

# Atacicept: targeting B cells in multiple sclerosis

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**Abstract:** Multiple sclerosis (MS) has traditionally been considered to be a T-cell-mediated disease. However, there is an increasing body of evidence for the involvement of B cells and autoantibodies in the pathology of this disease, providing a rationale for treatments directed against B cells. In this paper we summarize evidence for the key role of B cells in the immunopathology of MS and review data supporting the use of a novel B-cell targeted therapy, atacicept, in this condition. Atacicept is a human recombinant fusion protein that comprises the binding portion of a receptor for both BLYS (B-Lymphocyte Stimulator) and APRIL (A Proliferation-Inducing Ligand), two cytokines that have been identified as important regulators of B-cell maturation, function and survival. Atacicept has shown selective effects on cells of the B-cell lineage, acting on mature B cells and blocking plasma cells and late stages of B-cell development while sparing B-cell progenitors and memory cells. The efficacy of atacicept in animal models of autoimmune disease and the biological activity of atacicept in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) has been demonstrated. Clinical studies were initiated to investigate the safety, tolerability and efficacy of atacicept in patients with MS. An unexpected increase in inflammatory activity in one of the trials, however, led to suspension of all atacicept trials in MS.

**Keywords:** multiple sclerosis, B lymphocytes, B cells, treatment, immunotherapies, atacicept

## Introduction

Multiple sclerosis (MS) is a progressive inflammatory disease of the central nervous system (CNS) [Lassmann *et al.* 2007] in which leukocytes and antibodies attack myelin sheaths and axons in the CNS, resulting in axonal demyelination, damage and destruction [Kornek *et al.* 2000].

The pathology of MS appears to be heterogeneous, and distinct patterns of disease have been described. Key features include the presence of T cells and macrophages, B cells, immunoglobulins (Igs) and complement activation products, myelin protein loss, oligodendrocyte destruction, and the location and extension of plaques within the CNS [Lucchinetti *et al.* 2000]. These patterns may reflect the underlying autoimmune pathology in the individual patient.

The exact cause of MS is still unknown, but several aetiological factors have been proposed, including environmental [Marrie, 2004], immunological [Hohlfeld and Wekerle, 2004] and genetic factors [Barcellos *et al.* 2003; Willer *et al.* 2003]. It seems

probable that MS is a multifactorial disease in which environmental factors trigger an autoimmune response in genetically susceptible individuals [Handel *et al.* 2010; Ramagopalan *et al.* 2009]. Myelin basic protein and myelin oligodendrocyte glycoprotein (MOG) might represent relevant targets of autoimmune responses, but the heterogeneous nature of MS suggests that there may be many and varied targets in different individuals. Immunological mechanisms proposed to induce the autoimmune response seen in MS include [Sospedra and Martin, 2005]:

- molecular mimicry: activation of autoreactive cells by cross-reactivity between self-antigens and foreign antigens;
- bystander activation: activation of autoreactive cells by nonspecific inflammatory events that occur during infection.

Until recently, MS was considered to be primarily a T-cell-mediated disease [Sospedra and Martin, 2005]. Both CD4+ and CD8+ T cells are present in MS lesions, and have been shown to be essential

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features of MS pathology [Chitnis, 2007; Sospedra and Martin, 2005]. Activated CD4+ Th1 cells contribute to inflammation in the CNS and may increase the permeability of the blood–brain barrier (BBB) [Delgado and Sheremata, 2006; Hemmer *et al.* 2002], whereas CD8+ T cells can damage axons directly [McDole *et al.* 2006; Medana *et al.* 2001]. Existing therapies for MS aim to prevent autoimmune destruction of the CNS, and all either target T cells or produce more generalized suppression of the immune system. Likewise, therapies for many other autoimmune disorders have generally focused on suppressing or modifying T-cell responses. However, growing evidence for a central role of B cells in MS suggests that B-cell targeted therapies might represent interesting and relevant treatment strategies that may broaden our limited therapeutic armamentarium.

Several potential therapies for MS that affect B cells or both T and B cells are in clinical development:

- Agents that target both T and B cells include:
  - fingolimod, which affects lymphocyte trafficking [Cohen *et al.* 2010, Chun and Hartung, 2010; Brinkmann, 2009; Brown *et al.* 2007; Hemmer and Hartung, 2007; Chofflon, 2005];
  - alemtuzumab, which binds surface CD52 causing profound lymphocyte depletion [Coles *et al.* 2008; Cree, 2006];
  - teriflunomide, an antimetabolite that blocks production of T and B cells [Zeyda *et al.* 2005].
- Specific B-cell targeting agents include:
  - rituximab, a chimeric monoclonal antibody against CD20 that is expressed on the surface of B cells, but not terminally differentiated plasma cells [Hauser *et al.* 2008; Simpson and Coles, 2007];
  - ocrelizumab and ofatumumab, fully humanized anti-CD20 monoclonal antibody that target the same cells as rituximab, but with different binding sites [Genovese *et al.* 2008];
  - belimumab, a humanized monoclonal antibody targeting the soluble B-cell activating factor;
  - LY2127399, a fully human IgG4 monoclonal antibody targeting both membrane-bound and soluble B-cell activating factor;
  - atacept, a fusion protein that blocks plasma cell function and the late stages of B-cell development.

Rituximab, ocrelizumab, and ofatumumab produce profound, selective depletion of all

circulating CD20+ B cells but do not directly affect T cells [Stüve *et al.* 2009; Genovese *et al.* 2008; Liossis and Sfrikakis, 2008; Silverman, 2006].

Indirect effects on T cells have been reported, based on the observation that T-cell numbers are decreased in patients treated with rituximab [Cross *et al.* 2006]. In contrast, atacept selectively inhibits antigen-driven B-cell responses and plasma cell survival, while sparing B-cell progenitors and memory cells.

In this article we summarize the evidence for B-cell involvement in MS and provide a rationale for the use of B-cell targeting therapies in this disease. The mechanism of action of atacept will be reviewed alongside preclinical evidence of activity in animal models of MS, and early clinical results with atacept in autoimmune diseases will be presented.

### Review criteria

A search of PubMed was performed to identify English-language articles published on ‘B cell’ AND ‘multiple sclerosis’ AND ‘therapy’ in the last 10 years. Additional searches for ‘B cell’ AND ‘EAE’, and ‘atacept’ were also performed. An informal review of these articles was then performed to identify those considered most relevant to the focus of the article (i.e. evidence for B cells in the pathogenesis of MS; targets of B cell therapy; current B-cell targeting therapies for autoimmune diseases; evidence for efficacy of B-cell targeting therapies in animal models of autoimmune disease). Additional searches were performed as needed to identify relevant articles relating to the biological functions of BLYS and APRIL, and primary papers were cited. Information on the ongoing clinical development of atacept was sourced from published abstracts from the relevant congress, and information contained within associated posters where available.

### B cells: key players in MS pathogenesis

In MS and other autoimmune diseases, B cells have traditionally been considered to play a secondary T-cell-dependent role, producing pathogenic autoreactive antibodies that promote tissue destruction by recruiting macrophages and through activation of the complement pathway [Hawker, 2008]. However, B cells may play a more central role in MS immunopathogenesis. In addition to producing antibodies, activated B cells can act as antigen-specific antigen-presenting cells for T cells; this may be crucial for rapid

responses to B-cell targeted therapies. Within the T-cell–B-cell synapse, B cells produce costimulatory molecules that can influence the differentiation of T cells to Th1 or Th2 cells [Zouali, 2008]. B cells also produce cytokines (interleukin [IL]-6 and IL-10, and tumour necrosis factor [TNF]- $\alpha$ ) that activate macrophages and, in the case of IL-6 and IL-10, stimulate further B-cell proliferation.

This key role of B cells in MS is corroborated by evidence from the experimental autoimmune encephalomyelitis (EAE) mouse model of MS. When EAE is induced in B-cell deficient mice, a characteristic feature of the disease is a lack of demyelination [Svensson *et al.* 2002]. There is now considerable evidence from clinical studies that also indicates that B cells play a central role in the pathogenesis of MS (Box 1).

#### *B cells and autoantibodies in the CNS in MS*

Patients with MS generally have normal numbers of circulating B cells and plasma cells, but increased B-cell numbers in the CNS. B cells in the CNS of patients with MS are mainly memory cells and short-lived plasmablasts, and a consequent relative reduction in naive B cells is observed [Cepok *et al.* 2005; Corcione *et al.* 2004]. Plasmablasts persist in the cerebrospinal fluid (CSF) throughout the course of MS, and numbers of these cells correlate with intrathecal IgG synthesis and with active inflammatory parenchymal disease, as assessed by magnetic resonance imaging (MRI) [Cepok *et al.* 2005], suggesting that these short-lived plasmablasts could be a major effector B-cell population in MS.

The presence of oligoclonal Ig bands in the CSF is a hallmark of MS and reflects ongoing, persistent humoral immune responses. Sequence analysis of antibodies in the CSF of patients with MS

**Box 1.** Evidence supporting the key role of B cells in the pathogenesis of multiple sclerosis (MS).

- Clonal expansion of B cells in the central nervous system (CNS)
- Oligoclonal bands in the cerebrospinal fluid
- Presence of B cells in MS lesions
- Autoantibody production against CNS components
- Presence of antibodies in MS lesions
- Intrathecal ectopic germinal centres
- Histopathological evidence of antibody-mediated pathology
- Efficacy of plasmapheresis and B-cell targeting therapies

has revealed a high frequency of clonally expanded B cells, providing evidence of somatic hypermutation and antigen-driven B-cell selection [Owens *et al.* 2006]. This clonal expansion of B cells occurs early in demyelinating disease: expanded B- and plasma-cell clones can be found in the CSF of some patients only a few months after the onset of clinically isolated syndrome (CIS) [Qin *et al.* 2003]. The antigen target of these antibodies has yet to be identified, but myelin components, lipids, oligodendrocyte proteins and viruses have been proposed. For example, the presence of intrathecal antimyelin IgG and IgM has been associated with rapidly progressing disease [Franciotta *et al.* 2008; Zouali, 2008; Lambracht-Washington *et al.* 2007; Kolln *et al.* 2006; Owens *et al.* 2006; Perini *et al.* 2006; Villar *et al.* 2005; Archelos *et al.* 2000].

Several features of MS lesions suggest that B cells and antibodies contribute to their development [Archelos *et al.* 2000]. B cells and plasma cells have been detected in MS lesions, indicating that B cells can cross the BBB, and their numbers are highest in active lesions and during the late stages of the disease. Autoantibodies specific for myelin components have also been found in MS lesions. In addition, the capping of surface IgG on microglia/macrophages engaged in myelin breakdown [Prineas and Graham, 1981], and the codeposition of IgG and activated complement fragments and membrane attack complexes at the borders of active MS lesions [Archelos *et al.* 2000], strongly implicate antibodies as effectors of demyelination. Vesicles enriched with membrane attack complex have also been demonstrated in the CSF of patients with MS [Scolding *et al.* 1989] indicating that complement contributes to myelin damage.

It has been suggested that different pathophysiological mechanisms in MS result in specific patterns of demyelination in individual patients [Lucchinetti *et al.* 2000]. Among the patterns of demyelination in active lesions described by Lucchinetti and colleagues, types I and II were histologically similar to T-cell-mediated and T-cell plus antibody-mediated EAE, respectively. Thus, antibody-mediated demyelination may be a predominant pathogenic mechanism in the formation of white-matter MS lesions in a proportion of patients [Lucchinetti *et al.* 2000].

### B-cell activation and maturation in the CNS

The enrichment of B-cell subsets that are normally found in germinal centres of secondary lymphoid follicles has been reported within the CSF of patients with MS, indicating that B-cell affinity maturation may occur or recur in the CNS [Krumbholz *et al.* 2006; Cepok *et al.* 2005]. High levels of chemokines known to support germinal-centre formation and function are also present in the CSF of patients with MS [Scolding *et al.* 1989]. Indeed, ectopic lymphoid follicles have been detected in the CNS of patients with progressive MS [Serafini *et al.* 2004]. In a post-mortem study of 29 patients with secondary progressive MS (SPMS) and seven patients with primary progressive MS (PPMS), B-cell follicles were found in the meninges entering the cerebral sulci in 41.4% of patients with SPMS, but not in patients with PPMS [Magliozzi *et al.* 2007].

These data suggest that an immunopathogenic mechanism exists whereby B-cell follicles developing in the brain have a major detrimental impact on the integrity of cortical structures. Emerging evidence suggests that, as the disease evolves into the progressive stage, the immune response, in particular that driven by B cells, is compartmentalized and anatomically and functionally remote from control by systemic immune factors.

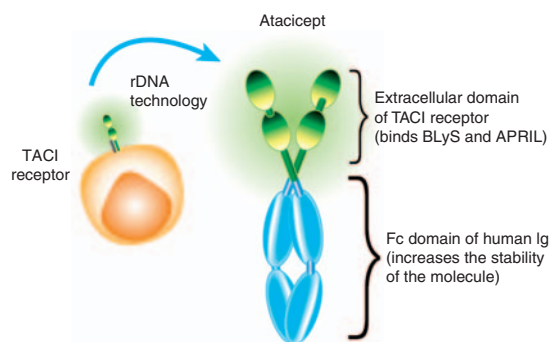
Many factors that promote B-cell differentiation, function and survival have been identified within MS lesions, including TNF- $\alpha$ , IL-1, IL-2, IL-4, IL-6 and IL-10 [Franciotta *et al.* 2008]. In addition, T cells expressing CD40L (CD154), which is essential for T-cell dependent B-cell activation, have been found in MS lesions. Elevated levels of nerve growth factor, which promotes the survival of memory B cells, have also been reported in the CSF of patients with MS. B-Lymphocyte Stimulator (BLyS; also called B-cell Activating Factor of the TNF Family [BAFF]; CD257) and APRIL (A Proliferation-Inducing Ligand; CD256) are members of the TNF superfamily that play an important role in B-cell survival and proliferation [Dillon *et al.* 2006; MacKay and Tangye, 2004]. BLyS is usually expressed in the brain at levels about 10% of those in lymphatic tissues. In MS lesions, however, BLyS expression is strongly upregulated to levels observed in lymphatic tissues [Krumbholz *et al.* 2005]. Increased APRIL expression in astrocytes has been noted in the brain of patients with MS compared with healthy controls

[Thangarajh *et al.* 2007]. Elevated expression of both BLyS and APRIL has also been reported in the monocytes and T cells of patients with MS [Thangarajh *et al.* 2005, 2004]. BLyS has been found to be localized to astrocytes, close to immune cells expressing its receptor, BAFF-R [Krumbholz *et al.* 2005]. Thus, astrocytes appear to be a nonimmune source of BLyS, and CNS-produced BLyS may support B-cell survival in inflammatory diseases such as MS.

Further evidence for a role of B cells in the immunopathology of MS is the efficacy of B-cell- and antibody-directed therapies, such as plasmapheresis and rituximab, in treating some cases of MS [Hauser *et al.* 2008; Hemmer and Stüve, 2007; Weinshenker *et al.* 1999]. Interestingly, B cells may also promote repair in the CNS: activated B cells secrete brain-derived neurotrophic factor in the MS lesion, which is known to prevent axonal loss after neuronal injury and in neurodegenerative disorders [Kerschensteiner *et al.* 1999].

### B-cell targeting in autoimmune disease

Atacept is a novel, soluble, fully human recombinant fusion protein containing the extracellular ligand-binding portion of the TACI (Transmembrane Activator and CAML [calcium-modulator and cyclophilin-ligand]-Interactor) receptor and a modified Fc portion of human IgG [Gross *et al.* 2000] (Figure 1). Atacept, therefore, contains the binding portion of a receptor that binds both BLyS and APRIL, two important cytokine



**Figure 1.** The structure of atacept: a recombinant fusion protein comprising the extracellular ligand-binding domain of the naturally occurring TACI (Transmembrane Activator and CAML [calcium-modulator and cyclophilin-ligand]-Interactor) receptor, linked to a recombinant Fc domain of human immunoglobulin (Ig). BLyS, B-Lymphocyte Stimulator; APRIL, A Proliferation-Inducing Ligand.



regulators of B-cell maturation, function and survival. Atacicept has high affinity and specificity for these two cytokines, acting as an antagonist by preventing receptor binding [Dillon *et al.* 2006; Thangarajh *et al.* 2005; Weinschenker *et al.* 1999]. Atacicept was developed specifically for the treatment of B-cell-mediated diseases, and is being evaluated for the treatment of the autoimmune diseases systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

#### *BLyS, APRIL and their receptors*

BLyS and APRIL are members of the TNF cytokine superfamily. BLyS is a potent stimulator of B-cell maturation, function and survival, and is expressed by monocytes, dendritic cells, neutrophils and T cells; BLyS exists in membrane-bound and secreted, soluble forms [Thangarajh *et al.* 2004; Schneider *et al.* 1999]. APRIL is a structural homologue of BLyS that is secreted as a soluble protein by monocytes, macrophages, dendritic cells, neutrophils and T cells [Thangarajh *et al.* 2004], and it shares some of the biological properties of BLyS [Dillon *et al.* 2006; Schneider *et al.* 1999].

Three receptors have been identified that have unique binding affinities for BLyS and APRIL [Marsters *et al.* 2000]. These are:

- TACI;
- BCMA (B-cell maturation antigen);
- BAFF-R.

TACI and BCMA bind homotrimers of BLyS and APRIL, whereas BAFF-R binds only homotrimers of BLyS with high affinity [Roschke *et al.* 2002] APRIL and BLyS also form heterotrimers that bind only to TACI (Figure 2). *In vitro* studies with Ig-fusion proteins for all three receptors have shown that only TACI-Ig blocks the biological activity of the heterotrimeric complexes [Yan *et al.* 2001], indicating that these heterotrimers exert their effects via this receptor. Studies with TACI-deficient mice indicate that TACI plays a critical role in B-cell homeostasis [Seshasayee *et al.* 2003; Yan *et al.* 2001] and is a key mediator of Ig class switching [Castigli *et al.* 2005b]. Mutations in TACI have also been associated with common variable immunodeficiency and IgA deficiency [Castigli *et al.* 2005a]. TACI is, therefore, an important receptor in B-cell function and survival. The expression of the three receptors varies in different B-cell subsets: BAFF-R is expressed earliest, being present on

immature B cells, but not on terminally differentiated plasma cells, whereas TACI and BCMA are expressed on mature B cells and plasma cells [Hsu *et al.* 2002]. BAFF-R, which is exclusively expressed on B lymphocytes, is thought to be the primary receptor through which BLyS exerts its effects on cell survival [Thompson *et al.* 2001].

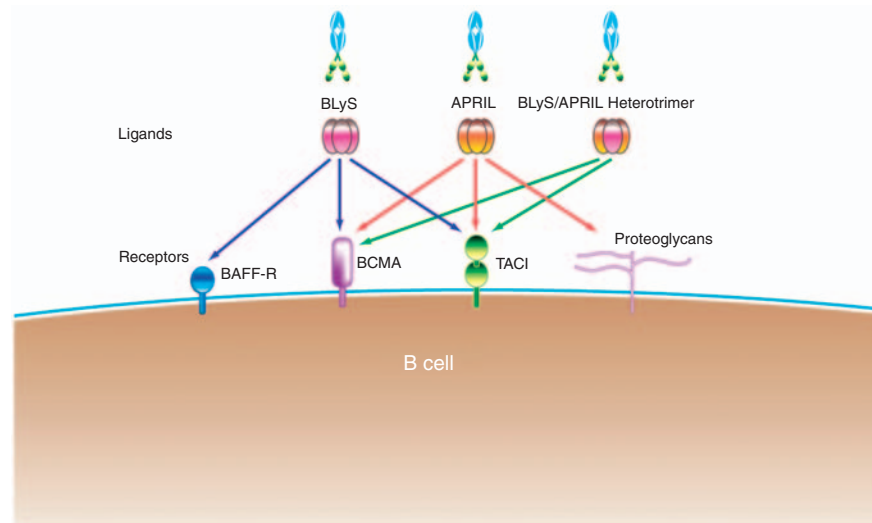
BLyS and APRIL have been implicated in the pathogenesis of several autoimmune diseases including MS, SLE and RA. Both BLyS and APRIL are overexpressed, locally and systemically [Dillon *et al.* 2006], and circulating, biologically active, heterotrimeric forms have been detected in individuals with systemic autoimmune diseases [Roschke *et al.* 2002].

#### *Mechanism of action of atacicept*

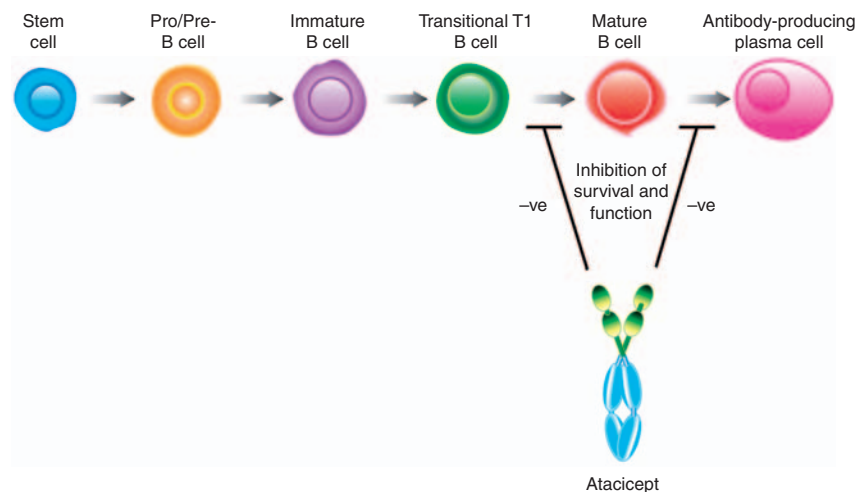
Atacicept binds to BLyS and APRIL on their cognate receptors, and has been shown to neutralize all forms of BLyS and APRIL homo/heterotrimers, inhibiting their effects on B-cell survival and key B-cell functions. Blockade of both BLyS and APRIL is needed to target antibody-secreting plasma cells, with preclinical data suggesting that BLyS and APRIL are both important for the survival of long-lived bone marrow plasma cells [Benson *et al.* 2008]. Atacicept indirectly targets mature B cells and short-lived antibody-producing plasma cells by inhibiting B-cell survival at stages after the T1 transitional stage, while sparing B-cell progenitors and memory B cells (Figure 3) [Dillon *et al.* 2006; Gross *et al.* 2001]. Thus, survival of short-lived plasma cells and serum Ig levels are reduced, as documented in healthy volunteers and in patients with SLE or RA [Tak *et al.* 2008; Dall'era *et al.* 2007; Munafo *et al.* 2007]. Studies in mice have shown that the ability to eliminate viral infections is retained during atacicept treatment [Heffernan *et al.* 2008].

#### *Targeting BLyS and APRIL in disease models*

In animal models, the overexpression of BLyS has been associated with autoimmune disease onset and severity [Gross *et al.* 2000; MacKay *et al.* 1999], highlighting BLyS antagonism as a potential therapeutic approach. Transgenic mice overexpressing BLyS have increased B-cell numbers and enlarged lymphoid organs, and develop an autoimmune condition similar to SLE [Do *et al.* 2000; MacKay *et al.* 1999]. These mice



**Figure 2.** Mechanism of action of atacept: binding of BlyS (B-Lymphocyte Stimulator) and APRIL (A Proliferation-Inducing Ligand) via their common receptor, TACI (Transmembrane Activator and CAML [calcium-modulator and cyclophilin-ligand]-Interactor). BAFF-R, B-cell Activating Factor of the TNF Family receptor; BCMA, B-Cell Maturation Antigen. Modified from Dillon *et al.* [2006] with permission.



**Figure 3.** Effect of atacept on B cells: atacept inhibits memory B cell survival and function, a B-cell population after the T1 transitional stage in the development of B lymphocytes. Theoretically, there might also be an inhibitory effect of atacept on antibody-producing plasma cells. Both target cell populations are antigen experienced, whereas all stages prior to that are antigen naive.

also develop a secondary, age-related pathology reminiscent of Sjögren’s syndrome. In contrast, mice deficient in BlyS or with a mutation in BAFF-R have reduced numbers of peripheral mature B cells but normal immature B cells and bone-marrow function [Munafa *et al.* 2007]. The role of APRIL in *in vivo* B-cell biology remains somewhat unclear. Transgenic mice deficient in APRIL retain B cells, suggesting that this growth factor does not play a critical role in B-cell development [Varfolomeev *et al.* 2004]. APRIL does, however, play an important role in several key

B-cell functions, including antigen presentation and Ig class switching [Dillon *et al.* 2006].

*In vivo* experimental studies confirm that targeting BlyS/APRIL–TACI interactions affects B-cell responses. Overexpression of soluble TACI (TACI-Ig) in transgenic mice has been shown to result in fewer mature B cells and reduced circulating antibody levels than in wild-type mice [Gross *et al.* 2001]. Modulation of B-cell survival by atacept has been demonstrated in *in vivo* preclinical studies. Normal mice treated with

atacept produced markedly fewer mature B cells and lower circulating antibody levels than untreated controls [Carbonatto *et al.* 2008; Gross *et al.* 2001]. Similar effects have been reported in healthy monkeys treated with atacept [Carbonatto *et al.* 2008]. In mouse models of collagen-induced arthritis and of SLE, atacept was able to inhibit the development of pathogenic B cells and antibodies, and improve disease features [Dillon *et al.* 2006; Gross *et al.* 2001]. These preclinical results indicate that atacept may provide a novel approach to treating autoimmune diseases.

#### *Atacept in SLE and RA*

The biological activity of atacept has been confirmed in clinical studies in patients with SLE or RA [Nestorov *et al.* 2010, 2008; Munafo *et al.* 2007; Kalled, 2005]. The pathological role of B cells in both these autoimmune conditions has been established [Martinez-Gamboa *et al.* 2006; Anolik and Sanz, 2004].

The safety and tolerability of subcutaneous atacept has been assessed in a phase Ib, multicentre, double-blind, placebo-controlled, dose-escalation study of 49 patients with SLE [Dall'Era *et al.* 2007]. Atacept was well tolerated, and produced rapid and sustained reductions in circulating Igs after the first treatment dose. Effects on mature and total B-cell numbers were also seen. The effects of atacept were most pronounced in the cohorts of patients who received repeated (4-weekly) doses. Importantly, the rate of infections did not differ between patients receiving atacept or placebo. Recent findings in another phase Ib study of 24 patients with mild-to-moderate SLE that received three single doses, multiple doses of atacept by intravenous route or placebo corroborated these findings [Pena-Rossi *et al.* 2009].

A phase Ib, exploratory, multicentre, double-blind, placebo-controlled, dose-escalating, single- and repeat-dose study has also been performed to assess the safety and pharmacokinetics of atacept in patients with RA [Nestorov *et al.* 2008; Tak *et al.* 2008]. Subcutaneous atacept was well tolerated, both systemically and locally, and treatment produced rapid reductions in Ig levels in the peripheral blood; the largest reduction was seen in IgM. Levels of circulating IgA, IgG and IgM rheumatoid factor were also lowered. Atacept treatment produced biphasic effects on total (defined by CD19+), mature

(CD19+, IgD+, CD27-), memory (CD19+, CD20+, CD27+, CD38-), immature (CD19+, IgD-, CD27-) and 'naive' (CD19+, CD20+, CD27-, CD38-) B cells. An initial dose-related increase in cell numbers followed the first dose of atacept, which was mainly accounted for by an increase in memory B cells. A later, sustained dose-related reduction in B-cell concentrations to below predose levels was seen, with the effect on mature B-cell numbers being particularly pronounced.

In the phase Ib studies described above, atacept was found to be well tolerated locally and systemically. The most frequently observed adverse events (AEs), both in patients with RA and those with SLE, included nausea, fatigue, headache, rhinitis, nasopharyngitis and chronic pyelonephritis. Severe AEs were not observed in patients with SLE treated with either single- or repeated-dose atacept; the only severe AE reported in this patient population involved a patient receiving placebo treatment [Do *et al.* 2000]. In contrast, severe AEs were reported in 5% of patients with RA exposed to atacept, although half were considered to be unrelated or unlikely to be related to the study drug [Carbonatto *et al.* 2008]. Overall, both for the patients with SLE and those with RA, the nature and frequency of AEs was similar among patients exposed to atacept or placebo. Among patients with SLE or RA, injection-site reactions (ISRs, which includes redness and swelling) were more common in the atacept arm of each trial than in the placebo arm [Carbonatto *et al.* 2008; Thompson *et al.* 2001]. In addition, patients with RA who received atacept experienced more frequent skin and subcutaneous tissue disorders than those who received placebo, although the small number of patient included in the trial did not allow a causal relationship to be established [Carbonatto *et al.* 2008]. Good local and systemic tolerability were also observed with single-dose atacept among healthy volunteers [Do *et al.* 2000]. Indeed, in the healthy-volunteer study all reported treatment-emergent AEs were transient and mild or moderate [Do *et al.* 2000]. Furthermore, no clinically significant changes in vital signs or laboratory parameters were observed over the course of the study [MacKay *et al.* 1999]. Taken together, evidence from the phase I trials in healthy volunteers and patients with systemic autoimmune diseases suggest that atacept is generally well tolerated, but may be associated with ISRs.

### Atacept in experimental models of MS

In addition to the role of B cells in MS, several lines of evidence suggest that atacept has therapeutic potential in this disease. BLYS and APRIL have been shown to be upregulated in peripheral blood monocytes and T cells of patients with MS [Thangarajh *et al.* 2005, 2004], and BLYS is strongly expressed on astrocytes within MS lesions [Krumbholz *et al.* 2005], suggesting that the targets of atacept are involved in MS pathogenesis.

Administration of an antagonist of BLYS has been shown to delay the onset and reduce the severity of EAE [Pena-Rossi *et al.* 2009; Huntington *et al.* 2006]. The activity of atacept as prophylaxis or treatment is currently being assessed in two mouse EAE models of MS: the primarily B-cell dependent model using sensitization with recombinant MOG (rMOG), and the primarily T-cell dependent MOG peptide-EAE model. In both models, prophylactic atacept produced marked reductions in circulating mature B-cell numbers and in serum IgM and IgG levels, and significantly delayed disease onset compared with that in vehicle-treated controls. Significant reductions in disease incidence and severity were seen after the administration of atacept in the rMOG-EAE model, which were associated with reduced B-cell infiltration into the CNS. Atacept, therefore, can inhibit pathological B-cell-dependant processes in EAE with a consequent reduction in disease activity.

### Atacept: clinical development in MS

Two phase II studies of atacept in MS were initiated, one in patients with MS and one in patients with optic neuritis (ON) as a first demyelinating event suggestive of MS.

#### *The ATAMS study*

The ATAMS (ATacept in Multiple Sclerosis) study (IMP28063, ClinicalTrials.gov identifier: NCT00642902) was designed to assess the safety and tolerability of atacept and its effects on CNS inflammation in relapsing MS, and determine a minimally effective dose. Patients were eligible for the study if they had a diagnosis of relapsing–remitting MS (RRMS), an Expanded Disability Status Scale (EDSS) score of 0–5.5 and fulfil one of the following criteria: at least two documented relapses during the previous 2 years; at least one documented relapse in the year prior to enrolment, or at least one T1 gadolinium (Gd)-enhanced lesion on MRI at

screening. The study aimed to recruit 300 patients, randomized 1:1:1:1 to receive one of three doses of subcutaneous atacept or placebo. The primary endpoint was the mean number of T1 Gd-enhancing lesions per patient per scan between weeks 12 and 36, inclusive. Secondary endpoints included the number of new T1 hypointense lesions and the proportion of patients who remain relapse-free over the course of the study.

In the ATAMS study an increase in inflammatory disease activity was reported. This led to a suspension of all atacept trials in MS. Patients are currently being followed up to obtain further safety information and the analysis of the resulting data will be published when available.

#### *The ATON study*

A complementary Phase II study to ATAMS was performed in patients with ON. The ATON (ATacept in Optic Neuritis) study (IMP28156, ClinicalTrials.gov identifier: NCT00624468) was initiated to assess the safety and tolerability of atacept in patients with ON. This study should also explore the ability of atacept to preserve retinal nerve fibre layer (RNFL) thickness, as assessed by optical coherence tomography (OCT). Reduced RNFL thickness is associated with visual impairment and brain atrophy in MS, with increasing overall neurological impairment (as shown by changes in EDSS and Multiple Sclerosis Functional Composite scores) and with MS disease duration [Gordon-Lipkin *et al.* 2007; Fisher *et al.* 2006]. Thus, the assessment of degenerative changes of the optic nerve/RNFL by OCT can be used as a marker of CNS neurodegeneration and is a recognized model system to test neuroprotective treatment strategies [Frohmann *et al.* 2006]. Patients diagnosed with unilateral symptomatic ON as a CIS were randomized 1:1 to receive either subcutaneous atacept, 150 mg every week with a 4-week loading dose, or placebo for a total of 36 weeks. The target sample size was 82 patients. The primary endpoint was the change in RNFL thickness in the affected eye between baseline and week 36. Secondary endpoints included the difference in RNFL thickness between the affected and unaffected eye, changes in macular thickness and volume over 36 weeks, visual function and the incidence of treatment-emergent AEs.



## Conclusions

B cells play a key role in the pathogenesis of MS, and therefore represent a promising potential target for treatments. Currently, all approved MS treatments target T-cell-mediated processes alone or produce global effects on immune function, leaving key B-cell-mediated pathogenic processes largely unaffected. There is apparently a need for B-cell targeting therapies in MS. Such therapies may provide wider treatment options for patients with progressive disease, and may also benefit those in whom current treatments achieve suboptimal outcomes. Therapies that target novel pathways also provide the opportunity for combination therapy; it is logical to speculate that in a disease such as MS with a complicated pathology, targeting multiple pathways will be necessary to achieve optimal outcomes for patients.

The specific, selective effects of atacept on mature B cells, and particularly plasma cells, made this drug appear as a promising candidate for targeting pathogenic B lymphocytes in MS. In contrast to other B-cell targeting therapies in development, atacept does not cause generalized depletion of B cells, but affects only mature, antibody-secreting cells. This specific effect on mature B cells suggests that atacept theoretically may have limited impact on the immune system leaving beneficial immune response intact. However, an unexpected increase in disease activity in the ATAMS trial led to the suspension of all atacept trials in MS. At present, reasons for the observed increase in disease activity remain unknown but are currently under investigation. This underlines the difficulties in translating experimental insights successfully from bench to bedside [Hohlfeld and Wiendl, 2001].

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## Conflict of interest statement

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