REGENERATION AND REMYELINATION ARE POSSIBLE IN MS LESIONS – NO

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Multiple sclerosis (MS) is a chronic autoimmune condition of the central nervous system predominantly affecting young females in their child-bearing age. For a long time regarded as almost exclusively demyelinating disease that spares the axons, recent evidence has unambiguously made clear that MS is as well a neurodegenerative disease with substantial loss of neurons and axons from the very beginning. New imaging modalities such as ultrahigh field magnetic resonance imaging (MRI) and optical coherence tomography (OCT) have helped to impressively visualize early neuro-axonal damage. Moreover, progressive disability seems rather to be associated with neurodegeneration and brain atrophy than with white matter demyelination. Some very powerful anti-inflammatory drugs that impressively reduce relapse activity and inflammatory MRI lesions have not proven to reduce or halt relentlessly progressing neurodegeneration and thus irreversible accrual of neurological disability.

Neuropathological studies have shown that there may be extensive remyelination in at least a subset of MS patients, however, we do not know if remyelination is sufficient to prevent axonal loss. Numerous animal studies have shown remyelination and the enhancement thereof by therapeutic interventions, but animal experiments poorly model the human disease. In patients with MS, attempts to depict remyelination by MRI have remained equivocal. Although there are clinical trials underway with compounds that suggest a remyelinating capacity through their mode of action (anti-LINGO-1 antibodies) we do neither know whether remyelination in humans is substantial to prevent axonal damage and to leverage regeneration nor do we know how to measure remyelination *in vivo* or which treatment duration would be required for successful remyelination.

References

Expert recommendations to personalization of medical approaches in treatment of multiple sclerosis: an overview of family planning and pregnancy.Borisow N, Döring A, Pfueller CF, **Paul** F, Dörr J, Hellwig K. **EPMA** J. 2012 Jun 22;3(1):9. doi: 10.1186/1878-5085-3-9.

Optic neuritis is associated with inner nuclear layer thickening and microcystic macular edema independently of multiple sclerosis. Kaufhold F, Zimmermann H, Schneider E, Ruprecht K, **Paul** F, Oberwahrenbrock T, Brandt AU. PLoS One. 2013 Aug 6;8(8):e71145. doi: 10.1371/journal.pone.0071145. Print 2013.

Retinal ganglion cell and inner plexiform layer thinning in clinically isolated syndrome. Oberwahrenbrock T, Ringelstein M, Jentschke S, Deuschle K, Klumbies K, Bellmann-Strobl J, Harmel J, Ruprecht K, Schippling S, Hartung HP, Aktas O, Brandt AU, **Paul** F. Mult Scler. 2013 Dec;19(14):1887-95. doi: 10.1177/1352458513489757. Epub 2013 May 23.

Optic neuritis interferes with **optical coherence tomography** and magnetic resonance imaging correlations. Zimmermann H, Freing A, Kaufhold F, Gaede G, Bohn E, Bock M, Oberwahrenbrock T, Young KL, Dörr J, Wuerfel JT, Schippling S, **Paul** F, Brandt AU. Mult Scler. 2013 Apr;19(4):443-50. doi: 10.1177/1352458512457844. Epub 2012 Aug 30.

Retinal damage in multiple sclerosis disease subtypes measured by high-resolution **optical coherence tomography**. Oberwahrenbrock T, Schippling S, Ringelstein M, Kaufhold F, Zimmermann H, Keser N, Young KL, Harmel J, Hartung HP, Martin R, **Paul** F, Aktas O, Brandt AU. Mult Scler Int. 2012;2012:530305. doi: 10.1155/2012/530305. Epub 2012 Jul 25.

Primary retinal pathology in multiple sclerosis as detected by **optical coherence tomography**.Brandt AU, Oberwahrenbrock T, Ringelstein M, Young KL, Tiede M, Hartung HP, Martin R, Aktas O, **Paul** F, Schippling S. Brain. 2011 Nov;134(Pt 11):e193; author reply e194. doi: 10.1093/brain/awr095. Epub 2011 May 19. No abstract available.

Metabolic changes in the visual cortex are linked to retinal nerve fiber layer thinning in multiple sclerosis. Pfueller CF, Brandt AU, Schubert F, Bock M, Walaszek B, Waiczies H, Schwenteck T, Dörr J, Bellmann-Strobl J, Mohr C, Weinges-Evers N, Ittermann B, Wuerfel JT, **Paul** F.

Impairment of contrast visual acuity as a functional correlate of retinal nerve fibre layer thinning and total macular volume reduction in multiple sclerosis. Bock M, Brandt AU, Kuchenbecker J, Dörr J, Pfueller CF, Weinges-Evers N, Gaede G, Zimmermann H, Bellmann-Strobl J, Ohlraun S, Zipp F, **Paul** F. Br J Ophthalmol. 2012 Jan;96(1):62-7. doi: 10.1136/bjo.2010.193581. Epub 2011 Mar 3.

Time domain and spectral domain **optical coherence tomography** in multiple sclerosis: a comparative cross-sectional study. Bock M, Brandt AU, Dörr J, Pfueller CF, Ohlraun S, Zipp F, **Paul** F. Mult Scler. 2010 Jul;16(7):893-6. doi: 10.1177/1352458510365156. Epub 2010 Mar 29.

Association of retinal and macular damage with brain atrophy in multiple sclerosis. Dörr J, Wernecke KD, Bock M, Gaede G, Wuerfel JT, Pfueller CF, Bellmann-Strobl J, Freing A, Brandt AU, Friedemann P. **PLoS One**. **2011** Apr 8;6(4):e18132. doi: 10.1371/journal.pone.0018132.

Multiple sclerosis lesions and irreversible brain tissue damage: a comparative ultrahigh-field strength magnetic resonance imaging study. **Sinnecker T**, Mittelstaedt P, Dörr J, Pfueller CF, Harms L, Niendorf T, Paul F, Wuerfel J. Arch Neurol. 2012 Jun;69(6):739-45. doi: 10.1001/archneurol.2011.2450.

Promoting remyelination in **multiple sclerosis**-recent advances. Jolanda Münzel E, **Williams** A. Drugs. 2013 Dec;73(18):2017-29. doi: 10.1007/s40265-013-0146-8.

Clinico-pathological evidence that axonal loss underlies disability in progressive multiple sclerosis. Tallantyre EC, Bø L, Al-Rawashdeh O, Owens T, Polman CH, Lowe JS, Evangelou N. Mult Scler. 2010 Apr;16(4):406-11. doi: 10.1177/1352458510364992. Epub 2010 Mar 9.

Remyelination is extensive in a subset of multiple sclerosis patients. Patrikios P, Stadelmann C, Kutzelnigg A, Rauschka H, Schmidbauer M, Laursen H, Sorensen PS, Brück W, Lucchinetti C, Lassmann H. Brain. 2006 Dec;129(Pt 12):3165-72. Epub 2006 Aug 18.