SLOWING PROGRESSIVE MS, REMYELINATION, NEURAL PROTECTION, NEURAL REPAIR

Gavin Giovannoni MBBCh, PhD, FCP, FRCP, FRCPath
Blizard Institute
Barts and The London School of Medicine and Dentistry
Queen Mary University of London
London, UNITED KINGDOM

g.giovannoni@qmul.ac.uk

Objectives

After this lecture you will have an understanding of:

1. Current dogma concerning the pathogenesis of progressive multiple sclerosis and the key pathological processes responsible for the progressive phases of the disease
2. Key therapeutic targets
3. The MS therapeutic pyramid and the rationale for combination therapies in MS
4. Current neuroprotective and remyelination therapy targets and trials
5. Alternative hypotheses, in particular the premature ageing and viral theories

Background

Although multiple sclerosis (MS) typically begins with a relapsing course, over the lifetime of an individual, MS is dominated by the progressive phase of the disease. There is considerable overlap between the relapsing and progressive phases of the disease with a significant number of patients in the secondary progressive phase having relapses (Cohen et al. 2002). A minority of people present with a primary progressive course from the outset (PPMS). Despite presenting without relapses at onset ~5% of people with PPMS go onto have superimposed relapses (Wolinsky et al. 2007). Against the backdrop of such substantial overlap between clinically described disease phases and/or MS phenotypes MS-related disability is driven by three separate, but related, pathological phenomenon, which are: 1) inflammation, which can be acute and focal in new lesions/plaques, with accompanying demyelination, or more chronic and diffuse affecting lesions as well as non-lesional tissue; 2) acute neuro-axonal damage, be it directly due to inflammation or as a result of other processes (Ferguson 1997; Trapp et al. 1998); and 3) delayed neuroaxonal loss, or neurodegeneration, of chronically demyelinated or vulnerable neuroaxonal tracts.

Progressive disease as characterized by worsening disability, independent of relapses, is intricately driven by the focal and diffuse inflammation and delayed neuroaxonal loss (pathological processes 1 & 3 above). Limited methodological approaches have been explored in clinical trials to disentangle these two related drivers of progression. At present there are a limited number of options to modify progressive MS; the current therapies only have an impact on clinically defined progression if there is evidence of ongoing relapses or focal MRI activity (Hawker et al. 2009; Montalban et al. 2017). Therefore, a significant unmet need persists for people with progressive MS, i.e. treatments targeting the delayed neurodegenerative component of the disease.

The definition of progressive MS disease has remained largely a clinical one based on the qualitative observation of “steadily increasing objectively documented neurologic dysfunction/disability without unequivocal recovery”. There is currently no consensus metric to identify and quantify progressive disease (Jacques and Lublin 2015). Evidence suggests the pathological substrates underlying progressive MS are chronic, widespread, inflammation, microglia activation (Frischer et al. 2009), demyelination, gliosis, and

particularly neuroaxonal loss (Frischer et al. 2009; Lassmann et al. 2012). However, all these processes can be detected from disease onset when disease progression is not clinically apparent. MRI studies indicate progressive brain volume loss, or accelerated brain atrophy, from disease onset and occurs on average at a similar rates in the early, and the late, stages of the disease (De Stefano et al. 2010). Other studies have shown that progressive brain atrophy can even be observed in people with radiologically-isolated syndromes (RIS), or pre-symptomatic MS (Amato et al. 2012; Rojas et al. 2014). These observations underpin the impression that there is no sudden transition, or switch, between the relapsing and progressive phases of the disease. Rather, there is interplay over months and years of pathological processes leading to what we observe as “chronic disease progression”. In reality this transition occurs over a period or months to years and is commonly recognised retrospectively (Kremenchutzky et al. 2006). These observations imply that we need to target progressive MS from the outset.

Clinical observations suggest that neuronal domains with longer central axonal projections are more likely to be involved early in the clinically apparent progressive phase of the disease, for example the bladder and corticospinal, or pyramidal, projections to the lower limbs (Kremenchutzky et al. 2006). Involvement of these domains early in the course of the disease predict a poorer outcome (Simone et al. 2002). If the distribution of MS lesions occurred randomly the functional subdomains, subserved by longer axons, are more likely to accumulate the greatest number of focal inflammatory lesions and hence be at the vanguard of the clinically-apparent progressive phase of the disease (Kremenchutzky et al. 2006). What protects neuronal domains from clinically progressive disease may be reserve capacity, i.e. the ability to compensate for neuroaxonal loss and the capacity for repair (Schwartz et al. 2013). A corollary is the shorter the neuronal pathway the less likely it is to have accumulated sufficient focal lesions and axonal loss to exhaust its reserve capacity. This might explain why the upper limb and brain stem motor function, and the visual system appear to be rarely involved initially in clinically-apparent progressive disease. The exception to the latter being progressive visual failure in women carriers of Leber’s hereditary optic neuropathy (LHON) who have a clinical phenotype that is indistinguishable from MS (Harding et al. 1992). The latter condition though is arguably not MS, but a separate disease that mimics MS. The progressive visual failure that occurs in carriers of the mitochondrial DNA mutations which cause LHON hints at mitochondria, and energetics, as playing a major role in delayed axonal loss and underpins the therapeutic strategy of using high-dose biotin to improve neurological function in advanced MS (Peyro Saint Paul et al. 2016; Sedel et al. 2015a; Tourbah et al. 2016) . This length-dependent central axonopathy hypothesis to explain progressive MS is not novel and has been proposed before (Garbern et al. 2002; Herndon 2002) and has been described in Pelizaeus-Merzbacher disease, a central demyelinating syndrome in which patients lack the major CNS myelin protein, proteolipid protein 1 (Garbern et al. 2002).

These and other observations make a strong case of targeting multiple pathological processes synchronously in multiple sclerosis, i.e. by using (1) anti-inflammatory agents to control, or switch-off, focal autoimmune inflammation (adaptive immunity) and to target secondary or delayed glial activation (innate immunity), (2) neuroprotective agents to protect vulnerable damage axons both as part of acute and delayed inflammation, (3) remyelinating agents to promote remyelination and restore conduction and finally (4) to restore or enhance recovery (neuroreparation).

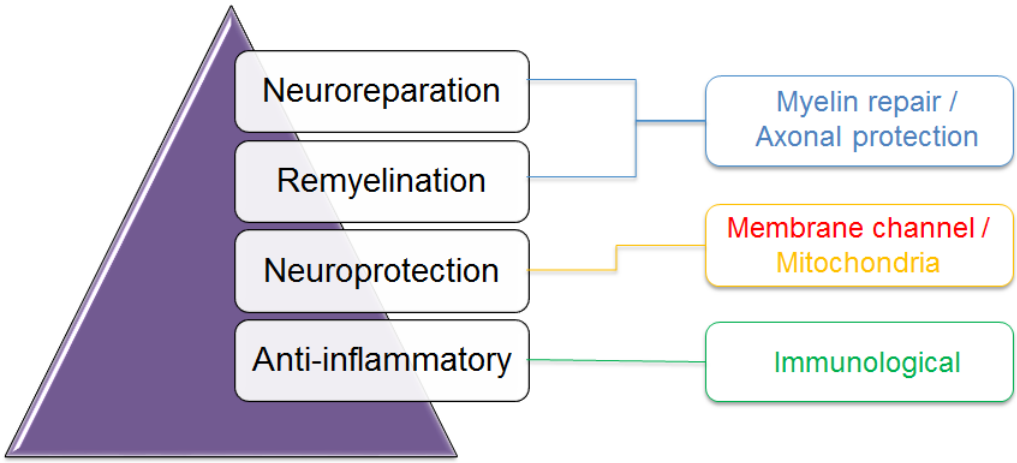

Figure 1: The therapeutic pyramid in multiple sclerosis supporting the concept of combination therapies. There is little point in using neuroprotection strategies unless this is in combination with anti-inflammatory platform to switch off autoimmune driven focal inflammation that is the main driver or both acute and chronic, or delayed, neuroaxonal loss. Similarly, remyelination strategies will only work if there is preservation of axons that target of remyelination. Similarly, what is the point of promoting remyelination if the initial autoimmune drive inflammatory events are not suppressed? The newly formed myelin may simply become a target for further rounds of inflammatory attack. The therapeutic pyramid therefore provides a conceptual framework for designing and testing combination therapy strategies in MS.

Neuroprotection

Evidence suggests that functional domains of the brain and spinal cord have reserve capacity. Functional domain can sometimes compensate for a substantial degree of neuro-axonal loss before progressive disease becomes clinically apparent (G. Giovannoni 2011; Schwartz et al. 2013). Functional reserve, and partial or complete recovery from focal lesions, both contribute to complexity, and difficulty, in reliably detecting and monitoring disease progression early in the course of the disease. A widely accepted theory suggests axons that have survived and attack of focal inflammatory demyelination may become vulnerable and degenerate overtime. The proposed mechanisms underlying such delayed axonal degeneration include excitotoxicity, functional energy deficits, persistent demyelination, delayed axonal transport, age-related neurodegeneration (Paz Soldán et al. 2015), ongoing focal inflammation that may occur proximal or distal to previous MS lesions and diffuse innate inflammation (Rao, Guy, and Sheffield 1981; Friese, Schattling, and Fugger 2014; Campbell, Worrall, and Mahad 2014). It is clear that based on these insight neuroprotective strategies are needed both acutely, in actively inflammed lesions, and chronically to target delayed, secondary, neurodegeneration. Similarly, neuroprotection is indicated in all stages of the disease to try and delay, and prevent, neuroaxonal loss to maintain reserve capacity. Putative neuroprotective therapies that are currently being assessed in MS include sodium channel blockers (phenytoin, lamotrigine, riluzole, oxcarbazepine) (Raftopoulos et al. 2016; Gnanapavan et al. 2013; Kalkers et al. 2004; Lidster et al. 2013), acid-sensing ion channel 1 (ASIC1) blockers (amiloride) (Arun et al. 2013), selective serotonin reuptake inhibitors (SSRIs) fluoxetine (Arun et al. 2013; Vesterinen et al. 2015), phosphodiesterase inhibitors (Ibudilast) (Vesterinen et al. 2015), microglial inhibitors (laquinimod, minocycline) (Vesterinen et al. 2015; Mishra et al. 2014) and drugs targeting mitochondrial function (biotin, idebenone, MitoQ) (Shirani, Okuda, and Stüve 2016; Sedel et al. 2015b; Mao et al. 2013).

Remyelination

Advancements in our understanding of the molecular mechanisms regulating myelination and remyelination have lead to the identification of several putative remyelination therapies that are currently in preclinical and/or early clinical development. In parallel, MRI and PET imaging techniques and evoked potentials are being used to assess whether or not remyelination strategies are feasible in vivo. The most advanced remyelination

therapy targets LINGO-1 (Pepinsky et al. 2014); LINGO-1 interacts with the Nogo receptor to inhibit myelination. It is selectively expressed in the CNS on both oligodendrocytes and neurons and negatively regulates oligodendrocyte differentiation and myelination, neuronal survival and axonal regeneration by activating ras homolog gene family member A (RhoA) and inhibiting protein kinase B (Akt) phosphorylation signalling pathways. LINGO-1 expression is increased in oligodendrocyte progenitor cells in post-mortem demyelinated white matter MS lesions. Across several animal models LINGO-1 inhibition has been shown to promote neuron and oligodendrocyte survival, axon regeneration, oligodendrocyte differentiation, remyelination and functional recovery (Mi, Pepinsky, and Cadavid 2013). The inhibition of LINGO-1 therefore presents a novel therapeutic approach for the treatment of MS. In a randomized, double-blind, placebo-controlled study (RENEW - NCT01721161) subjects with a first episode of unilateral acute optic neuritis treated with anti-LINGO-1 showed improved optic nerve conduction latency at Week 24 in the per protocol analysis, which is consistent with remyelination following a first episode of acute optic neuritis (Cadavid et al. 2015). In addition to anti-LINGO-1, RXR (retinoid X receptor) agonists (baroxetine, IRX4204) (G. Giovannoni 2011; Schwartz et al. 2013; Huang et al. 2011), muscarinic antagonists (benztropine) (Deshmukh et al. 2013), anti-histamine H3 antagonists (GSK239512, clemastine) (Giesser 2016) and anti-SEMA-4D (VX15) (Leonard et al. 2015) and biotin (Sedel et al. 2015b).

Neurorestoration

Up until quite recently most people would have described treatment to restore function in multiple sclerosis as being science fiction. However, it is quite clear that a significant proportion of patients with active MS treated with highly-active DMTs actually see improvements in disability that are not necessarily limited to one functional domain (Burt et al. 2015; Jones et al. 2010; Kalincik et al. 2017; Fox et al. 2016; Wickström, Nyström, and Svenningsson 2013; Florio and Maniscalco 2011; Lublin et al. 2014). Whether these improvements are due to functional plasticity or true neurorestoration is a moot point. Some investigators' suggest, for example in the case of alemtuzumab (Jones et al. 2010) that specific changes to immune system occur that increase production of brain-derived neurotrophic factor, platelet derived growth factor and ciliary neurotrophic factor , which are responsible for neurorestoration. A new therapeutic target in MS is repulsive guidance molecule A (RGMa) an inhibitor of neuronal regeneration and a regulator of cell death (Demicheva et al. 2015). In autopsy material from progressive MS patients, RGMa is found in active and chronic lesions, as well as in normal-appearing gray and white matter, and is expressed by cellular meningeal infiltrates (Demicheva et al. 2015). In animal models of MS, anti-RGMa antibody stimulated regeneration and remyelination of damaged nerve fibers, accelerated functional recovery, and protected the retinal nerve fiber layer as measured by clinically relevant optic coherence tomography (Demicheva et al. 2015).

Alternative Hypotheses

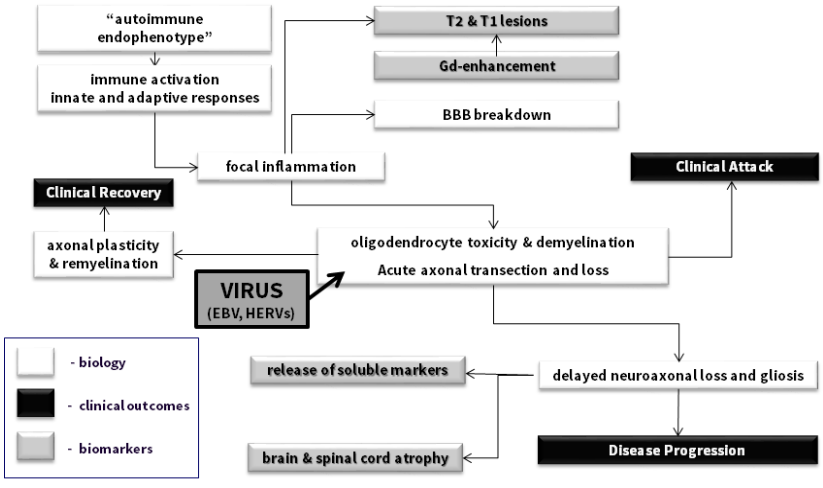

Figure 2 : The current dogma underpinning the immunopathogenesis of multiple sclerosis.

Viruses: The working hypothesis is that MS is complex disease due the interaction of genetic and environmental factors that establishes a latent autoimmune state. Some factor, possibly local or systemic, activates the immune system that results in a focal inflammatory lesion that sets up a cascade that is responsible for the clinical course of multiple sclerosis. An alternative hypothesis, the viral hypothesis, is that the primary event is damage (necrosis or apoptosis) of the oligodendrocyte due to direct viral infection, which secondarily triggers a focal inflammatory reaction. The intensity and anatomical location of the focal inflammatory lesions is responsible for the MS clinical phenotype. Against this hypothesis has been the failure to consistently find evidence of a specific virus in the brains of people with MS. Despite lack of firm pathological evidence of a viral infection epidemiological observations suggest that EBV is strongly associated with MS, which many argue is causal (G. Giovannoni 2011). As EBV resides in B-cells some commentators suggest that B-cell depleting agents, such as rituximab (Hauser et al. 2008a), ocrelizumab (Hauser et al. 2008b; Kappos et al. 2011; Montalban et al. 2017; Hauser et al. 2017) and ofatumumab (Hauser et al. 2008a; Kappos et al. 2011; Sorensen et al. 2014), may be working as anti-EBV agents. Other hypothesise that MS is due to a deficiency of anti-EBV cytotoxic T lymphocytes (CTLs) and MS is due to poorly controlled CNS infection with EBV (M. P. Pender et al. 2009) and are exploring adoptive transfer studies of anti-EBV CTLs (Michael P. Pender et al. 2014).

Similarly, there an association with transactivation of human endogenous retroviruses (HERVs) and MS; whether this is simply an association secondary to inflammation or causal is speculative. Activation of HERV families (HERV-H/F and HERV-W or MS-associated retrovirus) have been reported in cells from the peripheral blood and in the central nervous system of people with MS (Christensen 2016; van Horssen et al. 2016). In particular envelope genes and their gene products (Envs) are associated with MS (Perron and Lang 2010); MSRV-Env, a HERV protein, is expressed in MS lesions and has been shown to be pro-inflammatory and to inhibit oligodendrocyte precursor cell differentiation. Based on these observations GNbAC1, a humanized monoclonal antibody targeting MSRV-Env, is currently being investigated as a DMT in MS (Perron and Lang 2010; Derfuss et al. 2015).

Two epidemiological studies suggest that the rate of developing MS in people with HIV, relative to those without HIV, is reduced. Whether this observation is due to diagnostic or ascertainment bias, immunological effects of HIV or the effect of treatment with highly-active antiretrovirals (HAART) is unknown. This has prompted some investigators to suggest HERV-directed antiretrovirals as a potential novel therapeutic approach to treating MS.

Premature ageing: A fact of life is that as we get older our nervous systems degenerate. If we live long enough we will all develop age-related neurological problems, these include unsteadiness of gait, loss of memory, reduced vision, loss of hearing and poor coordination to highlight a few problems.

What protects people with MS from becoming disabled and developing age-related neurodegeneration are brain and cognitive reserve. Brain reserve is simply the size of your brain or the number of nerve cells you have. Cognitive reserve in comparison relates to how well these nerves function and is associated with your level of education and how well you enrich your lives by using your brain. From about 35 years of age our brains start to shrink. In MS this brain shrinkage is in general much greater than normal. The reduction in brain and cognitive reserve that occurs in MS almost certainly primes the nervous system to age earlier in people with MS. This is one of the reasons why people with MS continue to worsen, or develop worsening disability later on the course of their disease. This insight is one of the main reasons why I promote early effective treatment of MS to protect, and maintain, brain and cognitive reserve (Gavin Giovannoni et al., n.d.). This is why there is such a current focus on the holistic management of MS with a focus on actively treating comorbidities and optimizing lifestyle factors to maximise brain health. Figure 3 summarises some of the factors that are important targeting all of these factors.

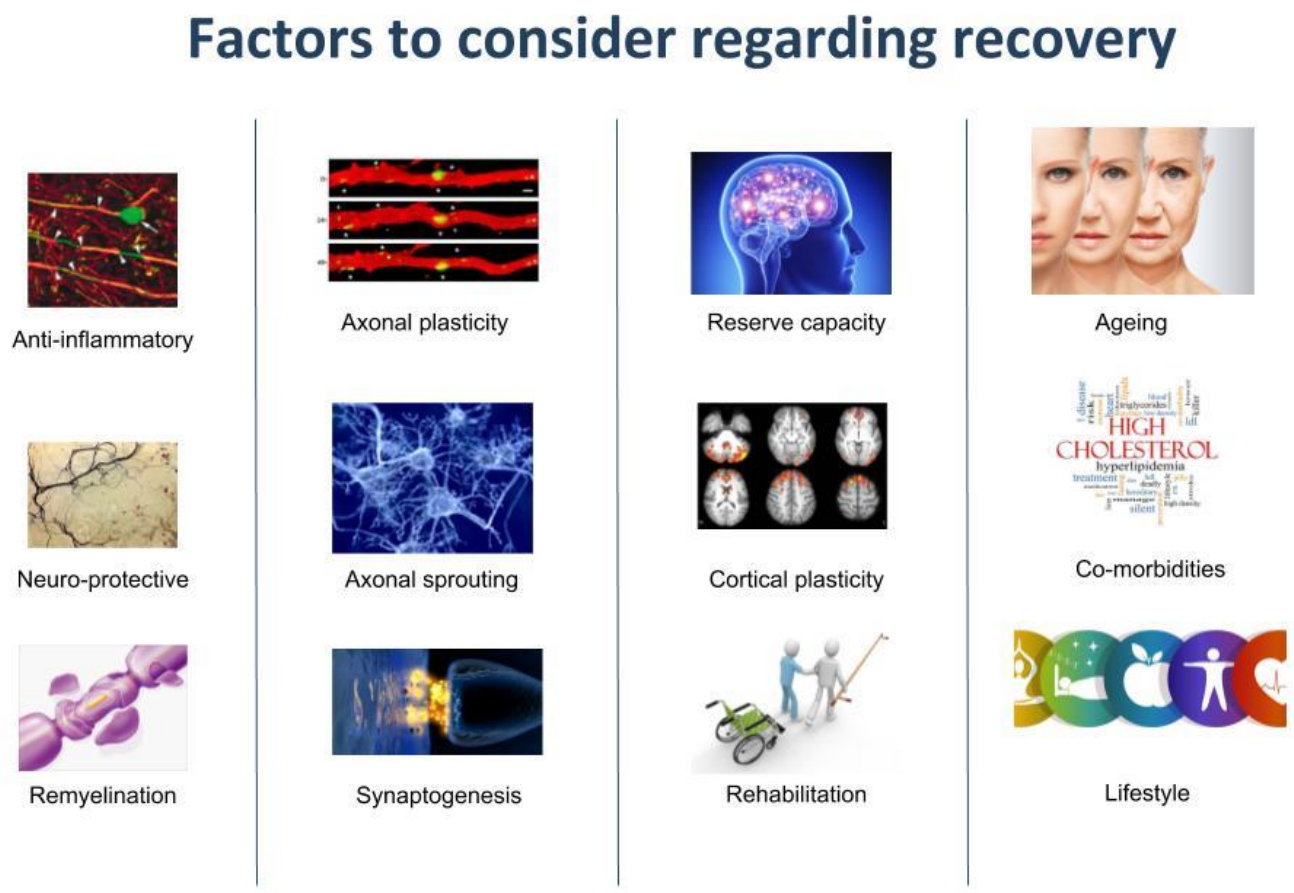

Figure 3 : Factors to consider when targeting restoration of function in multiple sclerosis; many of the treatment targets are not MS specific and include comorbidities and lifestyle factors.

Conclusions

In conclusion our understanding of MS within the current pathogenic dogma suggests we need to a multi-layered approach to target the pathogenic processes that underpin progressive MS. This includes anti-inflammatory therapies targeting both adaptive and innate immune mechanisms, neuroprotective therapies and remyelination strategies. Finally, the aim of neuroreparation would be restore lost function. At present we are aware of improvements in disability that is likely to occur endogenously from mechanism related to axonal and cortical/synaptic plasticity. Whether these mechanisms can be enhanced by physical and pharmacological interventions remains an area of active research. Finally, the sceptics in the field remain open to the possibility that MS may not an autoimmune disease and is rather caused by an exogenous agent, for example a virus. On way of proving, or disproving, the viral hypothesis is through well-designed clinical trials.

References

Amato, M. P., B. Hakiki, B. Goretti, F. Rossi, M. L. Stromillo, A. Giorgio, M. Roscio, et al. 2012. “Association of MRI Metrics and Cognitive Impairment in Radiologically Isolated Syndromes.” *Neurology* 78 (5): 309–14.

Arun, Tarunya, Valentina Tomassini, Emilia Sbardella, Michiel B. de Ruiter, Lucy Matthews, Maria Isabel Leite, Rose Gelineau-Morel, et al. 2013. “Targeting ASIC1 in Primary Progressive Multiple Sclerosis: Evidence of Neuroprotection with Amiloride.” *Brain: A Journal of Neurology* 136 (Pt 1): 106–15.

Burt, Richard K., Roumen Balabanov, Xiaoqiang Han, Basil Sharrack, Amy Morgan, Kathleeen Quigley, Kim Yaung, et al. 2015. “Association of Nonmyeloablative Hematopoietic Stem Cell Transplantation with Neurological Disability in Patients with Relapsing-Remitting Multiple Sclerosis.” *JAMA: The Journal of the American Medical Association* 313 (3): 275–84.

Cadavid, Diego, Laura Balcer, Steven Galetta, Orhan Aktas, Tjalf Ziemssen, Ludo Vanopdenbosch, Helmut Butzkueven, et al. 2015. “Efficacy Analysis of the Anti-LINGO-1 Monoclonal Antibody BIIB033 in Acute Optic Neuritis: The RENEW Trial (P7.202).” *Neurology* 84 (14 Supplement). http://www.neurology.org/content/84/14_Supplement/P7.202.abstract.

Campbell, Graham R., Joseph T. Worrall, and Don J. Mahad. 2014. “The Central Role of Mitochondria in Axonal Degeneration in Multiple Sclerosis.” *Multiple Sclerosis* 20 (14): 1806–13.

Christensen, Tove. 2016. “Human Endogenous Retroviruses in Neurologic Disease.” *APMIS: Acta Pathologica, Microbiologica, et Immunologica Scandinavica* 124 (1-2): 116–26.

Cohen, J. A., G. R. Cutter, J. S. Fischer, A. D. Goodman, F. R. Heidenreich, M. F. Kooijmans, A. W. Sandrock, et al. 2002. “Benefit of Interferon Beta-1a on MSFC Progression in Secondary Progressive MS.” *Neurology* 59 (5): 679–87.

Demicheva, Elena, Yi-Fang Cui, Philip Bardwell, Stefan Barghorn, Martina Kron, Axel H. Meyer, Martin Schmidt, et al. 2015. “Targeting Repulsive Guidance Molecule A to Promote Regeneration and Neuroprotection in Multiple Sclerosis.” *Cell Reports* 10 (11): 1887–98.

Derfuss, Tobias, François Curtin, Claudia Guebelin, Claire Bridel, Maria Rasenack, Alain Matthey, Renaud Du Pasquier, et al. 2015. “A Phase IIa Randomised Clinical Study of GNbAC1, a Humanised Monoclonal Antibody against the Envelope Protein of Multiple Sclerosis-Associated Endogenous Retrovirus in Multiple Sclerosis Patients.” *Multiple Sclerosis* 21 (7): 885–93.

Deshmukh, Vishal A., Virginie Tardif, Costas A. Lyssiotis, Chelsea C. Green, Bilal Kerman, Hyung Joon Kim, Krishnan Padmanabhan, et al. 2013. “A Regenerative Approach to the Treatment of Multiple Sclerosis.” *Nature* 502 (7471): 327–32.

De Stefano, N., A. Giorgio, M. Battaglini, M. Rovaris, M. P. Sormani, F. Barkhof, T. Korteweg, et al. 2010. “Assessing Brain Atrophy Rates in a Large Population of Untreated Multiple Sclerosis Subtypes.” *Neurology* 74 (23): 1868–76.

Ferguson, B. 1997. “Axonal Damage in Acute Multiple Sclerosis Lesions.” *Brain: A Journal of Neurology* 120 (3): 393–99.

Florio, Ciro, and Giorgia Teresa Maniscalco. 2011. “Improvement of Visual Acuity in Patients with Severe Visual Loss Affected by Multiple Sclerosis Treated with Natalizumab: A Case Report.” *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 31 Suppl 3 (January): 325–27.

Fox, Edward J., Daniel Wynn, Alasdair J. Coles, Jeffrey Palmer, David H. Margolin, and CAMMS223 Investigators. 2016. “Alemtuzumab Improves Neurological Functional Systems in Treatment-Naive Relapsing-Remitting Multiple Sclerosis Patients.” *Journal of the Neurological Sciences* 363 (April): 188–94.

Friese, Manuel A., Benjamin Schattling, and Lars Fugger. 2014. “Mechanisms of Neurodegeneration and Axonal Dysfunction in Multiple Sclerosis.” *Nature Reviews. Neurology* 10 (4): 225–38.

Frischer, Josa M., Stephan Bramow, Assunta Dal-Bianco, Claudia F. Lucchinetti, Helmut Rauschka, Manfred Schmidbauer, Henning Laursen, Per Soelberg Sorensen, and Hans Lassmann. 2009. “The Relation between Inflammation and Neurodegeneration in Multiple Sclerosis Brains.” *Brain: A Journal of Neurology* 132 (Pt 5): 1175–89.

Garbern, James Y., Donald A. Yool, Gregory J. Moore, Ian B. Wilds, Michael W. Faulk, Matthias Klugmann, Klaus-Amin Nave, et al. 2002. “Patients Lacking the Major CNS Myelin Protein, Proteolipid Protein 1, Develop Length-Dependent Axonal Degeneration in the Absence of Demyelination and Inflammation.” *Brain: A Journal of Neurology* 125 (Pt 3): 551–61.

Giesser, Barbara S. 2016. *Primer on Multiple Sclerosis*. Oxford University Press.

Giovannoni, G. 2011. “Epstein-Barr Virus and MS.” *International MS Journal / MS Forum* 17 (2): 44–49.

Giovannoni, Gavin, Helmut Butzkueven, Suhayl Dhib-Jalbut, Jeremy Hobart, Gisela Kobelt, George Pepper, Maria Pia Sormani, Christoph Thalheim, Anthony Traboulsee, and Timothy Vollmer10. n.d. “Time Matters in Multiple Sclerosis--International Consensus Recommendations on Diagnosis, Management and Access to Treatment.” http://www.msbrainhealth.org/ECTRIMSposter.

Gnanapavan, Sharmilee, Donna Grant, Steve Morant, Julian Furby, Tom Hayton, Charlotte E. Teunissen, Valerio Leoni, et al. 2013. “Biomarker Report from the Phase II Lamotrigine Trial in Secondary Progressive MS - Neurofilament as a Surrogate of Disease Progression.” *PloS One* 8 (8): e70019.

Harding, A. E., M. G. Sweeney, D. H. Miller, C. J. Mumford, H. Kellar-Wood, D. Menard, W. I. McDonald, and D. A. Compston. 1992. “Occurrence of a Multiple Sclerosis-like Illness in Women Who Have a Leber’s Hereditary Optic Neuropathy Mitochondrial DNA Mutation.” *Brain: A Journal of Neurology* 115 (Pt 4) (August): 979–89.

Hauser, Stephen L., Amit Bar-Or, Giancarlo Comi, Gavin Giovannoni, Hans-Peter Hartung, Bernhard Hemmer, Fred Lublin, et al. 2017. “Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis.” *The New England Journal of Medicine* 376 (3): 221–34.

Hauser, Stephen L., Emmanuelle Waubant, Douglas L. Arnold, Timothy Vollmer, Jack Antel, Robert J. Fox, Amit Bar-Or, et al. 2008a. “B-Cell Depletion with Rituximab in Relapsing-Remitting Multiple Sclerosis.” *The New England Journal of Medicine* 358 (7): 676–88.

———. 2008b. “B-Cell Depletion with Rituximab in Relapsing-Remitting Multiple Sclerosis.” *The New England Journal of Medicine* 358 (7): 676–88.

Hawker, Kathleen, Paul O’Connor, Mark S. Freedman, Peter A. Calabresi, Jack Antel, Jack Simon, Stephen Hauser, et al. 2009. “Rituximab in Patients with Primary Progressive Multiple Sclerosis: Results of a Randomized Double-Blind Placebo-Controlled Multicenter Trial.” *Annals of Neurology* 66 (4): 460–71.

Herndon, Robert M. 2002. “Multiple Sclerosis: The Search for the Cause.” *International Journal of MS Care* 4 (1): 8–9.

Horssen, Jack van, Susanne van der Pol, Philip Nijland, Sandra Amor, and Hervé Perron. 2016. “Human Endogenous Retrovirus W in Brain Lesions: Rationale for Targeted Therapy in Multiple Sclerosis.” *Multiple Sclerosis and Related Disorders* 8 (July): 11–18.

Huang, Jeffrey K., Andrew A. Jarjour, Brahim Nait Oumesmar, Christophe Kerninon, Anna Williams, Wojciech Krezel, Hiroyuki Kagechika, et al. 2011. “Retinoid X Receptor Gamma Signaling Accelerates CNS Remyelination.” *Nature Neuroscience* 14 (1): 45–53.

Jacques, F. H., and F. D. Lublin. 2015. “Defining the Clinical Course of Multiple Sclerosis: The 2013 Revisions.” *Neurology* 84 (9): 963–963.

Jones, Joanne L., Jane M. Anderson, Chia-Ling Phuah, Edward J. Fox, Krzysztof Selmaj, David Margolin, Stephen L. Lake, et al. 2010. “Improvement in Disability after Alemtuzumab Treatment of Multiple Sclerosis Is Associated with Neuroprotective Autoimmunity.” *Brain: A Journal of Neurology* 133 (Pt 8): 2232–47.

Kalincik, Tomas, J. William L. Brown, Neil Robertson, Mark Willis, Neil Scolding, Claire M. Rice, Alastair Wilkins, et al. 2017. “Treatment Effectiveness of Alemtuzumab Compared with Natalizumab, Fingolimod, and Interferon Beta in Relapsing-Remitting Multiple Sclerosis: A Cohort Study.” *Lancet Neurology*, February. doi:10.1016/S1474-4422(17)30007-8.

Kalkers, N., F. Barkhof, L. Bergers, R. Van Schijndel, and C. Polman. 2004. “Neuroprotective Treatment in Primary Progressive Multiple Sclerosis: A Phase I/II Study with Riluzole.” In *Early Indicators Early Treatments Neuroprotection in Multiple Sclerosis*, 41–47.

Kappos, Ludwig, David Li, Peter A. Calabresi, Paul O’Connor, Amit Bar-Or, Frederik Barkhof, Ming Yin, et al. 2011. “Ocrelizumab in Relapsing-Remitting Multiple Sclerosis: A Phase 2, Randomised, Placebo-Controlled, Multicentre Trial.” *The Lancet* 378 (9805): 1779–87.

Kremenchutzky, M., G. P. A. Rice, J. Baskerville, D. M. Wingerchuk, and G. C. Ebers. 2006. “The Natural History of Multiple Sclerosis: A Geographically Based Study 9: Observations on the Progressive Phase of the Disease.” *Brain: A Journal of Neurology* 129 (Pt 3): 584–94.

Lassmann, Hans, Lassmann Hans, Jack van Horssen, and Mahad Don. 2012. “Progressive Multiple Sclerosis: Pathology and Pathogenesis.” *Nature Reviews. Neurology* 8 (11): 647–56.

Leonard, John E., Terrence L. Fisher, Laurie A. Winter, Chad A. Cornelius, Christine Reilly, Ernest S. Smith, and Maurice Zauderer. 2015. “Nonclinical Safety Evaluation of VX15/2503, a Humanized IgG4 Anti-SEMA4D Antibody.” *Molecular Cancer Therapeutics* 14 (4): 964–72.

Lidster, Katie, Samuel J. Jackson, Zubair Ahmed, Peter Munro, Pete Coffey, Gavin Giovannoni, Mark D. Baker, and David Baker. 2013. “Neuroprotection in a Novel Mouse Model of Multiple Sclerosis.” *PloS One* 8 (11): e79188.

Lublin, Fred D., Gary Cutter, Gavin Giovannoni, Amy Pace, Nolan R. Campbell, and Shibeshih Belachew. 2014. “Natalizumab Reduces Relapse Clinical Severity and Improves Relapse Recovery in MS.” *Multiple Sclerosis and Related Disorders* 3 (6): 705–11.

Mao, Peizhong, Maria Manczak, Ulziibat P. Shirendeb, and P. Hemachandra Reddy. 2013. “MitoQ, a Mitochondria-Targeted Antioxidant, Delays Disease Progression and Alleviates Pathogenesis in an Experimental Autoimmune Encephalomyelitis Mouse Model of Multiple Sclerosis.” *Biochimica et Biophysica Acta* 1832 (12): 2322–31.

Mi, Sha, R. Blake Pepinsky, and Diego Cadavid. 2013. “Blocking LINGO-1 as a Therapy to Promote CNS Repair: From Concept to the Clinic.” *CNS Drugs* 27 (7): 493–503.

Mishra, Manoj Kumar, Janet Wang, Michael B. Keough, Yan Fan, Claudia Silva, Scott Sloka, Liat Hayardeny, Wolfgang Brück, and V. Wee Yong. 2014. “Laquinimod Reduces Neuroaxonal Injury through Inhibiting Microglial Activation.” *Annals of Clinical and Translational Neurology* 1 (6): 409–22.

Montalban, Xavier, Stephen L. Hauser, Ludwig Kappos, Douglas L. Arnold, Amit Bar-Or, Giancarlo Comi, Jérôme de Seze, et al. 2017. “Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis.” *The New England Journal of Medicine* 376 (3): 209–20.

Paz Soldán, M. Mateo, Martina Novotna, Nuhad Abou Zeid, Nilufer Kale, Melih Tutuncu, Daniel J. Crusan, Elizabeth J. Atkinson, et al. 2015. “Relapses and Disability Accumulation in Progressive Multiple Sclerosis.” *Neurology* 84 (1): 81–88.

Pender, Michael P., Peter A. Csurhes, Corey Smith, Leone Beagley, Kaye D. Hooper, Meenakshi Raj, Alan Coulthard, Scott R. Burrows, and Rajiv Khanna. 2014. “Epstein–Barr Virus-Specific Adoptive Immunotherapy for Progressive Multiple Sclerosis.” *Multiple Sclerosis Journal*, February. doi:10.1177/1352458514521888.

Pender, M. P., P. A. Csurhes, A. Lenarczyk, C. M. M. Pfluger, and S. R. Burrows. 2009. “Decreased T Cell Reactivity to Epstein–Barr Virus Infected Lymphoblastoid Cell Lines in Multiple Sclerosis.” *Journal of Neurology, Neurosurgery, and Psychiatry* 80 (5). BMJ Publishing Group Ltd: 498–505.

Pepinsky, R. Blake, Joseph W. Arndt, Chao Quan, Yan Gao, Omar Quintero-Monzon, Xinhua Lee, and Sha Mi. 2014. “Structure of the LINGO-1-Anti-LINGO-1 Li81 Antibody Complex Provides Insights into the Biology of LINGO-1 and the Mechanism of Action of the Antibody Therapy.” *The Journal of Pharmacology and Experimental Therapeutics* 350 (1): 110–23.

Perron, Hervé, and Alois Lang. 2010. “The Human Endogenous Retrovirus Link between Genes and Environment in Multiple Sclerosis and in Multifactorial Diseases Associating Neuroinflammation.” *Clinical Reviews in Allergy & Immunology* 39 (1): 51–61.

Peyro Saint Paul, Laure, Danièle Debruyne, Delphine Bernard, Donald M. Mock, and Gilles L. Defer. 2016. “Pharmacokinetics and Pharmacodynamics of MD1003 (high-Dose Biotin) in the Treatment of Progressive Multiple Sclerosis.” *Expert Opinion on Drug Metabolism & Toxicology* 12 (3): 327–44.

Raftopoulos, Rhian, Simon J. Hickman, Ahmed Toosy, Basil Sharrack, Shahrukh Mallik, David Paling, Daniel R. Altmann, et al. 2016. “Phenytoin for Neuroprotection in Patients with Acute Optic Neuritis: A Randomised, Placebo-Controlled, Phase 2 Trial.” *Lancet Neurology* 15 (3): 259–69.

Rao, N. A., J. Guy, and P. S. Sheffield. 1981. “Effects of Chronic Demyelination on Axonal Transport in Experimental Allergic Optic Neuritis.” *Investigative Ophthalmology & Visual Science* 21 (4): 606–11.

Rojas, Juan Ignacio, Liliana Patrucco, Jimena Miguez, Cristina Besada, and Edgardo Cristiano. 2014. “Brain Atrophy as a Non-Response Predictor to Interferon-Beta in Relapsing-Remitting Multiple Sclerosis.” *Neurological Research* 36 (7): 615–18.

Schwartz, Carolyn E., Brian R. Quaranto, Brian C. Healy, Ralph H. Benedict, and Timothy L. Vollmer. 2013. “Cognitive Reserve and Symptom Experience in Multiple Sclerosis: A Buffer to Disability Progression over Time?” *Archives of Physical Medicine and Rehabilitation* 94 (10): 1971–81.

Sedel, Frédéric, Caroline Papeix, Agnès Bellanger, Valérie Touitou, Christine Lebrun-Frenay, Damien Galanaud, Olivier Gout, Olivier Lyon-Caen, and Ayman Tourbah. 2015a. “High Doses of Biotin in Chronic Progressive Multiple Sclerosis: A Pilot Study.” *Multiple Sclerosis and Related Disorders* 4 (2): 159–69.

———. 2015b. “High Doses of Biotin in Chronic Progressive Multiple Sclerosis: A Pilot Study.” *Multiple Sclerosis and Related Disorders* 4 (2): 159–69.

Shirani, Afsaneh, Darin T. Okuda, and Olaf Stüve. 2016. “Therapeutic Advances and Future Prospects in Progressive Forms of Multiple Sclerosis.” *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics* 13 (1): 58–69.

Simone, I. L., D. Carrara, C. Tortorella, M. Liguori, V. Lepore, F. Pellegrini, A. Bellacosa, A. Ceccarelli, I. Pavone, and P. Livrea. 2002. “Course and Prognosis in Early-Onset MS: Comparison with Adult-Onset Forms.” *Neurology* 59 (12): 1922–28.

Sorensen, Per S., Steen Lisby, Richard Grove, Frederick Derosier, Steve Shackelford, Eva Havrdova, Jelena Drulovic, and Massimo Filippi. 2014. “Safety and Efficacy of Ofatumumab in Relapsing-Remitting Multiple Sclerosis: A Phase 2 Study.” *Neurology* 82 (7): 573–81.

Tourbah, Ayman, Christine Lebrun-Frenay, Gilles Edan, Michel Clanet, Caroline Papeix, Sandra Vukusic, Jerome De Sèze, et al. 2016. “MD1003 (high-Dose Biotin) for the Treatment of Progressive Multiple Sclerosis: A Randomised, Double-Blind, Placebo-Controlled Study.” *Multiple Sclerosis* 22 (13): 1719–31.

Trapp, B. D., J. Peterson, R. M. Ransohoff, R. Rudick, S. Mörk, and L. Bö. 1998. “Axonal Transection in the Lesions of Multiple Sclerosis.” *The New England Journal of Medicine* 338 (5): 278–85.

Vesterinen, Hanna M., Peter Connick, Cadi M. J. Irvine, Emily S. Sena, Kieren J. Egan, Gary G. Carmichael, Afiyah Tariq, et al. 2015. “Drug Repurposing: A Systematic Approach to Evaluate Candidate Oral Neuroprotective Interventions for Secondary Progressive Multiple Sclerosis.” *PloS One* 10 (4): e0117705.

Wickström, Anne, Josefina Nyström, and Anders Svenningsson. 2013. “Improved Ability to Work after One Year of Natalizumab Treatment in Multiple Sclerosis. Analysis of Disease-Specific and Work-Related Factors That Influence the Effect of Treatment.” *Multiple Sclerosis* 19 (5): 622–30.
Wolinsky, Jerry S., Ponnada A. Narayana, O ’connor Paul, Patricia K. Coyle, Ford Corey, Johnson Kenneth, Miller Aaron, et al. 2007. “Glatiramer Acetate in Primary Progressive Multiple Sclerosis: Results of a Multinational, Multicenter, Double-Blind, Placebo-Controlled Trial.” *Annals of Neurology* 61 (1): 14–24.