## Experimental autoimmune encephalomyelitis (EAE) rat/mouse models for the human inflammatory demyelinating disease, multiple sclerosis (MS)

***Species*:** rats and mice

***Fields of application:*** Autoimmune diseases, Inflammation

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).

Experimental autoimmune encephalomyelitis (EAE) is a widely-used rodent model for MS, but a single model can hardly capture and adequately incorporate all features of MS. A number of different EAE models are available, resulting in different disease-progression patterns and clinical features. Dependent on the antigen and rodent strain used, the animals develop different disease processes. In addition to studies with drugs and test compounds, we also investigate responses in knockout mice.

At Fraunhofer IME-TMP several EAE models are available to test compounds:

- monophasic EAE in Lewis rats (induced by myelin basic protein, MBP),
- protracted-relapsing EAE (PR-EAE) in Dark Agouti (DA) rats (induced by spinal cord homogenate, SCH)
- chronic progressive EAE (CP-EAE) in C57BL/6 mice (induced by myelin oligodendrocyte protein, MOG)
- relapsing-remitting EAE (RR EAE) in SJL mice (induced by proteolipid protein, PLP)

***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 clinical score readouts, but we also offer the possibility to study more subtle and objective readouts that potentially could have a higher translational value.

***Readout parameters***

Clinical signs and ascending paralysis in EAE are commonly assessed on a grading scale. In addition to this, we assess other variables that may be more predictive for the study of disease progression and drug efficacy, also during periods when no clinical scores can be registered, such as the remission interval between two clinical score peaks. More subtle and objective measurements of balance, motor coordination and muscle strength can be investigated using (semi) automated setups such as rotarod, threadmills and grip strength meter.

MS co-morbid 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 EAE animal models using setups such as the Mouse Touch Screen Chambers (Campden Instruments Ltd.).

We additionally offer fluorescence-activated cell sorting (FACS) / immunohistochemistry (IHC) analysis of spinal cord, brain, lymph organs and circulating immune cells; analysis of cytokines / chemokines / lipid profile in spinal cord, brain and blood samples and microglia activation; measurements of demyelination and remyelination. In addition, in collaboration with the Institute of Clinical Pharmacology (Pharmazentrum Frankfurt/ZAFES, Frankfurt am Main) we offer the use of multi Epitope Ligand Carthography (MELC) which allows staining of the same tissue section with up to 100 fluorescent markers.

Pharmacokinetics and determination of drug concentrations by LC-MS/MS: PK/PD studies of drugs, including chiral compounds, in rodent models

Bioluminescent imaging: The IVIS Spectrum (Caliper Life Sciences) is used as optical imaging technology to facilitate non-invasive longitudinal monitoring of disease progression (e.g. inflammation), cell trafficking and gene expression patterns in living animals.

***Quality management and validation:*** The models have been validated with the clinical reference compound FTY720 (fingolimod).

***References:***

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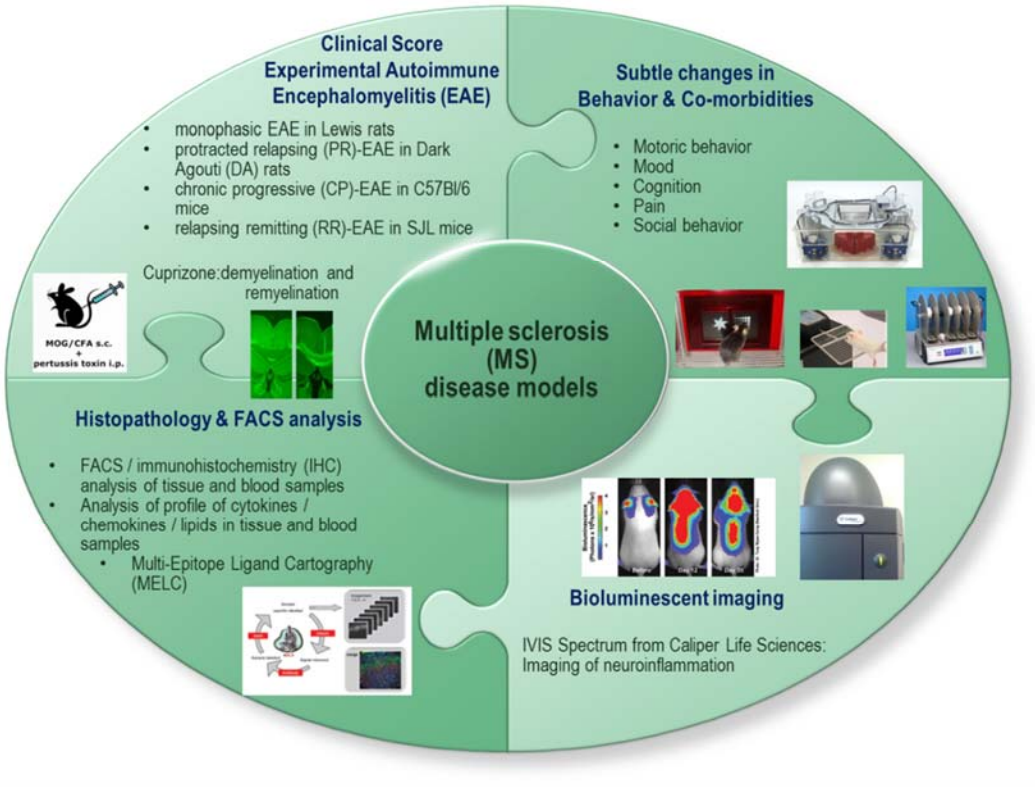


Figure: Various EAE animal models for MS and relevant readouts at Fraunhofer-TMP

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