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Datasheet for the decision of 12 December 2008

Case Number: T 1540/07 - 3.3.08

Application Number: 99912330.0

Publication Number: 1093457

IPC: C07H 21/04

Language of the proceedings: EN

Title of invention:
Cytokine receptor common gamma chain like

Applicant:
Human Genome Sciences

Headword:
Cytokine receptor/HUMAN GENOME SCIENCES

Relevant legal provisions:
EPC Art. 56, 57

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request - inventive step (yes)"
"Main request - industrial application (yes)"

Decisions cited:
T 0898/05

Catchword:
-

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Case Number: T 1540/07 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 12 December 2008

Appellant: Human Genome Sciences
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 13 February 2007 refusing European application No. 99912330.0 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
C. Heath

Summary of Facts and Submissions

I. European patent application no. 99 912 330, published under the International publication number WO 99/47538 (referred to in this decision as "*the application as filed*"), was refused by the examining division on the basis of Article 97(1) EPC 1973. The examining division considered that the main request filed during the oral proceedings on 8 November 2006 did not fulfil the requirements of Articles 56, 83 and 84 EPC.

II. The applicant (appellant) filed a notice of appeal and paid the appeal fee. With the statement setting out the grounds of appeal, the appellant filed auxiliary requests I and II and maintained, as a main request, the request refused by the examining division.

III. The examining division did not rectify its decision and the appeal was remitted to the boards of appeal (Article 109 EPC 1973).

IV. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) accompanying the summons to oral proceedings, the board indicated its preliminary, non-binding opinion on substantive matters, in particular with reference to Article 57 EPC.

V. In a letter dated 12 November 2008, the appellant replied to the board's communication and filed thirty new documents (D33 to D62), including a declaration of Dr. Gerard Zurawski signed on 11 November 2008 (D58). A new main request and auxiliary requests I and II were also filed in replacement of the other requests on file.

VI. At the oral proceedings that took place on 12 December 2008, the appellant filed a new main request and withdrew all previous requests on file.

VII. Claim 1 of the **main request** read as follows:

"A polynucleotide comprising a nucleic acid sequence selected from the group consisting of:

(a) a nucleic acid sequence encoding the full-length Cytokine Receptor Common Gamma Chain Like polypeptide comprising amino acid residues +1 to +371 as set forth in SEQ ID NO: 2;

(b) a nucleic acid sequence encoding the mature Cytokine Receptor Common Gamma Chain Like polypeptide comprising amino acid residues +23 to +371 as set forth in SEQ ID NO: 2;

(c) an allelic variant of the nucleic acid sequence defined in (a) or (b); and

(d) the polynucleotide complementary to the nucleic acid sequence of any one of (a) to (c)."

Claims 2 to 8 concerned embodiments of claim 1. Claims 9 to 10 and claim 11 were directed, respectively, to vectors comprising the polynucleotides of claims 1 to 8 and to a method of producing a host cell comprising these polynucleotides or vectors. Host cells were the subject-matter of claims 12 to 13. Claim 14 related to a method of producing a polypeptide comprising culturing the host cells of claims 12 or 13. Claims 15

to 22 and claims 23 to 27 were directed, respectively, to a polypeptide encoded by the polynucleotides of claims 1 to 8 and to antibodies specifically recognizing these polypeptides. Claim 28 related to an anti-idiotypic antibody to the antibody of claim 23. Claim 29 was directed to a polynucleotide which specifically hybridized under stringent conditions to a sequence of claim 1 and which did not consist of a nucleotide sequence indicated in the claim. Claim 30 related to an antisense nucleic acid or to a ribozyme and claim 31 was directed to a composition comprising the claimed polynucleotides, polypeptides, antisense, ribozyme or antibodies. A pharmaceutical composition comprising the same components as in claim 31, except for the antibodies, was the subject-matter of claim 32.

VIII. The main request differed from the request refused by the examining division in the wording of claim 1(c) which in the latter request read: "*a nucleic acid sequence encoding a polypeptide having an amino acid sequence at least 90% identical to the polypeptide defined in (a) or (b), wherein said nucleic acid sequence encodes a polypeptide that increases the proliferation and/or differentiation of cells*". Claim 1(d) of the request refused by the examining division read "*a polynucleotide...*" instead of "*the polynucleotide...*" found in the main request before the board. Other amendments were also made in the request refused by the examining division in order to overcome objections raised under Articles 123(2) and 84 EPC.

IX. The following documents are cited in this decision:

D4: T. Takeshita et al., Science, 1992, Vol. 257, pages 379 to 382;

D16: K. Fujio et al., Blood, 1 April 2000, Vol. 95, pages 2204 to 2211;

D20: J.F. Bazan, Proc. Natl. Acad. Sci. USA, 1990, Vol. 87, pages 6934 to 6938;

D46: I. Rochman et al., J. Immunol., 2007, Vol. 178, pages 6720 to 6724.

X. The reasons of the examining division for the refusal may be summarized as follows:

Article 56 EPC

Document D20 disclosed the cytokine receptor family and the motifs shared by its members. Although the homology between different members of this family was low, there were conserved domains that provided the skilled person with means (probes) to isolate new members of this family. The "cytokine receptor common gamma chain-like" (CRCGCL) sequence disclosed in the application was identified by computer-assisted methods as sharing partial homology with members of this cytokine receptor family. The closest structural homologous protein, with a 25% sequence identity, was the human interleukin-2 receptor gamma chain (hIL-2Rγ chain) disclosed in document D4. The appellant, however, did not attempt to isolate new cytokine receptors but only to perform a general screening in activated T-cells for identifying sequences of potential interest. Thus, the starting point for inventive step was a huge collection of

sequences, namely the cDNAs contained in a library of activated T-cells. Since the screening of cDNA libraries to identify potential sequences of interest was common general knowledge in the art (random sequence selection from a library and use of known analytical methods to assign putative functions) and the application failed to disclose any purposeful method for selecting the CRCGCL sequence and it did not disclose any functional data on the encoded CRCGCL protein, the technical problem to be solved was the provision of a further sequence of potential interest. The disclosed SEQ ID NOs: 1 and 2, which were found to contain elements typical of a cytokine receptor by standard sequence analysis algorithms (BLAST), solved this technical problem.

In the absence of a surprising or unexpected effect, the mere provision of a new cDNA sequence was not inventive, since only obvious steps were used in its selection and in the methods used for its characterization. The CRCGCL sequence disclosed in the application represented an arbitrary selection from all possible potential sequences that could be provided. The minimal characterization shown in the application (sequence and expression pattern) was not enough to elucidate a physiological function or involvement in pathologies nor did it provide any surprising effect. It was not inventive to speculate on potential applications of a sequence only on the basis of its expression pattern or of its putative functional assignment, since such speculations were obvious and they were made only on the basis of information available in the art.

Articles 83 and 84 EPC

The objections raised under these articles related to the functional feature present in claim 1(c) of the request refused by the examining division (cf. point VIII *supra*).

XI. The appellant's submissions may be summarized as follows:

Article 56 EPC

The CRCGL sequence disclosed in the application encoded a new member of the cytokine receptor family isolated from a library of activated T-cells and characterized by its cDNA expression pattern and the presence of conserved sequence motifs present in the members of this family. The closest homologous cytokine receptor, with a 25% sequence identity, was the hIL-2Rγ chain of document D4, the closest prior art document. Starting from this prior art, the technical problem to be solved was the provision of a further member of the cytokine receptor family or, alternatively, the provision of a marker specific for activated T-cells. There was evidence on file showing that the CRCGCL sequence solved both problems.

There was no suggestion in document D4 that a new cytokine receptor related to the IL-2Rγ chain could exist and no motivation was provided to look for such a receptor. Nor was this motivation derivable from other prior art on file, such as that disclosing two EST sequences, since these sequences did not provide sufficient alignment with predictive portions of the

CRCGCL sequence so as to indicate that they were members of the cytokine receptor family. On the contrary, they were identified as a sequence attaching loops of nuclear and mitochondrial DNA to underlying structures in cells and as a member of the family of tyrosine-kinase receptors. This prior art taught the skilled person away from the cytokine receptor family. Moreover, the authors of post-published document D16 were unable to use the DNA sequence encoding the mouse homolog of the CRCGCL sequence (39% sequence identity) as a probe to isolate the human CRCGCL homolog by low stringency hybridization. They were also unable to identify any human EST homolog to the mouse sequence by computer searching. Thus, traditional hybridization methods and computing searching of public databases did not result in the identification of the CRCGCL sequence disclosed in the application.

Northern blot analysis showed that the CRCGCL sequence was expressed in activated T-cells but not in T-cells at rest (Molt-4 cells, peripheral blood leukocytes). Based on this expression pattern, the application proposed to use the CRCGCL sequence, the encoded CRCGCL polypeptide and derived antibodies for identifying activated T-cells. There was no prior art on file from which the skilled person could have derived the use of the CRCGL sequence as a specific marker for activated T-cells allowing the skilled person to select these cells from the overall population of T-cells or from blood (leukocyte) cells.

Article 57 EPC

The CRCGCL sequence displayed the majority of the features set forth in the prior art for characterizing the members of the cytokine receptor family. The limited number of features which were not present in the CRCGCL sequence were irrelevant for its assignment to this family and the differences shown in the sequence were known deviations that were found in other members of this family and which were not sufficient to impede the assignment. Thus, the CRCGCL sequence was plausibly disclosed in the application as a cytokine receptor and there was no evidence on file showing that this CRCGCL sequence contained an element that would contradict the family assignment. The skilled person would have found plausible that the CRCGCL sequence was a new member of the cytokine receptor family, implying thereby corresponding diagnostic and therapeutic applications, i.e. possessing the activities asserted in the application and confirmed by post-published documents on file. The application further disclosed the use of CRCGCL as a specific marker for activated T-cells and there was evidence on file showing the use of such a marker as a valuable tool for diagnostic purposes.

XII. The appellant (applicant) requested that the decision under appeal be set aside and, as a sole claim request, that a patent be granted on the basis of the main request comprising claims 1 to 32 filed during the oral proceedings on 12 December 2008.

Reasons for the Decision

Main and sole request
Article 123(2) EPC

1. The subject-matter of claim 1(c) has a formal basis on page 14, lines 14 to 17 and on claim 1(g) of the application as filed. Claim 28 directed to specific anti-idiotypic antibodies has a basis on page 27, lines 17 to 18 of the application as filed. No objections were raised under this article by the examining division nor does the board see any reason to raise any of its own.

Articles 83 and 84 EPC and Article 54 EPC

2. The objections raised by the examining division under Articles 83 and 84 were directed to the functional feature of claim 1(c) of the refused request. This feature is no longer present in the request under consideration and therefore these objections have become moot (cf. points VII and VIII *supra*).

3. No objections have been raised under Article 54 EPC in the decision under appeal nor, with the evidence on file, sees the board any reason to raise any of its own.

Article 56 EPC
Closest prior art

4. To assess inventive step, the boards apply the "problem and solution approach" which requires as a first step the identification of the closest prior art, normally a document disclosing subject-matter conceived for the

same purpose as the claimed invention and having the most relevant technical features in common (cf. "Case Law of the Boards of Appeal of the EPO", 5th edition 2006, I.D.2 et seq., page 120).

5. Document D4, identified as the closest prior art, discloses the cloning and sequence of the γ chain of the human IL-2 receptor (IL-2Rγ chain). Based on conserved structural motifs, such as a signal sequence, predicted extracellular (with four conserved Cys and a WS motif near a transmembrane region) and cytoplasmic domains, the γ chain is characterized as a member of the cytokine receptor family (cf. page 380, Figure 2 and page 381, left-hand column to right-hand column). The document reports the expression pattern of the γ chain by Northern blot analysis (cf. page 381, Figure 3 and paragraph bridging middle and right-hand column) and its effect on the formation of three IL-2R isoforms differing in their IL-2 binding affinities. These studies show that the γ chain does not bind IL-2 by itself but is necessary for the formation of a high (αβγ heteromer) and an intermediate-affinity (βγ heteromer) receptor (cf. page 381, right-hand column to page 382, middle column). With a 24% sequence identity, the hIL-2Rγ chain is the closest homolog to the CRCGCL sequence disclosed in the application.

6. Based on computer analysis and homology comparison, the CRCGCL sequence, isolated from an activated T-cell cDNA library, is characterized by a predicted transmembrane domain, WS and Jak Box motifs (although no perfect matches) and a cytoplasmic domain. The CRCGCL sequence is identified in the application as a member of the cytokine receptor family with homology to bovine Il-2Rγ

(cf. page 7, lines 24 to 34). The CRCGCL expression pattern by Northern analysis is consistent with immune specific expression (cf. page 7, lines 15 to 23 and page 8, lines 28 to 30) and, based on these results, several diagnostic and therapeutic uses in immune and autoimmune diseases are suggested for this CRCGCL sequence (cf. page 8, lines 28 to 37 and page 55, line 22 to page 67, line 30). However, none of the suggested CRCGL biological activities is actually exemplified in the application nor is, apart from the expression pattern and the CRCGCL sequences, any other experimental data disclosed therein.

Technical problem to be solved and the proposed solution

7. Starting from the closest prior art, the objective technical problem to be solved is the provision of a further member of the cytokine receptor family. The claimed subject-matter, namely the CRCGCL nucleic acid sequence and the encoded CRCGCL protein (SEQ ID NO: 1 and 2, respectively) solve this problem.

8. Although, as acknowledged in the application, several conserved domains (hallmark motifs) of the cytokine receptor family are altered in the disclosed CRCGCL sequence, such as an altered WS motif, the presence of only two of the four conserved Cys, an imperfect Jak box motif with only box 1 and the absence of box 2, there is evidence on file showing that these structural differences are within the frame of variation of the members of this family. The observed structural deviations coincide with those of other known members of the family and they only reflect functional differences among them. In fact, the examining division

has not questioned this identification in its decision nor, in the light of the evidence on file, is there any reason for the board to conclude otherwise. On the basis of the information provided in the application and the related prior art, the identification of the CRCGCL sequence as a member of the cytokine receptor family is a plausible teaching to the skilled person. There are also post-published documents on file confirming this assignment.

Non-obviousness of the proposed solution

9. Document D4 refers to the complex formation of functional cytokine receptors as requiring several subunits and further states that the high affinity hIL-2R isoform is unusual among the cytokine receptors because it consists of three distinct subunits, namely the α, β and the γ chain (cf. page 382, paragraph bridging left-hand and middle column). The unusual character of this isoform holds also true for the γ chain itself which is shared with other cytokine receptors and is designated therefore γ common chain (γ_c). There is, however, no indication in document D4 that might suggest to the skilled person to look for other cytokine receptors in general let alone for receptors similar to the γ chain. Nevertheless, it might well be that the skilled person, driven by its naturally present scientific curiosity, would be incited to look for these receptors. In that case, there is evidence on file, namely post-published document D16, showing that the teachings of document D4 would not allow the skilled person to achieve the CRCGCL sequence in an obvious manner.

10. Post-published document D16 discloses the murine homolog of the human CRCGCL sequence (39% sequence identity) and the identity of this receptor to other known cytokine receptors, in particular to the mouse common γ receptor (γ_c) (cf. page 2206, paragraph bridging left and right-hand columns and page 2207, Figure 2). In spite of the high degree of identity and even though the authors of document D16 were well aware of standard methods for cloning new members of the cytokine receptor family (cf. page 2204, first paragraph, right-hand column), they were unable to obtain a human homolog of the disclosed murine receptor both by cross-hybridization screening or by searching for homolog human EST sequences (cf. page 2209, right-hand column, third full paragraph). Contrary to the assertions of the examining division for which there are no evidence on file, document D16 shows that, even one year after the filing date of the application, the use of standard methods failed to identify the human CRCGCL sequence. The observed structural deviations of the CRCGCL sequence and the low degree of identity to other known members of the cytokine receptor family might have prevented a straight identification, cloning and characterization.

Technical effect of the proposed solution

11. According to the application, the human CRCGCL sequence, isolated from an activated T-cell library, is expressed specifically on activated T-cells but not in T-cells at rest (Molt-4, peripheral blood leukocytes), its expression pattern being consistent with immune specific expression (cf. point 6 ***supra***). This pattern is completely different from that of the hIL-2Rγ chain

of document D4 since, although present in immune cells including T-cells, it does not differentiate activated T-cells from T-cells at rest (cf. page 381, Figure 3 and paragraph bridging middle and right-hand column). Post-published document D16 shows that, contrary to the human CRCGCL sequence, the murine homolog is expressed in many tissues, including heart, brain, spleen, lung, kidney and testis as well as immune cells, even though a "***slight up-regulation of the expression by T-cell activation was observed in both T-cell cultures***" (cf. page 2207, Figure 3 and paragraph bridging left and right-hand columns). The ability to differentiate activated T-cells from T-cells at rest is described in the application as a basis for using the human CRCGCL sequence as a specific marker for activated T-cells (cf. page 8, lines 17 to 21 and page 43, lines 15 to 21). The relevance of a specific marker for detecting activated T-cells is known in the art as shown by extensive evidence on file, ***inter alia*** post-published document D46 which shows the absence of the CRCGCL receptor in non-stimulated T-cells and its induction by T-cell stimulation.

12. Thus, the claimed human CRCGCL receptor provides a specific and useful technical effect, which is also directly derivable from the application.

Further issues raised by the examining division

13. For the sake of completeness, the board notes that the examining division has also followed another line of argumentation when applying the "problem and solution approach" with reference to a huge collection of cDNA sequences, namely those contained in an activated

T-cell cDNA library, as the appropriate starting point for assessing inventive step. In this case, the technical problem to be solved is the provision of a further sequence of potential interest (cf. pages 7 and 8 of the decision under appeal). The examining division, however, has not identified in its decision any document as closest prior art when following this approach nor is there any reference to the technical effect associated with the human CRCGCL sequence (cf. point 11 *supra*). Although the closest prior art could be represented by some of the documents filed by the appellant for showing the relevance of a specific marker in the detection of activated T-cells, the observed structural deviations of the disclosed CRCGCL sequence do not render its identification obvious or straightforward to the skilled person (cf. point 10 *supra*). The less so in view of the different expression pattern of the closest related homologous sequence, i.e. the hIL-2Rγ chain of document D4, or of the murine homolog cytokine receptor of post-published document D16 (cf. point 11 *supra*). On the evidence on file (or lack thereof), the board cannot agree with the approach taken by the examining division.

14. It follows from all the above that the main request fulfils the requirements of Article 56 EPC.

Article 57 EPC

15. According to the established case law, for an application or a patent to fulfil the requirements of Article 57 EPC it must disclose the purpose of the invention in definite technical terms and how it can be used in industrial practice to solve a given technical

problem, i.e. it must disclose an immediate concrete benefit (cf. decision T 898/05 of 7 July 2006, point 6 of the Reasons).

16. The application discloses the CRCGCL nucleic acid sequence (SEQ ID NO: 1), the predicted encoded CRCGCL amino acid sequence (SEQ ID NO: 2) and the CRCGCL expression pattern. Based on computer-assisted sequence homology studies and on its expression pattern, the CRCGCL sequence is identified as a putative member of the cytokine receptor family. The probative value of these methods has not been questioned and is given in the present case (cf. point 8 *supra*, and decision T 898/06, supra, point 22 of the Reasons). The appellant has also provided compelling evidence demonstrating that the CRCGCL sequence finds a useful application as a specific marker for activated T-cells (cf. point 11 *supra*) and thus, it has an immediate concrete benefit as defined in the established case law.

17. Therefore, the main request fulfils the requirements of Article 57 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted back to the first instance with the order to grant a patent based on the sole claim request as filed in the oral proceedings on 12 December 2008, comprising claims 1 to 32, and a description and drawings to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani