



Wilkins, A., & Scolding, N. (2017). Can the optic nerve be repaired? *Lancet Neurology*, 16(3), 172-173. [https://doi.org/10.1016/S1474-4422\(16\)30402-1](https://doi.org/10.1016/S1474-4422(16)30402-1)

Peer reviewed version

License (if available):
CC BY-NC-ND

Link to published version (if available):
[10.1016/S1474-4422\(16\)30402-1](https://doi.org/10.1016/S1474-4422(16)30402-1)

[Link to publication record on the Bristol Research Portal](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via <http://www.sciencedirect.com/science/article/pii/S1474442216304021>. Please refer to any applicable terms of use of the publisher.

University of Bristol – Bristol Research Portal

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: <http://www.bristol.ac.uk/red/research-policy/pure/user-guides/brp-terms/>

Can the optic nerve be repaired?

Alastair Wilkins, Reader in Neurology

and

Neil Scolding, Burden Professor of Clinical Neurosciences and Director, *Bristol Neuroscience*

University of Bristol and North Bristol NHS Trust

Forty years ago, Bill Blakemore showed that transplanted exogenous Schwann cells successfully repaired spinal cord myelin following experimental demyelination (1). The research, presciently funded by the UK Multiple Sclerosis Society, opened the field of cell therapy for MS. Ironically, while this field has developed fruitfully in various directions (and generated regular 'miracle cure' headlines in the lay media), there has never in the intervening four decades been a single published trial of myelinating cell transplantation in MS. There is nonetheless a direct link spanning Blakemore's pioneering work and the optic neuritis monoclonal antibody trial RENEW published today (2, 3).

In MS relapses, patches of inflammation in the brain and spinal cord cause myelin damage and consequently disrupted conduction of nerve impulses with, depending on the site, impaired neurological function. Remission is seen when inflammation settles (either spontaneously, or therapeutically accelerated by high dose corticosteroids) and spontaneous myelin repair occurs. Remyelination is more successful and widespread than originally considered (4), and is achieved by oligodendrocyte progenitors (likely derived from endogenous neural stem cells (5)) proliferating, migrating into inflammatory lesions, and differentiating into myelin-forming mature oligodendrocytes (3).

LINGO-1 is a receptor expressed on oligodendrocytes and neurons, and acts to inhibit oligodendrocyte differentiation and remyelination (6). Antagonising this inhibitor might be predicted to enhance remyelination, and in pre-clinical studies anti-LINGO-1 antibodies do indeed augment myelin repair in various experimental paradigms (6). These pre-clinical results lead to first-in-man phase 1 studies of the monoclonal anti-Lingo-1 antibody *opicinumab* in healthy volunteers and adults with MS, which supported its tolerability and safety (7), and then to RENEW, a randomised, double-blind, placebo-controlled phase 2 study of *opicinumab* in patients with a first episode of optic neuritis.

Eighty-two patients at 33 sites across Europe, Australia, and Canada were randomised to receive (in a 1:1 ratio) either placebo or intravenous *opicinumab* once monthly for 20 weeks (six treatments). In the event, 33 completed treatment with *opicinumab*, and 36 placebo. The primary endpoint indirectly assessed remyelination by measuring optic nerve conduction velocity using visual evoked potential recording (VEP), inferring recovery by comparing the P100 latency in the affected eye with the unaffected fellow eye at baseline. (The affected eye's baseline/pre-optic neuritis VEP was naturally unavailable, but VEP measurements usually have a very small inter-eye latency variation in healthy eyes, and are highly reproducible.) The trial appears to have been conducted with considerable care; rigorous efforts were made in particular to ensure reproducibility and consistency of VEP recording in the various trial sites.

The intention-to-treat analysis revealed no significant difference in the primary outcome measure, change in VEP latency at week 24 between the *opicinumab* and placebo groups. None of the secondary outcome measures reached statistical significance. However, in pre-specified per-protocol (PP) analyses, and also in some post-hoc analyses, significant differences were observed. The authors concluded that remyelination was not significantly different between the *opicinumab* and placebo groups in the ITT population, but that these other analyses suggest remyelination enhancement in the human CNS with *opicinumab* may be possible, and that further study is required.

For 'magic bullets', monoclonal antibodies can inflict surprising collateral damage, and so safety signals are particularly important. Two *opicinumab* subjects experienced clinical episodes of inflammatory demyelination, compared to none in the placebo, and there were in the *opicinumab* group greater increases in T2 lesion volume (*opicinumab* mean 0.20mL, placebo mean 0.05mL) and in Gd+ lesion number (*opicinumab* 0.32, placebo 0.14); but reassuringly none of these differences was statistically significant.

What messages can clinicians take? It is an important study, a landmark in the determined and committed evolution of the anti-lingo-1 story from its first discovery in studies of the biology of remyelination ultimately consequent to Blakemore's research, to the finding that blocking lingo-1 enhanced myelin repair, through phase I studies to this phase II clinical trial. That it is an essentially negative trial result is naturally disappointing, for researchers, for Biogen, the pharmaceutical company involved, and most of all for patients. But a 'hole in one' was never a realistic likelihood, and there are many positives in this study. Much invaluable information about conducting a multi-centre trial exploring CNS repair has been gained. The potential, hitherto insufficiently tapped, of neurophysiological outcome measures has been both developed and re-emphasised. It is impressive that the great majority of this work has been driven and funded commercially, the pharmaceutical industry previously having concentrated almost exclusively on blocking inflammation in MS. And as the authors imply, there must be a significant possibility of a type II error: the absence of efficacy has not been proven.

Additionally, Lingo-1, as mentioned above, is expressed on neuronal populations as well as oligodendrocytes, and lingo-1 blockade can be neuroprotective. RENEW partially explored this possibility, retinal ganglion cell and axon preservation assessed as a secondary outcome measure using OCT, with non-significant results. Raftopoulos et al also explored neuroprotection of the retina in optic neuritis using phenytoin (8); they reported statistically significant changes also using OCT measurements, though no visual function benefit. Future work might concentrate on this potentially important activity, and indeed on the question of whether remyelination or neuroprotection – or both – should be the principal aim of studies seeking ultimately to help prevent disability in progressive MS.

References

1. Blakemore WF. Remyelination of CNS axons by Schwann cells transplanted from the sciatic nerve. *Nature*. 1977;266(5597):68-9.
2. Cadavid D, Balcer, L, . Safety and efficacy of opicinumab in acute optic neuritis (RENEW): a randomised, placebo-controlled trial. *Lancet Neurology*. 2017 in press.
3. Franklin RJ, ffrench-Constant C, Edgar JM, Smith KJ. Neuroprotection and repair in multiple sclerosis. *Nature reviews Neurology*. 2012 Nov 05;8(11):624-34. PubMed PMID: 23026979.
4. Patani R, Balaratnam M, Vora A, Reynolds R. Remyelination can be extensive in multiple sclerosis despite a long disease course. *NeuropatholApplNeurobiol*. 2007;33(3):277-87.
5. Snethen H, Love S, Scolding N. Disease-responsive neural precursor cells are present in multiple sclerosis lesions. *RegenMed*. 2008;3(6):835-47.
6. Mi S, Pepinsky RB, Cadavid D. Blocking LINGO-1 as a therapy to promote CNS repair: from concept to the clinic. *CNS Drugs*. 2013 Jul;27(7):493-503. PubMed PMID: 23681979.
7. Tran JQ, Rana J, Barkhof F, Melamed I, Gevorkyan H, Wattjes MP, et al. Randomized phase I trials of the safety/tolerability of anti-LINGO-1 monoclonal antibody BIIB033. *Neurology(R) neuroimmunology & neuroinflammation*. 2014 Aug;1(2):e18. PubMed PMID: 25340070. Pubmed Central PMCID: 4202679.
8. Raftopoulos R, Hickman SJ, Toosy A, Sharrack B, Mallik S, Paling D, et al. Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016 Mar;15(3):259-69. PubMed PMID: 26822749.