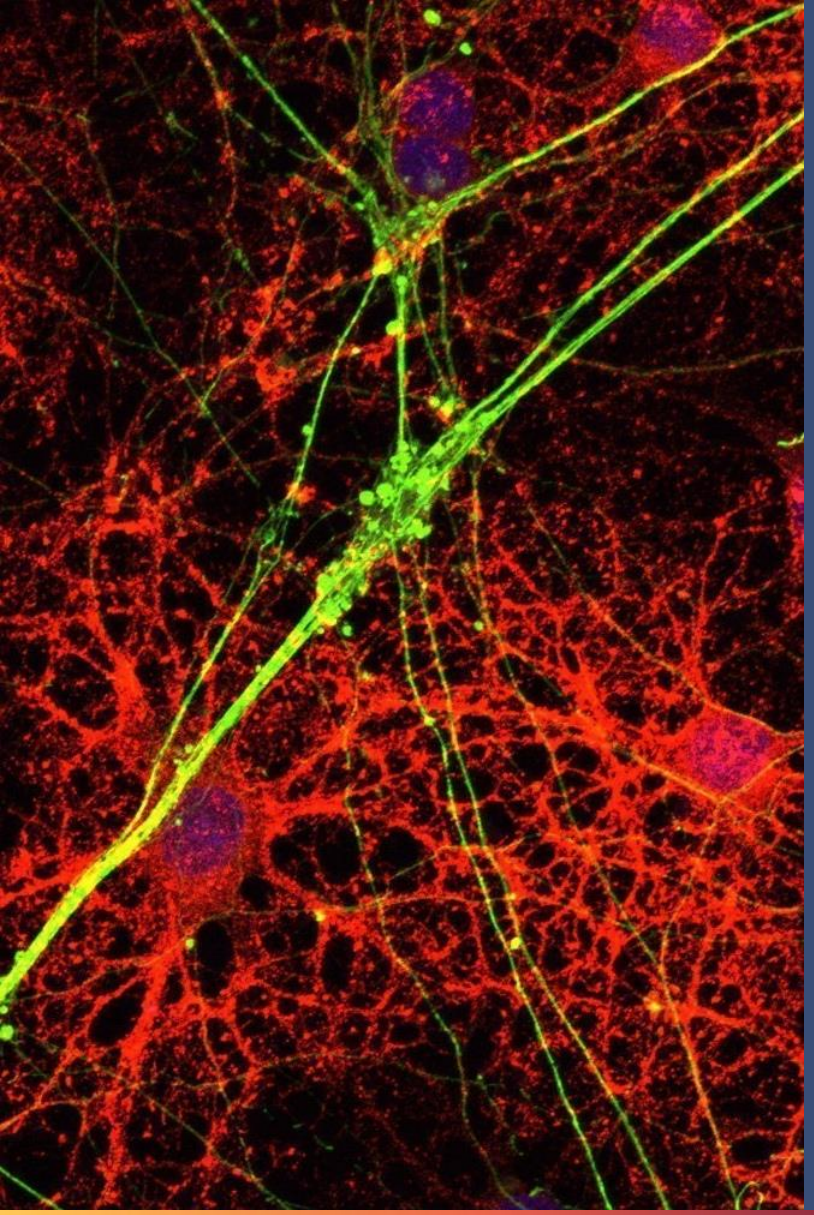

Regenerative Medicine for the Treatment of Multiple Sclerosis: Enhancing Repair to Prevent Progression

Luke Lairson, PhD

Department of Chemistry
Scripps Research

THE FRONT ROW
at Scripps Research

Outline

- Recent developments and breakthrough therapies in relapsing-remitting forms of MS (RRMS)

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- The potential of a regenerative medicine-based approach (remyelination) to treating progressive forms of MS

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- Recent developments and breakthrough therapies in relapsing-remitting forms of MS (RRMS)
- The potential of a regenerative medicine-based approach (remyelination) to treating progressive forms of MS
- The essential role of academic science in the discovery and development of new medicines

UT Southwestern
Medical Center

- Globally, multiple sclerosis (MS) impacts ~2.8 million people

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- Rates of MS are higher in regions further from the equator

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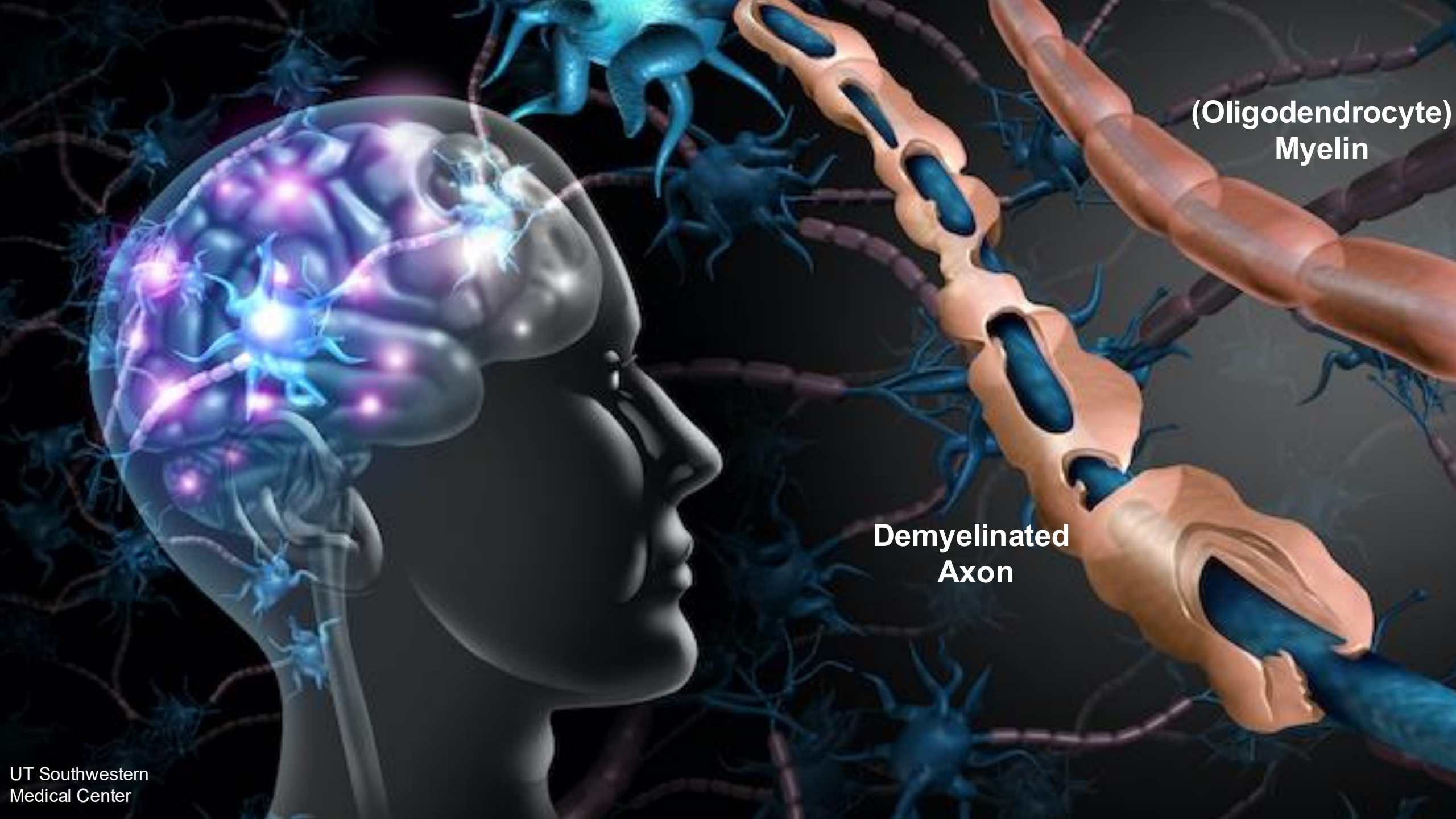
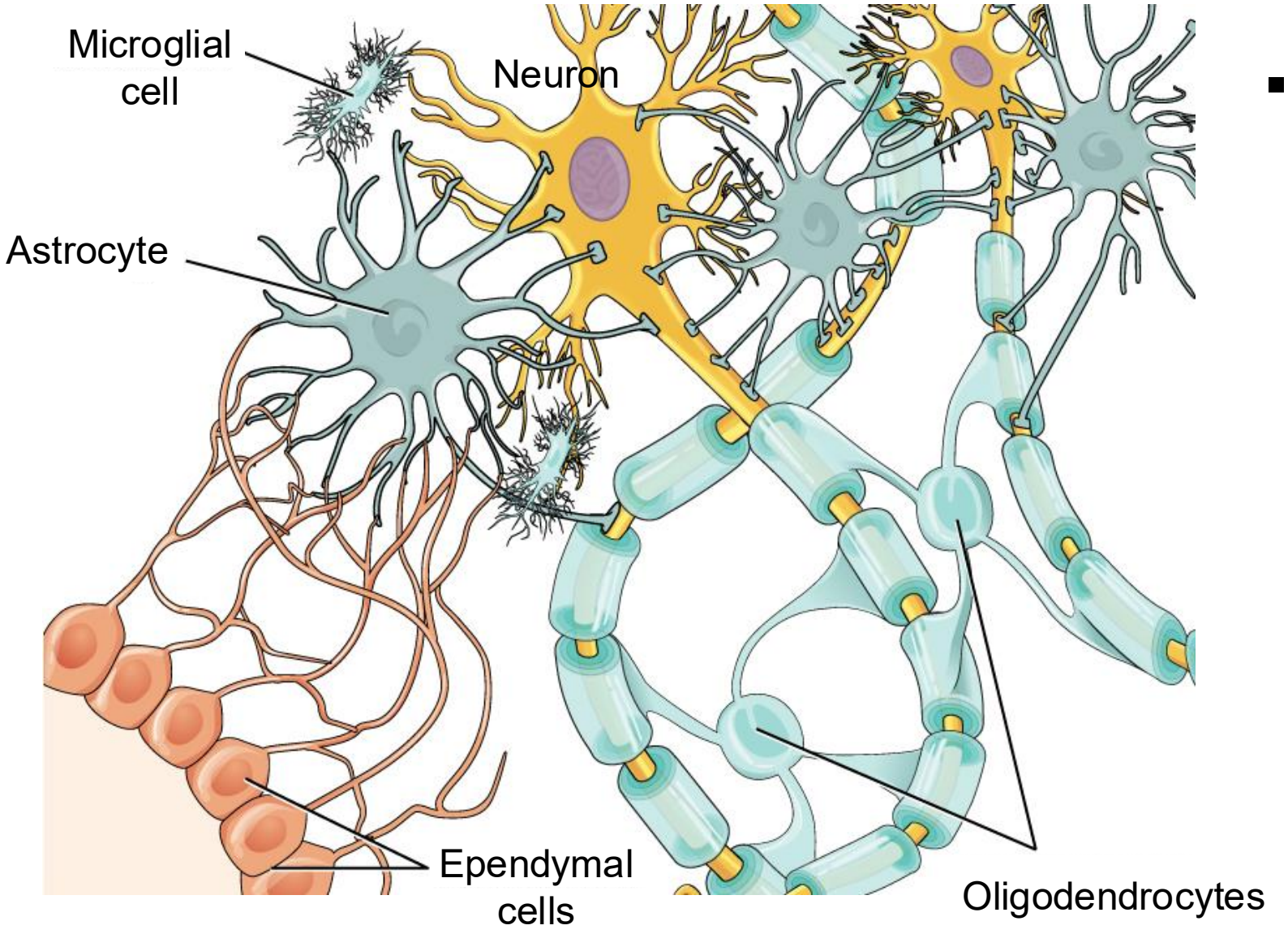
- Rates of MS are higher in regions further from the equator
- Women or ~3 times more likely than men to be diagnosed with MS

UT Southwestern
Medical Center



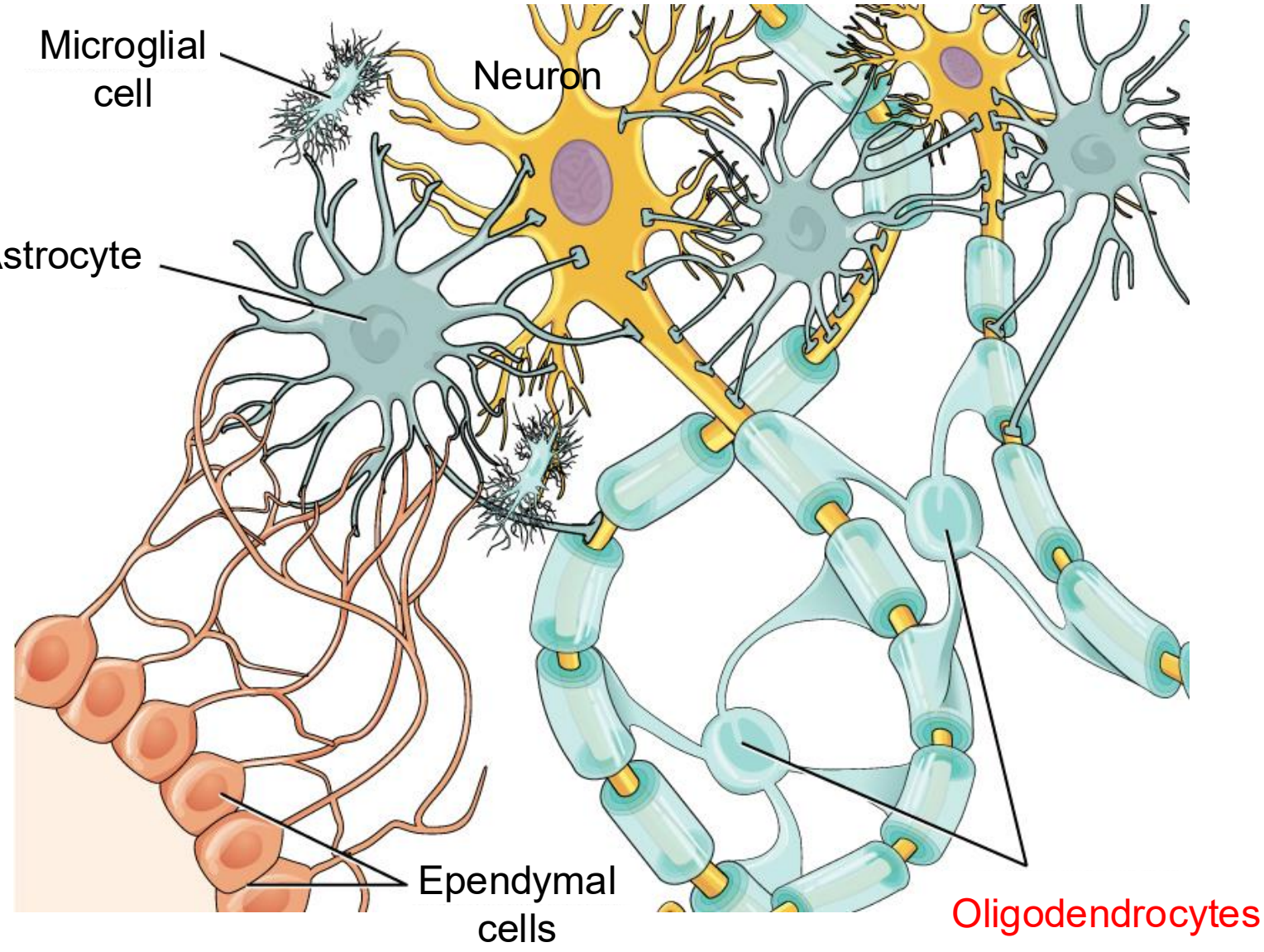
UT Southwestern
Medical Center

Oligodendrocytes Wrap the Axons of Neurons (Myelination)



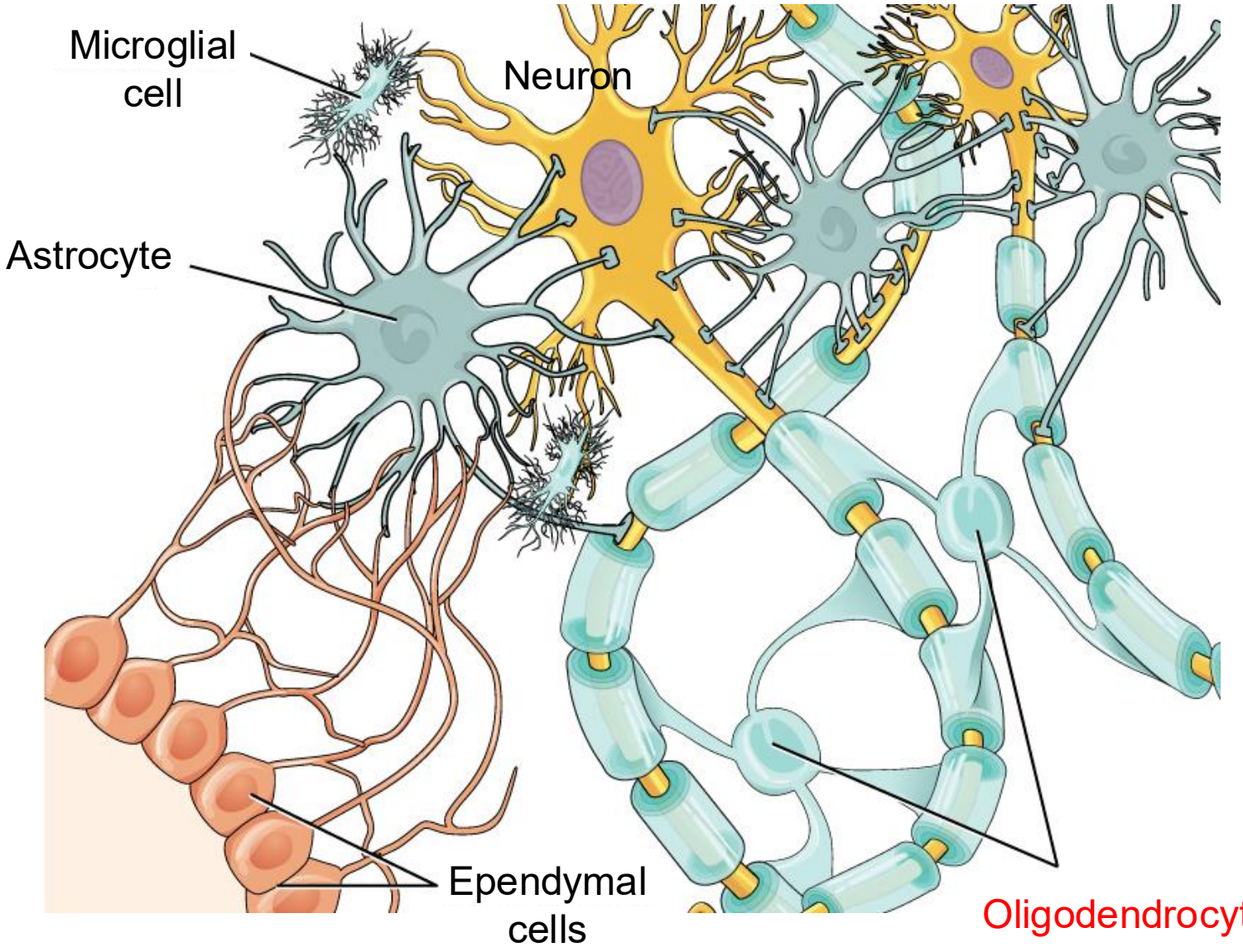
- CNS is composed of neuronal and glial cells
  - Neurons
  - Astrocytes
  - Microglia
  - Oligodendrocytes

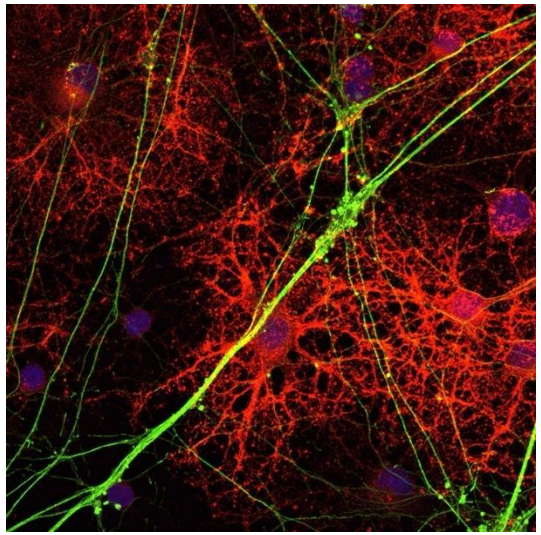
Oligodendrocytes Wrap the Axons of Neurons (Myelination)



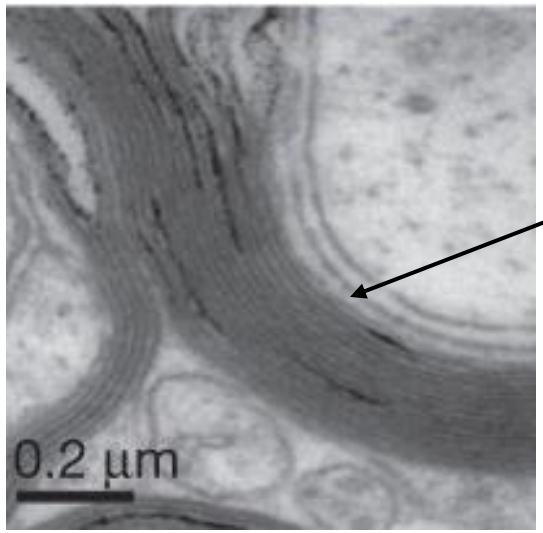
- CNS is composed of neuronal and glial cells
- Lipid rich myelin sheaths are required for neuronal survival and function

Oligodendrocytes Wrap the Axons of Neurons (Myelination)

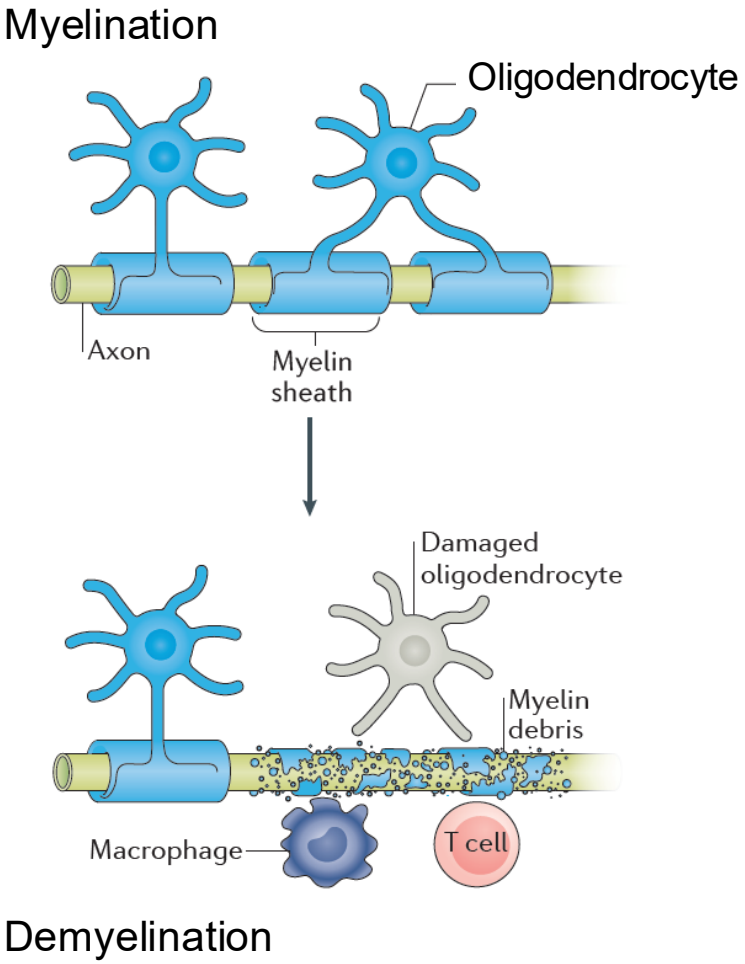




MBP (Oligodendrocytes)
TUJ1 (Neurons)



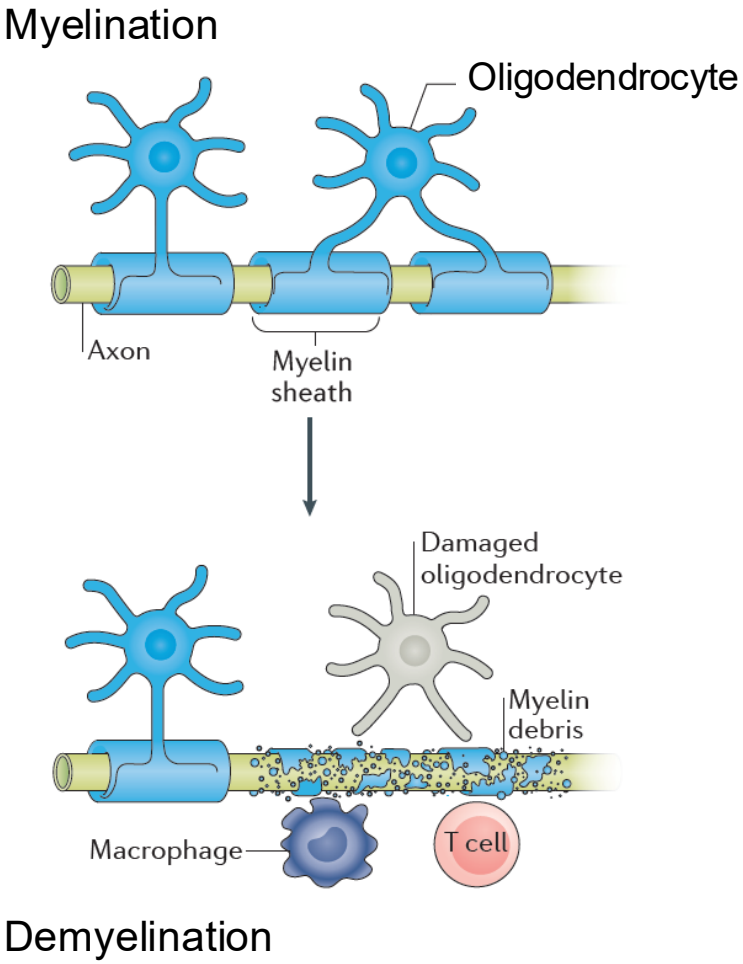
MS is Characterized by Adaptive Immune Responses to Oligodendrocytes



- Adaptive auto-immune (self destructive) responses target and destroy oligodendrocytes
- Loss of oligodendrocytes leads to the demyelination of axons

Franklin, R.J.M and ffrench-Constant, C. (2017)
Nat. Rev. Neurosci. **18**:753.

MS is Characterized by Adaptive Immune Responses to Oligodendrocytes



- Adaptive auto-immune (self destructive) responses target and destroy oligodendrocytes
- Loss of oligodendrocytes leads to the demyelination of axons
- Permanent loss of myelin results in the loss of axons and permanent neurological dysfunction

Franklin, R.J.M and ffrench-Constant, C. (2017)
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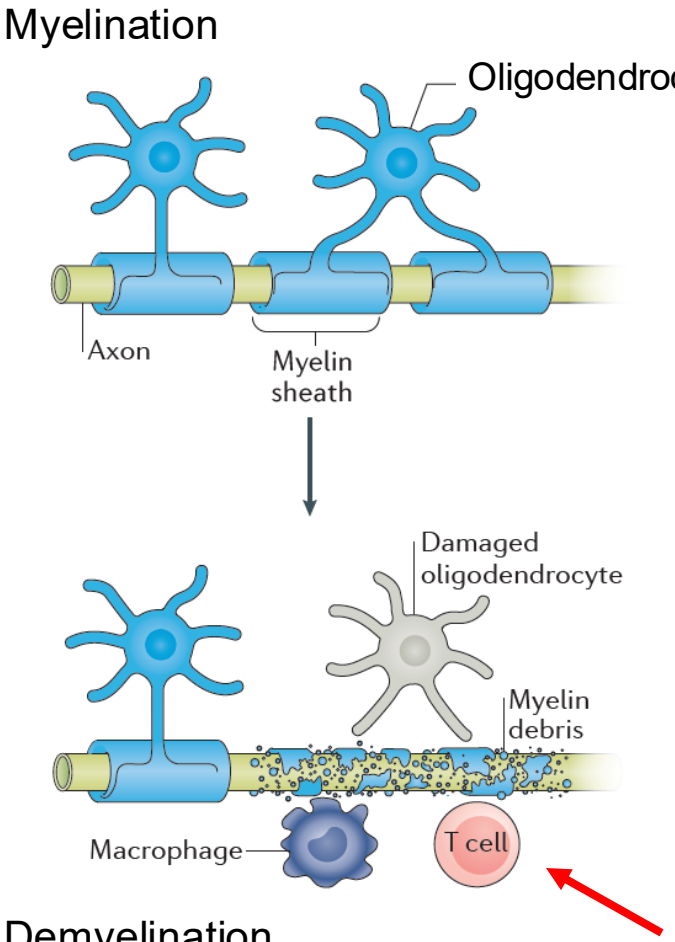
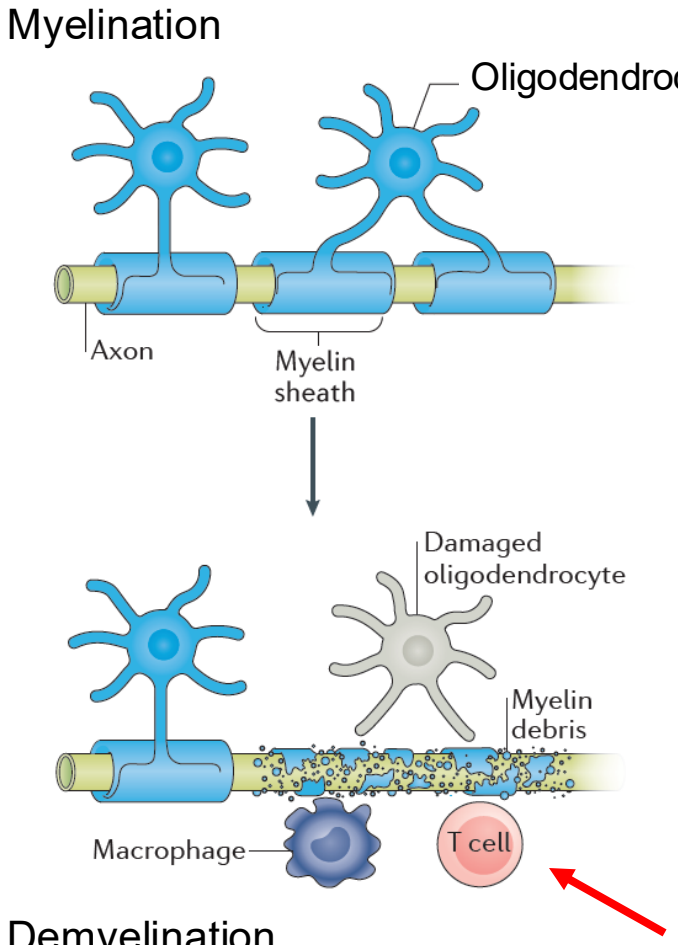
Therapeutic Approaches to the Treatment of MS: Targeting T Cells



- 2010, approval of Fingolimod (Gilenya, Novartis) – effective orally available treatment for RRMS

- S1PR therapies were a breakthrough for relapsing-remitting MS (RRMS)

Therapeutic Approaches to the Treatment of MS: Targeting T Cells

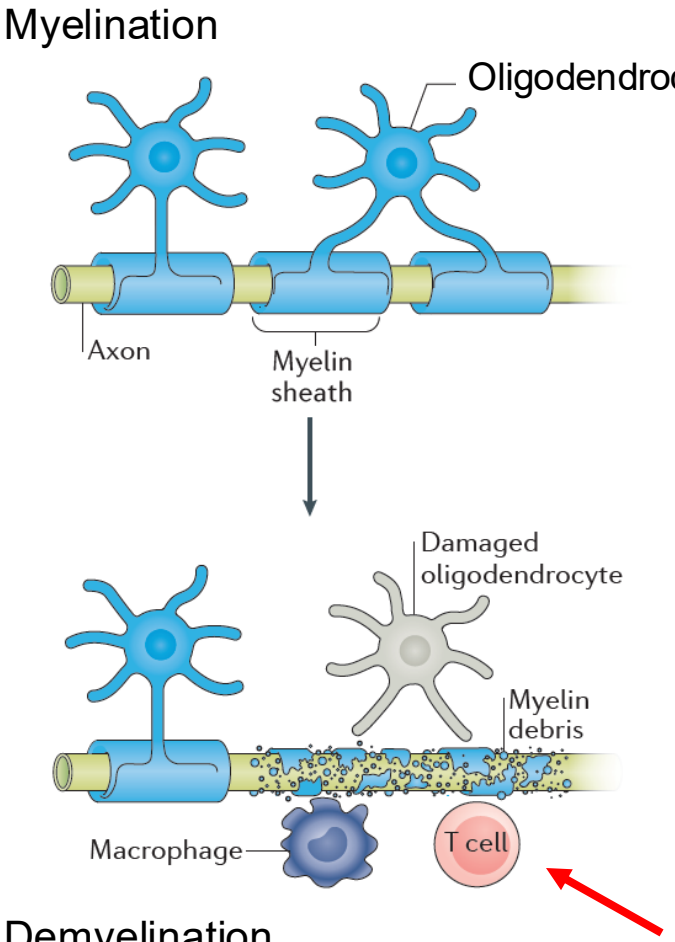


- 2020, Ozanimod (Receptos / Scripps) approved for RRMS

Developed by
Hugh Rosen (Chair of Molecular and Cellular Biology) with Edward Roberts

- S1PR therapies were a breakthrough for relapsing-remitting MS (RRMS)

Therapeutic Approaches to the Treatment of MS: Targeting T Cells

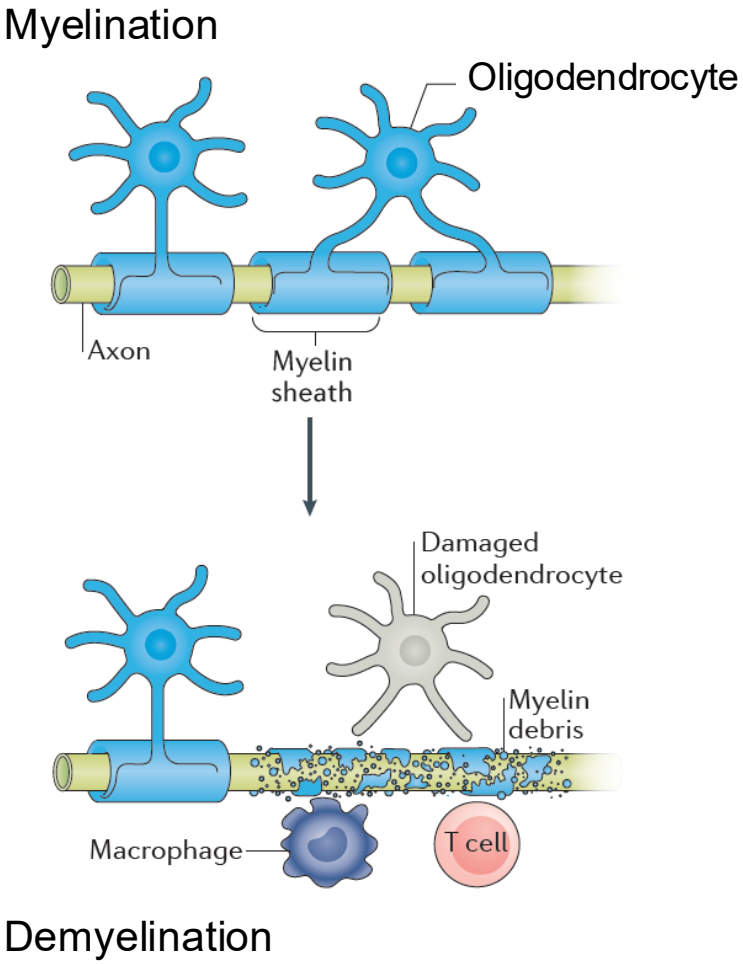


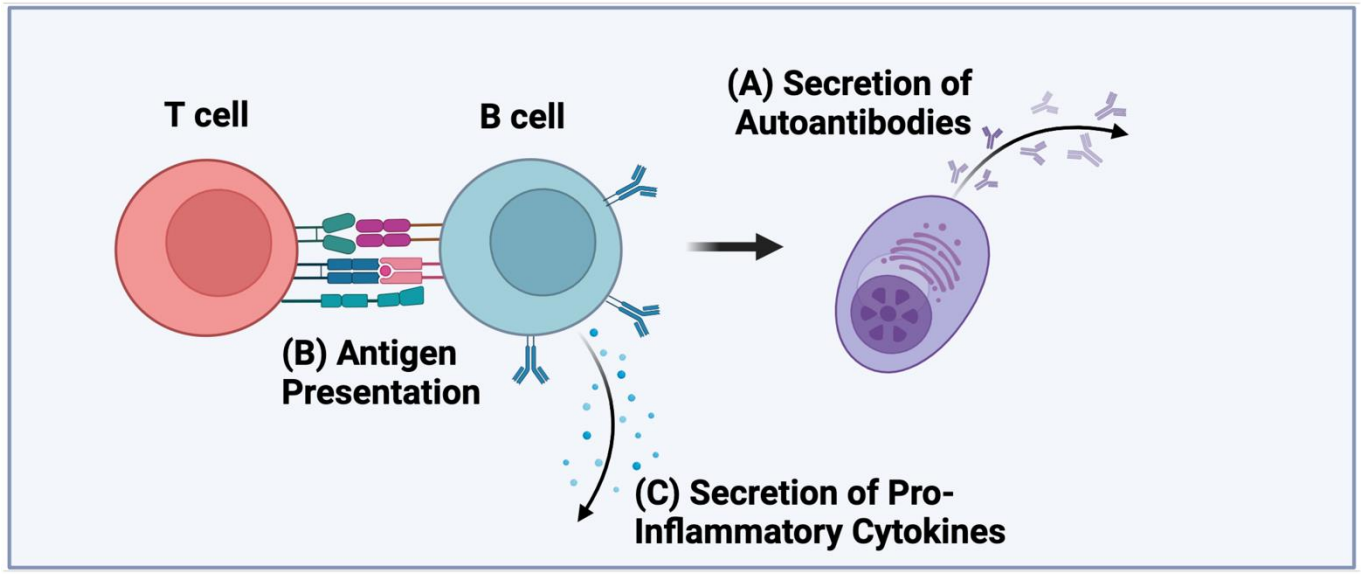
- 2019, Siponimod (BAF312) approved for RRMS and SPMS

Developed at GNF under the guidance of Pete Schultz (President and CEO)

- S1PR therapies were a breakthrough for relapsing-remitting MS (RRMS)

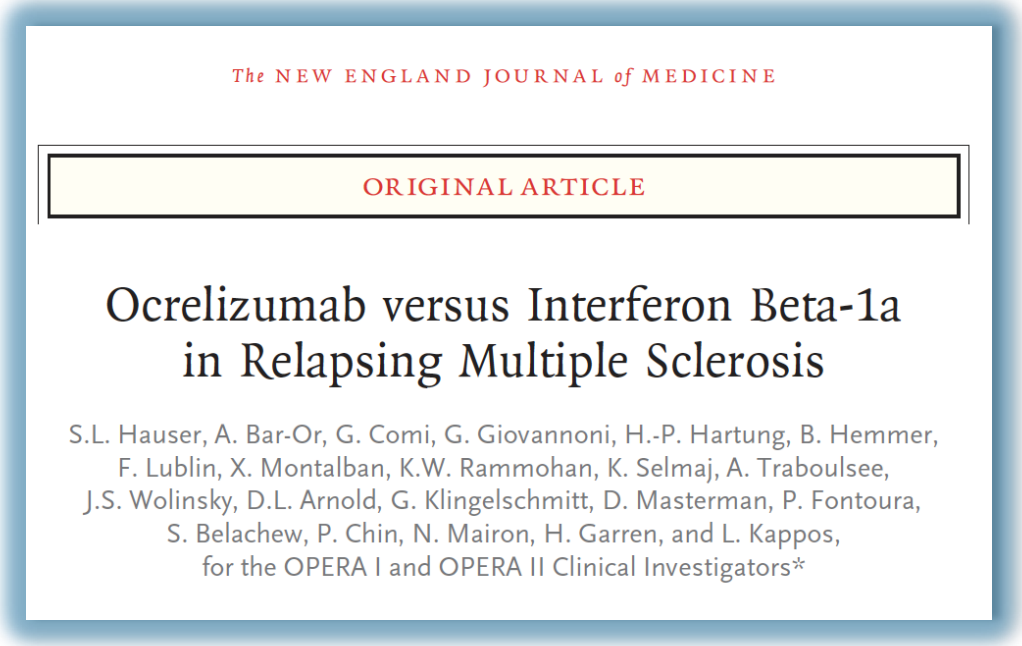
Therapeutic Approaches to the Treatment of MS: Targeting B Cells





- B cell depleting antibodies (e.g, Ocrelizumab) are highly effective in RRMS

Therapeutic Approaches to the Treatment of MS: Targeting B Cells



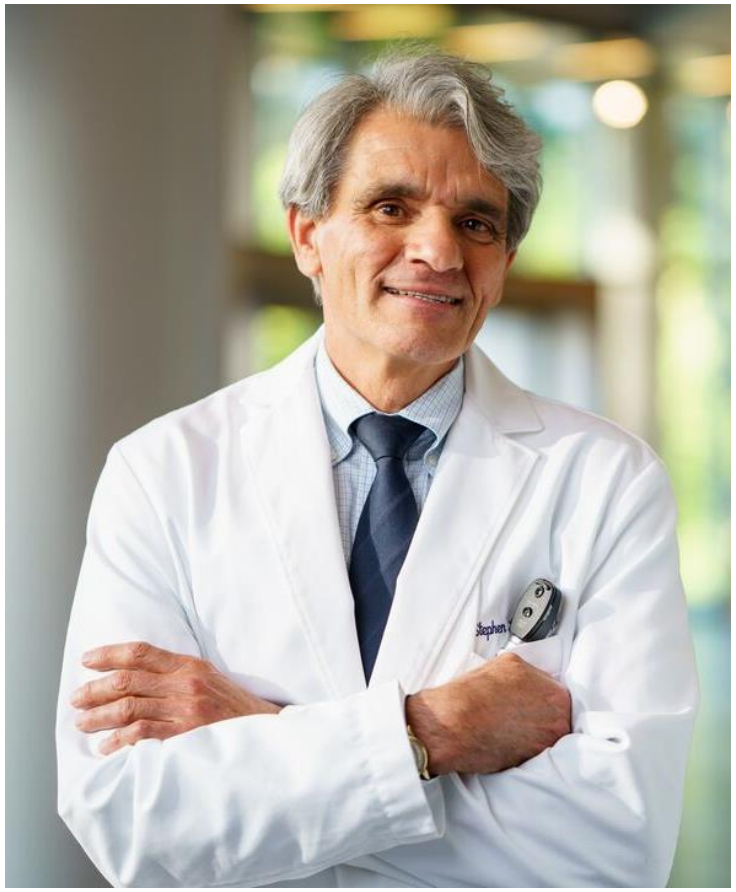
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis

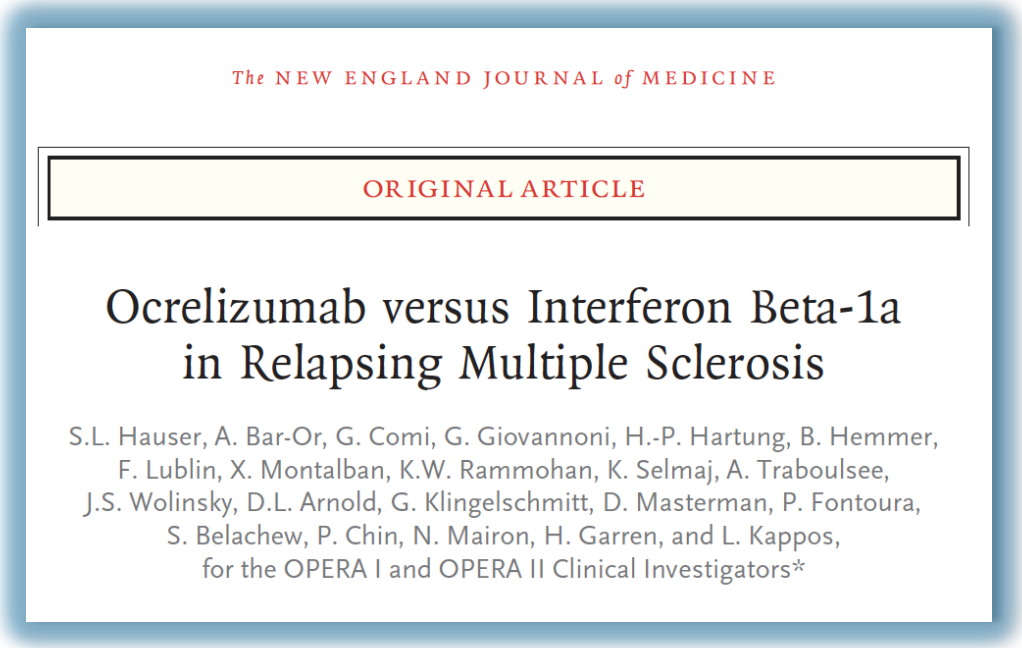
S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee, J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura, S. Belachew, P. Chin, N. Mairon, H. Garren, and L. Kappos, for the OPERA I and OPERA II Clinical Investigators*

Hauser, S.L. et al. (2017) *New England Journal of Medicine.* ***376***: 221.



Dr. Stephen Hauser (UCSF)

Therapeutic Approaches to the Treatment of MS: Targeting B Cells



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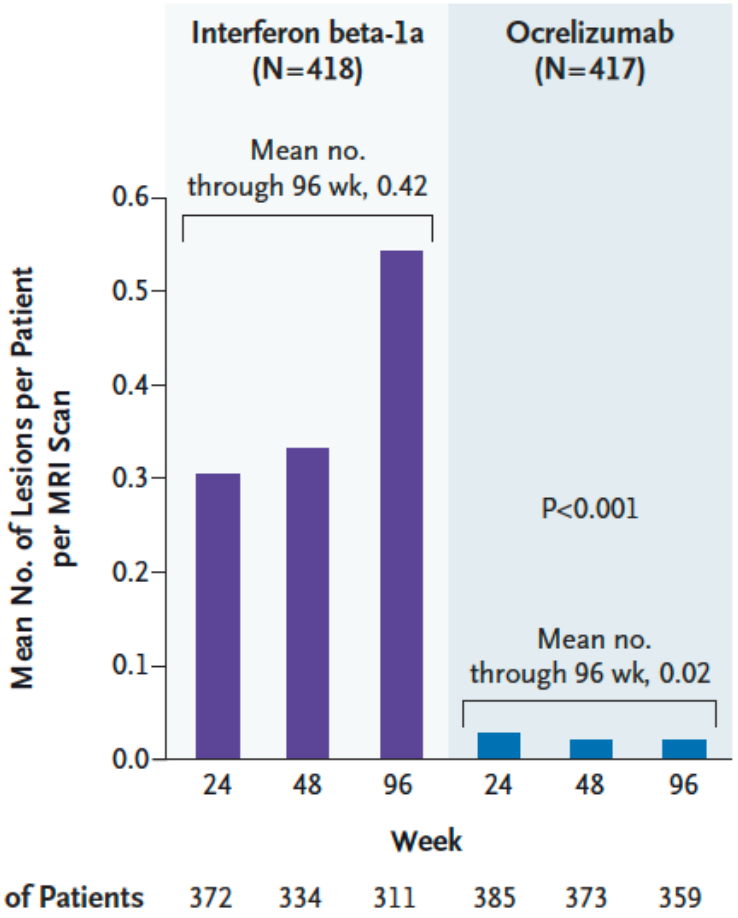
Impact of B cell depletion on MS lesions in RRMS patients



Therapeutic Approaches to the Treatment of MS: Targeting B Cells

- B cell depleting antibody treatment results in significantly reduced rates of MS disease relapse (46% compared to a previous standard of care)
- B cell depleting antibody treatment results in statistically significant reduction in disease progression

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- B cell depleting antibody treatment results in significantly reduced rates of MS disease relapse (46% compared to a previous standard of care)
- B cell depleting antibody treatment results in statistically significant reduction in disease progression
- 2017, Ocrelizumab fast-tracked and approved for the treatment of RRMS and PPMS

Epstein-Bar Virus (EBV) as the Leading Cause of MS

REPORT

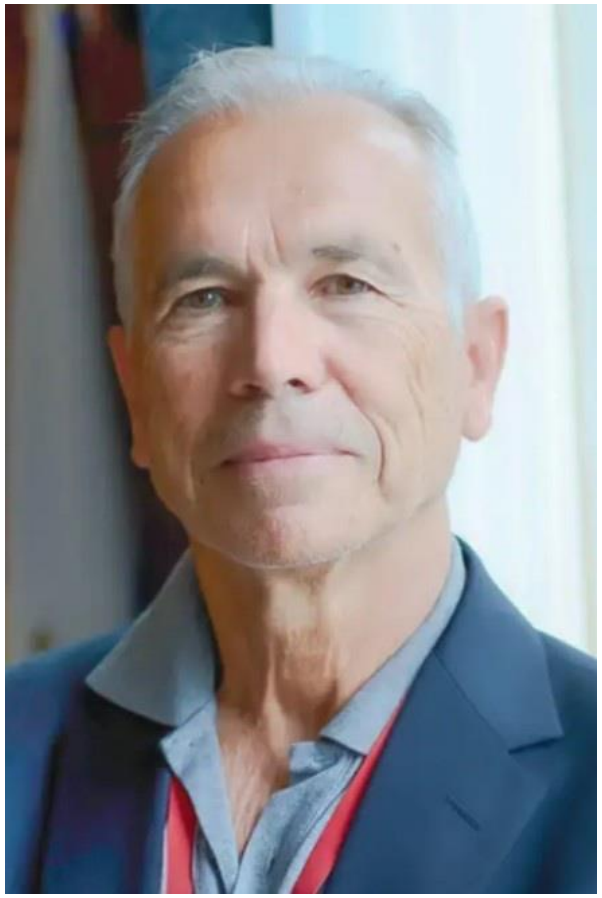
MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

Bjornevik, K., Cortese, M., …, Munger, K.L., Ascherio, A. (2022) *Science.* ***375***: 296.



Dr. Alberto Ascherio
(Harvard School of Public Health)

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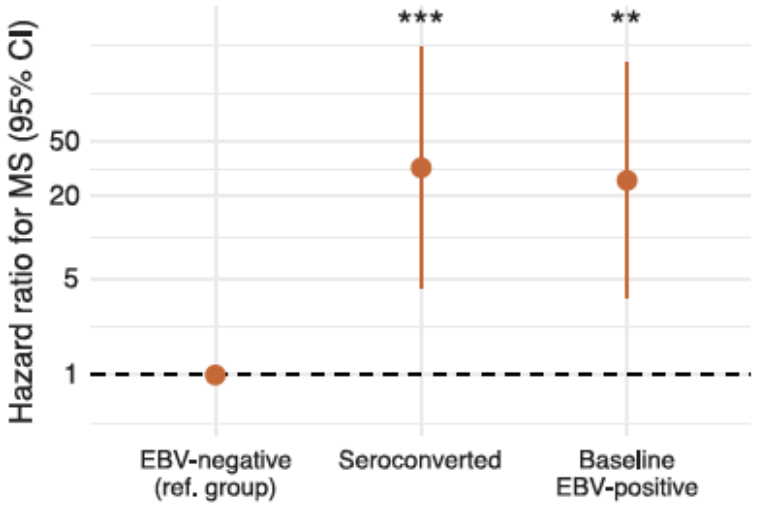
Risk ratio for MS according to EBV status



- Analysis of 10 million US military adults (955 diagnosed with MS *during* their service)
- Risk of MS increased 32-fold following EBV infection (unique amongst all viruses tested)

2025 Breakthrough Prize: Roles of EBV and B cells in MS

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2022 Breakthrough Prize in Life Sciences: Jeff Kelly

Jeffery W. Kelly

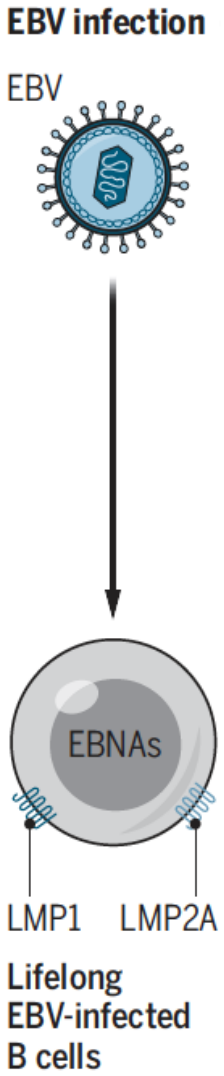
Scripps Research Institute

2022 Breakthrough Prize in Life Sciences

For elucidating the molecular basis of neurodegenerative and cardiac transthyretin diseases, and for developing tafamidis, a drug that slows their progression.

Scripps Research

Epstein-Bar Virus (EBV) as the Leading Cause of MS: Why?



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Robinson, W.H., and Steinman, L. (2022) *Science.* ***375***: 6578.

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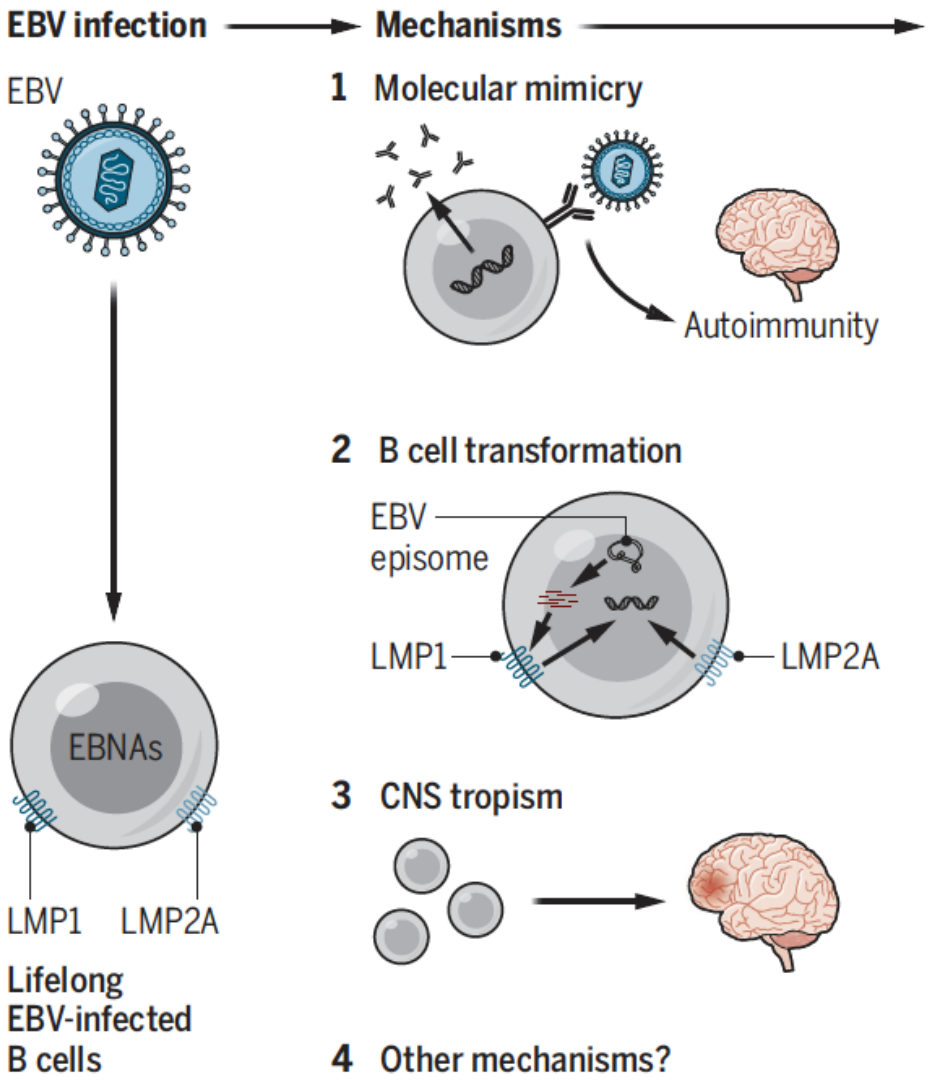

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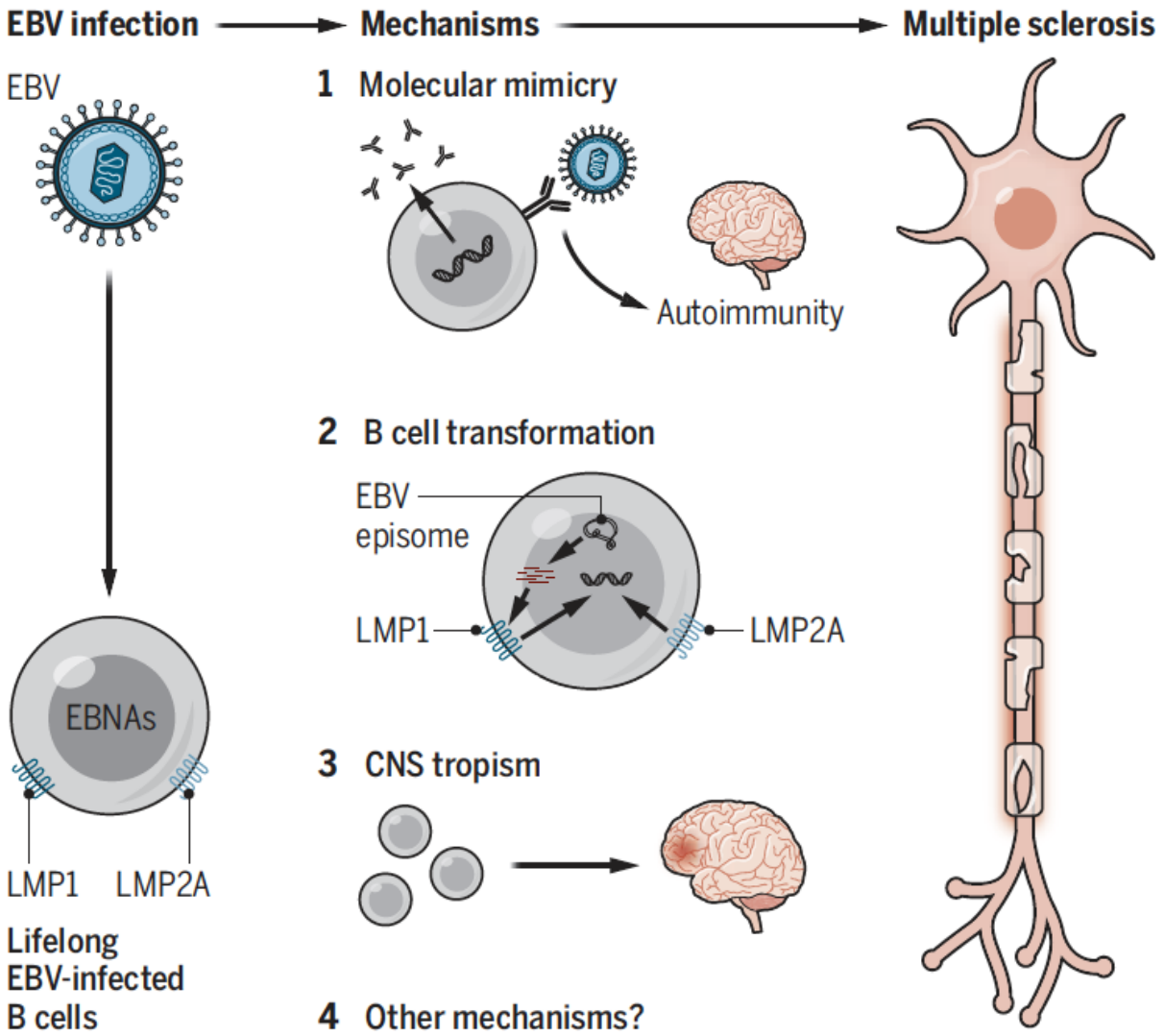

- EBV primarily targets B cells and permanently transforms them
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- B cell transformation can lead to the presentation of antigens that mimic self

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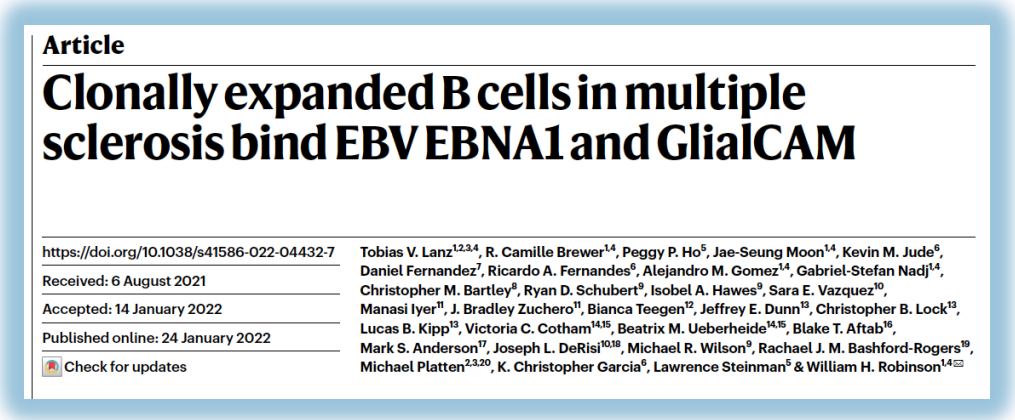
Epstein-Bar Virus (EBV) as the Leading Cause of MS: Why?



Article

Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM

https://doi.org/10.1038/s41586-022-04432-7

Received: 6 August 2021

Accepted: 14 January 2022

Published online: 24 January 2022

Check for updates

Tobias V. Lanz[1,2,3,4], R. Camille Brewer[1,4], Peggy P. Ho[5], Jae-Seung Moon[1,4], Kevin M. Jude[6], Daniel Fernandez[7], Ricardo A. Fernandes[6], Alejandro M. Gomez[1,4], Gabriel-Stefan Nadj[1,4], Christopher M. Bartley[8], Ryan D. Schubert[9], Isobel A. Hawes[9], Sara E. Vazquez[10], Manasi Iyer[11], J. Bradley Zuchero[11], Bianca Teegen[12], Jeffrey E. Dunn[13], Christopher B. Lock[13], Lucas B. Kipp[13], Victoria C. Cotham[14,15], Beatrix M. Ueberheide[14,15], Blake T. Aftab[16], Mark S. Anderson[17], Joseph L. DeRisi[10,18], Michael R. Wilson[9], Rachael J. M. Bashford-Rogers[19], Michael Platten[2,3,20], K. Christopher Garcia[6], Lawrence Steinman[5] & William H. Robinson[1,4]✉

Lanz, T., …, Steinman, L. Robinson, W. (2022) *Nature.* ***375***: 296.

- Self-recognizing EBV cross-reactive antibodies identified in MS patients

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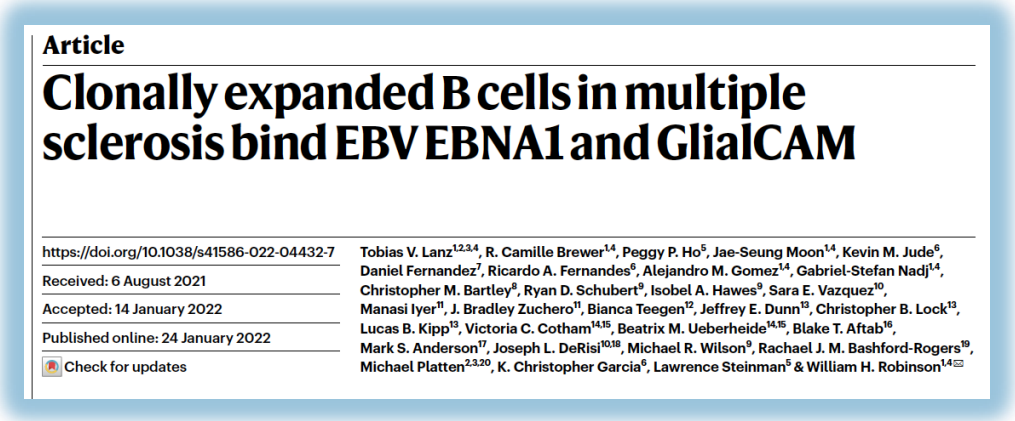

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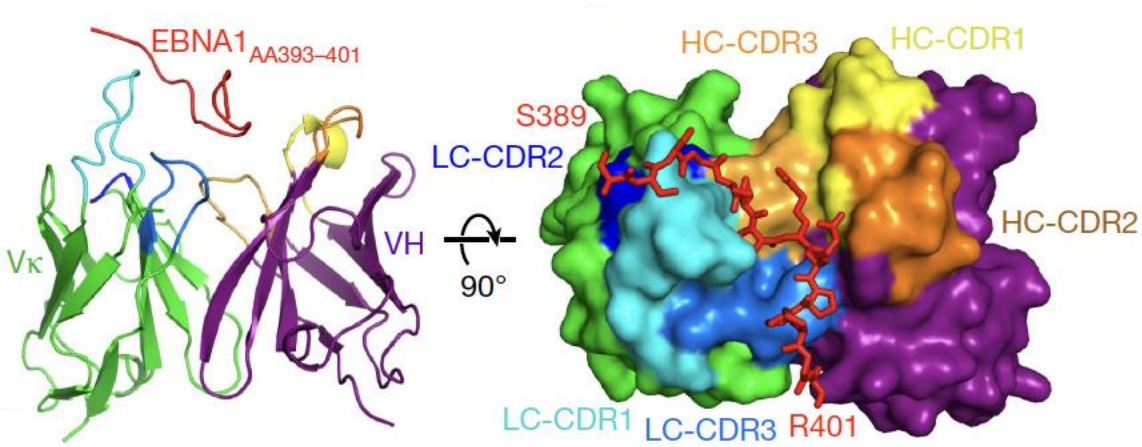
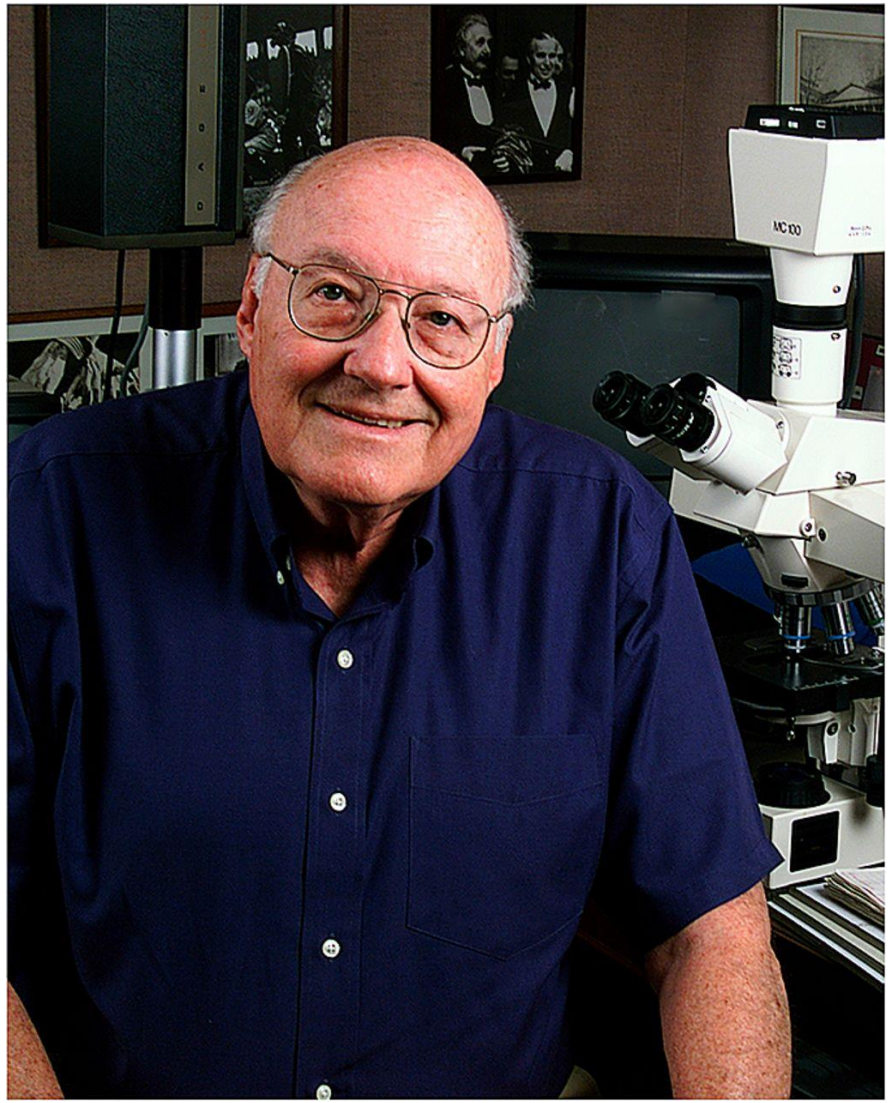
EBV protein (EBNA1) recognition by B cell antibodies in MS CSF



- Self-recognizing EBV cross-reactive antibodies identified in MS patients
- High affinity molecular mimicry between EBV EBNA1 and CNS protein GlialCAM 1



Dr. Michael B.A. Oldstone (1932-2023)
(Scripps Research)

Science

BACK TO VOL. 230, NO. 4729

REPORT

Amino Acid Homology Between the Encephalitogenic Site of Myelin Basic Protein and Virus: Mechanism for Autoimmunity

ROBERT S. FUJINAMI AND MICHAEL B. A. OLDSTONE Authors Info & Affiliations

SCIENCE • 29 Nov 1985 • Vol 230, Issue 4729 • pp. 1043-1045

Molecular Basis of Demyelination in MS

- EBV-infected B cells as drivers of MS disease
- Molecular mimicry between defined EBV and CNS proteins as basis for auto-immune response

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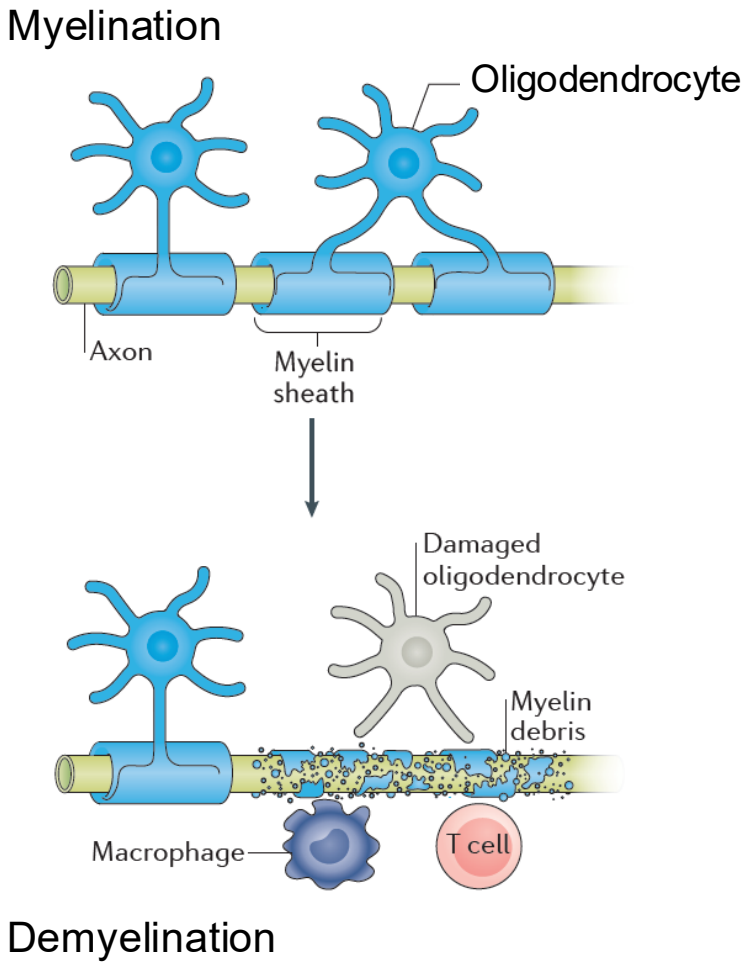
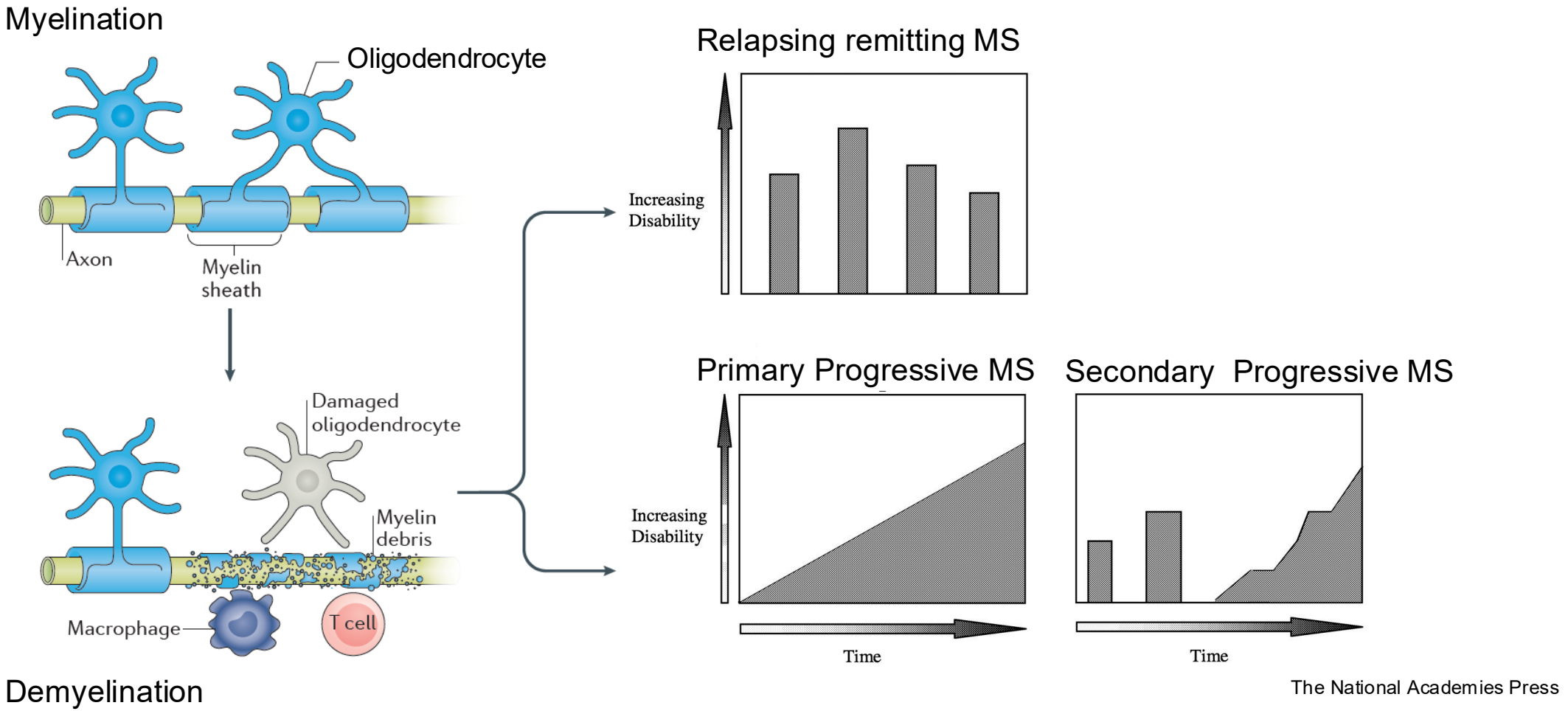
- EBV-infected B cells as drivers of MS disease
- Molecular mimicry between defined EBV and CNS proteins as basis for auto-immune response
- Repurposed B cell depleting antibodies display incredible efficacy in RRMS patients
- B cell therapies are minimally-effective in progressive forms of MS - treatments for progressive MS are completely lacking

Therapeutic Approaches to the Treatment of MS: Remyelination



- A promising complementary treatment approach for MS is the identification of agents that directly stimulate the regenerative process of remyelination

Therapeutic Approaches to the Treatment of MS: Remyelination



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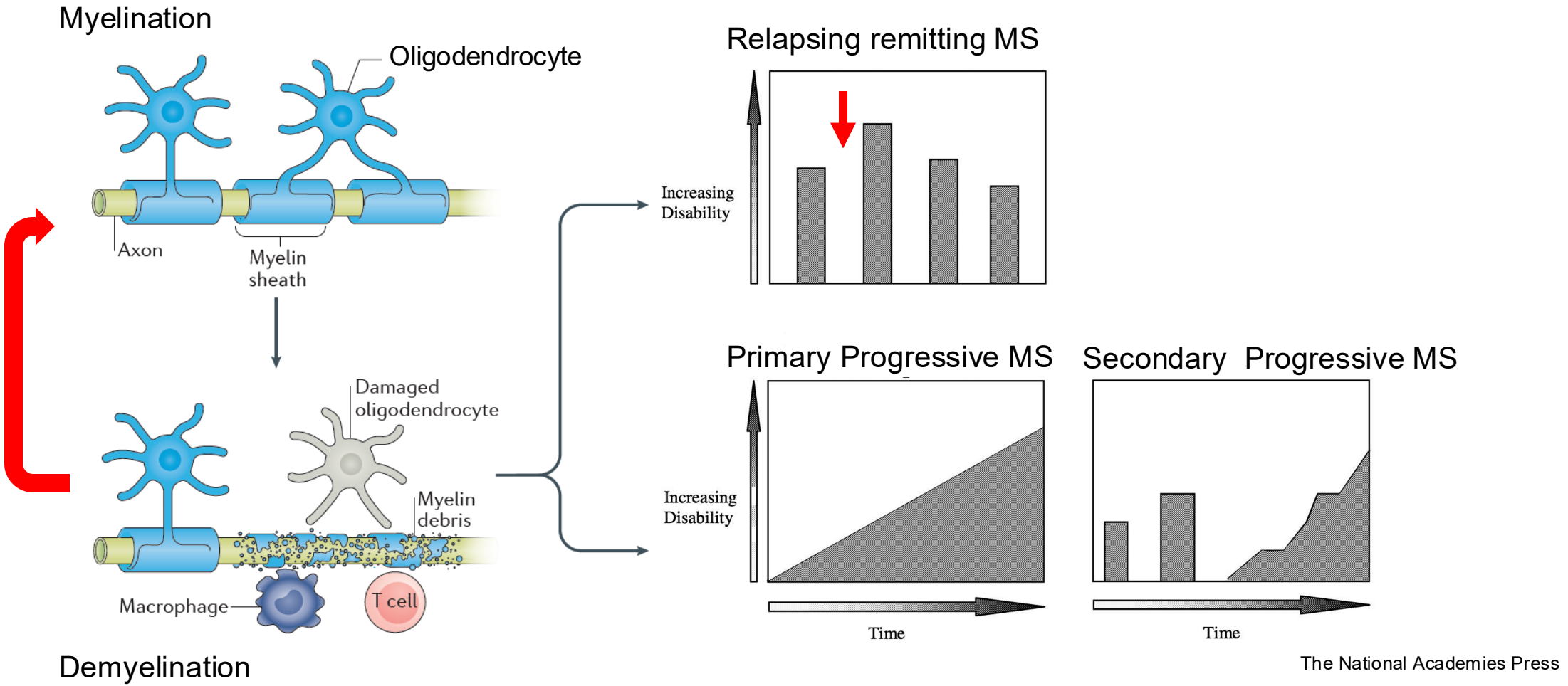

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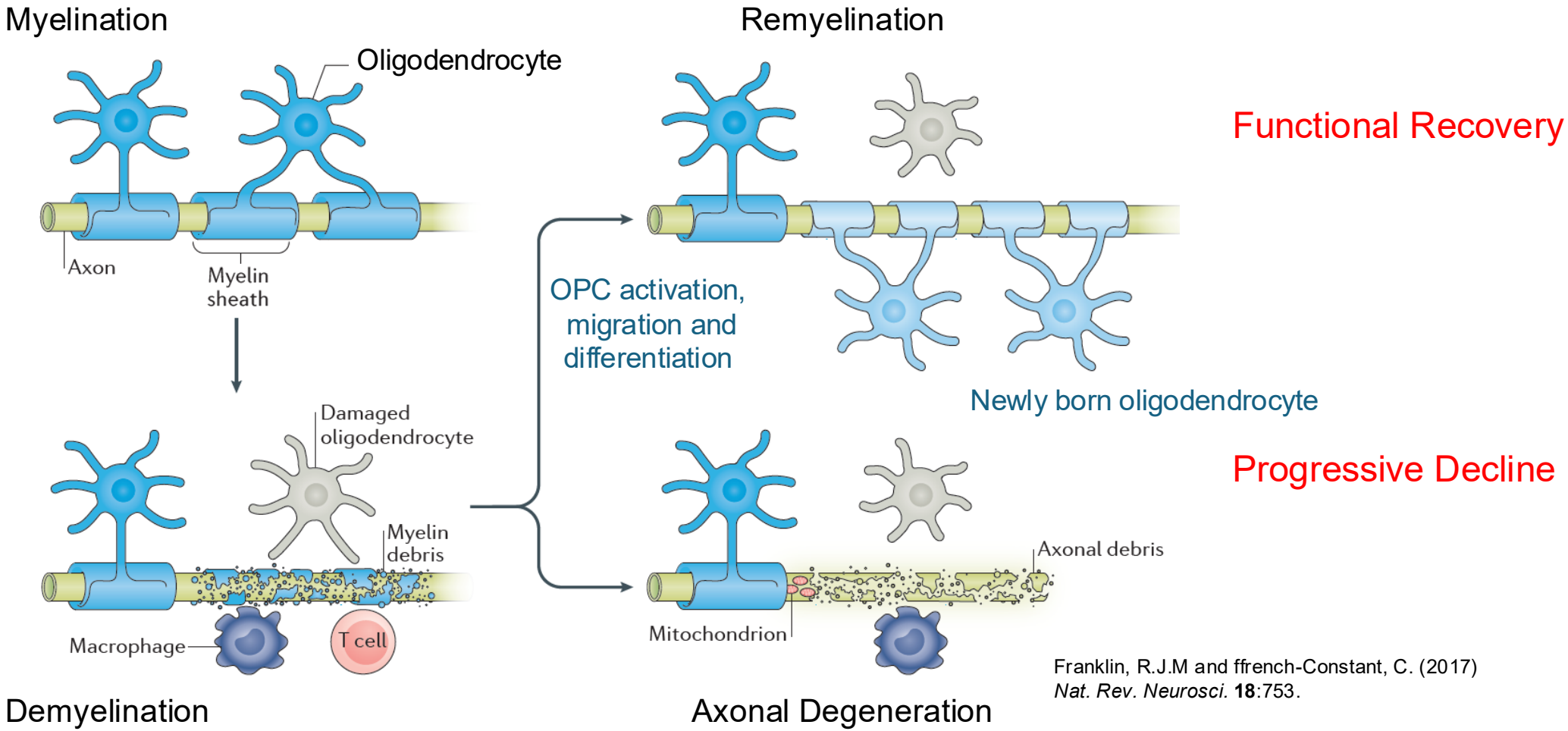
Remyelination is Defined by Functional OPC Differentiation

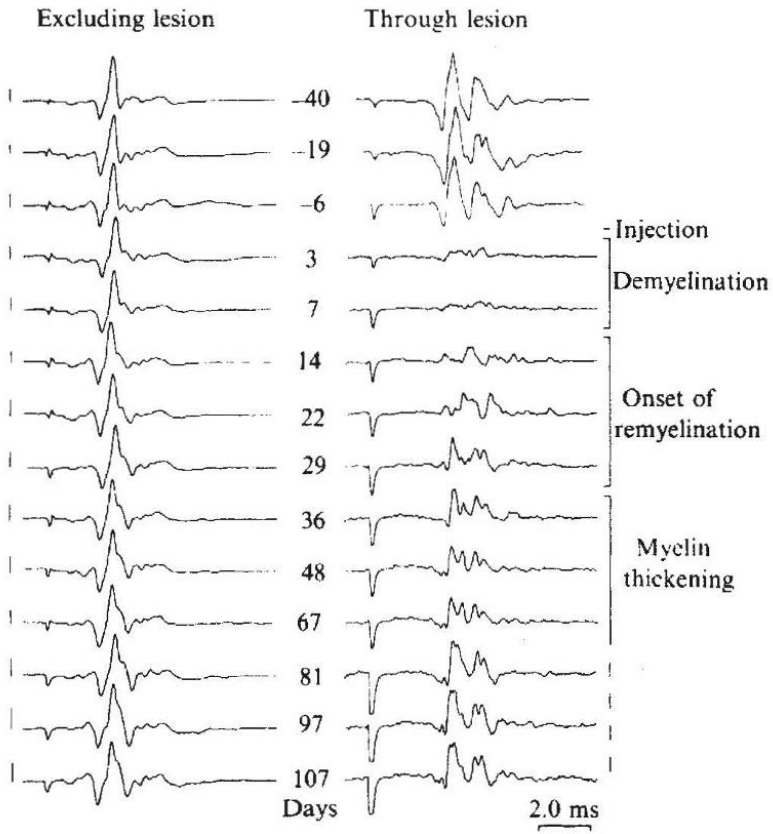


Franklin, R.J.M and ffrench-Constant, C. (2017) *Nat. Rev. Neurosci.* **18**:753.

- Remyelination persists throughout adulthood in the CNS and involves activation, migration and differentiation of oligodendrocyte progenitor cells (OPCs)

Remyelination and Functional Recovery

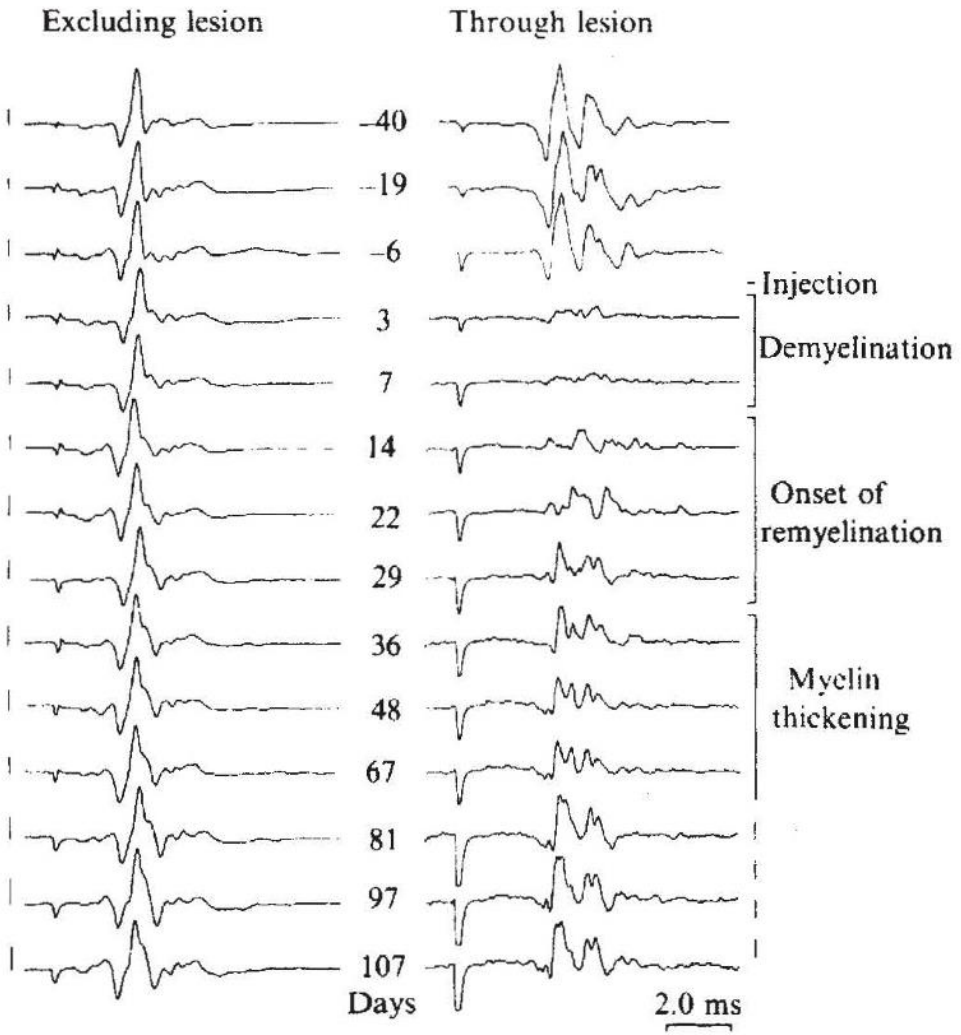
- 1906, Marburg first suggested that spontaneous remyelination may occur in the CNS to facilitate disease remission in MS.



- 1979, Smith et *al*. demonstrate that remyelination restores efficient impulse conduction to demyelinated axons in animals.

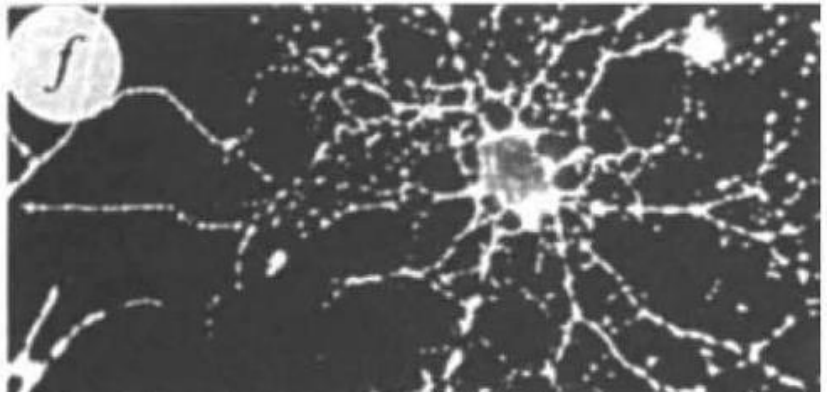
Smith, K.J., Blakemore, W.F., and McDonald, W.I. (1979) *Nature.* ***280***: 395.

Functional Recovery and the Identification of OPCs



Smith, Blakemore, and McDonald (1979) *Nature.*

GC$^+$ Oligodendrocyte (Adult)

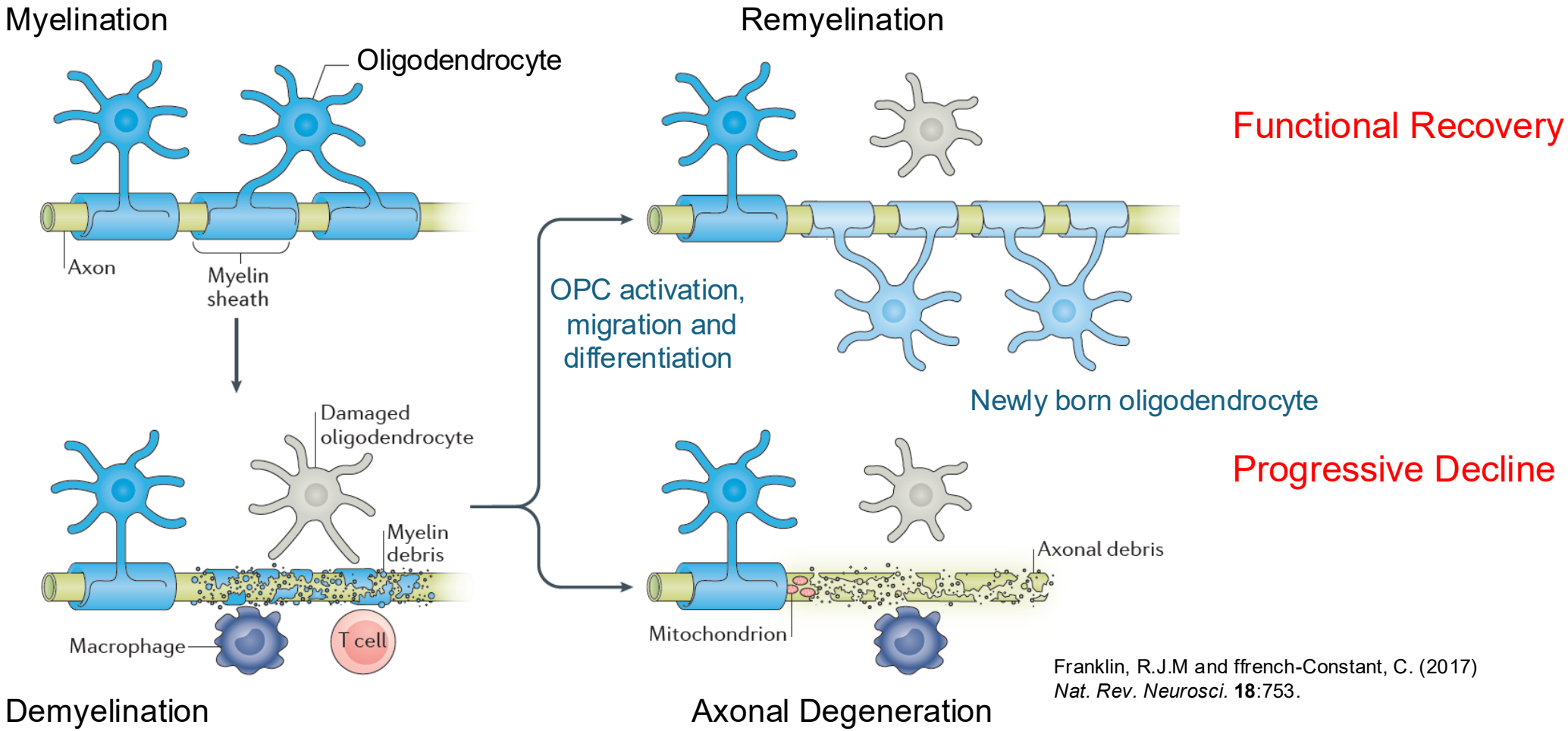


ffrench-Constant and Raff (1986) *Nature.* ***319***: 499.

- 1986, adult rat optic nerve contains progenitor cells that can differentiate under defined conditions into an oligodendrocytes

See also: Raff, M.C., Miller, R.H. and Noble, M. (1983) *Nature.* ***302***: 390.

Remyelination is Defined by Functional OPC Differentiation



Franklin, R.J.M and ffrench-Constant, C. (2017) *Nat. Rev. Neurosci.* **18**:753.

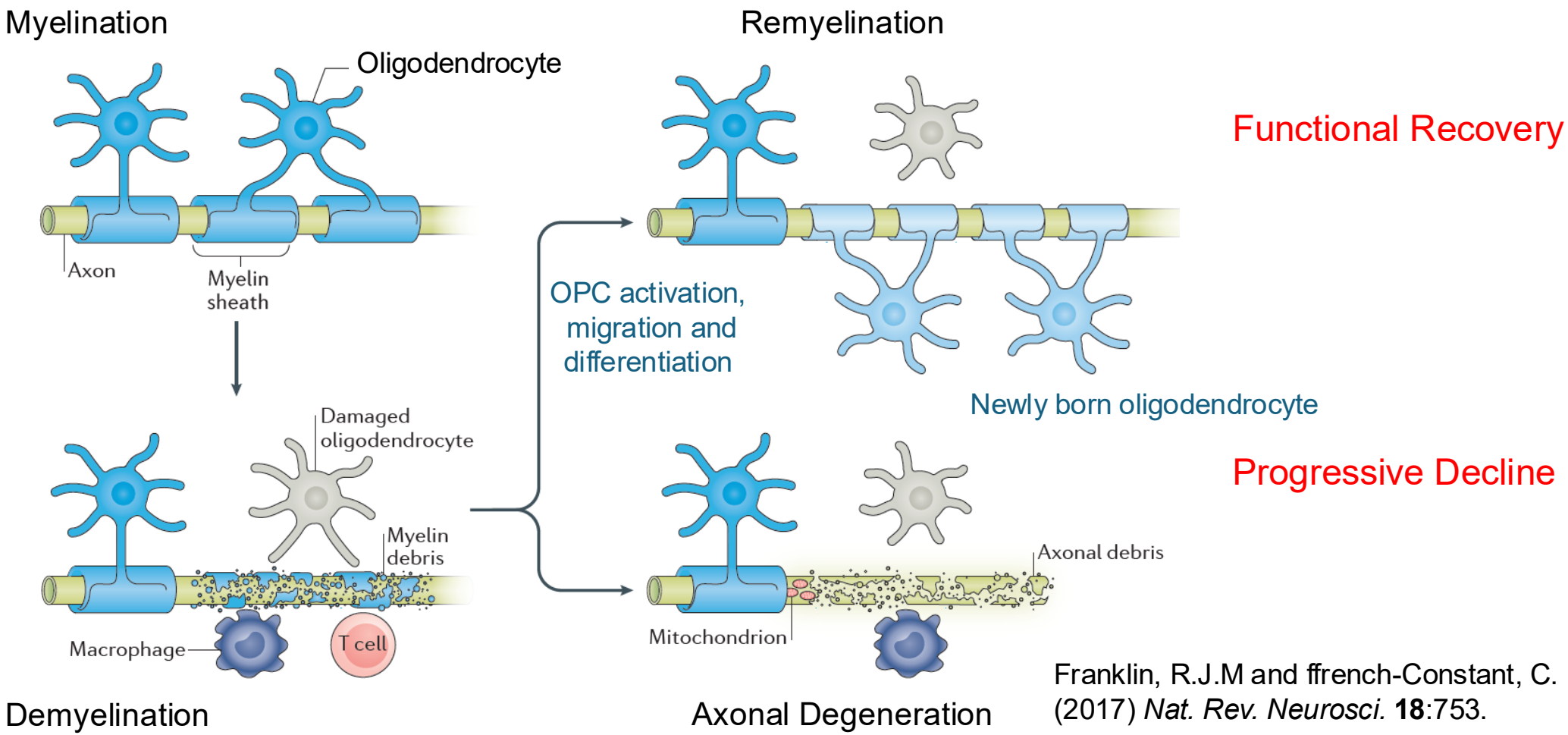
- Remyelination persists throughout adulthood in the CNS and involves activation, migration and differentiation of oligodendrocyte progenitor cells (OPCs)

Remyelination is Defined by Functional OPC Differentiation

Robin Franklin, PhD
(University of Cambridge
now Altos)

Charles ffrench-Constant, PhD
(Edinburgh University)

Remyelination is Defined by Functional OPC Differentiation



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Regenerative Medicine-Based Therapies: Considerations

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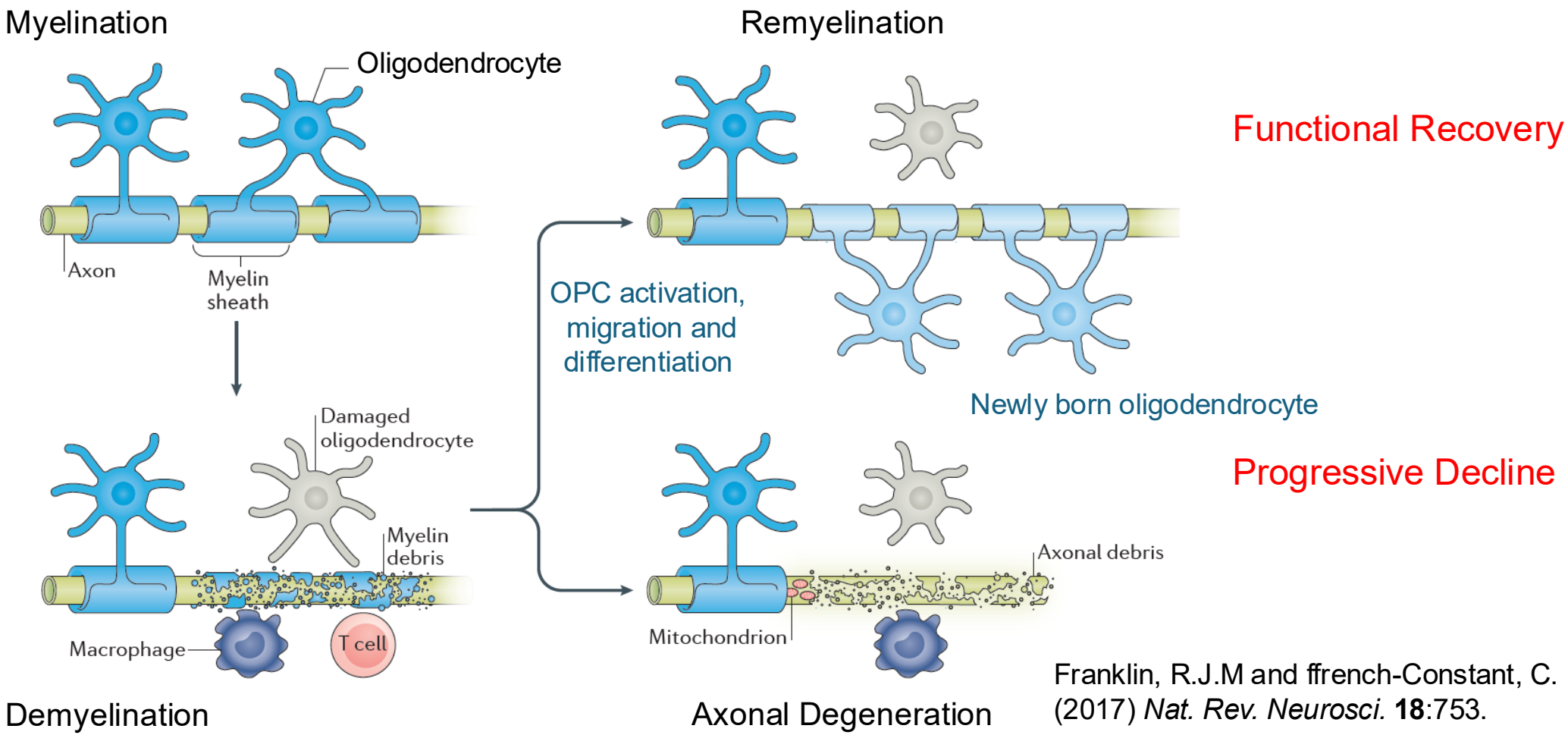
- Relative timing, compatibility and duration of treatments?

Remyelination is Defined by Functional OPC Differentiation



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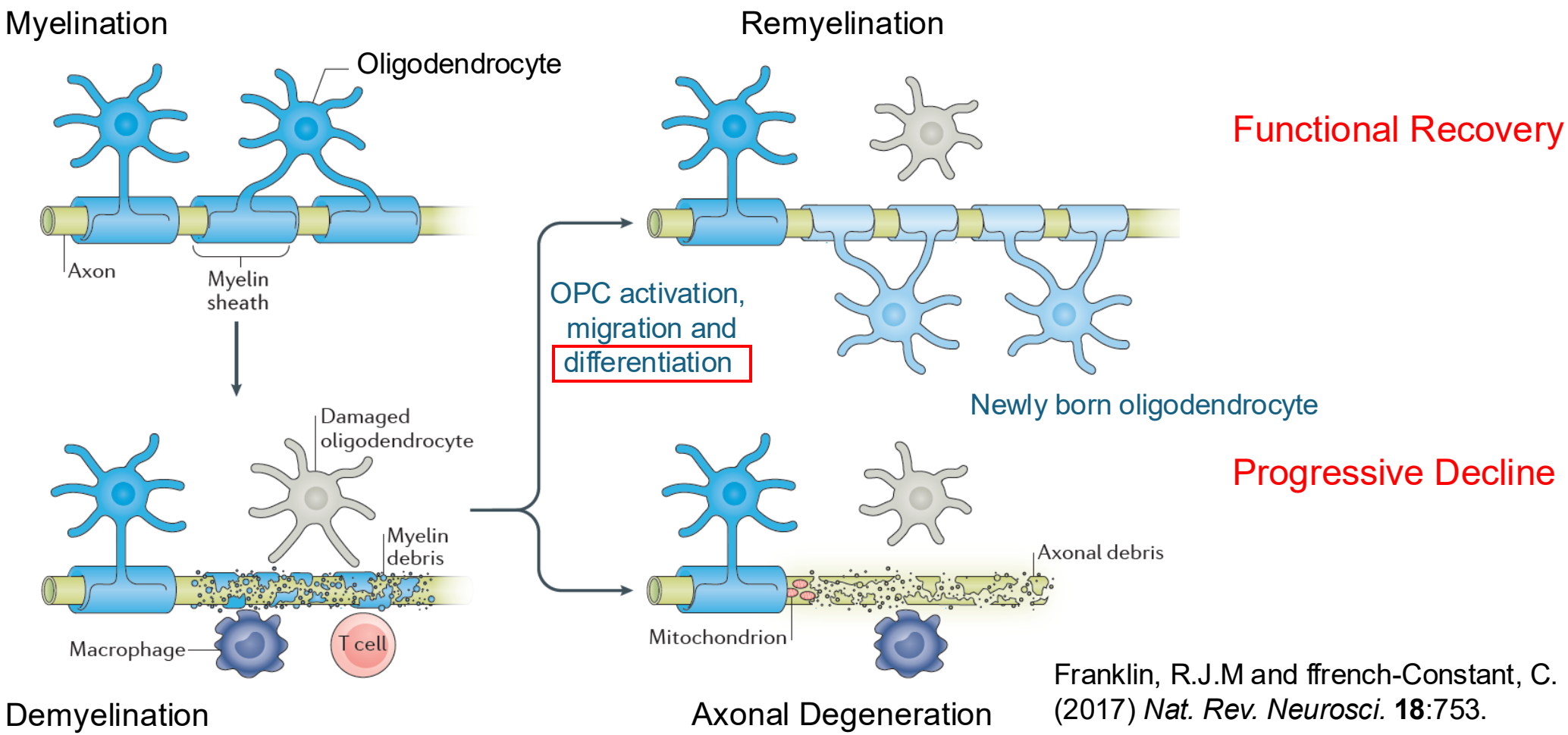

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Defined Stages of OPC Differentiation

Emery (2014) *Science*.
Sock & Wagner (2019) Glia.

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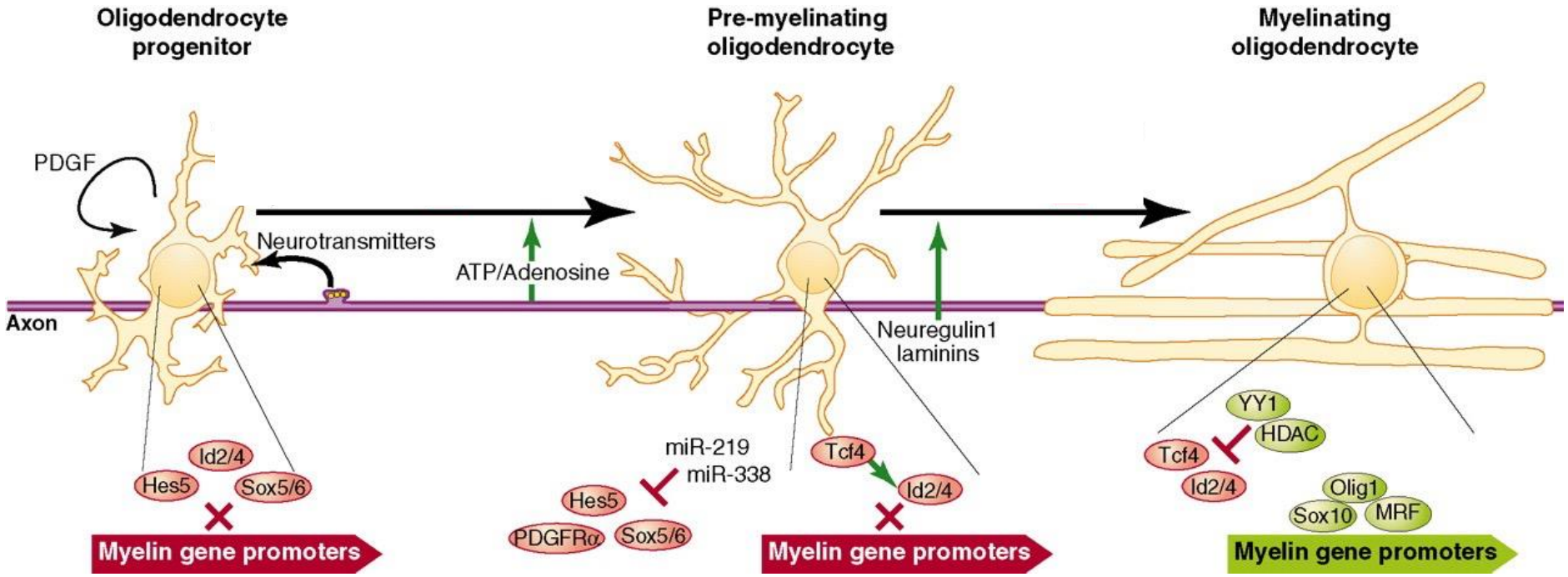

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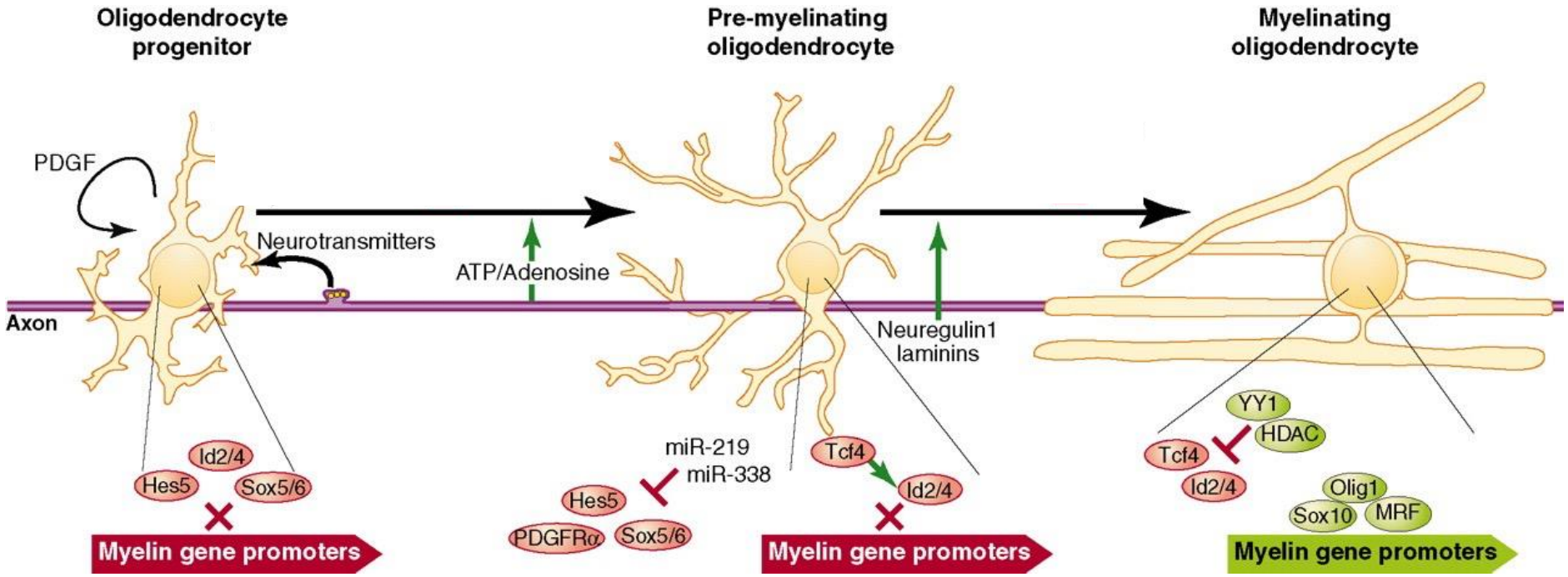
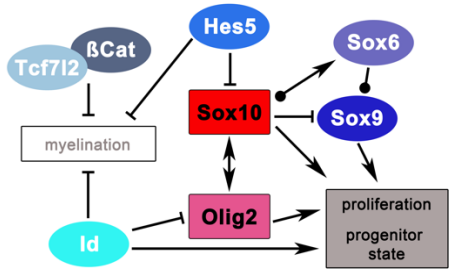
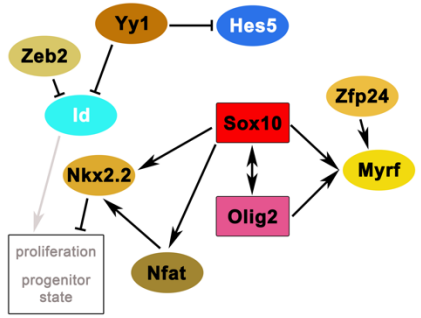
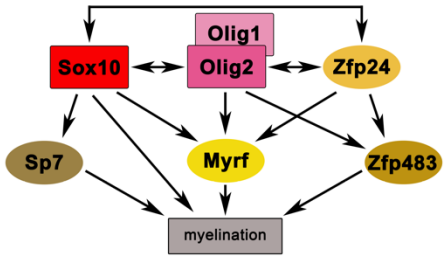






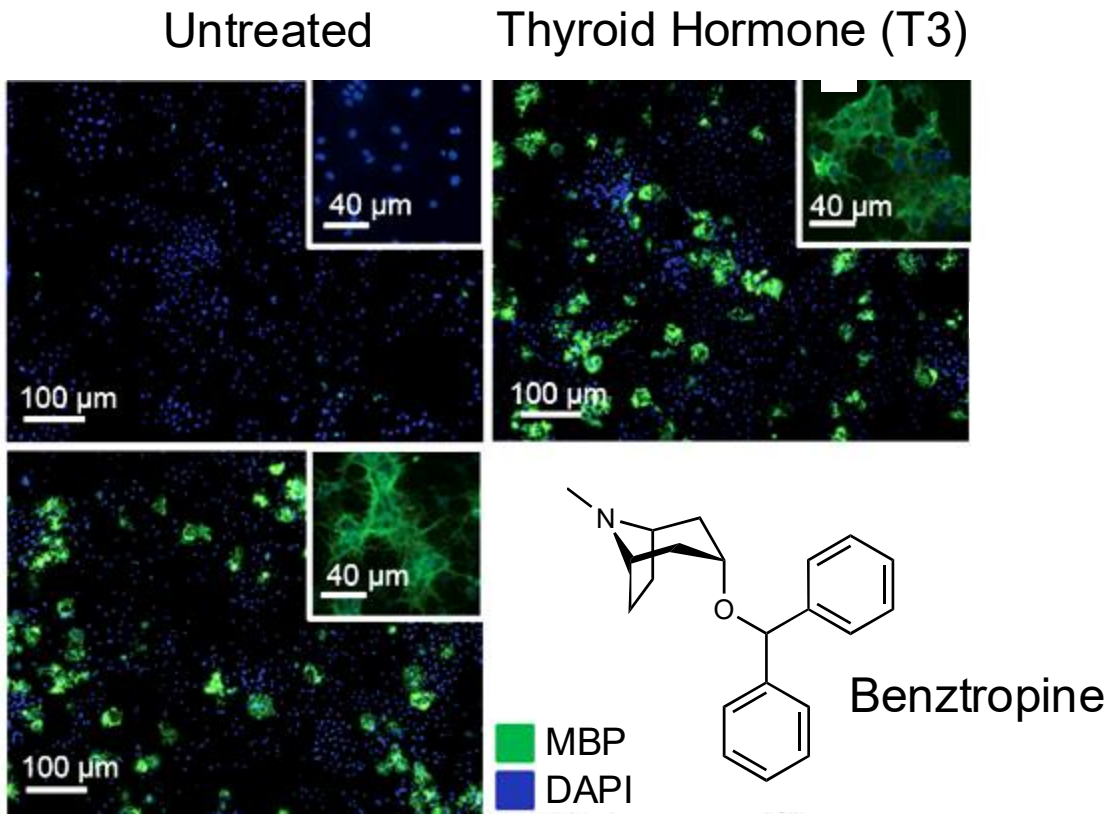


Emery (2014) *Science*.
Sock & Wagner (2019) Glia.

- Unbiased phenotype-based (target agnostic) high throughput discovery, combined with target identification, to generate testable hypotheses

Use nature's response to molecular structure to formulate unbiased testable hypotheses

Benztropine (M1R Antagonist) Enhances Functional OPC Differentiation



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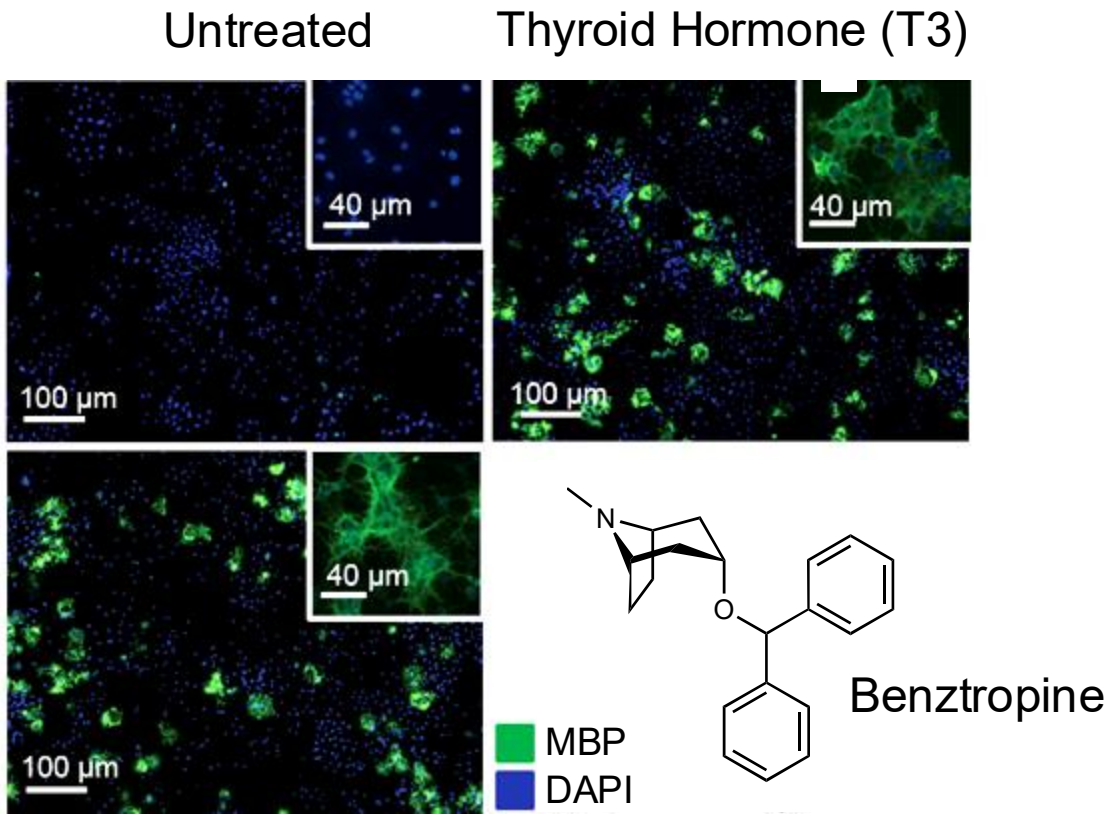

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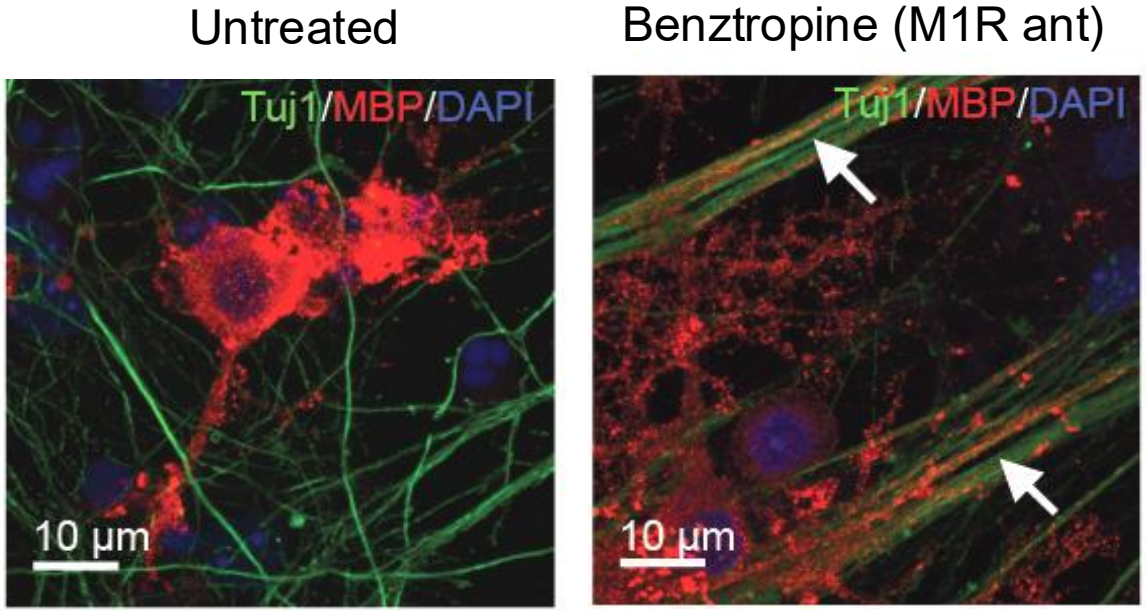

- Oligodendrocytes derived using M1R antagonists (e.g., benztropine) myelinate co-cultured axons

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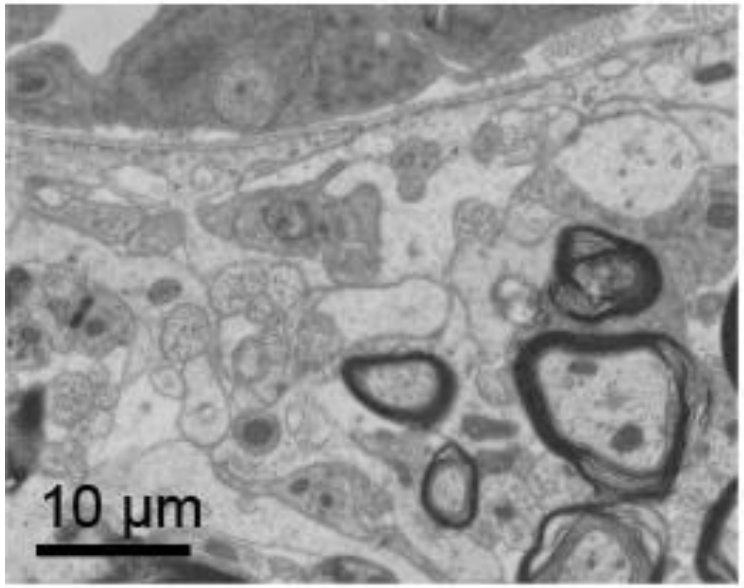
Benztropine (M1R Antagonist) Enhances Remyelination In Vivo

Untreated



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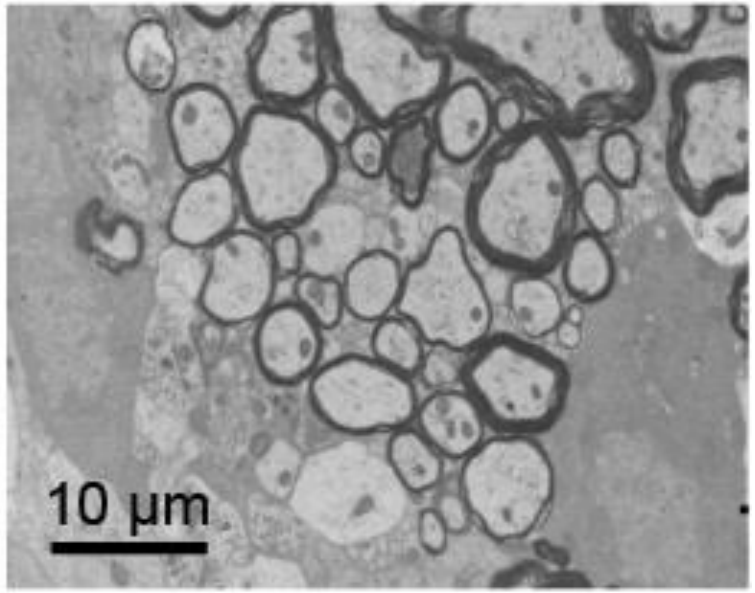

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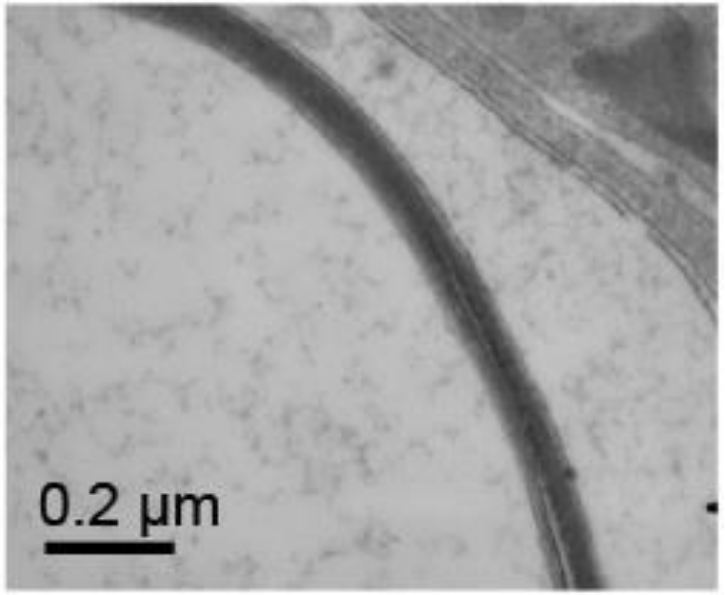

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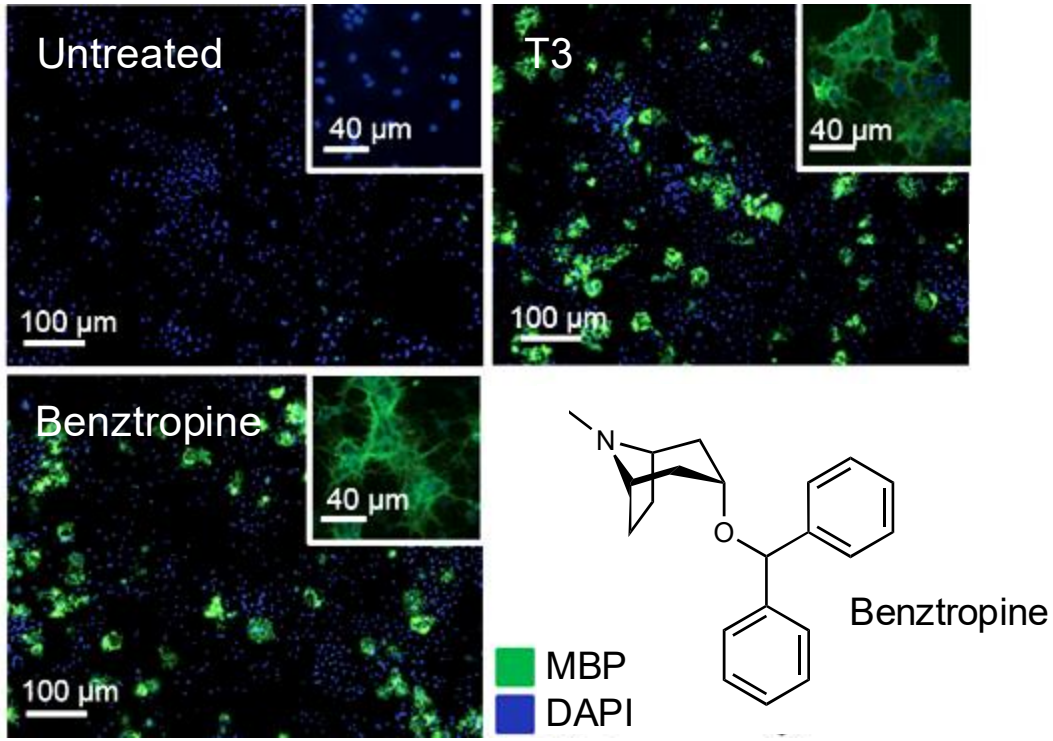

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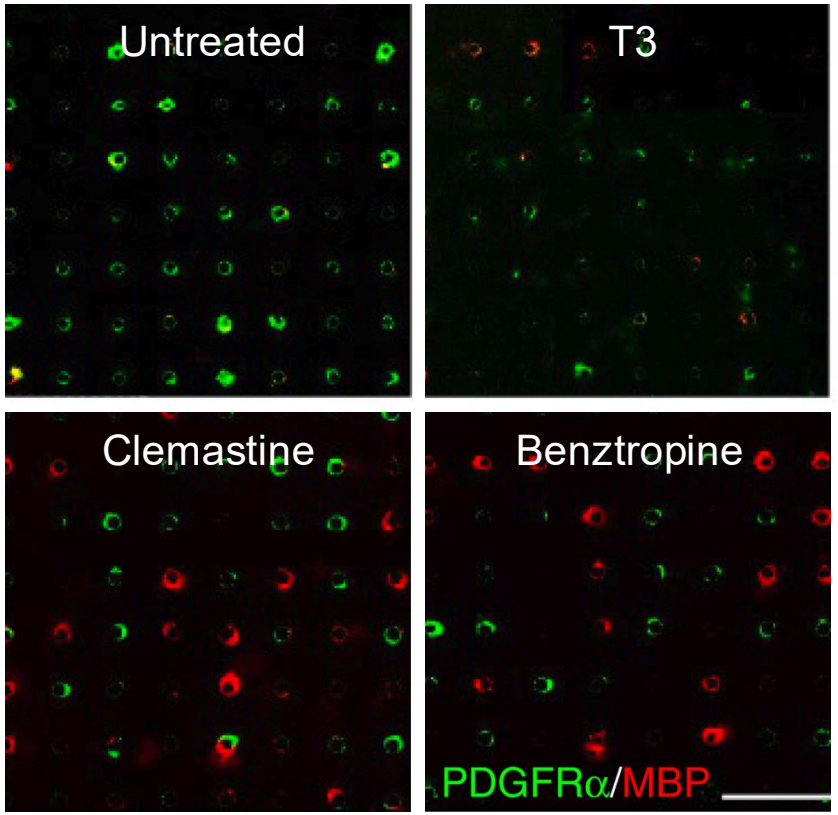

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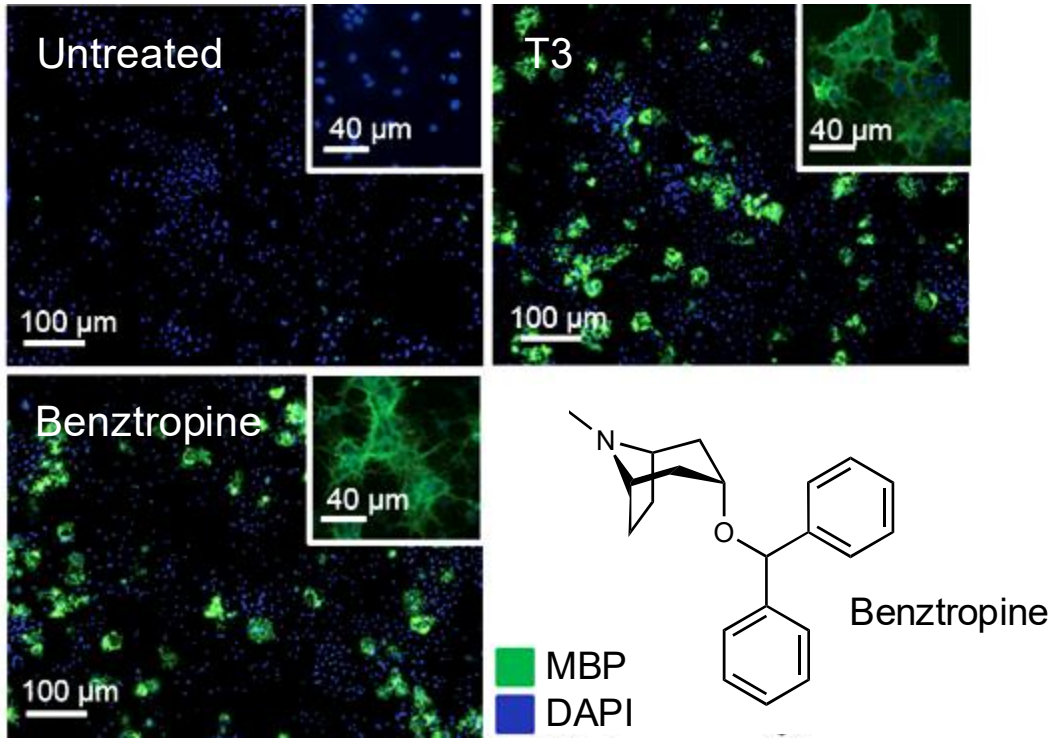

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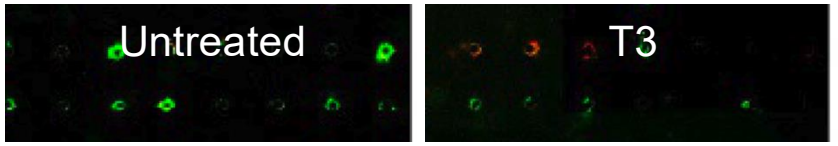
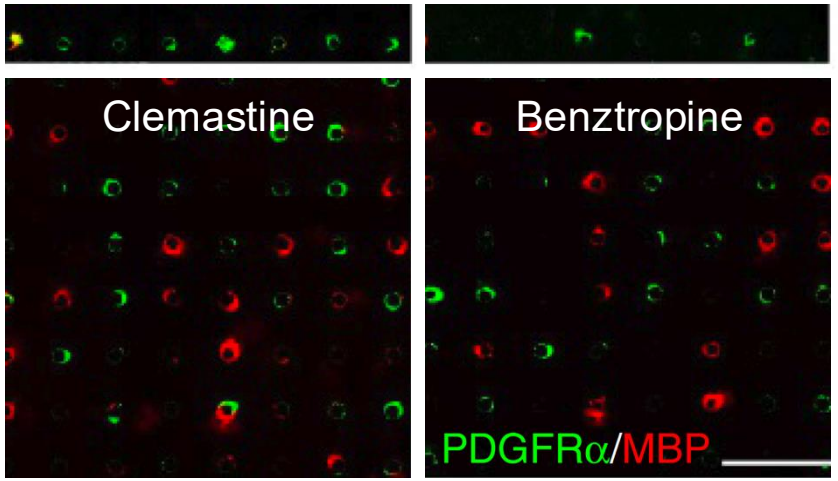


Chan laboratory (UCSF) converges on M1R antagonists as inducers of OPC differentiation



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Phenotype-Based Discovery: Evaluation of Clemastine in MS Patients

Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial

Ari J Green, Jeffrey M Gelfand, Bruce A Cree, Carolyn Bevan, W John Boscardin, Feng Mei, Justin Inman, Sam Arnow, Michael Devereux, Aya Abounasr, Hiroko Nobuta, Alyssa Zhu, Matt Friessen, Roy Gerona, Hans Christian von Büdingen, Roland G Henry, Stephen L Hauser, Jonah R Chan

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Lancet 2017; 390: 2481–89

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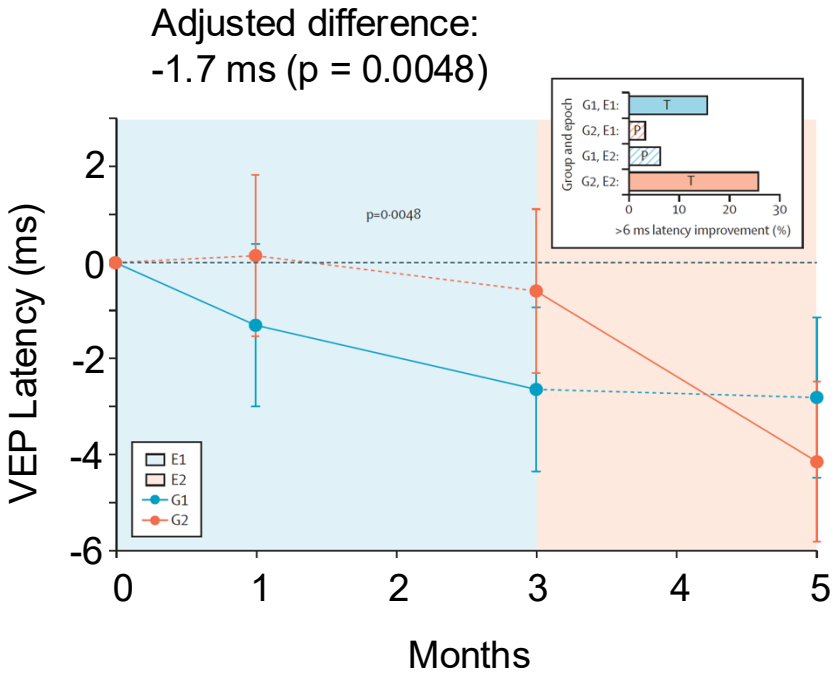
See Comment page 2421

Department of Neurology (A J Green MD, J M Gelfand MD, B A Cree MD, C Bevan MD, F Mei PhD, J Inman BS, S Arnow BS, M Devereux BS, A Abounasr BS, A Zhu BS, H C von Büdingen MD, Prof R G Henry PhD, Prof S L Hauser MD, Prof J R Chan PhD), **Department of Ophthalmology** (A J Green), **Department of Epidemiology and Biostatistics** (Prof W J Boscardin PhD), **Program in Neuroscience** (F Mei, Prof S L Hauser, Prof J R Chan), **Department of**

Clemastine Treatment Reduces VEP Latency Delay in MS Patients



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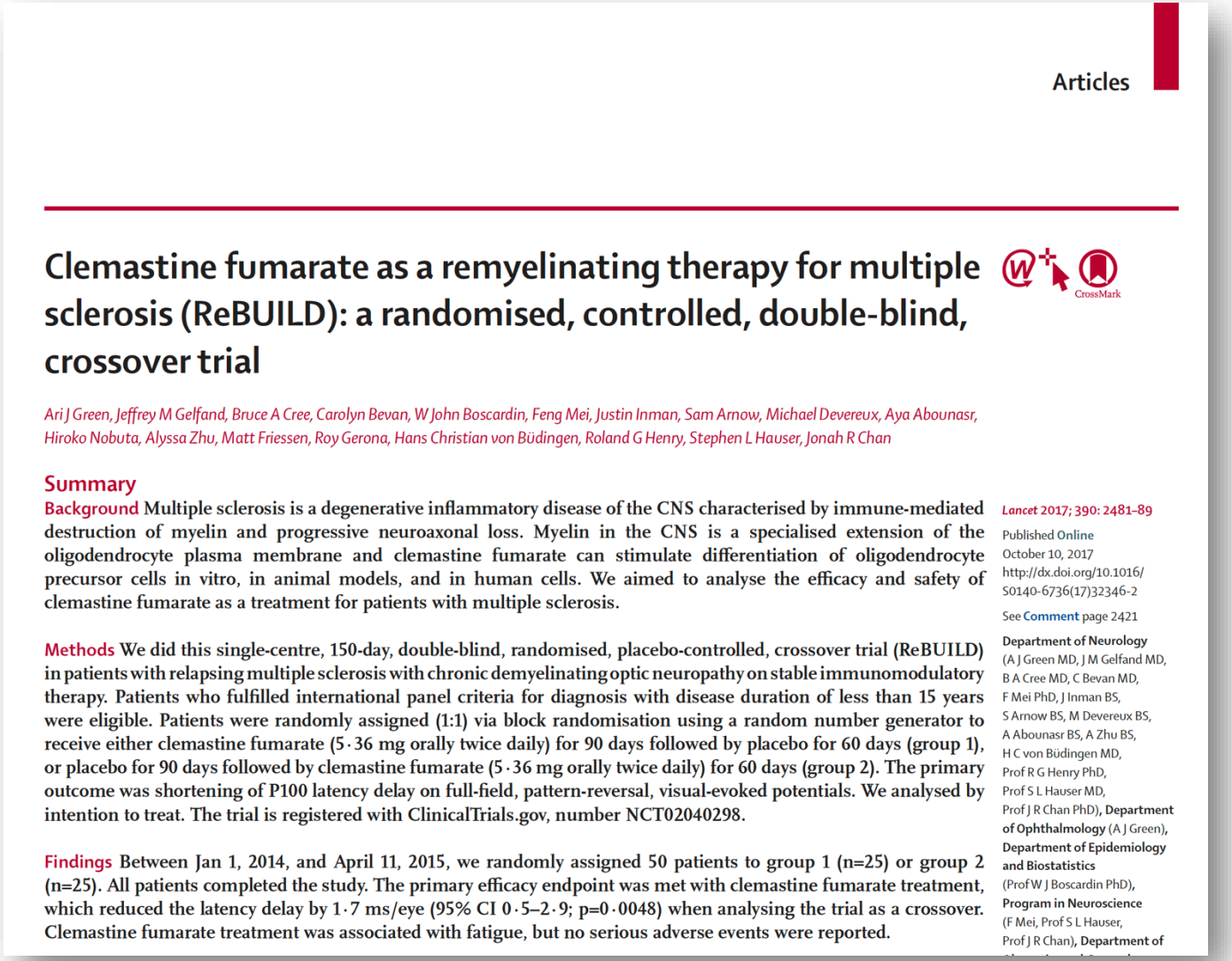

Articles

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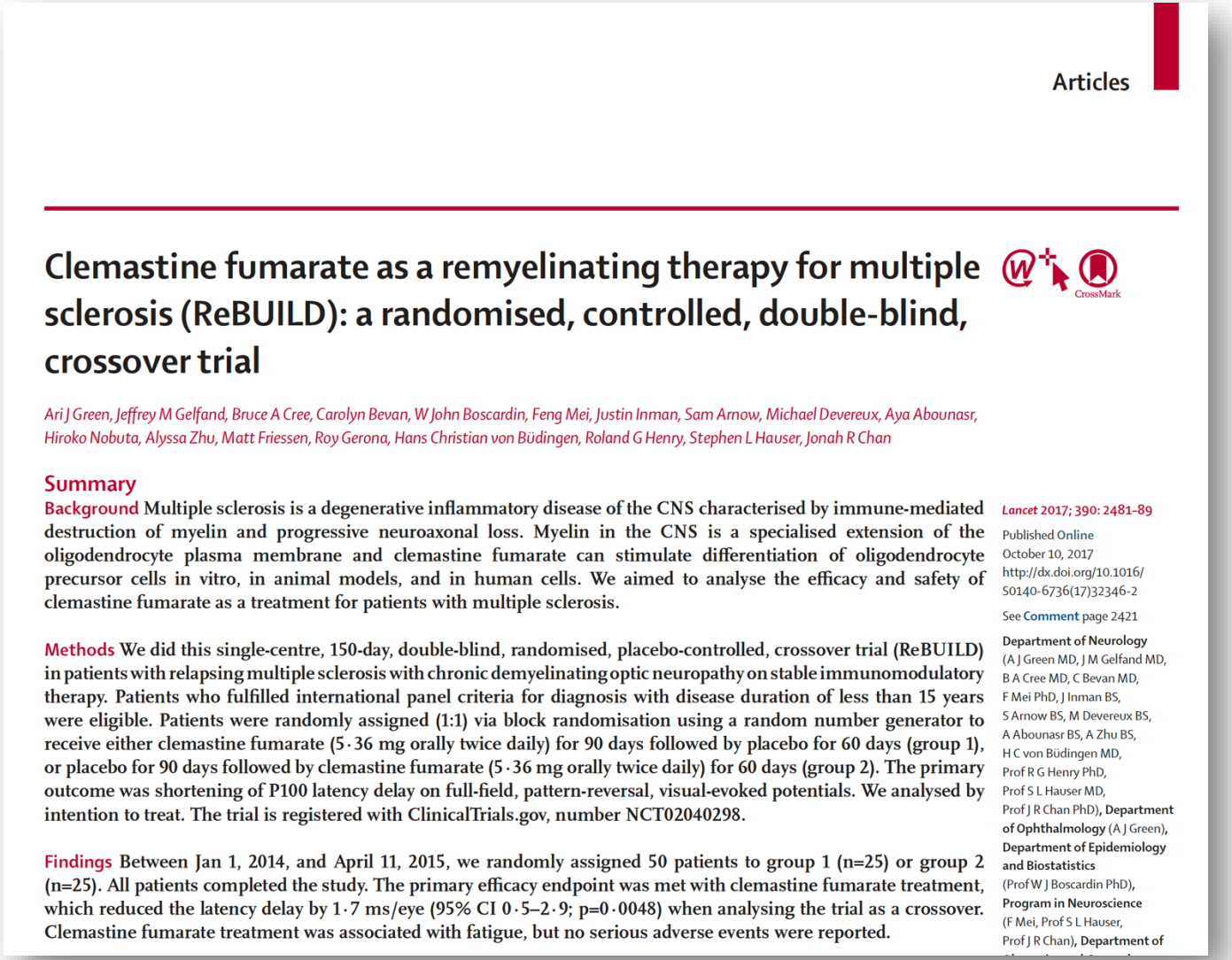

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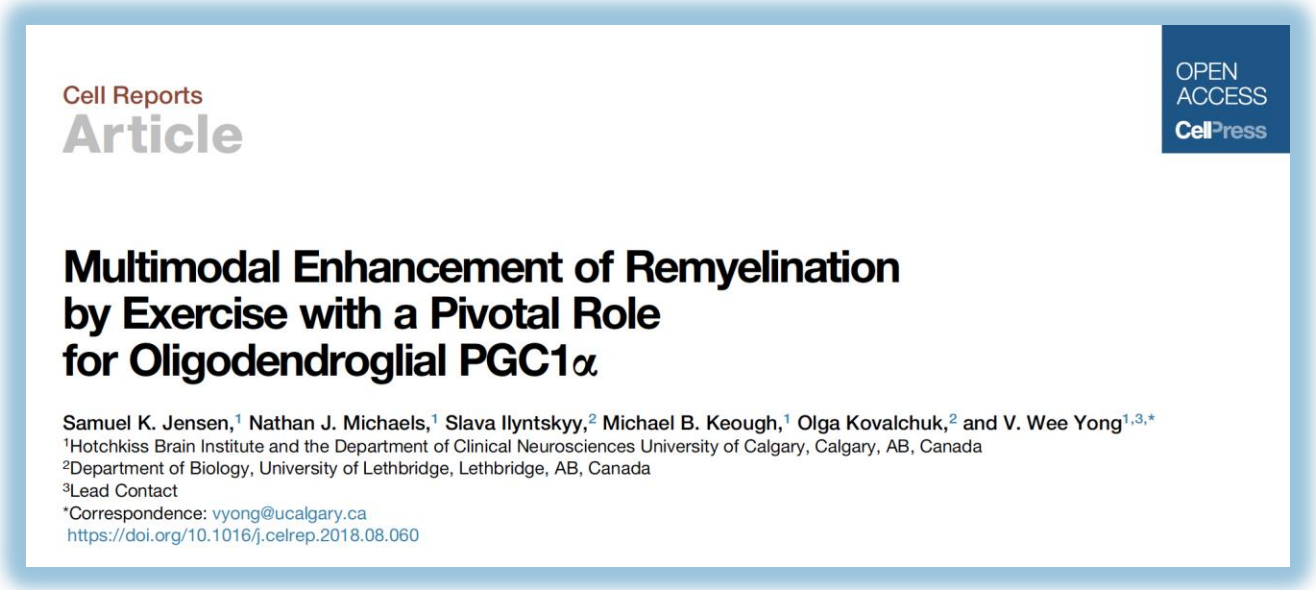
- First demonstration of evidence for drug-induced remyelination in MS patients
- 3 subsequent clinical trials evaluating clemastine in MS patients are ongoing

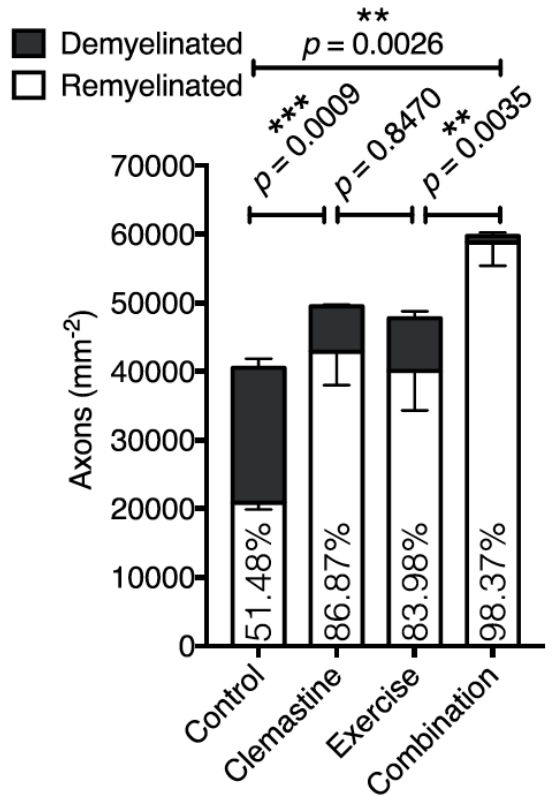
Green, A., …, Chan, J. (2017) *Lancet*.

Physical Activity Enhances Remyelination and Myelin Sheath Thickness



Jensen, S.K., …, Yong, V.W. (2018) *Cell Reports.* **24**: 3167.

Impact of combining clemastine treatment with exercise



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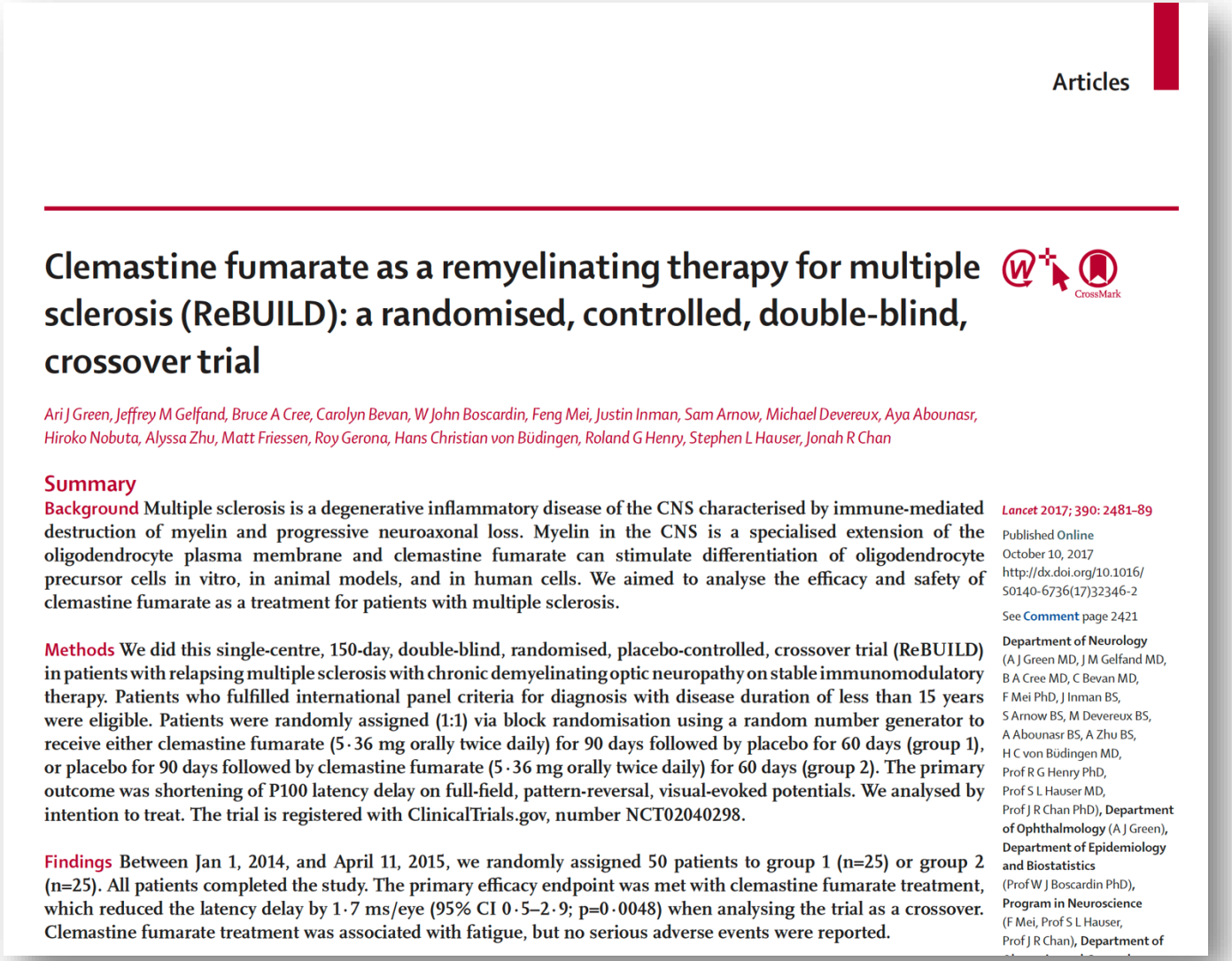

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Findings Between Jan 1, 2014, and April 11, 2015, we randomly assigned 50 patients to group 1 (n=25) or group 2 (n=25). All patients completed the study. The primary efficacy endpoint was met with clemastine fumarate treatment, which reduced the latency delay by 1·7 ms/eye (95% CI 0·5–2·9; p=0·0048) when analysing the trial as a crossover. Clemastine fumarate treatment was associated with fatigue, but no serious adverse events were reported.

Lancet 2017; 390: 2481–89

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See Comment page 2421

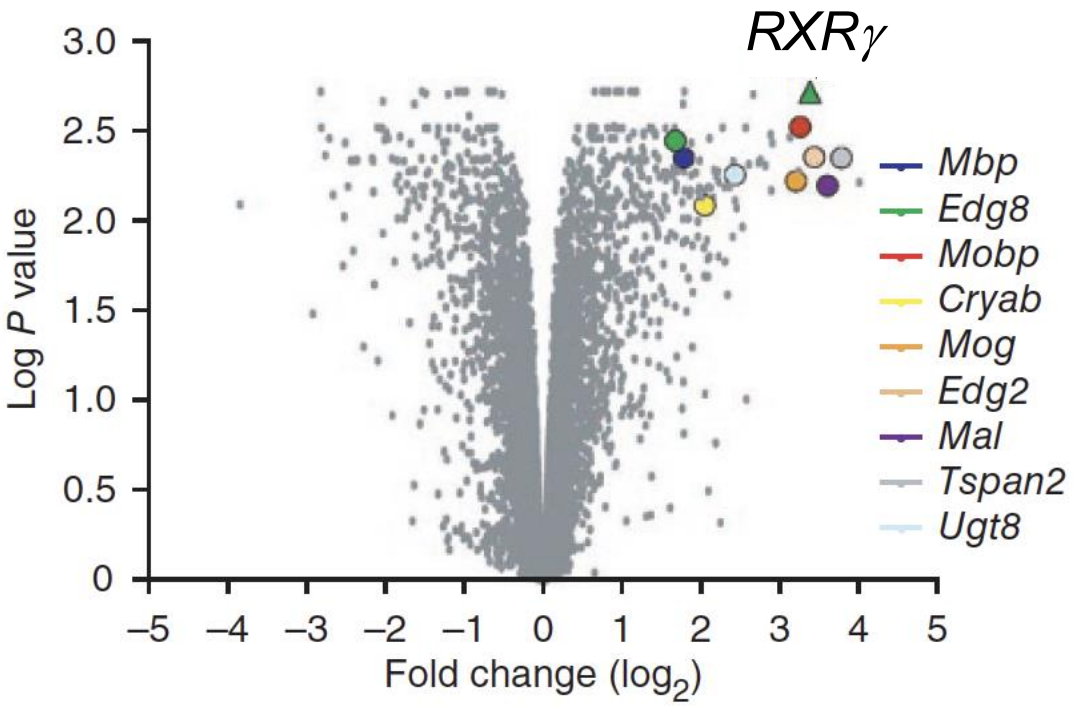
Department of Neurology (A J Green MD, J M Gelfand MD, B A Cree MD, C Bevan MD, F Mei PhD, J Inman BS, S Arnow BS, M Devereux BS, A Abounasr BS, A Zhu BS, H C von Büdingen MD, Prof R G Henry PhD, Prof S L Hauser MD, Prof J R Chan PhD), **Department of Ophthalmology** (A J Green), **Department of Epidemiology and Biostatistics** (Prof W J Boscardin PhD), **Program in Neuroscience** (F Mei, Prof S L Hauser, Prof J R Chan), **Department of**

- First demonstration of evidence for drug-induced remyelination in MS patients
- Molecules identified from phenotypic screens translate to human patients

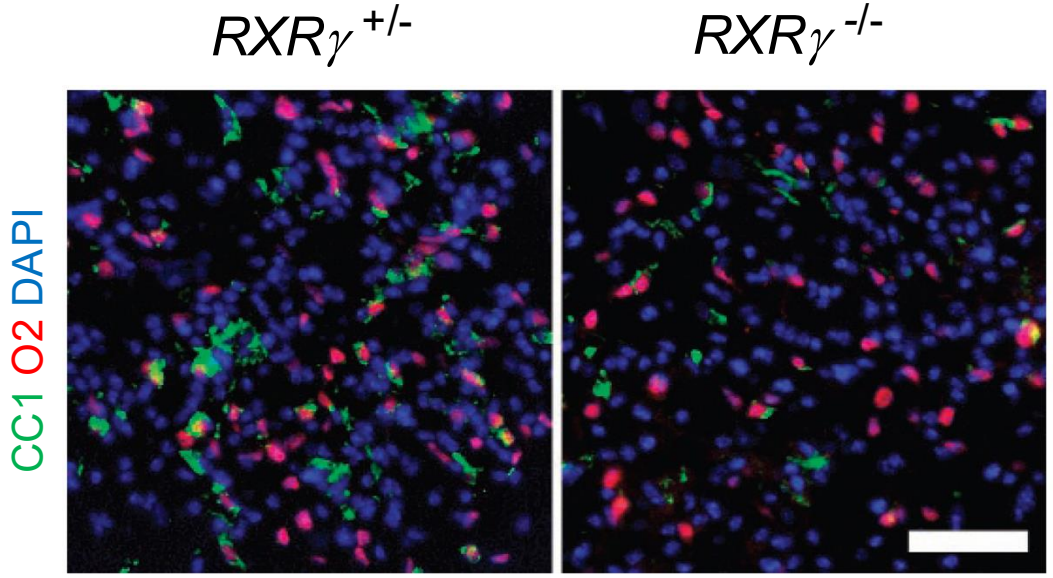
Green, A., …, Chan, J. (2017) *Lancet*.

RXRγ is a Positive Regulator of Remyelination

RXRγ transcripts are upregulated in demyelinated lesions



Loss of RXRγ impairs remyelination



Huang, …, ffrench-Constant, Franklin (2011) *Nature Neuroscience.*

Target-Based Approach: Clinical Evaluation of Bexarotene in MS Patients

Articles

Safety and efficacy of bexarotene in patients with relapsing-remitting multiple sclerosis (CCMR One): a randomised, double-blind, placebo-controlled, parallel-group, phase 2a study

J William L Brown, Nick G Cunniffe*, Ferran Prados, Baris Kanber, Joanne L Jones, Edward Needham, Zoya Georgieva, David Rog, Owen R Pearson, James Overell, David MacManus, Rebecca S Samson, Jonathan Stutters, Charles ffrench-Constant, Claudia A M Gandini Wheeler-Kingshott, Carla Moran, Paul D Flynn, Andrew W Michell, Robin J M Franklin, Siddharthan Chandran, Daniel R Altmann, Declan T Chard, Peter Connick, Alasdair J Coles*

Summary

Background Progressive disability in multiple sclerosis occurs because CNS axons degenerate as a late consequence of demyelination. In animals, retinoic acid receptor RXR-gamma agonists promote remyelination. We aimed to assess the safety and efficacy of a non-selective retinoid X receptor agonist in promoting remyelination in people with multiple sclerosis.

Methods This randomised, double-blind, placebo-controlled, parallel-group, phase 2a trial (CCMR One) recruited patients with relapsing-remitting multiple sclerosis from two centres in the UK. Eligible participants were aged 18–50 years and had been receiving dimethyl fumarate for at least 6 months. Via a web-based system run by an independent statistician, participants were randomly assigned (1:1), by probability-weighted minimisation using four binary factors, to receive 300 mg/m² of body surface area per day of oral bexarotene or oral placebo for 6 months. Participants, investigators, and outcome assessors were masked to treatment allocation. MRI scans were done at baseline and at 6 months. The primary safety outcome was the number of adverse events and withdrawals attributable to bexarotene. The primary efficacy outcome was the patient-level change in mean lesional magnetisation transfer ratio between baseline and month 6 for lesions that had a baseline magnetisation transfer ratio less than the within-patient median. We analysed the primary safety outcome in the safety population, which comprised participants who received at least one dose of their allocated treatment. We analysed the primary efficacy outcome

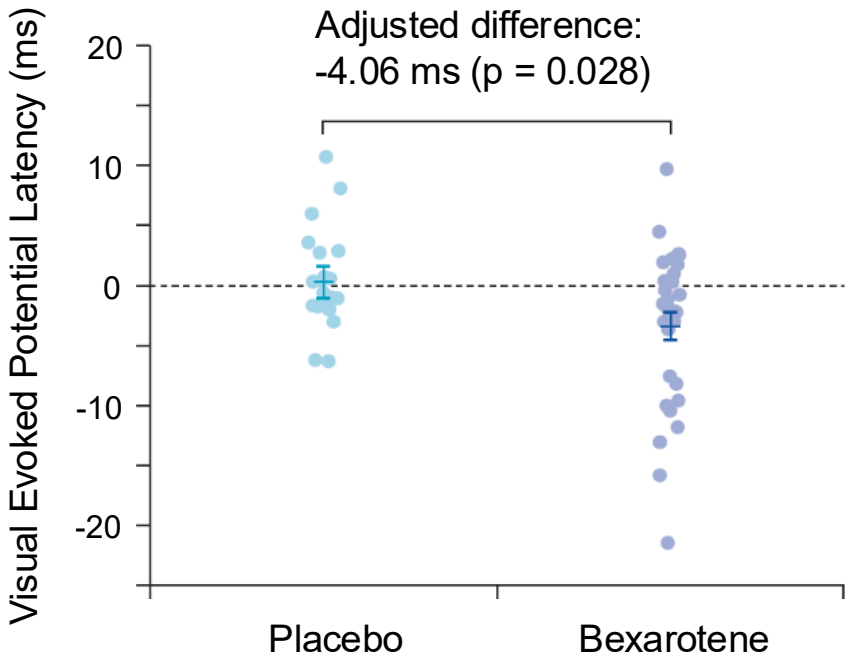
Lancet Neurol 2021; 20: 709–20

See Comment page 686

*Contributed equally and co-first authors

Department of Clinical Neurosciences (J W L Brown PhD, N G Cunniffe MBBChir, J L Jones PhD, E Needham PhD, Z Georgieva MBBS, A W Michell PhD, Prof R J M Franklin PhD, Prof A J Coles PhD), **Wellcome Trust-MRC Institute of Metabolic Science** (C Moran PhD), **Division of Cardiovascular Medicine, Department of Medicine** (P D Flynn PhD), **and Wellcome-**

Bexarotene Treatment Reduces VEP Latency Delay in MS Patients



Brown, Cunniffe, …, Coles (2021) *Lancet Neurology*.

Remyelination-Inducing Therapies

- The field has progressed from concept, to the identification of repurposed OPC differentiation-inducing agents, to evidence for remyelination in MS for 2 unique mechanisms

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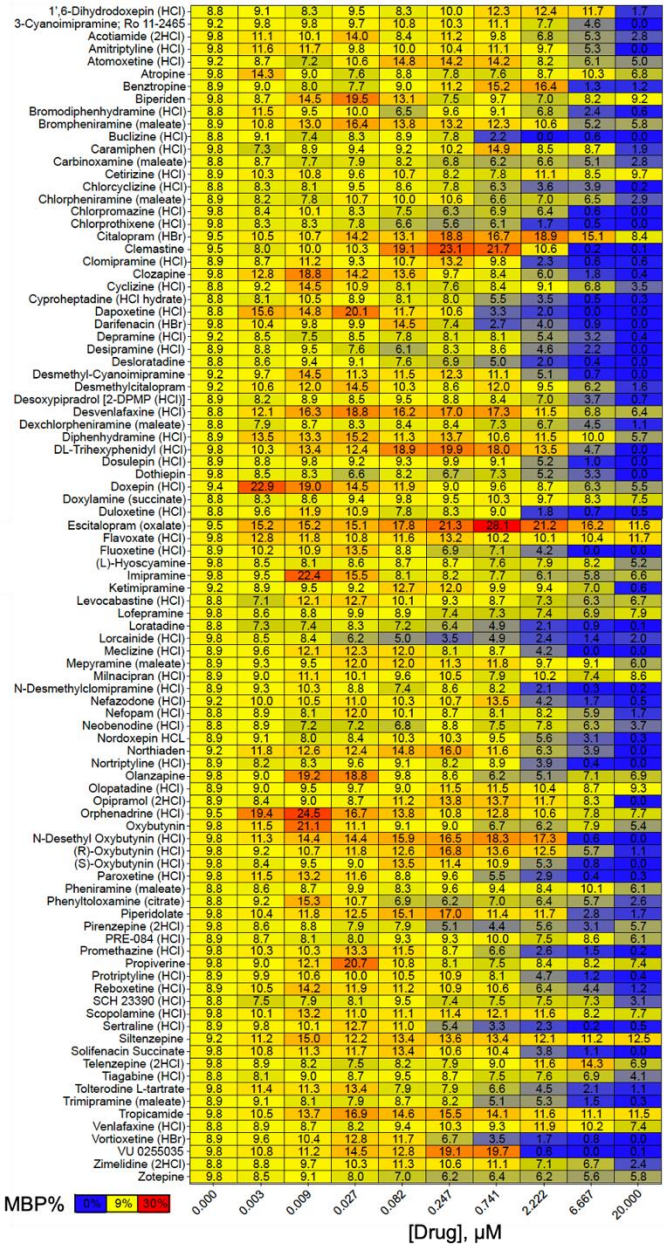
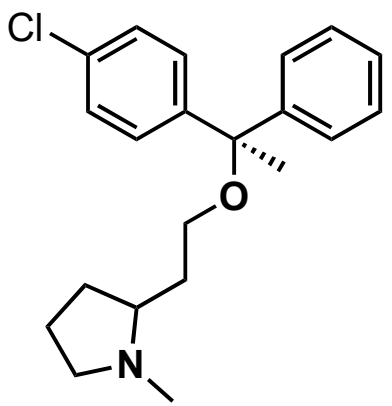
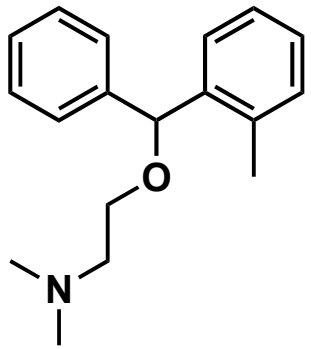
- Dose-related toxicity and therapeutic index limiting for both clemastine and bexarotene

Alternative OPC Differentiation-Inducing M1R Antagonists

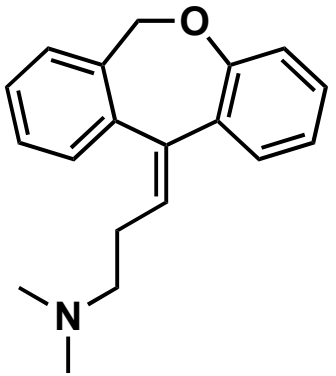




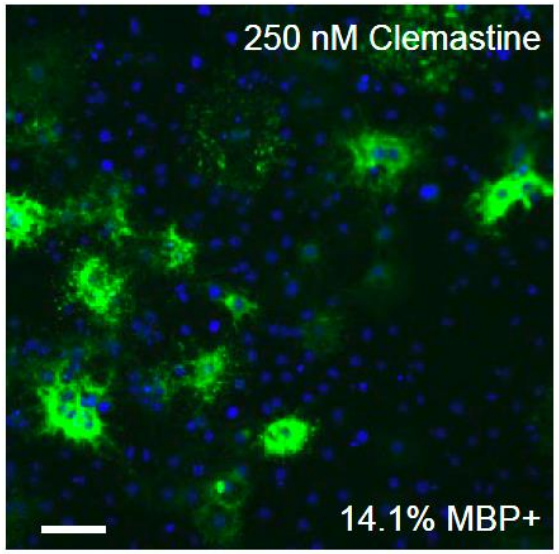
Clemastine
OPC EC_{50} = 270 nM

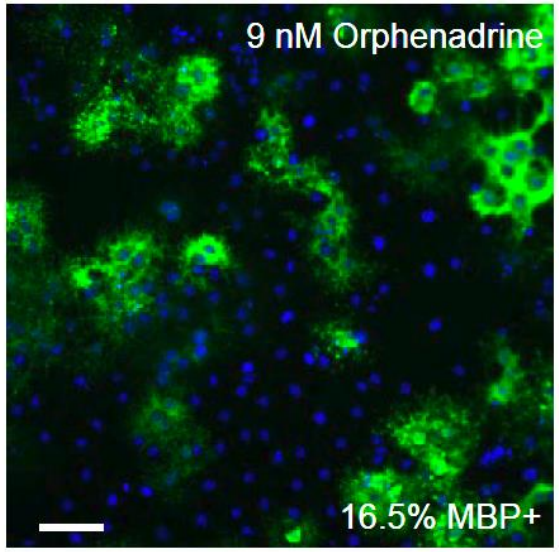


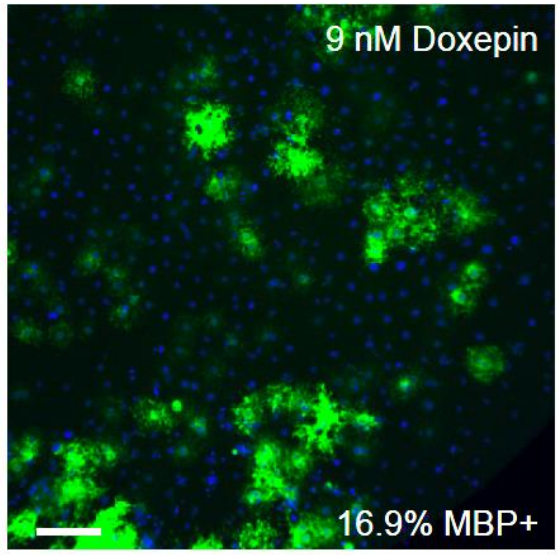
Orphenadrine
OPC EC_{50} = 4.4 nM



Doxepin
OPC EC_{50} = 2.6 nM







Beyer, B.A., …, Lairson, L.L. (2023) bioRxiv.

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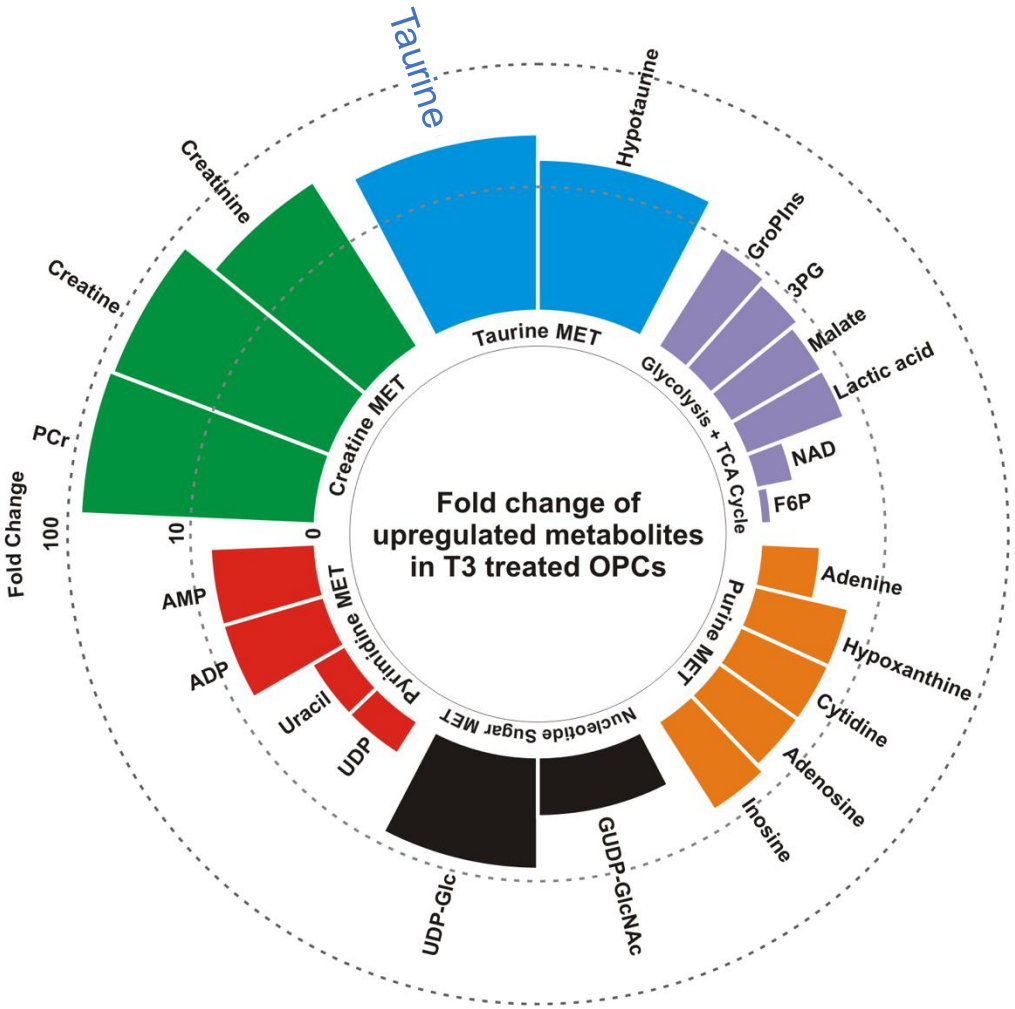
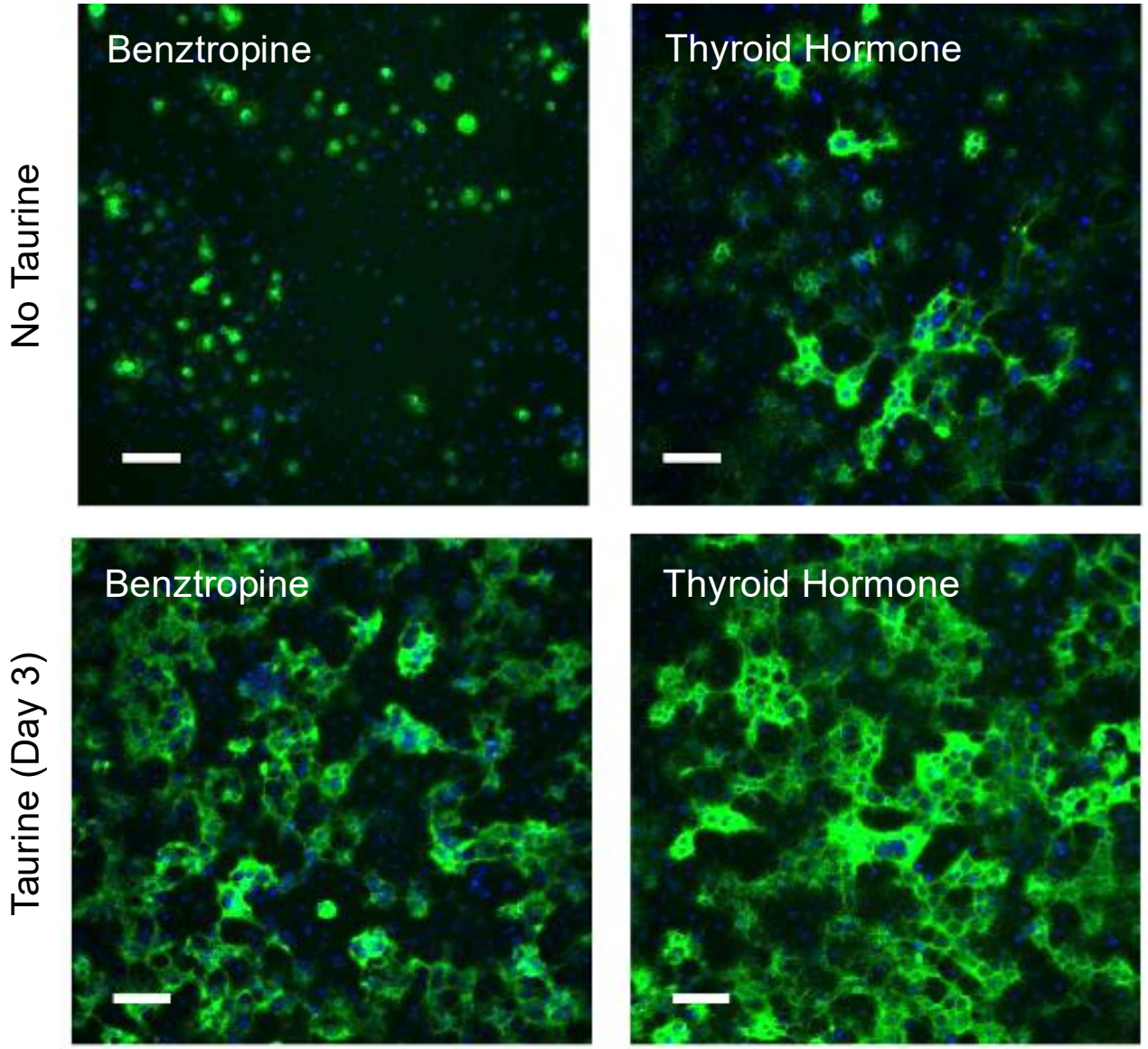
- The field has progressed from concept, to the identification of repurposed OPC differentiation-inducing agents, to evidence for remyelination in MS for 2 unique mechanisms
- Dose-related toxicity and therapeutic index limiting for both clemastine and bexarotene
- Can a single mechanism achieve maximal efficacy?
- Will a single mechanism work for all disease contexts?

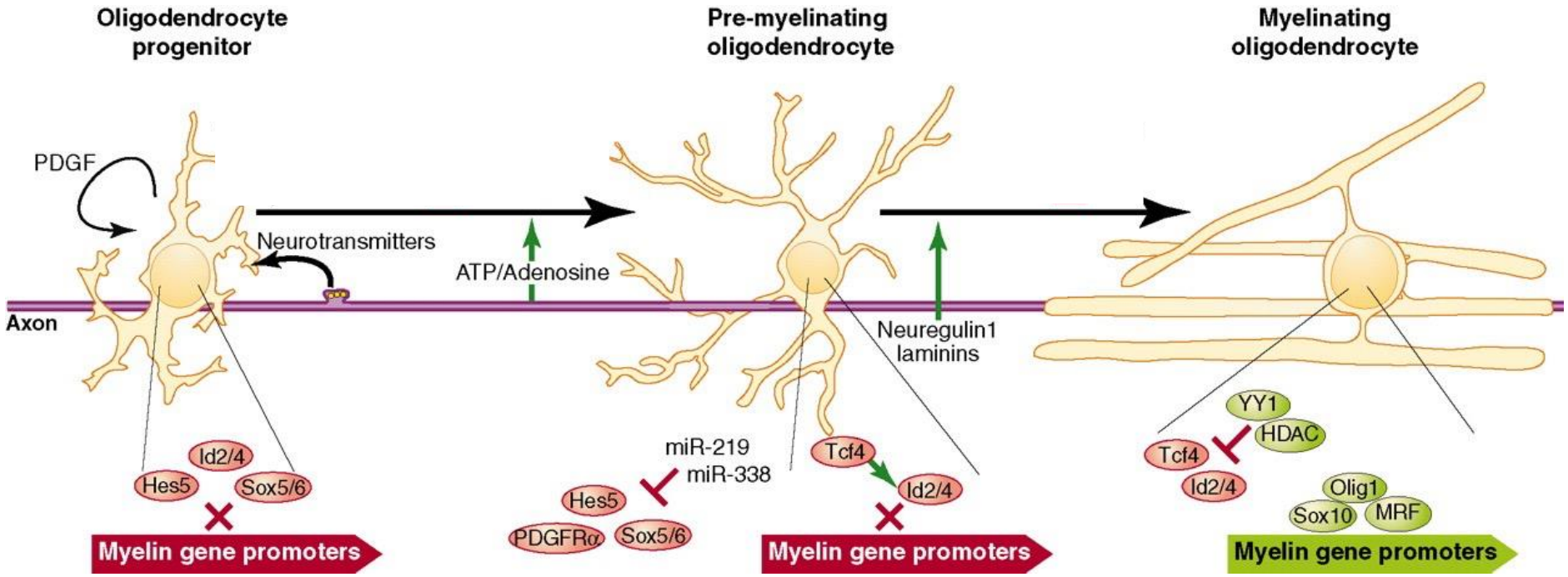
Impact of Taurine on OPC Differentiation

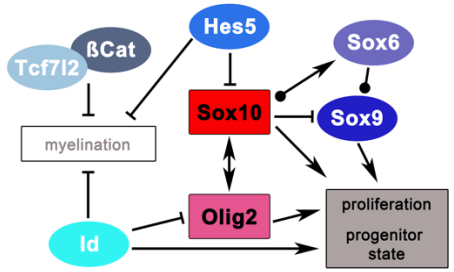


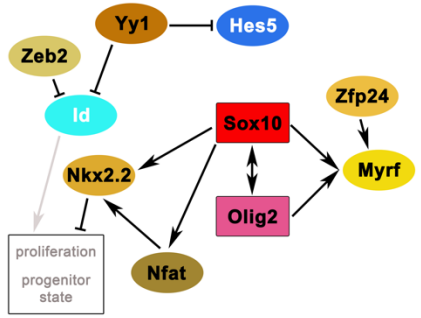


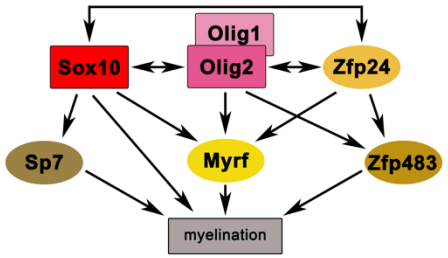
Beyer, …, Siuzdak, Lairson (2018) *Nature Chemical Biology*.

Defined Stages of OPC Differentiation









Emery (2014) *Science*.
Sock & Wagner (2019) Glia.

Can we improve efficacy levels for drug-induced remyelination using a combination of agents that target alternative mechanisms?

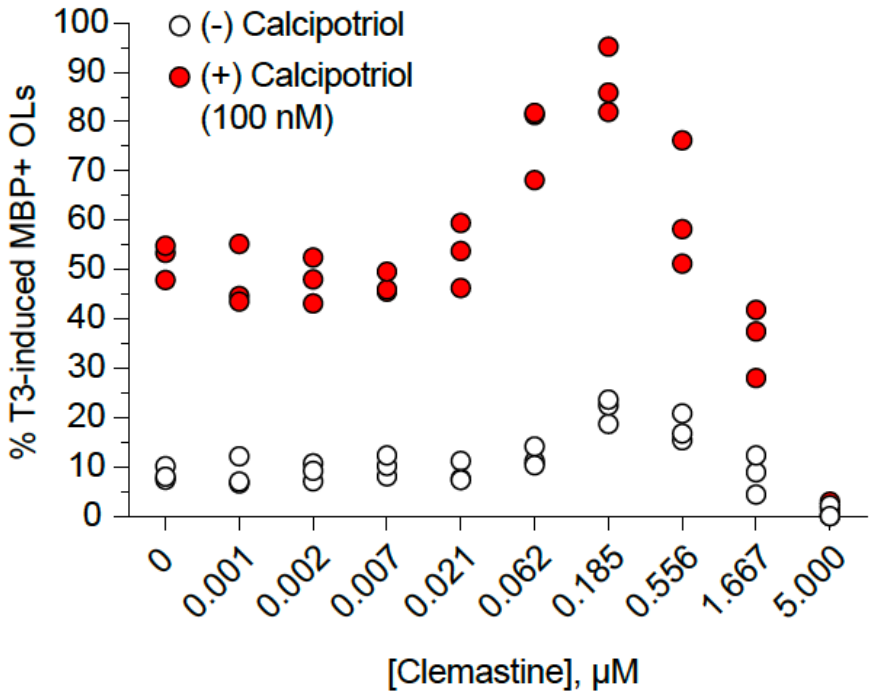
Brittney Beyer, PhD

Can we improve efficacy levels for drug-induced remyelination using a combination of agents that target alternative mechanisms?

Pairwise combinatorial drug screening using representative members from identified classes of OPC differentiation-inducing agents

Vitamin D receptor (VDR) Agonist / M1R Antagonist Combination

Clemastine (M1R antagonist) + Calcipotriol (VDR agonist)



- VDR agonists enhance the ability of clemastine to induce OPC differentiation

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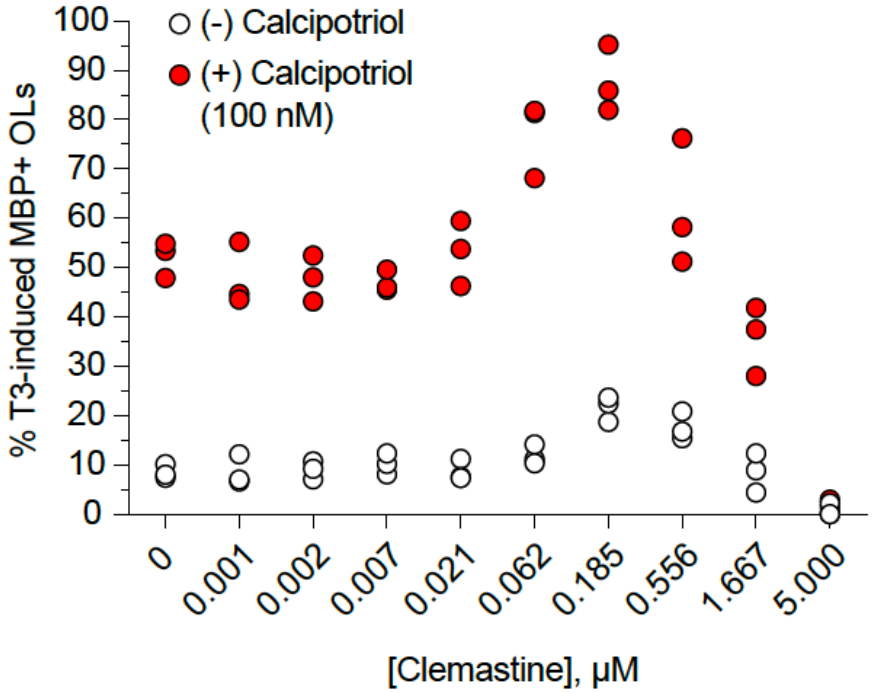
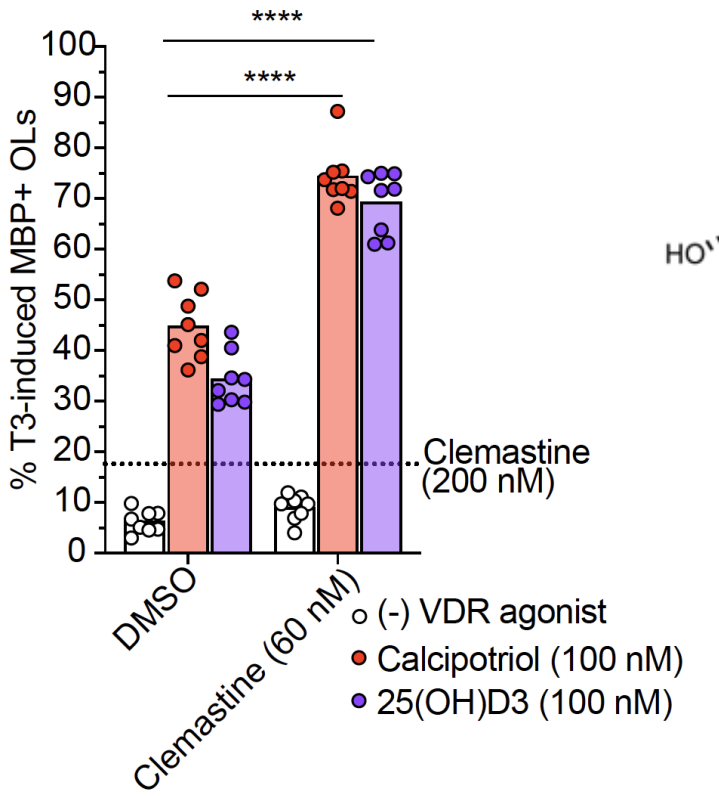
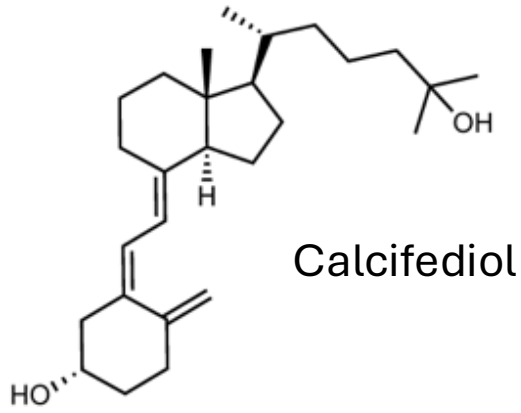
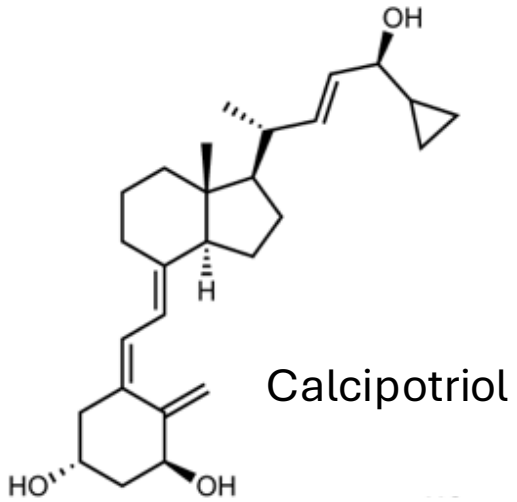


Impact of 25(OH)D3 (calcifediol)







- OPCs can metabolize calcifediol to form active metabolite (Cyp24A1)

Role of Vitamin D in Conversion to Clinically Defined MS (CDMS)

Original Investigation

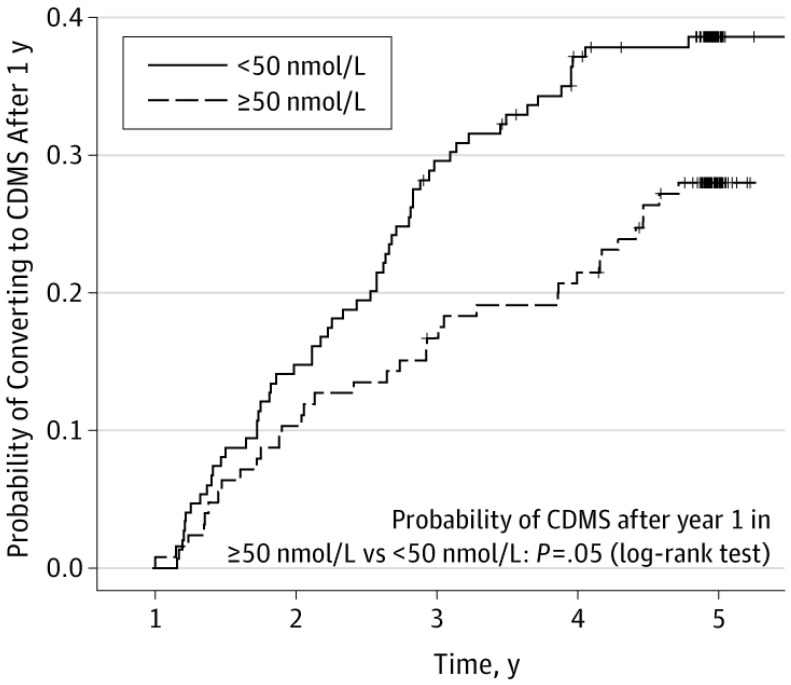
March 2014

Vitamin D as an Early Predictor of Multiple Sclerosis Activity and Progression

Alberto Ascherio, MD, DrPH[1]; Kassandra L. Munger, ScD[1]; Rick White, MSc[2]; Karl Köchert, PhD[3]; Kelly Claire Simon, ScD[1]; Chris H. Polman, MD[4]; Mark S. Freedman, MD[5]; Hans-Peter Hartung, MD[6]; David H. Miller, MD[7]; Xavier Montalbán, MD[8]; Gilles Edan, MD[9]; Frederik Barkhof, MD[4]; Dirk Pleimes, MD[10]; Ernst Wilhelm Radü, MD[11]; Rupert Sandbrink, MD[3,6]; Ludwig Kappos, MD[11]; Christoph Pohl, MD[3,12]

Ascherio, …, Kappos, Pohl (2014) *JAMA.*

Correlation of Vitamin D levels with conversion to CDMS



High Dose Vitamin D: Impact on Transition to Clinically Defined MS

New Online Views 31,725 | Citations 0 | Altmetric 484

Original Investigation

March 10, 2025

High-Dose Vitamin D in Clinically Isolated Syndrome Typical of Multiple Sclerosis

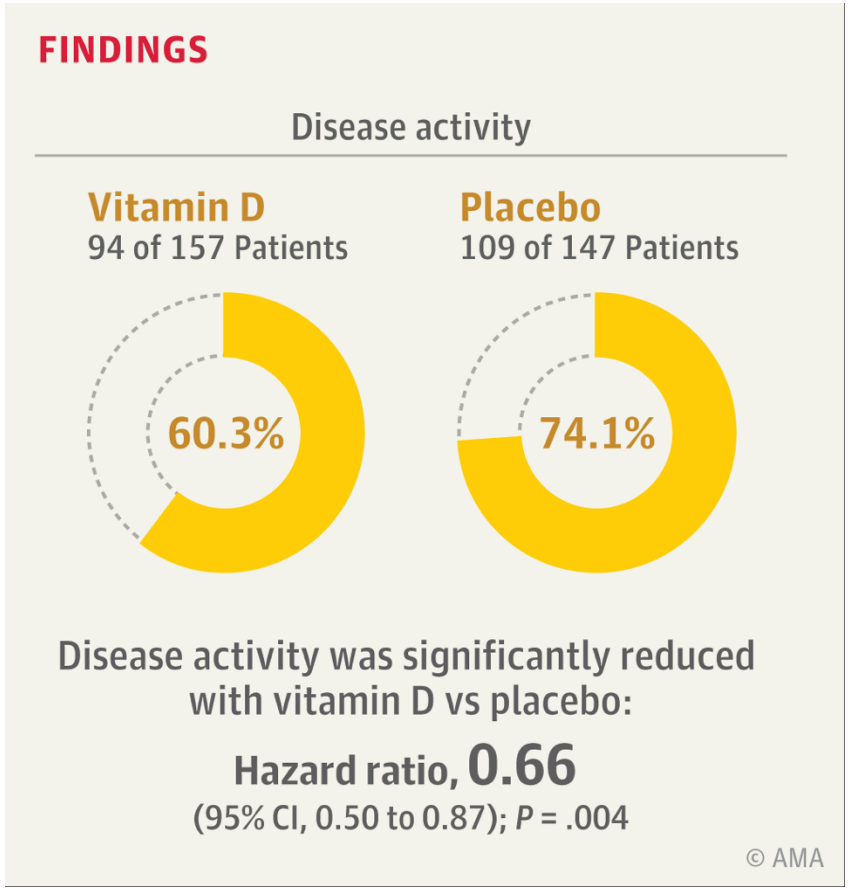
The D-Lay MS Randomized Clinical Trial

Eric Thouvenot, MD, PhD[1,2]; David Laplaud, MD, PhD[3]; Christine Lebrun-Frenay, MD, PhD[4]; et al

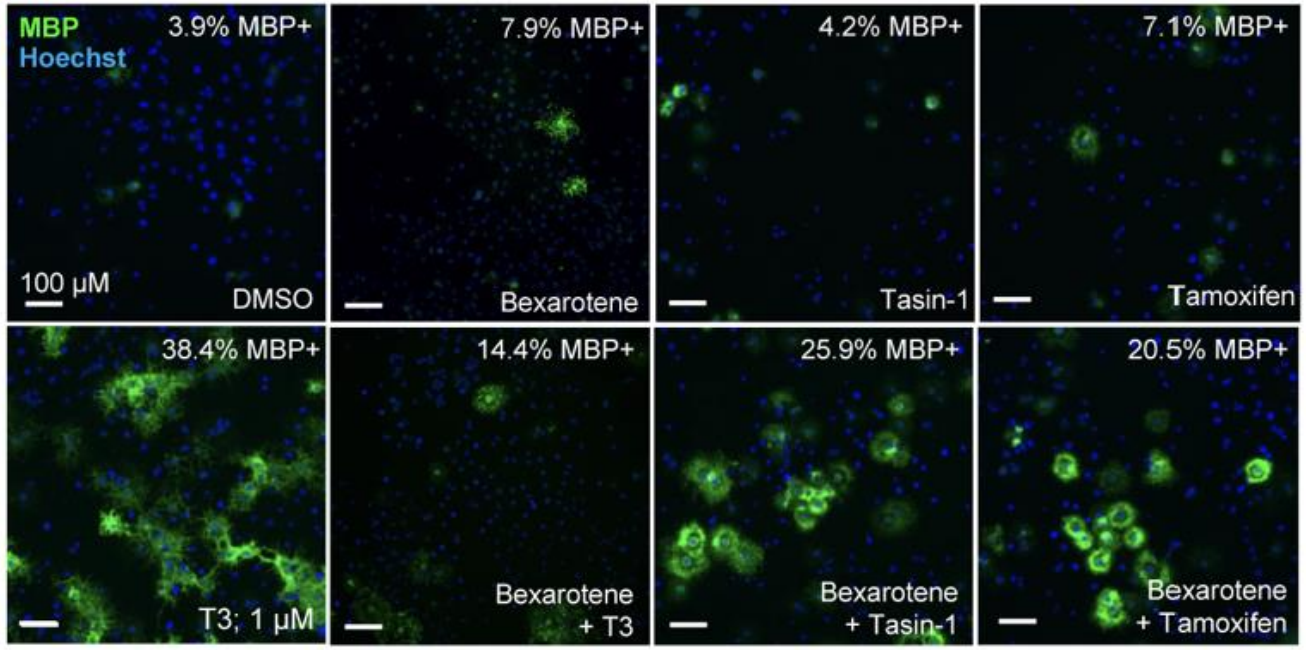
» Author Affiliations

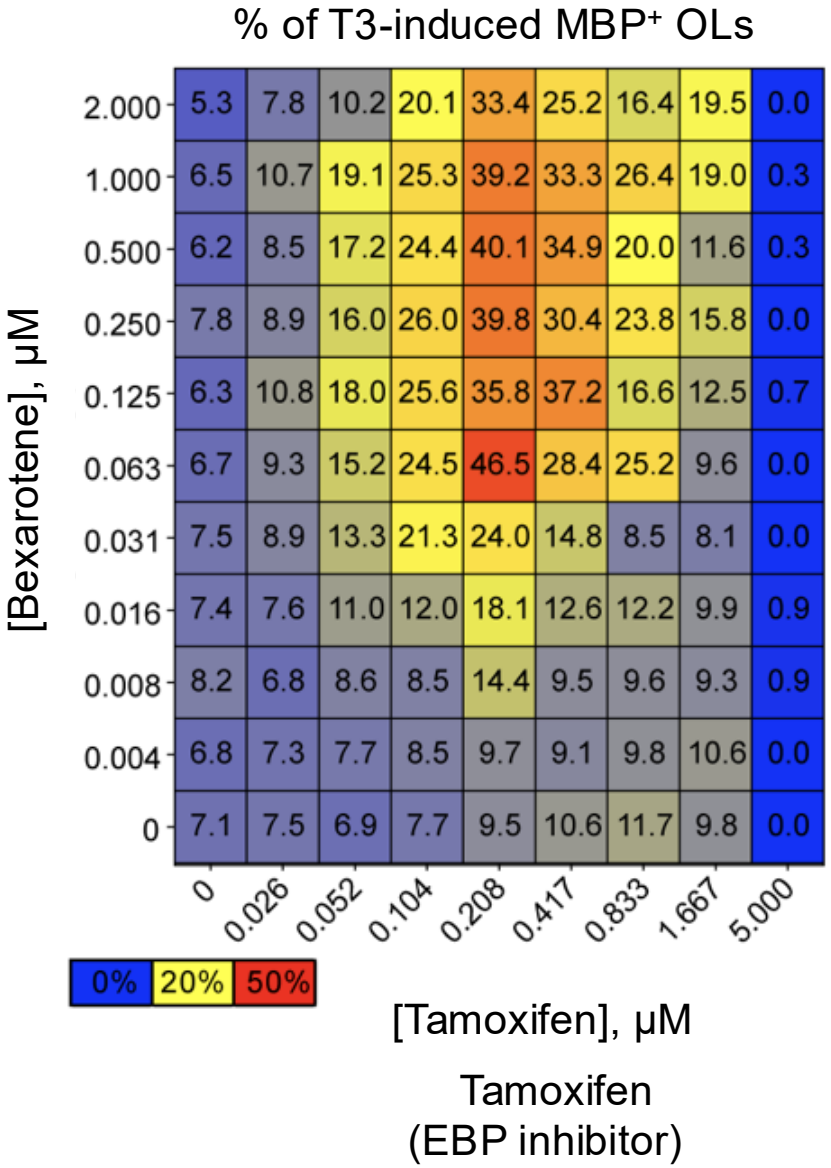
JAMA. Published online March 10, 2025. doi:10.1001/jama.2025.1604

Thouvenot, …, D-Lay investigators (2025) *JAMA.*



EBP* Inhibitors Synergize with Bexarotene (RXRγ Agonist)





* See: Hubler, …, Adams (2018) *Nature.*

Summary of Recent Work

- Based on known safe human exposure levels and predicted therapeutic indices, “next generation” M1R antagonists may be more efficacious than clemastine

Summary of Recent Work

- Based on known safe human exposure levels and predicted therapeutic indices, “next generation” M1R antagonists may be more efficacious than clemastine

- Combination-based drug screening identified 2 clinical hypotheses:
  - Vitamin D + M1R antagonist (e.g. clemastine)
  - Bexarotene + Tamoxifen (EBP inhibitor)

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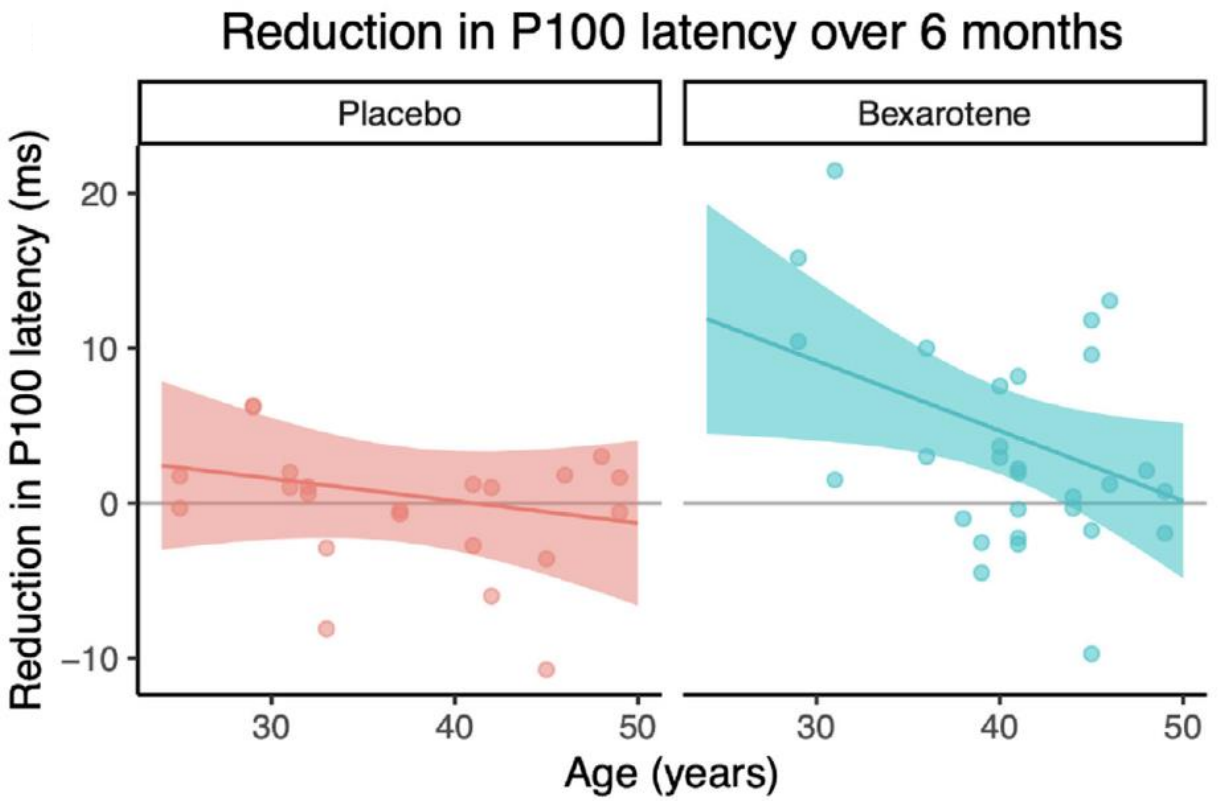
Remyelination Capacity is Very Clearly Age-Dependent

- Remyelination capacity in rodents and humans deteriorates with age
- Responses to bexarotene (and other MS drugs) correlates with age



McMurran, …, Coles, Cunniffe (2022) *Ann. Clin. Transl. Neurol.*

Remyelination Capacity is Very Clearly Age-Dependent

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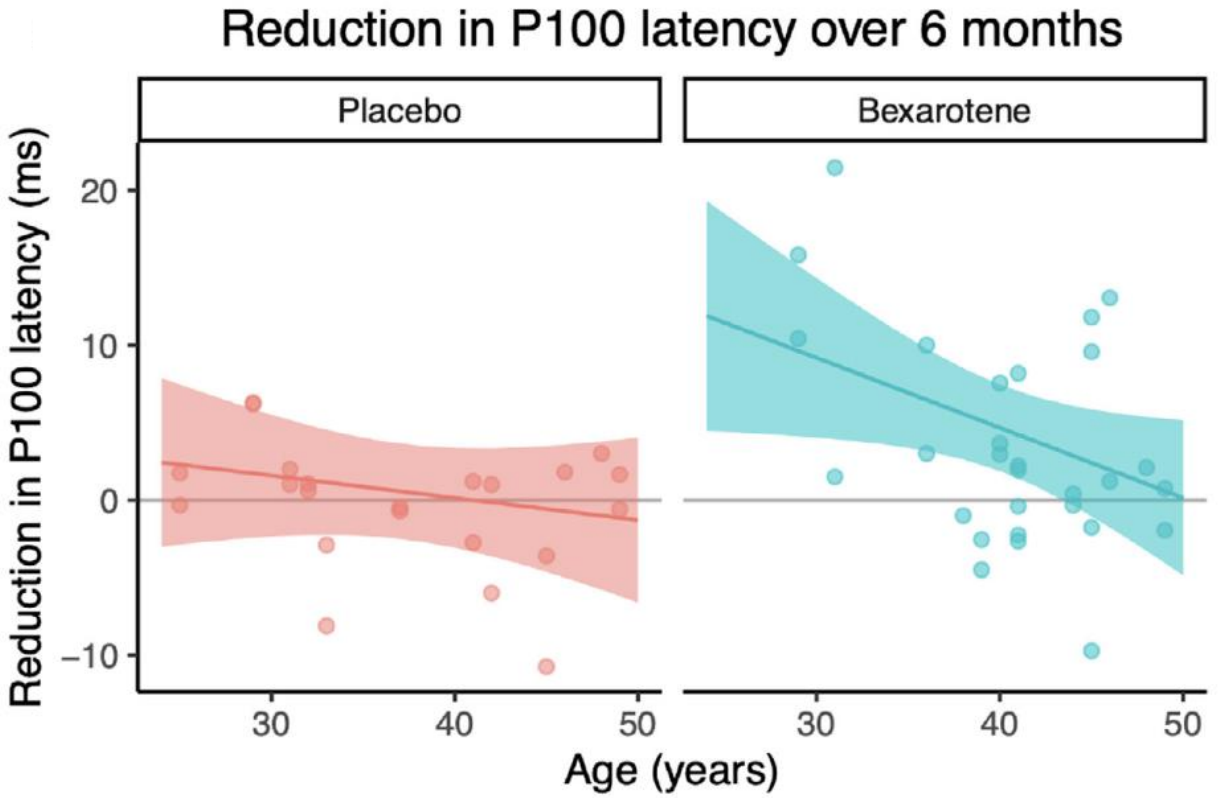
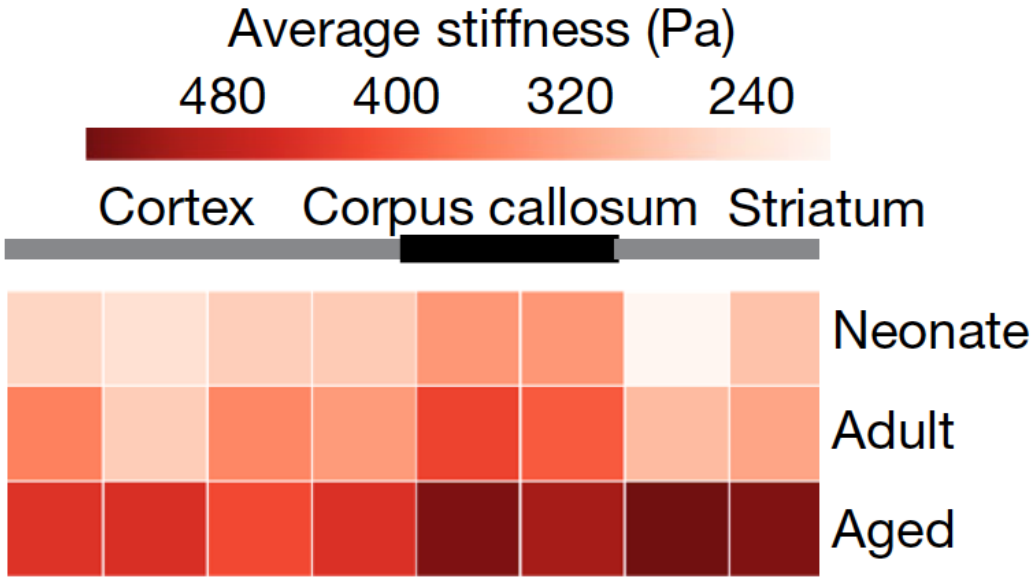
- Responses to bexarotene (and other MS drugs) correlates with age
- Change is not the result of depletion or an inherent limitation of aged OPCs



McMurran, …, Coles, Cunniffe (2022) *Ann. Clin. Transl. Neurol.*

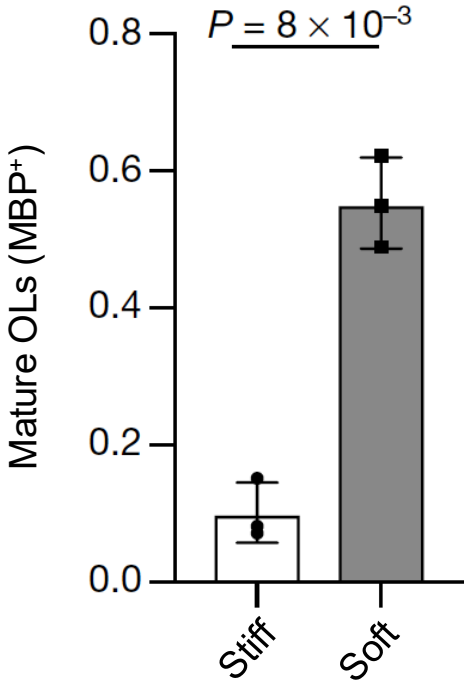
Matrix stiffness of aged OPC niche limits activation

- The OPC niche (and CNS in general) becomes stiffer with age



Segel, …, Franklin, Chalut (2019) *Nature.*

- Culture of aged OPCs on matrices that mimic young stiffness restores function



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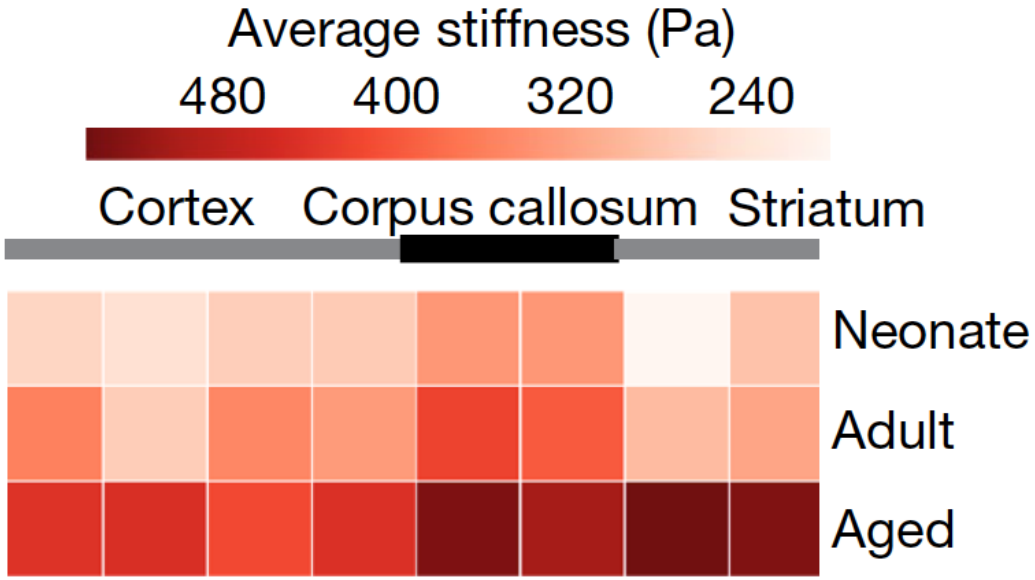
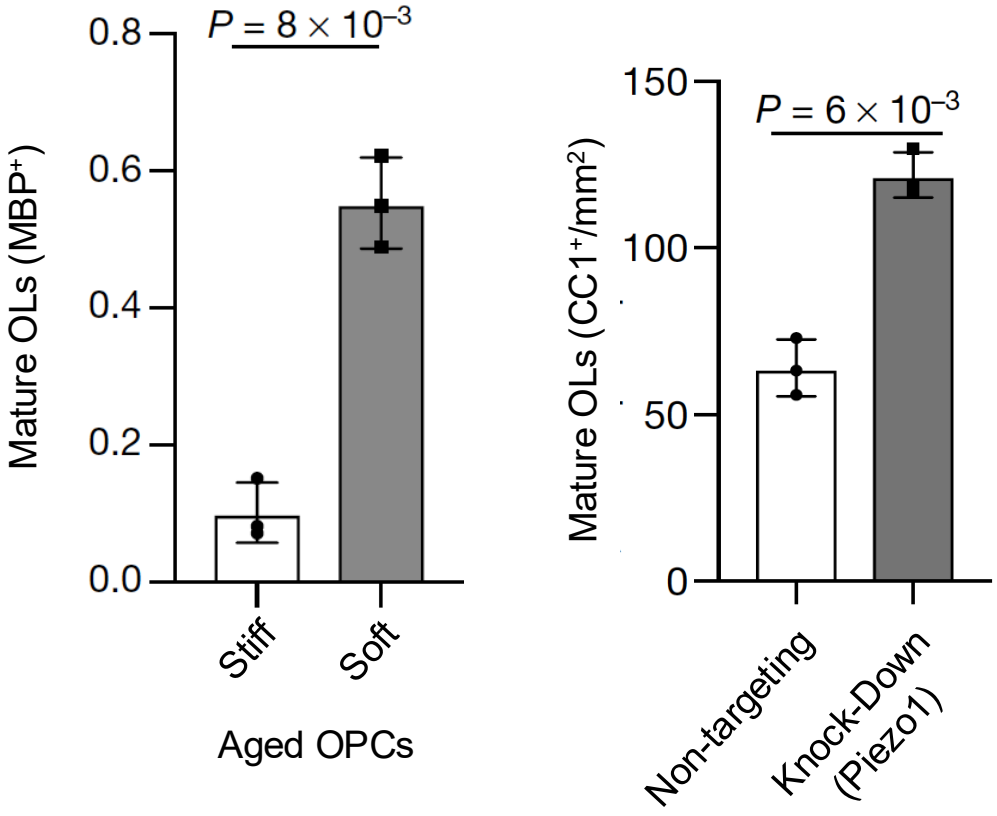
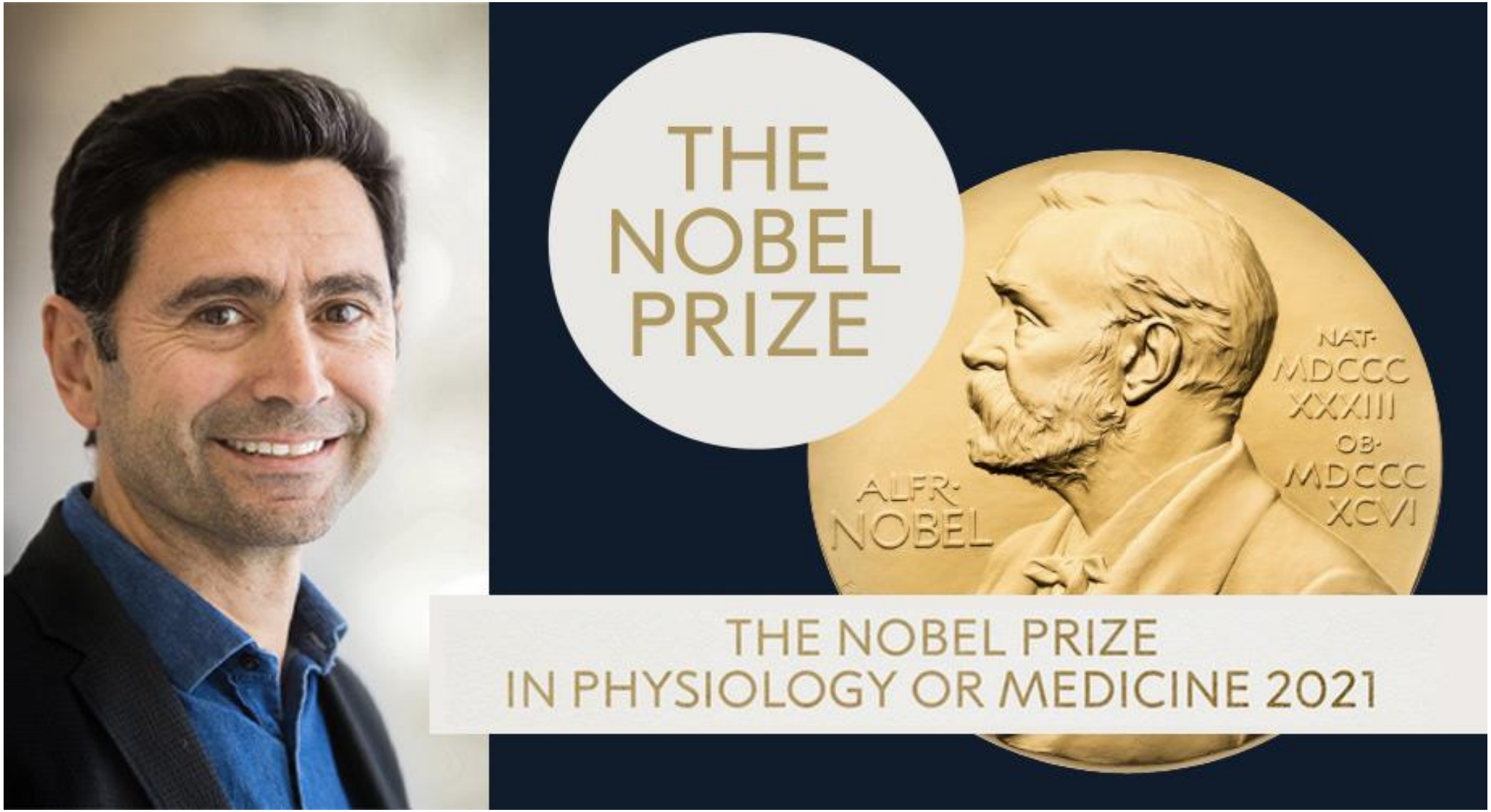


Segel, …, Franklin, Chalut (2019) *Nature.*

- OPC-restricted Piezo1 knockdown restores remyelination in aged CNS





Ardem Patapoutian (Department of Neuroscience), 2021 Noble Prize for the discovery of receptors associated with the sensing of temperature and touch (PIEZO1, PIEZO2)

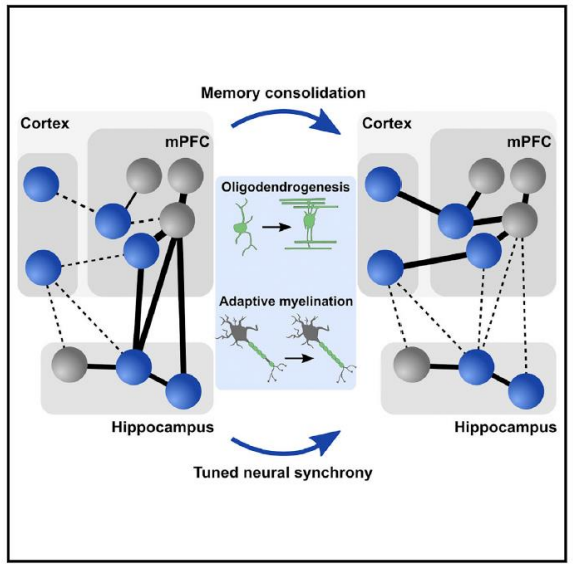
Beyond MS Disease

Article

Neuron

Disruption of Oligodendrogenesis Impairs Memory Consolidation in Adult Mice

Graphical Abstract



Authors

Patrick E. Steadman, Frances Xia, Moriam Ahmed, ..., Michelle Monje, Sheena A. Josselyn, Paul W. Frankland

Correspondence

paul.frankland@sickkids.ca

In Brief

Experience-dependent *de novo* myelination may fine-tune activated circuits by promoting brain synchrony, important for memory consolidation. Steadman et al. find that blocking this form of adaptive myelination prevents learning-induced increases in coordinated activity and impairs memory consolidation.

Steadman, …, Frankland (2020) *Neuron.*

nature neuroscience

ARTICLES

https://doi.org/10.1038/s41593-020-0637-3

Check for updates

Motor learning promotes remyelination via new and surviving oligodendrocytes

Clara M. Bacmeister[1,4], Helena J. Barr[1,4], Crystal R. McClain[1,4], Michael A. Thornton[1], Dailey Nettles[1,2,3], Cristin G. Welle[2,3] and Ethan G. Hughes[1]✉

Oligodendrocyte loss in neurological disease leaves axons vulnerable to damage and degeneration, and activity-dependent myelination may represent an endogenous mechanism to improve remyelination following injury. Here we report that, while learning a forelimb reach task transiently suppresses oligodendrogenesis, it subsequently increases oligodendrocyte precursor cell differentiation, oligodendrocyte generation and myelin sheath remodeling in the forelimb motor cortex. Immediately following demyelination, neurons exhibit hyperexcitability, learning is impaired and behavioral intervention provides no benefit to remyelination. However, partial remyelination restores neuronal and behavioral function, allowing learning to enhance oligodendrogenesis, remyelination of denuded axons and the ability of surviving oligodendrocytes to generate new myelin sheaths. Previously considered controversial, we show that sheath generation by mature oligodendrocytes is not only possible but also increases myelin pattern preservation following demyelination, thus presenting a new target for therapeutic interventions. Together, our findings demonstrate that precisely timed motor learning improves recovery from demyelinating injury via enhanced remyelination from new and surviving oligodendrocytes.

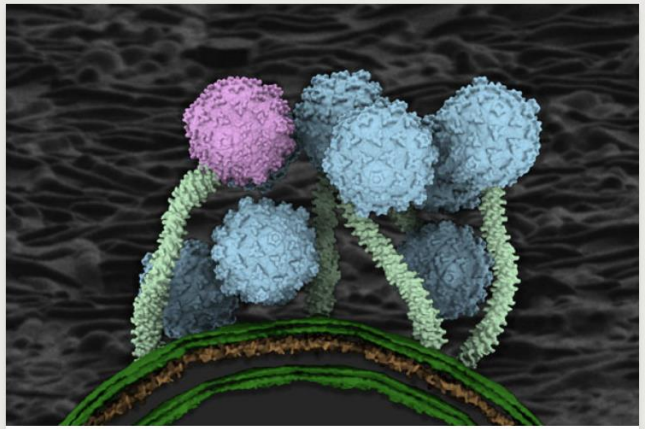
Bacmeister, …, Hughes (2020) *Nature Neuroscience.*

- Experience-dependent OPC differentiation and myelination contributes to motor learning and memory consolidation

Summary

- Role of EBV-infected B cells is MS disease and the related efficacy of repurposed B cell depleting antibodies in RRMS

News from Scripps Research



April 15, 2025

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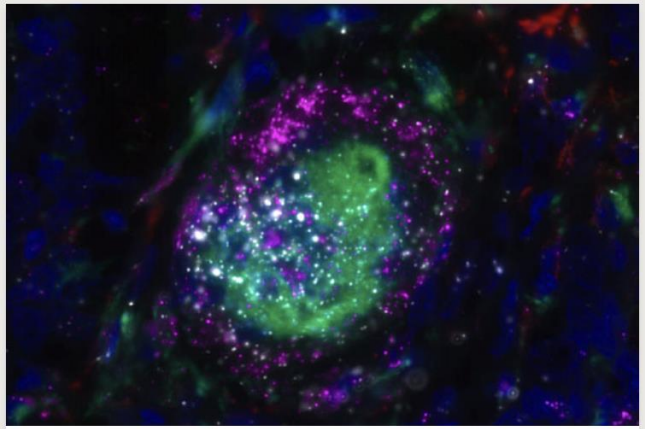

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Scripps Research and aTyr Pharma scientists have revealed how the protein HARS^{WHEP} calms inflammation associated with sarcoidosis.

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Molecular Medicine

Schimmel, Paul

Summary

- Role of EBV-infected B cells is MS disease and the related efficacy of repurposed B cell depleting antibodies in RRMS

Summary

- Role of EBV-infected B cells is MS disease and the related efficacy of repurposed B cell depleting antibodies in RRMS

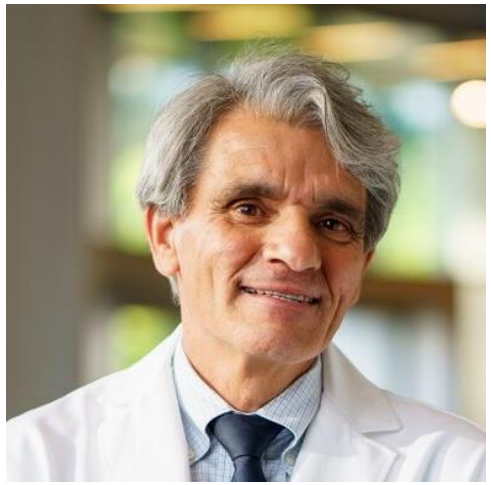
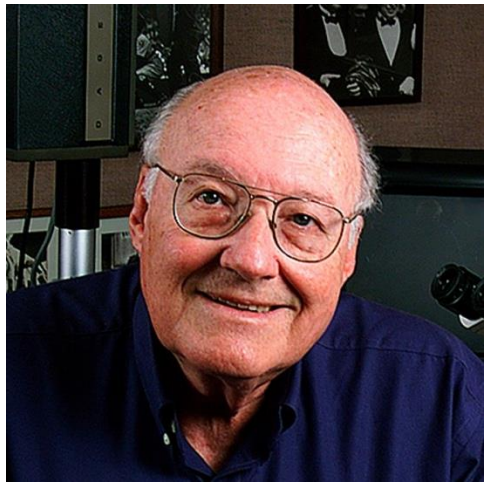
- Effective treatments for progressive MS are completely lacking

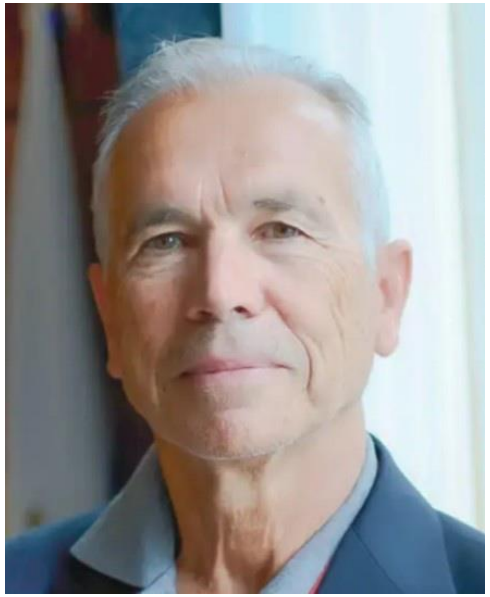
Summary

- Role of EBV-infected B cells is MS disease and the related efficacy of repurposed B cell depleting antibodies in RRMS
- Effective treatments for progressive MS are completely lacking
- Remyelination promoting therapies hold tremendous promise for progressive forms of MS
- The field has progressed from concept to evidence for remyelination in MS for 2 unique mechanisms

Summary

- Based on known human safety data, “next generation” M1R antagonists may be more efficacious than clemastine
- Combination-based drug screening identified 2 clinical hypotheses:
  - Vitamin D + M1R antagonist (e.g. clemastine)
  - Bexarotene + Tamoxifen (EBP inhibitor)

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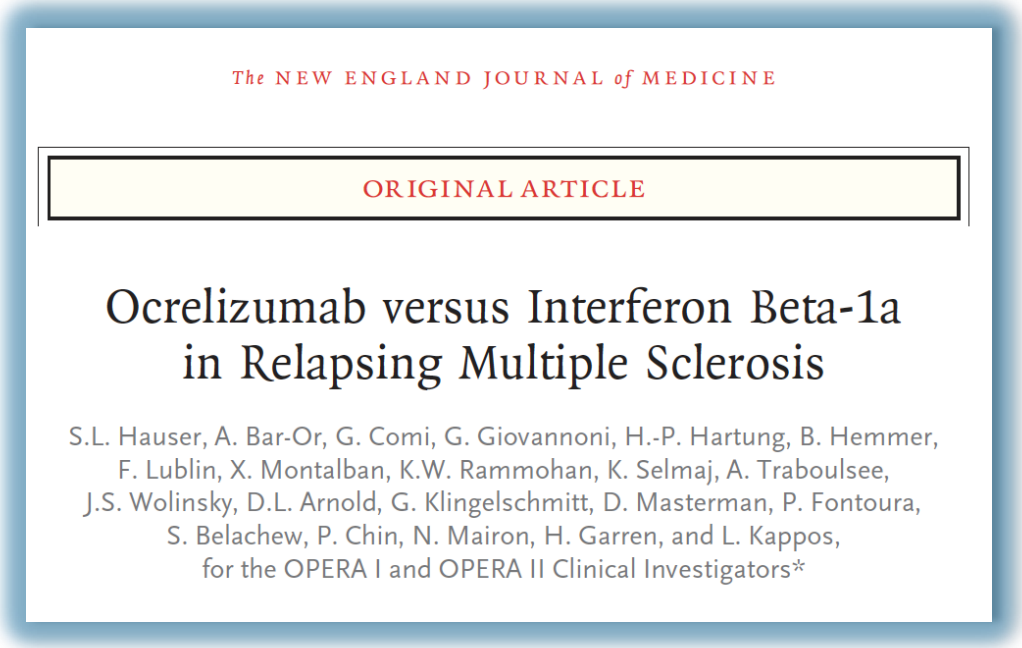
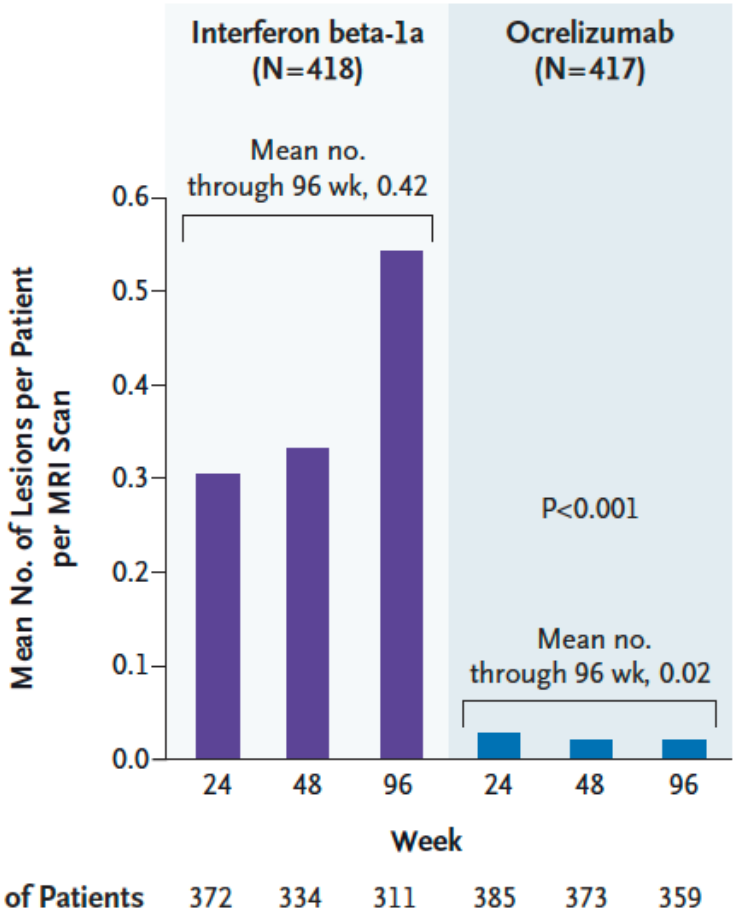
Therapeutic Approaches to the Treatment of MS: Targeting B Cells

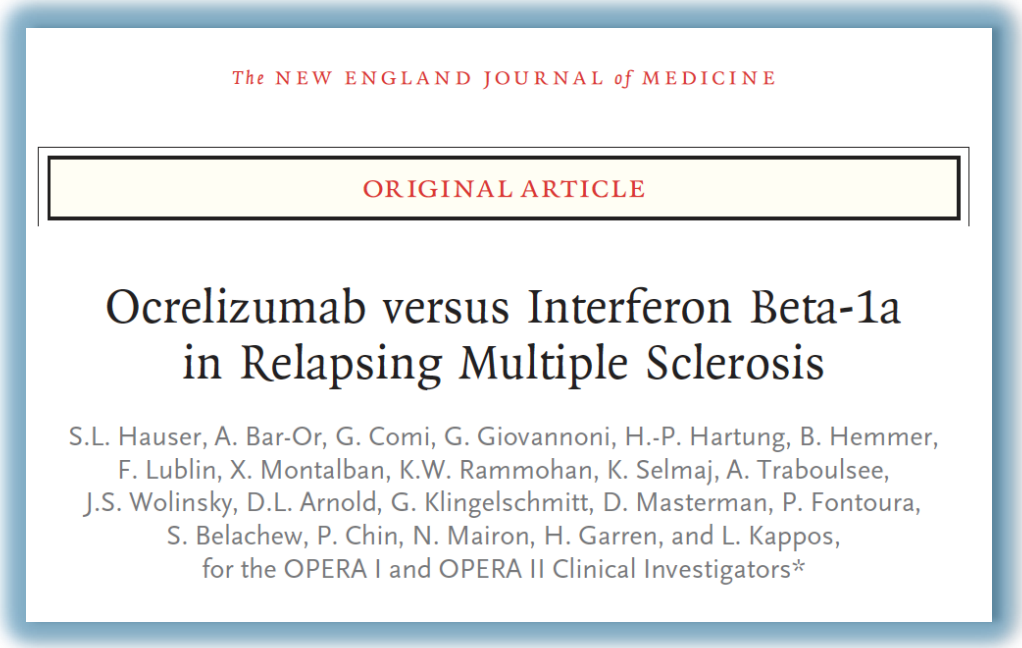


Hauser, S.L. et al. (2017) *New England Journal of Medicine.* ***376***: 221.

Impact of B cell depletion on MS lesions in RRMS patients



Therapeutic Approaches to the Treatment of MS: Targeting B Cells



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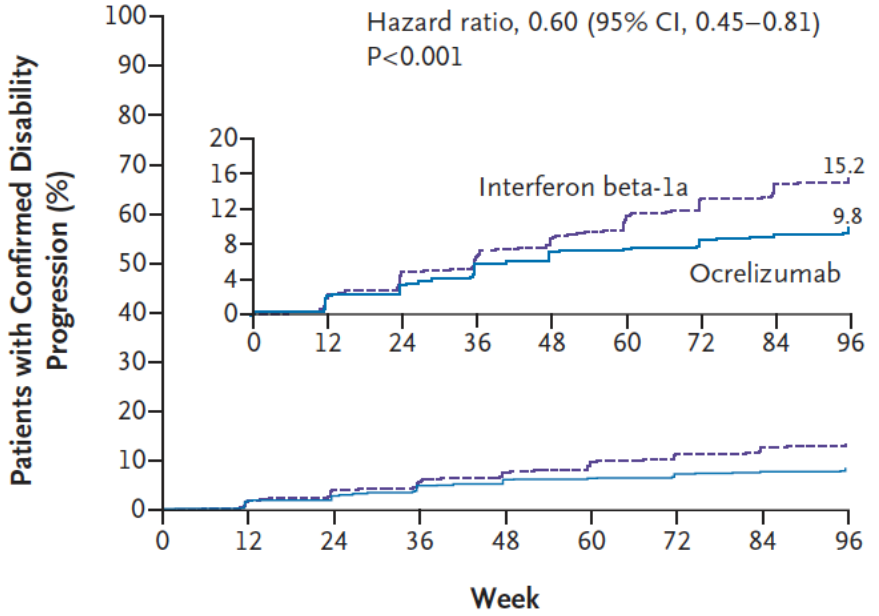
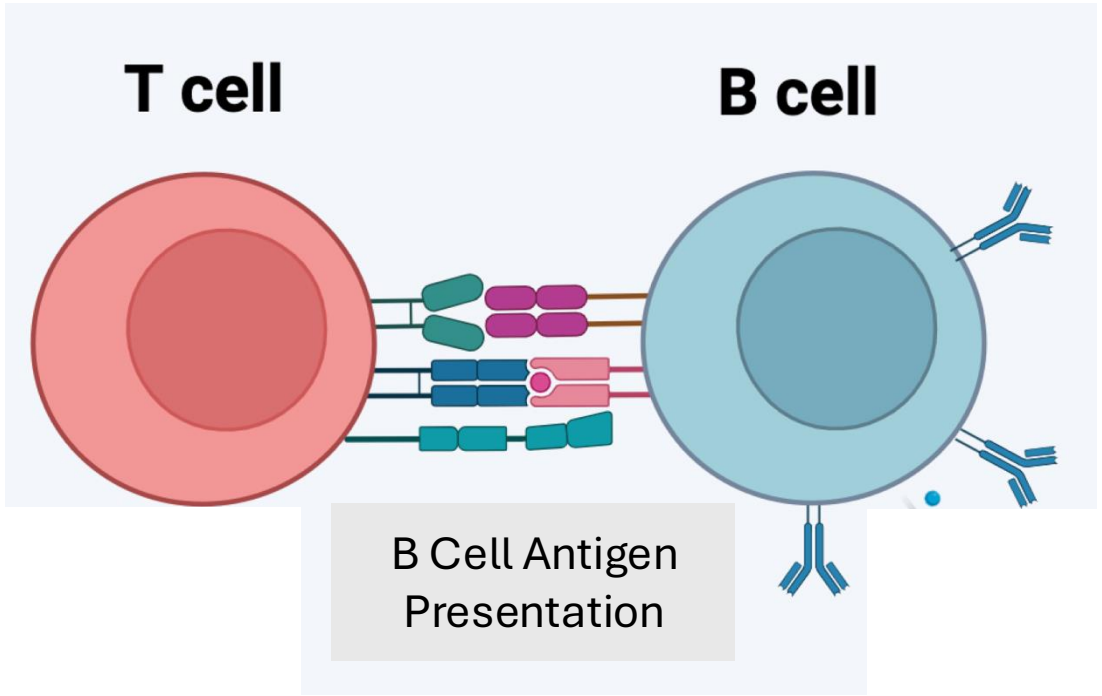
Impact of B cell depletion on disease progression in RRMS patients



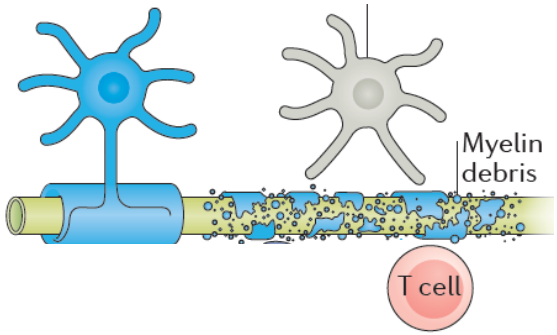
Brutus



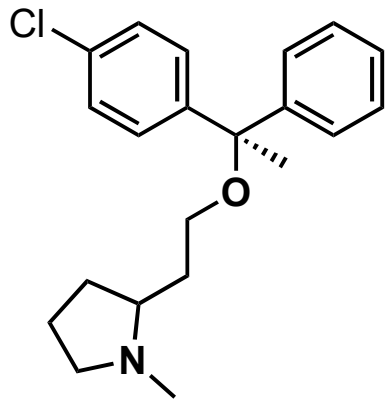
B Cell Antigen Presentation

Cassius

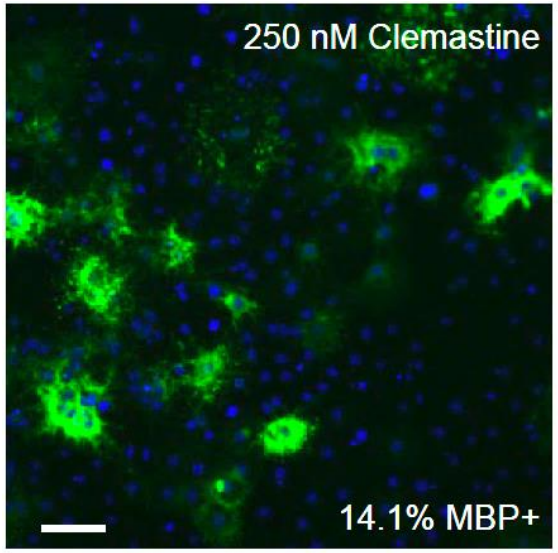
Caesar



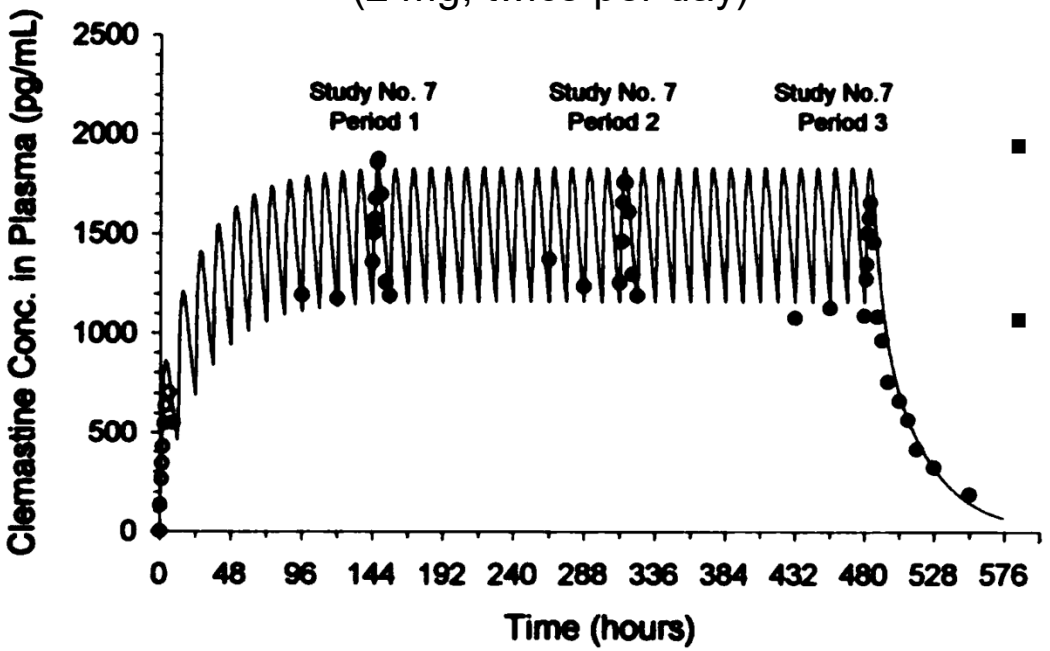
Alternative OPC Differentiation-Inducing M1R Antagonists



Clemastine
OPC EC_{50} = 270 nM



Clemastine Human Pharmacokinetics
(2 mg, twice per day)



- Steady state systemic [clemastine] ~7 nM
- H1R K_i = 0.26 nM

Schran, H.F., et *al*. (1996) *J. Clin. Pharmacol*.

- Clemastine is marketed as an H1R histamine antagonist
- Max tolerated human dose ~10 mg/day (plasma level <20 nM)

Alternative OPC Differentiation-Inducing M1R Antagonists

	0.000	0.003	0.009	0.027	0.082	0.247	0.741	2.222	6.667	20.000
1',6-Dihydrodoxepin (HCl)	8.8	9.1	8.3	9.5	8.3	10.0	12.3	12.4	11.7	1.7
3-Cyanoimipramine; Ro 11-2465	9.2	9.8	9.8	9.7	10.8	10.3	11.1	7.7	4.6	0.0
Acotiamide (2HCl)	9.8	11.1	10.1	14.0	8.4	11.2	9.8	6.8	5.3	2.8
Amitriptyline (HCl)	9.8	11.6	11.7	9.8	10.0	10.4	11.1	9.7	5.3	0.0
Atomoxetine (HCl)	9.2	8.7	7.2	10.6	14.8	14.2	14.2	8.2	6.1	5.0
Atropine	9.8	14.3	9.0	7.6	8.8	7.8	7.6	8.7	10.3	6.8
Benztropine	8.9	9.0	8.0	7.7	9.0	11.2	15.2	16.4	1.3	1.2
Biperiden	9.8	8.7	14.5	19.5	13.1	7.5	9.7	7.0	8.2	9.2
Bromodiphenhydramine (HCl)	8.8	11.5	9.5	10.0	6.5	9.6	9.1	6.8	2.4	0.6
Brompheniramine (maleate)	8.9	10.8	13.0	16.4	13.8	13.2	12.3	10.6	5.2	5.8
Buclizine (HCl)	8.8	9.1	7.4	8.3	8.9	7.8	2.2	0.0	0.6	0.0
Caramiphen (HCl)	9.8	7.3	8.9	9.4	9.2	10.2	14.9	8.5	8.7	1.9
Carbinoxamine (maleate)	8.8	8.7	7.7	7.9	8.2	6.8	6.2	6.6	5.1	2.8
Cetirizine (HCl)	8.9	10.3	10.8	9.6	10.7	8.2	7.8	11.1	8.5	9.7
Chlorcyclizine (HCl)	8.8	8.3	8.1	9.5	8.6	7.8	6.3	3.6	3.9	0.2
Chlorpheniramine (maleate)	8.9	8.2	7.8	10.7	10.0	10.6	6.6	7.0	6.5	2.9
Chlorpromazine (HCl)	9.8	8.4	10.1	8.3	7.5	6.3	6.9	6.4	0.6	0.0
Chlorprothixene (HCl)	9.8	8.3	8.3	7.8	6.6	5.6	6.1	1.7	0.5	0.0
Citalopram (HBr)	9.5	10.5	10.7	14.2	13.1	18.8	16.7	18.9	15.1	8.4
Clemastine	9.5	8.0	10.0	10.3	19.1	23.1	21.7	10.6	0.2	0.1
Clomipramine (HCl)	8.9	8.7	11.2	9.3	10.7	13.2	9.8	2.3	0.6	0.6
Clozapine	9.8	12.8	18.8	14.2	13.6	9.7	8.4	6.0	1.8	0.4
Cyclizine (HCl)	8.8	9.2	14.5	10.9	8.1	7.6	8.4	9.1	6.8	3.5
Cyproheptadine (HCl hydrate)	8.8	8.1	10.5	8.9	8.1	8.0	5.5	3.5	0.5	0.3
Dapoxetine (HCl)	8.8	15.6	14.8	20.1	11.7	10.6	3.3	2.0	0.0	0.0
Darifenacin (HBr)	9.8	10.4	9.8	9.9	14.5	7.4	2.7	4.0	0.9	0.0
Depramine (HCl)	9.2	8.5	7.5	8.5	7.8	8.1	8.1	5.4	3.2	0.4
Desipramine (HCl)	8.9	8.8	9.5	7.6	6.1	8.3	8.6	4.6	2.2	0.0
Desloratadine	8.8	8.6	9.4	9.1	7.6	6.9	5.0	2.0	0.4	0.0
Desmethyl-Cyanoimipramine	9.2	9.7	14.5	11.3	11.5	12.3	11.1	5.1	0.7	0.0
Desmethylcitalopram	9.2	10.6	12.0	14.5	10.3	8.6	12.0	9.5	6.2	1.6
Desoxypipradrol [2-DPMP (HCl)]	8.9	8.2	8.9	8.5	9.5	8.8	8.4	7.0	3.7	0.7
Desvenlafaxine (HCl)	8.8	12.1	16.3	18.8	16.2	17.0	17.3	11.5	6.8	6.4
Dexchlorpheniramine (maleate)	8.8	7.9	8.7	8.3	8.4	8.4	7.3	6.7	4.5	1.1
Diphenhydramine (HCl)	8.9	13.5	13.3	15.2	11.3	13.7	10.6	11.5	10.0	5.7
DL-Trihexyphenidyl (HCl)	9.8	10.3	13.4	12.4	18.9	19.9	18.0	13.5	4.7	0.0
Dosulepin (HCl)	8.9	8.8	9.8	9.2	9.3	9.9	9.1	5.2	1.0	0.0
Dothiepin	9.8	8.5	8.3	6.6	8.2	6.7	7.3	5.2	3.3	0.0
Doxepin (HCl)	9.4	22.9	19.0	14.5	11.9	9.0	9.6	8.7	6.3	5.5
Doxylamine (succinate)	8.8	8.3	8.6	9.4	9.8	9.5	10.3	9.7	8.3	7.5
Duloxetine (HCl)	8.8	9.6	11.9	10.9	7.8	8.3	9.0	1.8	0.7	0.5
Escitalopram (oxalate)	9.5	15.2	15.2	15.1	17.8	21.3	28.1	21.2	16.2	11.6
Flavoxate (HCl)	9.8	12.8	11.8	10.8	11.6	13.2	10.2	10.1	10.4	11.7
Fluoxetine (HCl)	8.9	10.2	10.9	13.5	8.8	6.9	7.1	4.2	0.0	0.0
(L)-Hyoscyamine	9.8	8.5	8.1	8.6	8.7	8.7	7.6	7.9	8.2	5.2
Imipramine	9.8	9.5	22.4	15.5	8.1	8.2	7.7	6.1	5.8	6.6
Ketimipramine	9.2	8.9	9.5	9.2	12.7	12.0	9.9	9.4	7.0	0.6

MBP% 0% 9% 30%

[Drug], μM

	0.000	0.003	0.009	0.027	0.082	0.247	0.741	2.222	6.667	20.000
Levocabastine (HCl)	8.8	7.1	12.1	12.7	10.1	9.3	8.7	7.3	6.3	6.7
Lofepramine	9.8	8.6	8.8	9.9	8.9	7.4	7.3	7.4	6.9	7.9
Loratadine	8.8	7.3	7.4	8.3	7.2	6.4	4.9	2.1	0.9	0.1
Lorcainide (HCl)	9.8	8.5	8.4	6.2	5.0	3.5	4.9	2.4	1.4	2.0
Meclizine (HCl)	8.9	9.6	12.1	12.3	12.0	8.1	8.7	4.2	0.0	0.0
Mepyramine (maleate)	8.9	9.3	9.5	12.0	12.0	11.3	11.8	9.7	9.1	6.0
Milnacipran (HCl)	8.9	9.0	11.1	10.1	9.6	10.5	7.9	10.2	7.4	8.6
N-Desmethylclomipramine (HCl)	8.9	9.3	10.3	8.8	7.4	8.6	8.2	2.1	0.3	0.2
Nefazodone (HCl)	9.2	10.0	10.5	11.0	10.3	10.7	13.5	4.2	1.7	0.5
Nefopam (HCl)	8.8	8.9	8.1	12.0	10.1	8.7	8.1	8.2	5.9	1.7
Neobenodine (HCl)	8.8	8.9	7.2	7.2	6.8	8.8	7.5	7.8	6.3	3.7
Nordoxepin HCL	8.9	9.1	8.0	8.4	10.3	10.3	9.5	5.6	3.1	0.3
Northiaden	9.2	11.8	12.6	12.4	14.8	16.0	11.6	6.3	3.9	0.0
Nortriptyline (HCl)	8.9	8.2	8.3	9.6	9.1	8.2	8.9	3.9	0.4	0.0
Olanzapine	9.8	9.0	19.2	18.8	9.8	8.6	6.2	5.1	7.1	6.9
Olopatadine (HCl)	8.9	9.0	9.5	9.7	9.0	11.5	11.5	10.4	8.7	9.3
Opipramol (2HCl)	8.9	8.4	9.0	8.7	11.2	13.8	13.7	11.7	8.3	0.0
Orphenadrine (HCl)	9.5	19.4	24.5	16.7	13.8	10.8	12.8	10.6	7.8	7.7
Oxybutynin	9.8	11.5	21.1	11.1	9.1	9.0	6.7	6.2	7.9	5.4
N-Desethyl Oxybutynin (HCl)	9.8	11.3	14.4	14.4	15.9	16.5	18.3	17.3	0.6	0.0
(R)-Oxybutynin (HCl)	9.8	9.2	10.7	11.8	12.6	16.8	13.6	12.5	5.7	1.1
(S)-Oxybutynin (HCl)	9.8	8.4	9.5	9.0	13.5	11.4	10.9	5.3	0.8	0.0
Paroxetine (HCl)	9.8	11.5	13.2	11.6	8.8	9.6	5.5	2.9	0.4	0.3
Pheniramine (maleate)	8.8	8.6	8.7	9.9	8.3	9.6	9.4	8.4	10.1	6.1
Phenyltoloxamine (citrate)	8.8	9.2	15.3	10.7	6.9	6.2	7.0	6.4	5.7	2.6
Piperidolate	9.8	10.4	11.8	12.5	15.1	17.0	11.4	11.7	2.8	1.7
Pirenzepine (2HCl)	9.8	8.6	8.8	7.9	7.9	5.1	4.4	5.6	3.1	5.7
PRE-084 (HCl)	8.9	8.7	8.1	8.0	9.3	9.3	10.0	7.5	8.6	6.1
Promethazine (HCl)	9.8	10.3	10.3	13.3	11.5	8.7	6.6	2.6	1.5	0.2
Propiverine	9.8	9.0	12.1	20.7	10.8	8.1	7.5	8.4	8.2	7.4
Protriptyline (HCl)	8.9	9.9	10.6	10.0	10.5	10.9	8.1	4.7	1.2	0.4
Reboxetine (HCl)	8.9	10.5	14.2	11.9	11.2	10.9	10.6	6.4	4.4	1.2
SCH 23390 (HCl)	8.8	7.5	7.9	8.1	9.5	7.4	7.5	7.5	7.3	3.1
Scopolamine (HCl)	9.8	10.1	13.2	11.0	11.1	11.4	12.1	11.6	8.2	7.7
Sertraline (HCl)	8.9	9.8	10.1	12.7	11.0	5.4	3.3	2.3	0.2	0.5
Siltenzepine	9.2	11.2	15.0	12.2	13.4	13.6	13.4	12.1	11.2	12.5
Solifenacin Succinate	9.8	10.8	11.3	11.7	13.4	10.6	10.4	3.8	1.1	0.0
Telenzepine (2HCl)	9.8	8.9	8.2	7.5	8.2	7.9	9.0	11.6	14.3	6.9
Tiagabine (HCl)	8.8	8.1	9.0	8.7	9.5	8.7	7.5	7.6	6.9	4.1
Tolterodine L-tartrate	9.8	11.4	11.3	13.4	7.9	7.9	6.6	4.5	2.1	1.1
Trimipramine (maleate)	8.9	9.1	8.1	7.9	8.7	8.2	5.1	5.3	1.5	0.3
Tropicamide	9.8	10.5	13.7	16.9	14.6	15.5	14.1	11.6	11.1	11.5
Venlafaxine (HCl)	8.8	8.9	8.7	8.2	9.4	10.3	9.3	11.9	10.2	7.4
Vortioxetine (HBr)	8.9	9.6	10.4	12.8	11.7	6.7	3.5	1.7	0.8	0.0
VU 0255035	9.8	10.8	11.2	14.5	12.8	19.1	19.7	0.6	0.0	0.1
Zimelidine (2HCl)	8.8	8.8	9.7	10.3	11.3	10.6	11.1	7.1	6.7	2.4
Zotepine	9.8	8.5	9.1	8.0	7.0	6.2	6.4	6.2	5.6	5.8

MBP% 0% 9% 30%

[Drug], μM

Alternative OPC Differentiation-Inducing M1R Antagonists

1',6-Dihydrodoxepin (HCl)	8.8	9.1	8.3	9.5	8.3	10.0	12.3	12.4	11.7	1.7
3-Cyanoimipramine; Ro 11-2465	9.2	9.8	9.8	9.7	10.8	10.3	11.1	7.7	4.6	0.0
Acotiamide (2HCl)	9.8	11.1	10.1	14.0	8.4	11.2	9.8	6.8	5.3	2.8
Amitriptyline (HCl)	9.8	11.6	11.7	9.8	10.0	10.4	11.1	9.7	5.3	0.0
Atomoxetine (HCl)	9.2	8.7	7.2	10.6	14.8	14.2	14.2	8.2	6.1	5.0
Atropine	9.8	14.3	9.0	7.6	8.8	7.8	7.6	8.7	10.3	6.8
Benztropine	8.9	9.0	8.0	7.7	9.0	11.2	15.2	16.4	1.3	1.2
Biperiden	9.8	8.7	14.5	19.5	13.1	7.5	9.7	7.0	8.2	9.2
Bromodiphenhydramine (HCl)	8.8	11.5	9.5	10.0	6.5	9.6	9.1	6.8	2.4	0.6
Brompheniramine (maleate)	8.9	10.8	13.0	16.4	13.8	13.2	12.3	10.6	5.2	5.8
Buclizine (HCl)	8.8	9.1	7.4	8.3	8.9	7.8	2.2	0.0	0.6	0.0
Caramiphen (HCl)	9.8	7.3	8.9	9.4	9.2	10.2	14.9	8.5	8.7	1.9
Carbinoxamine (maleate)	8.8	8.7	7.7	7.9	8.2	6.8	6.2	6.6	5.1	2.8
Cetirizine (HCl)	8.9	10.3	10.8	9.6	10.7	8.2	7.8	11.1	8.5	9.7
Chlorcyclizine (HCl)	8.8	8.3	8.1	9.5	8.6	7.8	6.3	3.6	3.9	0.2
Chlorpheniramine (maleate)	8.9	8.2	7.8	10.7	10.0	10.6	6.6	7.0	6.5	2.9
Chlorpromazine (HCl)	9.8	8.4	10.1	8.3	7.5	6.3	6.9	6.4	0.6	0.0
Chlorprothixene (HCl)	9.8	8.3	8.3	7.8	6.6	5.6	6.1	1.7	0.5	0.0
Citalopram (HBr)	9.5	10.5	10.7	14.2	13.1	18.8	16.7	18.9	15.1	8.4
Clemastine	9.5	8.0	10.0	10.3	19.1	23.1	21.7	10.6	0.2	0.1
Clomipramine (HCl)	8.9	8.7	11.2	9.3	10.7	13.2	9.8	2.3	0.6	0.6
Clozapine	9.8	12.8	18.8	14.2	13.6	9.7	8.4	6.0	1.8	0.4
Cyclizine (HCl)	8.8	9.2	14.5	10.9	8.1	7.6	8.4	9.1	6.8	3.5
Cyproheptadine (HCl hydrate)	8.8	8.1	10.5	8.9	8.1	8.0	5.5	3.5	0.5	0.3
Dapoxetine (HCl)	8.8	15.6	14.8	20.1	11.7	10.6	3.3	2.0	0.0	0.0
Darifenacin (HBr)	9.8	10.4	9.8	9.9	14.5	7.4	2.7	4.0	0.9	0.0
Depramine (HCl)	9.2	8.5	7.5	8.5	7.8	8.1	8.1	5.4	3.2	0.4
Desipramine (HCl)	8.9	8.8	9.5	7.6	6.1	8.3	8.6	4.6	2.2	0.0
Desloratadine	8.8	8.6	9.4	9.1	7.6	6.9	5.0	2.0	0.4	0.0
Desmethyl-Cyanoimipramine	9.2	9.7	14.5	11.3	11.5	12.3	11.1	5.1	0.7	0.0
Desmethylcitalopram	9.2	10.6	12.0	14.5	10.3	8.6	12.0	9.5	6.2	1.6
Desoxypipradrol [2-DPMP (HCl)]	8.9	8.2	8.9	8.5	9.5	8.8	8.4	7.0	3.7	0.7
Desvenlafaxine (HCl)	8.8	12.1	16.3	18.8	16.2	17.0	17.3	11.5	6.8	6.4
Dexchlorpheniramine (maleate)	8.8	7.9	8.7	8.3	8.4	8.4	7.3	6.7	4.5	1.1
Diphenhydramine (HCl)	8.9	13.5	13.3	15.2	11.3	13.7	10.6	11.5	10.0	5.7
DL-Trihexyphenidyl (HCl)	9.8	10.3	13.4	12.4	18.9	19.9	18.0	13.5	4.7	0.0
Dosulepin (HCl)	8.9	8.8	9.8	9.2	9.3	9.9	9.1	5.2	1.0	0.0
Dothiepin	9.8	8.5	8.3	6.6	8.2	6.7	7.3	5.2	3.3	0.0
Doxepin (HCl)	9.4	22.9	19.0	14.5	11.9	9.0	9.6	8.7	6.3	5.5
Doxylamine (succinate)	8.8	8.3	8.6	9.4	9.8	9.5	10.3	9.7	8.3	7.5
Duloxetine (HCl)	8.8	9.6	11.9	10.9	7.8	8.3	9.0	1.8	0.7	0.5
Escitalopram (oxalate)	9.5	15.2	15.2	15.1	17.8	21.3	28.1	21.2	16.2	11.6
Flavoxate (HCl)	9.8	12.8	11.8	10.8	11.6	13.2	10.2	10.1	10.4	11.7
Fluoxetine (HCl)	8.9	10.2	10.9	13.5	8.8	6.9	7.1	4.2	0.0	0.0
(L)-Hyoscyamine	9.8	8.5	8.1	8.6	8.7	8.7	7.6	7.9	8.2	5.2
Imipramine	9.8	9.5	22.4	15.5	8.1	8.2	7.7	6.1	5.8	6.6
Ketimipramine	9.2	8.9	9.5	9.2	12.7	12.0	9.9	9.4	7.0	0.6
Levocabastine (HCl)	8.8	7.1	12.1	12.7	10.1	9.3	8.7	7.3	6.3	6.7
Lofepramine	9.8	8.6	8.8	9.9	8.9	7.4	7.3	7.4	6.9	7.9
Loratadine	8.8	7.3	7.4	8.3	7.2	6.4	4.9	2.1	0.9	0.1
Lorcainide (HCl)	9.8	8.5	8.4	6.2	5.0	3.5	4.9	2.4	1.4	2.0
Meclizine (HCl)	8.9	9.6	12.1	12.3	12.0	8.1	8.7	4.2	0.0	0.0
Mepyramine (maleate)	8.9	9.3	9.5	12.0	12.0	11.3	11.8	9.7	9.1	6.0
Milnacipran (HCl)	8.9	9.0	11.1	10.1	9.6	10.5	7.9	10.2	7.4	8.6
N-Desmethylclomipramine (HCl)	8.9	9.3	10.3	8.8	7.4	8.6	8.2	2.1	0.3	0.2
Nefazodone (HCl)	9.2	10.0	10.5	11.0	10.3	10.7	13.5	4.2	1.7	0.5
Nefopam (HCl)	8.8	8.9	8.1	12.0	10.1	8.7	8.1	8.2	5.9	1.7
Neobenodine (HCl)	8.8	8.9	7.2	7.2	6.8	8.8	7.5	7.8	6.3	3.7
Nordoxepin HCL	8.9	9.1	8.0	8.4	10.3	10.3	9.5	5.6	3.1	0.3
Northiaden	9.2	11.8	12.6	12.4	14.8	16.0	11.6	6.3	3.9	0.0
Nortriptyline (HCl)	8.9	8.2	8.3	9.6	9.1	8.2	8.9	3.9	0.4	0.0
Olanzapine	9.8	9.0	19.2	18.8	9.8	8.6	6.2	5.1	7.1	6.9
Olopatadine (HCl)	8.9	9.0	9.5	9.7	9.0	11.5	11.5	10.4	8.7	9.3
Opipramol (2HCl)	8.9	8.4	9.0	8.7	11.2	13.8	13.7	11.7	8.3	0.0
Orphenadrine (HCl)	9.5	19.4	24.5	16.7	13.8	10.8	12.8	10.6	7.8	7.7
Oxybutynin	9.8	11.5	21.1	11.1	9.1	9.0	6.7	6.2	7.9	5.4
N-Desethyl Oxybutynin (HCl)	9.8	11.3	14.4	14.4	15.9	16.5	18.3	17.3	0.6	0.0
(R)-Oxybutynin (HCl)	9.8	9.2	10.7	11.8	12.6	16.8	13.6	12.5	5.7	1.1
(S)-Oxybutynin (HCl)	9.8	8.4	9.5	9.0	13.5	11.4	10.9	5.3	0.8	0.0
Paroxetine (HCl)	9.8	11.5	13.2	11.6	8.8	9.6	5.5	2.9	0.4	0.3
Pheniramine (maleate)	8.8	8.6	8.7	9.9	8.3	9.6	9.4	8.4	10.1	6.1
Phenyltoloxamine (citrate)	8.8	9.2	15.3	10.7	6.9	6.2	7.0	6.4	5.7	2.6
Piperidolate	9.8	10.4	11.8	12.5	15.1	17.0	11.4	11.7	2.8	1.7
Pirenzepine (2HCl)	9.8	8.6	8.8	7.9	7.9	5.1	4.4	5.6	3.1	5.7
PRE-084 (HCl)	8.9	8.7	8.1	8.0	9.3	9.3	10.0	7.5	8.6	6.1
Promethazine (HCl)	9.8	10.3	10.3	13.3	11.5	8.7	6.6	2.6	1.5	0.2
Propiverine	9.8	9.0	12.1	20.7	10.8	8.1	7.5	8.4	8.2	7.4
Protriptyline (HCl)	8.9	9.9	10.6	10.0	10.5	10.9	8.1	4.7	1.2	0.4
Reboxetine (HCl)	8.9	10.5	14.2	11.9	11.2	10.9	10.6	6.4	4.4	1.2
SCH 23390 (HCl)	8.8	7.5	7.9	8.1	9.5	7.4	7.5	7.5	7.3	3.1
Scopolamine (HCl)	9.8	10.1	13.2	11.0	11.1	11.4	12.1	11.6	8.2	7.7
Sertraline (HCl)	8.9	9.8	10.1	12.7	11.0	5.4	3.3	2.3	0.2	0.5
Siltenzepine	9.2	11.2	15.0	12.2	13.4	13.6	13.4	12.1	11.2	12.5
Solifenacin Succinate	9.8	10.8	11.3	11.7	13.4	10.6	10.4	3.8	1.1	0.0
Telenzepine (2HCl)	9.8	8.9	8.2	7.5	8.2	7.9	9.0	11.6	14.3	6.9
Tiagabine (HCl)	8.8	8.1	9.0	8.7	9.5	8.7	7.5	7.6	6.9	4.1
Tolterodine L-tartrate	9.8	11.4	11.3	13.4	7.9	7.9	6.6	4.5	2.1	1.1
Trimipramine (maleate)	8.9	9.1	8.1	7.9	8.7	8.2	5.1	5.3	1.5	0.3
Tropicamide	9.8	10.5	13.7	16.9	14.6	15.5	14.1	11.6	11.1	11.5
Venlafaxine (HCl)	8.8	8.9	8.7	8.2	9.4	10.3	9.3	11.9	10.2	7.4
Vortioxetine (HBr)	8.9	9.6	10.4	12.8	11.7	6.7	3.5	1.7	0.8	0.0
VU 0255035	9.8	10.8	11.2	14.5	12.8	19.1	19.7	0.6	0.0	0.1
Zimelidine (2HCl)	8.8	8.8	9.7	10.3	11.3	10.6	11.1	7.1	6.7	2.4
Zotepine	9.8	8.5	9.1	8.0	7.0	6.2	6.4	6.2	5.6	5.8

MBP% 0% 9% 30%

0.000 0.003 0.009 0.027 0.082 0.247 0.741 2.222 6.667 20.000

[Drug], µM