



¹ Myelin proteolipid protein (PLP or lipophilin) is the major myelin protein from the central nervous system, here in corpus callosum © Fraunhofer IME / Martine Hofmann, Mike Schmidt.

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CUPRIZONE DEMYELINATION OF MURINE CORPUS CALLOSUM, A MODEL OF MULTIPLE SCLEROSIS NEURODEGENERATION

Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating, inflammatory and degenerative neurological disease often occurring in early adulthood. It results in disabling physical symptoms. With progression of the disease, the likelihood increases that comorbid conditions occur (such as cognitive deficits, depression and fatigue).

Cuprizone intoxication

Cuprizone intoxication is a commonly used model to study experimental remyelination, with the corpus callosum being the most frequently investigated white matter tract. In this model, mice are fed with the copper chelator cuprizone (bis-cyclohexanone oxal-dihydrazone), which leads to a primary oligodendrocyte (OL) apoptosis and secondary

demyelination within weeks. After removal of the toxin, spontaneous remyelination occurs, thus making the cuprizone model appropriate for studying compounds which can prevent demyelination and/or stimulate remyelination.

Endpoints/Outcome parameters

It is important to consider which in vivo readouts are relevant for the evaluation of drug effects. We develop animal models for MS and try to mimic the symptoms of MS in animals in order to better predict efficacy of compounds in patients. Our approach is not only to use standard readouts, but we also offer the possibility to study more subtle and objective readouts that potentially could have a higher translational value.

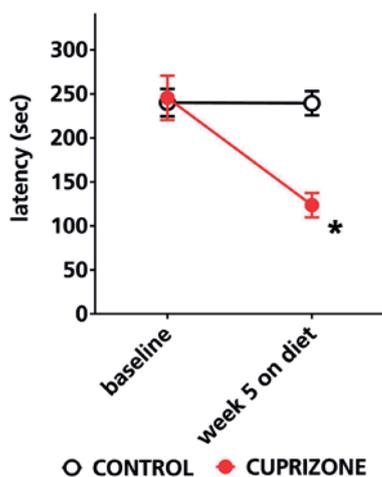


Readout parameters

The myelin staining method is used as a primary measure for demyelination and remyelination.

In addition to the myelin measure, we assess other variables that may be more predictive for the study of drug efficacy. More subtle and objective measurements of balance, motor coordination and muscle strength can be investigated using (semi) automated setups, rotarod, treadmills and grip strength meter.

For example, we use the **rotarod** test which is based on a rotating rod with forced motor activity being applied.



Rotarod accelerated version (16–32 rpm, 300 sec cut-off) Male C57Bl6 mice, 0.3 % cuprizone diet versus control diet (latency to fall, sec).

MS comorbid symptoms such as cognitive impairment, fatigue and mood disturbances are often untreated and therefore represent potential therapeutic targets. For example, clinical studies have revealed discrete cognitive dysfunction in MS patients already at an early stage of the disease. About 60% of individuals with MS experience significant cognitive dysfunction. We offer the opportunity to test effects of compounds on cognitive impairment in the cuprizone animal model using setups such as the **Mouse Touch Screen Chambers** (Campden Instruments Ltd.).

Quality management and validation

All current drugs work by decreasing inflammation through modulation of the immune system and while they have been very efficient in reducing the rate of relapses, their impact on the chronic disease course is unknown. A current thought in the MS therapeutics community is that drugs that enhance remyelination may be more effective in reducing long-term disability. We are presently testing existing and novel compounds in the model in order to investigate their effects on remyelination.

Selected publications

- de Bruin NMWJ, Schmitz K, Schiffmann S, Tafferner N, Schmidt M, Jordan H, Häußler A, Tegeder I, Geisslinger G, Parnham MJ. Multiple rodent models and behavioral measures reveal unexpected responses to FTY720 and DMF in experimental autoimmune encephalomyelitis. *Behav Brain Res* 2016;300:160–74. doi:10.1016/j.bbr.2015.12.006.
- Schmitz K, de Bruin N, Bishay P, Manich J, Haussler A, Altmann C, Ferreirós N, Lötsch J, Ultsch A, Parnham MJ, Geisslinger G, Tegeder I. R-flurbiprofen attenuates experimental autoimmune encephalomyelitis in mice. *EMBO Mol Med* 2014;6:1398–422. doi:10.15252/emmm.201404168.