AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Ludwig Institute for Cancer Research**, the applicant/Nominated Person in respect of Application No. 37790/93 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventors by assignment.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person is the assignee of the applicants in respect of the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this EIGHTH day of SEPTEMBER 1994

.....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1686800)

AU9337790

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NUCLEIC ACID SEQUENCES CODING FOR OR COMPLEMENTARY TO NUCLEIC ACID SEQUENCES CODING FOR INTERLEUKIN 9 RECEPTOR

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C12N 015/70 C12Q 001/00 G01N 033/68 A61K 039/395

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(56) Prior Art Documents
US 4675285
US 4707443
US 5116951

(57) Claim

1. Isolated nucleic acid molecule which encodes or is complementary to a nucleic acid molecule which encodes an interleukin-9 receptor which shows at least 53% homology to any one of SEQ ID Nos. 1-6.

15. Cell line transfected with the nucleic acid molecule of any one of claims 1 to 3.

16. The cell line of claim 15, wherein said cell line is a eukaryotic cell line.

24. Process for producing an antibody which specifically binds to interleukin 9 receptor comprising immunizing a subject animal with the cell line of claim 16 under conditions favoring generation of antibodies which specifically bind to interleukin 9 receptor and isolating said antibodies from said animal.

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(54) Title: NUCLEIC ACID SEQUENCES CODING FOR OR COMPLEMENTARY TO NUCLEIC ACID SEQUENCES CODING FOR INTERLEUKIN 9 RECEPTOR

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m MALGRCIAEGWTLERVAVKQV--SWFLIYSWVCSGVCRGVSVPEQGGGGQKAGAFTCLSNSIYRIDCHWSAPELGQESRAWLLFTSNQVTEIKHKCTF  96
h MGLGRCIWEGWTLESEALRRDMGTWLLACICICTCVCLGVSVTGEGQGPR-SRTFTCLTNNILRIDCHWSAPELGQGSSPWLLFTSNQAPGGTHKCIL  97

m WDSMCTLVLPKEEVFLPFDNFTITLHRCIMGQEQVSLVDSQYLPRRHIKLDPPSDLQSNVSSGRCVLTWGINLALEPLITSLSYELAFKRQEEAWE-A 193
h RGSECTVVLPPEAVLVPSDNFTITFHHCMSGREQVSLVDPEYLPRRHVKLDPPSDLQSNISSGHCILTWSISPALEPMTTLLSYELAFKKQEEAWEQA 195

m RHKDRIVGVTWLILEAVELNPGSIYEARLRVQM-TLESYEDKTEGEYYKSHWSEWSQPVSFPSPQRRQGLLVPRWQWSASILVVVPIFLLLTGFVHLL 290
h QHRDHIVGVTWLILEAFELDPGFIHEARLRVQMATLEDDVV--EEERYTGQWSEWSQPVCFQAPQ-RQGPLIPPWGWPGNTLVAVSIFLLLTGPTYLL 290

m FKLSPRLKRIFYQNIPSPEAFFHPLYSVYHGDFQSWTGARRAGPQARQNGVSTSSAGSESSIWEAVATLTYSPACPVQFACLKWEATAPGFPGLPG-- 386
h FKLSPRVKRIFYQNVPSPAMFFQPLYSVHNGNFQTWMGAHRAGVLLSQDCAGTPQGALEPCVQEATALLTCGPARPWKSVALEEEQEGPGTRLPGNLS 388

m SEHVLPAGCLELEGQPSAYLPQEDWAPLGSARPPPPDS---DSGSS--------DYCMLDCCEECHLSAFPGHTESPELTLAQPVALPVSSRA      468
h SEDVLPAGCTEWRVQTLAYLPQEDWAPTSLTRPAPPDSEGSRSSSSSSSSSNNNNYCALGCYGGWHLSALPGNTQSSGPIPALACGLSCDHQGLETQQ 486

h GVANVLAGHCQRPGLHEDLQGMLLPSVLSKARSWTF                                                                  522
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(57) Abstract

The invention describes nucleic acid sequences which code for the interleukin 9 receptor (IL9-R) molecule. These sequences may be used as probes to identify cells expressing the molecule, and as agents to transfect recipient cells.

NUCLEIC ACID SEQUENCES CODING FOR OR COMPLEMENTARY TO NUCLEIC ACID SEQUENCES CODING FOR INTERLEUKIN 9 RECEPTOR

FIELD OF THE INVENTION

This invention relates to the reception of the cytokine known as interleukin 9 by cells, via its receptor. More particularly, it relates to the isolation of nucleic acid sequences which code for interleukin 9 receptor molecules ("IL-9R" hereafter). These sequences can be used, e.g. as a source for IL-9 receptor, and as probes for cells which respond to the cytokine. The complementary sequences can be used to inhibit expression as well as to probe for the coding sequences.

BACKGROUND AND PRIOR ART

The last decade has seen knowledge of the immune system and its regulation expand tremendously. One area of particular interest has been that of research on the proteins and glycoproteins which regulate the immune system. Perhaps the best known of these molecules, which are generically referred to as "growth factors", "cytokines", "leukotrienes", "lymphokines", etc., is interleukin-2 ("IL-2"). See, e.g., U.S. Patent No. 4,778,879 to Mertelsmann et al.; U.S. Patent No. 4,490,289, to Stern; U.S. Patent No. 4,518,584, to Mark et al.; and U.S. Patent No. 4,851,512 to Miyaji et al. Additional patents have issued which relate to interleukin 1 - ("IL-1"), such as U.S. Patent No. 4,808,611, to Cosman. The disclosure of all of these patents are incorporated by reference herein.

In order for molecules such as IL-2 and IL-1 to exert their effect on cells, it is now pretty much accepted that these must interact with molecules, located on cell membranes, referred to as receptors. Patents which exemplify disclosures of interleukin receptors

include Honjo et al., U.S. Patent No. 4,816,565; and Urdal et al., U.S. Patent No. 4,578,335, the disclosures of which are incorporated by reference. Recently, Fanslow, et al., Science 248: 739-41 (May 11, 1990) presented data showing that the effect of IL-1 in vivo could be regulated via the administration of a soluble form of its receptor. The last paragraph of the Fanslow paper, the disclosure of which is incorporated by reference, describes the types of therapeutic efficacy administration of soluble IL-1 receptor ("IL-1R") is expected to have.

The lymphokine IL-9, previously referred to as "P40", is a T-cell derived molecule which was originally identified as a factor which sustained permanent antigen independent growth of T4 cell lines. See, e.g., Uyttenhove, et al., Proc. Natl. Acad. Sci. 85: 6934 (1988), and Van Snick et al., J. Exp. Med. 169: 363 (1989), the disclosures of which are incorporated by reference, as is that of Simpson et al., Eur. J. Biochem. 183: 715 (1989).

The activity of IL-9 was at first observed to act on restricted T4 cell lines, failing to show activity on CTLs or freshly isolated T cells. See, e.g., Uyttenhove et al., supra, and Schmitt et al., Eur. J. Immunol. 19: 2167 (1989). This range of activity was expanded when experiments showed that IL-9 and the molecule referred to as T cell growth Factor III ("TCGF III") are identical. IL-9 enhances the proliferative effect of bone marrow derived mast cells to "IL-3", as is described by Hültner et al., Eur. J. Immunol. 20: 1413-1416 (1990) and in U.S. Patent No. 5,164,317 the disclosures of both being incorporated by reference herein. It was also found that the human form of IL-9 stimulates proliferation of megakaryoblastic leukemia. See Yang et al., Blood 74: 1880 (1989). Recent work on IL9 has shown that it also supports erythroid colony formation (Donahue et al., Blood 75(12): 2271-2275 (6-15-90)); promotes the

proliferation of myeloid erythroid burst formation (Williams et al., Blood 76: 306-311 (9-1-90)); and supports clonal maturation of BFU.E's of adult and fetal origin (Holbrook et al., Blood 77(10): 2129-2134 (5/15/91)). Expression of IL9 has also been implicated in Hodgkin's disease and large cell anaplastic lymphoma (Merz et al., Blood 78(8): 1311-1317 (9-1-90)).

The art teaches the cloning of receptors for various members of the interleukin family. Moseley et al. Cell 59: 335-348 (1989), teach the isolation of cDNA coding for IL-4 receptors, and analysis of both genomic DNA and RNA for these molecules. To do this, Moseley et al. worked with cells exhibiting up to 1 million receptor molecules per cell, and an N-terminal amino acid sequence for IL-4 receptor. Holmes et al., Science 253: 1278-1280 (1991), and Murphy et al., Science 253: 1280-1282 (1991) discuss cDNA for the IL-8 receptor. Murphy et al. proceeded via hybridization studies, using an oligonucleotide probe based upon rabbit IL-8R amino acid sequences to isolate the human counterpart. Holmes et al. used human neutrophil cDNA libraries followed by transfection in COS cells.

Gillis, "T-cell Derived Lymphokines" in Paul, ed., Fundamental Immunology, Second Edition (New York, 1989), at pages 632 et seq. gives an overview of interleukin receptors. This reference describes cDNA for the IL1 receptor, the IL2 receptor and the IL-6 receptor.

These studies indicate that several factors are important in attempting to identify and isolate a nucleic acid sequence coding for an interleukin receptor. Ideally, one has both the amino acid sequence for the receptor and a cell type with a high degree of expression of the receptor molecule.

In the case of the interleukin 9 receptor, while Druez et al., J. Immunol. 145: 2494-2499 (1990) have identified and characterized the receptor as a glycoprotein with a molecular weight of 64 kilodaltons

the protein portion of which has a molecular weight of 54 kilodaltons as determined by SDS-PAGE, an amino acid sequence of the molecule is not yet available. In addition, very few cell types are known which express IL9-R (Druez, supra), and those that do, express it at very low levels. Thus, it is surprising that it now possible to identify and to isolate nucleic acid sequences which code for the interleukin 9 receptor. This is the key feature of the invention described herein, as will be seen from the disclosure which follows.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 presents Scatchard analysis of expression of murine IL9 receptor following transfection of COS cells. Figure 2 aligns deduced human and murine IL-9R amino acid sequences.

Figure 3 compares the response of TS1 cells, both before and after transfection with DNA coding for human IL-9R.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Example 1

The murine T cell clone, TS1, described by, e.g., Uyttenhove et al., Proc. Natl. Acad. Sci. 85: 6934-6938 (1988) the disclosure of which is incorporated by reference, expresses approximately 200 high affinity binding sites for IL-9, i.e., it expresses the IL-9 receptor molecule. See Druez et al., J. Immunol. 145: 2494-2499 (1990). This cell line, while presenting few receptor molecules does show the highest density of IL9R of all cells tested, and thus was selected as a source of mRNA for constructing a cDNA library.

Poly(A)+ mRNA was extracted from TS1 cells, and was then converted to double stranded cDNA using random hexanucleotide primers, following Grubler et al, Gene 25:

263-269 (1983), the disclosure of which is incorporated by reference.

Following this, EcoRI adaptors were attached, and any cDNA larger than 1.5 kilobases was isolated by fractionation on a 5-20% potassium acetate gradient, following Aruffo et al., Proc. Natl. Acad. Sci. 84: 8573-8577 (1987).

The size selected cDNA was then inserted into the ECORI site of expression vector pCDSRα taught by Takebe et al., Mol. Cell Biol. 8: 466-472 (1988). This was then transfected into E. coli strain XL1-blue using standard transformation procedures. (Maniatis). In order to screen for clones expressing IL-9R, plasmid DNA from the cDNA library was tested for the ability to express IL-9 binding activity by expression in COS cells. Basically, the cDNA library was subfractionated into 100 pools of about 500 clones each, and the DNA was transfected using the DEAE-dextran-chloroquine method of Aruffo et al., supra, into 1.5 x 10^5 COS cells, seeded on glass microscope slides. Cells were allowed to grow for 2-3 days, and were then tested for expression of IL-9R with ^{125}I labelled, purified recombinant murine IL9. This labeled material was prepared following Bolton et al., Biochem. J. 133: 529-539 (1973). The cells were incubated for three hours at 20°C with 0.2 nM of this material, washed briefly, fixed, and then dipped into liquid photographic emulsion. The slides were exposed for 10 days, then developed and examined microscopically for autoradiographic grains.

This screening resulted in two positive pools out of 100. One positive pool showed a single positive cell, and the second one showed 33 positive cells. This latter pool was selected for further testing, and was divided, first into 100 pools of 15 clones each, after which a single positive pool was selected, and divided into 100 single clones.

Example 2

Following the separating and replating described at the end of example 1, supra, the screening methodology described therein was employed on the replated cells, and led to identification of a clone containing a plasmid referred to as p9RA1. Since the "source" plasmid pCDSRα was known and characterized, it was possible using standard methodologies to identify the insert as 1900 base pairs in length.

Example 3

Using the p9RA1 1900 base pair segment as a probe, additional screening was carried out to identify additional murine IL9R receptor cDNA clones. The methodology followed was that of Maniatis et al., Molecular Cloning, a Laboratory Manual (Cold Spring Harbor Laboratory, New York, 1982), where the p9RA1 probe was hybridized to two further cDNA libraries which were generated in the BstXI site of vector pCDM8 (Aruffo et al, supra), using oligo T or random primers, followed by high stringency washes.

This methodology resulted in the identification of six additional clones. Two of these were oligo-dT primed cDNAs, and are referred to as p9RB1, and p9RB3, and four random primed clones p9RC2, p9RC3, p9RC4 and p9RC9. The sizes of these clones are as follows:

p9RB1	1600 bp
p9RB3	900 bp
p9RC2	2000 bp
p9RC3	1000 bp
p9RC4	3000 bp
p9RC9	2100 bp.

Example 4

In order to make sure that clone p9RA1 and all subsequent clones did in fact express IL9R, Scatchard analysis was carried out on transfected COS cells,

following Goodwin et al., Cell 60: 941-951 (1990). This analysis, shown in figure 1, identified a single class of binding sites with a Kd of 194 pM, when p9RA1 was used. This is slightly higher than the dissociation constant measured on TS1 cells previously, i.e., 67 pM.

When the largest cDNA was tested (i.e., the C4 clone), high affinity binding sites for IL9 were also identified, with a Kd of 126 pM.

Example 5

Following the isolation of murine clones, tests were also carried out to isolate analogous human material. To do this, a megakaryoblast cell line, i.e., Mo7E was used as a source of mRNA to make double stranded cDNA as per example 1. The plasmid pRC/RSV was used to receive the cDNA. This cDNA library was screened, using p9RA1 as a probe, and hybridization was carried out using the same conditions described supra, except washes were carried out at low stringency (2 x SSC, 0.1% SDS, 55°C). Six clones were isolated, i.e., ph9RA2, 3, 4, 5, 6 and 9, and sequenced. The clone ph9RA3 contained a 1566 base pair open reading frame, which showed 66% identity with murine p9RC4. The deduced murine and human protein sequences are shown in figure 2, with a 53% identity over 522 amino acids.

Example 6

In order to test whether clone ph9RA3 actually did code for a human IL9 receptor, the clone was transfected into murine cell line TS1, using double pulse electroporation. In brief, 5 x 10^6 TS1 cells were resuspended at 37°C in 0.8 ml of Dulbecco's modified Eagle's medium, supplemented with 10% fetal bovine serum, 50 mM 2-mercaptoethanol, 0.55 mM L-arginine, 0.24 mM L-asparagine, and 1.25 mM L-glutamine. Plasmid DNA (50 ug) was added to the cells in 0.4 cm cuvettes just before electroporation. After a double electric pulse (750 V,

7452Ω, 40 μF and 100 V, 74Ω, 2100 μF), cells were immediately diluted in fresh medium supplemented with murine IL9. After 24 hours, cells were washed and cultured in the presence of G418, and mouse IL9. These conditions resulted in a frequency of transfection of approximately 1/10,000. Following selection with G418, transfected cells were maintained in human IL9, and a TS1 proliferation assay was performed using the methodology of Uyttenhove et al., Proc. Natl., Acad. Sci. USA 85: 6934-6938 (1988). If the cDNA expresses hIL9R, then cells should proliferate, while those which do not contain it should not.

Figure 3 shows that original TS1 cells, unresponsive to 100 units/ml of human IL9, became responsive and proliferated after transfection with the human IL9R cDNA.

Example 7

The sequence of clone p9RC4, presented as SEQ ID NO: 1, shows an open reading frame coding a 468 amino acid protein. The deduced amino acid sequence predicts two hydrophobic regions, one of which spans amino acids 15-40, and probably represents a signal peptide. The probability weight matrix of von Heyne, Nucl. Acids Res. 14: 4683-4690 (1986) predicts a cleavage site for the signal peptide between positions 37 and 39. The second hydrophobic domain spans amino acids 271-291. This is presumed to constitute the transmembrane domain.

The putative extracellular domain contains 233 amino acids, including 6 cysteine residues and two potential N-linked glycosylation sites at positions 116 and 155. A 'WSEWS" motif, i.e., "Trp-Ser-Glu-Trp-Ser", typical of the hematopoietin receptor superfamily described by Idzerda et al., J. Exp. Med. 171: 861-873 (1990), is found at positions 244-248.

The cytoplasmic portion of the molecule is characterized by a high percentage of serine (13%), and proline (12.4%), as well as three potential protein

kinase C phosphorylation sites at positions 294, 416 and 465.

Comparison of the various clones indicates that p9RA1 and p9RB3 contain an additional glutamine between position 192 and 193 as compared to p9RC4, but without a frameshift. This residue lies in the extracellular domain, but as example 4, supra shows, it does not appear to affect the affinity for ligand. There is a 22 nucleotide deletion at this position in p9RC2. These features, and a potential intronic sequence in p9RC9, suggest alternate splicing events.

The analysis of p9RB3 implies the existence of a soluble form of IL9R. The cDNA for this clone contains a large part of extracellular domain, but lacks nucleotides 651-1719, which code the end of the N-terminal domain, the transmembrane and the cytoplasmic domain.

Clone p9RA1 is different from all other clones in that there is a stop codon after alanine (378), which is followed by a 736 base pair sequence unrelated to any other cDNA's sequenced.

The sequences for the murine cDNA described in this example is provided as follows:

p9RC4 (SEQ ID NO: 1)
p9RA1 (SEQ ID NO: 2)
p9RB3 (SEQ ID NO: 3).

Example 8

The cDNA for human IL9-R was also analyzed. As indicated supra, clone ph9RA3 showed 66% identity with murine p9RC4 and 53% homology on the amino acid sequence level. A putative cleavage site is positioned between amino acids 39 and 40. This site is conserved between species, as is the transmembrane domain, the two potential N-glycosylation sites, and the consensus sequence for the hematopoietic superfamily, all of which are described in Example 7.

The cytoplasmic portion of the protein seemed less conserved, and was much larger (231 amino acids) than the murine counterpart (177 residues). Due to a stretch of 9 consecutive serines in positions 431-439, there is a high percentage of serine in the molecule (11.2%).

Clones ph9RA2, 4, 6 and 9 confirmed the sequence derived from ph9RA3. The clone ph9RA5, however, has an 85 nucleotide deletion in positions 1063-1147, suggesting a truncated protein. The putative truncated protein would be 307 amino acids long, and contain the complete extracellular and transmembrane regions of IL9-R, 5 amino acids of the cytoplasmic domain, and 11 unrelated residues.

The clone referred to as pH9RA6 contains a short intervening sequence at the beginning of the DNA, which leads into a stop codon, in frame with the normal initiative codon. It also creates a new ATG triplet in frame with the downstream portion of the coding sequence. In the IL9R molecule, this yields a transcript with a unique N-terminal sequence, the rest of the sequence being identical to pH9RA3. Comparison of pH9RA6 and pH9RA3 shows that, after the initial methionine common to both clones, pH9RA6 contains an insert of 22 amino acids. These are followed by the sequence "GWTLESE ..." which is the sequence beginning at position 10 of pH9RA3.

The nucleic acid sequences for pH9RA3, pH9RA5 and pH9RA6 are presented as SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively.

The foregoing teaches the isolation of a nucleic acid sequence which codes for the interleukin-9 receptor. Both murine and the homology found therebetween (53%, with up to 67% in the extracellular region) suggests that nucleic acid sequences coding for IL9-R from other species could also be identified.

The preceding data deal with cDNA, but it will be seen that the sequences of the cDNA put one in possession of mRNA, as the latter can be derived from the former

based on well known rules regarding construction of the sequences. Given the cDNA information, it is presumed that one could also secure the genomic analogs of the cDNAs.

The information provided herein also teaches construction of vectors, such as plasmids, which contain the nucleic acid sequences of interest, i.e., those coding for mammalian IL9R. Such vectors may contain components in addition to the coding sequence, such as promoters operably linked to the coding sequence, "markers", such as genes for antibiotic resistance or selection, including the thymidine kinase or "TK" gene, as well as others which will be known to the skilled artisan. The nucleic acid sequences and vectors may be used - as has been shown - to transfect various cell types, such as "COS", "CHO", Spodoptera frugiperda or other insect cell lines. The sequences, either alone or in appropriate vectors, can be used to transfect a panoply of prokaryotic and eukaryotic cells.

The isolation of nucleic acid sequences coding for the IL9 receptor makes it possible for investigators to carry out several lines of investigation which were not possible or much more difficult without these. For example, as pointed out supra, even on these cells which express it best, expression of IL-9R is low. Isolation of the gene makes it possible to transfect recipient cells, followed by overexpression, amplification, etc. This leads to sufficient expression on cell surfaces to permit immunization with these cells, and generation of an immunogenic response to IL-9R, including the production of antibodies. Isolation of the antibody producing cells, followed by standard techniques of hybridoma biology leads to production of IL-9R specific monoclonal antibodies.

The antibodies produced, be they polyclonal or monoclonal, can then be used in therapeutic methods to block IL-9 from binding to IL-9R molecules. As binding

of IL-9 to cell surfaces is implicated in several pathological conditions, this is an important therapeutic goal.

In addition IL-9R specific antibodies can be used for both qualitative and quantitative measurement of IL-9R expression on cells, following known immunoassay protocols.

The examples supra show the existence of a soluble form of IL-9R. As with other soluble interleukin receptor molecules (see Fanslow et al., supra), this molecule can be used to prevent the binding of IL-9 to cell bound receptor, and thus interfere with the affect of IL-9 on a cell type, subpopulation, etc. As such, soluble IL-9R may be said to be an antagonist for IL-9.

Recent work has shown that the soluble form of one interleukin receptor, i.e., IL-6R, functions as an agonist. See Taga et al., Cell 58: 573-591 (8-11-89). The soluble form of IL-9R might function in a similar manner. In addition the IL-9R molecule, either the soluble form or a solubilized form of the molecule may be used as an immunogen for generation of IL-9R specific antibodies. Either the entire receptor molecule, or an immunogenic portion thereof, can be used in an appropriate animal, such as a mouse, rabbit or guinea pig, to generate an immune response which includes antibody formation. The antibodies can then be purified using standard techniques. Alternatively, antibody producing B cells can be isolated and utilized in any of the standard methods for producing hybridomas, so as to lead to the generation of IL-9R specific monoclonal antibodies.

An assay is described supra, in Example 6, in which IL-9R cDNA expression is assayed by measuring the responsiveness of a transfected cell line to IL9. This assay methodology provides a means for screening for various agonists and antagonists. In brief, a transfected cell sample containing a sequence coding for

IL9R is contacted with a compound of interest. If the compound is an agonist, it will bind to the IL-9R molecule on the cell surface, and lead to the series of events usually associated with IL-9/IL-9R binding. To the same end, an antagonist can be assayed by combining the compound of interest with IL-9 and the cell sample to determine whether the IL-9 has diminished impact, or no impact. The assay for agonist/antagonist may be viewed as part of a broader invention wherein one may assay for molecules which compete for binding to IL-9R.

In addition to the coding sequences discussed herein, the invention also embraces sequences complementary to the coding sequences. These complements, which can be derived from the coding sequences themselves, may be used, e.g., as probes or as "anti-sense" inhibitors to prevent expression of the IL9R coding sequences. Other aspects of the invention will be clear to the skilled artisan, and do not require elaboration here.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.

(1) GENERAL INFORMATION:

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Druez, Catherine
Van Snick, Jacques

(ii) TITLE OF INVENTION: Nucleic Acid Sequences Coding For Or Complementary To Nucleic Acid Sequences Coding For Interleukin 9 Receptor

(iii) NUMBER OF SEQUENCES: 6

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette, 5.25 inch, 360 kb storage
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(C) OPERATING SYSTEM: PC-DOS
(D) SOFTWARE: Wordperfect

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(2) INFORMATION FOR SEQ ID NO: 1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2281 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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CTCC                                                                    4
ATG GCC CTG GGA AGA TGC ATT GCG GAA GGT TGG ACC TTG GAG                 46
Met Ala Leu Gly Arg Cys Ile Ala Glu Gly Trp Thr Leu Glu
                  5                  10
AGA GTG GCG GTG AAA CAG GTC TCC TGG TTC CTG ATC TAC AGC                 88
Arg Val Ala Val Lys Gln Val Ser Trp Phe Leu Ile Tyr Ser
15                  20                  25
TGG GTC TGC TCT GGA GTC TGC CGG GGA GTC TCG GTC CCA GAG                 130
Trp Val Cys Ser Gly Val Cys Arg Gly Val Ser Val Pro Glu
     30                  35                  40
CAA GGA GGA GGA GGG CAG AAG GCT GGA GCA TTC ACC TGT CTC                 172
Gln Gly Gly Gly Gly Gln Lys Ala Gly Ala Phe Thr Cys Leu
         45                  50                  55
AGC AAC AGT ATT TAC AGG ATC GAC TGC CAC TGG TCG GCT CCA                 214
Ser Asn Ser Ile Tyr Arg Ile Asp Cys His Trp Ser Ala Pro
                 60                  65                  70
GAG CTG GGC CAG GAA TCC AGG GCC TGG CTC CTC TTT ACC AGT                 256
Glu Leu Gly Gln Glu Ser Arg Ala Trp Leu Leu Phe Thr Ser
                 75                  80
AAC CAG GTG ACT GAA ATC AAA CAC AAA TGC ACC TTC TGG GAC                 298
Asn Gln Val Thr Glu Ile Lys His Lys Cys Thr Phe Trp Asp
 85                  90                  95
AGT ATG TGT ACC CTG GTG CTG CCT AAA GAG GAG GTG TTC TTA                 340
Ser Met Cys Thr Leu Val Leu Pro Phe Glu Glu Val Phe Leu
    100                 105                 110
CCT TTT GAC AAC TTC ACC ATC ACA CTT CAC CGC TGC ATC ATG                 382
Pro Phe Asp Asn Phe Thr Ile Thr Leu His Arg Cys Ile Met
        115                 120                 125
GGA CAG GAA CAG GTC AGC CTG GTG GAC TCA CAG TAC CTG CCC                 424
Gly Gln Glu Gln Val Ser Leu Val Asp Ser Gln Tyr Leu Pro
            130                 135                 140
AGG AGA CAC ATC AAG TTG GAC CCA CCC TCT GAT CTG CAG AGC                 466
Arg Arg His Ile Lys Leu Asp Pro Pro Ser Asp Leu Gln Ser
                145                 150
AAT GTC AGC TCT GGG CGT TGT GTC CTG ACC TGG GGT ATC AAT                 508
Asn Val Ser Ser Gly Arg Cys Val Leu Thr Trp Gly Ile Asn
155                 160                 165
CTT GCC CTG GAG CCA TTG ATC ACA TCC CTC AGC TAC GAG CTG                 550
Leu Ala Leu Glu Pro Leu Ile Thr Ser Leu Ser Tyr Glu Leu
    170                 175                 180

GCC TTC AAG AGG CAG GAA GAG GCC TGG GAG GCC CGG CAC AAG                 592
Ala Phe Lys Arg Gln Glu Glu Ala Trp Glu Ala Arg His Lys
        185                 190                 195
```

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GAC CGT ATC GTT GGA GTG ACC TGG CTC ATC CTT GAA GCC GTC       634
Asp Arg Ile Val Gly Val Thr Trp Leu Ile Leu Glu Ala Val
            200                 205                 210
GAA CTG AAT CCT GGT TCC ATC TAC GAG GCC AGG CTG CGT GTC       676
Glu Leu Asn Pro Gly Ser Ile Tyr Glu Ala Arg Leu Arg Val
                215                 220
CAG ATG ACT TTG GAG AGT TAT GAG GAC AAG ACA GAG GGG GAA       718
Gln Met Thr Leu Glu Ser Tyr Glu Asp Lys Thr Glu Gly Glu
225                 230                 235
TAT TAT AAG AGC CAT TGG AGT GAG TGG AGC CAG CCC GTG TCC       760
Tyr Tyr Lys Ser His Trp Ser Glu Trp Ser Gln Pro Val Ser
    240                 245                 250
TTT CCT TCT CCC CAG AGG AGA CAG GGC CTC CTG GTC CCA CGC       802
Phe Pro Ser Pro Gln Arg Arg Gln Gly Leu Leu Val Pro Arg
        255                 260                 265
TGG CAA TGG TCA GCC AGC ATC CTT GTA GTT GTG CCC ATC TTT       844
Trp Gln Trp Ser Ala Ser Ile Leu Val Val Val Pro Ile Phe
            270                 275                 280
CTT CTG CTG ACT GGC TTT GTC CAC CTT CTG TTC AAG CTG TCA       886
Leu leu Leu Thr Gly Phe Val His Leu Leu Phe Lys Leu Ser
                285                 290
CCC AGG CTG AAG AGA ATC TTT TAC CAG AAC ATT CCA TCT CCC       928
Pro Arg Leu Lys Arg Ile Phe Tyr Gln Asn Ile Pro Ser Pro
295                 300                 305
GAG GCG TTC TTC CAT CCT CTC TAC AGT GTG TAC CAT GGG GAC       970
Glu Ala Phe Phe His Pro Leu Tyr Ser Val Tyr His Gly Asp
    310                 315                 320
TTC CAG AGT TGG ACA GGG GCC CGC AGA GCC GGA CCA CAA GCA      1012
Phe Gln Ser Trp Thr Gly Ala Arg Arg Ala Gly Pro Gln Ala
        325                 330                  335
AGA CAG AAT GGT GTC AGT ACT TCA TCA GCA GGC TCA GAG TCC      1054
Arg Gln Asn Gly Val Ser Thr Ser Ser Ala Gly Ser Glu Ser
            340                 345                 350
AGC ATC TGG GAG GCC GTC GCC ACA CTC ACC TAT AGC CCG GCA      1096
Ser Ile Trp Glu Ala Val Ala Thr Leu Thr Tyr Ser Pro Ala
                 355                360
TGC CCT GTG CAG TTT GCC TGC CTG AAG TGG GAG GCC ACA GCC      1138
Cys Pro Val Gln Phe Ala Cys Leu Lys Trp Glu Ala Thr Ala
365                 370                 375
CCG GGC TTC CCA GGG CTC CCA GGC TCA GAG CAT GTG CTG CCG      1180
Pro Gly Phe Pro Gly Leu Pro Gly Ser Glu His Val Leu Pro
    380                 385                 390
GCA GGG TGT CTG GAG TTG GAA GGA CAG CCA TCT GCC TAC CTG      1222
Ala Gly Cys Leu Glu Leu Glu Gly Gln Pro Ser Ala Tyr Leu
        395                 400                 405
CCC CAG GAG GAC TGG GCC CCA CTG GGC TCT GCC AGG CCC CCT      1264
Pro Gln Glu Asp Trp Ala Pro Leu Gly Ser Ala Arg Pro Pro
            410                 415                 420
CCT CCA GAC TCA GAC AGC GGC AGC AGC GAC TAT TGC ATG TTG      1306
Pro Pro Asp Ser Asp Ser Gly Ser Ser Asp Tyr Cys Met Leu
                425                 430
GAC TGC TGT GAG GAA TGC CAC CTC TCA GCC TTC CCA GGA CAC      1348
Asp Cys Cys Glu Glu Cys His Leu Ser Ala Phe Pro Gly His
435                 440                 445
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ACC GAG AGT CCT GAG CTC ACG CTA GCT CAG CCT GTG GCC CTT     1390
Thr Glu Ser Pro Glu Leu Thr Leu Ala Gln Pro Val Ala Leu
    450                 455                 460
CCT GTG TCC AGC AGG GCC TGA                             1411
Pro Val Ser Ser Arg Ala
        465
CACCTACCAA GGGATGTGGG CATTCTCTTC CCTCCTATCC TCGGATGGCA      1461
CCAGACACAG TCTCTGCGTG TCTCTGCTAG GTGCACCATG TCTGTTTTGG      1511
GGAGATGAAC GAAAGGCCCC AGGCTGACCC TGGGGTGCGT GTGGAACTCC      1561
GGAGAGGAGG CAGCTGTGCA CGGATCAGAG GCAATGCGGA TGGAAGCAGT      1611
AGACTGTGCC TTACCCCCCT GCTCTGCCTT TGTGGTGGGG ATGCCTCCAG      1661
GGTCAGCATC TTAACATCGC CTTCGCTTCT CTTGTCTTTC TGGCTCTGTC      1711
CCAGGCCTGA AAAAAGAATG TGACAAGCAG CCTGGTCTGT TCTTCCACCC      1761
CTAAAGGGCT GGCCTGGGCC CAGGGACACT GATGAGACAA CATTGGTGAA      1811
GTGTCCCTTT TCAGTGCCTT TCCCATTAAG ACCAGAAGGG ACGCTTTTGA      1861
CTGCAGGCTG TGGGTGGCTG GGTACGGAGG GAATGATGGA GCTTTGAGCA      1911
GGTGGGGTTG TCCATCTTTG AGCTTTTGGG GTTCCAAGAT CAGCTGGAAG      1961
GAGTCTCACC GACTGATTCA AAGAAGTCTT ACCCATCTGT GATATTTTCT      2011
TTCCTGGTGC CGTGATAAAA CACCGTGACC AAAAATGACT TACAAAAGGA      2061
AGAGTTGGCT TGGTTTAAGG TTCCAGAGGT GTGGAGACAT GGCAGCCAGC      2111
GGCACACATG GCAGTGAGGA CAGGAAGCTG AGAGCTCACA TCTCAACCAA      2161
AAGTTGAGTG AACTGAAAGT ACTATCCCCT CCCCCACCCC AACTCCAGCA      2211
AGGCTCCACC CCCCTGAAGG TTCCATGCCT CCCTAAACAG CTCGGCCAAA      2261
TAGAGACCAA GTGTTCAAAT                                    2281
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1905 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

```
CACCTCCTGG CTGGGGCTGC CTGAGACTCT CC                        32
ATG GCC CTG GGA AGA TGC ATT GCG GAA GGT TGG ACC TTG GAG     74
Met Ala Leu Gly Arg Cys Ile Ala Glu Gly Trp Thr Leu Glu
                5                   10
AGA GTG GCG GTG AAA CAG GTC TCC TGG TTC CTG ATC TAC AGC    116
Arg Val Ala Val Lys Gln Val Ser Trp Phe Leu Ile Tyr Ser
15                  20                  25
TGG GTC TGC TCT GGA GTC TGC CGG GGA GTC TCG GTC CCA GAG    158
Trp Val Cys Ser Gly Val Cys Arg Gly Val Ser Val Pro Glu
    30                  35                  40
CAA GGA GGA GGA GGG CAG AAG GCT GGA GCA TTC ACC TGT CTC    200
Gln Gly Gly Gly Gly Gln Lys Ala Gly Ala Phe Thr Cys Leu
        45                  50                  55
AGC AAC AGT ATT TAC AGG ATC GAC TGC CAC TGG TCG GCT CCA    242
Ser Asn Ser Ile Try Arg Ile Asp Cys His Trp Ser Ala Pro
            60                  65                  70
GAG CTG GGC CAG GAA TCC AGG GCC TGG CTC CTC TTT ACC AGT    284
Glu Leu Gly Gln Glu Ser Arg Ala Trp Leu Leu Phe Thr Ser
                75                  80
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AAC CAG GTG ACT GAA ATC AAA CAC AAA TGC ACC TTC TGG GAC      326
Asn Gln Val Thr Glu Ile Lys His Lys Cys Thr Phe Trp Asp
 85                  90                  95
AGT ATG TGT ACC CTG GTG CTG CCT AAA GAG GAG GTG TTC TTA      368
Ser Met Cys Thr Leu Val Leu Pro Phe Glu Glu Val Phe Leu
    100                 105                 110
CCT TTT GAC AAC TTC ACC ATC ACA CTT CAC CGC TGC ATC ATG      410
Pro Phe Asp Asn Phe Thr Ile Thr Leu His Arg Cys Ile Met
        115                 120                 125
GGA CAG GAA CAG GTC AGC CTG GTG GAC TCA CAG TAC CTG CCC      452
Gly Gln Glu Gln Val Ser Leu Val Asp Ser Gln Tyr Leu Pro
            130                 135                 140
AGG AGA CAC ATC AAG TTG GAC CCA CCC TCT GAT CTG CAG AGC      494
Arg Arg His Ile Lys Leu Asp Pro Pro Ser Asp Leu Gln Ser
                145                 150
AAT GTC AGC TCT GGG CGT TGT GTC CTG ACC TGG GGT ATC AAT      536
Asn Val Ser Ser Gly Arg Cys Val Leu Thr Trp Gly Ile Asn
155                 160                 165
CTT GCC CTG GAG CCA TTG ATC ACA TCC CTC AGC TAC GAG CTG      578
Leu Ala Leu Glu Pro Leu Ile Thr Ser Leu Ser Tyr Glu Leu
    170                 175                 180
GCC TTC AAG AGG CAG GAA GAG GCC TGG GAG CAG GCC CGG CAC      620
Ala Phe Lys Arg Gln Glu Glu Ala Trp Glu Gln Ala Arg His
        185                 190                 195
AAG GAC CGT ATC GTT GGA GTG ACC TGG CTC ATC CTT GAA GCC      662
Lys Asp Arg Ile Val Gly Val Thr Trp Leu Ile Leu Glu Ala
            200                 205                 210
GTC GAA CTG AAT CCT GGT TCC ATC TAC GAG GCC AGG CTG CGT      704
Val Glu Leu Asn Pro Gly Ser Ile Tyr Glu Ala Arg Leu Arg
                215                 220
GTC CAG ATG ACT TTG GAG AGT TAT GAG GAC AAG ACA GAG GGG      746
Val Gln Met Thr Leu Glu Ser Tyr Glu Asp Lys Thr Glu Gly
225                 230                 235
GAA TAT TAT AAG AGC CAT TGG AGT GAG TGG AGC CAG CCC GTG      788
Glu Tyr Tyr Lys Ser His Trp Ser Glu Trp Ser Gln Pro Val
    240                 245                 250
TCC TTT CCT TCT CCC CAG AGG AGA CAG GGC CTC CTG GTC CCA      830
Ser Phe Pro Ser Pro Gln Arg Arg Gln Gly Leu Leu Val Pro
        255                 260                 265
CGC TGG CAA TGG TCA GCC AGC ATC CTT GTA GTT GTG CCC ATC      872
Arg Trp Gln Trp Ser Ala Ser Ile Leu Val Val Val Pro Ile
            270                 275                 280
TTT CTT CTG CTG ACT GGC TTT GTC CAC CTT CTG TTC AAG CTG      914
Phe Leu Leu Leu Thr Gly Phe Val His Leu Leu Phe Lys Leu
                285                 290
TCA CCC AGG CTG AAG AGA ATC TTT TAC CAG AAC ATT CCA TCT      956
Ser Pro Arg Leu Lys Arg Ile Phe Tyr Gln Asn Ile Pro Ser
295                 300                 305
CCC GAG GCG TTC TTC CAT CCT CTC TAC AGT GTG TAC CAT GGG      998
Pro Glu Ala Phe Phe His Pro Leu Tyr Ser Val Tyr His Gly
    310                 315                 320
GAC TTC CAG AGT TGG ACA GGG GCC CGC AGA GCC GGA CCA CAA     1040
Asp Phe Gln Ser Trp Thr Gly Ala Arg Arg Ala Gly Pro Gln
        325                 330                 335
```

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GCA AGA CAG AAT GGT GTC AGT ACT TCA TCA GCA GGC TCA GAG      1082
Ala Arg Gln Asn Gly Val Ser Thr Ser Ser Ala Gly Ser Glu
            340                 345                 350
TCC AGC ATC TGG GAG GCC GTC GCC ACA CTC ACC TAT AGC CCG      1124
Ser Ser Ile Trp Glu Ala Val Ala Thr Leu Thr Tyr Ser Pro
                355                 360
GCA TGC CCT GTG CAG TTT GCC TGC CTG AAG TGG GAG GCC ACA      1166
Ala Cys Pro Val Gln Phe Ala Cys Leu Lys Trp Glu Ala Thr
365                 370                 375
GCG TGA                                                     1172
Ala
GAAGGGACAG CCAGCCACTC AGTGCGTGGG CTTAGATTGG GAAGAGACCT      1222
CCCAAGCAGC TTCCCCTCCT CCCCAGCCCC TGCCATTCAC CCCTGCTGGC      1272
CGTCCATCCC CAGGATCCAC TGTGGAGCCA AGCCCACAGA CCCGGCCTGA      1322
TTCAGCTCTG ACACTCGCTG CGCTGCTCCG TTGTGAACTT TGGCCAAGTC      1372
ACCACTTTTA CCTCAGCTTC CTCCTGTGAG AACAGGGTTG CCTTAGAGTT      1422
GCCTAATCCC TAAGGAGACT GAGACAAACT TGTCTGCAAA TATCTATCCG      1472
ATGTATATTG TTAGGAGCTC GAGGGTCCGT GGGTGGGCGG GGCAGGGGGG      1522
TGGGGATGCG GTTGGCGCAT ATCACTGTGT CAACAGCCAG AGCCTTCCTC      1572
CATGTCTCAA CCAACACTCT CCAAGCTGAA TTCTCAGGCT GAACTCACTG      1622
TCACCTGTGA AGTAAACCCC GGCAGACCTG GAAGATTGGT GGTAGGATTG      1672
TGGAGGTTGC AGGGAGCATG CTCAGTGGGC ACTAGTTGCC TGCTGGGTAC      1722
CAGGAGATGC TTGTGCCCTG AGGTATCTTT AAGAACTATC ACGGAATTGG      1772
ACTGGGAGCT CAGGAGAGAG CTTGGTAGAC TGGCAGTGTC AGTGAAACAG      1822
TTATTTAGCC AAGAACAACA TTCCTGGGGC TGGGGACAGT GGCTCGGTGA      1872
AACCAACCTG GAACATGGGA GGTTGTAAGT TCG                        1905
```

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1214 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
ATG GCC CTG GGA AGA TGC ATT GCG GAA GGT TGG ACC TTG GAG       42
Met Ala Leu Gly Arg Cys Ile Ala Glu Gly Trp Thr Leu Glu
                  5                  10
AGA GTG GCG GTG AAA CAG GTC TCC TGG TTC CTG ATC TAC AGC       84
Arg Val Ala Val Lys Gln Val Ser Trp Phe Leu Ile Tyr Ser
15                  20                  25
TGG GTC TGC TCT GGA GTC TGC CGG GGA GTC TCG GTC CCA GAG      126
Trp Val Cys Ser Gly Val Cys Arg Gly Val Ser Val Pro Glu
     30                  35                  40
CAA GGA GGA GGA GGG CAG AAG GCT GGA GCA TTC ACC TGT CTC      168
Gln Gly Gly Gly Gly Gln Lys Ala Gly Ala Phe Thr Cys Leu
         45                  50                  55
AGC AAC AGT ATT TAC AGG ATC GAC TGC CAC TGG TCG GCT CCA      210
Ser Asn Ser Ile Try Arg Ile Asp Cys His Trp Ser Ala Pro
             60                  65                  70
```

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GAG CTG GGC CAG GAA TCC AGG GCC TGG CTC CTC TTT ACC AGT      252
Glu Leu Gly Gln Glu Ser Arg Ala Trp Leu Leu Phe Thr Ser
                 75                  80
AAC CAG GTG ACT GAA ATC AAA CAC AAA TGC ACC TTC TGG GAC      294
Asn Gln Val Thr Glu Ile Lys His Lys Cys Thr Phe Trp Asp
 85                  90                  95
AGT ATG TGT ACC CTG GTG CTG CCT AAA GAG GAG GTG TTC TTA      336
Ser Met Cys Thr Leu Val Leu Pro Phe Glu Glu Val Phe Leu
    100                 105                 110
CCT TTT GAC AAC TTC ACC ATC ACA CTT CAC CGC TGC ATC ATG      378
Pro Phe Asp Asn Phe Thr Ile Thr Leu His Arg Cys Ile Met
        115                 120                 125
GGA CAA GAA CAG GTC AGC CTG GTG GAC TCA CAG TAC CTG CCC      420
Gly Gln Glu Gln Val Ser Leu Val Asp Ser Gln Tyr Leu Pro
            130                 135                 140
AGG AGA CAC ATC AAG TTG GAC CCA CCC TCT GAT CTG CAG AGC      462
Arg Arg His Ile Lys Leu Asp Pro Pro Ser Asp Leu Gln Ser
        145                 150
AAT GTC AGC TCT GGG CGT TGT GTC CTG ACC TGG GGT ATC AAT      504
Asn Val Ser Ser Gly Arg Cys Val Leu Thr Trp Gly Ile Asn
155                 160                 165
CTT GCC CTG GAG CCA TTG ATC ACA TCC CTC AGC TAC GAG CTG      546
Leu Ala Leu Glu Pro Leu Ile Thr Ser Leu Ser Tyr Glu Leu
    170                 175                 180
GCC TTC AAG AGG CAG GAA GAG GCC TGG GAG CAG GCC CGG CAC      588
Ala Phe Lys Arg Gln Glu Glu Ala Trp Glu Ala Arg His Lys
        185                 190                 195
AAG GAC CGT ATC GTT GGA GTG ACC TGG CTC ATC CTT GAA GCC      630
Lys Asp Arg Ile Val Gly Val Thr Trp Leu Ile Leu Glu Ala
            200                 205                 210
GTC GAA CTG AAT CCT GAA AAA AGA ATG TGA                      660
Val Glu Leu Asn Pro Glu Lys Arg Met
        215

CAAGCAGCCT GGTCTGTTCT TCCACCCCTA AAGGGCTGGC CTGGGCCCAG       710
GGACACTGAT GAGACAACAT TGGTGAAGTG TCCCTTTTCA GTGCCTTTCC       760
CATTAAGACC AGAAGGGACG CTTTTGACTG CAGGCTGTGG GTGGCTGGGT       810
ACGGAGGGAA TGATGGAGCT TTGAGCAGGT GGGGTTGTCC ATCTTTGAGC       860
TTTTGGGTTC CAAGATCAGC TGGAAGGAGT CTCACCGACT GATTCAAAGA       910
AGTCTTACCC ATCTGTGATA TTTTCTTTCC TGGTGCCGTG ATAAAACACC       960
GTGACCAAAA ATGACTTACA AAAGGAAGAG TTGGCTTGGT TTAAGGTTCC      1010
AGAGGTGTGG AGACATGGCA GCCAGCGGCA CACATGGCAG TGAGGACAGG      1060
AAGCTGAGAG CTCACATCTC AACCAAAAGT TGAGTGAACT GAAAGTACTA      1110
TCCCCTCCCC CACCCCAACT CCAGCAAGGC TCCACCCCCC TGAAGGTTCC      1160
ATGCCTCCCT AAACAGCTCG GCCAAATAGA GACCAAGTGT TCAAATAAAA      1210
AAAA                                                       1214
```

(2) INFORMATION FOR SEQ ID NO: 4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1947 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
AGCAGCTCTG TAATGCGCTT GTGGTTTCAG ATGTGGGCGG CCTGTGTGAA          50
CCTGTCGTGC AAAGCTCACG TCACCAACTG CTGCAGTTAT CTCCTGAATC         100
AGGCTGAGGG TCTTTGCTGT GCACCCAGAG ATAGTTGGGT GACAAATCAC         150
CTCCAGGTTG GGGATGCCTC AGACTTGTG                                179
ATG GGA CTG GGC AGA TGC ATC TGG GAA GGC TGG ACC TTG GAG        221
Met Gly Leu Gly Arg Cys Ile Trp Glu Gly Trp Thr Leu Glu
                  5                  10
AGT GAG GCC CTG AGG CGA GAC ATG GGC ACC TGG CTC CTG GCC        263
Ser Glu Ala Leu Arg Arg Asp Met Gly Thr Trp Leu Leu Ala
 15                  20                  25
TGC ATC TGC ATC TGC ACC TGT GTC TGC TTG GGA GTC TCT GTC        305
Cys Ile Cys Ile Cys Thr Cys Val Cys Leu Gly Val Ser Val
     30                  35                  40
ACA GGG GAA GGA CAA GGG CCA AGG TCT AGA ACC TTC ACC TGC        347
Thr Gly Glu Gly Gln Gly Pro Arg Ser Arg Thr Phe Thr Cys
         45                  50                  55
CTC ACC AAC AAC ATT CTC AGG ATC GAT TGC CAC TGG TCT GCC        389
Leu Thr Asn Asn Ile Leu Arg Ile Asp Cys His Trp Ser Ala
             60                  65                  70
CCA GAG CTG GGA CAG GGC TCC AGC CCC TGG CTC CTC TTC ACC        431
Pro Glu Leu Gly Gln Gly Ser Ser Pro Trp Leu Leu Phe Thr
                 75                  80
AGC AAC CAG GCT CCT GGC GGC ACA CAT AAG TGC ATC TTG CGG        473
Ser Asn Gln Ala Pro Gly Gly Thr His Lys Cys Ile Leu Arg
 85                  90                  95
GGC AGT GAG TGC ACC GTC GTG CTG CCA CCT GAG GCA GTG CTC        515
Gly Ser Glu Cys Thr Val Val Leu Pro Pro Glu Ala Val Leu
    100                 105                 110
GTG CCA TCT GAC AAT TTC ACC ATC ACT TTC CAC CAC TGC ATG        557
Val Pro Ser Asp Asn Phe Thr Ile Thr Phe His His Cys Met
        115                 120                 125
TCT GGG AGG GAG CAG GTC AGC CTG GTG GAC CCG GAG TAC CTG        599
Ser Gly Arg Glu Gln Val Ser Leu Val Asp Pro Glu Tyr Leu
            130                 135                 140
CCC CGG AGA CAC GTT AAG CTG GAC CCG CCC TCT GAC TTG CAG        641
Pro Arg Arg His Val Lys Leu Asp Pro Pro Ser Asp Leu Gln
                145                 150
AGC AAC ATC AGT TCT GGC CAC TGC ATC CTG ACC TGG AGC ATC        683
Ser Asn Ile Ser Ser Gly His Cys Ile Leu Thr Trp Ser Ile
155                 160                 165
AGT CCT GCC TTG GAG CCA ATG ACC ACA CTT CTC AGC TAT GAG        725
Ser Pro Ala Leu Glu Pro Met Thr Thr Leu Leu Ser Tyr Glu
    170                 175                 180
```

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CTG GCC TTC AAG AAG CAG GAA GAG GCC TGG GAG CAG GCC CAG      767
Leu Ala Phe Lys Lys Gln Glu Glu Ala Trp Glu Gln Ala Gln
        185                 190                 195
CAC AGG GAT CAC ATT GTC GGG GTG ACC TGG CTT ATA CTT GAA      809
His Arg Asp His Ile Val Gly Val Thr Trp Leu Ile Leu Glu
            200                 205                 210
GCC TTT GAG CTG GAC CCT GGC TTT ATC CAT GAG GCC AGG CTG      851
Ala Phe Glu Val Asp Pro Gly Phe Ile His Glu Ala Arg Leu
                215                 220
CGT GTC CAG ATG GCC ACA CTG GAG GAT GAT GTG GTA GAG GAG      893
Arg Val Gln Met Ala Thr Leu Glu Asp Asp Val Val Glu Glu
225                 230                 235
GAG CGT TAT ACA GGC CAG TGG AGT GAG TGG AGC CAG CCT GTG      935
Glu Arg Tyr Thr Gly Gln Trp Ser Glu Trp Ser Gln Pro Val
    240                 245                 250
TGC TTC CAG GCT CCC CAG AGA CAA GGC CCT CTG ATC CCA CCC      977
Cys Phe Gln Ala Pro Gln Arg Gln Gly Pro Leu Ile Pro Pro
        255                 260                 265
TGG GGG TGG CCA GGC AAC ACC CTT GTT GCT GTG TCC ATC TTT     1019
Trp Gly Trp Pro Gly Asn Thr Leu Val Ala Val Ser Ile Phe
            270                 275                 280
CTC CTG CTG ACT GGC CCG ACC TAC CTC CTG TTC AAG CTG TCG     1061
Leu Leu Leu Thr Gly Pro Thr Tyr Leu Leu Phe Lys Leu Ser
                285                 290
CCC AGG GTG AAG AGA ATC TTC TAC CAG AAC GTG CCC TCT CCA     1103
Pro Arg Val Lys Arg Ile Phe Tyr Gln Asn Val Pro Ser Pro
295                 300                 305
GCG ATG TTC TTC CAG CCC CTC TAC AGT GTA CAC AAT GGG AAC     1145
Ala Met Phe Phe Gln Pro Leu Tyr Ser Val His Asn Gly Asn
    310                 315                 320
TTC CAG ACT TGG ATG GGG GCC CAC AGG GCC GGT GTG CTG TTG     1187
Phe Gln Thr Trp Met Gly Ala His Arg Ala Gly Val Leu Leu
        325                 330                 335
AGC CAG GAC TGT GCT GGC ACC CCA CAG GGA GCC TTG GAG CCC     1229
Ser Gln Asp Cys Ala Gly Thr Pro Gln Gly Ala Leu Glu Pro
            340                 345                 350
TGC GTC CAG GAG GCC ACT GCA CTG CTC ACT TGT GGC CCA GCG     1271
Cys Val Gln Glu Ala Thr Ala Leu Leu Thr Cys Gly Pro Ala
                355                 360
CGT CCT TGG AAA TCT GTG GCC CTG GAG GAG GAA CAG GAG GGC     1313
Arg Pro Trp Lys Ser Val Ala Leu Glu Glu Glu Gln Glu Gly
365                 370                 375
CCT GGG ACC AGG CTC CCG GGG AAC CTG AGC TCA GAG GAT GTG     1355
Pro Gly Thr Arg Leu Pro Gly Asn Leu Ser Ser Glu Asp Val
    380                 385                 390
CTG CCA GCA GGG TGT ACG GAG TGG AGG GTA CAG ACG CTT GCC     1397
Leu Pro Ala Gly Cys Thr Glu Trp Arg Val Gln Thr Leu Ala
        395                 400                 405
TAT CTG CCA CAG GAG GAC TGG GCC CCC ACG TCC CTG ACT AGG     1439
Tyr Leu Pro Gln Glu Asp Trp Ala Pro Thr Ser Leu Thr Arg
            410                 415                 420
CCG GCT CCC CCA GAC TCA GAG GGC AGC AGG AGC AGC AGC AGC     1481
Pro Ala Pro Pro Asp Ser Glu Gly Ser Arg Ser Ser Ser Ser
                425                 430
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AGC AGC AGC AGC AGC AAC AAC AAC AAC TAC TGT GCC TTG GGC     1523
Ser Ser Ser Ser Ser Asn Asn Asn Asn Tyr Cys Ala Leu Gly
435                 440                 445
TGC TAT GGG GGA TGG CAC CTC TCA GCC CTC CCA GGA AAC ACA     1565
Cys Tyr Gly Gly Trp His Leu Ser Ala Leu Pro Gly Asn Thr
    450                 455                 460
CAG AGC TCT GGG CCC ATC CCA GCC CTG GCC TGT GGC CTT TCT     1607
Gln Ser Ser Gly Pro Ile Pro Ala Leu Ala Cys Gly Leu Ser
        465                 470                 475
TGT GAC CAT CAG GGC CTG GAG ACC CAG CAA GGA GTT GCC TGG     1649
Cys Asp His Gln Gly Leu Glu Thr Gln Gln Gly Val Ala Trp
            480                 485                 490
GTG CTG GCT GGT CAC TGC CAG AGG CCT GGG CTG CAT GAG GAC     1691
Val Leu Ala Gly His Cys Gln Arg Pro Gly Leu His Glu Asp
                495                 500
CTC CAG GGC ATG TTG CTC CCT TCT GTC CTC AGC AAG GCT CGG     1733
Leu Gln Gly Met Leu Leu Pro Ser Val Leu Ser Lys Ala Arg
505                 510                 515
TCC TGG ACA TTC TAG                                        1748
Ser Trp Thr Phe
    520
GTCCCTGACT CGCCAGATGC ATCATGTCCA TTTTGGGAAA ATGGACTGAA      1798
GTTTCTGGAG CCCTTGTCTG AGACTGAACC TCCTGAGAAG GGGCCCCTAG      1848
CAGCGGTCAG AGGTCCTGTC TGGATGGAGG CTGGAGGCTC CCCCCTCAAC      1898
CCCTCTGCTC AGTGCCTGTG GGGAGCAGCC TCTACCCTCA GCATCCTGG       1947
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1683 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
ATG GGA CTG GGC AGA TGC ATC TGG GAA GGC TGG ACC TTG GAG      42
Met Gly Leu Gly Arg Cys Ile Trp Glu Gly Trp Thr Leu Glu
                5                   10
AGT GAG GCC CTG AGG CGA GAC ATG GGC ACC TGG CTC CTG GCC      84
Ser Glu Ala Leu Arg Arg Asp Met Gly Thr Trp Leu Leu Ala
 15                  20                  25
TGC ATC TGC ATC TGC ACC TGT GTC TGC TTG GGA GTC TCT GTC     126
Cys Ile Cys Ile Cys Thr Cys Val Cys Leu Gly Val Ser Val
     30                  35                  40
ACA GGG GAA GGA CAA GGG CCA AGG TCT AGA ACC TTC ACC TGC     168
Thr Gly Glu Gly Gln Gly Pro Arg Ser Arg Thr Phe Thr Cys
         45                  50                  55
CTC ACC AAC AAC ATT CTC AGG ATC GAT TGC CAC TGG TCT GCC     210
Leu Thr Asn Asn Ile Leu Arg Ile Asp Cys His Trp Ser Ala
             60                  65                  70
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CCA GAG CTG GGA CAG GGC TCC AGC CCC TGG CTC CTC TTC ACC        252
Pro Glu Leu Gly Gln Gly Ser Ser Pro Trp Leu Leu Phe Thr
                75                  80
AGC AAC CAG GCT CCT GGC GGC ACA CAT AAG TGC ATC TTG CGG        294
Ser Asn Gln Ala Pro Gly Gly Thr His Lys Cys Ile Leu Arg
 85                  90                  95
GGC AGT GAG TGC ACC GTC GTG CTG CCA CCT GAG GCA GTG CTC        336
Gly Ser Glu Cys Thr Val Val Leu Pro Pro Glu Ala Val Leu
    100                 105                 110
GTG CCA TCT GAC AAT TTC ACC ATC ACT TTC CAC CAC TGC ATG        378
Val Pro Ser Asp Asn Phe Thr Ile Thr Phe His His Cys Met
        115                 120                 125
TCT GGG AGG GAG CAG GTC AGC CTG GTG GAC CCG GAG TAC CTG        420
Ser Gly Arg Glu Gln Val Ser Leu Val Asp Pro Glu Tyr Leu
            130                 135                 140
CCC CGG AGA CAC GTT AAG CTG GAC CCG CCC TCT GAC TTG CAG        462
Pro Arg Arg His Val Lys Leu Asp Pro Pro Ser Asp Leu Gln
                145                 150
AGC AAC ATC AGT TCT GGC CAC TGC ATC CTG ACC TGG AGC ATC        504
Ser Asn Ile Ser Ser Gly His Cys Ile Leu Thr Trp Ser Ile
155                 160                 165
AGT CCT GCC TTG GAG CCA ATG ACC ACA CTT CTC AGC TAT GAG        546
Ser Pro Ala Leu Glu Pro Met Thr Thr Leu Leu Ser Tyr Glu
    170                 175                 180
CTG GCC TTC AAG AAG CAG GAA GAG GCC TGG GAG CAG GCC CAG        588
Leu Ala Phe Lys Lys Gln Glu Glu Ala Trp Glu Gln Ala Gln
        185                 190                 195
CAC AGG GAT CAC ATT GTC GGG GTG ACC TGG CTT ATA CTT GAA        630
His Arg Asp His Ile Val Gly Val Thr Trp Leu Ile Leu Glu
            200                 205                 210
GCC TTT GAG CTG GAC CCT GGC TTT ATC CAT GAG GCC AGG CTG        672
Ala Phe Glu Val Asp Pro Gly Phe Ile His Glu Ala Arg Leu
                215                 220
CGT GTC CAG ATG GCC ACA CTG GAG GAT GAT GTG GTA GAG GAG        714
Arg Val Gln Met Ala Thr Leu Glu Asp Asp Val Val Glu Glu
225                 230                 235
GAG CGT TAT ACA GGC CAG TGG AGT GAG TGG AGC CAG CCT GTG        756
Glu Arg Tyr Thr Gly Gln Trp Ser Glu Trp Ser Gln Pro Val
    240                 245                 250
TGC TTC CAG GCT CCC CAG AGA CAA GGC CCT CTG ATC CCA CCC        798
Cys Phe Gln Ala Pro Gln Arg Gln Gly Pro Leu Ile Pro Pro
        255                 260                 265
TGG GGG TGG CCA GGC AAC ACC CTT GTT GCT GTG TCC ATC TTT        840
Trp Gly Trp Pro Gly Asn Thr Leu Val Ala Val Ser Ile Phe
            270                 275                 280
CTC CTG CTG ACT GGC CCG ACC TAC CTC CTG TTC AAG CTG TCG        882
Leu Leu Leu Thr Gly Pro Thr Tyr Leu Leu Phe Lys Leu Ser
                285                 290
CCC AGA CTT GGA TGG GGG CCC ACA GGG CCG GTG TGC TGT TGA        924
Pro Arg Leu Gly Trp Gly Pro Thr Gly Pro Val Cys Cys
295                 300                 305
GCCAGGACTG TGCTGGCACC CCACAGGGAG CCTTGGAGCC CTGCGTCCAG        974
GAGGCCACTG CACTGCTCAC TTGTGGCCCA GCGCGTCCTT GGAAATCTGT       1024
GGCCCTGGAG GAGGAACAGG AGGGCCCTGG GACCAGGCTC CCGGGGAACC       1074
TGAGCTCAGA GGATGTGCTG CCAGCAGGGT GTACGGAGTG GAGGGTACAG       1124
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ACGCTTGCCT ATCTGCCACA GGAGGACTGG GCCCCCACGT CCCTGACTAG        1174
GCCGGCTCCC CCAGACTCAG AGGGCAGCAG GAGCAGCAGC AGCAGCAGCA        1224
GCAGCAGCAA CAACAACAAC TACTGTGCCT TGGGCTGCTA TGGGGGATGG        1274
CACCTCTCAG CCCTCCCAGG AAACACACAG AGCTCTGGGC CCATCCCAGC        1324
CCTGGCCTGT GGCCTTTCTT GTGACCATCA GGGCCTGGAG ACCCAGCAAG        1374
GAGTTGCCTG GGTGCTGGCT GGTCACTGCC AGAGGCCTGG GCTGCATGAG        1424
GACCTCCAGG GCATGTTGCT CCCTTCTGTC CTCAGCAAGG CTCGGTCCTG        1474
GACATTCTAG GTCCCTGACT CGCCAGATGC ATCATGTCCA TTTTGGGAAA        1524
ATGGACTGAA GTTTCTGGAG CCCTTGTCTG AGACTGAACC TCCTGAGAAG        1574
GGGCCCCTAG CAGCGGTCAG AGGTCCTGTC TGGATGGAGG CTGGAGGCTC        1624
CCCCCTCAAC CCCTCTGCTC AGTGCCTGTG GGGAGCAGCC TCTACCCTCA        1674
GCATCCTGG                                                    1683
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1997 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

```
CCAGGTTGGG GATGCCTCAG ACTTGTGATG GGACTGGGCA GATGCATCTG         50
GGAAGGTCCT GGTGGTGACT CCAACCCTGC CCTCACATAT CCCAAGAGCA        100
GGCTGACTGC CTTCCCCATT CCCACCTTTC CAGTAACTGC TGCAAGAACG        150
GACAGACACT GCTGCAGAGA ACTTGCCACG GTGTTTC                     187
ATG CTG TGG CTG GTG GTT CCA GGC TGC ACG CTC CAT TCT AGG       229
Met Leu Trp Leu Val Val Pro Gly Cys Thr Leu His Ser Arg
                 5                  10
AAA GGG GCC CTC AGC CAG TCC CTT GCA GGC TGG ACC TTG GAG       271
Lys Gly Ala Leu Ser Gln Ser Leu Ala Gly Trp Thr Leu Glu
 15                  20                  25
AGT GAG GCC CTG AGG CGA GAC ATG GGC ACC TGG CTC CTG GCC       313
Ser Glu Ala Leu Arg Arg Asp Met Gly Thr Trp Leu Leu Ala
     30                  35                  40
TGC ATC TGC ATC TGC ACC TGT GTC TGC TTG GGA GTC TCT GTC       355
Cys Ile Cys Ile Cys Thr Cys Val Cys Leu Gly Val Ser Val
         45                  50                  55
ACA GGG GAA GGA CAA GGG CCA AGG TCT AGA ACC TTC ACC TGC       397
Thr Gly Glu Gly Gln Gly Pro Arg Ser Arg Thr Phe Thr Cys
             60                  65                  70
CTC ACC AAC AAC ATT CTC AGG ATC GAT TGC CAC TGG TCT GCC       439
Leu Thr Asn Asn Ile Leu Arg Ile Asp Cys His Trp Ser Ala
                 75                  80
CCA GAG CTG GGA CAG GGC TCC AGC CCC TGG CTC CTC TTC ACC       481
Pro Glu Leu Gly Gln Gly Ser Ser Pro Trp Leu Leu Phe Thr
 85                  90                  95
AGC AAC CAG GCT CCT GGC GGC ACA CAT AAG TGC ATC TTG CGG       523
Ser Asn Gln Ala Pro Gly Gly Thr His Lys Cys Ile Leu Arg
     100                 105                 110
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GGC AGT GAG TGC ACC GTC GTG CTG CCA CCT GAG GCA GTG CTC      565
Gly Ser Glu Cys Thr Val Val Leu Pro Pro Glu Ala Val Leu
        115                 120                 125
GTG CCA TCT GAC AAT TTC ACC ATC ACT TTC CAC CAC TGC ATG      607
Val Pro Ser Asp Asn Phe Thr Ile Thr Phe His His Cys Met
            130                 135                 140
TCT GGG AGG GAG CAG GTC AGC CTG GTG GAC CCG GAG TAC CTG      649
Ser Gly Arg Glu Gln Val Ser Leu Val Asp Pro Glu Tyr Leu
                145                 150
CCC CGG AGA CAC GTT AAG CTG GAC CCG CCC TCT GAC TTG CAG      691
Pro Arg Arg His Val Lys Leu Asp Pro Pro Ser Asp Leu Gln
155                 160                 165
AGC AAC ATC AGT TCT GGC CAC TGC ATC CTG ACC TGG AGC ATC      733
Ser Asn Ile Ser Ser Gly His Cys Ile Leu Thr Trp Ser Ile
    170                 175                 180
AGT CCT GCC TTG GAG CCA ATG ACC ACA CTT CTC AGC TAT GAG      775
Ser Pro Ala Leu Glu Pro Met Thr Thr Leu Leu Ser Tyr Glu
        185                 190                 195
CTG GCC TTC AAG AAG CAG GAA GAG GCC TGG GAG CAG GCC CAG      817
Leu Ala Phe Lys Lys Gln Glu Glu Ala Trp Glu Gln Ala Gln
            200                 205                 210
CAC AGG GAT CAC ATT GTC GGG GTG ACC TGG CTT ATA CTT GAA      859
His Arg Asp His Ile Val Glu Val Thr Trp Leu Ile Leu Glu
                215                 220
GCC TTT GAG CTG GAC CCT GGC TTT ATC CAT GAG GCC AGG CTG      901
Ala Phe Glu Leu Gln Pro Gly Phe Ile His Glu Ala Arg Leu
225                 230                 235
CGT GTC CAG ATG GCC ACA CTG GAG GAT GAT GTG GTA GAG GAG      943
Arg Val Gln Met Ala Thr Leu Gly Asp Asp Val Val Glu Glu
    240                 245                 250
GAG CGT TAT ACA GGC CAG TGG AGT GAG TGG AGC CAG CCT GTG      985
Glu Arg Tyr Thr Gly Gln Trp Ser Glu Trp Ser Gln Pro Val
        255                 260                 265
TGC TTC CAG GCT CCC CAG AGA CAA GGC CCT CTG ATC CCA CCC     1027
Cys Phe Gln Arg Pro Gln Arg Gln Gly Pro Leu Ile Pro Pro
            270                 275                 280
TGG GGG TGG CCA GGC AAC ACC CTT GTT GCT GTG TCC ATC TTT     1069
Trp Gly Trp Pro Gly Asn Thr Leu Val Ala Val Ser Ile Phe
                285                 290
CTC CTG CTG ACT GGC CCG ACC TAC CTC CTG TTC AAG CTG TCG     1111
Leu Leu Leu Thr Gly Pro Thr Tyr Leu Leu Phe Lys Leu Ser
295                 300                 305
CCC AGG GTG AAG AGA ATC TTC TAC CAG AAC GTG CCC TCT CCA     1153
Pro Arg Val Lys Arg Ile Phe Tyr Gln Asn Val Pro Ser Pro
    310                 315                 320
GCG ATG TTC TTC CAG CCC CTC TAC AGT GTA CAC AAT GGG AAC     1195
Ala Met Phe Phe Gln Pro Leu Tyr Ser Val His Asn Gly Asn
        325                 330                 335
TTC CAG ACT TGG ATG GGG GCC CAC AGG GCC GGT GTG CTG TTG     1237
Phe Gln Thr Trp Met Gly Ala His Arg Ala Gly Val Leu Leu
            340                 345                 350
AGC CAG GAC TGT GCT GGC ACC CCA CAG GGA GCC TTG GAG CCC     1279
Ser Gln Asp Cys Ala Gly Thr Pro Gln Gly Ala Leu Gly Pro
                355                 360
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TGC GTC CAG GAG GCC ACT GCA CTG CTC ACT TGT GGC CCA GCG      1321
Cys Val Gln Glu Ala Thr Ala Leu Leu Thr Cys Gly Pro Ala
365                 370                 375
CGT CCT TGG AAA TCT GTG GCC CTG GAG GAG GAA CAG GAG GGC      1363
Arg Pro Trp Lys Ser Val Ala Leu Gly Glu Glu Gln Glu Gly
    380                 385                 390
CCT GGG ACC AGG CTC CCG GGG AAC CTG AGC TCA GAG GAT GTG      1405
Pro Gly Thr Arg Leu Pro Gly Asn Leu Ser Ser Glu Asp Val
        395                 400                 405
CTG CCA GCA GGG TGT ACG GAG TGG AGG GTA CAG ACG CTT GCC      1447
Leu Pro Ala Gly Cys Thr Glu Trp Arg Val Gln Thr Leu Ala
            410                 415                 420
TAT CTG CCA CAG GAG GAC TGG GCC CCC ACG TCC CTG ACT AGG      1489
Tyr Leu Pro Gln Glu Asp Trp Ala Pro Thr Ser Leu Thr Arg
                425                 430
CCG GCT CCC CCA GAC TCA GAG GGC AGC AGG AGC AGC AGC AGC      1531
Pro Ala Pro Pro Asp Ser Glu Gly Ser Arg Ser Ser Ser Ser
435                 440                 445
AGC AGC AGC AGC AGC AAC AAC AAC AAC TAC TGT GCC TTG GGC      1573
Ser Ser Ser Ser Ser Asn Asn Asn Asn Tyr Cys Ala Leu Gly
    450                 455                 460
TGC TAT GGG GGA TGG CAC CTC TCA GCC CTC CCA GGA AAC ACA      1615
Cys Tyr Gly Gly Trp His Leu Ser Ala Leu Pro Gly Asn Thr
        465                 470                 475
CAG AGC TCT GGG CCC ATC CCA GCC CTG GCC TGT GGC CTT TCT      1657
Gln Ser Ser Gly Pro Ile Pro Ala Leu Ala Cys Gly Leu Ser
            480                 485                 490
TGT GAC CAT CAG GGC CTG GAG ACC CAG CAA GGA GTT GCC TGG      1699
Cys Asp His Gln Gly Leu Glu Thr Gln Gln Gly Val Ala Trp
                495                 500
GTG CTG GCT GGT CAC TGC CAG AGG CCT GGG CTG CAT GAG GAC      1741
Val Leu Ala Gly His Cys Gln Arg Pro Gly Leu His Glu Asp
505                 510                 515
CTC CAG GGC ATG TTG CTC CCT TCT GTC CTC AGC AAG GCT CGG      1783
Leu Gln Gly Met Leu Leu Pro Ser Val Leu Ser Lys Ala Arg
    520                 525                 530
TCC TGG ACA TTC TAG                                         1798
Ser Trp Thr Phe
        535
GTCCCTGACT CGCCAGATGC ATCATGTCCA TTTTGGGAAA ATGGACTGAA      1848
GTTTCTGGAG CCCTTGTCTG AGACTGAACC TCCTGAGAAG GGGCCCCTAG      1898
CAGCGGTCAG AGGTCCTGTC TGGATGGAGG CTGGAGGCTC CCCCCTCAAC      1948
CCCTCTGCTC AGTGCCTGTG GGGAGCAGCC TCTACCCTCA GCATCCTGG       1997
```

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Isolated nucleic acid molecule which encodes or is complementary to a nucleic acid molecule which encodes an interleukin-9 receptor which shows at least 53% homology to any one of SEQ ID Nos. 1-6.

2. An isolated nucleic acid molecule which encodes an interleukin-9 receptor and which hybridises to the nucleotide sequence set forth in SEQ ID No. 1 or a complementary nucleotide sequence thereof in 2 x SSC, 0.1% (w/v) SDS at 55°C.

3. An isolated nucleic acid molecule according to claim 2, further comprising a sequence of nucleotides which is at least 53% identical to any one of SEQ ID Nos. 1-6.

4. The isolated nucleic acid molecule of any one of claims 1 to 3, wherein said sequence is cDNA.

5. The isolated nucleic acid molecule of any one of claims 1 to 3, wherein said sequence codes for human interleukin-9 receptor.

6. The isolated nucleic acid molecule of any one of claims 1 to 3, wherein said sequence codes for murine interleukin-9 receptor.

7. The isolated nucleic acid molecule of any one of claims 1 to 3, selected from the group consisting of: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6.

8. The isolated nucleic acid molecule of any one of claims 1 to 3, wherein said sequence is genomic DNA.

9. Vector comprising the isolated nucleic acid molecule of any one of claims 1 to 3, operably linked to a promoter.

10. The vector of claim 9, further comprising a marker sequence.

11. The vector of claim 10, wherein said marker sequence is a resistance marker.

12. The vector of claim 9, wherein said vector is a plasmid.

13. Microorganism transfected with the nucleic acid molecule of any one of claims 1 to 3.

14. The microorganism of claim 13, wherein said microorganism is Escherichia coli.

15. Cell line transfected with the nucleic acid molecule of any one of claims 1 to 3.

16. The cell line of claim 15, wherein said cell line is a eukaryotic cell line.

17. The cell line of claim 16, wherein said eukaryotic cell line is a CHO cell line.

18. The cell line of claim 16, wherein said eukaryotic cell line is a COS cell line.

19. The cell line of claim 16, wherein said eukaryotic cell line is a yeast cell line.

20. The cell line of claim 16, wherein said cell line is an insect cell line.

21. The cell line of claim 20, wherein said cell line is Spodoptera frugiperda.

22. The cell line of claim 20, wherein said nucleic acid molecule is incorporated into an expression vector.

23. The cell line of claim 22, wherein said expression vector is a baculovirus vector.

24. Process for producing an antibody which specifically binds to interleukin 9 receptor comprising immunizing a subject animal with the cell line of claim 16 under conditions favoring generation of antibodies which specifically bind to interleukin 9 receptor and isolating said antibodies from said animal.

25. Purified antibody produced by the process of claim 24.

26. Method for inhibiting effect of interleukin 9 on a subject comprising administering an amount of the antibody of claim 25 sufficient to inhibit binding of interleukin-9 to cells expressing interleukin 9 receptor, to a subject in need of inhibition of interleukin 9.

27. Method for determining a substance which binds to interleukin 9 receptor comprising contacting the cell line of claim 16 with a substance to be tested and determining binding or lack thereof to said cell line.

28. Method for determining an interleukin 9 receptor agonist comprising contacting the cell line of claim 16 with a substance to be tested and determining the affect thereon, wherein an effect characteristic of interleukin 9 is indicative of an interleukin 9 receptor agonist.

29. Method for determining an interleukin 9 antagonist comprising contacting the cell line of claim 16 with interleukin 9 receptor and a substance to be tested and determining if said substance interferes with effect of interleukin-9 on said cell line, wherein interference therewith is indicative of an antagonist for interleukin-9.

30. Method for producing an antibody which specifically binds to an interleukin 9 receptor comprising immunizing a non-human animal with an immunogenically effective form of the interleukin 9 receptor set forth in any one of SEQ ID Nos. 1-6 or an interleukin 9 receptor which is at least 53% identical thereto in an amount sufficient to generate an antibody specific for interleukin 9 receptor, and purifying said antibody.

DATED the SIXTH day of MAY 1996

LUDWIG INSTITUTE FOR CANCER RESEARCH

by its Patent Attorneys
DAVIES COLLISON CAVE

FIG. 1

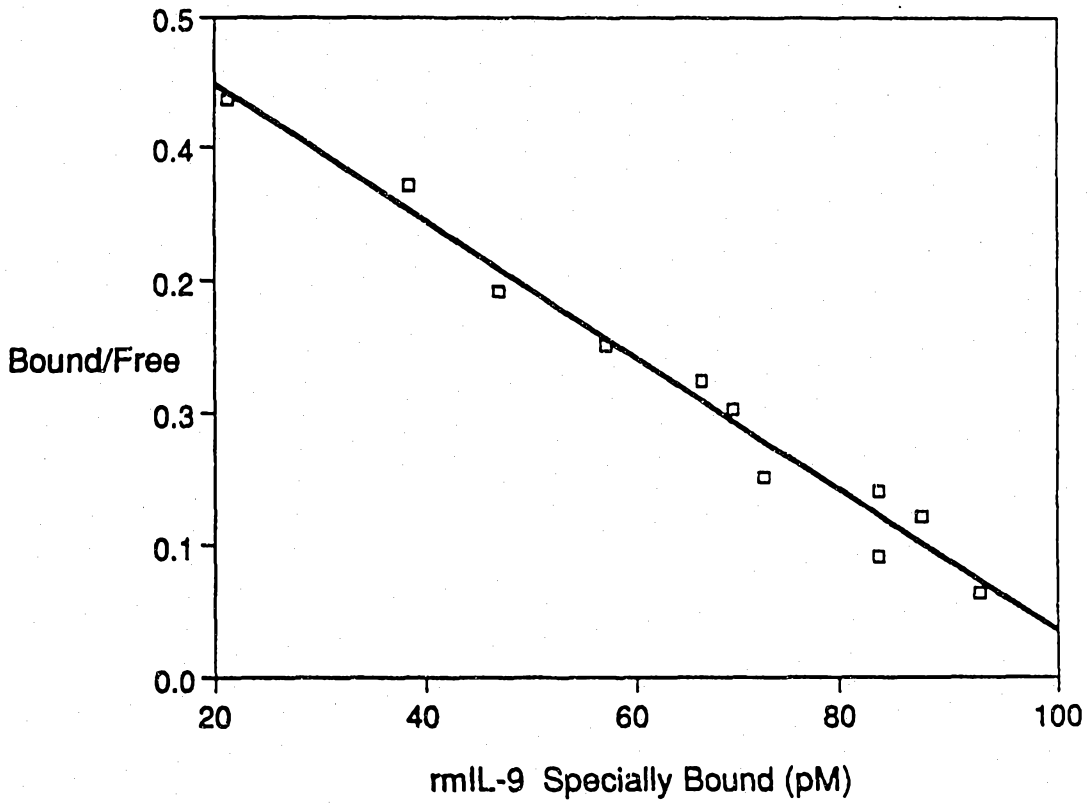
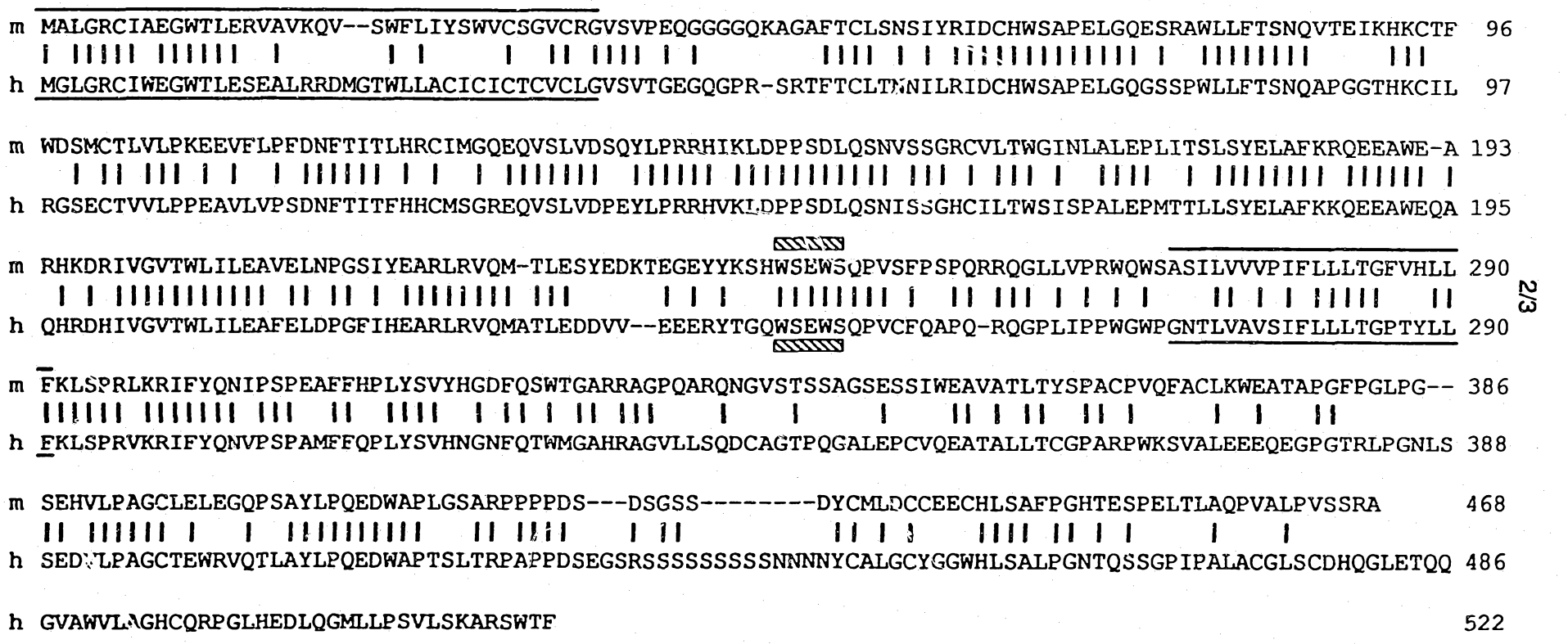

0.5
0.4
0.2
0.3
0.1
0.0
Bound/Free
20
40
60
80
100
rmIL-9 Specially Bound (pM)

FIG. 2



SUBSTITUTE SHEET

FIG. 3A

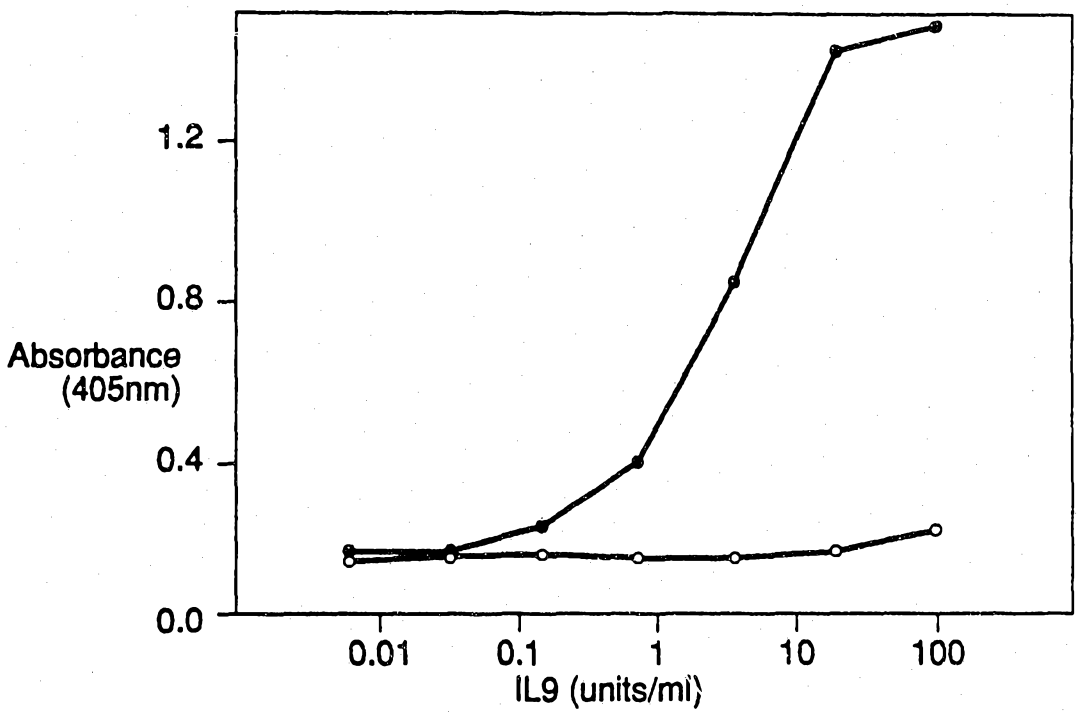
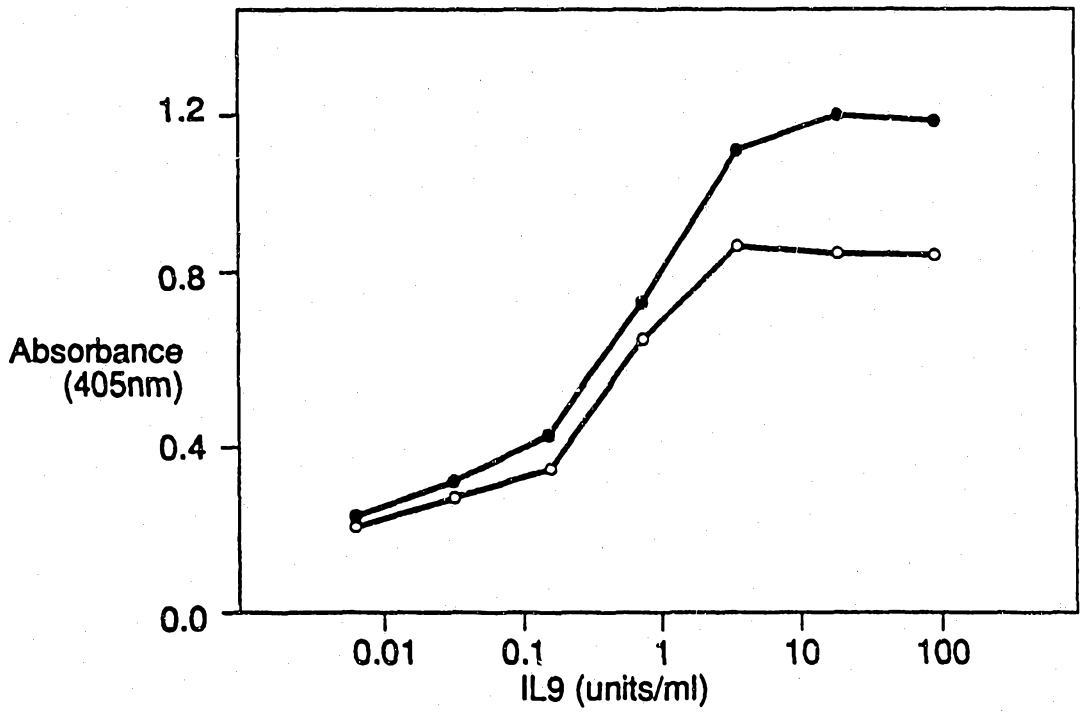

1.2
0.8
0.4
0.0
Absorbance
(405nm)
0.01
0.1
1
10
100
IL9 (units/ml)

FIG. 3B


1.2
0.8
0.4
0.0
Absorbance
(405nm)
0.01
0.1
1
10
100
IL9 (units/ml)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01720

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
US CL :536/23.5; 435/7.2, 240.1, 320.1; 530/389.2; 424/85.8
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.5; 435/7.2; 240.1, 320.1; 530/389.2; 424/85.8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Sequence search of Sequence ID No's. 1-6; and antibodies to IL-9R

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US, A, 5,116,951 (Druez et al), 26 May 1992, see all.	1-29
X	The Journal of Immunology, Vol. 145, Number 8, issued 15 October 1990, Druez et al, "Function and Biochemical Characterization of Mouse P40/IL-9 Receptors," pages 2494-2499, see all.	1-29
X	US, A, 4,675,285, (Clark et al), 23 June 1987, see all.	1-22
X	US, A, 5,030,576, (Dull et al), 09 July 1991, see all.	26-28

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 26 MAY 1993	Date of mailing of the international search report 08 JUN 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer GARNETTE D. DRAPER, PRIMARY EXAMINER Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01720

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Clin. Chem., Vol. 27, No. 11, issued 1981, Sevier et al, "Monoclonal Antibodies in Clinical Immunology," pages 1797-1806, see all.	23-25, 29
X	US, A, 4,707,443, (Nelson et al), 17 November 1987, see all.	23-25, 29
X	US, A, 4,636,463, (Altman et al), 13 January 1987, see all.	23-25,29
A,P	US, A, 5,132,109, (Dugas et al), 21 July 1992, see all.	1-29
A	Blood Reviews, Vol. 5, issued 1991, Kaczmarski et al, "The Cytokine Receptor Superfamily", pages 193-203, see all.	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01720

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(Telephone Practice)
Group I, claims 1-22 and 26-28, drawn to nucleic acids (NA), vectors, cell lines, and methods of receptor binding, and agonist/antagonist, classified in classes 536 and 435, subclasses 23.5, and 7.2, 240.1
Group II, claims 23-24 and 29, drawn to antibodies and a process of preparing such, classified in class 530, subclass 389.2
Group III, claim 25, drawn to a method of inhibiting IL-9 activity with anti-IL-9(R), classified in class 424, subclass 85.8

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01720

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

C07H 15/12; C12N 5/00, 15/70; C07K 15/28; A61K 39/395; C12Q 1/00