



(86) Date de dépôt PCT/PCT Filing Date: 1995/06/19
(87) Date publication PCT/PCT Publication Date: 1996/01/18
(45) Date de délivrance/Issue Date: 2008/11/18
(85) Entrée phase nationale/National Entry: 1996/12/24
(86) N° demande PCT/PCT Application No.: EP 1995/002358
(87) N° publication PCT/PCT Publication No.: 1996/001274
(30) Priorité/Priority: 1994/07/01 (DEP 44 23 131.8)

(51) Cl.Int./Int.Cl. *C07K 14/54* (2006.01),
A61K 38/20 (2006.01), *A61P 37/02* (2006.01),
A61P 37/08 (2006.01)

(72) Inventeurs/Inventors:
WILD, HANNO, DE;
HANKO, RUDOLF, DE;
DORSCHUG, MICHAEL, DE;
HORLEIN, HANS-DIETRICH, DE;
BEUNINK, JURGEN, DE;
APELER, HEINER, DE;
WEHLMANN, HERMANN, DE;
SEBALD, WALTER, DE

(73) Propriétaire/Owner:

(54) Titre : NOUVELLES PROTEINES MUTANTES DE L'IL-4 HUMAINE UTILISEES COMME ANTAGONISTES OU AGONISTES PARTIELS DE L'INTERLEUKINE HUMAINE 4
(54) Title: NEW hIL-4 MUTANT PROTEINS USED AS ANTAGONISTS OR PARTIAL AGONISTS OF HUMAN INTERLEUKIN 4

(57) **Abrégé/Abstract:**

The present invention relates to novel hIL-4 mutant proteins, to processes for preparing them, and to their use as medicaments, in particular in overshooting, falsely regulated immune reactions and autoimmune diseases.



(73) **Propriétaires(suite)/Owners(continued):**BAYER AKTIENGESELLSCHAFT, DE

(74) **Agent:** FETHERSTONHAUGH & CO.

Novel hIL-4 mutant proteins as antagonists or partial agonists of human interleukin 4

Abstract

The present invention relates to novel hIL-4 mutant proteins, to processes for preparing them, and to their use as medicaments, in particular in overshooting, falsely regulated immune reactions and autoimmune diseases.

NEW hIL-4 MUTANT PROTEINS USED AS ANTAGONISTS OR PARTIAL
AGONISTS OF HUMAN INTERLEUKIN 4

5 The present invention relates to novel hIL-4 mutant proteins, to processes for preparing them, and to their use as medicaments, in particular in association with overshooting, falsely regulated immune reactions and autoimmune diseases.

PCT WO 93/10235 already discloses therapeutic agents which are or which contain antagonists or partial agonists of hIL-4, with the antagonists or partial agonists
10 being hIL-4 mutant proteins.

Human interleukin 4 (hIL-4) is one of the many cytokines which induce and coordinate the proliferation, maturation, survival and differentiation of lymphoid and myeloid cells. In particular, hIL-4 is involved in the IgE-mediated immune
15 reaction and directly accelerates the proliferation of thymocytes and activated T cells. A high-affinity IL-4 receptor protein of Mr 140,000 has been identified which, according to its cDNA sequence, consists of 800 amino acid residues. This protein belongs to a recently described group of receptors which are designated the haematopoietin receptor superfamily.

20

Based on the cloned cDNA, the amino acid sequence of the mature IL-4 consists of 129 residues. The cDNA has been expressed in E. coli and yeast. Recombinant IL-4 having high biological activity can be isolated from these sources.

25 Very recently, a monoclonal antibody has been disclosed which exhibits antagonistic properties towards human interleukin 4. This antibody contains a Fab fragment and is produced by a human/human hybridoma cell line. A hybridoma cell line from the spleen cells of a rat which was immunized against (non-)glycosylated human IL-4 also produces monoclonal antibodies against hIL-4.

30

The role of interleukin 4 in allergic processes provides grounds for hoping that substances which inhibit interleukin 4-mediated processes, or compete with hIL-4, might interrupt the disease-triggering reaction chain.

30725-98

- 2a -

acid between the N-terminal methionine and the natural N-terminus of the hIL-4 mutant protein. More preferably, the inserted amino acid is alanine, glycine, proline, serine, threonine or valine.

5 In another aspect of the present invention, there is provided a therapeutic composition comprising: a) the mutant human hIL-4 protein as described herein; and b) a physiologically acceptable carrier.

 According to yet another aspect of the present
10 invention, there is provided use of the mutant hIL-4 protein as described herein for antagonizing or partially agonizing the effect of human interleukin-4 (hIL-4).

 According to still another aspect of the present invention, there is provided use of the mutant hIL-4 protein
15 as described herein in the manufacture of a medicament for antagonizing or partially agonizing the effect of human interleukin-4 (hIL-4).

 For this, the amino acids which naturally occur in the wild type are deleted, or replaced by other amino acids,
20 at one or more positions, or else additional amino acids are inserted, at the C terminus or at the N terminus as well, or else one or more of the amino acids is/are substituted by various non-protein polymers, for example polyethylene glycol and its derivatives, or by glycosyl residues.

25 Within the context of the invention, amino acids are generally

Ala	L-alanine
Arg	L-arginine
Asn	L-asparagine

30725-98

- 2b -

	Asp	L-aspartic acid
	Cys	L-cysteine
	Gln	L-glutamine
	Glu	L-glutamic acid
5	Gly	L-glycine
	His	L-histidine
	Ile	L-isoleucine
	Leu	L-leucine
	Lys	L-lysine

