HUMAN MONOCLONAL ANTIBODIES AGAINST HUMAN IL-4

The present invention relates to antibodies which are specific for human interleukin-4 (hIL-4).

Allergic diseases such as atopic dermatitis, allergic rhinitis, asthma and food allergies are characteristically associated with exacerbated Th2 cell responses to innocuous environmental antigens (allergens). Allergens are captured by antigen presenting cells, processed and presented in the context of MHC Class II molecules to allergen-specific T helper (Th) cells. Allergen specific Th cells belong to the Th2 phenotype and develop from precursor T cells under the influence of interleukin-4 (IL-4). Once Th2 cells are activated, they secrete IL-4 and interleukin-13 (IL-13), which together with surface bound signals induce B cells to switch to IgE producing plasma cells. IgE molecules bind to high affinity FcεR on mast cells and, after subsequent encounter with allergen, induce mast cell activation and the release of mediators of allergic reactions. Th2 cytokines also promote the survival of eosinophils and the growth of mast cells which, after degranulation, also release additional Th2 cytokines capable of augmenting IgE production, Th2 cell differentiation and eosinophil survival. Thus, Th2 cells play a pivotal role in the induction and development of allergic responses and therefore, antagonizing their development and/or their effector functions would be an efficient way to intervene in allergic responses.

IL-4 and IL-13 share many biological activities due to the fact that both cytokines use the IL-4 receptor (IL-4R)-alpha chain as a component of their respective receptor complexes. IL-13 signals through an heterodimeric complex consisting of an IL-13 binding chain (IL-13Rα1) and the IL-4Rα chain. IL-4 utilizes this IL-4Rα/IL-13Rα1 complex, called type II IL-4R, as an alternative to the type I IL-4R, consisting of IL-4Rα chain and the common γ chain (cγ) shared by receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and thymic stromal lymphopoietin (TSLP). Because T cells do not express IL-13Rα1, IL-13 in contrast to IL-4 does not support T cell proliferation and cannot induce the differentiation of naïve human Th cells towards the Th2 phenotype (see e.g. J. E. de Vries et al., Encyclopedia of Hormones and related cell regulators, Academic Press, 2002). IL-4 plays a pivotal role in T cell proliferation and thus in the development and maintenance of allergic diseases. IL-4 gene deficient mice or mice lacking IL-4 (see e.g. Kuhn R. et al., Science, 1991 (5032) 707:10) or the downstream signaling factor STAT6 (see e.g. Kaplan M.H. et al., Immunity, 1996 (3) 313-9). do not develop significant numbers of Th2 cells and have reduced IgE responses.

We have now found antibodies with a high affinity for human IL-4 and a strong inhibitory potential of IL-4 mediated IgE synthesis by naïve human B cells.

In one aspect the present invention provides an human IL-4 specific antibody which binds to human IL-4 with a dissociation constant K_d of equal or less than 800 pM, such as e.g. equal or less than 200 pM.

In another aspect the present invention provides an antibody having a first domain comprising in sequence the hypervariable regions CDR1, CDR2 and CDR3 and a second domain comprising in sequence the hypervariable regions CDR1', CDR2' and CDR3' selected from the group consisting of an antibody wherein

a) said CDR1 has the amino acid sequence Gly-Phe-Thr-Phe-Ser-Ser-Tyr-Ala-Met-His (GFTFSSYAMH),
said CDR2 has the amino acid sequence Phe-Ile-Trp-Asp-Asp-Gly-Ser-Phe-Lys-Tyr-Tyr-Ala-Glu-Ser-Val-Lys-Gly (FIWDDGSFKYYAESVKG),
said CDR3 has the amino acid sequence Glu-Gly-Ser-Trp-Ser-Pro-Asp-Ile-Phe (EGSWSPDIF),
said CDR1' has the amino acid sequence Ser-Gln-Gly-Ile-Ser-Arg-Ala (SQGISRA),
said CDR2' has the amino acid sequence Asp-Ala-Ser (DAS),
said CDR3' has the amino acid sequence Phe-Asn-Ser-Tyr-Pro-Ile (FNSYPI),

b) said CDR1 has the amino acid sequence Gly-Phe-Thr-Leu-Ser-Ser-Phe-Gly-Met-His (GFTLSSFGMH),
said CDR2 has the amino acid sequence Val-Ile-Trp-Tyr-Asp-Gly-Ser-Asn-Glu-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly (VIWYDGSNEYYADSVKG),
said CDR3 has the amino acid sequence Glu-Gly-Ser-Trp-Ser-Pro-Asp-Ile-Phe (EGSWSPDIF),
said CDR1' has the amino acid sequence Ser-Gln-Gly-Ile-Arg-Ser-Ala (SQGIRSA),
said CDR2' has the amino acid sequence Asp-Ala-Ser (DAS),
said CDR3' has the amino acid sequence Phe-Asn-Ser-Tyr-Pro-Val (FNSYPV),

c) said CDR1 has the amino acid sequence Gly-Phe-Thr-Leu-Ser-Ser-Tyr-Gly-Met-His (GFTLSSYGMH),
said CDR2 has the amino acid sequence Val-Ile-Trp-Tyr-Asp-Gly-Asn-Asn-Gln-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly (VIWYDGNNQYYADSCKG),
said CDR3 has the amino acid sequence Glu-Gly-Ser-Trp-Ser-Pro-Asp-Ile-Phe (EGSWSPDIF),
said CDR1' has the amino acid sequence Ser-Gln-Gly-Ile-Ser-Ser-Tyr (SQGISSY),
said CDR2' has the amino acid sequence Asp-Ala-Ser (DAS),
said CDR3' has the amino acid sequence Phe-Asn-Ser-Tyr-Pro (FNSYP),

d) said CDR1 has the amino acid sequence Gly-Asp-Thr-Phe-Ser-Ser-Tyr-Ala-Ile-Ser (GDTFSSYAIS),

said CDR2 has the amino acid sequence Gly-Ile-Ile-Ile-Pro-Val-Ile-Gly-Thr-Val-Asn-Tyr-Glu-Glu-Arg-Phe-Gln-Asp-Arg (GIIIPVIGTVNYEERFQD),
said CDR3 has the amino acid sequence Glu–Glu-Gly-Phe-Leu (EEGFL),
said CDR1' has the amino acid sequence Ser-Gln-Gly-Ile-Ser-Ser-Ala (SQGISSA),
said CDR2' has the amino acid sequence Asp-Ala-Ser (DAS),
said CDR3' has the amino acid sequence Phe-Asn-Ser-Tyr-Pro-Leu (FNSYPL),

e) said CDR1 has the amino acid sequence Gly-Phe-Thr-Phe-Ser-Cys-Cys-Gly-Met-His (GFTFSCCGMH),
said CDR2 has the amino acid sequence Val-Ile-Trp-Tyr-Asp-Gly-Ser-Asn-Lys-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly (VIWYDGSNKYYADSVKG),
said CDR3 has the amino acid sequence Asp-Ser-Ser-Gly-Ser-Phe-Tyr-Glu-Tyr-Phe (DSSGSFYEYF),
said CDR1' has the amino acid sequence Ser-Gln-Gly-Ile-Asn-Ser-Ala (SQGINSA),
said CDR2' has the amino acid sequence Asp-Ala-Ser (DAS),
said CDR3' has the amino acid sequence Phe-Asn-Ser-Tyr-Pro-Tyr (FNSYPY), and

f) said CDR1 has the amino acid sequence Gly-Phe-Thr-Phe-Ser-Gly-Tyr-Gly-Met-His (GFTFSGYGMH),
said CDR2 has the amino acid sequence Val-Val-Trp-Tyr-Asp-Gly-Gly-Tyr- Lys- Phe-Tyr-Ala-Asp-Ser-Val-Lys-Gly (VVWYDGGYKFYADSVKG),
said CDR3 has the amino acid sequence Asp-Ser-Ser-Gly-Ser-Phe-Tyr-Glu-Tyr-Leu (DSSGSFYEYL),
said CDR1' has the amino acid sequence Ser-Gln-Gly-Ile-Ser-Ser-Ala (SQGISSA),
said CDR2' has the amino acid sequence Asp-Ala-Ser (DAS),
said CDR3' has the amino acid sequence Phe-Asn-Ser-Tyr-Pro-His (FNSYPH).

CDR1, CDR2 and CDR3 are part of the amino acid sequence of the heavy chain of such antibody and CDR1', CDR2' and CDR3' are part of the amino acid sequence of the light chain of such antibody.

We also have found an antibody comprising:

- the amino acid sequence of the heavy chain of a mature polypeptide of SEQ ID NO:1 and the amino acid sequence of the light chain of a mature polypeptide of SEQ ID NO:2, or
- the amino acid sequence of the heavy chain of a mature polypeptide of SEQ ID NO:9 and the amino acid sequence of the light chain of a mature polypeptide of SEQ ID NO:10, or
- the amino acid sequence of the heavy chain of a mature polypeptide of SEQ ID NO:17 and the amino acid sequence of the light chain of a mature polypeptide of SEQ ID NO:18, or
- the amino acid sequence of the heavy chain of a mature polypeptide of SEQ ID NO:25 and the

amino acid sequence of the light chain of a mature polypeptide of SEQ ID NO:26, or
- the amino acid sequence of the heavy chain of a mature polypeptide of SEQ ID NO:33 and the amino acid sequence of the light chain of a mature polypeptide of SEQ ID NO:34, or
- the amino acid sequence of the heavy chain of a mature polypeptide of SEQ ID NO:41 and the amino acid sequence of the light chain of a mature polypeptide of SEQ ID NO:42.

In a further aspect the present invention provides an antibody comprising
a) a polypeptide of SEQ ID NO:1 and a polypeptide of SEQ ID NO:2, or
b) a polypeptide of SEQ ID NO:9 and a polypeptide of SEQ ID NO:10, or
c) a polypeptide of SEQ ID NO:17 and a polypeptide of SEQ ID NO:18, or
d) a polypeptide of SEQ ID NO:25 and a polypeptide of SEQ ID NO:26, or
e) a polypeptide of SEQ ID NO:33 and a polypeptide of SEQ ID NO:34, or
f) a polypeptide of SEQ ID NO:41 and a polypeptide of SEQ ID NO:42.

We further have found an antibody comprising:
- the amino acid sequence of the heavy chain of a polypeptide of SEQ ID NO:1 further containing a leader sequence (= SEQ ID NO:3) and the amino acid sequence of the light chain of a polypeptide of SEQ ID NO:2 further containing a leader sequence (= SEQ ID NO:4), or
- the amino acid sequence of the heavy chain of a polypeptide of SEQ ID NO:9 further containing a leader sequence (= SEQ ID NO:11) and the amino acid sequence of the light chain of a polypeptide of SEQ ID NO:10 further containing a leader sequence (= SEQ ID NO:12), or
- the amino acid sequence of the heavy chain of a polypeptide of SEQ ID NO:17 further containing a leader sequence (= SEQ ID NO:19) and the amino acid sequence of the light chain of a polypeptide of SEQ ID NO:18 further containing a leader sequence (= SEQ ID NO:20), or
- the amino acid sequence of the heavy chain of a polypeptide of SEQ ID NO:25 further containing a leader sequence (= SEQ ID NO:27) and the amino acid sequence of the light chain of a polypeptide of SEQ ID NO:26 further containing a leader sequence (= SEQ ID NO:28), or
- the amino acid sequence of the heavy chain of a polypeptide of SEQ ID NO:33 further containing a leader sequence (= SEQ ID NO:35) and the amino acid sequence of the light chain of a polypeptide of SEQ ID NO:34 further containing a leader sequence (= SEQ ID NO:36), or
- the amino acid sequence of the heavy chain of a polypeptide of SEQ ID NO:41 further containing a leader sequence (= SEQ ID NO:43) and the amino acid sequence of the light chain of a polypeptide of SEQ ID NO:42 further containing a leader sequence (= SEQ ID NO:44).

In a further aspect the present invention provides an antibody comprising
a) a polypeptide of SEQ ID NO:3 and a polypeptide of SEQ ID NO:4, or
b) a polypeptide of SEQ ID NO:11 and a polypeptide of SEQ ID NO:12, or

c) a polypeptide of SEQ ID NO:19 and a polypeptide of SEQ ID NO:20, or
d) a polypeptide of SEQ ID NO:27 and a polypeptide of SEQ ID NO:28, or
e) a polypeptide of SEQ ID NO:35 and a polypeptide of SEQ ID NO:36, or
f) a polypeptide of SEQ ID NO:43 and a polypeptide of SEQ ID NO:44.

Antibodies provided by the present invention are hereinafter also designated as "compound(s) of (according to) the present invention".

In another aspect the present invention provides a compound of the present invention which is selected from the group consisting of an human IL-4 specific monoclonal antibody (hIL-4 mAb), a fragment thereof and an analog thereof.

An hIL-4 mAb is an antibody which specifically recognizes human IL-4, i.e. includes antigen binding sites specific for human IL-4, and which has specifically its CDRs but also other parts of the heavy and light chain derived from human immunoglobulins.
The antibody may be of any isotype including IgG1, IgG2, IgG3 and IgG4, preferably of isotype IgG1.

"A fragment thereof" means a part of the heavy and light chain variable sequence of a hIL-4 mAb, which retains the same antigen binding specificity and/or neutralizing ability as the molecule from which the fragments are derived, e.g. a Fab fragment or a $F(ab')_2$ fragment derived from hIL-4 mAb.
A Fab fragment contains the entire light chain and amino terminal portions of the heavy chain; a $F(ab`)_2$ fragment is the fragment formed by 2 Fab fragments bound by disulfide bonds. Such fragments can be obtained by conventional means, e.g. cleavage of the monoclonal antibodies with the appropriate proteolytic enzymes, papain and/or pepsin, or by recombinant methods, and the fragments themselves are useful as therapeutic and/or prophylactic agents.

"An analog thereof" means a hIL-4 mAb with an amino acid sequence which is modified by at least one amino acid outside of the CDR regions, e.g. outside of CDR1, CDR2 and CDR3 of the heavy chain or outside of CDR1', CDR2' and CDR3' of the light chain. Said modification includes a chemical modification, a substitution or a rearrangement of one or a few amino acids, i.e. no more than 10 amino acids, which modification permits the amino acid sequence to retain the biological characteristics, e.g. antigen specificity and affinity, of the unmodified sequence. For example silent mutations can be constructed via substitution to create endonuclease restriction sites within or surrounding the CDR regions.

An analog may also arise as allelic variation. An "allelic variation or modification" is an alteration in the nucleic acid sequence encoding an antibody of the present invention outside of the CDR regions. Such alterations or modifications may be due to the degeneracies of the genetic code or may be liberately engineered to provide desired characteristics. Such variations or modifications may or may not result in alterations in any encoded amino acid sequence, but retain the biological activities, e.g. antigen specificity and affinity.

We have also found polynucleotides encoding compounds of the present invention.

In another aspect the present invention provides isolated polynucleotides comprising polynucleotides encoding a compound of the present invention.

In another aspect the present invention provides polynucleotides encoding the amino acid sequence of CDR1, CDR2 and CDR3 of a compound of the present invention and polynucleotides encoding the amino acid sequence of CDR1', CDR2' and CDR3' of a compound of the present invention.

In another aspect the present invention provides polynucleotides comprising
a) a polynucleotide of SEQ ID NO:5 and a polynucleotide of SEQ ID NO:6, or
b) a polynucleotide of SEQ ID NO:13 and a polynucleotide of SEQ ID NO:14, or
c) a polynucleotide of SEQ ID NO:21 and a polynucleotide of SEQ ID NO:22, or
d) a polynucleotide of SEQ ID NO:29 and a polynucleotide of SEQ ID NO:30, or
e) a polynucleotide of SEQ ID NO:37 and a polynucleotide of SEQ ID NO:38, or
f) a polynucleotide of SEQ ID NO:45 and a polynucleotide of SEQ ID NO:46.

In another aspect the present invention provides polynucleotides encoding
a) a polypeptide of SEQ ID NO:7 and SEQ ID NO:8, or
b) a polypeptide of SEQ ID NO:15 and SEQ ID NO:16, or
c) a polypeptide of SEQ ID NO:23 and SEQ ID NO:24, or
d) a polypeptide of SEQ ID NO:31 and SEQ ID NO:32, or
e) a polypeptide of SEQ ID NO:39 and SEQ ID NO:40, or
f) a polypeptide of SEQ ID NO:47 and SEQ ID NO:48.

SEQ ID NO:5 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:1.
SEQ ID NO:6 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:2.
SEQ ID NO:7 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:3.

SEQ ID NO:8 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:4.
SEQ ID NO:13 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:9.
SEQ ID NO:14 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:10.
SEQ ID NO:15 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:11.
SEQ ID NO:16 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:12.
SEQ ID NO:21 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:17.
SEQ ID NO:22 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:18.
SEQ ID NO:23 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:19.
SEQ ID NO:24 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:20.
SEQ ID NO:29 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:25.
SEQ ID NO:30 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:26.
SEQ ID NO:31 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:27.
SEQ ID NO:32 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:28.
SEQ ID NO:37 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:33.
SEQ ID NO:38 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:34.
SEQ ID NO:39 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:35.
SEQ ID NO:40 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:36.
SEQ ID NO:45 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:41.
SEQ ID NO:46 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:42.
SEQ ID NO:47 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:43.
SEQ ID NO:48 is a polynucleotide encoding an amino acid sequence of SEQ ID NO:44.

A compound of the present invention may be produced by recombinant DNA techniques. Thus, one or more DNA molecules encoding the antibody, a fragment thereof or an analog thereof may be constructed, placed under appropriate control sequences in an appropriate vector and transferred into a suitable host (organism) for expression. The compound of the present invention may be obtained according, e.g. analogously, to a method as conventional together with the information provided herein, e.g. with the knowledge of the amino acid sequence of the hypervariable and/or variable regions and the polynucleotides encoding these regions. A method for constructing a variable domain gene is e.g. described in EP 239 400 and may be briefly summarized as follows:

A replicable expression vector including a suitable promoter operably linked to a polynucleotide sequence of interest, e.g. encoding at least a variable domain of an immunoglobulin heavy or light chain comprising CDRs, is prepared, a suitable cell line is transformed with said expression vector, the transformed cell line is cultured and the corresponding immunoglobulin is obtained.

In another aspect the present invention provides an expression vector comprising a polynucleotide encoding a compound of the present invention, e.g. at least one polynucleotide of SEQ ID NO:5, SEQ ID NO: 6, SEQ ID NO:7, SEQ ID No:8, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID No:16, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID No:24, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID No:40, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47 or SEQ ID No:48.
Naturally an expression vector can comprise more than one polynucleotide.

In another aspect the present invention provides

- An expression system comprising a polynucleotide encoding a compound of the present invention wherein said expression system or part thereof is capable of producing a compound of the present invention, e.g. a hIL-4 mAb, when said expression system or part thereof is present in a compatible host cell; and
- An isolated host cell comprising an expression system as defined above.

Expression vectors, e.g. comprising suitable promoter(s) and genes encoding heavy and light chain constant parts are known, e.g. and are commercially available and include e.g. heavy chain vector IgG1 and light chain vector human kappa. A conventional expression vector or recombinant plasmid may be produced by placing the respective polynucleotide in operative association with conventional regulatory control sequences capable of controlling the replication and expression in, and/or secretion from, a host cell. Regulatory sequences include promoter sequences, e.g. CMV promoter, LCK promoter, and appropriate signal sequences.

A selected host cell may be transfected by conventional techniques with the vector of interest to create a transfected host cell, which then may be cultured by conventional techniques to produce the compounds of the present invention.
Appropriate cell lines may be found according, e.g. analogously, to a method as conventional.
Appropriate hosts are known or may be found according, e.g. analogously, to a method as conventional and include cell cultures or transgenic animals.
Suitable host cells or cell lines for the expression of the compounds of the present invention are preferably eukaryotic cells such as e.g. CHO, COS, a fibroblast cell (e.g. 3T3) and myeloid cells among others, preferably a mammalian cell, such as a CHO cell or SP2/0.

The compounds of the present invention exhibit pharmacological activity and are therefore useful as pharmaceuticals. E.g., the compounds of the present invention interfere strongly with the binding of IL-4 to an IL-4 receptor and are herein also referred to as IL-4 blocking or neutralizing compounds of the present invention, including hIL-4 mAb(s). Compounds of the present invention

show activity and their affinity can be determined in the TEST:AFFINITY MEASUREMENT as described in Example 1.

A compound of the present invention thus shows therapeutic activity against IL-4 and/or IgE mediated diseases, such as

- various allergic diseases, e.g. including urticaria, allergic reactions to medication, rhinitis, e.g. allergic rhinitis, conjunctivitis, e.g. rhinoconjunctivitis, dermatitis, e.g. atopic dermatitis, asthma, e.g. atopic asthma and allergic asthma, anaphylactic shock;
  preferably atopic dermatitis, allergic asthma, allergic rhinitis, allergic rhinoconjunctivitis, such as allergic asthma or atopic dermatitis;
- autoimmune diseases, including e.g. Kawasaki disease, Grave`s disease, Sjorgen`s syndrome, autoimmune lymphoproliferative syndrome, autoimmune haemolytic anemia, autoimmune uveitis, myasthenia gravis, Lupus Erythematosis and Bullous pemphigoid;
- disorders of the digestive system in which IL-4 and/or IgE play a role, including e.g. ulcers, gastric inflammation, mucosal inflammation, ulcerative colitis, Crohn`s disease, inflammatory bowel disease and other disorders of the digestive system in which IL-4 and/or IgE play a role;
- diseases wherein IL-4 and/or IgE are overproduced and considered to contribute to pathology, including e.g. systemic sclerosis (scleroderma), septic arthritis and reactive arthritis.

In another aspect the present invention provides a compound of the present invention, e.g. a hIL-4 mAb, for use as a pharmaceutical, e.g. against IL-4 and/or IgE mediated diseases, e.g. allergic diseases, e.g. atopic dermatitis, allergic asthma, allergic rhinitis, preferably atopic dermatitis.

In another aspect the present invention provides the use of the present invention of a compound of the present invention which is selected from the group consisting of a hIL-4 mAb, a fragment thereof and an analog thereof.

For pharmaceutical use a compound of the present invention includes one or more, preferably one, compounds of the present invention, e.g. a combination of two or more compounds of the present invention.

In another aspect the present invention provides the use of a compound of the present invention for the manufacture of a medicament, e.g. a pharmaceutical composition, for the treatment of diseases mediated by IL-4 and/or IgE, e.g. allergic diseases, e.g. allergic rhinoconjunctivitis, atopic dermatitis, allergic asthma, allergic rhinitis, preferably allergic asthma or atopic dermatitis, such as atopic dermatitis.

In a further aspect the present invention provides the use of a compound of the present invention for the manufacture of a medicament, e.g. a pharmaceutical composition, for the treatment of a disease as described above, e.g. selected from the group consisting of atopic dermatitis, allergic asthma and allergic rhinitis.

In a further aspect the present invention provides a compound of the present invention for the uses as mentioned above, wherein the compound of the present invention is selected from the group consisting of a hIL-4 mAb, a fragment thereof and an analog thereof.

It has, for example been determined that the affinity constant of a compound of the present invention, e.g. a hIL-4 mAb, a fragment thereof or an analog thereof, for human IL-4 is equal or less than 800 pM, e.g. is equal or less than 200 pM, such as of about 30 pM to about 200 pM, preferably of about 45 pM to about 170 pM, such as about 100 pM, more preferred about 50 pM, such as about 45 pM.
It has, for example also been determined that the affinity constant of a compound of the present invention, e.g. a hIL-4 mAb, a fragment thereof or an analog thereof, for human IL-4 is of 30 pM to 200 pM, preferably of 45 pM to 170 pM, such as 100 pM, more preferred 50 pM, such as 45 pM.
It is therefore, indicated that for the treatment of diseases mediated by IL-4, the compounds of the present invention may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally used with monoclonal antibodies.

In another aspect the present invention provides an antibody which binds to human IL-4 with a dissociation constant of equal or less than 200 pM, e.g. 30 to 200 pM.

In a further aspect of the present invention the antibody for the uses as mentioned above is a hIL-4 mAb, a fragment thereof or an analog thereof which binds to human IL-4 with a dissociation constant K_d of equal or less than 200 pM, e.g. 30 to 200 pM.

In a further aspect the present invention provides a method of treatment of diseases which are mediated by IL-4 and/or IgE, e.g. allergic diseases, e.g. atopic dermatitis, allergic asthma, allergic rhinitis, preferably atopic dermatitis, which treatment comprises administering to a subject in need of such treatment an effective amount of a compound of the present invention; e.g. in the form of a pharmaceutical composition.

In a further aspect of the present invention a compound of the present invention is administered in combination with another pharmaceutically active agent either simultaneously or in sequence.

Treatment includes treatment and prophylaxis.
For such treatment, the appropriate dosage will, of course, vary depending upon, for example, the chemical nature and the pharmacokinetic data of an antibody of the present invention employed, the individual host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from, e.g. about, 0.1 ng/kg to, e.g. about, 10 mg/kg, such as from, e.g. about, 100 ng/kg to, e.g. about, 2 mg/kg of a compound of the present invention; conveniently administered, for example, in divided doses up to four times a day.
A compound of the present invention may be administered by any conventional route, for example parenterally, e.g. including intravenous, intradermal, intramuscular, subcutaneous, intranasal administration, injectable solutions or suspensions or inhaler powder.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of the present invention in association with at least one pharmaceutical excipient, e.g. appropriate carrier and/or diluent, e.g. including fillers, binders, disintegrators, flow conditioners, lubricants, sugars and sweeteners, fragrances, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers.

In another aspect the present invention provides a pharmaceutical composition according to the present invention further comprising another pharmaceutically active agent.

Such compositions may be manufactured according, e.g. analogously to a method as conventional, e.g. by mixing, granulating, coating, dissolving or lyophilizing processes. Unit dosage forms may contain, for example, from, e.g. about, 0.5 mg to, e.g. about, 1000 mg, such as 1 mg to about 500 mg.

A compound of the present invention may be used for pharmaceutical treatment according to the present invention alone or in combination with one or more other pharmaceutically active agents. Such other pharmaceutically active agents include e.g. other antibodies, e.g. such as antibodies neutralizing IgE, cytokines or cytokine receptors, which are chosen according to the particular condition to be treated.

Combinations include fixed combinations, in which two or more pharmaceutically active agents are in the same formulation; kits, in which two or more pharmaceutically active agents in separate formulations are sold in the same package, e.g. with instruction for co-administration; and free combinations in which the pharmaceutically active agents are packaged separately, but instruction for simultaneous or sequential administration are given.

In another aspect the present invention also provides a method for diagnosing allergies and other conditions associated with excess IgE production in a human which comprises

a) contacting a sample of a biological fluid with an antibody of the present invention, and

b) assaying for the occurrence of binding between said antibody and human IL-4.

In the following Examples all temperatures are in degrees Celsius (°C) and are uncorrected.

The following abbreviations are used:

FACS buffer	PBS, 2% FCS and 0.2% NaN_3
FCS	fetal calf serum
FITC	fluoroescein isothiocyanat
IC_{50}	inhibitory concentration
KLH	keyhole limpet hemocyanin
mAb	monoclonal antibody
MTX	methotrexate
PBS	phosphate buffered saline
sIgD	surface Immunoglobulin D
rmIL-3	recombinant murine interleukin-3
rhIL-4	recombinant human interleukin-4
rhIL-13	recombinant human interleukin-13
rpm	revolutions per minute
RPMI	Roswell Park Memorial Institute medium
RT	room temperature
TF-buffer	272 mM sucrose, 1 mM $MgCl_2$, 7 mM phosphate buffer pH 7.4

EXAMPLES

EXAMPLE 1:

a) Antibody production

Plasmids encoding the variable regions of the sequence SEQ ID NO: 5 or 7 (= heavy chain) and the sequence SEQ ID NO: 6 or 8 (= light chain) of the antibody are cloned into expression cassettes for human kappa light chains and human IgG1 heavy chains.

The specificity determining regions are combined with the necessary elements to generate complete monoclonal antibodies, i.e. promoter, leader sequence and splice donor sites for splicing to the antibody constant region exons that are required for the expression of functional immunoglobulin proteins. The variable region cassettes for the heavy and light chain antibodies, encoding for leader sequences, variable region and 3'- prime splice donor sites for splicing the constant region exons CH1-CH4 and kappa, are transferred into mammalian expression vetors HC (heavy chain vector, human IgG1) and LC (light chain vector, human kappa).

The light chain containing plasmid and the heavy chain containing plasmid are introduced into Sp2/0 cells in a co-transfection approach. E.g. for transfection, cells in exponential growth phase with a viability of about 95% are used. Cells are washed twice with cold TF-buffer and cell concentration is adjusted to 2 x 10^7 cells/ml in TF-buffer. 0.8 ml cell suspension obtained are mixed with 15 µg each of the heavy chain and light chain plasmid and placed on ice for 10 minutes. Transfection is done by electroporation using the Biorad Gene Pulser (280 V and 25 µF). After electroporation, cells are placed on ice for 15 minutes, transferred into 50 ml cold culture medium and incubated for 1 day at 37° and 5% CO_2. For clonal amplification, the G418 resistant cells obtained are cultivated in the presence of 200 nM MTX. An aliquot of the heterogeneous cell pool is seeded into 96-well plates at clonal density of 1 viable cell/well in culture medium containing 200 nM MTX allowing selection of clonal populations of amplified cells. Limiting dilution cloning is applied to generate clonal cell lines after amplification and adaptation to serum-free culture conditions. Cells are seeded into two 96-well plates at a concentration of 0.5 cell/well. Wells are screened microscopically for clonality one day after seeding. Only monoclonal antibodies are used for further testing.

The antibody obtained comprises an amino acid sequence of SEQ ID NO:1 and SEQ ID NO:2.

b) Affinity measurements

Affinity measurements of human mAbs of the present invention are carried on a BIAcore™ 2000 instrument. Anti-human IgG is coated onto a BIAcore sensorchip CM-5 (BIAcore), so that application of defined amounts of human mAbs results in capturing on this prepared surface and hence in a change of refractory properties that are measured. A subsequent application of rhIL-4 results in a further change of the refractory properties, which allows determination of the association rate (K_{on}, on rate) as well as the dissociation rate (K_{off}, off rate) and the product of these two, the affinity (K_d, dissociation constant, given in pM), according to the BIAevaluation 3.0

software. Using several concentrations of rhIL-4 in BIAbuffer, an affinity of 43 pM of an mAb as defined by CDRs as described in claim 2a) is determined.

c) Determination of inhibitory potential on IL-4 mediated IgE

c1) Cell sources

Human B cells are isolated from peripheral blood, respectively, buffy coats by Ficoll-paque density centrifugation, followed by magnetic separation with MACS beads (Miltenyi Biotech) specific for human CD19 or human CD22 on an AutoMACS device.

Naïve human B cells are similarly isolated using anti-human sIgD FITC labeled goat $F(ab')_2$ antibodies followed by anti-FITC MACS beads.

c2) Cell culture/maintenance

Transfectants (BaF/3 transfectants carrying the IL-4Rα and the IL-13Rα1) are cultured in RPMI 1640 medium supplemented with Glutamax (Invitrogen), 10% FCS, 1% penicillin/streptomycin and 10 ng/ml rhIL-4 (Novartis). Cells are split 1:1 twice weekly, washed with fresh medium without rhIL-4 and kept in such medium overnight (=starved cells).

Human ex vivo (naïve) B cell cultures are incubated in X-Vivo medium (Cambrex, XV15) supplemented with Glutamax, 10% FCS, 1% penicillin/streptomycin in 96-well plates (Costar).

c3) BAF cell proliferation assay

Starved cells as described in b) are collected, washed with fresh medium, counted and adjusted to 2 x 105 cells/ml of which 100 µl per well are distributed to 96-well plates (Costar). For titration series the cytokines rhIL-4, rhIL-13 and rmIL-3 are prepared in 4 times the desired final concentration in the same medium.

For titration series antibodies are either used as cell culture supernatants with ELISA determined concentrations or from purified material at 4 times the desired concentrations in the same medium. The pre-dilutions of cytokines and antibodies are mixed at equal volumes and 100 µl of the pre-mix are transferred to the well prepared with cells. Controls are set up for background proliferation (medium without cytokine and without antibody = 100% inhibition) and maximum proliferation (medium with cytokine only = 0% inhibition).

After overnight incubation at 37° in the presence of 5% CO_2, [methyl-^{3}H]thimidine (Amersham TRK120) 1 µCi per well is added in 10 µl of medium and incubated for 8 hours. Following a freeze/thaw cycle cells are harvested from the plates on filter mats using a Tomtek harvester. Filter mats are dried in a microwave oven for 2 minutes at 650 W and transferred to a sample bag together with a sheet of Meltilex Scintillation Wax (Wallac). Wax is melted through the filter and filters obtained are placed inside appropriate cassettes and inserted into a micro-beta reader (Wallac) for scintillation counting using a program measuring 30 seconds per field and extrapolating to counts per minutes.

An IC_{50} of 30 pM is measured in this test system for the antibody.

c4) IL-4 induced CD23 up-regulation on B cells

MACS separated B cells are adjusted to 0.5-1 x 106 cells/ml in XV15 and plated out in 100µl per well of 96 well round bottom plates. Cytokines (1 ng/ml final) and mAb (2 µg/ml – 2 ng/ml final) are pre-diluted and pre-mixed as described above and added in 100 µl to reach a final volume of 200 µl.

After culturing overnight at 37° in the presence of 5% CO_2 cells are transferred to 96-well plates (Costar) and centrifuged at 2200 rpm (~1000 x g) for 1 minute after flicking off the supernatant washed with FACS buffer.

Florochrome labeled mAbs [HLA-DR FITC (Caltag#MHLDR01 1:800), CD19 PE (Caltag#MHCD1904 1:200) and CD23 APC (Caltag#MHCD2305 1:200)] are prepared in FACS buffer and distributed in 50µl per well. After 30-60 minutes incubation at RT, wells are filled up with FACS buffer, centrifuged and the centrifugation residue obtained is washed with FACS buffer. Cells are re-suspended in FACS buffer with 2µg/ml propidium iodide and analyzed on a dual laser FacsCalibur flow cytometer (BD Biosciences). Cells are gated according to their forward scatter and side scatter properties as well as their ability to exclude propidium iodide and their CD19 expression. Mean fluorescence intensities and percentage of cells above arbitrary threshold (set on un-induced cells) in CD23 expression are determined. Baseline expression (100% inhibition) is determined on cells without cytokine, whereas 0% inhibition is set on cells incubated with cytokine but without mAb.

An IC50 of 334 pM for this antibody is determined for IL-4 induced CD23 expression on the cells as described above in the presence of 70 pM recombinant human IL-4.

c5) IL-4 induced IgE production by naïve B cells

Magnetically sorted naïve B cells are adjusted to 3 x 105 cells per ml in XV15 and plated out in 100µl per well of 96-well plates in a 6 x 6 array in the center of the plate, surrounded by PBS filled wells during the 10 days of culture at 37° in the presence of 5% CO_2. One plate each is prepared per mAb to be tested, consisting of 3 wells each un-induced and induced controls and quintuplicate repeats of mAb titrations starting at 7µg/ml and running in 3-fold dilution down to 29ng/ml final concentrations added in 50µl four times concentrated pre-dilution. Inducing conditions are rhIL-4 at 20 ng/ml plus anti-CD40 mAb (Novartis) at 0.5µg/ml final concentrations also added in 50µl of four times concentrated pre-dilution. IgE concentrations are determined at the end of the culture period by a standard sandwich ELISA method.

An IC50 of 2806 pM for this antibody is determined for IL-4 induced IgE on the cells as described above.

Examples 2 to 6:

Antibodies are obtained analogously as described in example 1 and comprise the following amino acid sequences:

Example 2 is an antibody comprising amino acid sequence SEQ ID NO:9 and SEQ ID NO:10.

Example 3 is an antibody comprising amino acid sequence SEQ ID NO:17 and SEQ ID NO:18.
Example 4 is an antibody comprising amino acid sequence SEQ ID NO:25 and SEQ ID NO:26.
Example 5 is an antibody comprising amino acid sequence SEQ ID NO:33 and SEQ ID NO:34.
Example 6 is an antibody comprising amino acid sequence SEQ ID NO:41 and SEQ ID NO:42.

Table 1 summarizes the IC_{50} values of the antibodies in the various test systems as described in Example 1b to c.

TABLE 1:

	K_d [pM]	IC50 [pM] measured in the particular assays		
		BAF cell proliferation	IL-4 induced CD23	IL-4 induced IgE
Ex. 1	43	30	334	2806
Ex. 2	59	50	463	5339
Ex. 3	89	84	873	7813
Ex. 4	66	688	848	7570
Ex. 5	84	218	2835	9944
Ex. 6	170	167	2869	2648

SEQUENCE LISTING

SEQ ID NO:1

(amino acid sequence of the mature polypeptide of the heavy chain, underlined amino acids correspond to CDR1, CDR2 and CDR3)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVTFIWDDGSFKYYAES
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGSWSPDIFDIWGQGTMVTVSS

SEQ ID NO:2

(amino acid sequence of the mature polypeptide of the light chain, underlined amino acids correspond to CDR1', CDR2' and CDR3')

AIQLTQSPSSLSASVGDRVTITCRASQGISRALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSG
SGTDFTLTISSLQPEDFATYYCQQFNSYPITFGQGTRLEIKRT

SEQ ID NO:3

(amino acid sequence of the polypeptide of SEQ ID NO:1 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MEFGLNWVFLVALFRGVHCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGK
GLEWVTFIWDDGSFKYYAESVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGSWSPDIFDI
WGQGTMVTVSS

SEQ ID NO:4

(amino acid sequence of the polypeptide of SEQ ID NO:2 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MDMRVPAQLLGLLLLWLPGARCAIQLTQSPSSLSASVGDRVTITCRASQGISRALAWYQQKPGK
APKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPITFGQGTRLEIKRT

SEQ ID NO:5

(nucleotides encoding an amino acid sequence of SEQ ID NO:1)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
CCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGCCATGCACTGGGTCCGCCAGGCTCCA
GGCAAGGGGCTGGAGTGGGTGACATTTATATGGGATGATGGAAGTTTTAAATATTATGCAGAG
TCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATTTGCAAATG
AACAGCCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGAGGGCAGCTGGTCTCC
TGATATATTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

SEQ ID NO:6

(nucleotides encoding an amino acid sequence of SEQ ID NO:2)

GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATC
ACTTGCCGGGCAAGTCAGGGCATTAGCAGAGCTTTAGCCTGGTATCAGCAGAAACCAGGGAA
AGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAG
CGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGC
AACTTATTACTGTCAACAGTTTAATAGTTACCCCATCACCTTCGGCCAAGGGACACGACTGGA
GATTAAACGAACT

SEQ ID NO:7

(nucleotides encoding an amino acid sequence of SEQ ID NO:3)

ATGGAGTTTGGGCTGAACTGGGTTTTCCTCGTTGCTCTTTTCAGAGGTGTCCACTGTCAGGTG
CAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTG
CAGCGTCTGGATTCACCTTCAGTAGCTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAG
GGGCTGGAGTGGGTGACATTTATATGGGATGATGGAAGTTTTAAATATTATGCAGAGTCCGTG
AAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATTTGCAAATGAACAGC
CTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGAGGGCAGCTGGTCTCCTGATAT
ATTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

SEQ ID NO:8

(nucleotides encoding an amino acid sequence of SEQ ID NO:4)

ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTTCTGCTGCTCTGGCTCCCAGGTGCCAG
ATGTGCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCAC
CATCACTTGCCGGGCAAGTCAGGGCATTAGCAGAGCTTTAGCCTGGTATCAGCAGAAACCAG
GGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGT
TCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGAT

TTTGCAACTTATTACTGTCAACAGTTTAATAGTTACCCCATCACCTTCGGCCAAGGGACACGAC
TGGAGATTAAACGAACT

SEQ ID NO:9

(amino acid sequence of the mature polypeptide of the heavy chain, underlined amino acids correspond to CDR1, CDR2 and CDR3)

QVQLVESGGGVVQPGRSLRLSCAASGFTLSSFGMHWVRQAPGKGLEWVAVIWYDGSNEYYADS
VKGRFTTSRDNSKNTLYLQMNSLRAEDTAVYYCAREGSWSPDIFDIWGQGTMVTVSS

SEQ ID NO:10

(amino acid sequence of the mature polypeptide of the light chain, underlined amino acids correspond to CDR1', CDR2' and CDR3')

AIQLTQSPSSLSASVGDRVTITCRTSQGIRSALAWYQQNPGKAPKLLIYDASSLESGVPSRFSGSG
SGTDFTLTISSLQPEDFATYYCQQFNSYPVTFGQGTRLEIKRT

SEQ ID NO:11

(amino acid sequence of the polypeptide of SEQ ID NO:9 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTLSSFGMHWVRQAPGK
GLEWVAVIWYDGSNEYYADSVKGRFTTSRDNSKNTLYLQMNSLRAEDTAVYYCAREGSWSPDIF
DIWGQGTMVTVSS

SEQ ID NO:12

(amino acid sequence of the polypeptide of SEQ ID NO:10 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MDMRVPAQLLGLLLLWLPGARCAIQLTQSPSSLSASVGDRVTITCRTSQGIRSALAWYQQNPGK
APKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPVTFGQGTRLEIKRT

SEQ ID NO:13

(nucleotides encoding an amino acid sequence of SEQ ID NO:9)

CAGGTGCAACTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTC
TCCTGTGCAGCGTCTGGATTCACCTTAAGTAGCTTTGGCATGCACTGGGTCCGCCAGGCTCC
AGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATGAATACTATGCAG
ACTCCGTGAAGGGCCGATTCACCACCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAA
ATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGGCAGCTGGT
CTCCTGATATTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

SEQ ID NO:14

(nucleotides encoding an amino acid sequence of SEQ ID NO:10)

GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATC
ACTTGCCGGACAAGTCAGGGCATTCGCAGTGCTTTAGCCTGGTATCAGCAGAACCCCGGGAA
AGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAG
CGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTG

CAACTTATTACTGTCAACAGTTTAATAGTTACCCCGTCACCTTCGGCCAAGGGACACGACTGG
AGATTAAACGAACT

SEQ ID NO:15

(nucleotides encoding an amino acid sequence of SEQ ID NO:11)

ATGGAGTTTGGGCTGAGCTGGGTTTTCCTCGTTGCTCTTTTAAGAGGTGTCCAGTGTCAGGTG
CAACTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTG
CAGCGTCTGGATTCACCTTAAGTAGCTTTGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAG
GGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATGAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCACCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACA
GCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGGCAGCTGGTCTCCTGA
TATTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

SEQ ID NO:16

(nucleotides encoding an amino acid sequence of SEQ ID NO:12)

ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTTCTGCTGCTCTGGCTCCCAGGTGCCA
GATGTGCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCA
CCATCACTTGCCGGACAAGTCAGGGCATTCGCAGTGCTTTAGCCTGGTATCAGCAGAACCCC
GGGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAG
GTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG
ATTTTGCAACTTATTACTGTCAACAGTTTAATAGTTACCCCGTCACCTTCGGCCAAGGGACACG
ACTGGAGATTAAACGAACT

SEQ ID NO:17

(amino acid sequence of the mature polypeptide of the heavy chain, underlined amino acids correspond to CDR1, CDR2 and CDR3)

QVQLVESGGGMVQPGRSLRLSCAASGFTLSSYGMHWVRQAPGKGLEWVTVIWYDGNNQYYAD
SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGSWSPDIFDIWGQGTMVTVSS

SEQ ID NO:18

(amino acid sequence of the mature polypeptide of the light chain, underlined amino acids correspond to CDR1', CDR2' and CDR3')

AIQLTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSG
SGTDFTLTISSLQPEDFATYYCQQFNSYPITFGQGTRLEIKRT

SEQ ID NO:19

(amino acid sequence of the polypeptide of SEQ ID NO:17 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MEFGLSWVFLVALLRGVQCQVQLVESGGGMVQPGRSLRLSCAASGFTLSSYGMHWVRQAPGK
GLEWVTVIWYDGNNQYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGSWSPDIF
DIWGQGTMVTVSS

SEQ ID NO:20

(amino acid sequence of the polypeptide of SEQ ID NO:18 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MDMRVPAQLLGLLLLWLPGARCAIQLTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGK
APKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPITFGQGTRLEIKRT

SEQ ID NO:21

(nucleotides encoding an amino acid sequence of SEQ ID NO:17)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCATGGTCCAGCCTGGGAGGTCCCTGAGACTCT
CCTGTGCAGCGTCTGGATTCACCCTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCA
GGCAAGGGGCTGGAGTGGGTGACAGTTATATGGTATGATGGAAATAATCAATACTATGCAGA
CTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAAT
GAACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGAGGGCAGCTGGTCT
CCTGATATTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

SEQ ID NO:22

(nucleotides encoding an amino acid sequence of SEQ ID NO:18)

GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATC
ACTTGCCGGGCAAGTCAGGGCATTAGCAGTTATTTAGCCTGGTATCAGCAGAAACCAGGGAA
AGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAG
CGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTG
CAACTTATTACTGTCAACAGTTTAATAGTTACCCCATCACCTTCGGCCAAGGGACACGACTGG
AGATTAAACGAACT

SEQ ID NO:23

(nucleotides encoding an amino acid sequence of SEQ ID NO:19)

ATGGAGTTTGGGCTGAGCTGGGTTTTCCTCGTTGCTCTTTTAAGAGGTGTCCAGTGTCAGGTG
CAGCTGGTGGAGTCTGGGGGAGGCATGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTG
CAGCGTCTGGATTCACCCTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAG
GGGCTGGAGTGGGTGACAGTTATATGGTATGATGGAAATAATCAATACTATGCAGACTCCGTG
AAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGAGGGCAGCTGGTCTCCTGATAT
TTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

SEQ ID NO:24

(nucleotides encoding an amino acid sequence of SEQ ID NO:20)

ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTTCTGCTGCTCTGGCTCCCAGGTGCCA
GATGTGCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCA
CCATCACTTGCCGGGCAAGTCAGGGCATTAGCAGTTATTTAGCCTGGTATCAGCAGAAACCA
GGGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAG
GTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG

ATTTTGCAACTTATTACTGTCAACAGTTTAATAGTTACCCCATCACCTTCGGCCAAGGGACACG
ACTGGAGATTAAACGAACT

SEQ ID NO:25

(amino acid sequence of the mature polypeptide of the heavy chain, underlined amino acids correspond to CDR1, CDR2 and CDR3)

QVQLVQSGAEVKKPGSSVKVSCKASGDTFSSYAISWVRQAPGQGFEWMGGIIPVIGTVNYEERF
QDRVTITADNSTSTAYMELTSLRSEDTAVYFCGREEGFLDYWGQGTLVTVSS

SEQ ID NO:26

(amino acid sequence of the mature polypeptide of the light chain, underlined amino acids correspond to CDR1', CDR2' and CDR3')

AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSG
SGTDFTLTISSLQPEDFATYYCQQFNSYPLLTFGGGTKVEIKRT

SEQ ID NO:27

(amino acid sequence of the polypeptide of SEQ ID NO:25 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MDWTWRFLFVVAAATGVQSQVQLVQSGAEVKKPGSSVKVSCKASGDTFSSYAISWVRQAPGQ
GFEWMGGIIPVIGTVNYEERFQDRVTITADNSTSTAYMELTSLRSEDTAVYFCGREEGFLDYWGQ
GTLVTVSS

SEQ ID NO:28

(amino acid sequence of the polypeptide of SEQ ID NO:26 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MDMRVPAQLLGLLLLWLPGARCAIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKP
GKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPLLTFGGGTK
VEIKRT

SEQ ID NO:29

(nucleotides encoding an amino acid sequence of SEQ ID NO:25)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCT
CCTGCAAGGCTTCTGGAGACACCTTCAGCAGTTATGCTATCAGTTGGGTGCGACAGGCCCCT
GGACAAGGGTTTGAGTGGATGGGAGGGATCATCCCTGTCATTGGTACAGTAAATTATGAAGA
GAGATTCCAGGACAGAGTCACGATTACCGCGGACAATTCCACGAGCACAGCCTACATGGAGT
TGACTAGTCTGAGATCTGAAGACACGGCCGTGTATTTTTGTGGGAGAGAAGAGGGCTTCCTT
GACTATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

SEQ ID NO:30

(nucleotides encoding an amino acid sequence of SEQ ID NO:26)

ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTTCTGCTGCTCTGGCTCCCAGGTGCCA
GATGTGCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCA
CCATCACTTGCCGGGCAAGTCAGGGCATTAGCAGTGCTTTAGCCTGGTATCAGCAGAAACCA

GGGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAG
GTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG
ATTTTGCAACTTATTACTGTCAACAGTTTAATAGTTACCCTCTTCTCACTTTCGGCGGAGGGAC
CAAGGTGGAGATCAAACGTACG

SEQ ID NO:31

(nucleotides encoding an amino acid sequence of SEQ ID NO:27)

ATGGACTGGACCTGGAGGTTCCTCTTTGTGGTGGCAGCAGCTACAGGTGTCCAGTCCCAGGT
CCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGC
AAGGCTTCTGGAGACACCTTCAGCAGTTATGCTATCAGTTGGGTGCGACAGGCCCCTGGACA
AGGGTTTGAGTGGATGGGAGGGATCATCCCTGTCATTGGTACAGTAAATTATGAAGAGAGATT
CCAGGACAGAGTCACGATTACCGCGGACAATTCCACGAGCACAGCCTACATGGAGTTGACTA
GTCTGAGATCTGAAGACACGGCCGTGTATTTTTGTGGGAGAGAAGAGGGCTTCCTTGACTATT
GGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

SEQ ID NO:32

(nucleotides encoding an amino acid sequence of SEQ ID NO:28)

ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTTCTGCTGCTCTGGCTCCCAGGTGCCA
GATGTGCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCA
CCATCACTTGCCGGGCAAGTCAGGGCATTAGCAGTGCTTTAGCCTGGTATCAGCAGAAACCA
GGGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAG
GTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG
ATTTTGCAACTTATTACTGTCAACAGTTTAATAGTTACCCTCTTCTCACTTTCGGCGGAGGGAC
CAAGGTGGAGATCAAACGTACG

SEQ ID NO:33

(amino acid sequence of the mature polypeptide of the heavy chain, underlined amino acids correspond to CDR1, CDR2 and CDR3)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSCCGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD
SVKGRFTISRDTSKNTLYLQMNSLRAEDTAVYYCATDSSGSFYEYFQHWGQGTLVTVSS

SEQ ID NO:34

(amino acid sequence of the mature polypeptide of the light chain, underlined amino acids correspond to CDR1', CDR2' and CDR3')

AIQLTQSPSSLSASVGDRVTITCRASQGINSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSG
SGTDFTLTISSLQPEDFATYYCQQFNSYPYTFGQGTKLEIKRT

SEQ ID NO:35

(amino acid sequence of the polypeptide of SEQ ID NO:33 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSCCGMHWVRQAPGK
GLEWVAVIWYDGSNKYYADSVKGRFTISRDTSKNTLYLQMNSLRAEDTAVYYCATDSSGSFYEYF
QHWGQGTLVTVSS

SEQ ID NO:36

(amino acid sequence of the polypeptide of SEQ ID NO:34 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MDMRVPAQLLGLLLLWLPGARCAIQLTQSPSSLSASVGDRVTITCRASQGINSALAWYQQKPGK
APKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPYTFGQGTKLEIKRT

SEQ ID NO:37

(nucleotides encoding an amino acid sequence of SEQ ID NO:33)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
CCTGTGCAGCGTCTGGATTCACCTTCAGTTGCTGTGGCATGCACTGGGTCCGCCAGGCTCCA
GGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGA
CTCCGTGAAGGGCCGATTCACCATCTCCAGAGACACTTCCAAGAACACGCTGTATCTGCAAAT
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SEQ ID NO:38

(nucleotides encoding an amino acid sequence of SEQ ID NO:34)

GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATC
ACTTGCCGGGCAAGTCAGGGCATTAACAGTGCTTTAGCCTGGTATCAGCAGAAACCAGGGAA
AGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAG
CGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTG
CAACTTATTACTGTCAACAGTTTAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTGG
AGATCAAACGAACT

SEQ ID NO:39

(nucleotides encoding an amino acid sequence of SEQ ID NO:35)

ATGGAGTTTGGGCTGAGCTGGGTTTTCCTCGTTGCTCTTTTAAGAGGTGTCCAGTGTCAGGTG
CAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTG
CAGCGTCTGGATTCACCTTCAGTTGCTGTGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAG
GGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACACTTCCAAGAACACGCTGTATCTGCAAATGAACA
GCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGACAGATAGTTCGGGGAGTTTTTAT
GAATACTTCCAGCACTGGGGCCAGGGCACCCTGGTCACCGTCTCCTCA

SEQ ID NO:40

(nucleotides encoding an amino acid sequence of SEQ ID NO:36)

ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTTCTGCTGCTCTGGCTCCCAGGTGCCA
GATGTGCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCA

CCATCACTTGCCGGGCAAGTCAGGGCATTAACAGTGCTTTAGCCTGGTATCAGCAGAAACCA
GGGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAG
GTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG
ATTTTGCAACTTATTACTGTCAACAGTTTAATAGTTACCCGTACACTTTTGGCCAGGGGACCAA
GCTGGAGATCAAACGAACT

SEQ ID NO:41

(amino acid sequence of the mature polypeptide of the heavy chain, underlined amino acids correspond to CDR1, CDR2 and CDR3)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGRGLDWVAVVWYDGGYKFYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSSGSFYEYLQHWGQGTLVTVSS

SEQ ID NO:42

(amino acid sequence of the mature polypeptide of the light chain, underlined amino acids correspond to CDR1', CDR2' and CDR3')

AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSG
SGTDFTLTISSLQPEDFATYYCQQFNSYPHFWPGDQAGDQTNCG

SEQ ID NO:43

(amino acid sequence of the polypeptide of SEQ ID NO:41 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGR
GLDWVAVVWYDGGYKFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSSGSFYEY
LQHWGQGTLVTVSS

SEQ ID NO:44

(amino acid sequence of the polypeptide of SEQ ID NO:42 with leader sequence, amino acids marked in bold correspond to the leader sequence)

MDMRVPAQLLGLLLLWLPGARCAIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGK
APKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPHFWPGDQAGDQT
NCG

SEQ ID NO:45

(nucleotides encoding an amino acid sequence of SEQ ID NO:41)

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
CCTGTGCAGCGTCTGGATTCACCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCA
GGCAGGGGGCTGGACTGGGTGGCAGTTGTGTGGTATGATGGAGGTTATAAGTTCTATGCAGA
CTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAAT
GAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATAGTTCGGGGAGTT
TTTATGAATACTTACAACATTGGGGCCAGGGCACCCTGGTCACCGTCTCCTCA

SEQ ID NO:46

(nucleotides encoding an amino acid sequence of SEQ ID NO:42)

GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATC
ACTTGCCGGGCAAGTCAGGGCATTAGCAGTGCTTTAGCCTGGTATCAGCAGAAACCAGGGAA
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CGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTG
CAACTTATTACTGTCAACAGTTTAATAGTTACCCTCACTTTTGGCCAGGGGACCAAGCTGGAG
ATCAAACGAACT

SEQ ID NO:47

(nucleotides encoding an amino acid sequence of SEQ ID NO:43)

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CAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTG
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GGGGCTGGACTGGGTGGCAGTTGTGTGGTATGATGGAGGTTATAAGTTCTATGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACA
GCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATAGTTCGGGGAGTTTTTAT
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SEQ ID NO:48

(nucleotides encoding an amino acid sequence of SEQ ID NO:44)

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CCATCACTTGCCGGGCAAGTCAGGGCATTAGCAGTGCTTTAGCCTGGTATCAGCAGAAACCA
GGGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAG
GTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG
ATTTTGCAACTTATTACTGTCAACAGTTTAATAGTTACCCTCACTTTTGGCCAGGGGACCAAGC
TGGAGATCAAACGAACT

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An anti-IL-4 antibody having a first domain comprising in sequence the hypervariable regions CDR1, CDR2 and CDR3 and a second domain comprising in sequence the hypervariable regions CDR1', CDR2' and CDR3' selected from the group consisting of an antibody wherein

   said CDR1 has the amino acid sequence Gly-Phe-Thr-Phe-Ser-Ser-Tyr-Ala-Met-His,

   said CDR2 has the amino acid sequence Phe-Ile-Trp-Asp-Asp-Gly-Ser-Phe-Lys-Tyr-Tyr-Ala-Glu-Ser-Val-Lys-Gly,

   said CDR3 has the amino acid sequence Glu-Gly-Ser-Trp-Ser-Pro-Asp-Ile-Phe,

   said CDR1' has the amino acid sequence Ser-Gln-Gly-Ile-Ser-Arg-Ala,

   said CDR2' has the amino acid sequence Asp-Ala-Ser,

   said CDR3' has the amino acid sequence Phe-Asn-Ser-Tyr-Pro-Ile.

2. An anti-IL-4 antibody of claim 1 comprising a polypeptide of SEQ ID NO: 1 and a polypeptide of SEQ ID NO: 2.

3. An antibody of claims 1 or 2 which is selected from the group consisting of an human IL-4 specific monoclonal antibody, a fragment thereof and an analog thereof.

4. Isolated polynucleotides encoding an antibody of claim 1 or 2.

5. Isolated polynucleotides comprising a polynucleotide of SEQ ID NO: 5 and a polynucleotide of SEQ ID NO: 6.

6. An expression vector comprising polynucleotides of claims 4 or 5.

7. An isolated host cell comprising an expression system of claim 6.

8. Use of an antibody of claims 1 or 2 as a pharmaceutical.

9. Use of an antibody of claims 1 or 2 for the manufacture of a medicament for the treatment of diseases mediated by IL-4 and/or IgE.

10. Use of claim 9 wherein the disease is selected from the group consisting of atopic dermatitis, allergic asthma and allergic rhinitis.

11. Use of any one of claims 8 to 10 wherein the antibody is selected from the group consisting of an human IL-4 monoclonal antibody, a fragment thereof and an analog thereof.

12. A pharmaceutical composition comprising an antibody of claims 1 or 2 in association with at least one pharmaceutically acceptable excipient.

SEQUENCE LISTING

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<130> 4-33746A/NFI 8059

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            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Thr Phe Ile Trp Asp Asp Gly Ser Phe Lys Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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

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Gly Thr Met Val Thr Val Ser Ser
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            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
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Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Ile
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            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

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

Glu Trp Val Thr Phe Ile Trp Asp Asp Gly Ser Phe Lys Tyr Tyr Ala
65                  70                  75                  80

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

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

Tyr Tyr Cys Ala Arg Glu Gly Ser Trp Ser Pro Asp Ile Phe Asp Ile
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            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Gly Ile Ser Arg Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Phe Asn Ser Tyr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
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Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ser Lys Asn Thr 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 Arg Glu Gly Ser Trp Ser Pro Asp Ile Phe Asp Ile Trp Gly Gln
            100                 105                 110

Gly Thr Met Val Thr Val Ser Ser
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            20                  25                  30

Leu Ala Trp Tyr Gln Gln Asn Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

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Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr
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Asp Ser Val Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ser Lys Asn
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Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
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35 40 45

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

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

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gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtat attactgtgc gagagagggc 300

agctggtctc ctgatatttt tgatatctgg ggccaaggga caatggtcac cgtctcttca 360

<210> 22
<211> 327
<212> DNA
<213> Homo sapiens

<400> 22
gccatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattagc agttatttag cctggtatca gcagaaacca 120

gggaaagctc ctaagctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag tttaatagtt accccatcac cttcggccaa 300

gggacacgac tggagattaa acgaact 327

<210> 23
<211> 417
<212> DNA
<213> Homo sapiens

<400> 23
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag 60

gtgcagctgg tggagtctgg gggaggcatg gtccagcctg ggaggtccct gagactctcc 120

tgtgcagcgt ctggattcac cctcagtagc tatggcatgc actgggtccg ccaggctcca 180

ggcaaggggc tggagtgggt gacagttata tggtatgatg gaaataatca atactatgca 240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtatatt actgtgcgag agagggcagc 360

tggtctcctg atatttttga tatctggggc caagggacaa tggtcaccgt ctcttca 417

<210> 24
<211> 393
<212> DNA
<213> Homo sapiens

<400> 24
atggacatga gggtccccgc tcagctcctg gggcttctgc tgctctggct cccaggtgcc 60

agatgtgcca tccagttgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga 120

gtcaccatca cttgccgggc aagtcagggc attagcagtt atttagcctg gtatcagcag 180

aaaccaggga aagctcctaa gctcctgatc tatgatgcct ccagtttgga aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ctctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttattactgt caacagttta atagttaccc catcaccttc 360

ggccaaggga cacgactgga gattaaacga act 393

<210> 25
<211> 116
<212> PRT
<213> Homo sapiens

<400> 25

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asp Thr Phe Ser Ser Tyr
20 25 30

```
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Phe Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Val Ile Gly Thr Val Asn Tyr Glu Glu Arg Phe
    50                  55                  60

Gln Asp Arg Val Thr Ile Thr Ala Asp Asn Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

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

Gly Arg Glu Glu Gly Phe Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115


<210>  26
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  26

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Leu
                85                  90                  95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210>  27
<211>  135
<212>  PRT
<213>  Homo sapiens

<400>  27

Met Asp Trp Thr Trp Arg Phe Leu Phe Val Val Ala Ala Ala Thr Gly
```

1 5 10 15

Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asp Thr Phe
35 40 45

Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Phe
50 55 60

Glu Trp Met Gly Gly Ile Ile Pro Val Ile Gly Thr Val Asn Tyr Glu
65 70 75 80

Glu Arg Phe Gln Asp Arg Val Thr Ile Thr Ala Asp Asn Ser Thr Ser
85 90 95

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

Tyr Phe Cys Gly Arg Glu Glu Gly Phe Leu Asp Tyr Trp Gly Gln Gly
115 120 125

Thr Leu Val Thr Val Ser Ser
130 135

<210> 28
<211> 132
<212> PRT
<213> Homo sapiens

<400> 28

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Ser Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Phe Asn Ser Tyr Pro Leu Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
115 120 125

Ile Lys Arg Thr
130

<210> 29
<211> 348
<212> DNA
<213> Homo sapiens

<400> 29
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60

tcctgcaagg cttctggaga caccttcagc agttatgcta tcagttgggt gcgacaggcc 120

cctggacaag ggtttgagtg gatgggaggg atcatccctg tcattggtac agtaaattat 180

gaagagagat tccaggacag agtcacgatt accgcggaca attccacgag cacagcctac 240

atggagttga ctagtctgag atctgaagac acggccgtgt atttttgtgg gagagaagag 300

ggcttccttg actattgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 30
<211> 396
<212> DNA
<213> Homo sapiens

<400> 30
atggacatga gggtccccgc tcagctcctg gggcttctgc tgctctggct cccaggtgcc 60

agatgtgcca tccagttgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga 120

gtcaccatca cttgccgggc aagtcagggc attagcagtg ctttagcctg gtatcagcag 180

aaaccaggga aagctcctaa gctcctgatc tatgatgcct ccagtttgga aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ctctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttattactgt caacagttta atagttaccc tcttctcact 360

ttcggcggag ggaccaaggt ggagatcaaa cgtacg 396

<210> 31
<211> 405
<212> DNA
<213> Homo sapiens

<400> 31
atggactgga cctggaggtt cctctttgtg gtggcagcag ctacaggtgt ccagtcccag 60

gtccagctgg tgcagtctgg ggctgaggtg aagaagcctg ggtcctcggt gaaggtctcc 120

tgcaaggctt ctggagacac cttcagcagt tatgctatca gttgggtgcg acaggcccct 180

ggacaagggt ttgagtggat gggagggatc atccctgtca ttggtacagt aaattatgaa 240

gagagattcc aggacagagt cacgattacc gcggacaatt ccacgagcac agcctacatg 300

gagttgacta gtctgagatc tgaagacacg gccgtgtatt tttgtgggag agaagagggc 360

ttccttgact attggggcca gggaaccctg gtcaccgtct cctca 405

<210> 32
<211> 396
<212> DNA
<213> Homo sapiens

<400> 32
atggacatga gggtccccgc tcagctcctg gggcttctgc tgctctggct cccaggtgcc 60

agatgtgcca tccagttgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga 120

gtcaccatca cttgccgggc aagtcagggc attagcagtg ctttagcctg gtatcagcag 180

aaaccaggga aagctcctaa gctcctgatc tatgatgcct ccagtttgga aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ctctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttattactgt caacagttta atagttaccc tcttctcact 360

ttcggcggag ggaccaaggt ggagatcaaa cgtacg 396

<210> 33
<211> 121
<212> PRT
<213> Homo sapiens

<400> 33

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Cys Cys
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr 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 Thr Asp Ser Ser Gly Ser Phe Tyr Glu Tyr Phe Gln His Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 34
<211> 109
<212> PRT
<213> Homo sapiens

<400> 34

```
Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asn Ser Ala
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr
            100                 105
```

<210> 35
<211> 140
<212> PRT
<213> Homo sapiens

<400> 35

```
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                  10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Cys Cys Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

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

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

Tyr Tyr Cys Ala Thr Asp Ser Ser Gly Ser Phe Tyr Glu Tyr Phe Gln
        115                 120                 125
```

```
His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140


<210>  36
<211>  131
<212>  PRT
<213>  Homo sapiens

<400>  36

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Pro Gly Ala Arg Cys Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser
            20                  25                  30


Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45


Gln Gly Ile Asn Ser Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60


Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65                  70                  75                  80


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95


Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110


Phe Asn Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
        115                 120                 125


Lys Arg Thr
    130


<210>  37
<211>  363
<212>  DNA
<213>  Homo sapiens

<400>  37
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc     60

tcctgtgcag cgtctggatt caccttcagt tgctgtggca tgcactgggt ccgccaggct    120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat    180

gcagactccg tgaagggccg attcaccatc tccagagaca cttccaagaa cacgctgtat    240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gacagatagt    300

tcggggagtt tttatgaata cttccagcac tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363
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<210> 38
<211> 327
<212> DNA
<213> Homo sapiens

<400> 38
gccatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaac agtgctttag cctggtatca gcagaaacca 120

gggaaagctc ctaagctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag tttaatagtt acccgtacac ttttggccag 300

gggaccaagc tggagatcaa acgaact 327

<210> 39
<211> 420
<212> DNA
<213> Homo sapiens

<400> 39
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag 60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc 120

tgtgcagcgt ctggattcac cttcagttgc tgtggcatgc actgggtccg ccaggctcca 180

ggcaaggggc tggagtgggt ggcagttata tggtatgatg gaagtaataa atactatgca 240

gactccgtga agggccgatt caccatctcc agagacactt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgac agatagttcg 360

gggagttttt atgaatactt ccagcactgg ggccagggca ccctggtcac cgtctcctca 420

<210> 40
<211> 393
<212> DNA
<213> Homo sapiens

<400> 40
atggacatga gggtccccgc tcagctcctg gggcttctgc tgctctggct cccaggtgcc 60

agatgtgcca tccagttgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga 120

gtcaccatca cttgccgggc aagtcagggc attaacagtg ctttagcctg gtatcagcag 180

aaaccaggga aagctcctaa gctcctgatc tatgatgcct ccagtttgga aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ctctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttattactgt caacagttta atagttaccc gtacactttt 360

ggccagggga ccaagctgga gatcaaacga act 393

<210> 41
<211> 121
<212> PRT
<213> Homo sapiens

<400> 41

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Asp Trp Val
        35                  40                  45

Ala Val Val Trp Tyr Asp Gly Gly Tyr Lys Phe Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Arg Asp Ser Ser Gly Ser Phe Tyr Glu Tyr Leu Gln His Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120

<210>  42
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  42

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro His
                85                  90                  95

Phe Trp Pro Gly Asp Gln Ala Gly Asp Gln Thr Asn Cys Gly
            100                 105                 110
```

<210> 43
<211> 140
<212> PRT
<213> Homo sapiens

<400> 43

```
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                  10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

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

Asp Trp Val Ala Val Val Trp Tyr Asp Gly Gly Tyr Lys Phe Tyr Ala
65                  70                  75                  80

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

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

Tyr Tyr Cys Ala Arg Asp Ser Ser Gly Ser Phe Tyr Glu Tyr Leu Gln
        115                 120                 125

His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140
```

<210> 44
<211> 132
<212> PRT
<213> Homo sapiens

<400> 44

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Pro Gly Ala Arg Cys Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Gly Ile Ser Ser Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65                  70                  75                  80
```

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Phe Asn Ser Tyr Pro His Phe Trp Pro Gly Asp Gln Ala Gly Asp Gln
115 120 125

Thr Asn Cys Gly
130

<210> 45
<211> 363
<212> DNA
<213> Homo sapiens

<400> 45
caggtgcagt tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt ggctatggca tgcactgggt ccgccaggct 120

ccaggcaggg ggctggactg ggtggcagtt gtgtggtatg atggaggtta taagttctat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatagt 300

tcggggagtt tttatgaata cttacaacat tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> 46
<211> 325
<212> DNA
<213> Homo sapiens

<400> 46
gccatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattagc agtgctttag cctggtatca gcagaaacca 120

gggaaagctc ctaagctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag tttaatagtt accctcactt ttggccaggg 300

gaccaagctg gagatcaaac gaact 325

<210> 47
<211> 420
<212> DNA
<213> Homo sapiens

<400> 47
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag 60

gtgcagttgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc 120

tgtgcagcgt ctggattcac cttcagtggc tatggcatgc actgggtccg ccaggctcca 180

ggcaggggc tggactgggt ggcagttgtg tggtatgatg gaggttataa gttctatgca 240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agatagttcg 360

gggagttttt atgaatactt acaacattgg ggccagggca ccctggtcac cgtctcctca 420

<210> 48
<211> 391
<212> DNA
<213> Homo sapiens

<400> 48
atggacatga gggtccccgc tcagctcctg gggcttctgc tgctctggct cccaggtgcc 60

agatgtgcca tccagttgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga 120

gtcaccatca cttgccgggc aagtcagggc attagcagtg ctttagcctg gtatcagcag 180

aaaccaggga aagctcctaa gctcctgatc tatgatgcct ccagtttgga aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ctctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttattactgt caacagttta atagttaccc tcacttttgg 360

ccaggggacc aagctggaga tcaaacgaac t 391