The CME program will start on the hour.

Translational Research:

Biological Aging and Progressive Multiple Sclerosis

Current Topics in MS

Translational Research: Biological Aging and Progressive Multiple Sclerosis

Benjamin M. Segal, M.D.
Chair of Neurology
Director, Neuroscience Research Institute
Co-Director, Neurological Institute
Ohio State University

National Multiple Sclerosis Society

VA | U.S. Department of Veterans Affairs
Veterans Health Administration
Multiple Sclerosis Centers of Excellence

Diversity, Equity & Inclusion Statement

The National Multiple Sclerosis Society is a movement by and for all people affected by MS. Our voices and actions reflect diversity, equity and inclusion.

We welcome and value diverse perspectives.

We actively seek out and embrace differences.

We want everyone to feel respected and be empowered to bring their whole selves to ensure we make the best decisions to achieve our mission.

National Multiple Sclerosis Society

Together We Are Stronger.

Vision & Mission Statements

Our Vision:

A World Free of MS.

Our Mission:

We will cure MS while empowering people affected by MS to live their best lives.

National Multiple Sclerosis Society

Together We Are Stronger.

VA MS Centers of Excellence Mission

- Improve the quality and consistency of health care services delivered to Veterans with MS across the US.
- Expand care coordination between VA medical facilities through the development of a national network of MS providers within the Veterans Health Administration.

VA

U.S. Department of Veterans Affairs

Veterans Health Administration

Multiple Sclerosis Centers of Excellence

Your feedback is important to us!

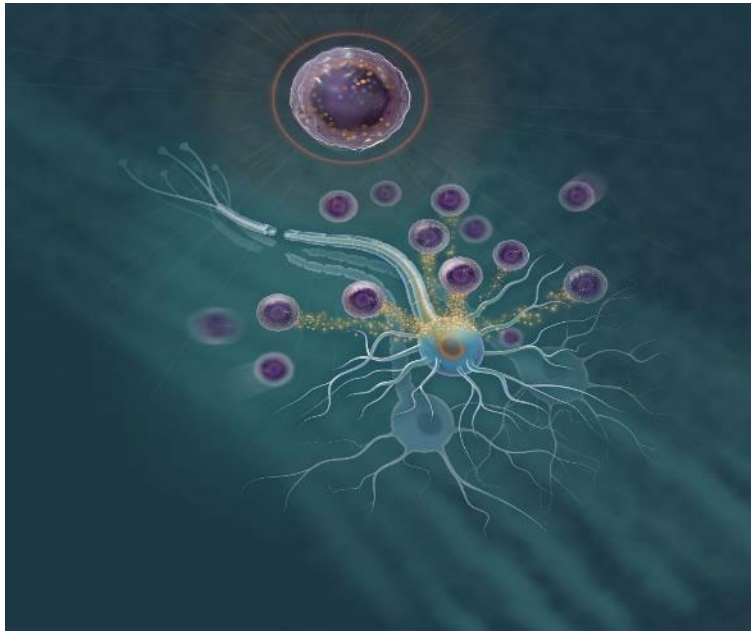
At the end of the program, please take the survey in the TRAIN or TMS websites. This will give you access to your CME/CE certificate.

Dr. Benjamin Segal is Chair of the Department of Neurology, Director of the Neurological Research Institute, and co-Director of the Neurological Institute at Ohio State University. He was also appointed the Stanley D. and Joan H. Ross Professor of Neuromodulation. On the international level, he is a Director of the Americas Committee for Treatment and Research in MS (ACTRIMS).

In the past, Dr. Segal served as Chair of the Scientific Program Committee of MSVirtual 2020, the largest international academic conference on MS and related diseases. He was co-Chair of the Clinical Neuroimmunology and Brain Tumors study section and Chair of the NIAID Investigator Initiated Program Project Applications Study Section of the National Institute of Health, Chair of the Canada Foundation for Innovation- Expert Committee on Neurosciences, and Chair of the Scientific Advisory Board, VA MS Centers of Excellence-East. He was the Program Chair for the ACTRIMS forum between 2016-2018, and created the ACTRIMS Neurology Resident Summit in MS. In 2018 he developed the annual ACTRIMS Young Scientist Summit in Clinical Neuroimmunology.

Dr. Segal has received numerous honors for his research, including the Commendation Medal for Excellence from the Public Health Service, the Harry Weaver Junior Faculty Award from the National MS Society, the Stanley Aronson Award for Excellence in the Clinical Neurosciences, and the Kenneth P. Johnson Lectureship at ACTRIMS. In 2014 he was inducted into the University of Michigan League of Research Excellence. He was a Senior Scholar of the A. Alfred Taubman Medical Research Institute. For the past 10 years, he has consistently been named among the Best Doctors in America.

Biological Aging and Progressive Multiple Sclerosis



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THE OHIO STATE UNIVERSITY

Disclosures

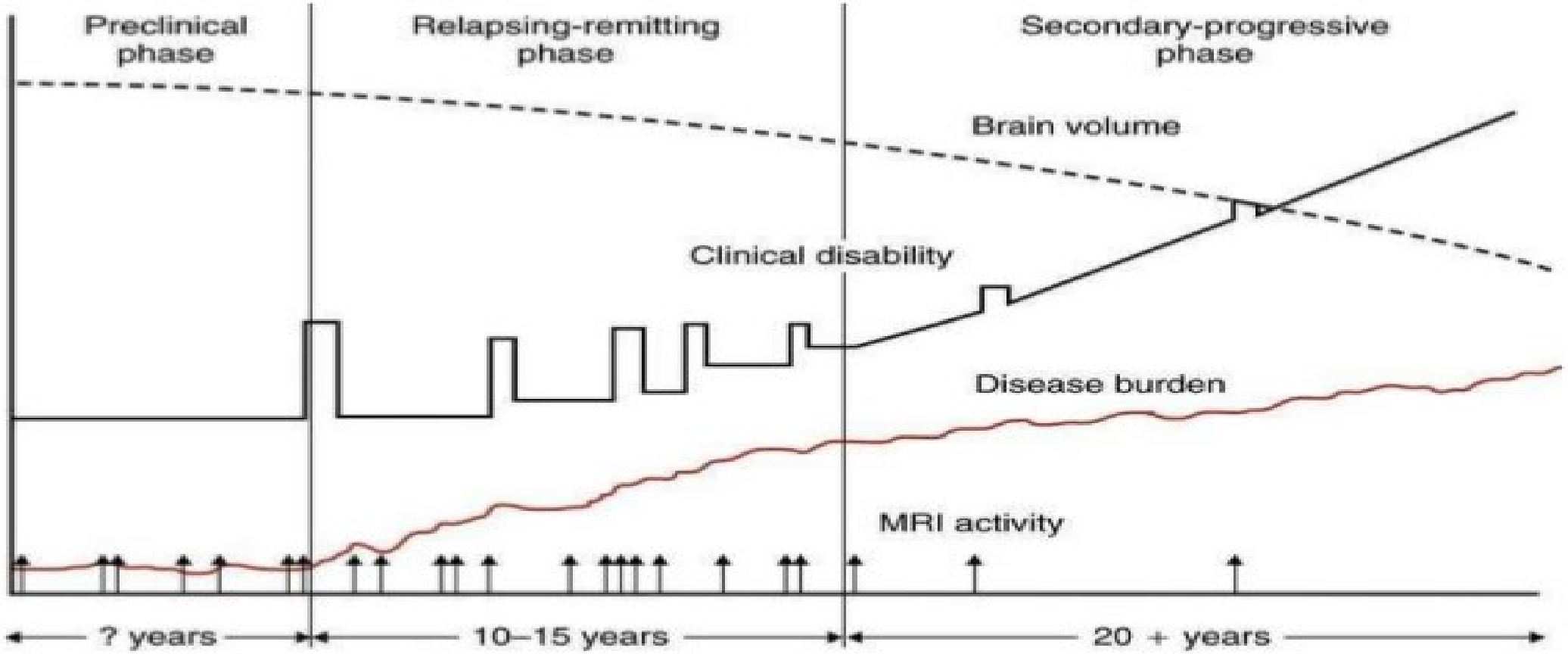
- Consultant: Neurodeim, Banner Life Sciences and Send Biosciences.
- Member of Data Safety Monitoring Board: Eli Lily

The MS Spectrum

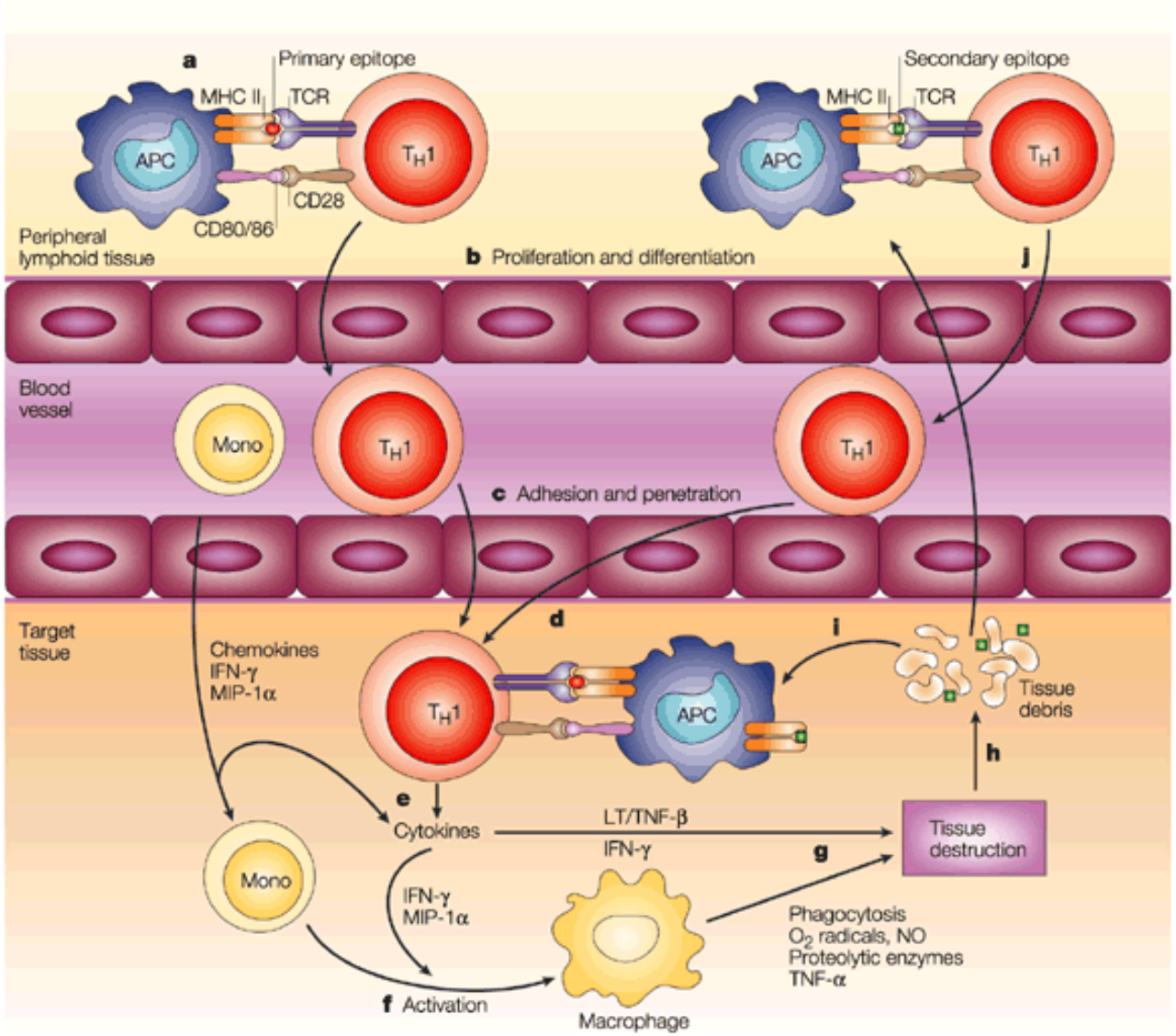
2 general patterns of neurological disability in MS:

i. Recurrent, self limited episodes of neurological deficits, followed by full or partial recovery, and separated by periods of clinical stability ("relapsing-remitting")

ii. Steady, insidious neurological deterioration spanning years to decades ("progression")



“T CELL- CENTRIC” MODEL OF MS PATHOGENESIS



Nature Reviews | Immunology

New generation DMT in RRMS are designed to target lymphocytes

- Natalizumab (Tysabri®) is a monoclonal antibody against α4 integrin that blocks lymphocyte trafficking across the blood-brain-barrier

- Fingolimod (Gilenya®) and Siponimod (Mayzent®) are sphingosine-1-phosphate receptor modulators that inhibit the egress of lymphocytes from lymph nodes to the circulation, thereby curtailing their migration to the CNS

- Alemtuzamab (Lemtrada®) is a monoclonal antibody against CD52 that depletes lymphocytes

- Ocrelizumab (Ocrevus®) is a monoclonal antibody that depletes B cells

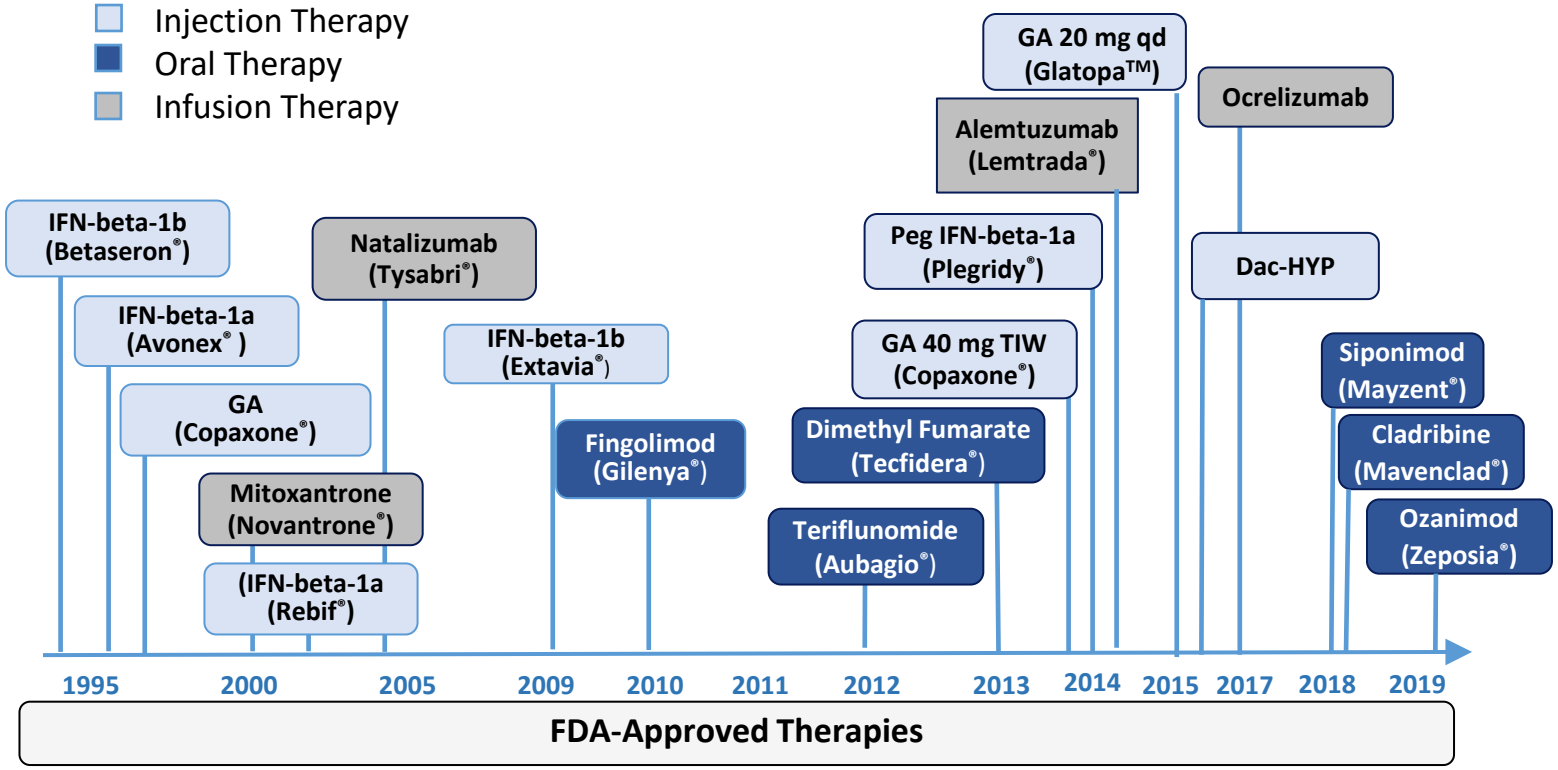
- Cladribine (Mavenclad®) is a purine analog and global immunosuppressant

Challenges

None are cures. Response rates range from 25-68%.

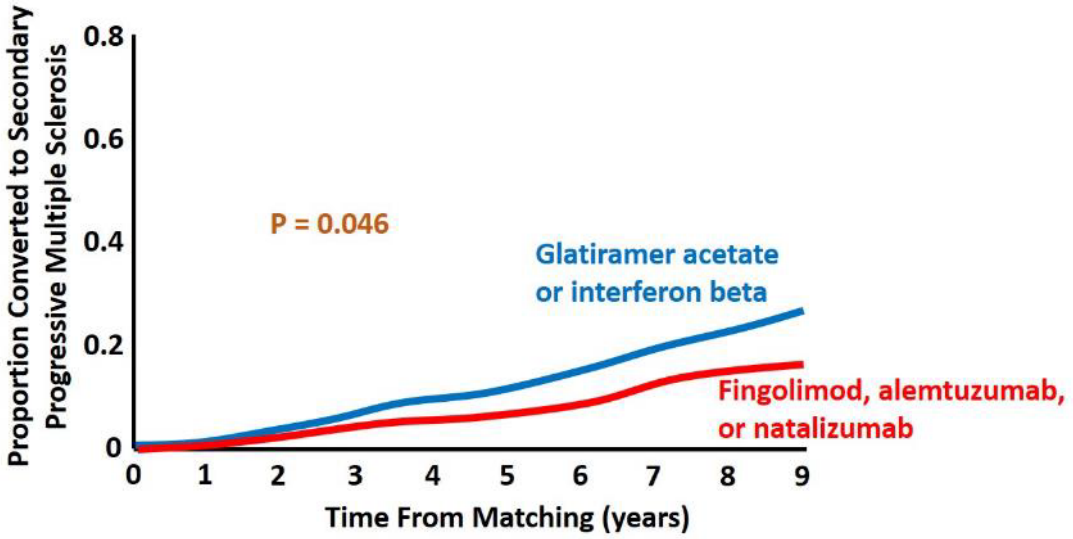
There is a paucity of effective treatments for PMS

Evolving relapsing MS treatment landscape



Adapted from Wingerchuk DM, Weinshenker BG. *BMJ* 2016;354:13518

Initial DMT and rate of conversion to SPMS



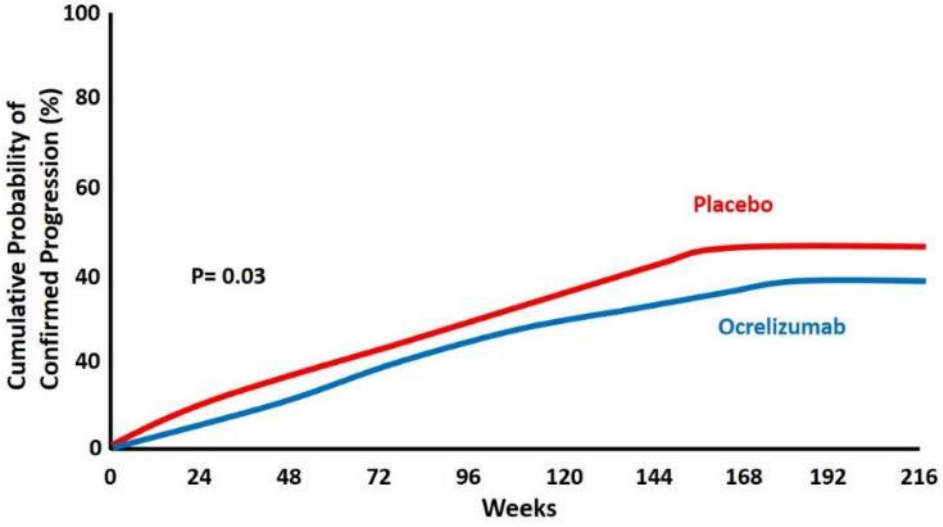
- Propensity matched cohort of 1555 patients RRMS at 68 centers commencing DMT or monitoring 1988-2012 with 4-yrs followup
- Lower risk of SPMS in patients treated initially with fingolimod, alemtuzumab, or natalizumab vs IFN/GA HR=0.66

Brown JWL et al. JAMA 2019;321:175-187

DMT for progressive MS

Oratorio

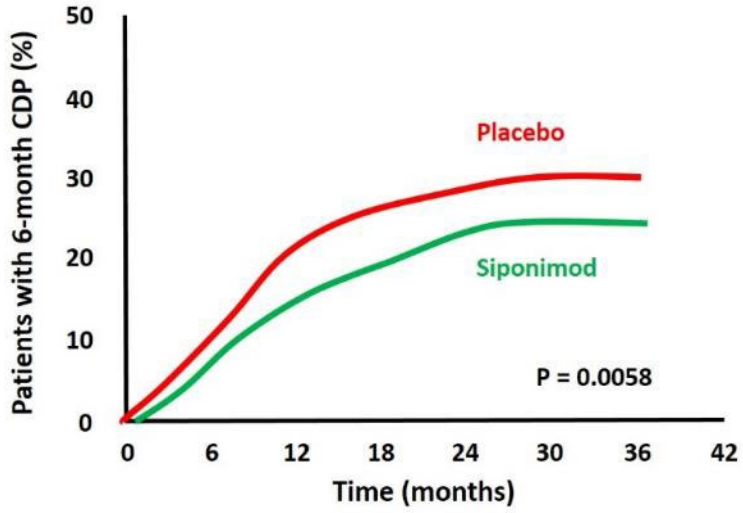
Tx: Ocrelizumab
Primary Endpoint: 12-Week Confirmed Disability Worsening
Subjects: PPMS (< 50 y.o.; + OCBs)



Montalban X et al. NEJM 2017;376:209-20

EXPAND

Tx: Siponimod
Primary Endpoint: 6 month Confirmed Disability Worsening
Subjects: SPMS (mean age 48, mean time since conversion- 3.9 y)



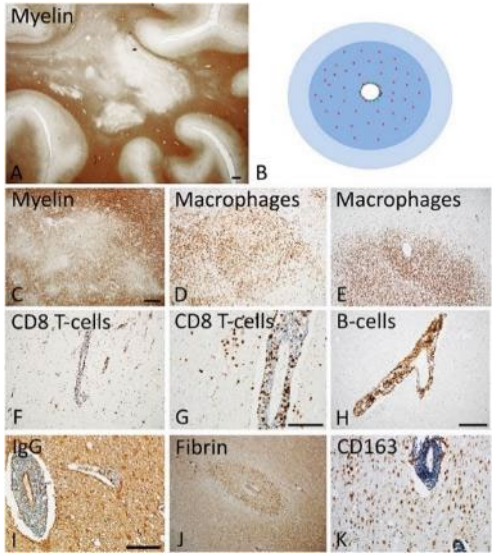
Kappos L et al. Lancet 2018;391:1263-73

Both studies indicate that patients with progressive MS who are younger, with shorter disease duration, and signs of active inflammatory activity (superimposed relapses, gad enhancing lesions) are more likely to benefit.

Pathological Hallmarks of Relapsing & Progressive MS: White Matter

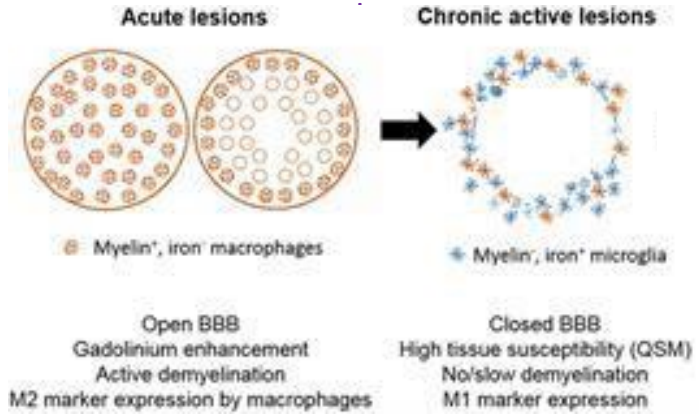
"Relapsing" course

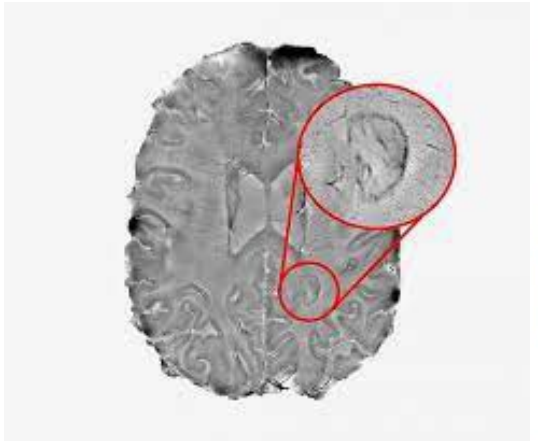
- Acute white matter lesions:
  - perivenular lymphocytic infiltrates composed of CD8+ T cells and B cells
  - Parenchymal invasion by hematogeneous myeloid cells
  - Active demyelination, axonopathy
  - focal BBB breakdown

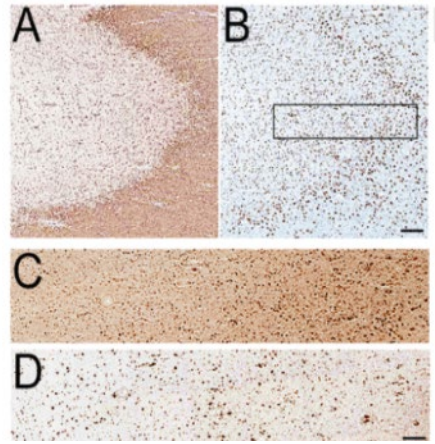


"Progressive" course

- Slowly expanding (smoldering/chronic active) lesions
  - inactive core – axonopathy, gliosis
  - rim of activated myeloid cells (predominantly microglial) with ongoing demyelination
  - Perivascular CD8+ infiltrates in lesion core



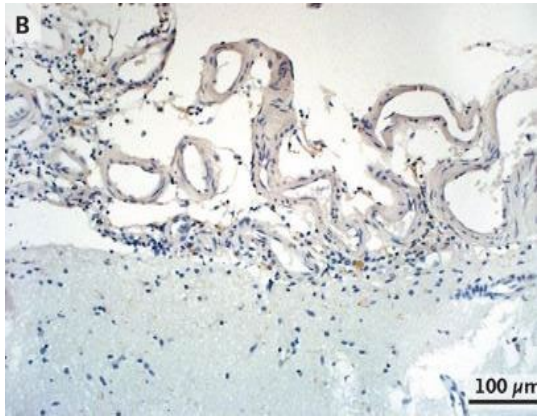




Pathological Hallmarks of Relapsing & Progressive MS: White Matter

"Relapsing" course

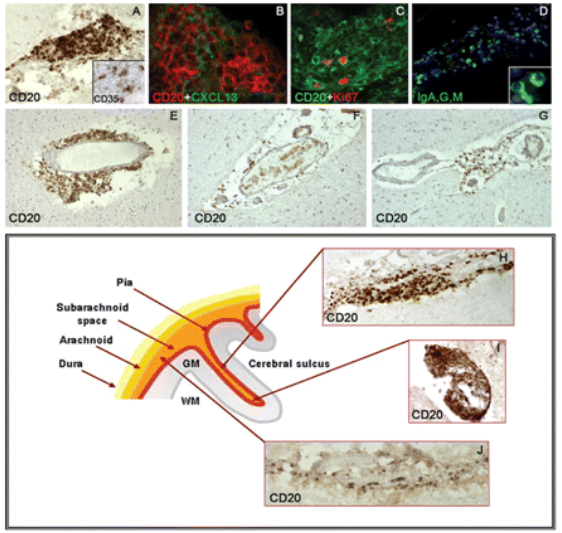
- Cortical lesions:
  - ➢ Diffuse meningeal infiltrates, composed of CD8 T cells, Bcells and plasmablasts abutting subpial lesions
  - ➢ Intracortical lesions have perivascular lymphocytic infiltrates composed of CD8 T cells and B cells



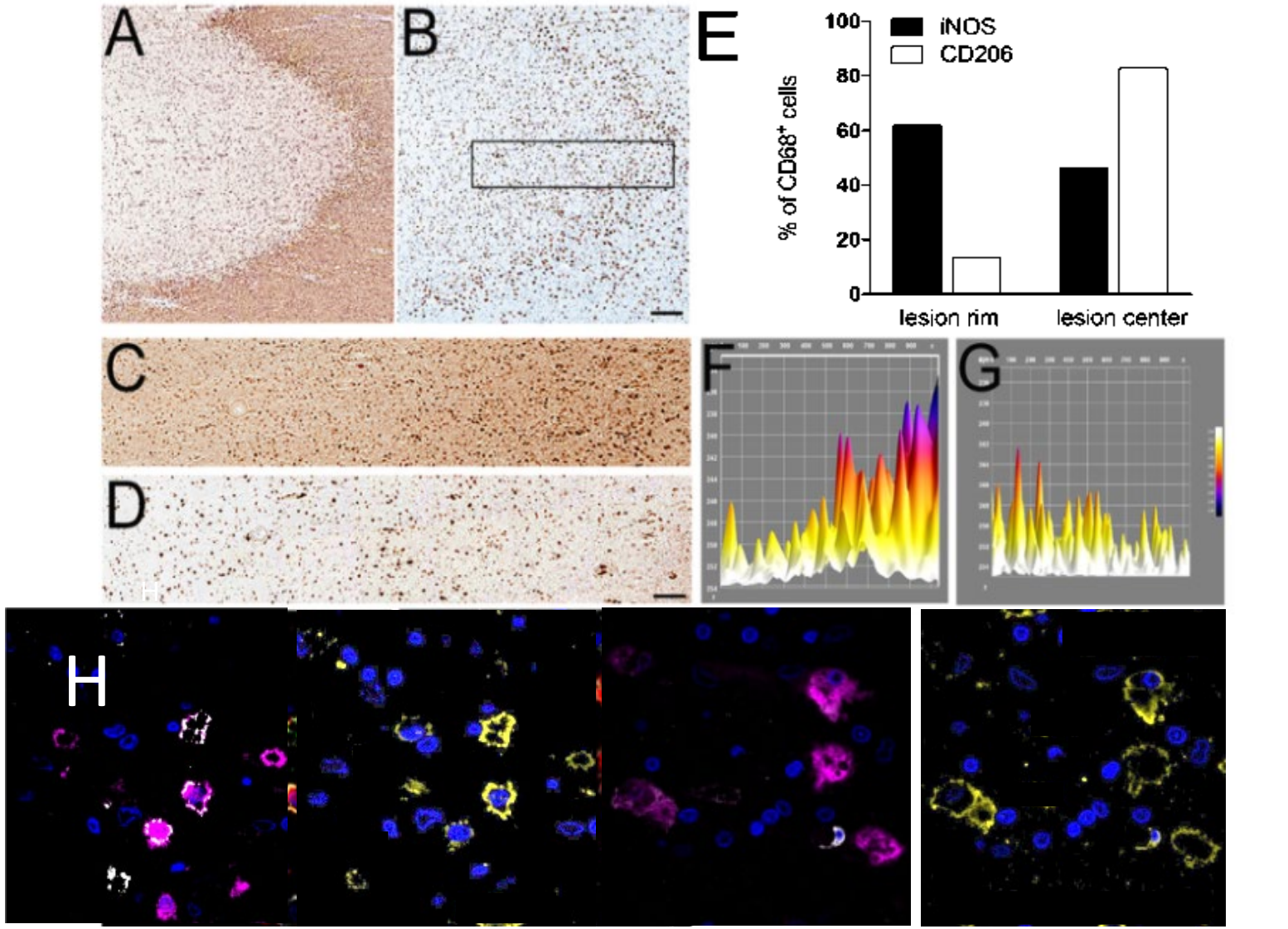
"Progressive" course

- Diffuse activation/ priming of microglia throughout grey and white matter

- Cortical lesions:
  - ➢ More prominent, organized meningeal infiltrates, sometimes in the form of tertiary follicles, composed of of CD8 T cells and proliferating Ig^+ plasma cells

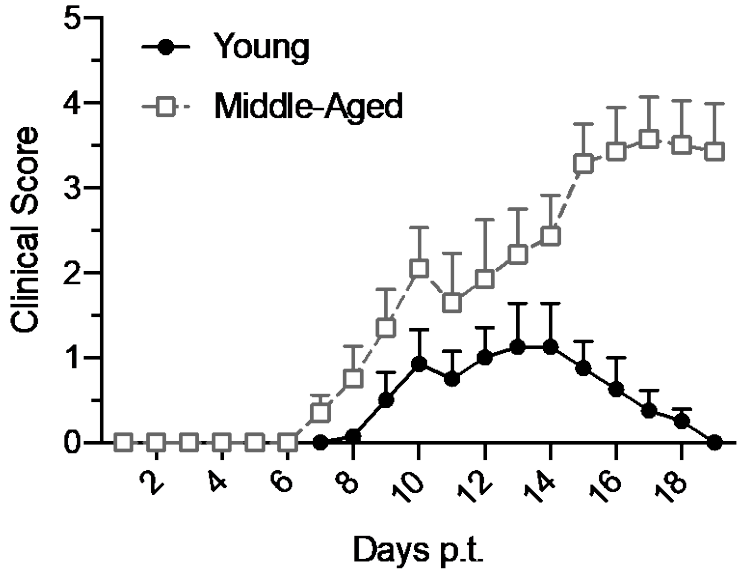


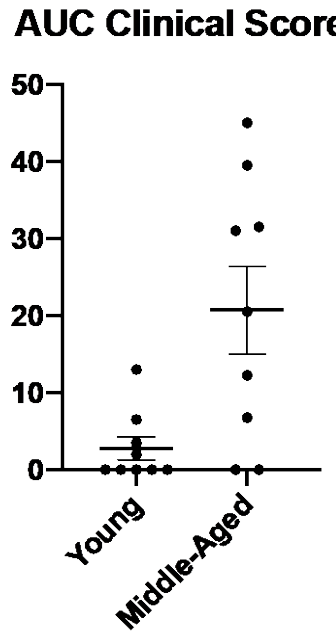
Active inflammation at the edge of smoldering MS lesions



Giles DA, et.al. Ann Neurol. 2018; 83:131.

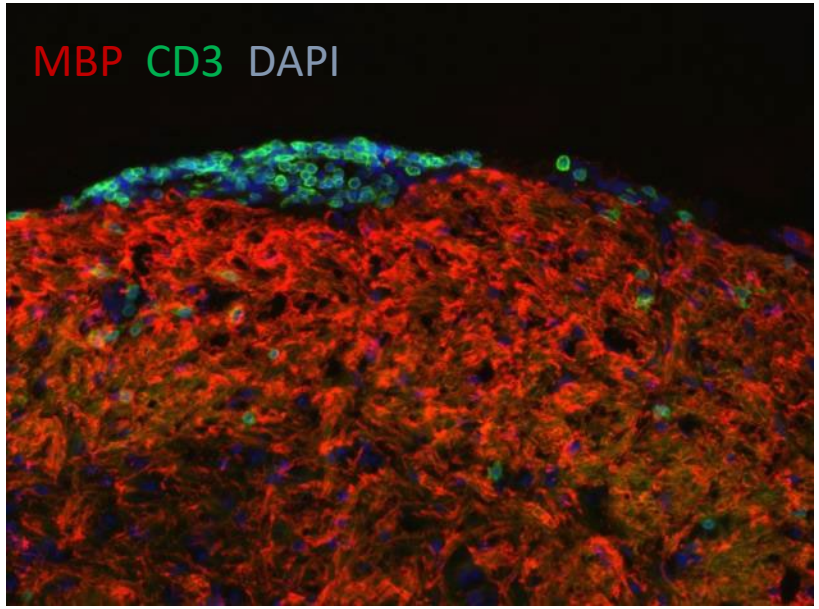
Middle aged mice are less likely to remit from EAE

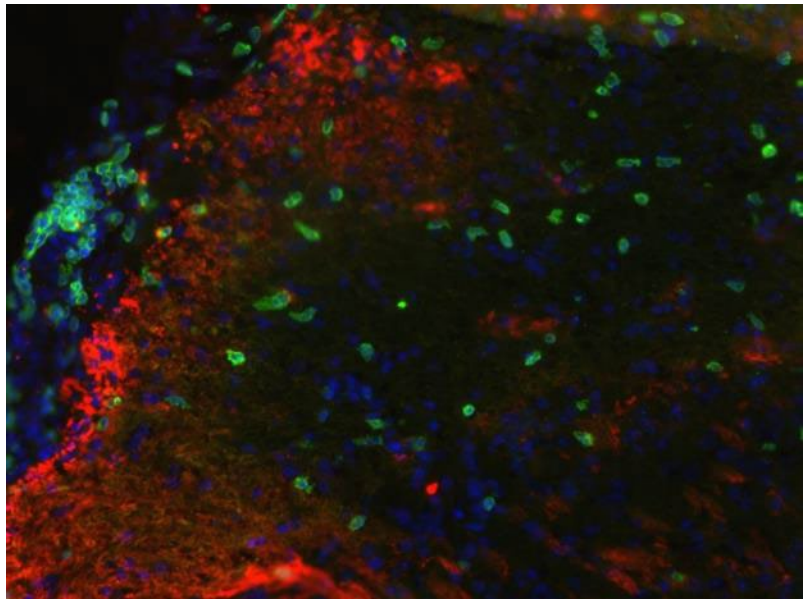




These data suggest that the immune status and CNS microenvironment of aged mice are conducive to the perpetuation of chronic neuroinflammation

Meningeal follicle-like structures in chronic EAE





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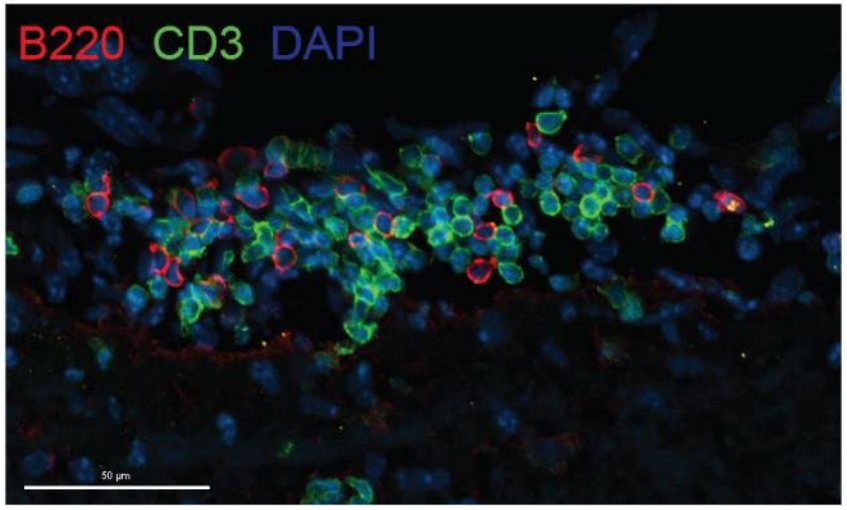
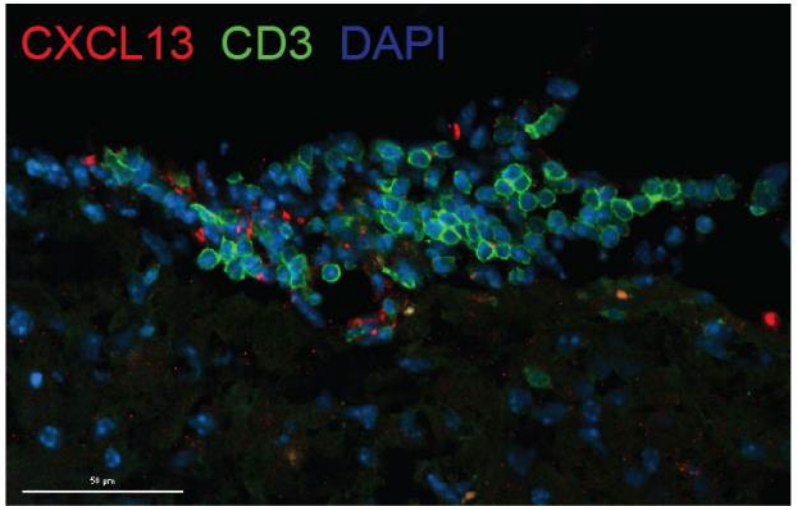
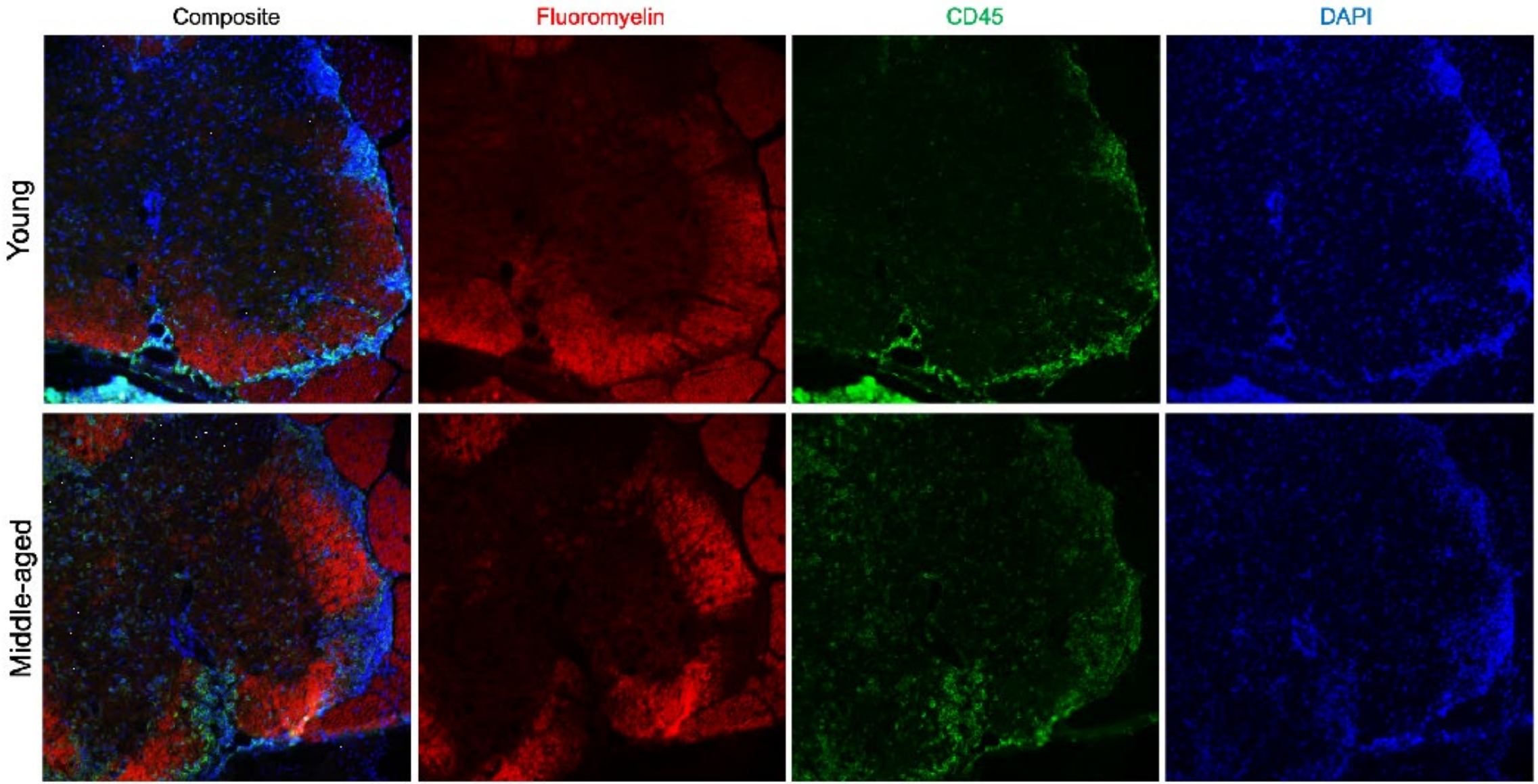
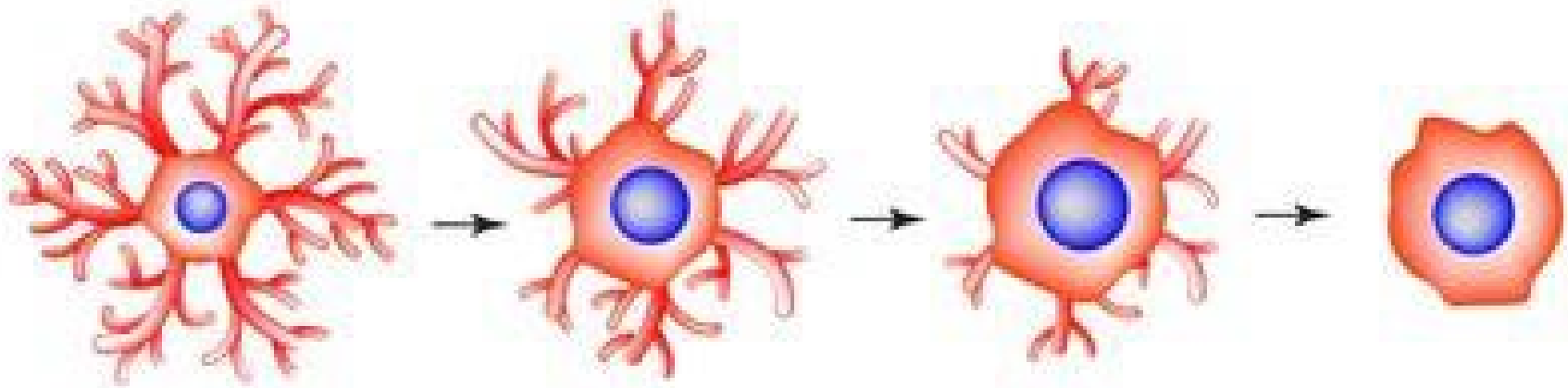


C

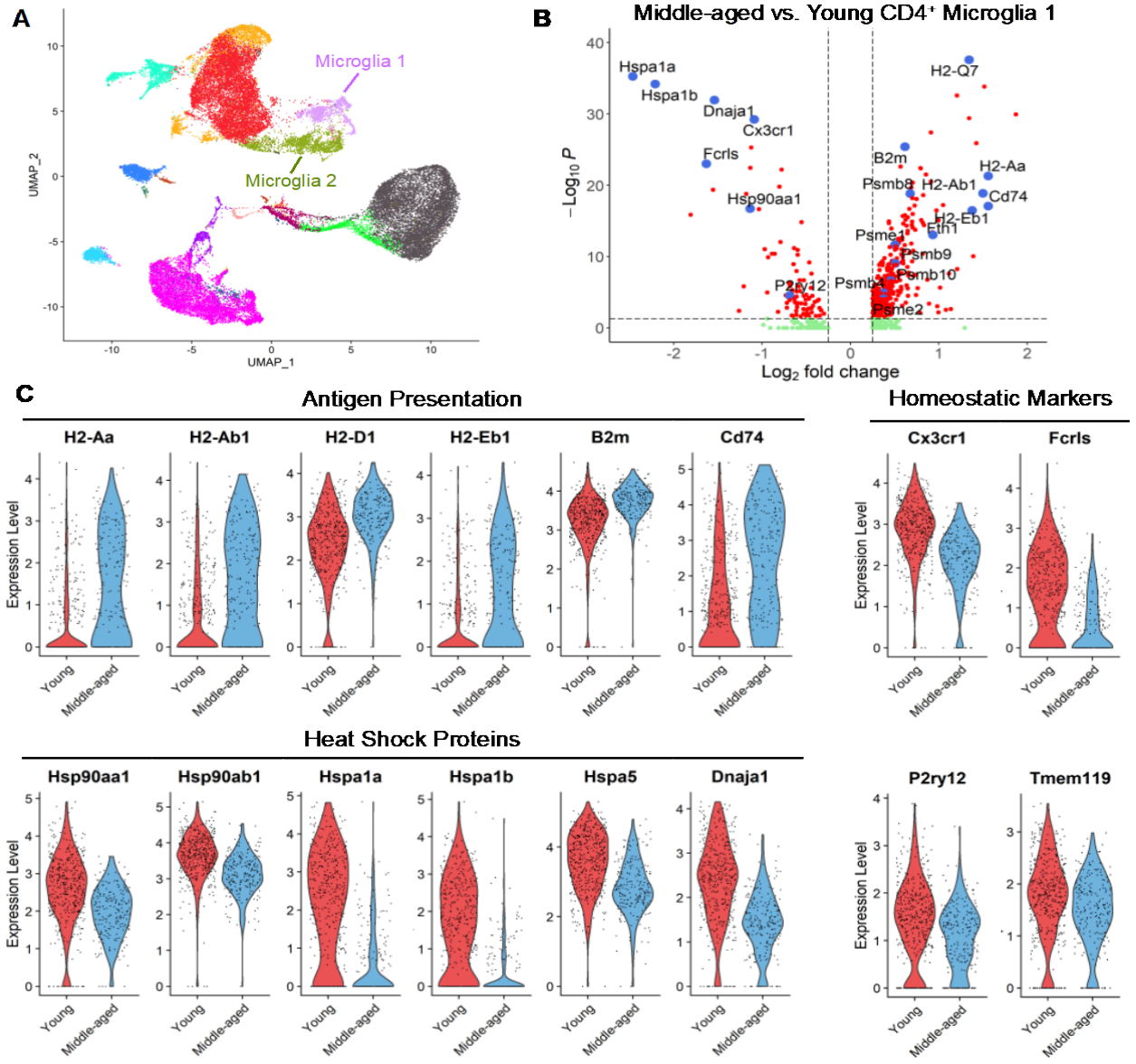


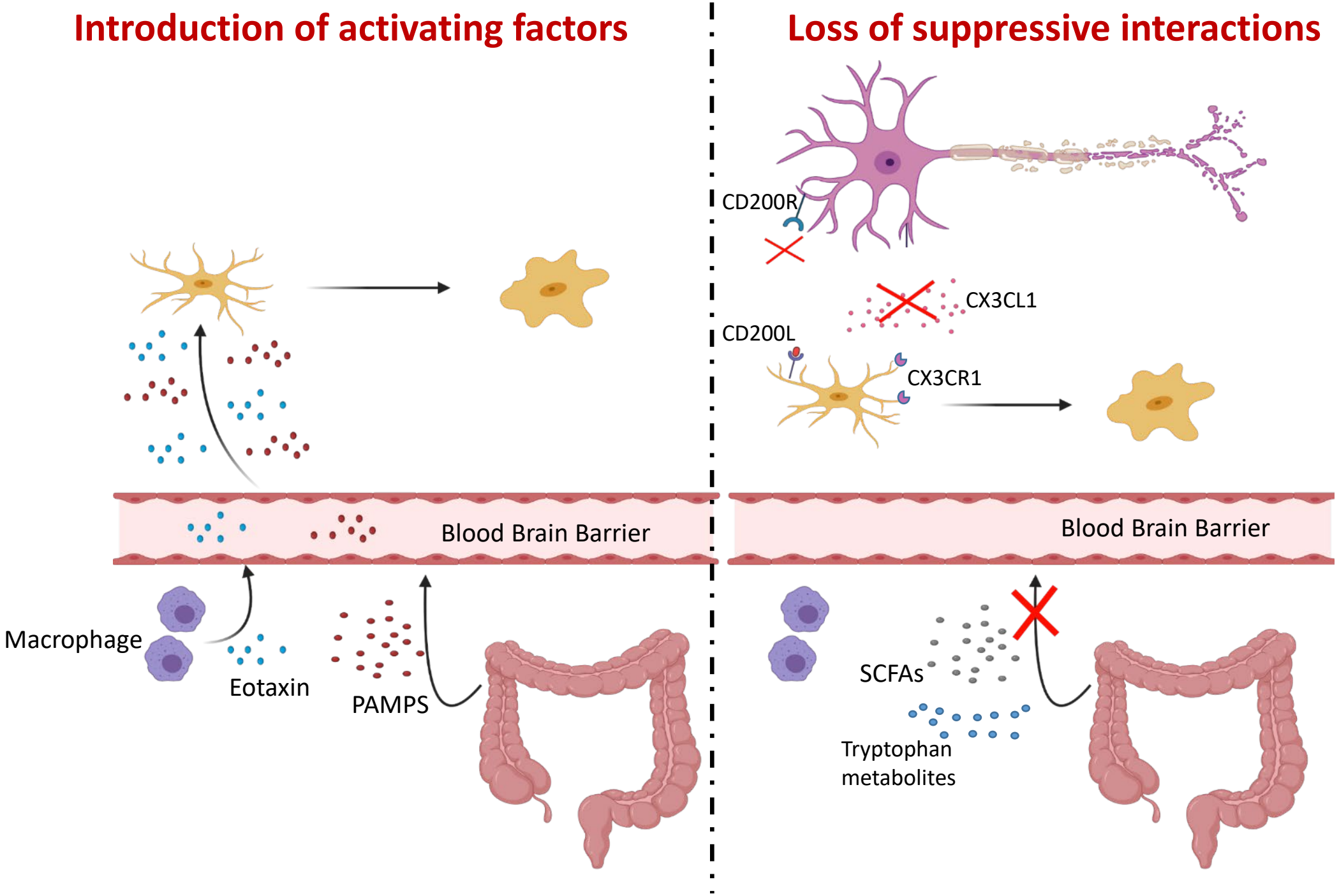

Composite
Fluoromyelin
CD45
DAPI
Young
Middle-aged

MICROGLIAL ACTIVATION



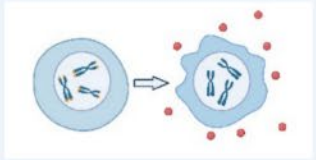
Microglia are “hyper”-activated in middle-aged mice



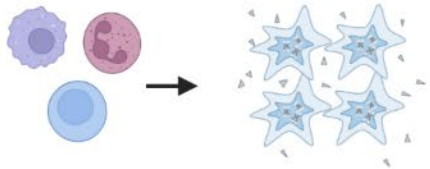

Introduction of activating factors
Loss of suppressive interactions
CD200R
CX3CL1
CD200L
CX3CR1
Blood Brain Barrier
Blood Brain Barrier
Macrophage
Eotaxin
PAMPS
SCFAs
Tryptophan
metabolites

Aging processes that impact MS pathology and treatment

Telomere attrition, peripheral immune and resident CNS senescent cell accumulation with chronic secretion of pro-inflammatory molecules (SASP)



Peripheral immune cell senescence and the senescenence associated secretory phenotype (SASP)



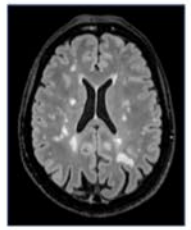
Secretion of cytokines, chemokines, matrix metalloproteinases, and other pro-inflammatory factors

Hypoxic stress, energy failure and mitochondrial dysfunction in multiple cell types

Pro-infammatory senescent microglia

Poor phagocytic activity ; iron accumulation; pro-inflammatory cytokines

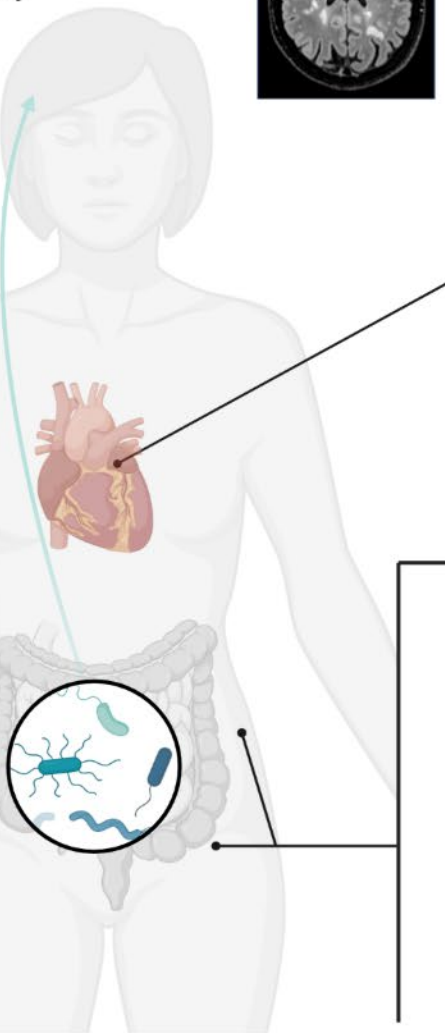
Poor OPC differentiation and remyelination



Aging related white matter changes and atrophy

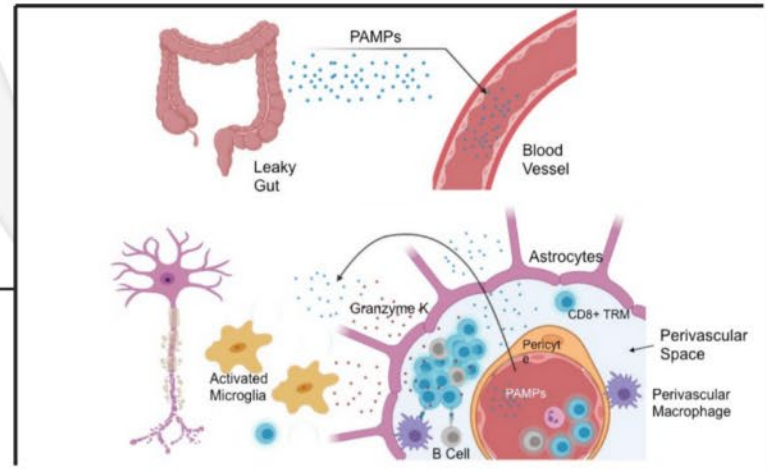
Comorbidity

Cardiovascular and neurovascular disease; Diabetes



Reproductive aging: Declines in AMH, estrogen, FSH, progesterone, testosterone

Microbiota and "leaky gut" with aging

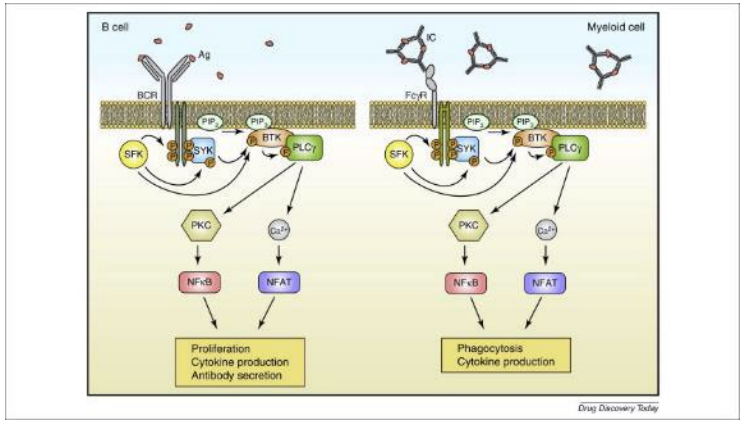


- **New Therapeutic Approaches- On the Horizon**

- BTKi Inhibitors
- Remyelinating Agents
- Immune Driven Repair

Bruton's Tyrosine Kinase (BTK): A novel therapeutic target in MS

- A member of the TEC family of cytoplasmic tyrosine kinases
- Expressed in all immune cells (other than T cells, NK cells and plasma cells), as well as alveolar epithelial cells.
- Plays a critical role in signaling pathways in B cells and myeloid cells (monocytes, macrophages, neutrophils, mast cells and microglia)
- BTK functions downstream of the B cell receptor on B cells and Fcγ/ Fcε receptors on myeloid cells
- BTK loss of function mutations cause nonlethal X-linked agammaglobulinemia, resulting in reduced B cells and immunoglobulin levels
- Ibrutinib, a small molecule BTK inhibitor (BTKi) is FDA approved for the treatment of B cell malignancies as well as GVHD.

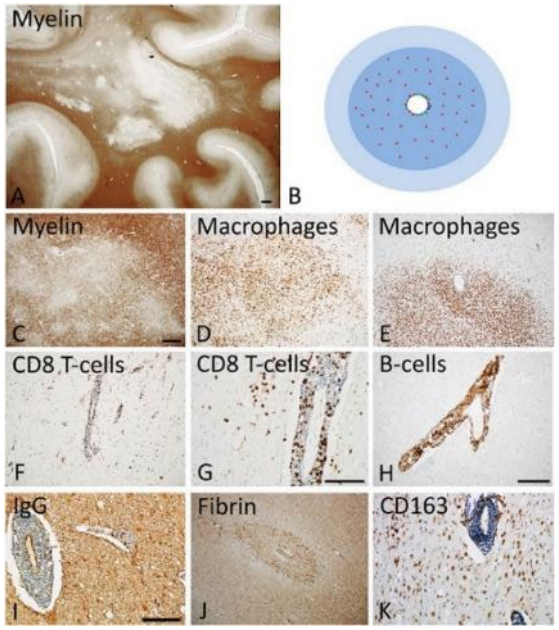


Whang JA and Chang BY. Drug Discovery Today. 2014; 19:1200

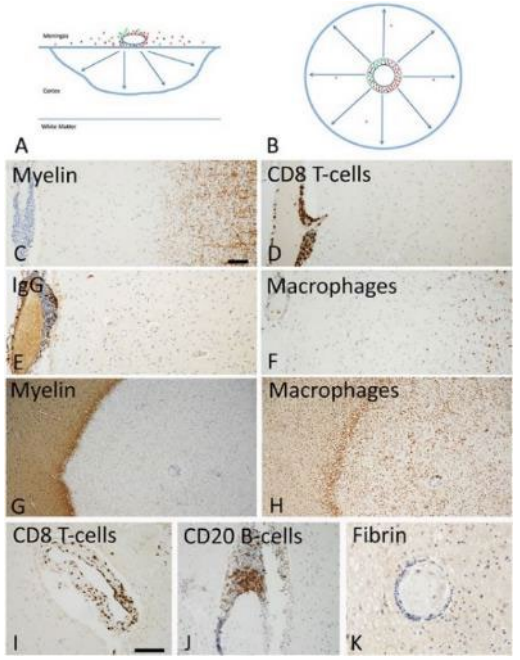
BTK inhibitors: Putative Mechanisms of Action in MS

- Blocking the proliferation and effector functions of pathogenic B cells, as well as their maturation into antibody producing plasma cells
- Suppressing antigen presentation (by B cells and/ or myeloid cells) to encephalitogenic T cells
- Blocking the activation of pro-inflammatory microglia and CNS-infiltrating myeloid cells
- Inhibiting microglial phagocytosis, including uptake of synaptosomes
- Suppressing mast cell degranulation and cytokine production

Relapsing MS



Progressive MS



Lassmann, H. *Front. Immunol*. 2019; 9:3116.

A Placebo Controlled Trial of Evobrutinib in Relapsing MS

- Double blind, randomized Phase 2 trial
- Placebo controlled phase: 24 weeks; blinded extension phase: 24 weeks
- Subjects: relapsing MS
  (87% RRMS, 13% active SPMS; 69% women; all white)
- 5 arms: placebo, evobrutinib x 3 doses, open label dimethyl fumarate
  (52-54 subjects/ arm)
- Primary outcome: total # of gad^{+} lesions on MRI at weeks 12, 16, 20 and 24
- Results: The total number of gad^{+} lesions, measured at weeks 12-24, was significantly lower among patients in the evobrutinib 75 mg once-daily group than in the placebo group
- Side effects: elevated LFTs; nasopharyngitis

Montalban X, et al. N Engl J Med. 2019; 380:2406

A Placebo Controlled Trial of SAR442168 (tolebrutinab) in Relapsing MS

- Double blind, randomized Phase 2b trial
- 12 week crossover
- Subjects: RRMS
- 5 arms: placebo, SAR442168 x 4 doses
  (52-54 subjects/ arm)
- Primary outcome: new gad+ lesions
- Results: 85% relative reduction in new gad^{+} lesions in the highest dose group
  89% relative reduction in new or enlarging T2 lesions (secondary outcome)

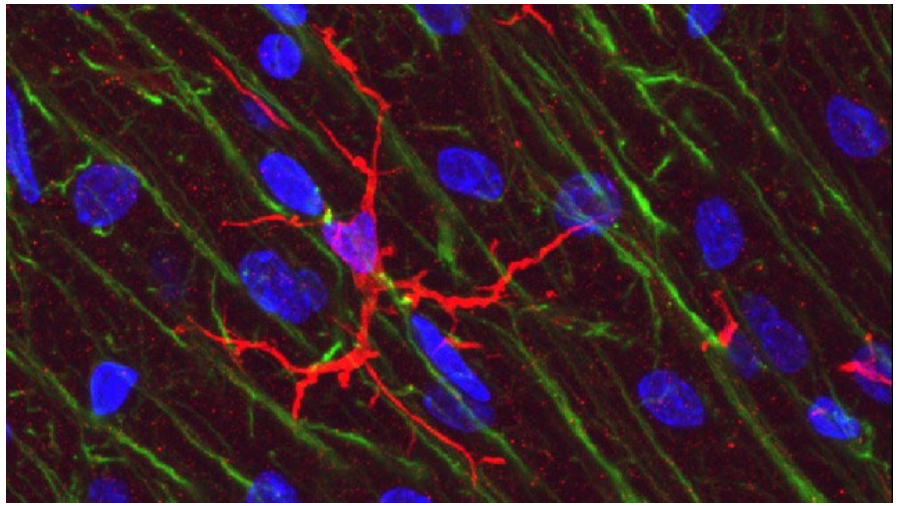
Reich DS, et al. Eur J Neurol. 2020; 27:1-102

Ongoing Clinical Trials of BTKi's in MS

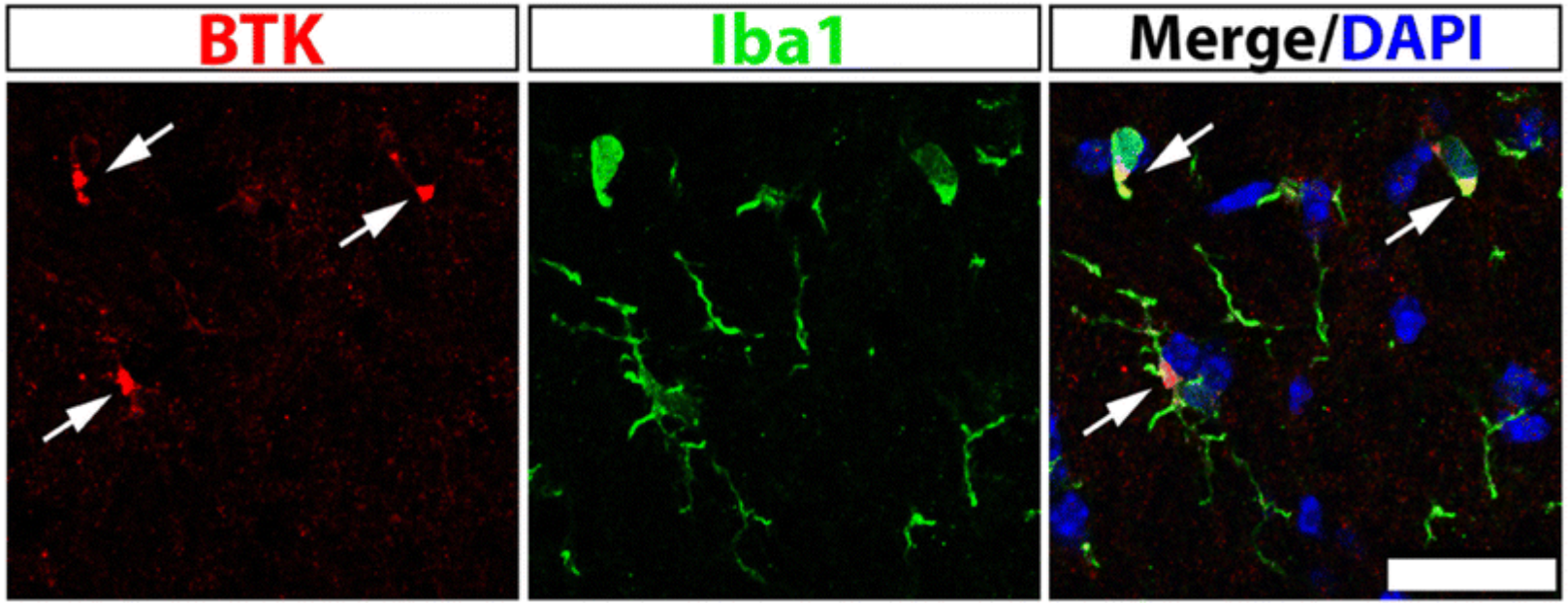
Compound	Clinical Trials.gov Identifier	Study Type	Subjects	Control Group
SAR442168 (Tolebrutinib)	NCT03889639	Phase 2b	Relapsing MS	Placebo
SAR442168	NCT04410991	Phase 3	Relapsing MS	Placebo, Teriflunomide
SAR442168	NCT04410978	Phase 3	Relapsing MS	Placebo, Teriflunomide
SAR442168	NCT04458051	Phase 3	PPMS	Placebo
SAR442168	NCT04411641	Phase 3	Non-relapsing SPMS	Placebo
M2951	NCT02975349	Phase 2	RRMS	Placebo, DMF
BIIB091	NCT03943056	Phase 1	Healthy volunteers	Placebo

Potential Mechanisms of Action of BTKi in Progressive MS

- Activated microglia in the rim of smoldering white matter lesions and in cortical lesions
- Activated microglia scattered through out the perilesional and NAWM



BTK is expressed in microglia



Kenay J et al. *J Neuroimmune Pharmacol*. 2019; 14:448

Side effects of BTKi: Experience from trials in cancer and GVHD

- In trials of ibrutinib in CLL, side effects were predominantly grade 1 or 2 and included transient diarrhea, fatigue and URIs. Most adverse events resolved without the need for a suspension of treatment. IgG and IgM levels remained relatively stable through out treatment, whereas IgA levels increased.

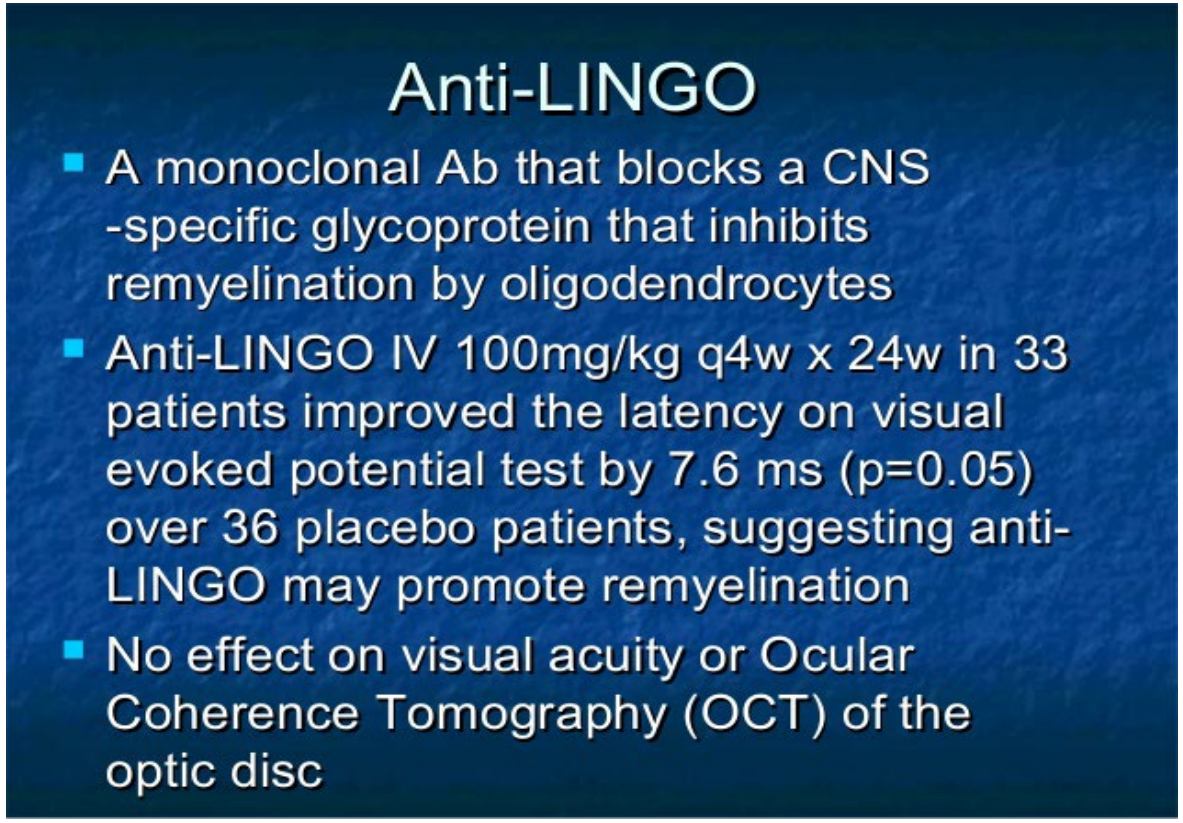
  Byrd JC, et al. *N Eng J Med*. 2013; 369: 32; Sun C, et al. Blood. 2015; 126:2213.

- In a clinical trial of chronic, refractory GVHD the most common adverse effects were fatigue, diarrhea, muscle spasms, nausea and bruising. Dose reductions were reported for 31% of patients; the most common reason being fatigue.

  Mikos D, et al. *Blood*. 2017; 130:2243.

- A review of EMRs of 378 patients with lymphoid cancers treated with ibrutinib revealed serious infections in 43 individuals (11.4%), primarily during the first year of treatment (bacterial infections in 23 and fungal infections in 16). The majority (84%) received ibrutinib as a monotherapy. Infection resulted in death in 6 of the 43 patients. Risk factors associated with development of serious infection included receipt of ≥3 prior antitumor regimens and the presence of neutropenia at any time during the course of ibrutinib.

  Varughese T, et al. *Clinical Infect Diseases*. 2018; 67:687.



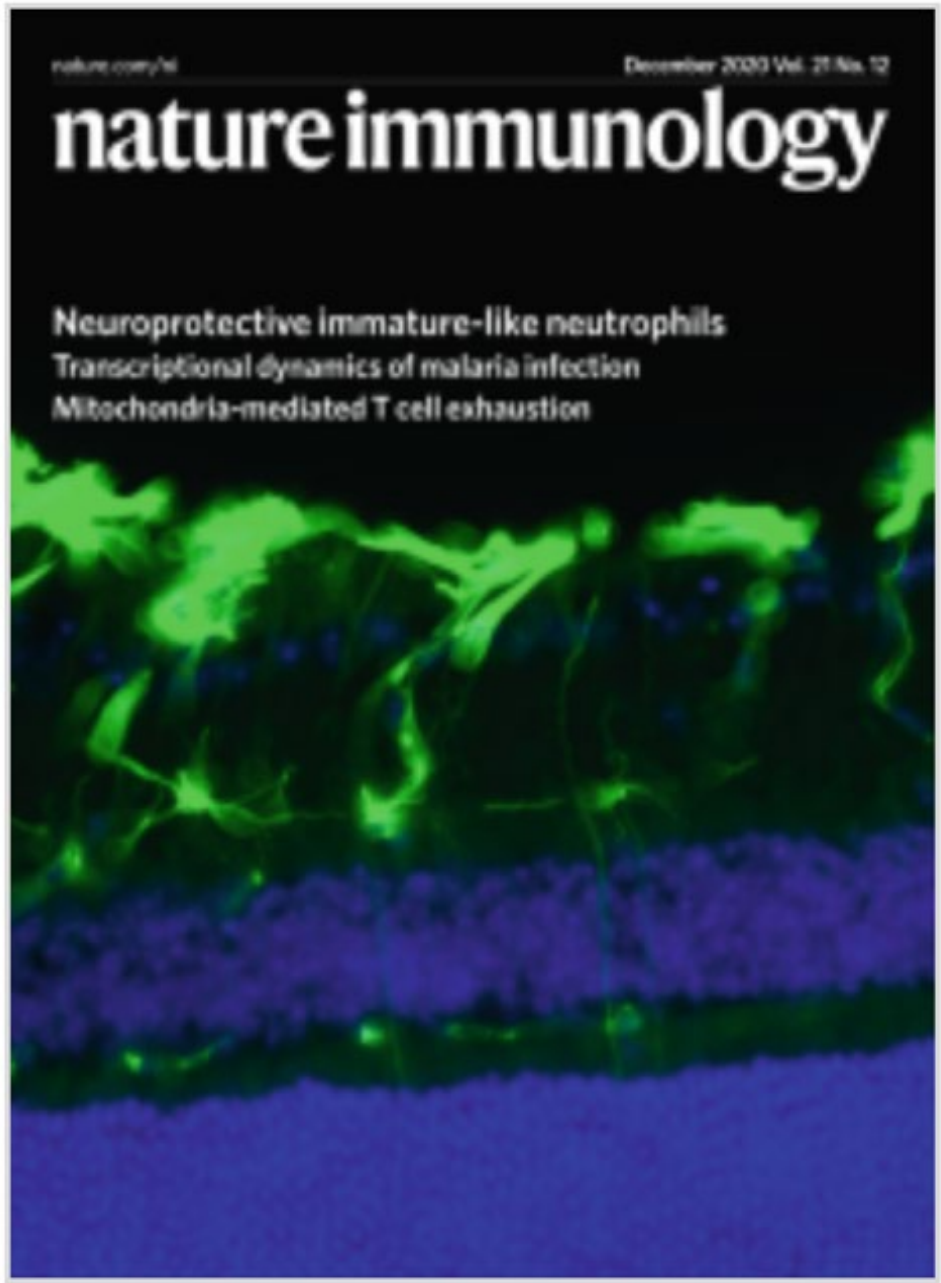
Opicinumab:
2 other Phase II clinical trials demonstrated no significant impact.
Biogen discontinued clinical development in October 2020.

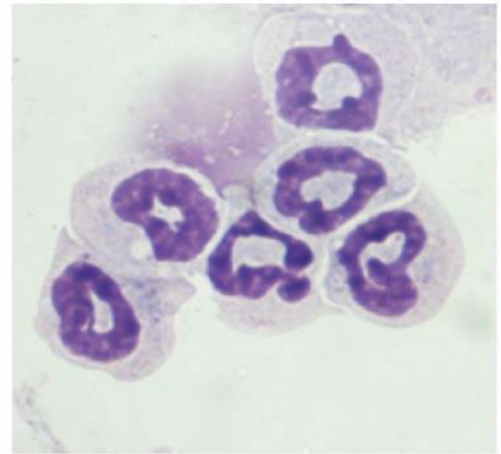
Muscarinic Receptor Antagonists/ Antihistamines as Remyelinating Agents

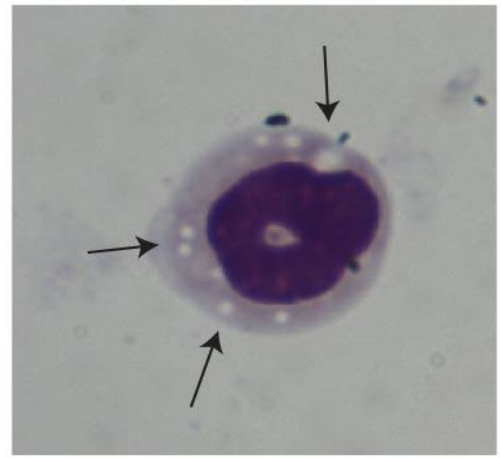
- Identified in high throughput screening assays of drug libraries for compounds that promote oligodendrocyte differentiation/ remyelination.

- In a randomized, single-center, placebo-controlled, crossover phase II trial (NCT02040298; ReBUILD) the effect of 10.72 mg/day orally administered **clemastine fumarate** was investigated in 50 patients with relapsing MS and a history of optic neuritis on stable immunomodulatory therapy. Outcome measure: shortening of p100 latency on VEP. Result: slight but significant reduction of latency delay by 1.7 msec, suggesting minimally faster axon conduction. A new Phase 2 trial of clemastine in acute optic neuritis is ongoing.

- Another oral antihistamine, **GSK239512**, has evaluated in a randomized, placebo-controlled, phase II trial (NCT01772199) as add-on to a preexisting disease-modifying therapy with intramuscular interferon-β1a or glatiramer acetate to assess its potential to drive remyelination in established MS lesions. Outcome measures were based on changes in magnetization transfer ratio (MTR), an MRI marker thought to reflect myelination. A small positive effect on MTR was observed, but the drug was poorly tolerated.


nature immunology
December 2020 Vol. 21 No. 12
Neuroprotective immature-like neutrophils
Transcriptional dynamics of malaria infection
Mitochondria-mediated T cell exhaustion





Symptomatic Treatment of Progressive MS

- Physical, occupational and speech therapy
- Cognitive Rehabilitation and Psychotherapy
- 4-aminopyridine
- Management of Fatigue

  Pharmaceutical, Cog. Rehab, tx of co-morbid sleep disorders
- Management of spasticity & dystonia

  Pharmaceutical, Botox, PT
- Management of bladder dysfunction
- Management of pain

Conclusions

- People with progressive MS (pMS) do not respond as well as people with RRMS to currently available DMTs
- There are fundamental differences in the pathology of pMS and RRMS. pMS is characterized by local microglial activation and compartmentalized inflammation (edge of smoldering lesions/ meningeal follicles)
- CNS-penetrant BTKi might be therapeutically effective in progressive MS by suppressing microglia and blocking B cell rich meningeal infiltrates
- Neurorestorative and pro-remyelinating therapies are potential strategies for mitigating and even reversing disability in pMS
- Symptomatic management is a critical component of therapeutic management

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Thank you and please join us for the next webinar on September 12, 2022!

Bladder Dysfunction in Multiple Sclerosis

Rebecca Lavelle, MD

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