ANIMAL MODELS IN MULTIPLE SCLEROSIS

Iris Martí Fernández. Grau en Genètica. Universitat Autònoma de Barcelona.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory and demyelization disease of the central nervous system (SNC). MS affects more than 2 millions of people, which a major rate among women (3:1). Clinical manifestation begins, in most cases, in the third or fourth decade of life. The patients have neurological deficits that exhibit a relapsing and remitting pattern.

There are four main pathological features in MS: (1) inflammation, which is believed to have an important role in CNS tissue damage in the majority of cases; (2) demyelination, the hallmark of MS, where the myelin sheath or the oligodendrocyte is destroyed by the inflammatory process; (3) axonal loss or damage; and (4) gliosis (astrocytic reaction to CNS damage)

Relapsing-Remitting MS (RRMS): relapses of disease separated by periods without clinical progression.

Primary Progressive (PPMS): neurological deterioration is present from the onset.

Secondary Progressive MS(SPMS): gradual neurological deterioration.

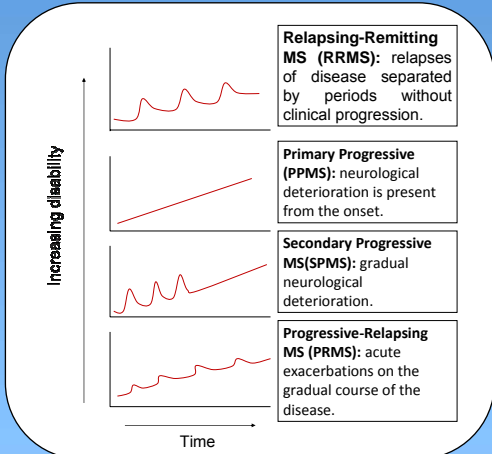**Progressive-Relapsing MS (PRMS):** acute exacerbations on the gradual course of the disease.

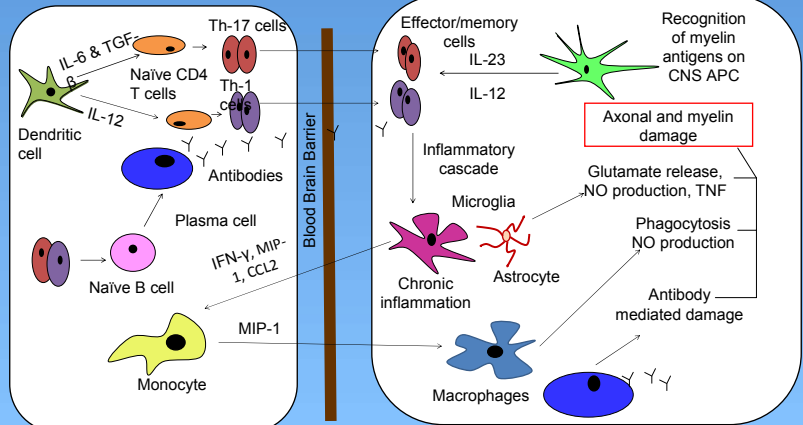Figure 1. Subtypes of MS depending on the clinical course

Figure 2. Schematic diagram of some of the key pathological features of EAE pathogenesis. Adapted of CS. Constantinescu, *et al. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS).* British Journal of Pharmacology 164 (2011) 1079-1106.
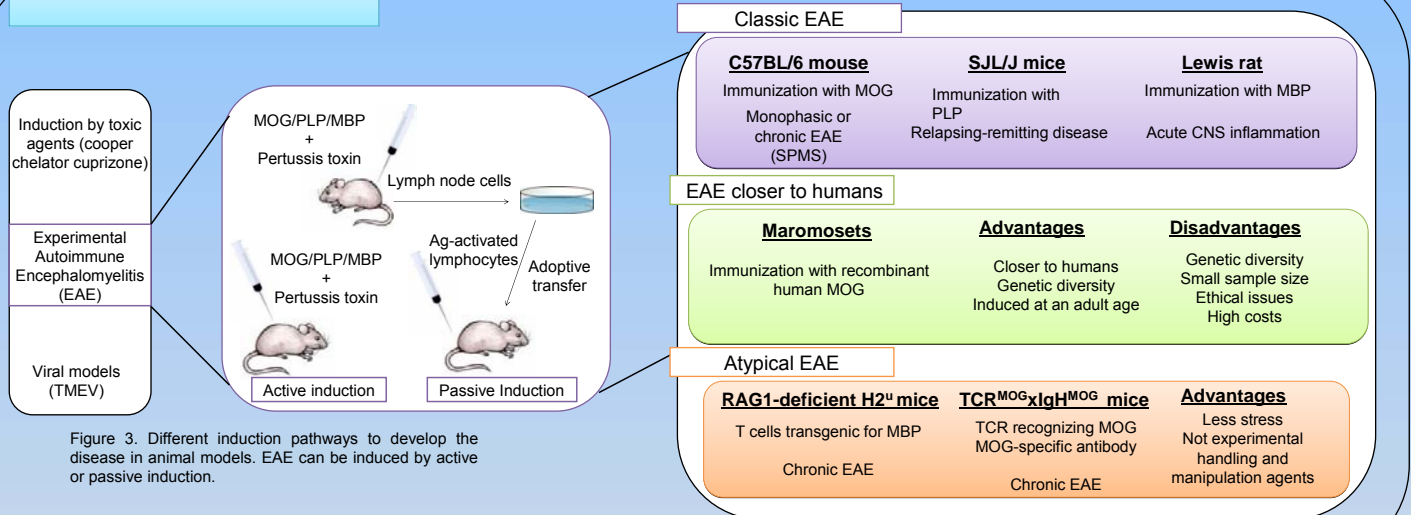
ANIMAL MODELS

Induction by toxic agents (cooper chelator cuprizone)

Experimental Autoimmune Encephalomyelitis (EAE)

Viral models (TMEV)

Figure 3. Different induction pathways to develop the disease in animal models. EAE can be induced by active or passive induction.

Classic EAE

C57BL/6 mouse	**SJL/J mice**	**Lewis rat**
Immunization with MOG	Immunization with PLP	Immunization with MBP
Monophasic or chronic EAE (SPMS)	Relapsing-remitting disease	Acute CNS inflammation

EAE closer to humans

Maromosets	**Advantages**	**Disadvantages**
Immunization with recombinant human MOG	Closer to humans Genetic diversity Induced at an adult age	Genetic diversity Small sample size Ethical issues High costs

Atypical EAE

RAG1-deficient H2^u mice	**TCR^{MOG}xIgH^{MOG} mice**	**Advantages**
T cells transgenic for MBP	TCR recognizing MOG MOG-specific antibody	Less stress Not experimental handling and manipulation agents
Chronic EAE	Chronic EAE	

Figure 4. Animal models in MS

TREATMENT EAE vs MS

1st generation DMT
- Type I IFN (α and β)
- Galtiramer acetat (GA)

Reduces relapses

Not SPMS, PPMS, PRMS

2nd generation DMT
- Natalizumab: Ac agains VLA-4 integrin

Severe complications

Clinical benefits in aggressive RRMS →outweigh the risk

- Oral administration of Ag→ no results in MS
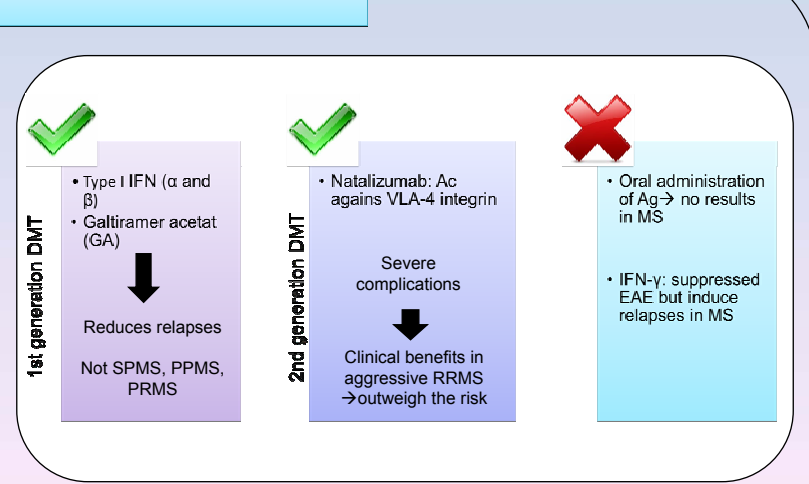- IFN-γ: suppressed EAE but induce relapses in MS

Figure 5. Treatment EAE vs MS: Success and discrepancies

CONCLUSIONS

Ms is a neurodegenerative disease that affects a lot people around the world, but we haven't found yet a treatment for it

In spite of all this models, it is still investigating to find a better animal model, which resembles more closely MS. If we can achieve this model, we may get more efficiency in the experiments and also is more probable that more treatments reach clinical trials. Maybe if we continue studying and improving animal models, in some years we will have a treatment for MS.