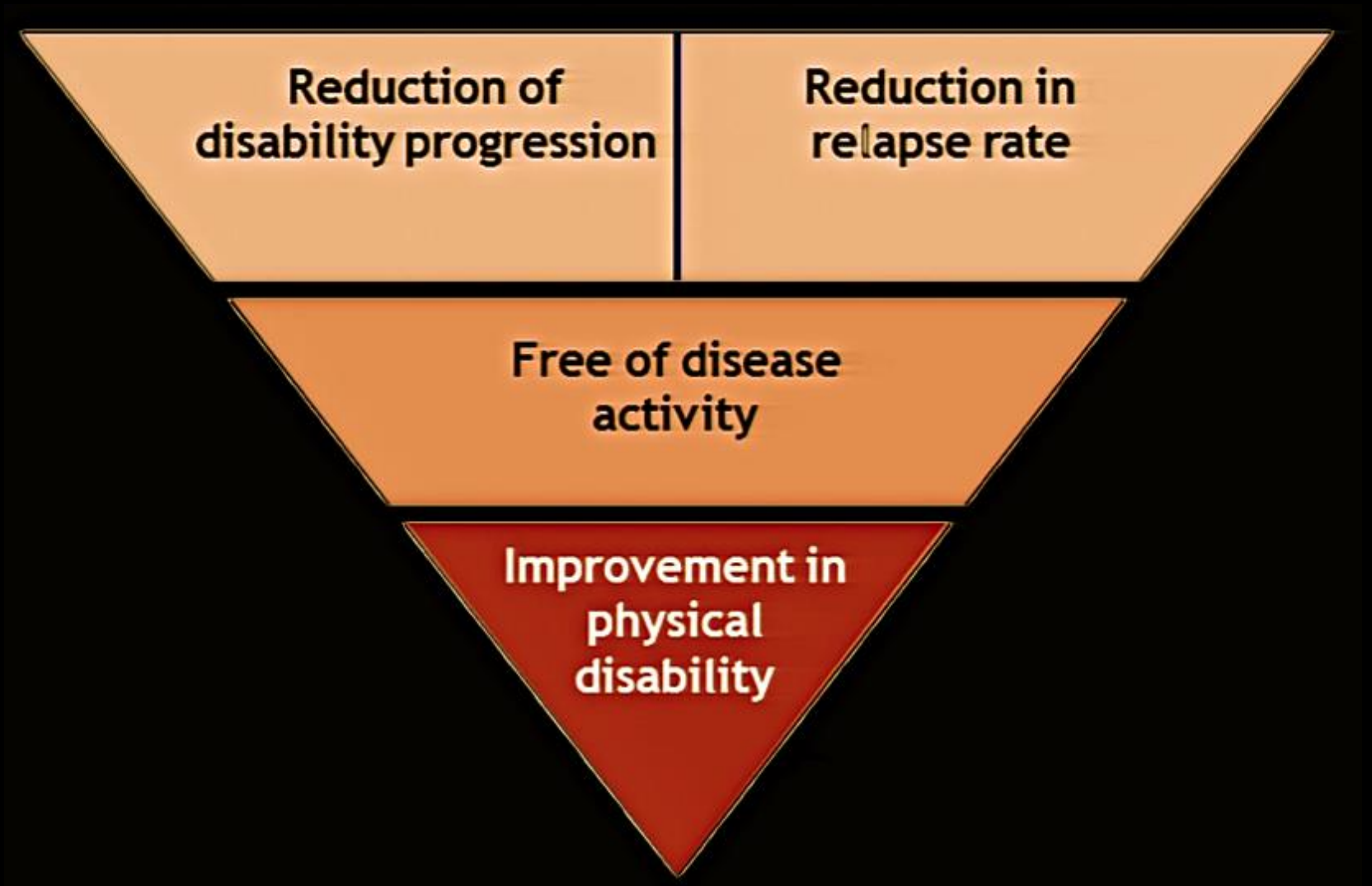
ECTRIMS EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS — ean

Clinical Guidelines on Multiple Sclerosis

20 recommandations

- **Possibilité de prescrire un traitement de fond dès le syndrome cliniquement isolé**
- Réaliser une IRM de contrôle 6 mois après le début d'un nouveau traitement de fond puis à un an et tous les ans.

Modern treatment goals



Hartung HP., ACTRIMS/ECTRIMS 2014

Future developments and research

- Better inflammation control
  - "trapped inflammation" and progression
- Personalized therapies
- Neuroprotection
- Natural remyelination promotion
- Immune system "re-programming"
- Repair
- Cellular therapy
- Better evaluation techniques
  - Diagnostic and follow-up surrogates

Sensibilisation – choquer pour avancer ?