NEURODEGENERATIVE DISEASES

Repurposing for remyelination

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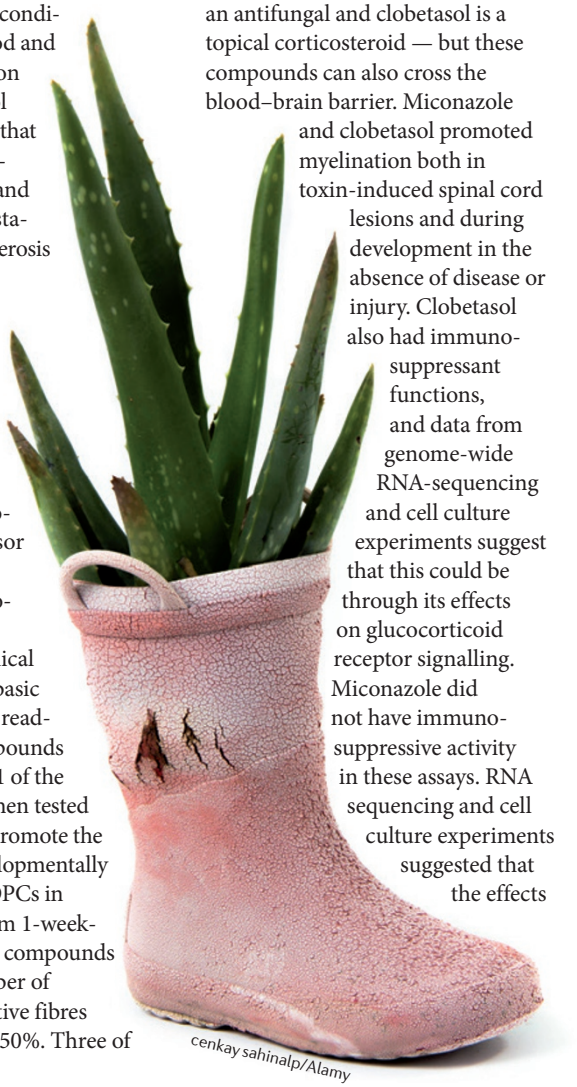
Most drugs for multiple sclerosis inhibit the immune-mediated destruction of myelin, oligodendrocytes and nerves, but they are unable to prevent disease progression. An alternative therapeutic strategy, promoting remyelination, could indeed reverse the disease and would thus be of substantial benefit. Towards this end, Najm *et al.* have now identified two drugs already approved for other conditions by the US Food and Drug Administration (FDA) — clobetasol and miconazole — that promote remyelination in cell culture and reverse the manifestations of multiple sclerosis in animal models.

Approximately 700 chemicals with a history of safe use in clinical trials were screened for their ability to aid the maturation of oligodendrocyte precursor cells (OPCs) into remyelinating oligodendrocytes, using immunohistochemical staining of myelin basic protein (MBP) as a readout. Of the 22 compounds identified as hits, 11 of the most potent were then tested for their ability to promote the maturation of developmentally immature mouse OPCs in cerebellar slices from 1-week-old mice; 4 of these compounds increased the number of aligned, MBP-positive fibres by approximately 150%. Three of these compounds were 1,3-diazoles monosubstituted at the 1 position, of which miconazole was the overall top performing hit.

Miconazole and clobetasol (the top performing hit from the steroids, which were also over-represented in the highest-ranking compounds) were then tested *in vivo*. Both of these drugs are approved for topical use — miconazole is an antifungal and clobetasol is a topical corticosteroid — but these compounds can also cross the blood–brain barrier. Miconazole and clobetasol promoted myelination both in toxin-induced spinal cord lesions and during development in the absence of disease or injury. Clobetasol also had immunosuppressant functions, and data from genome-wide RNA-sequencing and cell culture experiments suggest that this could be through its effects on glucocorticoid receptor signalling. Miconazole did not have immunosuppressive activity in these assays. RNA sequencing and cell culture experiments suggested that the effects of miconazole could be mediated by the extracellular signal-regulated kinase (ERK) signalling pathway.



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Two versions of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, were used to further analyse the therapeutic potential of miconazole and clobetasol. In the heavily immune-driven model (PLP139–151), only clobetasol was effective, probably owing to its immunosuppressant function. In a second model (MOG35–55), which more closely models chronic progressive demyelination and in which the immune system is relatively controlled, daily intraperitoneal injections with either miconazole or clobetasol, beginning at the peak of disease, markedly improved motor function, and nearly all the mice regained use of one or both hindlimbs. In the spinal cord of drug-treated mice, MBP expression was restored and demyelination was reduced relative to that of vehicle-treated mice.

Phase II trials are now being planned for one of the compounds identified in this screen. These drugs, or derivatives thereof, could be promising candidates to evaluate further for the treatment of chronic progressive multiple sclerosis, joining other potential remyelinating therapeutics such as an antibody targeting LINGO1 (leucine-rich repeat neuronal protein 1) that is being tested in clinical trials.

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ORIGINAL RESEARCH PAPER Najm, F. J. *et al.* Drug-based modulation of endogenous stem cells promotes functional remyelination *in vivo*. *Nature* http://dx.doi.org/10.1038/nature14335 (2015)
FURTHER READING Ledford, H. Drug that boosts nerve signals offers hope for multiple sclerosis. *Nature* **520**, 417 (2015)