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REVIEW ARTICLE

The value of animal models for drug development in multiple sclerosis

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The rodent model for multiple sclerosis, experimental allergic (autoimmune) encephalomyelitis (EAE), has been used to dissect molecular mechanisms of the autoimmune inflammatory response, and hence to devise and test new therapies for multiple sclerosis. Clearly, artificial immunization against myelin may not necessarily reproduce all the pathogenetic mechanisms operating in the human disease, but most therapies tested in multiple sclerosis patients are nevertheless based on concepts derived from studies in EAE. Unfortunately, several treatments, though successful in pre-clinical EAE trials, were either less effective in patients, worsened disease or caused unexpected, severe adverse events, as we review here. These discrepancies must, at least in part, be due to genetic and environmental differences, but the precise underlying reasons are not yet clear. Our understanding of EAE pathogenesis is still incomplete and so, therefore, are any implications for drug development in these models. Here, we suggest some potential explanations based on new thinking about key pathogenic concepts and differences that may limit extrapolation from EAE to multiple sclerosis. To try to circumvent these rodent–human dissimilarities more systematically, we propose that pre-clinical trials should be started in humanized mouse models.

Keywords: animal models; experimental allergic encephalomyelitis; immunomodulation; multiple sclerosis; treatments

Abbreviations: CFA = complete Freund's adjuvant; EAE = experimental allergic (autoimmune) encephalomyelitis; HSCT = haematopoietic stem cell transplantation; MBP = myelin basic protein; PDEs = phosphodiesterases; PML = progressive multifocal leukoencephalopathy; PPARs = peroxisome proliferator-activated receptors; TCR = T-cell receptor; T_H1 = T helper 1; TNF = tumour necrosis factor

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Introduction

Multiple sclerosis is the commonest neurological disease of young adults, afflicting at least 350 000 individuals in North America and 500 000 in Europe (Hafler *et al.*, 2005; Sospedra and Martin, 2005). Although multiple sclerosis does not usually shorten life expectancy, its socio-economic burden in young adults is second only to trauma (Sospedra and Martin, 2005). Its clinical signs and symptoms are very variable and depend on the parts of the CNS it affects, that is, the brain and spinal cord, and include motor, sensory, autonomic and cognitive disabilities (Noseworthy *et al.*, 2000*a*). It can run at least three clinical courses: (i) relapsing–remitting (RR) multiple sclerosis, which is most frequent (~85%) and characterized by discrete attacks (exacerbations) and subsequent periods of clinical stability. In most relapsing multiple sclerosis patients, (ii) a secondary progressive (SP) phase ensues, with continuously increasing deficits. About 10–15% of multiple sclerosis patients develop

steadily increasing neurological deficits from onset, (iii) the primary-progressive subtype (Noseworthy *et al.*, 2000*a*).

Neuropathologically, CNS tissue from multiple sclerosis patients shows discrete lesions (predominantly in the white matter) with inflammatory infiltrates, demyelination, astrogliosis and early axonal damage. Again, there is considerable heterogeneity in composition of cellular infiltrates and in involvement of antibodies and complement (Lassmann *et al.*, 2001). Multiple sclerosis is widely considered an autoimmune demyelinating disease, and the inflammatory infiltrates as pathogenically primary events. Its aetiology remains a mystery, but infectious agents have long been suspected as triggers (Marrie, 2004). The evidence for an autoimmune reaction targeting myelin is strong but not definitive. There are, for example, descriptions of primary oligodendrocyte apoptosis with microglial activation in early multiple sclerosis lesions in the absence of lymphocytes or myelin phagocytosis (Barnett and Prineas, 2004). Further, the decreasing inflammatory activity that is seen by MRI during the SP phase has led to the assumption that the pathology is inflammatory at first and degenerative later. Despite these uncertainties, it is generally accepted that multiple sclerosis involves an autoimmune reaction by myelin-specific $CD4^+$ T helper 1 (T_H1) cells, which initiate the neuropathology (Hafler *et al.*, 2005; Sospedra and Martin, 2005). This notion is based on the cellular composition of CNS- and CSF-infiltrating cells (Hauser *et al.*, 1986), on genetic studies in multiple sclerosis (Dyment *et al.*, 2004) and on one animal model of multiple sclerosis, experimental allergic (autoimmune) encephalomyelitis (EAE) (Zamvil and Steinman, 1990).

Dissecting the pathogenesis of a complex disease in man is fraught with many problems, particularly those associated with clinical and genetic heterogeneity. Not surprisingly, most of our current thinking about multiple sclerosis stems from EAE. This model originated from vaccination with rabies-infected rabbit spinal cord by Louis Pasteur (from 1885). About 1 in 1000 vaccinees had 'neuroparalytic incidents'; this acute demyelinating disorder later proved to be due to 'contamination' by spinal cord components in the inoculum. The EAE model has since evolved a long way; different variants, mice, rats or non-human primates are immunized with whole spinal cord, myelin proteins or even defined peptides, usually in complete Freund's adjuvant (CFA). This immunization leads to a disease that shares clinical and neuropathological changes with multiple sclerosis (Steinman, 1999). The course it takes ranges from acute monophasic (or even lethal) to chronic progressive or relapsing–remitting (Steinman, 1999). Typical $CD4^+$ T_H1 myelin-specific T cells have been implicated as the disease-initiating subset. In almost all models, they are sufficient to induce EAE; they can be isolated, cloned and used to transfer disease to naïve healthy animals (Zamvil and Steinman, 1990). These various EAE models have been used to dissect molecular mechanisms of the autoimmune inflammatory response, and hence to devise and test new therapies for multiple sclerosis. It is clear, however, that the artificial induction of a myelin-specific immune response may by-pass key pathogenetic mechanisms operating in human disease, as we do not even know the key target autoantigens in multiple sclerosis.

Limitations of current EAE models

Without doubt, EAE models are vital for studying general concepts as well as specific processes of autoimmunity, however rarely they predict success in clinical trials (*see* below). Nevertheless, their value is further challenged by our rudimentary understanding of the key pathogenetic mechanisms in EAE models, and their failure to forewarn us of adverse effects (reviewed below). As with other murine disease models, including the NOD model of type 1 diabetes (Roep *et al.*, 2004), it appears much easier to prevent, reverse or ameliorate EAE in mice than multiple sclerosis in man.

Furthermore, since EAE almost always has to be induced, it cannot mimic a spontaneous disease. The most important component in the inducing adjuvant CFA is heat-inactivated *Mycobacterium tuberculosis*, which always induces a prominent $CD4^+$ T_H1 response by activating certain toll-like receptors (Su *et al.*, 2005). This leaves little room for variability in disease pathways and certainly does not reflect heterogeneous inducing mechanisms in multiple sclerosis. Also, demyelination is not obvious in all models. Moreover, the time courses are very different. Since EAE develops over days in most models, they seem more similar to post-infectious acute demyelinating events (Steinman, 1999). Indeed, the mice are rarely monitored for late relapses and fatal adverse effects, such as those noted in marmosets (Genain *et al.*, 1996). Nevertheless, the same treatment can have a different degree of efficacy or even opposite effects at different stages in EAE, as has also been reported for other autoimmune models such as in NOD mice (Shoda *et al.*, 2005). In contrast, multiple sclerosis usually manifests insidiously over years, for example, in its relapsing–remitting and later chronic forms (Noseworthy *et al.*, 2000*a*), by when antibodies and complement may also be more important than in most mouse models. Indeed, many patients present after much more protracted epitope spreading than is usually seen in EAE mice (Vanderlugt and Miller, 2002). These and other obvious mouse : human differences are summarized in Table 1.

Many aspects of pathology and immunology differ between multiple sclerosis and EAE. These differences are fundamental, as ongoing imbalances in immune regulation must be crucial for the progression of multiple sclerosis; such orders of complexity have not yet been recapitulated in EAE models.

What can we learn from failures or successes in adapting therapies from EAE to multiple sclerosis?

Only very few therapeutics that were successful in pre-clinical EAE trials have shown similar efficacy in multiple sclerosis

Table 1 Immunological differences between mouse and human relevant for testing multiple sclerosis therapeutics

	Mouse	Human	References
General	Inbred; homozygous	Outbred; heterozygous	
	Short lifespan: high fecundity	Long lifespan: low fecundity	
	Fixed diet; pathogen-free	Varied diet; carriers of potential pathogens, e.g. EBV, JCV etc	
	Clean environment	Open access to new infections	
EAE and multiple sclerosis			
	May be monophasic	Different subtypes, usually relapsing	
	Mice tested while epitopes are spreading	Epitopes must often have spread long before diagnosis	Vanderlugt and Miller (2002)
Induction	Usually with CFA	Spontaneous	
Testing new therapeutics	Induction of EAE studied much more than ongoing disease	Ongoing disease	
	Only a few dozen mice tested	Hundreds of multiple sclerosis patients; some side-effects are too rare to be seen in mice	
Scrutiny	Less detailed	Detailed, would be missed in mice	
Follow-up	Often short-term only	Several years or life-long	
Molecular differences in immune response			
T-cell responses	Often stereotypical	Usually idiosyncratic, even to recurring epitope(s)	
Lymphocytes in peripheral blood	75–90%	30–50%	Doeing *et al.* (2003)
$CD4^+$ expression	Lymphocytes	Lymphocytes, macrophages	Crocker *et al.* (1987)
$CD8^+$ expression	Lymphocytes, dendritic cells	Lymphocytes	Banchereau *et al.* (2000)
IL-10 expression	T_H2	T_H1 and T_H2	Del Prete *et al.* (1993)
IFN-α response	No preferential T_H differentiation	Promotes T_H1 response	Farrar *et al.* (2000)
IL-4 and IFN-γ expression by T_H	Exclusively one or the other	Sometimes both	Gor *et al.* (2003)
CD28 expression	~100% of $CD4^+$ and $CD8^+$ T cells	~80% of $CD4^+$ T cells, 50% of $CD8^+$ T cells	Lenschow *et al.* (1996)
MHC class II expression	Absent on T cells and endothelial cells	Present on T cells and endothelial cells	Choo *et al.* (1997), Taams *et al.* (1999)
CD52 expression	Not found in mice	Lymphocytes	Tone *et al.* (1999)
Glucocorticoid-sensitivity	High	Low and variable	Claman (1972)

patients; the majority of new treatments were either less effective in these patients, worsened disease or caused severe adverse events. In Table 2 we list a subset of these therapies reflecting this discrepancy.

Antigen-specific therapies

Only one licensed multiple sclerosis therapy (Glatiramer acetate, GA), a synthetic amino acid copolymer (Glu, Ala, Lys and Tyr), emerged from findings in EAE (Teitelbaum *et al.*, 1971). It was designed to mimic encephalitogenic myelin basic protein (MBP) epitopes, but instead it suppresses EAE by other mechanisms in several species, and it reportedly reduces multiple sclerosis relapses by 30% (Johnson *et al.*, 1995). GA has many biological activities including bystander suppression via induction of T_H2 cells that partly cross-react with MBP, and/or upregulation of CNS growth factors (Arnon and Aharoni, 2004). However, its *in vivo* mechanisms are not clear and even its beneficial effects on the main outcome measures in multiple sclerosis (disease progression) have now been questioned in a systematic Cochrane review (Munari *et al.*, 2004).

A more specific therapeutic approach in EAE and multiple sclerosis has been based on an altered peptide ligand of MBP 85–99 that was modified at its main T-cell receptor (TCR) contact sites (Brocke *et al.*, 1996). Despite promising effects in EAE, subcutaneous administration of altered peptide ligand at high doses led to multiple sclerosis exacerbations in some patients, which could be linked to this treatment (Bielekova *et al.*, 2000). A trend towards improved MRI parameters was observed in another phase II trial (Kappos *et al.*, 2000), and an additional phase II study is under way. Its success in EAE may depend on the stereotyped T_H responses of inbred mice.

Oral administration of myelin antigens leads to specific immune hyporesponsiveness in mice. Different doses and feeding regimes have been demonstrated to induce different types of 'oral tolerance'/degrees of immune suppression in different EAE models (Faria and Weiner, 2005). 'Bystander suppression' directed against one tolerogen may suppress reactions against other myelin antigens *in situ*, a major advantage where the key autoimmunizing antigen(s) are not known. However, a large double-blind phase III trial of a single oral dose of bovine myelin in RR multiple sclerosis did not show differences in the number of relapses between placebo and treated groups (Faria and Weiner, 2005). Treatment failure could have been due to the unexpectedly strong

Table 2 Some immunomodulatory approaches of multiple sclerosis and their development from EAE or *in vitro* studies to clinical application*

Treatment approach	Based on clear hypothesis	Rationale confirmed	Efficacy in EAE	Efficacy in multiple sclerosis	Adverse event profile	Status of development	Reference
Glatiramer acetate	No	No	++	+	+++	Approved	Johnson *et al.* (1995)
Altered peptide ligand	Yes	No; i.d.	++	−; i.d.	±	No	Bielekova *et al.* (2000),Kappos *et al.* (2000)
Oral myelin	Yes	Yes	++	−	+++	Not continued after phase III owing to lack of efficacy	Faria and Weiner (2005)
Anti-α_4 integrin	Yes	Yes	+++	+++	±†	Taken off the market	Miller *et al.* (2003)
Anti-CD40L	Yes	Yes	+++	n.k.	±	No	Dumont (2002)
Anti-CD4	Yes	No	+++	±	±	Halted in phase II	van Oosten *et al.* (1997)
Anti-CD52	Yes	Yes	n.a.	++; i.d.	+	Approved for other indication	Coles *et al.* (1999*b*)
Anti-CD25	Yes	No	±	+++; i.d.	++	Approved for other indication	Bielekova *et al.* (2004)
CTLA-4-Ig	Yes	No; i.d.	+++	n.k.	n.k.	In phase III	Kremer (2004)
IFN-β	No	No	+	+	++	Approved	Paty and Li (1993)
IFN-γ	No	No	++	−	−	Stopped in phase I	Panitch *et al.*, 1987)
Anti-TNF antibodies	Yes	No	++(?)	−	−‡	Approved for other indication	van Oosten *et al.* (1996)
TNFR-Ig fusion protein	Yes	No	++(?)	−	− ‡	Approved for other indication	The Lenercept Multiple Sclerosis Study Group and The University of British Columbia multiple sclerosis/MRI Analysis Group (1999)
TGF-β2	Yes	Yes	++	i.d.	−	Stopped in phase I	Calabresi *et al.* (1998)
IL-10	Yes	No	±	i.d.	i.d.	Stopped in phase II	Wiendl *et al.* (2000)
IGF-I	Yes	Yes	+(+)	−; i.d.	++	Phase IIa, not continued	Frank *et al.* (2002)
PDE4 inhibitors	Yes	Yes	++	−; i.d.	+	Halted in phase II	R. Martin *et al.* (unpublished data)
PPARγ agonists	Yes	Yes	++	n.t.	n.a.	Not yet tested in multiple sclerosis	Diab *et al.* (2002), Feinstein *et al.* (2002)
Statins	Yes	Yes	+++	++; i.d.	+	Approved for other indication	Vollmer *et al.* (2004), Youssef *et al.* (2002)
Mitoxantrone	No§	No§	++	++	±	Approved	Hartung *et al.* (2002)
Linomide	No	No	++	++	±	Phase III stopped due to cardiotoxicity	Noseworthy *et al.* (2000*c*)
Laquinimod	No	No	++	++; i.d.	+	In phase II	Polman *et al.* (2005)
FTY720/SP-1 agonist	No	No	+++	++(+); i.d.	+	In phase II	Gonsette (2004), Rausch *et al.*, 2004)
Deoxyspergualin	No	No	+	−	+	After phase II stopped owing to lack of efficacy	Wiendl and Hohlfeld (2002)
Sulphasalazine	Yes	No	±	±	+	In phase III	Noseworthy *et al.* (1998)
IVIG	No	No	±	±	++	In phase II	Hommes *et al.* (2004), Sorensen *et al.* (2002)
Haematopoietic stem cell transplant	Yes	Yes	+	++;i.d.	±; i.d.	In phase III	Mancardi *et al.* (2005), Tyndall and Saccardi (2005)

i.d., insufficient data; n.a., not applicable; n.k., not known; n.t., not tested; *The table depicts whether a therapeutic approach was developed for multiple sclerosis on the basis of a clear and pre-formed hypothesis, whether the rationale for its clinical/EAE testing had later been shown and whether the therapy was effective in EAE and/or multiple sclerosis. Both the clinical efficacy and the tolerability and safety are depicted by + or − signs. In the context of the adverse events, + indicates a favourable profile. The relative weighting reflects the subjective perception of the authors either from own experience or the published literature; †Reasonable safety profile, but one specific severe adverse event (PML). ‡Development of demyelinating episodes and diseases in RA- and Crohn's patients; §Broad immunosuppressant; no specific target.

effects in the placebo group, wrong dose or type of antigen, or route of administration.

Adhesion molecules

Another promising strategy, using a blocking anti-α_4 integrin humanized antibody (natalizumab), emerged from EAE evidence that $\alpha_4\beta_1$ integrin is critical for T cell and monocyte homing to the CNS (Yednock *et al.*, 1992). This mAb was highly effective in pre-clinical EAE studies and successfully completed phase II and III testing in large numbers of multiple sclerosis patients. Because of its remarkable efficacy in multiple sclerosis (Miller *et al.*, 2003), natalizumab was approved by the Food and Drug Administration even before phase III trial data had been published, but was taken off the market four months later because of rare but very severe

adverse events. Three patients had developed progressive multifocal leukoencephalopathy (PML), an often lethal opportunistic infection of the CNS; two died, and one is recovering, though with considerable neurological deficits (Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould *et al.*, 2005; Van Assche *et al.*, 2005). A large *post facto* analysis estimated the risk of PML for a 2-year treatment period to 1 in 1000 patients (Yousry *et al.*, 2006). PML is caused by reactivation and mutation of the highly prevalent polyomavirus JC (JCV), which destroys oligodendrocytes. PML is almost exclusively observed in immunosuppressed individuals, and it is not clear what initiated its unexpected development under natalizumab treatment. JCV persists in kidneys and lymphoid organs, including bone marrow (Monaco *et al.*, 1998). During immunosuppression, latent infection can be reactivated, and JCV disseminates to the CNS (Tornatore *et al.*, 1992). That might have resulted either from compromised T-cell surveillance of the CNS or from mobilization of stem cells and JCV from the bone marrow (Papayannopoulou and Nakamoto, 1993; Ransohoff, 2005), where $\alpha_4\beta_1$ integrin serves as a retaining signal (Simmons *et al.*, 1992). Since JCV is not found in rodents, this adverse event could not have been anticipated from pre-clinical investigations. Therefore, this drug cannot be called a failure of prediction, especially as many thousand patients needed to be treated to unravel potential adverse effects. In addition, the recently published two-year phase III trials underline its compelling effects on relapse rate and clinical progression (Polman *et al.*, 2006; Rudick *et al.*, 2006). In March 2006, The Peripheral and CNS Drugs Advisory Committee, under The Food and Drug Administration, voted unanimously to recommend the return of natalizumab for the treatment of RR multiple sclerosis in a subset group of patients.

Co-stimulatory molecules

Despite its promise in EAE, anti-CD40 ligand (CD154) (Howard *et al.*, 1999) was not developed because of its thromboembolic complications in man (Kawai *et al.*, 2000), which result from its expression on human but not murine platelets. Anti-CD4 therapy was effective in EAE (Waldor *et al.*, 1985), but not in human studies (van Oosten *et al.*, 1997). Anti-CD52, which depletes both $CD8^+$ and $CD4^+$ T-cells (Coles *et al.*, 1999*b*), was never evaluated in EAE, but is very effective against new lesions in multiple sclerosis, though ~30% of treated multiple sclerosis patients develop autoimmune hyperthyroidism (Coles *et al.*, 1999*a*). On the other hand, IL-2 receptor blockade with the humanized anti-CD25 antibody (daclizumab) caused impressive reductions in MRI lesions and improvements in some clinical measures (Bielekova *et al.*, 2004). In this case, the theoretical role of CD25 in promoting T regulatory cells, and equivocal EAE data (Engelhardt *et al.*, 1989; Reddy *et al.*, 2004), might have argued against its use in multiple sclerosis. Interestingly, there is little evidence that it perturbs T regulatory or T_H function; indeed it may act by expanding immunoregulatory NK cells (Bielekova *et al.*, in review). CTLA-4-Ig interferes with co-stimulation from CD80/CD86 molecules on antigen-presenting cells (APCs) to the stimulatory or inhibitory ligands CD28 and CTLA-4 (Alegre *et al.*, 2001). Data in EAE indicate that CTLA-4-Ig is much more effective as a preventive pre-treatment (Cross *et al.*, 1995) than in therapy of ongoing disease (Cross *et al.*, 1999). Treatment with CTLA-4-Ig is also effective in other autoimmune diseases such as rheumatoid arthritis (Kremer *et al.*, 2003), and is currently being tested in a phase III trial in multiple sclerosis.

Cytokines

Cytokines have different effects at different stages of pathogenesis, for example, in the induction phase and the chronic/relapsing phase in EAE. These differences suggest a pleiotropic role in CNS inflammation and might explain some of the below-described discrepancies between EAE and multiple sclerosis.

Interferon-β (IFN-β), the first drug approved for multiple sclerosis, had not been previously tested in EAE. It exerts a wide variety of effects on the immune system: it inhibits both leukocyte proliferation and antigen presentation; it biases towards production of anti-inflammatory cytokines and it inhibits T-cell migration across the blood-brain barrier (Billiau *et al.*, 2004). Although widely used in multiple sclerosis, its long-term effectiveness and side-effects are still uncertain (Filippini *et al.*, 2003). With other cytokines, effects have seemed contradictory in EAE vis à vis multiple sclerosis. In the mid-1990s, it was found that *IFN*-γ knockout mice develop lethal EAE (Ferber *et al.*, 1996), and IFN-γ administration in EAE showed a protective effect on disease severity (Krakowski and Owens, 1996). By then, its use in multiple sclerosis patients had already led to a modest increase in disease exacerbations (Panitch *et al.*, 1987). Although this study is limited, it is unlikely that IFN-γ will ever be tested again in multiple sclerosis.

In contrast, tumour necrosis factor-α (TNF-α) has long been considered a key mediator of multiple sclerosis pathogenesis (Sharief and Hentges, 1991), and its blockade by antibodies or soluble TNF receptors prevents or reverses disease in EAE models (Ruddle *et al.*, 1990; Selmaj *et al.*, 1991, 1995). Paradoxically, this approach worsens disease in multiple sclerosis patients and had to be discontinued (The Lenercept Multiple Sclerosis Study Group and The University of British Columbia Multiple Sclerosis/MRI Analysis Group, 1999; van Oosten *et al.*, 1996). Indeed, a substantial number of cases developed their first demyelinating event while being treated with anti-TNF-α agents for other diseases such as rheumatoid arthritis or Crohn's disease (Hyrich *et al.*, 2004). Despite the data that TNF-α is an important component in the pathogenesis in EAE, a precise role for TNF-α in multiple sclerosis remains unclear. However, subsequent EAE experiments using TNF-α gene deleted mice ($TNF\text{-}\alpha^{-/-}$) surprisingly showed that $TNF\text{-}\alpha^{-/-}$ mice displayed profound neurological impairment and high mortality with extensive

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