Antibody molecules which bind IL-17A and IL-17F

The present invention relates to antibody molecules having specificity for antigenic determinants of both IL-17A and IL-17F. The present invention also relates to the therapeutic uses of the antibody molecules and methods for producing them.

IL-17A (originally named CTLA-8 and also known as IL-17) is a proinflammatory cytokine and the founder member of the IL-17 family (Rouvier *et al.* 1993, *J. Immunol.* 150: 5445-5456). Subsequently five additional members of the family have been identified (IL-17B – IL-17F) including the most closely related, IL-17F (ML-1) which shares approximately 55% amino acid sequence homology with IL-17A (Moseley *et al.,* 2003, *Cytokine Growth Factor Rev.* 14: 155-174). IL-17A and IL-17F are expressed by the recently defined autoimmune related subset of T helper cells, Th17, that also express IL-21 and IL-22 signature cytokines (Korn *et al.,* 2009, *Annu. Rev. Immunol.* 27:485-517.: 485-517). IL-17A and IL-17F are expressed as homodimers, but may also be expressed as the IL-17A/F heterodimer (Wright *et al.* 2008, *J. Immunol.* 181: 2799-2805). IL-17A and F signal through the receptors IL-17R, IL-17RC or an IL-17RA/RC receptor complex (Gaffen 2008, *Cytokine.* 43: 402-407). Both IL-17A and IL-17F have been associated with a number of autoimmune diseases.

Accordingly dual antagonists of IL-17A and IL-17F may be more effective than a sole antagonist in treating IL-17 mediated diseases. Antibodies which bind IL-17A and IL-17F have been described in WO2007/106769, WO2008/047134, WO2009/136286 and WO2010/025400.

The present invention provides an improved neutralising antibody which is capable of binding to both IL-17A and IL-17F with high affinity. In particular, the antibody of the present invention is capable of specifically binding to both IL-17A and IL-17F i.e. the antibody does not bind to other isoforms of IL-17. Preferably the antibody of the present invention also binds the IL-17A/IL-17F heterodimer. Preferably, the antibody of the present invention neutralises the activity of both IL-17A and IL-17F. In one embodiment the antibody of the present invention also neutralises the activity of the IL-17A/IL-17F heterodimer. The antibodies of the present invention therefore have the advantageous property that they can inhibit the biological activity of both IL-17A and IL-17F. Accordingly, the present invention also provides the use of such antibodies in the treatment of and/or

prophylaxis of a disease mediated by either or both of IL-17A or IL-17F such as autoimmune or inflammatory disease or cancer.

As used herein, the term 'neutralising antibody' describes an antibody that is capable of neutralising the biological signalling activity of both IL-17A and IL17F for example by blocking binding of IL-17A and IL17F to one or more of their receptors and by blocking binding of the IL-17A/IL-17F heterodimer to one or more of its receptors. It will be appreciated that the term 'neutralising' as used herein refers to a reduction in biological signalling activity which may be partial or complete. Further, it will be appreciated that the extent of neutralisation of IL-17A and IL-17F activity by the antibody may be the same or different. In one embodiment the extent of neutralisation of the activity of the IL-17A/IL-17F heterodimer may be the same or different as the extent of neutralisation of IL-17A or IL-17F activity.

In one embodiment the antibodies of the present invention specifically bind to IL-17A and IL-17F. Specifically binding means that the antibodies have a greater affinity for IL-17A and IL-17F polypeptides (including the IL-17A/IL-17F heterodimer) than for other polypeptides. Preferably the IL-17A and IL-17F polypeptides are human. In one embodiment the antibody also binds cynomolgus IL-17A and IL-17F.

IL-17A or IL-17F polypeptides or a mixture of the two or cells expressing one or both of said polypeptides can be used to produce antibodies which specifically recognise both polypeptides. The IL-17 polypeptides (IL-17A and IL-17F) may be 'mature' polypeptides or biologically active fragments or derivatives thereof which preferably include the receptor binding site. Preferably the IL-17 polypeptides are the mature polypeptides. IL-17 polypeptides may be prepared by processes well known in the art from genetically engineered host cells comprising expression systems or they may be recovered from natural biological sources. In the present application, the term "polypeptides" includes peptides, polypeptides and proteins. These are used interchangeably unless otherwise specified. The IL-17 polypeptide may in some instances be part of a larger protein such as a fusion protein for example fused to an affinity tag. Antibodies generated against these polypeptides may be obtained, where immunisation of an animal is necessary, by administering the polypeptides to an animal, preferably a non-human animal, using well-known and routine protocols, see for example Handbook of Experimental Immunology, D. M. Weir (ed.), Vol 4, Blackwell Scientific Publishers, Oxford, England, 1986). Many warm-blooded animals, such as rabbits,

mice, rats, sheep, cows or pigs may be immunized. However, mice, rabbits, pigs and rats are generally preferred.

Antibodies for use in the present invention include whole antibodies and functionally active fragments or derivatives thereof and may be, but are not limited to, monoclonal, multi-valent, multi-specific, bispecific, humanized or chimeric antibodies, domain antibodies e.g. VH, VL, VHH, single chain antibodies, Fv, Fab fragments, Fab' and $F(ab')_2$ fragments and epitope-binding fragments of any of the above. Other antibody fragments include those described in International patent applications WO2005003169, WO2005003170 and WO2005003171. Other antibody fragments include Fab-Fv and Fab-dsFv fragments described in WO2009040562 and WO2010035012 respectively. Antibody fragments and methods of producing them are well known in the art, see for example Verma *et al.*, 1998, Journal of Immunological Methods, 216, 165-181; Adair and Lawson, 2005. Therapeutic antibodies. *Drug Design Reviews - Online 2(3):209-217.*

Antibodies for use in the present invention include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.* molecules that contain an antigen binding site that specifically binds an antigen. The immunoglobulin molecules of the invention can be of any class (*e.g.* IgG, IgE, IgM, IgD and IgA) or subclass of immunoglobulin molecule.

Monoclonal antibodies may be prepared by any method known in the art such as the hybridoma technique (Kohler & Milstein, 1975, Nature, 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.,* 1983, Immunology Today, 4:72) and the EBV-hybridoma technique (Cole *et al.,* Monoclonal Antibodies and Cancer Therapy, pp77-96, Alan R Liss, Inc., 1985).

Antibodies for use in the invention may also be generated using single lymphocyte antibody methods by cloning and expressing immunoglobulin variable region cDNAs generated from single lymphocytes selected for the production of specific antibodies by for example the methods described by Babcook, J. *et al.*, 1996, Proc. Natl. Acad. Sci. USA 93(15):7843-7848l; WO92/02551; WO2004/051268 and International Patent Application number WO2004/106377.

Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule (see, *e.g.* US 5,585,089; WO91/09967).

Chimeric antibodies are those antibodies encoded by immunoglobulin genes that have been genetically engineered so that the light and heavy chain genes are composed of immunoglobulin gene segments belonging to different species. These chimeric antibodies are likely to be less antigenic.

Bivalent antibodies may be made by methods known in the art (Milstein *et al.*, 1983, Nature 305:537-539; WO 93/08829, Traunecker *et al.*, 1991, EMBO J. 10:3655-3659). Multi-valent antibodies may comprise multiple specificities or may be monospecific (see for example WO 92/22853 and WO05/113605).

The antibodies for use in the present invention can also be generated using various phage display methods known in the art and include those disclosed by Brinkman *et al.* (in J. Immunol. Methods, 1995, 182: 41-50), Ames *et al.* (J. Immunol. Methods, 1995, 184:177-186), Kettleborough *et al.* (Eur. J. Immunol. 1994, 24:952-958), Persic *et al.* (Gene, 1997 187 9-18), Burton *et al.* (Advances in Immunology, 1994, 57:191-280) and WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and US 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108. Techniques for the production of single chain antibodies, such as those described in US 4,946,778 can also be adapted to produce single chain antibodies which bind to IL-17A and IL-17F. Also, transgenic mice, or other organisms, including other mammals, may be used to express humanized antibodies.

Screening for antibodies can be performed using assays to measure binding to human IL-17A and human IL-17F, for example BIAcore™ assays described in the Examples herein. Suitable neutralisation assays are known in the art, see for example WO2008/047134 and the Examples herein.

The residues in antibody variable domains are conventionally numbered according to a system devised by Kabat *et al.* This system is set forth in Kabat *et al.*, 1987, in Sequences of Proteins of Immunological Interest, US Department of Health and Human Services, NIH, USA (hereafter "Kabat *et al.* (*supra*)"). This numbering system is used in the present specification except where otherwise indicated.

The Kabat residue designations do not always correspond directly with the linear numbering of the amino acid residues. The actual linear amino acid sequence may contain fewer or additional amino acids than in the strict Kabat numbering corresponding to a shortening of, or insertion into, a structural component, whether framework or

complementarity determining region (CDR), of the basic variable domain structure. The correct Kabat numbering of residues may be determined for a given antibody by alignment of residues of homology in the sequence of the antibody with a "standard" Kabat numbered sequence.

The CDRs of the heavy chain variable domain are located at residues 31-35 (CDR-H1), residues 50-65 (CDR-H2) and residues 95-102 (CDR-H3) according to the Kabat numbering system. However, according to Chothia (Chothia, C. and Lesk, A.M. J. Mol. Biol., 196, 901-917 (1987)), the loop equivalent to CDR-H1 extends from residue 26 to residue 32. Thus 'CDR-H1', as used herein, comprises residues 26 to 35, as described by a combination of the Kabat numbering system and Chothia's topological loop definition.

The CDRs of the light chain variable domain are located at residues 24-34 (CDR-L1), residues 50-56 (CDR-L2) and residues 89-97 (CDR-L3) according to the Kabat numbering system.

In one embodiment the present invention provides a neutralising antibody having specificity for human IL-17A and human IL-17F, comprising a light chain, wherein the variable domain of the light chain comprises the sequence given in SEQ ID NO:4 for CDR-L1, the sequence given in SEQ ID NO:5 for CDR-L2 and the sequence given in SEQ ID NO:6 for CDR-L3 (See Figure 1c).

The antibody molecules of the present invention preferably comprise a complementary heavy chain.

Accordingly, in one embodiment the present invention provides a neutralising antibody having specificity for human IL-17A and human IL-17F, further comprising a heavy chain, wherein the variable domain of the heavy chain comprises at least one of a CDR having the sequence given in SEQ ID NO:1 for CDR-H1, a CDR having the sequence given in SEQ ID NO:2 for CDR-H2 and a CDR having the sequence given in SEQ ID NO:3 for CDR-H3 (See Figure 1c).

In another embodiment the present invention provides a neutralising antibody having specificity for human IL-17A and human IL-17F, comprising a heavy chain, wherein at least two of CDR-H1, CDR-H2 and CDR-H3 of the variable domain of the heavy chain are selected from the following: the sequence given in SEQ ID NO:1 for CDR-H1, the sequence given in SEQ ID NO:2 for CDR-H2 and the sequence given in SEQ ID NO:3 for CDR-H3. For example, the antibody may comprise a heavy chain wherein CDR-H1 has the sequence

given in SEQ ID NO:1 and CDR-H2 has the sequence given in SEQ ID NO:2. Alternatively, the antibody may comprise a heavy chain wherein CDR-H1 has the sequence given in SEQ ID NO:1 and CDR-H3 has the sequence given in SEQ ID NO:3, or the antibody may comprise a heavy chain wherein CDR-H2 has the sequence given in SEQ ID NO:2 and CDR-H3 has the sequence given in SEQ ID NO:3. For the avoidance of doubt, it is understood that all permutations are included.

In another embodiment the present invention provides a neutralising antibody having specificity for human IL-17A and human IL-17F, comprising a heavy chain, wherein the variable domain of the heavy chain comprises the sequence given in SEQ ID NO:1 for CDR-H1, the sequence given in SEQ ID NO:2 for CDR-H2 and the sequence given in SEQ ID NO:3 for CDR-H3.

In one embodiment, an antibody according to the present invention comprises a heavy chain, wherein the variable domain of the heavy chain comprises the sequence given in SEQ ID NO:1 for CDR-H1, the sequence given in SEQ ID NO:2 for CDR-H2 and the sequence given in SEQ ID NO:3 for CDR-H3 and a light chain wherein the variable domain of the light chain comprises the sequence given in SEQ ID NO:4 for CDR-L1, the sequence given in SEQ ID NO:5 for CDR-L2 and the sequence given in SEQ ID NO:6 for CDR-L3.

In one embodiment the antibody provided by the present invention is a monoclonal antibody.

In one embodiment the antibody provided by the present invention is a CDR-grafted antibody molecule comprising each of the CDRs provided in SEQ ID NOS:1 to 6. As used herein, the term 'CDR-grafted antibody molecule' refers to an antibody molecule wherein the heavy and/or light chain contains one or more CDRs (including, if desired, one or more modified CDRs) from a donor antibody (e.g. a murine monoclonal antibody) grafted into a heavy and/or light chain variable region framework of an acceptor antibody (e.g. a human antibody). For a review, see Vaughan *et al*, Nature Biotechnology, 16, 535-539, 1998. In one embodiment rather than the entire CDR being transferred, only one or more of the specificity determining residues from any one of the CDRs described herein above are transferred to the human antibody framework (see for example, Kashmiri *et al.*, 2005, Methods, 36, 25-34). In one embodiment only the specificity determining residues from one or more of the CDRs described herein above are transferred to the human antibody framework. In another

embodiment only the specificity determining residues from each of the CDRs described herein above are transferred to the human antibody framework.

When the CDRs or specificity determining residues are grafted, any appropriate acceptor variable region framework sequence may be used having regard to the class/type of the donor antibody from which the CDRs are derived, including mouse, primate and human framework regions. Preferably, the CDR-grafted antibody according to the present invention has a variable domain comprising human acceptor framework regions as well as one or more of the CDRs or specificity determining residues described above. Thus, provided in one embodiment is a neutralising CDR-grafted antibody wherein the variable domain comprises human acceptor framework regions and non-human donor CDRs.

Examples of human frameworks which can be used in the present invention are KOL, NEWM, REI, EU, TUR, TEI, LAY and POM (Kabat *et al., supra*). For example, KOL and NEWM can be used for the heavy chain, REI can be used for the light chain and EU, LAY and POM can be used for both the heavy chain and the light chain. Alternatively, human germline sequences may be used; these are available at: http://vbase.mrc-cpe.cam.ac.uk/

In a CDR-grafted antibody of the present invention, the acceptor heavy and light chains do not necessarily need to be derived from the same antibody and may, if desired, comprise composite chains having framework regions derived from different chains.

The preferred framework region for the heavy chain of the CDR-grafted antibody of the present invention is derived from the human sub-group VH3 sequence 1-3 3-07 together with JH4, as previously described in WO2008/047134. Accordingly, provided is a neutralising CDR-grafted antibody comprising at least one non-human donor CDR wherein the heavy chain framework region is derived from the human subgroup sequence 1-3 3-07 together with JH4. The sequence of human JH4 is as follows: (YFDY)WGQGTLVTVSS . The YFDY motif is part of CDR-H3 and is not part of framework 4 (Ravetch, JV. *et al.*, 1981, *Cell*, 27, 583-591).

The preferred framework region for the light chain of the CDR-grafted antibody of the present invention is derived from the human germline sub-group VK1 sequence 2-1-(1) L4 together with JK1, as previously described in WO2008/047134. Accordingly, provided is a neutralising CDR-grafted antibody comprising at least one non-human donor CDR wherein the light chain framework region is derived from the human subgroup sequence VK1 2-1-(1) L4 together with JK1. The JK1 sequence is as follows: (WT)FGQGTKVEIK. The WT motif

is part of CDR-L3 and is not part of framework 4 (Hieter, PA., *et al.*, 1982, J. Biol. Chem., 257, 1516-1522).

Also, in a CDR-grafted antibody of the present invention, the framework regions need not have exactly the same sequence as those of the acceptor antibody. For instance, unusual residues may be changed to more frequently-occurring residues for that acceptor chain class or type. Alternatively, selected residues in the acceptor framework regions may be changed so that they correspond to the residue found at the same position in the donor antibody (see Reichmann *et al.*, 1998, Nature, 332, 323-324). Such changes should be kept to the minimum necessary to recover the affinity of the donor antibody. A protocol for selecting residues in the acceptor framework regions which may need to be changed is set forth in WO 91/09967.

Preferably, in a CDR-grafted antibody molecule of the present invention, if the acceptor heavy chain has the human VH3 sequence 1-3 3-07 together with JH4, then the acceptor framework regions of the heavy chain comprise, in addition to one or more donor CDRs, a donor residue at at least position 94 (according to Kabat et al.,(supra)). Accordingly, provided is a CDR-grafted antibody, wherein at least the residue at position 94 of the variable domain of the heavy chain is a donor residue.

Preferably, in a CDR-grafted antibody molecule according to the present invention, if the acceptor light chain has the human sub-group VK1 sequence 2-1-(1) L4 together with JK1, then no donor residues are transferred i.e. only the CDRs are transferred. Accordingly, provided is a CDR-grafted antibody wherein only the CDRs are transferred to the donor framework.

Donor residues are residues from the donor antibody, i.e. the antibody from which the CDRs were originally derived.

In the present invention the antibody known as CA028_0496 (previously described in WO2008/047134) was improved by changing five residues in the light chain. Three residues were in the CDRs and two in the framework. Accordingly in one embodiment the light chain variable domain comprises an arginine residue at position 30, a serine residue at position 54, an isoleucine residue at position 56, an aspartic acid residue at position 60 and an arginine residue at position 72.

Accordingly, in one embodiment, an antibody of the present invention comprises a light chain, wherein the variable domain of the light chain comprises the sequence given in SEQ ID NO:7 (gL7).

In another embodiment, an antibody of the present invention comprises a light chain, wherein the variable domain of the light chain comprises a sequence having at least 96% identity to the sequence given in SEQ ID NO:7. In one embodiment the antibody of the present invention comprises a light chain, wherein the variable domain of the light chain comprises a sequence having at least 97, 98 or 99% identity to the sequence given in SEQ ID NO:7.

In one embodiment, an antibody of the present invention comprises a heavy chain, wherein the variable domain of the heavy chain comprises the sequence given in SEQ ID NO:9 (gH9).

In another embodiment, an antibody of the present invention comprises a heavy chain, wherein the variable domain of the heavy chain comprises a sequence having at least 60% identity or similarity to the sequence given in SEQ ID NO:9. In one embodiment, an antibody of the present invention comprises a heavy chain, wherein the variable domain of the heavy chain comprises a sequence having at least 70%, 80%, 90%, 95%, 96, 97, 98 or 99% identity or similarity to the sequence given in SEQ ID NO:9.

In one embodiment an antibody of the present invention comprises a heavy chain, wherein the variable domain of the heavy chain comprises the sequence given in SEQ ID NO:9 and a light chain, wherein the variable domain of the light chain comprises the sequence given in SEQ ID NO:7.

In another embodiment of the invention, the antibody comprises a heavy chain and a light chain, wherein the variable domain of the heavy chain comprises a sequence having at least 60% identity or similarity to the sequence given in SEQ ID NO:9 and the variable domain of the light chain comprises a sequence having at least 96% identity to the sequence given in SEQ ID NO:7. Preferably, the antibody comprises a heavy chain, wherein the variable domain of the heavy chain comprises a sequence having at least 70%, 80%, 90%, 95%, 96%, 97%, 98 or 99% identity or similarity to the sequence given in SEQ ID NO:9 and a light chain, wherein the variable domain of the light chain comprises a sequence having at least 96, 97, 98 or 99% identity to the sequence given in SEQ ID NO:7.

"Identity", as used herein, indicates that at any particular position in the aligned sequences, the amino acid residue is identical between the sequences. "Similarity", as used herein, indicates that, at any particular position in the aligned sequences, the amino acid residue is of a similar type between the sequences. For example, leucine may be substituted

for isoleucine or valine. Other amino acids which can often be substituted for one another include but are not limited to:

- phenylalanine, tyrosine and tryptophan (amino acids having aromatic side chains);
- lysine, arginine and histidine (amino acids having basic side chains);
- aspartate and glutamate (amino acids having acidic side chains);
- asparagine and glutamine (amino acids having amide side chains); and
- cysteine and methionine (amino acids having sulphur-containing side chains). Degrees of identity and similarity can be readily calculated (Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing. Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991).

The antibody molecule of the present invention may comprise a complete antibody molecule having full length heavy and light chains or a fragment thereof, such as a domain antibody e.g. VH, VL, VHH, Fab, modified Fab, Fab', $F(ab')_2$, Fv or scFv fragment. Other antibody fragments include Fab-Fv and Fab-dsFv fragments described in WO2009040562 and WO2010035012 respectively. In one embodiment the antibody fragment of the present invention is selected from the group consisting of a Fab, Fab', $F(ab')_2$, scFv and Fv fragment.

It will be appreciated that the antibodies of the present invention, in particular the antibody fragments described above, may be incorporated into other antibody formats, in particular, multi-specific antibodies, such as bi or tri specific antibodies, where one specificity is provided by an antibody of the present invention i.e specificity for IL-17A and IL-17F (including IL-17A/F heterodimer). Accordingly, in one embodiment the present invention provides a multi-specific antibody comprising one or more of the antibody fragments described herein above.

Examples of multi-specific antibodies include bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies, bibodies and tribodies (see for example Holliger and Hudson, 2005, Nature Biotech 23(9): 1126-1136; Schoonjans *et al.*2001, Biomolecular Engineering, 17 (6), 193-202). Other multi-specific antibodies include Fab-Fv, Fab-dsFv, Fab-Fv-Fv. Fab-Fv-Fc and Fab-dsFv-PEG fragments described in WO2009040562, WO2010035012, WO2011/08609, WO2011/030107 and WO2011/061492 respectively.

The constant region domains of the antibody molecule of the present invention, if present, may be selected having regard to the proposed function of the antibody molecule, and in particular the effector functions which may be required. For example, the constant region domains may be human IgA, IgD, IgE, IgG or IgM domains. In particular, human IgG constant region domains may be used, especially of the IgG1 and IgG3 isotypes when the antibody molecule is intended for therapeutic uses and antibody effector functions are required. Alternatively, IgG2 and IgG4 isotypes may be used when the antibody molecule is intended for therapeutic purposes and antibody effector functions are not required, e.g. for simply blocking IL-17 activity. It will be appreciated that sequence variants of these constant region domains may also be used. For example IgG4 molecules in which the serine at position 241 has been changed to proline as described in Angal *et al.*, Molecular Immunology, 1993, 30 (1), 105-108 may be used. Particularly preferred is the IgG1 constant domain. It will also be understood by one skilled in the art that antibodies may undergo a variety of posttranslational modifications. The type and extent of these modifications often depends on the host cell line used to express the antibody as well as the culture conditions. Such modifications may include variations in glycosylation, methionine oxidation, diketopiperazine formation, aspartate isomerization and asparagine deamidation. A frequent modification is the loss of a carboxy-terminal basic residue (such as lysine or arginine) due to the action of carboxypeptidases (as described in Harris, RJ. *Journal of Chromatography* 705:129-134, 1995). Accordingly, the C-terminal lysine of the antibody heavy chain, for example as given in Figure 2 (a), SEQ ID NO: 15, may be absent

In one embodiment the antibody heavy chain comprises a CH1 domain and the antibody light chain comprises a CL domain, either kappa or lambda.

In a preferred embodiment the antibody provided by the present invention is a neutralising antibody having specificity for human IL-17A and human IL-17F in which the heavy chain constant region comprises the human IgG1 constant region. Accordingly, the present invention provides an antibody in which the heavy chain comprises or consists of the sequence given in SEQ ID NO:15 (See figure 2a).

In one embodiment of the invention, the antibody comprises a heavy chain, wherein the heavy chain comprises a sequence having at least 60% identity or similarity to the sequence given in SEQ ID NO:15. Preferably, the antibody comprises a heavy chain, wherein the heavy chain comprises a sequence having at least 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identity or similarity to the sequence given in SEQ ID NO:15

In one embodiment an antibody molecule according to the present invention comprises a light chain comprising the sequence given in SEQ ID NO:11 (See Figure 1d).

In one embodiment of the invention, the antibody comprises a light chain, wherein the light chain comprises a sequence having at least 60% identity or similarity to the sequence given in SEQ ID NO:11. Preferably, the antibody comprises a light chain, wherein the light chain comprises a sequence having at least 70%, 80%, 90%, 95% or 98% identity or similarity to the sequence given in SEQ ID NO:11.

In one embodiment the present invention provides an antibody in which the heavy chain comprises or consists of the sequence given in SEQ ID NO:15 and the light chain comprises or consists of the sequence given in SEQ ID NO:11.

In one embodiment of the invention, the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises a sequence having at least 60% identity or similarity to the sequence given in SEQ ID NO:15 and the light chain comprises a sequence having at least 60% identity or similarity to the sequence given in SEQ ID NO:11. Preferably, the antibody comprises a heavy chain, wherein the heavy chain comprises a sequence having at least 70%, 80%, 90%, 95% or 98% identity or similarity to the sequence given in SEQ ID NO:15 and a light chain, wherein the light chain comprises a sequence having at least 70%, 80%, 90%, 95% or 98% identity or similarity to the sequence given in SEQ ID NO:11.

The antibody molecule of any aspect of the present invention preferably has a high binding affinity, preferably picomolar. It will be appreciated that the binding affinity of an antibody according to the present invention for human IL-17A may be different from the binding affinity of the same antibody for human IL-17F and/or the IL-17A/F heterodimer. In one example the antibody molecule of the present invention has an affinity for IL-17A that is greater than its affinity for IL-17F. In one example the antibody molecule of the present invention has an affinity for IL-17A which is at least 5 fold greater than its binding affinity for IL-17F. In one example the antibody molecule of the present invention has an affinity for IL-17A that is the same as its affinity for IL-17F. In one example the antibody molecule of the present invention has a picomolar affinity for both IL-17A and IL-17F.

Affinity may be measured using any suitable method known in the art, including BIAcore™, as described in the Examples herein, using isolated natural or recombinant IL-17A and IL-17F which both exist as homodimers.

Preferably the antibody molecule of the present invention has a binding affinity for IL-17A of 50pM or less. In one embodiment the antibody molecule of the present invention has a binding affinity for IL-17A of 20pM or less. In one embodiment the antibody molecule of the present invention has a binding affinity for IL-17A of 10pM or less. In one embodiment the antibody molecule of the present invention has a binding affinity for IL-17A of 5pM or less. In one embodiment the antibody of the present invention has an affinity for IL-17A of 3.2pM.

Preferably the antibody molecule of the present invention has a binding affinity for IL-17F of 100pM or less. In one embodiment the antibody of the present invention has an affinity for IL-17F of 50pM or less. In one embodiment the antibody of the present invention has an affinity for IL-17F of 23pM.

It will be appreciated that the affinity of antibodies provided by the present invention may be altered using any suitable method known in the art. The present invention therefore also relates to variants of the antibody molecules of the present invention, which have an improved affinity for IL-17A and/or IL-17F. Such variants can be obtained by a number of affinity maturation protocols including mutating the CDRs (Yang *et al.*, J. Mol. Biol., 254, 392-403, 1995), chain shuffling (Marks *et al.*, Bio/Technology, 10, 779-783, 1992), use of mutator strains of *E. coli* (Low *et al.*, J. Mol. Biol., 250, 359-368, 1996), DNA shuffling (Patten *et al.*, Curr. Opin. Biotechnol., 8, 724-733, 1997), phage display (Thompson *et al.*, J. Mol. Biol., 256, 77-88, 1996) and sexual PCR (Crameri *et al.*, Nature, 391, 288-291, 1998). Vaughan *et al.* (*supra*) discusses these methods of affinity maturation.

If desired an antibody for use in the present invention may be conjugated to one or more effector molecule(s). It will be appreciated that the effector molecule may comprise a single effector molecule or two or more such molecules so linked as to form a single moiety that can be attached to the antibodies of the present invention. Where it is desired to obtain an antibody fragment linked to an effector molecule, this may be prepared by standard chemical or recombinant DNA procedures in which the antibody fragment is linked either directly or via a coupling agent to the effector molecule. Techniques for conjugating such effector molecules to antibodies are well known in the art (see, Hellstrom *et al.*, Controlled Drug Delivery, 2nd Ed., Robinson *et al.*, eds., 1987, pp. 623-53; Thorpe *et al.*, 1982 , Immunol. Rev., 62:119-58 and Dubowchik *et al.*, 1999, Pharmacology and Therapeutics, 83, 67-123). Particular chemical procedures include, for example, those described in WO 93/06231, WO 92/22583, WO 89/00195, WO 89/01476 and WO03031581. Alternatively, where the effector

molecule is a protein or polypeptide the linkage may be achieved using recombinant DNA procedures, for example as described in WO 86/01533 and EP0392745.

The term effector molecule as used herein includes, for example, antineoplastic agents, drugs, toxins, biologically active proteins, for example enzymes, other antibody or antibody fragments, synthetic or naturally occurring polymers, nucleic acids and fragments thereof e.g. DNA, RNA and fragments thereof, radionuclides, particularly radioiodide, radioisotopes, chelated metals, nanoparticles and reporter groups such as fluorescent compounds or compounds which may be detected by NMR or ESR spectroscopy.

Examples of effector molecules may include cytotoxins or cytotoxic agents including any agent that is detrimental to (*e.g.* kills) cells. Examples include combrestatins, dolastatins, epothilones, staurosporin, maytansinoids, spongistatins, rhizoxin, halichondrins, roridins, hemiasterlins, taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof.

Effector molecules also include, but are not limited to, antimetabolites (*e.g.* methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.* mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.* daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.* dactinomycin (formerly actinomycin), bleomycin, mithramycin, anthramycin (AMC), calichcamicins or duocarmycins), and anti-mitotic agents (*e.g.* vincristine and vinblastine).

Other effector molecules may include chelated radionuclides such as ^{111}In and ^{90}Y, Lu^{177}, Bismuth^{213}, Californium^{252}, Iridium^{192} and Tungsten^{188}/Rhenium^{188}; or drugs such as but not limited to, alkylphosphocholines, topoisomerase I inhibitors, taxoids and suramin.

Other effector molecules include proteins, peptides and enzymes. Enzymes of interest include, but are not limited to, proteolytic enzymes, hydrolases, lyases, isomerases, transferases. Proteins, polypeptides and peptides of interest include, but are not limited to, immunoglobulins, toxins such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin, a protein such as insulin, tumour necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor or tissue plasminogen activator, a thrombotic agent or an

anti-angiogenic agent, *e.g.* angiostatin or endostatin, or, a biological response modifier such as a lymphokine, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), nerve growth factor (NGF) or other growth factor and immunoglobulins.

Other effector molecules may include detectable substances useful for example in diagnosis. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive nuclides, positron emitting metals (for use in positron emission tomography), and nonradioactive paramagnetic metal ions. See generally U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics. Suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; suitable prosthetic groups include streptavidin, avidin and biotin; suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride and phycoerythrin; suitable luminescent materials include luminol; suitable bioluminescent materials include luciferase, luciferin, and aequorin; and suitable radioactive nuclides include ^{125}I, ^{131}I, ^{111}In and ^{99}Tc.

In another example the effector molecule may increase the half-life of the antibody *in vivo*, and/or reduce immunogenicity of the antibody and/or enhance the delivery of an antibody across an epithelial barrier to the immune system. Examples of suitable effector molecules of this type include polymers, albumin, albumin binding proteins or albumin binding compounds such as those described in WO05/117984.

Where the effector molecule is a polymer it may, in general, be a synthetic or a naturally occurring polymer, for example an optionally substituted straight or branched chain polyalkylene, polyalkenylene or polyoxyalkylene polymer or a branched or unbranched polysaccharide, e.g. a homo- or hetero- polysaccharide.

Particular optional substituents which may be present on the above-mentioned synthetic polymers include one or more hydroxy, methyl or methoxy groups.

Particular examples of synthetic polymers include optionally substituted straight or branched chain poly(ethyleneglycol), poly(propyleneglycol) poly(vinylalcohol) or derivatives thereof, especially optionally substituted poly(ethyleneglycol) such as methoxypoly(ethyleneglycol) or derivatives thereof.

Particular naturally occurring polymers include lactose, amylose, dextran, glycogen or derivatives thereof.

"Derivatives" as used herein is intended to include reactive derivatives, for example thiol-selective reactive groups such as maleimides and the like. The reactive group may be linked directly or through a linker segment to the polymer. It will be appreciated that the residue of such a group will in some instances form part of the product as the linking group between the antibody fragment and the polymer.

The size of the polymer may be varied as desired, but will generally be in an average molecular weight range from 500Da to 50000Da, preferably from 5000 to 40000Da and more preferably from 20000 to 40000Da. The polymer size may in particular be selected on the basis of the intended use of the product for example ability to localize to certain tissues such as tumors or extend circulating half-life (for review see Chapman, 2002, Advanced Drug Delivery Reviews, 54, 531-545). Thus, for example, where the product is intended to leave the circulation and penetrate tissue, for example for use in the treatment of a tumour, it may be advantageous to use a small molecular weight polymer, for example with a molecular weight of around 5000Da. For applications where the product remains in the circulation, it may be advantageous to use a higher molecular weight polymer, for example having a molecular weight in the range from 20000Da to 40000Da.

Particularly preferred polymers include a polyalkylene polymer, such as a poly(ethyleneglycol) or, especially, a methoxypoly(ethyleneglycol) or a derivative thereof, and especially with a molecular weight in the range from about 15000Da to about 40000Da.

In one example antibodies for use in the present invention are attached to poly(ethyleneglycol) (PEG) moieties. In one particular example the antibody is an antibody fragment and the PEG molecules may be attached through any available amino acid side-chain or terminal amino acid functional group located in the antibody fragment, for example any free amino, imino, thiol, hydroxyl or carboxyl group. Such amino acids may occur naturally in the antibody fragment or may be engineered into the fragment using recombinant DNA methods (see for example US 5,219,996; US 5,667,425; WO98/25971). In one example the antibody molecule of the present invention is a modified Fab fragment wherein the modification is the addition to the C-terminal end of its heavy chain one or more amino acids to allow the attachment of an effector molecule. Preferably, the additional amino acids form a modified hinge region containing one or more cysteine residues to which the effector molecule may be attached. Multiple sites can be used to attach two or more PEG molecules.

Preferably PEG molecules are covalently linked through a thiol group of at least one cysteine residue located in the antibody fragment. Each polymer molecule attached to the modified antibody fragment may be covalently linked to the sulphur atom of a cysteine residue located in the fragment. The covalent linkage will generally be a disulphide bond or, in particular, a sulphur-carbon bond. Where a thiol group is used as the point of attachment appropriately activated effector molecules, for example thiol selective derivatives such as maleimides and cysteine derivatives may be used. An activated polymer may be used as the starting material in the preparation of polymer-modified antibody fragments as described above. The activated polymer may be any polymer containing a thiol reactive group such as an α-halocarboxylic acid or ester, e.g. iodoacetamide, an imide, e.g. maleimide, a vinyl sulphone or a disulphide. Such starting materials may be obtained commercially (for example from Nektar, formerly Shearwater Polymers Inc., Huntsville, AL, USA) or may be prepared from commercially available starting materials using conventional chemical procedures. Particular PEG molecules include 20K methoxy-PEG-amine (obtainable from Nektar, formerly Shearwater; Rapp Polymere; and SunBio) and M-PEG-SPA (obtainable from Nektar, formerly Shearwater).

In one embodiment, the antibody is a modified Fab fragment which is PEGylated, *i.e.* has PEG (poly(ethyleneglycol)) covalently attached thereto, *e.g.* according to the method disclosed in EP 0948544 [see also "Poly(ethyleneglycol) Chemistry, Biotechnical and Biomedical Applications", 1992, J. Milton Harris (ed), Plenum Press, New York, "Poly(ethyleneglycol) Chemistry and Biological Applications", 1997, J. Milton Harris and S. Zalipsky (eds), American Chemical Society, Washington DC and "Bioconjugation Protein Coupling Techniques for the Biomedical Sciences", 1998, M. Aslam and A. Dent, Grove Publishers, New York; Chapman, A. 2002, Advanced Drug Delivery Reviews 2002, 54:531-545]. In one example PEG is attached to a cysteine in the hinge region. In one example, a PEG modified Fab fragment has a maleimide group covalently linked to a single thiol group in a modified hinge region. A lysine residue may be covalently linked to the maleimide group and to each of the amine groups on the lysine residue may be attached a methoxypoly(ethyleneglycol) polymer having a molecular weight of approximately 20,000 Da. The total molecular weight of the PEG attached to the Fab fragment may therefore be approximately 40,000 Da.

In one embodiment, the present invention provides a neutralising antibody molecule having specificity for human IL-17A and human IL-17F, which is a modified Fab fragment

having a heavy chain comprising the sequence given in SEQ ID NO:9 and a light chain comprising the sequence given in SEQ ID NO:7 and having at the C-terminal end of its heavy chain a modified hinge region containing at least one cysteine residue to which an effector molecule is attached. Preferably the effector molecule is PEG and is attached using the methods described in (WO98/25971 and WO2004072116) whereby a lysyl-maleimide group is attached to the cysteine residue at the C-terminal end of the heavy chain, and each amino group of the lysyl residue has covalently linked to it a methoxypoly(ethyleneglycol) residue having a molecular weight of about 20,000 Da. The total molecular weight of the PEG attached to the antibody is therefore approximately 40,000Da.

In another example effector molecules may be attached to antibody fragments using the methods described in International patent applications WO2005/003169, WO2005/003170 and WO2005/003171.

The present invention also provides an isolated DNA sequence encoding the heavy and/or light chain(s) of an antibody molecule of the present invention. Preferably, the DNA sequence encodes the heavy or the light chain of an antibody molecule of the present invention. The DNA sequence of the present invention may comprise synthetic DNA, for instance produced by chemical processing, cDNA, genomic DNA or any combination thereof.

DNA sequences which encode an antibody molecule of the present invention can be obtained by methods well known to those skilled in the art. For example, DNA sequences coding for part or all of the antibody heavy and light chains may be synthesised as desired from the determined DNA sequences or on the basis of the corresponding amino acid sequences.

DNA coding for acceptor framework sequences is widely available to those skilled in the art and can be readily synthesised on the basis of their known amino acid sequences.

Standard techniques of molecular biology may be used to prepare DNA sequences coding for the antibody molecule of the present invention. Desired DNA sequences may be synthesised completely or in part using oligonucleotide synthesis techniques. Site-directed mutagenesis and polymerase chain reaction (PCR) techniques may be used as appropriate.

Examples of suitable sequences are provided in SEQ ID NO:8; SEQ ID NO:10; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19.

The present invention also relates to a cloning or expression vector comprising one or more DNA sequences of the present invention. Accordingly, provided is a cloning or

expression vector comprising one or more DNA sequences encoding an antibody of the present invention. Preferably, the cloning or expression vector comprises two DNA sequences, encoding the light chain and the heavy chain of the antibody molecule of the present invention, respectively along with suitable signal sequences. Preferably, a vector according to the present invention comprises the sequences given in SEQ ID NO:14 and SEQ ID NO:18. In one embodiment a vector according to the present invention comprises the sequences given in SEQ ID NO:13 and SEQ ID NO:17.

General methods by which the vectors may be constructed, transfection methods and culture methods are well known to those skilled in the art. In this respect, reference is made to "Current Protocols in Molecular Biology", 1999, F. M. Ausubel (ed), Wiley Interscience, New York and the Maniatis Manual produced by Cold Spring Harbor Publishing.

Also provided is a host cell comprising one or more cloning or expression vectors comprising one or more DNA sequences encoding an antibody of the present invention. Any suitable host cell/vector system may be used for expression of the DNA sequences encoding the antibody molecule of the present invention. Bacterial, for example *E. coli*, and other microbial systems may be used or eukaryotic, for example mammalian, host cell expression systems may also be used. Suitable mammalian host cells include CHO, myeloma or hybridoma cells.

The present invention also provides a process for the production of an antibody molecule according to the present invention comprising culturing a host cell containing a vector of the present invention under conditions suitable for leading to expression of protein from DNA encoding the antibody molecule of the present invention, and isolating the antibody molecule.

The antibody molecule may comprise only a heavy or light chain polypeptide, in which case only a heavy chain or light chain polypeptide coding sequence needs to be used to transfect the host cells. For production of products comprising both heavy and light chains, the cell line may be transfected with two vectors, a first vector encoding a light chain polypeptide and a second vector encoding a heavy chain polypeptide. Alternatively, a single vector may be used, the vector including sequences encoding light chain and heavy chain polypeptides.

As the antibodies of the present invention are useful in the treatment and/or prophylaxis of a pathological condition, the present invention also provides a pharmaceutical

or diagnostic composition comprising an antibody molecule of the present invention in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier. Accordingly, provided is the use of an antibody according to the present invention for the manufacture of a medicament. The composition will usually be supplied as part of a sterile, pharmaceutical composition that will normally include a pharmaceutically acceptable carrier. A pharmaceutical composition of the present invention may additionally comprise a pharmaceutically-acceptable adjuvant.

The present invention also provides a process for preparation of a pharmaceutical or diagnostic composition comprising adding and mixing the antibody molecule of the present invention together with one or more of a pharmaceutically acceptable excipient, diluent or carrier.

The antibody molecule may be the sole active ingredient in the pharmaceutical or diagnostic composition or may be accompanied by other active ingredients including other antibody ingredients, for example anti-TNF, anti- IL-1β, anti-T cell, anti-IFNγ or anti-LPS antibodies, or non-antibody ingredients such as xanthines or a small molecule inhibitor.

The pharmaceutical compositions preferably comprise a therapeutically effective amount of the antibody of the invention. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent needed to treat, ameliorate or prevent a targeted disease or condition, or to exhibit a detectable therapeutic or preventative effect. For any antibody, the therapeutically effective amount can be estimated initially either in cell culture assays or in animal models, usually in rodents, rabbits, dogs, pigs or primates. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

The precise therapeutically effective amount for a human subject will depend upon the severity of the disease state, the general health of the subject, the age, weight and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities and tolerance/response to therapy. This amount can be determined by routine experimentation and is within the judgement of the clinician. Generally, a therapeutically effective amount will be from 0.01 mg/kg to 50 mg/kg, preferably 0.1 mg/kg to 20 mg/kg. Pharmaceutical compositions may be conveniently presented in unit dose forms containing a predetermined amount of an active agent of the invention per dose.

Compositions may be administered individually to a patient or may be administered in combination (*e.g.* simultaneously, sequentially or separately) with other agents, drugs or hormones.

The dose at which the antibody molecule of the present invention is administered depends on the nature of the condition to be treated, the extent of the inflammation present and on whether the antibody molecule is being used prophylactically or to treat an existing condition.

The frequency of dose will depend on the half-life of the antibody molecule and the duration of its effect. If the antibody molecule has a short half-life (e.g. 2 to 10 hours) it may be necessary to give one or more doses per day. Alternatively, if the antibody molecule has a long half life (e.g. 2 to 15 days) it may only be necessary to give a dosage once per day, once per week or even once every 1 or 2 months.

The pharmaceutically acceptable carrier should not itself induce the production of antibodies harmful to the individual receiving the composition and should not be toxic. Suitable carriers may be large, slowly metabolised macromolecules such as proteins, polypeptides, liposomes, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers and inactive virus particles.

Pharmaceutically acceptable salts can be used, for example mineral acid salts, such as hydrochlorides, hydrobromides, phosphates and sulphates, or salts of organic acids, such as acetates, propionates, malonates and benzoates.

Pharmaceutically acceptable carriers in therapeutic compositions may additionally contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents or pH buffering substances, may be present in such compositions. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries and suspensions, for ingestion by the patient.

Preferred forms for administration include forms suitable for parenteral administration, e.g. by injection or infusion, for example by bolus injection or continuous infusion. Where the product is for injection or infusion, it may take the form of a suspension, solution or emulsion in an oily or aqueous vehicle and it may contain formulatory agents, such as suspending, preservative, stabilising and/or dispersing agents. Alternatively, the

antibody molecule may be in dry form, for reconstitution before use with an appropriate sterile liquid.

Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals. However, it is preferred that the compositions are adapted for administration to human subjects.

The pharmaceutical compositions of this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, transcutaneous (for example, see WO 98/20734), subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, intravaginal or rectal routes. Hyposprays may also be used to administer the pharmaceutical compositions of the invention. Typically, the therapeutic compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared.

Direct delivery of the compositions will generally be accomplished by injection, subcutaneously, intraperitoneally, intravenously or intramuscularly, or delivered to the interstitial space of a tissue. The compositions can also be administered into a lesion. Dosage treatment may be a single dose schedule or a multiple dose schedule.

It will be appreciated that the active ingredient in the composition will be an antibody molecule. As such, it will be susceptible to degradation in the gastrointestinal tract. Thus, if the composition is to be administered by a route using the gastrointestinal tract, the composition will need to contain agents which protect the antibody from degradation but which release the antibody once it has been absorbed from the gastrointestinal tract.

A thorough discussion of pharmaceutically acceptable carriers is available in Remington's Pharmaceutical Sciences (Mack Publishing Company, N.J. 1991).

In one embodiment the formulation is provided as a formulation for topical administrations including inhalation.

Suitable inhalable preparations include inhalable powders, metering aerosols containing propellant gases or inhalable solutions free from propellant gases. Inhalable powders according to the disclosure containing the active substance may consist solely of the abovementioned active substances or of a mixture of the abovementioned active substances with physiologically acceptable excipient.

These inhalable powders may include monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextranes), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these with one another. Mono- or disaccharides are suitably used, the use of lactose or glucose, particularly but not exclusively in the form of their hydrates.

Particles for deposition in the lung require a particle size less than 10 microns, such as 1-9 microns for example from 0.1 to 5 μm, in particular from 1 to 5 μm. The particle size of the active ingredient (such as the antibody or fragment) is of primary importance.

The propellent gases which can be used to prepare the inhalable aerosols are known in the art. Suitable propellent gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The abovementioned propellent gases may be used on their own or in mixtures thereof.

Particularly suitable propellent gases are halogenated alkane derivatives selected from among TG 11, TG 12, TG 134a and TG227. Of the abovementioned halogenated hydrocarbons, TG134a (1,1,1,2-tetrafluoroethane) and TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof are particularly suitable.

The propellent-gas-containing inhalable aerosols may also contain other ingredients such as cosolvents, stabilisers, surface-active agents (surfactants), antioxidants, lubricants and means for adjusting the pH. All these ingredients are known in the art.

The propellant-gas-containing inhalable aerosols according to the invention may contain up to 5 % by weight of active substance. Aerosols according to the invention contain, for example, 0.002 to 5 % by weight, 0.01 to 3 % by weight, 0.015 to 2 % by weight, 0.1 to 2 % by weight, 0.5 to 2 % by weight or 0.5 to 1 % by weight of active ingredient.

Alternatively topical administrations to the lung may also be by administration of a liquid solution or suspension formulation, for example employing a device such as a nebulizer, for example, a nebulizer connected to a compressor (e.g., the Pari LC-Jet Plus(R) nebulizer connected to a Pari Master(R) compressor manufactured by Pari Respiratory Equipment, Inc., Richmond, Va.).

The antibody of the invention can be delivered dispersed in a solvent, e.g., in the form of a solution or a suspension. It can be suspended in an appropriate physiological solution, e.g., saline or other pharmacologically acceptable solvent or a buffered solution. Buffered solutions known in the art may contain 0.05 mg to 0.15 mg disodium edetate, 8.0 mg to 9.0 mg NaCl, 0.15 mg to 0.25 mg polysorbate, 0.25 mg to 0.30 mg anhydrous citric acid, and

0.45 mg to 0.55 mg sodium citrate per 1 ml of water so as to achieve a pH of about 4.0 to 5.0. A suspension can employ, for example, lyophilised antibody.

The therapeutic suspensions or solution formulations can also contain one or more excipients. Excipients are well known in the art and include buffers (e.g., citrate buffer, phosphate buffer, acetate buffer and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, proteins (e.g., serum albumin), EDTA, sodium chloride, liposomes, mannitol, sorbitol, and glycerol. Solutions or suspensions can be encapsulated in liposomes or biodegradable microspheres. The formulation will generally be provided in a substantially sterile form employing sterile manufacture processes.

This may include production and sterilization by filtration of the buffered solvent/solution used for the formulation, aseptic suspension of the antibody in the sterile buffered solvent solution, and dispensing of the formulation into sterile receptacles by methods familiar to those of ordinary skill in the art.

Nebulizable formulation according to the present disclosure may be provided, for example, as single dose units (e.g., sealed plastic containers or vials) packed in foil envelopes. Each vial contains a unit dose in a volume, e.g., 2 mL, of solvent/solutionbuffer.

The antibodies disclosed herein may be suitable for delivery via nebulisation.

It is also envisaged that the antibody of the present invention may be administered by use of gene therapy. In order to achieve this, DNA sequences encoding the heavy and light chains of the antibody molecule under the control of appropriate DNA components are introduced into a patient such that the antibody chains are expressed from the DNA sequences and assembled *in situ*.

The present invention also provides an antibody molecule for use in the control of inflammatory diseases. Preferably, the antibody molecule can be used to reduce the inflammatory process or to prevent the inflammatory process.

The present invention also provides the antibody molecule of the present invention for use in the treatment or prophylaxis of a pathological disorder that is mediated by IL-17A and/or IL-17F or is associated with an increased level of IL-17A and/or IL-17F. Preferably, the pathological condition is selected from the group consisting of infections (viral, bacterial, fungal and parasitic), endotoxic shock associated with infection, arthritis, rheumatoid arthritis, psoriatic arthritis, systemic onset juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), asthma, chronic obstructive airways disease (COAD), chronic obstructive pulmonary disease (COPD), acute lung injury, pelvic inflammatory

disease, Alzheimer's Disease, Crohn's disease, inflammatory bowel disease, irritable bwel syndrome, Ulcerative colitis, Castleman's disease, ankylosing spondylitis and other spondyloarthropathies, dermatomyositis, myocarditis, uveitis, exophthalmos, autoimmune thyroiditis, Peyronie's Disease, coeliac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, atopic dermatitis, vasculitis, surgical adhesions, stroke, autoimmune diabetes, Type I Diabetes, lyme arthritis, meningoencephalitis, immune mediated inflammatory disorders of the central and peripheral nervous system such as multiple sclerosis and Guillain-Barr syndrome, other autoimmune disorders, pancreatitis, trauma (surgery), graft-versus-host disease, transplant rejection, fibrosing disorders including pulmonary fibrosis, liver fibrosis, renal fibrosis, scleroderma or systemic sclerosis, cancer (both solid tumours such as melanomas, hepatoblastomas, sarcomas, squamous cell carcinomas, transitional cell cancers, ovarian cancers and hematologic malignancies and in particular acute myelogenous leukaemia, chronic myelogenous leukemia, chronic lymphatic leukemia, gastric cancer and colon cancer), heart disease including ischaemic diseases such as myocardial infarction as well as atherosclerosis, intravascular coagulation, bone resorption, osteoporosis, periodontitis and hypochlorhydia.

In one embodiment the antibody of the present invention is used in the treatment or prophylaxis of a pathological disorder selected from the group consisting of arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, systemic onset juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), asthma, chronic obstructive airway disease, chronic obstructive pulmonary disease, atopic dermatitis, scleroderma, systemic sclerosis, lung fibrosis, inflammatory bowel diseases, ankylosing spondylitis and other spondyloarthropathies and cancer.

In one embodiment the antibody of the present invention is used in the treatment or prophylaxis of a pathological disorder selected from the group consisting of arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, systemic onset juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), asthma, chronic obstructive airway disease, chronic obstructive pulmonary disease, atopic dermatitis, scleroderma, systemic sclerosis, lung fibrosis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and other spondyloarthropathies and cancer.

In one embodiment the antibody of the present invention is used in the treatment or prophylaxis of a pathological disorder selected from the group consisting of arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, systemic onset juvenile idiopathic arthritis

(JIA), systemic lupus erythematosus (SLE), asthma, chronic obstructive airway disease, chronic obstructive pulmonary disease, atopic dermatitis, scleroderma, systemic sclerosis, lung fibrosis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and other spondyloarthropathies.

In one embodiment the pathological disorder is rheumatoid arthritis.

In one embodiment the pathological disorder is Crohn's disease.

In one embodiment the pathological disorder is ulcerative colitis.

In one example the antibody of the present invention is used in the treatment of an inflammatory or immune related disease. In one example the inflammatory or immune related disease is selected from the group consisting of rheumatoid arthritis, Crohn's disease and ulcerative colitis.

The present invention also provides an antibody molecule according to the present invention for use in the treatment or prophylaxis of pain, particularly pain associated with inflammation.

The present invention further provides the use of an antibody molecule according to the present invention in the manufacture of a medicament for the treatment or prophylaxis of a pathological disorder that is mediated by IL-17A and/or IL-17F or associated with an increased level of IL-17A and/or IL-17F. Preferably the pathological disorder is one of the medical indications described herein above. The present invention further provides the use of an antibody molecule according to the present invention in the manufacture of a medicament for the treatment or prophylaxis of pain, particularly pain associated with inflammation.

An antibody molecule of the present invention may be utilised in any therapy where it is desired to reduce the effects of IL-17A and/or IL-17F in the human or animal body. IL-17 A and/or IL-17F may be circulating in the body or may be present in an undesirably high level localised at a particular site in the body, for example a site of inflammation.

An antibody molecule according to the present invention is preferably used for the control of inflammatory disease, autoimmune disease or cancer.

The present invention also provides a method of treating human or animal subjects suffering from or at risk of a disorder mediated by IL-17A and/or IL-17F, the method comprising administering to the subject an effective amount of an antibody molecule of the present invention.

An antibody molecule according to the present invention may also be used in diagnosis, for example in the *in vivo* diagnosis and imaging of disease states involving IL-17A and/or IL-17F.

The present invention is further described by way of illustration only in the following examples, which refer to the accompanying Figures, in which:

Figure 1 a) Light chain V region of antibody CA028_0496g3 (SEQ ID NO:7)

b) Heavy chain V region of antibody CA028_0496g3 (SEQ ID NO:9)

c) CDRH1 (SEQ ID NO:1), CDRH2 (SEQ ID NO:2), CDRH3 (SEQ ID NO:3), CDRL1 (SEQ ID NO:4), CDRL2 (SEQ ID NO:5), CDRL3 (SEQ ID NO:6) of antibody CA028_496g3.

d) Light chain of antibody CA028_496g3 (SEQ ID NO:11).

e) Light chain of antibody CA028_496g3 including signal sequence (SEQ ID NO:12).

Figure 2

a) Heavy chain of antibody CA028_496g3 (SEQ ID NO:15).

b) Heavy chain of antibody CA028_496g3 including signal sequence (SEQ ID NO:16).

c) DNA encoding light chain of antibody CA028_496g3 (no signal sequence) (SEQ ID NO:13).

Figure 3

a) DNA encoding light chain of antibody CA028_496g3 including signal sequence (SEQ ID NO:14)
b) DNA encoding light chain variable region of antibody CA028_496g3 (SEQ ID NO:8)
c) DNA encoding heavy chain variable region of antibody CA028_496g3 including signal sequence (SEQ ID NO:10)

Figure 4: DNA (including exons) encoding heavy chain of antibody CA028_496g3 without signal sequence (SEQ ID NO:17)

Figure 5: DNA (including exons and signal sequence) encoding heavy chain of antibody CA028_496g3 (SEQ ID NO:18)

Figure 6: c DNA encoding heavy chain of antibody CA028_496g3 including signal sequence (SEQ ID NO:19).

Figure 7: The effect of antibodies CA028_0496 (designated 496g1 in legend) and CA028_00496.g3 (designated 496.g3 in legend) on human IL-17F induced IL-6 production from Hela cells.

Example 1: Production of an improved neutralising antibody which binds IL-17A and IL-17F

The isolation and humanisation of antibody CA028_0496 has previously been described in WO2008/047134. CA028_0496 is a humanised neutralising antibody which binds both IL-17A and IL-17F and comprises the grafted variable regions gL7 and gH9, the sequences of which are provided in WO2008/047134. The heavy chain acceptor framework is the human germline sequence VH3 1-3 3-07 with framework 4 coming from this portion of the human JH-region germline JH4. The light chain acceptor framework is the human germline sequence VK1 2-1-(1) L4, with framework 4 coming from this portion of the human JK-region germline JK1.

Antibody CA028_00496 was affinity matured to improve the affinity of the antibody for IL-17F whilst retaining affinity for IL-17A. In contrast to antibody CA028_00496, the affinity matured antibody, known as CA028_00496.g3, was expressed as an IgG1 rather than an IgG4. Genes were modified to generate the affinity matured versions by oligonucleotide directed mutagenesis. The affinity matured light chain variable region (gL57) gene sequence was sub-cloned into the UCB Celltech human light chain expression vector pKH10.1, which contains DNA encoding the human C-Kappa constant region (Km3 allotype). The unaltered heavy chain variable region (gH9) sequence was sub-cloned into the UCB Celltech expression vector pVhg1 FL, which contains DNA encoding human heavy chain gamma-1 constant regions. Plasmids were co-transfected into CHO cells using the Lipofectamine™ 2000 procedure according to manufacturer's instructions (InVitrogen, catalogue No. 11668).

The final sequence of the affinity matured variable regions of antibody CA028_00496.g3 are given in Figures 1a and 1b. In antibody CA028_00496.g3 the heavy chain variable region sequence is the same as that of the parent antibody CA028_00496. In contrast, the light chain variable region differs by 5 amino acids. The five residues that differ between the light chain of antibody CA028_00496 and antibody CA028_00496.g3 are underlined in Figure 1a.

Example 2: BIACORE

As described below, the assay format was capture of the antibody CA028_00496.g3 by an immobilised anti-human IgG Fc-specific antibody, followed by titration of human IL-17A and human IL-17F over the captured surface.

Biamolecular Interaction Analysis was performed using a Biacore 3000 (Biacore AB). Assays were performed at 25°C. Affinipure $F(ab')_2$ fragment goat anti-human IgG Fc specific (Jackson ImmunoResearch) was immobilised on a CM5 Sensor Chip (Biacore AB) via amine coupling chemistry to a level of approximately 6000 response units (RU). HBS-EP buffer (10mM HEPES pH7.4, 0.15M NaCl, 3mM EDTA, 0.005% Surfactant P20, Biacore AB) was used as the running buffer with a flow rate of 10µL/minute (min). A 10µL injection of CA028_00496.g3 at 0.5µg/mL was used for capture by the immobilised anti-human IgG Fc. Human IL-17A (generated in house by UCB) was titrated over the captured CA028_00496.g3 from 5nM at a flow rate of 30µL/min for 3min followed by a 20min dissociation. Human IL-17F (R&D systems) was titrated over the captured CA028_00496.g3 from 10nM at a flow rate of 30µL/min for 3min followed by a 5min dissociation. The surface was regenerated at a flow rate of 10µL/min by a 10µL injection of 40mM HCl followed by a 5µL injection of 5mM NaOH.

Table 1 Affinity of CA028_496.g3 against human IL-17F and IL-17A

	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (M)	KD (pM)
hIL-17F	2.49E+06	8.74E-05	3.51E-11	**35**
	3.49E+06	5.08E-05	1.46E-11	**15**
	2.99E+06	6.91E-05	2.31E-11	**23**
hIL-17A	4.66E+06	2.04E-05	4.38E-12	**4.4**
	4.52E+06	8.66E-06	1.92E-12	**1.9**
	4.59E+06	1.45E-05	3.17E-12	**3.2**

Double referenced background subtracted binding curves were analysed using the BIAevaluation software (version 4.1) following standard procedures. Kinetic parameters were determined from the fitting algorithm. Data are detailed in Table 1, average values are highlighted in grey.

The affinity value determined for the original antibody CA028_0496 binding IL-17A was 16 pM and 1750pM for IL-17F. In contrast, the improved antibody CA028_0496 g3 has an affinity for IL-17A of 3.2pM and for IL-17F of 23pM. The affinity of antibody CA028_0496 for IL-17F was improved over 70 fold without reducing the affinity of the antibody for IL-17A. Infact, affinity for IL-17A was increased five fold.

The affinity of CA028_0496 g3 was also improved for IL-17A/F heterodimer (made as described in WO2008/047134) where affinity was found to be 26pM (data not shown).

Example 3

The potency of CA028_00496.g1 (previously described in WO2008/047134) and CA028_00496.g3 for the neutralisation of human IL-17F was determined using a HeLa cell bioassay. Hela cells were obtained from the cell bank at ATCC (ATCC CCL-2). Cells were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% foetal calf serum, penicillin, gentamycin and glutamine. $1x10^4$ cells were plated out into 96 well flat bottomed tissue culture plates. Cells were incubated overnight and washed once in assay buffer. HeLa cells were stimulated with a combination of recombinant human IL-17F (125ng/ml) and tumour necrosis factor-alpha (TNF-α) (1ng/ml) for 48 hours in the presence of varying concentrations of the antibodies. In the HeLa cell line, IL-17F synergises with TNF-alpha to induce the production of IL-6 which can be quantified using a specific MSD assay kit. The resulting amount of secreted IL-6 was measured using Meso Scale Discovery (MSD) assay technology and IC50 values calculated. CA028_00496.g1 and CA028_00496.g3 showed dose-dependent inhibition of the bioactivity of IL-17F as measured in the HeLa cell bioassay (Figure 7). The activity of CA028_00496.g1 and CA028_00496.g3 in the HeLa assay was expressed as the dose required to inhibit 50% of the activity of IL-17F (IC_{50}). The IC_{50} for CA028_00496.g1 is 92mg/mL and for CA0 496.g3 is 4ng/mL.

The ability of CA028_00496.g3 to neutralise IL-17A, as described previously for CA028_00496.g1 in WO2008/047134, was confirmed using the same assay in which IL-17F was replaced with IL-17A (data not shown).

CLAIMS:

1. A neutralising antibody which binds human IL-17A and human IL-17F having a light chain wherein the variable domain of the light chain comprises the sequence given in SEQ ID NO:7.

2. A neutralising antibody according to claim 1 additionally comprising a heavy chain wherein the variable domain of the heavy chain comprises the sequence given in SEQ ID NO:1 for CDR-H1, the sequence given in SEQ ID NO:2 for CDR-H2 and the sequence given in SEQ ID NO:3 for CDR-H3.

3. A neutralising antibody according to claim 2, wherein the variable domain of the heavy chain comprises the sequence given in SEQ ID NO:9.

4. An antibody according to any one of claims 1 to 3 which also binds the IL-17A/IL-17F heterodimer.

5. An antibody according to any one of claims 1 to 4, wherein the antibody is a whole antibody or functionally active fragment thereof.

6. The antibody according to claim 5 where the antibody fragment is selected from the group consisting of a Fab, Fab', $F(ab')_2$, scFv and Fv fragment.

7. An antibody according to any one of claims 1 to 4 wherein the antibody is a multi-specific antibody.

8. A neutralising antibody which binds human IL-17A and human IL-17F, having a heavy chain comprising the sequence given in SEQ ID NO:15 and a light chain comprising the sequence given in SEQ ID NO:11.

9. An isolated DNA sequence encoding the light chain of an antibody according to any one of claims 1 to 8.

10. An isolated DNA sequence encoding the heavy and the light chain of an antibody according to any one of claims 1 to 8.

11. A cloning or expression vector comprising the DNA sequence according to claim 9 or claim 10.

12. A vector according to claim 11, wherein the vector comprises the sequences given in SEQ ID NO:13 and SEQ ID NO:17.

13. A host cell comprising one or more cloning or expression vectors according to claim 11 or claim 12.

14. A process for the production of the antibody of any one of claims 1 to 8, comprising culturing the host cell of claim 13 and isolating the antibody.

15. A pharmaceutical composition comprising an antibody according to any one of claims 1 to 8, in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier.

16. A pharmaceutical composition according to claim 15, additionally comprising other active ingredients.

17. An antibody according to any one of claims 1 to 8 or a pharmaceutical composition according to claim 15 or 16, for use in therapy.

18. An antibody according to any one of claims 1 to 8 or a pharmaceutical composition according to claim 15 or claim 16, for use in the treatment or prophylaxis of a pathological condition selected from the group consisting of infections (viral, bacterial, fungal and parasitic), endotoxic shock associtated with infection, arthritis, rheumatoid arthritis, psoriatic arthritis, systemic onset juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), asthma, chronic obstructive airways disease (COAD), chronic obstructive pulmonary disease (COPD), acute lung injury, pelvic inflammatory disease, Alzheimer's Disease, Crohn's disease, inflammatory bowel disease, irritable bwel syndrome, Ulcerative colitis, Castleman's disease, ankylosing spondylitis and other spondyloarthropathies, dermatomyositis, myocarditis, uveitis, exophthalmos, autoimmune thyroiditis, Peyronie's Disease, coeliac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, atopic dermatitis, vasculitis, surgical adhesions, stroke, autoimmune diabetes, Type I Diabetes, lyme arthritis, meningoencephalitis, immune mediated inflammatory disorders of the central and peripheral nervous system such as multiple sclerosis and Guillain-Barr syndrome, other autoimmune disorders, pancreatitis, trauma (surgery), graft-versus-host disease, transplant rejection, fibrosing disorders including pulmonary fibrosis, liver fibrosis, renal fibrosis, scleroderma or systemic sclerosis, cancer (both solid tumours such as melanomas, hepatoblastomas, sarcomas, squamous cell carcinomas, transitional cell cancers, ovarian cancers and hematologic malignancies and in particular acute myelogenous leukaemia, chronic myelogenous leukemia, chronic lymphatic leukemia, gastric cancer and colon cancer), heart disease including ischaemic

diseases such as myocardial infarction as well as atherosclerosis, intravascular coagulation, bone resorption, osteoporosis, periodontitis and hypochlorhydia.

19. The use of an antibody according to any one of claims 1 to 8 or a pharmaceutical composition according to claim 15 or claim 16 in the manufacture of a medicament for the treatment or prophylaxis of a pathological disorder that is mediated by IL-17A and/or IL-17F, or that is associated with an increased level of IL-17A and/or IL-17F.

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Adams, Ralph
Baker, Terence
Lawson, Alastair

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35 40 45

Tyr Leu Val Ser Asn Ser Glu Ile Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Arg Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Trp Ser Asp Pro Trp
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aggttcagcg gcagtgggtc tggaactgac tttcgcctga caatctcctc actccagccc 240

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35 40 45

Ala Thr Ile Thr Tyr Glu Gly Arg Asn Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Pro Pro Gln Tyr Tyr Glu Gly Ser Ile Tyr Arg Leu Trp Phe
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cgggattcag tgaaagggcg atttaccatc agcagggata atgcaaagaa cagtctgtac 240

ctgcagatga actctctgag agctgaggac accgctgtct actattgtgc aagcccaccc 300

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20 25 30

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35 40 45

Tyr Leu Val Ser Asn Ser Glu Ile Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Arg Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Trp Ser Asp Pro Trp
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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
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Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala

130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
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Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
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Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Asp Glu Ser
35 40 45

Val Arg Thr Leu Met His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
50 55 60

Lys Leu Leu Ile Tyr Leu Val Ser Asn Ser Glu Ile Gly Val Pro Asp
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Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Arg Leu Thr Ile Ser
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Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Trp
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Ser Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
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Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
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Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
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Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
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Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
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Ala Thr Ile Thr Tyr Glu Gly Arg Asn Thr Tyr Tyr Arg Asp Ser Val
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Ser Pro Pro Gln Tyr Tyr Glu Gly Ser Ile Tyr Arg Leu Trp Phe
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Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
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Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
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Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
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Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
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Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
    290                 295                 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
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        35                  40                  45

Ser Asp Tyr Asn Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Thr Ile Thr Tyr Glu Gly Arg Asn Thr Tyr Tyr Arg
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Ser Pro Pro Gln Tyr Tyr Glu Gly Ser Ile Tyr Arg
        115                 120                 125

Leu Trp Phe Ala His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
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225                 230                 235                 240

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
                245                 250                 255

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
            260                 265                 270

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
        275                 280                 285

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    290                 295                 300

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        355                 360                 365

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
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Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
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Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            420                 425                 430

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
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<223> DNA (including exons) encoding heavy chain of antibody CA028_496g3

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agctgcgctg ccagtggctt cactttcagc gattacaata tggcctgggt gcgccaggcc 120

ccaggcaagg gtctggagtg ggtggccaca attacctatg agggcagaaa cacttattac 180

cgggattcag tgaaagggcg atttaccatc agcagggata atgcaaagaa cagtctgtac 240

ctgcagatga actctctgag agctgaggac accgctgtct actattgtgc aagcccaccc 300

cagtactatg agggctcaat ctacagattg tggtttgccc attggggcca gggaacactg 360

gtgaccgtct cgagcgcttc tacaaagggc ccatcggtct tcccctggc accctcctcc 420

aagagcacct ctgggggcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 480

ccggtgacgg tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggct 540

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc 600

ttgggcaccc agacctacat ctgcaacgtg aatcacaagc ccagcaacac caaggtcgac 660

aagaaagttg agcccaaatc ttgtgacaaa actcacacat gcccaccgtg cccagcacct 720

gaactcctgg ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 780

atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag 840

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 900

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 960

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agccccatc 1020

gagaaaacca tctccaaagc caaagcgcag ccccgagaac cacaggtgta caccctgccc 1080

ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1140

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1200

accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg 1260

gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1320

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1365

<210> 18
<211> 1422
<212> DNA
<213> Artificial

<220>
<223> DNA (including exons) encoding heavy chain of antibody CA028_496g3 with signal sequence

<400> 18
atggaatggt cctgggtctt cctgtttttc ctttctgtca caaccggggt gcacagcgag 60

gttcagctcg ttgaatccgg aggcggactc gtgcagcctg ggggctcctt gcggctgagc 120

tgcgctgcca gtggcttcac tttcagcgat tacaatatgg cctgggtgcg ccaggcccca 180

ggcaagggtc tggagtgggt ggccacaatt acctatgagg gcagaaacac ttattaccgg 240

gattcagtga aagggcgatt taccatcagc agggataatg caaagaacag tctgtacctg 300

cagatgaact ctctgagagc tgaggacacc gctgtctact attgtgcaag cccaccccag 360

tactatgagg gctcaatcta cagattgtgg tttgcccatt ggggccaggg aacactggtg 420

accgtctcga gcgcttctac aaagggccca tcggtcttcc ccctggcacc ctcctccaag 480

agcacctctg ggggcacagc ggccctgggc tgcctggtca aggactactt ccccgaaccg 540

gtgacggtgt cgtggaactc aggcgccctg accagcggcg tgcacacctt cccggctgtc 600

ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcagcttg 660

ggcacccaga cctacatctg caacgtgaat cacaagccca gcaacaccaa ggtcgacaag 720

aaagttgagc ccaaatcttg tgacaaaact cacacatgcc caccgtgccc agcacctgaa 780

ctcctggggg gaccgtcagt cttcctcttc cccccaaaac ccaaggacac cctcatgatc 840

tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc 900

aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 960

gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg 1020

ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc ccccatcgag 1080

aaaaccatct ccaaagccaa agcgcagccc cgagaaccac aggtgtacac cctgccccca 1140

tcccgggatg agctgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctat 1200

cccagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc 1260

acgcctcccg tgctggactc cgacggctcc ttcttcctct acagcaagct caccgtggac 1320

aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac 1380

aaccactaca cgcagaagag cctctccctg tctccgggta aa 1422

<210> 19
<211> 1422
<212> DNA
<213> Artificial

<220>
<223> CDNA encoding heavy chain of antibody CA028_496g3 including signal sequence

<400> 19
atggaatggt cctgggtctt cctgtttttc ctttctgtca caaccggggt gcacagcgag 60

gttcagctcg ttgaatccgg aggcggactc gtgcagcctg ggggctcctt gcggctgagc 120

tgcgctgcca gtggcttcac tttcagcgat tacaatatgg cctgggtgcg ccaggcccca 180

ggcaagggtc tggagtgggt ggccacaatt acctatgagg gcagaaacac ttattaccgg 240

gattcagtga aagggcgatt taccatcagc agggataatg caaagaacag tctgtacctg 300

cagatgaact ctctgagagc tgaggacacc gctgtctact attgtgcaag cccaccccag 360

tactatgagg gctcaatcta cagattgtgg tttgcccatt ggggccaggg aacactggtg 420

accgtctcga gcgcttctac aaagggccca tcggtcttcc ccctggcacc ctcctccaag 480

agcacctctg ggggcacagc ggccctgggc tgcctggtca aggactactt ccccgaaccg 540

gtgacggtgt cgtggaactc aggcgccctg accagcggcg tgcacacctt cccggctgtc 600

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ggcacccaga cctacatctg caacgtgaat cacaagccca gcaacaccaa ggtcgacaag 720

aaagttgagc ccaaatcttg tgacaaaact cacacatgcc caccgtgccc agcacctgaa 780

ctcctggggg gaccgtcagt cttcctcttc cccccaaaac ccaaggacac cctcatgatc 840

tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc 900

aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 960

gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg 1020

ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc ccccatcgag 1080

aaaaccatct ccaaagccaa agcgcagccc cgagaaccac aggtgtacac cctgccccca 1140

tcccgggatg agctgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctat 1200

cccagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc 1260

acgcctcccg tgctggactc cgacggctcc ttcttcctct acagcaagct caccgtggac 1320

aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac 1380

aaccactaca cgcagaagag cctctccctg tctccgggta aa 1422