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CELLULE BETA

(54) Title: FC GAMMA IIB RECEPTOR FOR THE TREATMENT OF B CELL MEDIATED MULTIPLE SCLEROSIS

(57) **Abrégé/Abstract:**

The invention relates to the Fc γ receptor (Fc gamma receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis. The invention relates to pharmaceutical compositions containing the Fc γ receptor (Fc gamma receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis.

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Abstract

The invention relates to the Fc γ receptor (Fc gamma receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis. The

5 invention relates to pharmaceutical compositions containing the Fc γ receptor (Fc gamma receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis.

FC GAMMA IIB RECEPTOR FOR THE TREATMENT OF B CELL MEDIATED MULTIPLE SCLEROSIS

FIELD OF THE INVENTION

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The invention is in the field of biotechnology and therapeutics. The invention relates to the Fc γ receptor (Fc-gamma receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis.

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BACKGROUND OF THE INVENTION

Current hypotheses favour the concept that T cells play a pivotal role in the pathogenesis of Multiple Sclerosis (MS), which was initially based upon the observation that T cells are the predominant lymphocyte class present in MS lesions (Windhagen, *et al.*, Cytokine, secretion of myelin basic protein reactive T cells in patients with multiple sclerosis, Journal of Neuroimmunology, 91:1-9, 1998; Hafler, D.A., *et al.*, Oral administration of myelin induces antigen-specific TGF-beta 1 secreting cells in patients with multiple sclerosis, Annals of the New York Academy of Science, 835:120-131, 1997; Lovett-Racke, A.E., *et al.*, Decreased dependence of myelin basic protein-reactive T cells on CD28-mediated costimulation in multiple sclerosis patients, Journal of Clinical Investigation, 101:725-730, 1998). This observation continues to be a cardinal hallmark of the disease, and is supported by a number of observations. For example, active CD4+ T helper cells bearing anti-myelin

25 T cell receptors (TCRs) are present in the cerebrospinal fluid (CSF) of patients with MS. In addition, elevated levels of Th1-like cytokines have been detected in the CSF of patients with MS and have been correlated with worsening of the disease in some cases (Calabresi *et al.*, Cytokine expression in cells derived from CSF of multiple sclerosis patients, Journal of Neuroimmunology, 89:198-205, 1998).

There has, however, also been evidence that B cells may be involved in the development and perpetuation of MS including:

- (1) elevated immunoglobulin levels in the CSF of MS patients (Link, H., *et al.*, Immunoglobulins in multiple sclerosis and infections of the nervous system, Archives of Neurology, 25:326-344, 1971; Link, H., *et al.*, Immunoglobulin class and light chain type of oligoclonal bands in CSF in multiple sclerosis determined by agarose gel electrophoresis and immunofixation, Ann. Neurol; 6(2):107-110, 1979; Perez, L., *et al.*, B cells capable of spontaneous IgG secretion in cerebrospinal fluid from patients with multiple sclerosis: dependency on local IL-6 production, Clinical Experimental Immunology, 101:449-452, 1995),
- (2) oligoclonal banding in the CSF of MS patients (Link, H., *et al.*, Immunoglobulin class and light chain type of oligoclonal bands in CSF in multiple sclerosis determined by agarose gel electrophoresis and immunofixation, Ann. Neurol., 6(2):107-110, 1979),
- (3) skewing of the $\kappa:\lambda$ ratio in the CSF of MS patients (Hauser, S.L., *et al.*, Clonally restricted B cells in peripheral blood of multiple sclerosis patients: kappa/lambda staining patterns, Annals of Neurology, 11:408-412, 1982),
- (4) the presence of anti-myelin antibodies in the CSF of MS patients (Sun, J. H., *et al.*, B cell responses to myelin-oligodendrocyte glycoprotein in multiple sclerosis, Journal of Immunology, 146:1490-1495, 1991), and
- (5) the demonstration that antibodies from the CSF of MS patients may contribute to the overall extent of tissue injury in these patients (Lassmann, H., *et al.*, Experimental allergic encephalomyelitis: the balance between encephalitogenic T lymphocytes and demyelinating antibodies determines size and structure of demyelinated lesions, Acta Neuropathology, 75:566-576, 1988).

A number of publications demonstrate such B cell mediation: Bourquin, *et al.*, The Journal of Immunology, 2003, 171:455-461; Stromnes *et al.* Nature Protocols, Vol. 1,

No. 4, 2006: 1810-1818; Stromnes et al Nature Protocols, Vol. 1, No. 4, 2006: 1952-19160; Oliver, et al., The Journal of Immunology, 2003, 171: 462-468;

The basic role of B cells in the immune system is to mediate Humoral Immune responses. That is, to secrete proteins called antibodies (or immunoglobulins) that bind to foreign bodies and mark them for elimination from the body by other immune cells such as NK cells and macrophages.

Intravenous Immune globulin (IVIG) has been demonstrated in multiple clinical trials reported in the medical literature to have an impact on two important considerations in relapsing-remitting multiple sclerosis. IVIG reduces the frequency of the acute exacerbation and it reduces the intensity and duration of the acute exacerbation. Seemingly, a subset of patients has a prominent B cell involvement in multiple sclerosis. Hence, it would be advantageous to have substances and methods for the treatment of such B cell mediated multiple sclerosis patients.

IVIG represents pooled human immune globulin from many donors. The exact mechanism by which IVIG ameliorates autoantibody mediated diseases is unknown. However, it could be shown that a) the efficacy of IVIG is dependant on Fc-receptor expression b) the ratio of autoantibodies to normal immune globulin (IVIG) is shifted, which leads to enhanced degradation of autoantibodies and c) the IVIG contains the complete human antibody and anti-idiotypic antibody network (antibodies against antibodies) which leads to the neutralization of autoantibodies."

SUMMARY OF THE INVENTION

The inventors have astonishingly found that the current hypothesis that T cells play a pivotal role in the pathogenesis of Multiple Sclerosis (MS) is at least not entirely correct. The inventors addressed the B cell mediated form of multiple sclerosis and are, astonishingly able to provide for a special treatment.

The invention relates to the Fc γ receptor (Fc gamma receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis. The invention

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relates to pharmaceutical compositions containing the Fc γ receptor (Fc gamma receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis.

- 5 Fc receptors (FcRs) play a key role in defending the human organism against infections. After pathogens have gained access to the blood circulation they are opsonized by immunoglobulins (Igs). The resulting immunocomplexes bind due to their multivalency with high avidity to FcR bearing cells leading to clustering of the FcRs, which triggers several effector functions. The receptor with high affinity for IgE,
10 Metzger, H., 1992, Immunol Rev. 1992 Feb;125:37-48. These include, depending on the expressed FcR type and associated proteins, endocytosis with subsequent neutralization of the pathogens and antigen presentation, antibody dependent cellular cytotoxicity (ADCC), secretion of mediators or the regulation of antibody production. (Structural Bases of Fc γ Receptor Functions, Wolf H. Fridman, Christian Bonnerot,
15 Marc Daeron, Sebastian Amigorena, Jean-Luc Teillaud, Catherine Sautes, 1992, Immunological Reviews No. 125; Human IgG Fc receptor heterogeneity: molecular aspects and clinical implications, Jan G.J. van de Winkel, Peter J.A. Capel, 1993, Immunology Today Volume 14, Issue 5, May 1993, Pages 215–221).

- Specific FcRs exist for all Ig classes, the ones for IgG being the most abundant with
20 the widest diversity. Together with the high affinity receptor for IgE (Fc ϵ RIa), Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIIIA (CD16) occur as type I transmembrane proteins or in soluble forms (sFcRs) but also a glycosylphosphatidylinositol anchored form of the Fc γ RIII (Fc γ RIIIb) exists. Furthermore, Fc γ Rs occur in various isoforms (Fc γ RIA, B1, B2, C; Fc γ RIIA1-2, B1-3, C) and alleles (Fc γ RIIA1-HR, -LR; Fc γ RIIIb-NA1, -NA2)
25 (van de Winkel, Peter J.A. Capel, 1993, Immunology Today Volume 14, Issue 5, May 1993, Pages 215-221). In contrast to the overall homologous extracellular parts, the membrane spanning and the cytoplasmic domains differ. They may be deleted entirely or be of a size of 8 kDa. They may contain either a 26 amino acid immunoreceptor tyrosine-based activation motif (ITAM) as in Fc γ RIIA or a respective

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13 amino acid inhibitory motif (ITIM) in FcγRIIB involved in signal transduction (Cytoplasmic domain heterogeneity and functions of IgG Fc receptors in B lymphocytes, Amigorena, S. et al. (1992) Science, 256, 1808-1812).

Herein, EAE is experimental autoimmune encephalomyelitis.

- 5 The present invention as claimed relates to recombinant non glycosylated human soluble FcγRIIB receptor (Fc-gamma RIIB receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the Fc γ receptor (Fc-gamma receptor) for use in treating
5 multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple
sclerosis and/or an autoantibody driven form of multiple sclerosis.

The B cell mediation of the multiple sclerosis and/or autoantibody driven form of
multiple sclerosis is characterized by one or more of the following features, (a) the
10 multiple sclerosis is ameliorated if the patient undergoes Intravenous immunoglobulin
(IVIG) treatment and/or, (b) the multiple sclerosis is ameliorated if the patient
undergoes anti-CD20 antibody treatment and/or, (c) the multiple sclerosis is
ameliorated if the patient undergoes plasmapheresis and/or, (d) the multiple
Sclerosis is ameliorated if the patient undergoes immunoadsorption (e) the presence
15 of auto-antibodies against the antigen Myelin Oligodendrocyte Glycoprotein (MOG)
and/or (f) the presence of auto-antibodies against the antigen myelin basic protein
(MBP) and/or (g) the presence of auto-antibodies against aquaporin 4.

Devic's disease is similar to MS in that the body's immune system attacks the myelin
20 surrounding nerve cells. Unlike standard MS, the attacks are not believed to be
mediated by the immune system's T cells but rather by antibodies called NMO-IgG.
These antibodies target a protein called aquaporin 4 in the cell membranes of
astrocytes which acts as a channel for the transport of water across the cell
membrane.

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In a preferred embodiment the B cell mediation of the multiple sclerosis and/or
autoantibody driven form of multiple sclerosis is determined prior to the use of the
Fc γ receptor by means of one or more of the following tests, (a) determining whether
the multiple sclerosis is ameliorated if the patient undergoes Intravenous
30 immunoglobulin (IVIG) treatment and/or, (b) the multiple sclerosis is ameliorated if
the patient undergoes anti-CD20 antibody treatment and/or, (c) the multiple sclerosis
is ameliorated if the patient undergoes plasmapheresis, (d) the multiple Sclerosis is
ameliorated if the patient undergoes immunoadsorption (e) determining whether
auto-antibodies against the antigen myelin oligodendrocyte glycoprotein (MOG) are

present in the patient and/or, (f) determining whether auto-antibodies against the antigen myelin basic protein (MBP) are present in the patient and/or (g) determining the presence of auto-antibodies against aquaporin 4. Preferably a selection of two of the test are performed, more preferably a selection of three of tests are performed,
5 more preferably a selection of four of the tests are performed.

One example of an anti-CD20 treatment is Rituximab. This is a monoclonal antibody. Sadly, it has severe side-effects which could be ameliorated if the present protein, *i.e.* polypeptides were used in place of Rituximab.

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During plasmapheresis, blood is initially taken out of the body through a needle or previously implanted catheter. Plasma is then removed from the blood by a cell separator. Three procedures are commonly used to separate the plasma from the blood:

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Discontinuous flow centrifugation:

One venous catheter line is required. Typically, a 300 ml batch of blood is removed at a time and centrifuged to separate plasma from blood cells.

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Continuous flow centrifugation

Two venous lines are used. This method requires slightly less blood volume to be out of the body at any one time as it is able to continuously spin out plasma.

Plasma filtration

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Two venous lines are used. The plasma is filtered using standard hemodialysis equipment. This continuous process requires less than 100 ml of blood to be outside the body at one time.

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During immunoadsorption the blood of a patient is cleared from immunoglobulin by an extra corporal affinity chromatography column.

Each method has its advantages and disadvantages. After plasma separation, the blood cells are returned to the person undergoing treatment, while the plasma, which contains the antibodies, is first treated and then returned to the patient in traditional

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plasmapheresis. (In plasma exchange, the removed plasma is discarded and the patient receives replacement donor plasma or saline with added proteins.) Medication to keep the blood from clotting (an anticoagulant) is generally given to the patient during the procedure. Plasmapheresis is used as a therapy in particular
5 diseases.

An important use of plasmapheresis is in the therapy of autoimmune disorders. However, the method is extremely strenuous for the patient.

10 WO 2008/017363 discloses means for testing for B cell mediation. In particular it discloses means of detecting auto-antibodies against MOG and aquaporin 4.

In a preferred embodiment of the invention the FcR receptor is of human origin. The
15 Fc γ receptor according to the invention is preferably selected from the group of, Fc γ RI (CD64), Fc γ RIIA (CD32), Fc γ RIIB1 (CD32), Fc γ RIIB2 (CD32), Fc γ RIIC (CD32), Fc γ RIIIA (CD16) and Fc γ RIIIB (CD16).

Fc γ RIIB1 (CD32) and Fc γ RIIB2 (CD32) are so called isoforms, i.e. the isoforms 1 and
20 2.

According to the present invention, the preparation of the soluble Fc receptors takes place in prokaryotic or eukaryotic cells. It may also take place in eukaryotic cells. If it takes place in prokaryotic cells (see EP-B1 1 135 486) insoluble inclusion bodies
25 containing the recombinant protein form, thus facilitating purification by separation of the inclusion bodies from other cell components before renaturation of the proteins contained therein takes place. The renaturation of the FcRs according to the present invention which are contained in the inclusion bodies can principally take place according to known methods. The advantage of the preparation in prokaryotic cells,
30 the production of inclusion bodies and the thus obtained recombinant soluble Fc receptors make it possible to obtain a very pure and, in particular, also very homogeneous FcR preparation. Also because of the absence of glycosylation the obtained product is of great homogeneity. However, in some cases glycosylation may be desired.

A host cell is genetically engineered with the polynucleotide or the vector encoding or carrying the FcR. The host cells that may be used for purposes of the invention include but are not limited to prokaryotic cells such as bacteria (for example, *E. coli* and *B. subtilis*), which can be transformed with, for example, recombinant bacteriophage DNA, plasmid DNA, or cosmid DNA expression vectors containing the polynucleotide molecules encoding the FcR; simple eukaryotic cells like yeast (for example, *Saccharomyces* and *Pichia*), which can be transformed with, for example, recombinant yeast expression vectors containing the polynucleotide molecule of the invention, *i.e.* the polynucleotide molecules encoding the FcR; insect cell systems like, for example, Sf9 or Hi5 cells, which can be infected with, for example, recombinant virus expression vectors (for example, baculovirus) containing the polynucleotide molecules of the invention; *Xenopus* oocytes, which can be injected with, for example, plasmids; plant cell systems, which can be infected with, for example, recombinant virus expression vectors (for example, cauliflower mosaic virus (CaMV) or tobacco mosaic virus (TMV)) or transformed with recombinant plasmid expression vectors (for example, Ti plasmid) containing a FcR or variant nucleotide sequence; or mammalian cell systems (for example, COS, CHO, BHK, HEK293, VERO, HeLa, MDCK, Wi38, Swiss 3T3 and NIH 3T3 cells), which can be transformed with recombinant expression constructs containing, for example, promoters derived, for example, from the genome of mammalian cells (for example, the metallothionein promoter) from mammalian viruses (for example, the adenovirus late promoter, CMV IE and the vaccinia virus 7.5K promoter) or from bacterial cells (for example, the tet-repressor binding is employed in the tet-on and tet-off systems). Also useful as host cells are primary or secondary cells obtained directly from a mammal and transfected with a plasmid vector or infected with a viral vector. Depending on the host cell and the respective vector used to introduce the polynucleotide of the invention the polynucleotide can integrate, for example, into the chromosome or the mitochondrial DNA or can be maintained extrachromosomally like, for example, episomally, or can be only transiently comprised in the cells.

In the sequence of FcγRIIB three potential N-glycosylation sites are found. All three sites are on the surface of the molecule and are accessible. They are located in the E loops (N61 and N142) of both domains and on strand E (N 135) of the C-terminal domain. FcRs isolated from mammalian cells are highly glycosylated. Since FcR is glycosylated *in vivo* it may be desirable to choose an expression system, which

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provides faithful glycosylation of the protein. Consequently, it is preferred to introduce the polynucleotides encoding the FcR of the present invention into higher eukaryotic cells, in particular into mammalian cells, e.g. COS, CHO, BHK, HEK293, VERO, HeLa, MDCK, Wi38, Swiss 3T3 or NIH 3T3 cells.

- 5 Preferably the Fc γ receptor according to the invention lacks the transmembrane domain and/or the signal peptide and is soluble. Soluble forms of Fc receptors (sFcR) such as Fc γ RIII mediate isotype-specific regulation of B cell growth and immunoglobulin production. In a murine model of myeloma, sFcR suppresses growth and immunoglobulin production of tumor cells. (T cells with Fc receptors in myeloma: suppression of growth and secretion of MOPC 315 by Ta cells, Müller, S. and Hoover, R.G, 1985, J. Immunol. 134, 644; Modulation of Ig gene expression by Ig binding factors. Suppression of alpha-H chain and lambda-2-L chain mRNA accumulation in MOPC-315 by IgA-binding factor, Roman S., Moore J.S., Darby C., Müller S., Hoover R.G., J Immunol. 1988 May 15;140(10):3622-30; Soluble Fc γ receptors II (Fc γ RII) are generated by cleavage of membrane Fc γ RII. Sautès C., Varin N., Teillaud C. et al, 1990, Eur. J. Immunol. 21:231-234). Furthermore, sFcR binds to surface IgG on cultures of human IgG-secreting myeloma cells and effects suppression of tumor cell growth and IgG secretion. Prolonged exposure of these cells to sFcR results in tumor cell cytolysis (Autoregulatory circuits in myeloma: Tumor cell cytotoxicity mediated by soluble CD16, Hoover, R.G., Lary, C., Page, R., Travis, P., Owens, R., Flick, J., Kornbluth, J. and Barlogie, B. (1995) J. Clin. Invest., 95, 241-247).

The Fc γ receptor polypeptides can be any of those described above but with not more than ten (e.g., not more than: ten, nine, eight, seven, six, five, four, three, two, or one) conservative substitutions. Conservative substitutions are known in the art and typically include substitution of, e.g. one polar amino acid with another polar amino acid and one acidic amino acid with another acidic amino acid. Accordingly, conservative substitutions preferably include substitutions within the following groups of amino acids: glycine, alanine, valine, proline, isoleucine, and leucine (non polar,

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aliphatic side chain); aspartic acid and glutamic acid (negatively charged side chain); asparagine, glutamine, methionine, cysteine, serine and threonine (polar uncharged side chain); lysine, histidine and arginine; and phenylalanine, tryptophan and tyrosine (aromatic side chain); and lysine, arginine and histidine (positively charged side chain).

- 5 It is well known in the art how to determine the effect of a given substitution, e.g. on pK_I etc. All that is required of a polypeptide having one or more conservative substitutions is that it has at least 50% (e.g., at least: 55%; 60%; 65%, 70%; 75%; 80%; 85%; 90%; 95%; 98%; 99%; 99.5%; or 100% or more) of the activity of the unaltered Fcγ receptor according to the invention.
- 10 Both polypeptides and peptides can be produced by standard *in vitro* recombinant DNA techniques and *in vivo* transgenesis, using nucleotide sequences encoding the

appropriate polypeptides or peptides. Methods well-known to those skilled in the art can be used to construct expression vectors containing relevant coding sequences and appropriate transcriptional/translational control signals. See, for example, the techniques described in Sambrook, *et al.*, Molecular Cloning: A Laboratory Manual (2nd Ed.) [Cold Spring Harbor Laboratory, N.Y., 1989], and Ausubel, *et al.*, Current Protocols in Molecular Biology [Green Publishing Associates and Wiley Interscience, N.Y., 1989].

Polypeptides and fragments of the invention, *i.e.* isolated polypeptides, also include those described above, but modified for *in vivo* use by the addition, at the amino- and/or carboxyl-terminal ends, of blocking agents to facilitate survival of the relevant polypeptide *in vivo*. This can be useful in those situations in which the peptide termini tend to be degraded by proteases prior to cellular up-take. Such blocking agents can include, without limitation, additional related or unrelated peptide sequences that can be attached to the amino and/or carboxyl terminal residues of the peptide to be administered. This can be done either chemically during the synthesis of the peptide or by recombinant DNA technology by methods familiar to artisans of average skill.

Alternatively, blocking agents such as pyroglutamic acid or other molecules known in the art can be attached to the amino and/or carboxyl terminal residues, or the amino group at the amino terminus or carboxyl group at the carboxyl terminus can be replaced with a different moiety. Likewise, the peptides can be covalently or non-covalently coupled to pharmaceutically acceptable "carrier" proteins prior to administration.

25

The term "isolated" polypeptide or peptide fragment as used herein refers to a polypeptide or a peptide fragment which either has no naturally-occurring counterpart or has been separated or purified from components which naturally accompany it, *e.g.*, in tissues such as tongue, pancreas, liver, spleen, ovary, testis, muscle, joint tissue, neural tissue, gastrointestinal tissue or tumor tissue, or body fluids such as blood, serum, or urine. Typically, the polypeptide or peptide fragment is considered "isolated" when it is at least 70%, by dry weight, free from the proteins and other naturally-occurring organic molecules with which it is naturally associated. Preferably, a preparation of a polypeptide (or peptide fragment thereof) of the invention is at

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least 80%, more preferably at least 90%, and most preferably at least 99%, by dry weight, the polypeptide (or the peptide fragment thereof), respectively, of the invention. Thus, for example, a preparation of polypeptide x is at least 80%, more preferably at least 90%, and most preferably at least 99%, by dry weight, polypeptide
5 x. Since a polypeptide that is chemically synthesized is, by its nature, separated from the components that naturally accompany it, the synthetic polypeptide is "isolated."

An isolated polypeptide (or peptide fragment) of the invention can be obtained, for example, by extraction from a natural source (e.g., from tissues or bodily fluids); by
10 expression of a recombinant nucleic acid encoding the polypeptide; or by chemical synthesis. A polypeptide that is produced in a cellular system different from the source from which it naturally originates is "isolated," because it will necessarily be free of components which naturally accompany it. The degree of isolation or purity can be measured by any appropriate method, e.g., column chromatography,
15 polyacrylamide gel electrophoresis, or HPLC analysis.

The Fcγ receptor according to the invention may be chemically modified (improved) by PEGylation and/or genetic engineering.

Known approaches involve the provision of additional glycosylation sites (see e.g.
20 WO 91/05867, WO 94/09257 and WO 01/81405). Such modified analogs may have at least one additional N-linked and/or O-linked carbohydrate chain. Other attempts to improve the half life may involve the addition of polyethylene glycol residues (PEG) of varying length to the amino acid backbone (see e.g. WO 00/32772, WO 01/02017, WO 03/029291). One may modify the molecules with at least one N-linked and/or O-
25 linked oligosaccharide which are further modified by oxidation, sulfation, phosphorylation, PEGylation or a combination thereof (see WO 2005/025606). All these approaches can equally be employed to extend the half life of the variants of the present invention and accordingly in a preferred embodiment of the Fcγ receptor according to the invention the modification is selected from the group consisting of
30 oxidation, sulfation, phosphorylation, addition of oligosaccharides or combinations thereof. If the addition of further N-linked or O-linked oligonucleotides is desired it is possible to introduce them by introducing additional glycosylation sites. It also preferred that the protein is affinity modulated.

In the practice of one aspect of the present invention, a pharmaceutical composition comprising the receptor of the invention may be administered to a mammal by any route which provides a sufficient level of activity. It can be administered systemically or locally. Such administration may be parenterally, transmucosally, e.g., orally, nasally, rectally, intravaginally, sub-lingually, submucosally or transdermally. Preferably, administration is parenteral, e.g. via intravenous or intraperitoneal injection, and also including, but is not limited to, intraarterial, intramuscular, intradermal and subcutaneous administration. If the pharmaceutical composition of the present invention is administered locally it can be injected directly into the organ or tissue to be treated. In cases of treating the nervous system this administration route includes, but is not limited to, the intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal and/or peri-spinal routes of administration, which can employ intracranial and intravertebral needles, and catheters with or without pump devices.

15

The receptor may also be glycosylated.

Most preferably the receptor is selected from the group of FCγRIIA/B/C (CD32) and FCγRIIIA/B (CD16B). The invention also relates to isoforms thereof and isoforms of the FcRs claimed herein in general.

20

In a preferred embodiment of pharmaceutical composition comprises an FcR receptor polypeptide in a dosage unit form for treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven form of multiple sclerosis, and the amount to administered to a patient in a single dose is between 1 and 20 mg/kg, preferably 2 and 10 mg/kg, more preferably between 2.5 and 5 mg/kg, even more preferably between 2.5 and 5 mg/kg.

25

A pharmaceutical composition may additionally comprise one or more of the following substances, a detergent and/or a sugar. A preferred detergent is Tween 20[®]. A preferred sugar is mannitol.

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The Fcγ receptor according to the invention preferably has sequence selected from the group of, SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID

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NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 and SEQ ID NO. 13. These are outlined in Table 1.

The Fc γ receptor according to the invention preferably comprises only the extra
 5 cellular domain of said sequences (soluble form of the receptor). Said domain is known from sequence alignments, is structurally characterized by x-ray crystallography and comprise the first two (CD16, CD32) or the first three (CD64) IgG-like domains of the mature receptor (Sondermann P., Kaiser J., Jacob U., Molecular basis for immune complex recognition: a comparison of Fc-receptor
 10 structures. J. Mol. Biol. 2001, 309, 737-749).

Table 1

Human Fc gamma RIA (SEQ ID NO. 1)	MWFLTTLLLVWPVDGQVDTTKAVIT LOPPWVSVFQEETVTLHCEVLHLPG SSSTQWFLNGTATQTSTPSY RITSASVNDSGEYRCQRGLSGRSDP IQLEIHRGWLLQVSSRVFTEGEPL ALRCHAWKDKLVYNVLYYRN GKAFKFFHWNSNLTILKTNISHNGT YHCSGMGKHRYTSAGISVTVKELFP APVLNASVTSPLLEGNLVT SCETKLLLQRPGLQLYFSFYMGSKT LRGRNTSSEYQILTARREDSGLYWC EAATEDGNVLKRSPELELQV LGLQLPTPVWFHVLFLYLAVGIMFLV NTVLWVTIRKELKRKKKWDLEISLD SGHEKKVISSLQEDRHLEEE LKCQEKEEQQLQEGVHRKEPQGAT	SEQ ID NO. 14 ATGTGGTTCTTGACAACTCTGCTCCTTTGGGTTCCAGT TGATGGGCAAGTGACACCACAAAGGCAGTGATCACTT TGCAGCCTCCATGGGTCAGCGTGTCCAAGAGGAAACC GTAACCTTGCACTGTGAGGTGCTCCATCTGCCTGGGAG CAGCTCTACACAGTGGTTTCTCAATGGCACAGCCACTC AGACCTCGACCCCACTACAGAATCACCTCTGCCAGT GTCAATGACAGTGGTGAATACAGGTGCCAGAGAGGTCT CTCAGGGCGAAGTGACCCCATACAGCTGGAAATCCACA GAGGCTGGCTACTACTGCAGGTCTCCAGCAGAGTCTTC ACGGAAGGAGAACCCTCTGGCCTTGAGGTGTGATGCGTG GAAGGATAAGCTGGTGTACAATGTGCTTTACTATCGAA ATGGCAAAGCCTTTAAGTTTTTCCACTGGAATTCCTAAC CTCACCATTCTGAAAACCAACATAAGTCACAATGGCAC CTACCATTGCTCAGGCATGGGAAAGCATCGCTACACAT CAGCAGGAATATCTGTCACTGTGAAAGAGCTATTTCCA GCTCCAGTGCTGAATGCATCTGTGACATCCCCACTCCT GGAGGGGAATCTGGTCAACCTGAGCTGTGAAACAAAGT TGCTCTTGCAAGAGGCTGGTTTGCAGCTTTACTTCTCC TTCTACATGGGCAGCAAGACCCTGCGAGGCAGGAACAC ATCCTCTGAATACCAATACTAAGTCTAGAAAGAGAAG ACTCTGGGTTATACTGGTGGAGGCTGCCACAGAGGAT GGAAATGTCCTTAAGCGCAGCCCTGAGTTGGAGCTTCA AGTGCTTGGCCTCCAGTTACCAACTCCTGTCTGGTTTC ATGTCCTTTTCTATCTGGCAGTGGGAATAATGTTTT TAGTGAACACTGTCTCTGGGTGACAATACGTAAAGAA CTGAAAAGAAAGAAAAGTGGGATTTAGAAATCTCTTT GGATTCTGGTCATGAGAAGAAGGTAATTTCCAGCCTTC AAGAAGACAGACATTTAGAAGAAGAGCTGAAATGTCAG GAACAAAAGAAGAACAGCTGCAGGAAGGGGTGCACCG GAAGGAGCCCCAGGGGGCCACGTAG
Human Fc gamma RIB (SEQ ID NO. 2)	MWFLTTLLLVGWLLQVSSRVFMEG EPLALRCHAWKDKLVYNVLYYRNGK AFKFFHWNSNLTILKTNISH NGTYHCSGMGKHRYTSAGISQYTVK GLQLPTPVWFHVLFLYLAVGIMFLVN TVLWVTIRKELKRKKKWNLE ISLDSGHEKKVISSLQEDRHLEEE KCQEKEEQQLQEGVHRKEPQGAT	SEQ ID NO. 15 ATGTGGTTCTTGACAACTCTGCTCCTTTGGGGCTGGCT ACTACTGCAGGTCTCCAGCAGAGTCTTCATGGAAGGAG AACCTCTGGCCTTGAGGTGTGATGCGTGGAAGGATAAG CTGGTGTACAATGTGCTTTACTATCGAAATGGCAAAGC CTTTAAGTTTTTCCACTGGAATTCCTAACCTCACCATT TGAAAACCAACATAAGTCACAATGGCACCTACCATTGC TCAGGCATGGGAAAGCATCGCTACACATCAGCAGGAAT ATCACAATACACTGTGAAAGGCCTCCAGTTACCAACTC CTGTCTGGTTTCATGTCTTTTCTATCTGGCAGTGGGA ATAATGTTTTTAGTGAACACTGTTCTCTGGGTGACAAT ACGTAAAGAACTGAAAAGAAAGAAAAGTGGAAATTTAG AAATCTCTTTGGATTCTGGTGTGAGAAGAAGGTAATT

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		TCCAGCCTTCAAGAAGACAGACATTTAGAAGAAGAGCT GAAATGTCAGGAACAAAAAGAAGACAGCTGCAGGAAG GGGTGCACCGGAAGGAGCCCCAGGGGGCCACGTAG
Human Fc gamma RIIb (SEQ ID NO. 3)	MWFLTTLTLLWVPVDGQVDITKAVIT LQPPWVSVFQEBTVTLHCEVLHLP SSSTQWFLNGTATQTSTPSY RITSASVNDSGEYRCQRGLSGRSDP IQLEIHRGWLLQVSSRVFMEGEPL ALRCHAWKDKLVYNVLYRN GKAFKFFHWNSNLTKTNISHNGT YHCSGMGKHRYTSAGISQYTVKGLQ LPTPVWFHVLFLAVGIMFL VNTVLWVTIRKELKRKKWNLKISL DSGHEKKVISSLQEDRHLEELKCO EQKEEQLEQGVHRKEPQGAT	SEQ ID NO. 16 ATGTGGTTCTTGACAACCTCTGCTCCTTTGGGTTCCAGT TGATGGGCAAGTGGACACCACAAAGGCAGTGATCACTT TGCAGCCTCCATGGGTCAGCGTGTTCAGAGGAAACC GTAACCTTGCACTGTGAGGTGCTCCATCTGCCTGGGAG CAGCTCCACACAGTGGTTTCTCAATGGCACAGCCACTC AGACCTCGACCCCCAGCTACAGAATCACCTCTGCCAGT GTCAATGACAGTGGTGAATACAGGTGCCAGAGAGGTCT CTCAGGGCGAAGTGACCCCATACAGCTGGAAATCCACA GAGGTGGCTACTACTGCAGGTCTCCAGCAGAGTCTTC ATGGAAGGAGAACCCTCTGGCCTTGAGGTGTATGCGTG GAAGGATAAGCTGGTGTACAATGTGCTTTACTATCGAA ATGGCAAAGCCTTTAAGTTTTTCCACTGGAATTCTAAC CTCACCATTCTGAAAACCAACATAAGTCACAATGGCAC CTACCATTGCTCAGGCATGGGAAAGCATCGCTACACAT CAGCAGGAATATCACAATACACTGTGAAAGGCCTCCAG TTACCAACTCCTGTCTGGTTTCATGTCTTTTCTATCT GGCAGTGGGAATAATGTTTTTAGTGAACACTGTTCTCT GGGTGACAATACGTAAAGAACTGAAAAGAAAGAAAAG TGGAATTTAGAAATCTCTTTGGATTCTGGTCATGAGAA GAAGGTAATTTCCAGCCTTCAAGAAGACAGACATTTAG AAGAAGAGCTGAAATGTCAGGAACAAAAAGAAGACAG CTGCAGGAAGGGGTGCACCGGAAGGAGCCCCAGGGGGC CACGTAG
Human Fc gamma RIIa (SEQ ID NO. 4)	MTMETQMSQNVCPRLWLLQPLTVL LLLASADSQAAPPKAVLKLEPPWIN VLQEDSVTLTCQARSPESD SIQWFHNGNLIPTHTQPSYRFKANN NDSGEYTCQTGQTSLSDPVHLTVLS EWLVLTQPHLEFQEGETIML RCHSWKDKPLVKVTFQNGKSQKFS HLDPTFSIPQANHSHSGDYHCTGNI GYTLFSSKPVITITVQVPSMG SSSPMGIIIVAVVIATAVAIIVAVV ALIYCRKKRISANSTDPVKAAQFEP PGRQMIARKRQLEETNNDY ETADGGYMTLNPRAPTDDDKNIYLT LPPNDHVNSNN	SEQ ID NO. 17 ATGACTATGGAGACCCAAATGTCTCAGAATGTATGTCC CAGAAACCTGTGGCTGCTTCAACCATTGACAGTTTTGC TGCTGCTGGCTCTTGACAGAGTCAAGCTGCTCCCCCA AAGGCTGTGCTGAAACTTGAGCCCCGTGGATCAACGT GCTCCAGGAGGACTCTGTGACTCTGACATGCCAGGGGG CTCGCAGCCCTGAGAGCGACTCCATTCACTGGTTCCAC AATGGGAATCTCATTTCCACCCACACGCAGCCAGCTA CAGGTTCAAGGCCAACAACAATGACAGCGGGGAGTACA CGTGCCAGACTGGCCAGACCAGCCTCAGCGACCTGTG CATCTGACTGTGCTTTCCGAATGGCTGGTGTCCAGAC CCCTCACCTGGAGTTCCAGGAGGGAGAAACCATCATGC TGAGGTGCCACAGCTGGAAGGACAAGCCTCTGGTCAAG GTCACATTCTTCCAGAATGGAAAATCCCAGAAATCTC CCATTTGGATCCCACCTTCTCCATCCCACAAGCAAACC ACAGTCACAGTGGTGATTACCACTGCACAGGAAACATA GGCTACACGCTGTTCTCATCCAAGCCTGTGACCATCAC TGTCGAAGTGCCCGAGCATGGGCAGCTCTTACCAATGG GGATCATTGTGGCTGTGGTCAATGGGACTGCTGTAGCA GCCATTGTGTGCTGTAGTGGCCTTGATCTACTGCAG GAAAAAGCGGATTTAGCCCAATTCACCTGATCCTGTGA AGGCTGCCCAATTTAGCCACCTGGACGTCAAATGATT GCCATCAGAAAGAGACAACCTGAAGAAACCAACAATGA CTATGAAACAGCTGACGGCGGCTACATGACTCTGAACC CCAGGGCACCTACTGACGATGATAAAACATCTACCTG ACTCTTCTCTCCAACGACCATGTCAACAGTAATAACTA A
Human Fc gamma RIIB Isoform 1 (SEQ ID NO. 5)	MGILSFLPVLATESDWADCKSPQPW GHMLLWTAFLFAPVAGTPAAPKA VLKLEPQWINVLQEDSVTLT CRGTHSPESDSIQWFHNGNLIPTHT QPSYRFKANNNDSGEYTCQTGQTS SDPVHLTVLSEWLVLQTPHL EFQEGETIVLRCHSWKDKPLVKVTF FQNGKSKKFSRSDPNFSIPQANSH SGDYHCTGNIQYTLVSSKPV TITVQAPSSSPMGIIIVAVVTGIAVA AIVAAVVALIYCRKKRISALPGYPE CREMGETLPEKPANPTNPDE ADKVGAEINTITYSLMHPDALEED DQNR	SEQ ID NO. 18 ATGGGAATCCTGTCACTTCTTACCTGTCTTGGCACTGA GAGTGACTGGGCTGACTGCAAGTCCCCCAGCCTTGGG GTCATATGCTTCTGTGGACAGCTGTGCTATTCTTGGCT CCTGTTGCTGGGACACCTGCAGCTCCCCCAAAGGCTGT GCTGAAACTCGAGCCCCAGTGGATCAACGTGCTCCAGG AGGACTCTGTGACTCTGACATGCCGGGGGACTCACAGC CCTGAGAGCGACTCCATTCACTGGTTCCACAATGGGA TCTCATTECCACCCACACGCAGCCAGCTACAGGTTCA AGGCCAACAACAATGACAGCGGGGAGTACAGTGCCAG ACTGGCCAGACCAGCCTCAGCGACCTGTGCATCTGAC TGTGCTTTCTGAGTGGCTGGTGTCTCCAGACCCCTCAC TGGAGTTCAGGAGGGAGAAACCATCGTGTGAGGTGC CACAGCTGGAAGGACAAGCCTCTGGTCAAGGTACATT CTTCCAGAATGGAAATCCAAGAAATTTCCCGTTCGG ATCCCAACTTCTCCATCCCACAAGCAAACCACAGTCAC AGTGGTGATTACCACTGCACAGGAAACATAGGCTACAC

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		GCTGTACTCATCCAAGCCTGTGACCATCACTGTCCAAG CTCCCAGCTCTTCACCGATGGGGATCATTGTGGCTGTG GTCAGTGGGATTGCTGTAGCGGCCATTGTTGCTGCTGT AGTGGCCTTGATCTACTGCAGGAAAAAGCGGATTTTCAG CTCTCCCAGGATACCCGTAGTGCAGGGAAATGGGAGAG ACCCCTCCCTGAGAAACCAGCCAATCCCACCTAATCCTGA TGAGGCTGACAAAGTTGGGGCTGAGAACACAATCACCT ATTCACCTTCTCATGCACCCGGATGCTCTGGAAGAGCCT GATGACCAGAACCGTATTTAG
Human Fc gamma RIIB Isoform 2 (SEQ ID NO. 6)	MGILSFLPVLATESDWADCKSPQPW GHMLLWTAFLAPVAGTPAPPKAV LKLEPQWINVLQEDSVTLTC RGTHSPESDSIQWFHNGNLIPTHTQ PSYRFKANNNDSEYTCQTGQTSLS DPVHLTVLSEWLVLQTPHLE FQEGETIVLRCHSWKDKPLVKVTF QNGKSKKFSRSDPNFSIPQANHSHS GDYHCTGNIGYTLYSSKPV ITVQAPSSSPMGIIVAVVTGIAVAA IVA AVVALIYCRKKRISANPTNPDE ADKVGAE NTITYSLLMHPDA LEEPDDQNRI	SEQ ID NO. 19 tctagcgagg tgacagcgta gaaccagaga atltgtttgc cctctagggt agaattccgcc aagctttgag agaaggctgt gactgctgtg ctctggggcgc cagctcgctc cagggagtg tgggaatcct gtcattctta cctgtccttg ccactgagag tgactgggct gactgcaagt ccccccagcc ttgggggtcat atgcttctgt ggacagctgt gctattcctg gctcctgttg ctgggacacc tgcagctccc ccaaaggctg tgctgaaact cgagccccag tggatcaacg tgctccagga ggactctgtg actctgacat gcccgggggac tcacagccct gagagcgact ccattcagtg gtccacaaat gggaaatctca ttcccaccca cagcagccc agctacaggt tcaaggccaa caacaatgac agcggggagt acacgtgcca gactggccag accagcctca gcgaccctgt gcactgact gtgctttctg agtggctggg gctccagacc cctcacctgg agttccagga gggagaaacc atcgtgctga gggtgccacag ctggaaagac aagcctctgg tcaaggtcac attcttccag aatggaaaat ccaagaaatt ttcccgttcg gatcccaact tctccatccc acaagcaaac cacagtecca gtgggtgatt accactgcac agggaaaaat agggctacac cctgtactca tccaagccct gtggaccatc actgttcaaa gctccccaac ttcttcacgg atggggga
Human Fc gamma RIIB Isoform 3 (SEQ ID NO. 7)	MGILSFLPVLATESDWADCKSPQPW GHMLLWTAFLAPVAGTPAAPPKA VLKLEPQWINVLQEDSVTLT CRGTHSPESDSIQWFHNGNLIPTHT QPSYRFKANNNDSEYTCQTGQTSLS SDPVHLTVLSEWLVLQTPHL EFQEGETIVLRCHSWKDKPLVKVTF FQNGKSKKFSRSDPNFSIPQANHSH SGDYHCTGNIGYTLYSSKPV TITVQAPSSSPMGIIVAVVTGIAVA AIVA AVVALIYCRKKRISANPTNPD EADKVGAE NTITYSLLMHPD ALEEPDDQNRI	SEQ ID NO. 20 ATGGGAATCCTGTCACTTCTTACCTGTCTTGGCACTGA GAGTGACTGGGCTGACTGCAAGTCCCCCAGCCTTGGG GTCATATGCTTCTGTGGACAGCTGTGCTATTCTGGCT CCTGTTGCTGGGACACCTGCAGCTCCCCCAAAGGCTGT GCTGAAACTCGAGCCCCAGTGGATCAACGTGCTCCAGG AGGACTCTGTGACTCTGACATGCCGGGGGACTCACAGC CCTGAGAGCGACTCCATTTCAGTGGTTCCACAATGGGAA TCTCATTTCCACCCACACGCAGCCCAGCTACAGGTTCA AGGCCAACAAATGACAGCGGGGAGTACACGTGCCAG ACTGGCCAGACAGCCTCAGCGACCCCTGTGCATCTGAC TGTGCTTTCTGAGTGGCTGGTGTCTCCAGACCCCTCACC TGGAGTTCCAGGAGGGAGAAACCATCGTGTGAGGTGC CACAGCTGGAAGGACAAGCCTCTGGTCAAGGTACATT CTTCCAGAATGGAAAATCCAAGAAATTTTCCCGTTCGG ATCCCAACTTCTCCATCCCACAAGCAAACACAGTCAC AGTGGTGATTACCACTGCACAGGAAACATAGGCTACAC GCTGTACTCATCCAAGCCTGTGACCATCACTGTCCAAG CTCCCAGCTCTTCACCGATGGGGATCATTGTGGCTGTG GTCAGTGGGATTGCTGTAGCGGCCATTGTTGCTGCTGT AGTGGCCTTGATCTACTGCAGGAAAAAGCGGATTTTCAG CCAATCCCACCTAATCCTGATGAGGCTGACAAAGTTGGG GCTGAGAACACAATCACCTATTCACTTCTCATGCACCC GGATGCTCTGGAAGAGCCTGATGACCAGAACCGTATTT AG
Human Fc gamma RIIB Isoform 4 (SEQ ID	mgilsflpvl atesdwadck spqpwwghml wtavflapv agtpappkav lklepqwinv lqedsvtltc rgthspesds iqwfhnngnli pthtqpsyrf kannndsgey tcqtgqtsls dpvhltvlse wlvltqphle fgegetivlr chswkdplv kvtfqngks kkfsrsdpnf	SEQ ID NO. 21 atgggaatcc tgctattctt acctgtcctt gccactgaga gtgactgggc tgactgcaag tccccccagc cttgggggtca tatgtctctg tggacagctg tgctattcct ggctcctgtt gctgggacac ctgctcccc aaaggctgtg ctgaaactcg agccccagt gatcaacgtg ctccaggagg actctgtgac tctgacatgc ggggggactc acagccctga gagcgactcc

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NO. 8)	sipqanhshs gdyhctgnig ytlysskpvt itvqapsssp mgiivavvtg iavaalvaav valiycrkk isalpgypec remgetlpek panptnpdea dkvgaentit ysllmhpdal eepddqnri	attcagtggt tccacaatgg gaatctcatt cccacccaca cgcagcccag ctacaggttc aaggccaaca acaatgacag cggggagtag acgtgccaga ctggccagac cagcctcagc gaccctgtgc atctgactgt gctttctgag tggctgggtgc tccagacccc tcacctggag ttccaggagg gagaaacat cgtgctgagg tgccacagct ggaaggacaa gcctctggtc aaggtcacat tcttccagaa tggaaaatcc aagaaathtt cccgttcgga toccaacttc tccatccac aagcaaacca cagtcacagt ggtgattacc actgcacagg aaacataggc tacacgctgt actcatccaa gcctgtgacc atcactgtcc aagctcccag ctcttcaccg atggggatca ttgtggctgt ggtcactggg attgctgtag cggccattgt tgctgctgta gtggccttga tctactgcag gaaaaagcgg atttcagctc tcccaggata ccttgagtgc agggaaatgg gagagaccct ccctgagaaa ccagccaatc ccaactaatcc tgatgaggct gacaaagttg gggctgagaa cacaatcacc tattcacctc tcatgcaccc ggatgctctg gaagagcctg atgaccagaa ccgtatttag
Human Fc gamma RIIc Isoform 1 (SEQ ID NO. 9)	MGILSFLPVLATESDWADCKSPQPW GHMLLWTAVLFLAPVAGTP AAPPKAVLKLEPQWINVLQEDSVTL TCRGTHSPESDSIPWFHNGNLIPTH TQPSYRFK ANNNDSGEYTCQTGQTSLSDPVHLT VLSEWLVLQTPHLEFQEGETIVLRC HSWKDKPL VKVTFFQNGKSKKFSRSDPNFSIPQ ANHSHSGDYHCTGNIGYTLYSSKPV TITVQAPS SSPMGIIVAVVTGIAVAAIVA AVVA LIYCRKKRISANSTDPVKAQFEPP GRQMIAIR KRQPEETNNDYETADGGYMTLNPRA PTDDDKNIYLTLPNDHVNSNN	SEQ ID NO. 22 atgggaatcc tgtcattctt acctgtcctt gccactgaga gtgactgggc tgactgcaag tccccccagc cttgggggtca tatgcttctg tggacagctg tgctattcct ggctcctgtt gctgggacac ctgcagctcc cccaaaggct gtgctgaaac tcgagcccca gtggatcaac gtgctccaag aggactctgt gactctgaca tgccggggga ctcacagccc tgagagcgac tccattccgt ggttccacaa tgggaatctc attccccacc acacgcagcc cagctacagg ttcaaggcca acaacaatga cagcggggag tacacgtgcc agactggcca gaccagcctc agcgaccctg tgcactctgac tgtgctttct gagtggctgg tgetccagac cctcaccctg gagttccagg agggagaaac catcgtgctg aggtgccaca gctggaagga caagcctctg gtcaaggcca cattcttcca gaatggaaaa tccaagaaat tttcccggtc ggatcccaac ttctccatcc cacaagcaaa ccacagtcac agtggtgatt accactgcac aggaacata ggctacacgc tgtactcatc caagcctgtg accatcactg tccaagctcc cagctcttca ccgatgggga tcattgtggc tgtggtcact gggattgctg tagcgcccat tgttgctgct gtagtggcct tgatctactg caggaaaaag eggatttcag ccaattccac tgatcctgtg aaggctgccc aatttgagcc acctggacgt caaatgattg ccatcagaaa gagacaacct gaagaaacca acaatgacta tgaacagct gacggcggtc acatgactct gaaccccagg gcacctactg acgatgataa aaacatctac ctgactcttc ctccaacga ccatgtcaac agtaataact aa
Human Fc gamma RIIC Isoform 2 (SEQ ID NO. 10)	MGILSFLPVLATESDWADCKSPQPW GHMLLWTAVLFLAPVAGTP AAPPKAVLKLEPQWINVLQEDSVTL TCRGTHSPESDSIPWFHNGNLIPTH TQPSYRFK ANNNDSGEYTCQTGQTSLSDPVHLT VLSEWLVLQTPHLEFQEGETIVLRC HSWKDKPL VKVTFFQNGKSKKFSRSDPNFSIPQ	SEQ ID NO. 23 atgggaatcc tgtcattctt acctgtcctt gccactgaga gtgactgggc tgactgcaag tccccccagc cttgggggtca tatgcttctg tggacagctg tgctattcct ggctcctgtt gctgggacac ctgcagctcc cccaaaggct gtgctgaaac tcgagcccca gtggatcaac gtgctccaag aggactctgt gactctgaca tgccggggga ctcacagccc tgagagcgac tccattccgt ggttccacaa tgggaatctc attccccacc acacgcagcc cagctacagg ttcaaggcca acaacaatga cagcggggag tacacgtgcc agactggcca gaccagcctc

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	ANHSMSGDYHCTGNIGYTLYSSKPV TITVQAPS SSPMGIIVAVVTGIAVAIAVAVVA LIYCRKKRISANSTDPVKAAQFEML SCTHLDVK	17 agcgaccctg tgcattctgac tgtgctttct gagtggctgg tgctccagac ccctcacctg gagttccagg agggagaaac catcgtgctg aggtgccaca gctggaagga caagcctctg gtcaagggtca cattcttcca gaatggaaaa tccaagaaat tttcccgttc ggatcccaac ttctccatcc cacaagcaaa ccacagtcac agtgggtgatt accactgcac aggaacata ggctacacgc tgtactcatc caagcctgtg accatcactg tccaagctcc cagctcttca ccgatgggga tcattgtggc tgtggctact gggattgctg tagcgcccat tgttgctgct gtagtggcct tgatctactg caggaaaaag cggatttcag ccaattccac tgatcctgtg aaggctgccc aatttgagat gctttcctgc accacctgg acgtcaaatg a
Human Fc gamma RIIC Isoform 3 (SEQ ID NO. 11)	MGILSFLPVLATESDWADCKSPQPW GHMLLWTAVLFLAPVAGTP AAPPKAVLKLEPQWINVLQEDSVTL TCRGTHSPESDSIPWFHNGNLIPTH TQPSYRFK ANNNDSEYTCQTGQTSLSDPVHLT VLSEWLVLQTPHLEFQEGETIVLRC HSWKDKPL VKVTFQNGKSKKFSRSDPNFSIPQ ANHSMSGDYHCTGNIGYTLYSSKPV TITVQAPS SSPMGIIVAVVTGIAVAIAVAVVA LIYCRKKRISATWTSNDCHQKETT	SEQ ID NO. 24 atgggaatcc tgcattctt acctgtcctt gccactgaga gtgactgggc tgactgcaag tccccccagc cttgggggtca tatgcttctg tggacagctg tgctattcct ggctcctgtt gctgggacac ctgcagctcc cccaaaggct gtgctgaaac tcgagcccca gtggatcaac gtgctccaag aggaactctgt gactctgaca tgccggggga ctacagaccc tgagagcgac tccattccgt ggttccacaa tgggaatctc attccccacc acacgcagcc cagctacagg ttcaaggcca acaacaatga cagcggggag tacacgtgcc agactggcca gaccagctc agcgaccctg tgcattctgac tgtgctttct gagtggctgg tgctccagac ccctcacctg gagttccagg agggagaaac catcgtgctg aggtgccaca gctggaagga caagcctctg gtcaagggtca cattcttcca gaatggaaaa tccaagaaat tttcccgttc ggatcccaac ttctccatcc cacaagcaaa ccacagtcac agtgggtgatt accactgcac aggaacata ggctacacgc tgtactcatc caagcctgtg accatcactg tccaagctcc cagctcttca ccgatgggga tcattgtggc tgtggctact gggattgctg tagcgcccat tgttgctgct gtagtggcct tgatctactg caggaaaaag cggatttcag ccacctggac gtcaaatgat tgccatcaga aagagacaac ctga
Human Fc gamma RIIIA (SEQ ID NO. 12)	MGGGAGERLFTSSCLVGLVPLGLRI SLVTCPLQCGIMWQLLLPTALLLLV SAGMRTEDLPAVVFLEPQW YRVLEKDSVTLKCQAYSPEDNSTQ WFHNESSLISQASSYFIDAATVDDS GEYRCQTNLSTLSDFVQLEV HIGWLLQAPRWVFKEEDPIHLRCH SWKNTALHKVTYLQNGKGRKYFHHN SDFYIPKATLKDSGSYFCRG LFGSKNVSETVNITITQGLAVSTI SSFFPPGYQVSFCLVMVLLFAVDTG LYFSVKTNIRSSTRDWKDHK FKWRKDPQDK	SEQ ID NO. 25 ATGGGTGGAGGGCTGGGGAAAGGCTGTTTACTTCCTC CTGTCTAGTCGGTTTGGTCCCTTTAGGGCTCCGGATAT CTTTGGTGACTTGTCCTCACTCCAGTGTGGCATCATGTGG CAGCTGCTCCTCCCAACTGCTCTGCTACTTCTAGTTTC AGCTGGCATGCGGACTGAAGATCTCCCAAGGCTGTGG TGTTCTTGGAGCCTCAATGGTACAGGGTGTCTGAGAAG GACAGTGTGACTCTGAAGTGCCAGGGAGCCTACTCCCC TGAGGACAATTCCACACAGTGGTTTCACAATGAGAGCC TCATCTCAAGCCAGGCTCGAGCTACTTCATTGACGCT GCCACAGTCGACGACAGTGGAGAGTACAGGTGCCAGAC AAACCTCTCCACCCTCAGTGACCCGGTGCAGCTAGAAG TCCATATCGGCTGGCTGTTGCTCCAGGCCCTCGGTGG GTGTTCAAGGAGGAAGACCCTATTACCTGAGGTGTCA CAGCTGGAAGAACTGCTCTGCATAAGGTACATATT TACAGAATGGCAAAGGCAGGAAGTATTTTCATCATAAT TCTGACTTCTACATTCCAAAAGCCACACTCAAAGACAG CGGCTCCTACTTCTGCAGGGGGCTTTTGGGAGTAAAA ATGTGTCCTCAGAGACTGTGAACATCACCATCACTCAA GGTTTGGCAGTGTCAACCATCTCATCTTCTTCCACC TGGGTACCAAGTCTCTTCTGCTTGGTGATGGTACTCC TTTTTGCAGTGGACACAGGACTATATTCTCTGTGAAG ACAAACATTGAAGCTCAACAAGAGACTGGAAGGACCA TAAATTTAAATGGAGAAAGGACCCTCAAGACAAATGA
Human Fc gamma RIIIB	MWQLLLPTALLLLVSAGMRTEDLPK AVVFLEPQWYSVLEKDSVTLKCQGA YSPEDNSTQWFHNEENLISSQ	SEQ ID NO. 26 ATGTGGCAGCTGCTCCTCCCAACTGCTCTGCTACTTCT AGTTTCAGCTGGCATGCGGACTGAAGATCTCCCAAGG

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(SEQ ID NO. 13)	ASSYFIDAATVNDSGEYRCQTNLST LSDPVQLEVHIGWLLQAPRWVFE EDPIHLRCHSWKNTALHKVT YLQNGKDRKYFHHNSDFHIPKATLK DSGSYFCRGLVGSKNVSETVNITI TQGLAVSTISSFSPPGYQVS FCLVMVLLFAVDLTGLYFSVKTNI	CTGTGGTGTTCCTGGAGCCTCAATGGTACAGCGTGCTT GAGAAGGACAGTGTGACTCTGAAGTGCCAGGGAGCCTA CTCCCCTGAGGACAATTCCACACAGTGGTTTCACAATG AGAACCCTCATCTCAAGCCAGGCCTCGAGCTACTTCATT GACGCTGCCACAGTCAACGACAGTGGAGAGTACAGGTG CCAGACAAACCTCTCCACCCTCAGTGACCCGGTGCAGC TAGAAGTCCATATCGGCTGGCTGTTGCTCCAGGCCCT CGGTGGGTGTTCAAGGAGGAAGACCCTATTACCTGAG GTGTCACAGCTGGAAGAACACTGCTCTGCATAAGGTCA CATATTTACAGAATGGCAAAGACAGGAAGTATTTTCAT CATAATTCTGACTTCCACATTCCAAAAGCCACACTCAA AGATAGCGGCTCCTACTTCTGCAGGGGGCTTGTGGGA GTAAAAATGTGTCTTCAGAGACTGTGAACATCACCATC ACTCAAGGTTTGGCAGTGTCAACCATCTCATATTCTC TCCACCTGGGTACCAAGTCTCTTTCTGCTTGGTGATGG TACTCCTTTTTCAGTGGACACAGGACTATATTTCTCT GTGAAGACAAACATTTGA
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The preferred FcRs are encoded by the following nucleic acids:

Human Fc gamma RIA (SEQ ID NO. 1) is encoded by the sequence according to SEQ ID NO. 14.

Human Fc gamma RIB (SEQ ID NO. 2) is encoded by the sequence according to SEQ ID NO. 15.

Human Fc gamma RIB (SEQ ID NO. 3) is encoded by the sequence according to SEQ ID NO. 16.

Human Fc gammaRIIA (SEQ ID NO. 4) is encoded by the sequence according to SEQ ID NO. 17.

Human Fc gammaRIIB Isoform 1 (SEQ ID NO. 5) is encoded by the sequence according to SEQ ID NO. 18.

15 Human Fc gammaRIIB Isoform 2 (SEQ ID NO. 6) is encoded by the sequence according to SEQ ID NO. 19.

Human Fc gammaRIIB Isoform 3 (SEQ ID NO. 7) is encoded by the sequence according to SEQ ID NO. 20.

Human Fc gammaRIIB Isoform 4 (SEQ ID NO. 8) is encoded by the sequence
20 according to SEQ ID NO. 21.

Human Fc gammaRIIC Isoform 1 (SEQ ID NO. 9) is encoded by the sequence according to SEQ ID NO. 22.

Human Fc gammaRIIC Isoform 2 (SEQ ID NO. 10) is encoded by the sequence according to SEQ ID NO. 23.

25 Human Fc gammaRIIC Isoform 3 (SEQ ID NO. 11) is encoded by the sequence according to SEQ ID NO. 24.

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Human FcgammaRIIA (SEQ ID NO. 12) is encoded by the sequence according to SEQ ID NO. 25.

Human Fc gamma RIIB (SEQ ID NO. 13) is encoded by the sequence according to SEQ ID NO. 26.

It is preferred that the FcγR is a recombinant non-glycosylated human soluble FcγRIIB preferably selected from the group of SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7 and SEQ ID NO. 8.

10 EXAMPLES

The biologically active compound, the recombinant human soluble FcγRIIB molecule, is produced in inclusion bodies by fermentation of genetically engineered *E. coli*.

15 sFcγRIIB is produced by fermentation in *E. coli* strain BL21 (DE3) which has been transformed with an optimized cDNA sequence for the expression of FcγRIIB.

The sFcγRIIB contains 4 cysteins to form 2 intra-molecular disulfide bonds between positions Cys26-Cys68 and Cys107-Cys151. The N-terminal sequence corresponds
20 to the consensus sequence of the eukaryotic signal peptidase. The C-terminus was generated by introduction of a stop codon after the SER-SER-PRO motive. No further modifications were introduced.

The sFcγRIIB has a molecular mass of 19,688.9 at native and of 19,692.9 at reducing
25 conditions.

An overview of the manufacturing process of the drug substance is given in Table 2:

Table 2

One vial of WCB
Fermentation of <i>E. coli</i> cell substrate
Harvest of <i>E. coli</i> cell substrate
Isolation of inclusion bodies

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20

Refolding of sFcγRIIB from inclusion bodies
Purification of sFcγRIIB to yield bulk material
Storage of sFcγRIIB bulk at -80°C

FIGURE CAPTIONS**Fig. 1**

5

EAE was induced on day zero in 6-8 week old C57/Bl6j female mice by subcutaneous injection of 100 µg rat MOG in complete Freund adjuvant (CFA). 250ng of pertussistoxin were given Intraperitoneally on day 0 and day 2. The mice were treated Intraperitoneally with 200 µg sFcγR after first symptoms appeared on day 8, 11 and 14. The scoring scheme was according to the degree of paralysis: 0=no paralysis, 1=tail paralysis, 2=hind legs paralysis, 3=front legs paralysis, 4=complete paralysis, 5=death.

Fig. 2

15

EAE was induced on day zero in 6-8 week old SJL female mice by subcutaneous injection of 100 µg rat MOG in complete Freund adjuvant (CFA). 250ng of pertussistoxin were given Intraperitoneally on day 0 and day 2. The mice were treated intraperitoneally with 200 µg sFcγR after first symptoms appeared on day 9, 12 and 15. The scoring scheme was according to the degree of paralysis: 0=no paralysis, 1=tail paralysis, 2=hind legs paralysis, 3=front legs paralysis, 4=complete paralysis, 5=death.

20

SEQUENCE LISTING IN ELECTRONIC FORM

In accordance with Section 111(1) of the Patent Rules, this description contains a sequence listing in electronic form in ASCII text format (file: 54097-4 Seq 10-MAR-11 v1.txt).

A copy of the sequence listing in electronic form is available from the Canadian Intellectual Property Office.

The sequences in the sequence listing in electronic form are reproduced in the following table.

SEQUENCE TABLE

<110> SuppreMol GmbH

<120> SUBSTANCES AND METHODS FOR THE TREATMENT OF B CELL MEDIATED MULTIPLE SCLEROSIS

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<170> PatentIn version 3.3

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Thr	Ser	Thr	Pro	Ser	Tyr	Arg	Ile	Thr	Ser	Ala	Ser	Val	Asn	Asp	Ser
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Gly	Glu	Tyr	Arg	Cys	Gln	Arg	Gly	Leu	Ser	Gly	Arg	Ser	Asp	Pro	Ile
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Val	Phe	Thr	Glu	Gly	Glu	Pro	Leu	Ala	Leu	Arg	Cys	His	Ala	Trp	Lys
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      195      200      205
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      210      215      220
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      260      265      270
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<213> Homo sapiens

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      145      150      155      160

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 130 135 140
 Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr Asn Ile
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 180 185 190
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 195 200 205
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 35 40 45
 Lys Ala Val Leu Lys Leu Glu Pro Gln Trp Ile Asn Val Leu Gln Glu
 50 55 60
 Asp Ser Val Thr Leu Thr Cys Arg Gly Thr His Ser Pro Glu Ser Asp
 65 70 75 80
 Ser Ile Gln Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln
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 Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser Gly Glu Tyr Thr
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 35 40 45
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 50 55 60
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 Ile Gln Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln Pro
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 50 55 60
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 180 185 190
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 195 200 205
 Pro Val Thr Ile Thr Val Gln Ala Pro Ser Ser Ser Pro Met Gly Ile
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 Ser Ile Pro Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln
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 180 185 190
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 Pro Val Thr Ile Thr Val Gln Ala Pro Ser Ser Ser Pro Met Gly Ile
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 Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
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20k

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 Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Val
 165 170 175
 Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
 180 185 190
 Gly Leu Ser Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
 195 200 205
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 Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr Val Asn Asp Ser Gly
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CLAIMS:

1. Recombinant non glycosylated human soluble FcγRIIB receptor (Fc-gamma RIIB receptor) for use in treating multiple sclerosis, wherein the multiple sclerosis is a B cell mediated form of multiple sclerosis and/or an autoantibody driven
5 form of multiple sclerosis.
2. FcγRIIB receptor according to claim 1, wherein the B cell mediation of the multiple sclerosis or autoantibody driven form of multiple sclerosis is characterized by one or more of the following features,
 - a. the multiple sclerosis is ameliorated if the patient undergoes
10 intravenous immunoglobulin (IVIG) treatment or,
 - b. the multiple sclerosis is ameliorated if the patient undergoes anti-CD20 antibody treatment or,
 - c. the multiple sclerosis is ameliorated if the patient undergoes plasmapheresis or,
 - d. the multiple sclerosis is ameliorated if the patient undergoes
15 immunoadsorption or,
 - e. the presence of autoantibodies against the antigen myelin oligodendrocyte glycoprotein (MOG) or,
 - f. the presence of autoantibodies against the antigen myelin basic
20 protein (MBP) or,
 - g. the presence of autoantibodies against aquaporin 4.
3. FcγRIIB receptor according to claim 1 or 2, wherein the B cell mediation of the multiple sclerosis or autoantibody driven form of multiple sclerosis is

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determined prior to the use of the FcγRIIB receptor by means of one or more of the following tests,

- a. determining whether the multiple sclerosis is ameliorated if the patient undergoes intravenous immunoglobulin (IVIG) treatment or,
 - 5 b. the multiple sclerosis is ameliorated if the patient undergoes anti-CD20 antibody treatment or,
 - c. the multiple sclerosis is ameliorated if the patient undergoes plasmapheresis or,
 - 10 d. the multiple sclerosis is ameliorated if the patient undergoes immunoadsorption or,
 - e. determining whether autoantibodies against the antigen myelin oligodendrocyte glycoprotein (MOG) are present in the patient or,
 - f. determining whether autoantibodies against the antigen myelin basic protein (MBP) are present in the patient or,
 - 15 g. determining whether autoantibodies against aquaporin 4 are present in the patient.
4. FcγRIIB receptor according to any one of claims 1 to 3, wherein the FcγRIIB is selected from the group consisting of FcγRIIB1 and FcγRIIB2.
 5. FcγRIIB receptor according to any one of claims 1 to 4, wherein the
20 receptor lacks the transmembrane domain and/or the signal peptide.
 6. FcγRIIB receptor according to any one of claims 1 to 5, wherein the receptor is chemically modified by PEGylation.

7. FcγRIIB receptor according to any one of claims 1 to 6, in an aqueous solution, wherein the amount to be administered to a patient in a single dose is between 1 and 20 mg FcγRIIB/kg patient.
8. FcγRIIB receptor according to any one of claims 1 to 7, wherein said
- 5 receptor has an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8.

Fig. 1

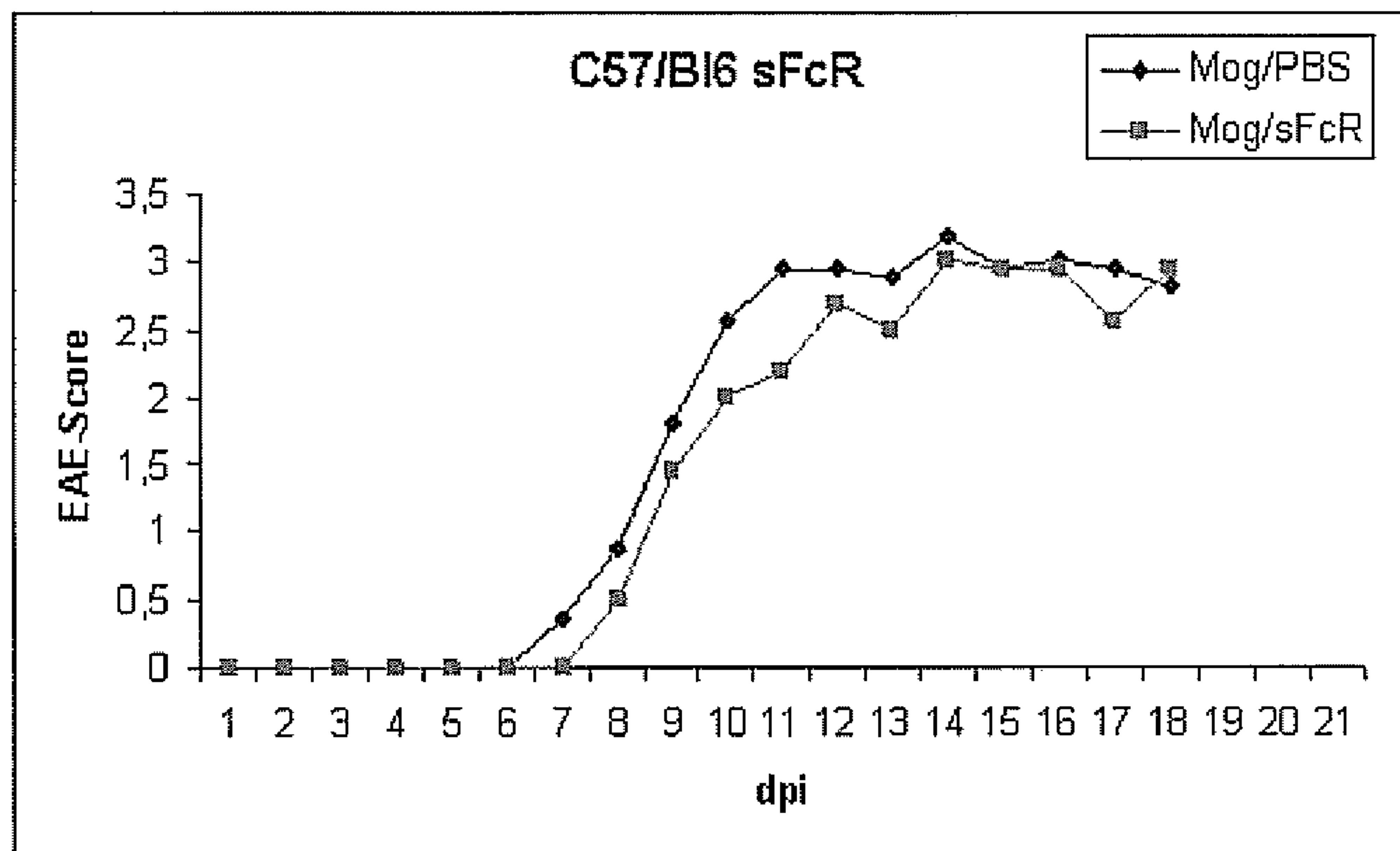


Fig. 2

