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Datasheet for the decision of 19 July 2007

Case Number: T 1165/06 - 3.3.08

Application Number: 00905517.9

Publication Number: 1141297

IPC: C12N 15/24

Language of the proceedings: EN

Title of invention:
Interleukin-17 related mammalian cytokines. Polynucleotides encoding them. Uses

Applicant:
SCHERING CORPORATION

Opponent:
-

Headword:
IL-17 related polypeptide/SCHERING

Relevant legal provisions:
EPC Art. 54, 56, 82, 83, 84, 87, 123(2)

Keyword:
"Amended claims - added matter (no)"
"Clarity and sufficiency of disclosure (yes)"
"Unity of invention (yes)"
"Novelty and inventive step (yes)"
"Industrial applicability (yes)"

Decisions cited:
T 0195/84, T 0886/02, T 0956/03, T 0604/04

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1165/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 19 July 2007

Appellant: SCHERING CORPORATION
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 24 January 2006 refusing European application No. 00905517.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
C. Heath

Summary of Facts and Submissions

I. European patent application No. 00 905 517.9 was filed as International application under the PCT on 10 January 2000, claiming the priority of US application Serial No. 09/228 822 of 11 January 1999. and was published as WO 00/42188 with the title "Interleukin-17 related mammalian cytokines. Polynucleotides encoding them. Uses".

II. By decision posted on 24 January 2006, the application was refused by the examining division under Article 97(1) EPC. The refusal was based on the grounds that the subject-matter of the claims of either the main request or the auxiliary request then on file did not involve an inventive step within the meaning of Article 56 EPC. Furthermore, the examining division found that the invention as claimed in the main request lacked unity (cf. Article 82 EPC).

III. The reasons given by the examining division to deny an inventive step may be summarized as follows:

Documents D1 and D2, which represented the closest prior art, disclosed IL-17 related proteins (designated PRO1031 and PRO1122 in D1 and CTLA-8 in D2). D2 also suggested to clone the gene encoding the CTLA-8 protein from other species by cross-hybridization or by the use of antibodies against the protein. The problem to be solved by the application could be seen in the provision of further IL-17 related nucleic acids and proteins. As already several IL-17 related proteins were known at the filing date, the selection of one (further) IL-17 related protein could not involve an

inventive step. In order to fulfil the requirements of Article 56 EPC, a selection must be justified by a technical purpose, ie. a hitherto unknown or unexpected technical effect resulting from those structural features which distinguish the compound claimed from all other possible solutions. However, the application neither provided any proof for a IL-17 related activity of the claimed protein nor showed any particular technical effect for the claimed protein. Since at the priority date screening DNA libraries was a matter of routine, the screening process described in the application, even though was time-consuming, did not required inventive skill, especially in view of the fact that D2 already gave the incentive to do so. Hence, neither the subject-matter of claim 1 of the main request nor that of the auxiliary request, which was restricted to primate IL-174 as shown in SEQ ID NO: 14, met the requirements of Article 56 EPC.

IV. The appellant (applicant) lodged an appeal against the refusal of the application. By the statement setting out the grounds of appeal, the main claim request considered by the examining division was re-filed as sole claim request, and additional documentary evidence in support of an inventive step was submitted. Oral proceedings were requested in the event that the main request was not considered to be allowable.

V. The examining division did not rectify its decision and, pursuant to Article 109(2) EPC, remitted the appeal to the boards of appeal.

VI. The appellant was summoned to oral proceedings. In a communication under Article 11(1) of the Rules of

Procedure of the Boards of Appeal ("RPBA") sent with the summons, the board expressed its preliminary, non-binding opinion on some of the issues to be discussed, and set a time limit for filing additional submissions and/or requests.

VII. One week before the time limit expired, the appellant appointed a new representative and requested that the scheduled oral proceedings were postponed in order to give the representative sufficient time for the preparation. The board decided not to grant the appellant's request, but nevertheless extended the time limit for filing a response by two weeks.

VIII. The appellant answered to the board's communication and filed an amended claim request as well as additional documentary evidence.

IX. At oral proceedings, which were held on 19 July 2007, the appellant submitted an amended claim request (claims 1 to 15) in replacement of the request previously on file.

X. Independent claims 1 and 8 of the claim request filed at oral proceedings read as follows:

"1. A polynucleotide comprising a sequence which encodes the mature IL-174 polypeptide comprised within SEQ ID NO: 14.

8. A polypeptide comprising the mature IL-174 polypeptide comprised within SEQ ID NO: 14."

Claim 2, which depended on claim 1, was directed to a polynucleotide comprising the entire mature coding portion of SEQ ID NO: 13. Independent claims 3 and 4 were directed to, respectively, a polynucleotide encoding at least 16 contiguous amino acids from the mature IL-174 polypeptide, and a polynucleotide comprising at least 33 contiguous nucleotides from SEQ ID NO: 13.

Independent claims 5, 6 and 7 concerned, respectively, an expression vector comprising the claimed polynucleotide, a host cell containing the vector and a method of making a IL-174 polypeptide.

Independent claim 9 was directed to a polypeptide comprising at least 16 contiguous amino acids from the mature IL-174 polypeptide comprised within SEQ ID NO: 14. Dependent claims 10 and 13 concerned various embodiments of the polypeptides of claims 9 and 13, respectively. Claims 11 and 12 were directed to the polypeptide of claim 9 attached to a solid substrate and as a fusion protein with a detection or purification tag, respectively. Finally, a sterile composition comprising the polypeptide of claim 9 and a method using the polypeptide of claim 8 were claimed in independent claims 13 and 14.

XI. The following documents are referred to in the present decision:

D1: WO 99/60127, published on 25 November 1999;

D2: WO 95/18826, published on 13 July 1995;

D4: WO 99/61617, published on 2 December 1999;

D5: M. Kawaguchi et al., December 2004, J. Allergy Clin. Immunol. Vol. 114, No. 6, pages 1265 to 1273.

XII. The arguments put forward by the appellant may be summarised as follows:

Articles 123(2) and 84 EPC

The deletion of the terms "isolated", "recombinant" or "substantially pure" did not introduce subject-matter which extended beyond the content of the application as filed, because the application as filed provided a basis for polynucleotides, polypeptides and host cells as claimed.

The amended claims referred to the "mature" form of the IL-174 polypeptide comprised *within* SEQ ID NO:14. This clarification was self-explanatory from, for example, SEQ ID NO:13 and SEQ ID NO:14. Specifically, sequence identifiers <221> and <222> in SEQ ID NO:13 indicated that the mature peptide ("mat_peptide") was encoded from nucleotide position (67) to (501). Accordingly, the skilled person would have understood that position (1) two (66) represented the nucleotide sequence encoding the "leader peptide". Moreover, the person skilled in the art knew that negative numbers as used in both SEQ ID NOs:13 and 14 indicated the presence of a leader sequence within a polypeptide, while positive numbers indicated the then-processed, ie. mature form of the polypeptide. Thus, the term "mature polypeptide" was clear within the meaning of Article 84 EPC.

Article 82 EPC

Since the claims had been restricted to subject-matter relating to SEQ ID NOs:13 and 14, ie. to human IL-174, no objection in respect of the unity of the invention could arise.

Article 56 EPC

Starting from document D4 as the closest prior art, the problem to be solved was the provision of a further human IL-17 family member. The solution provided in the application was human IL-174 nucleotide and amino acid sequences as defined in the claims.

Contrary to the view of the examining division, the existence of knowledge of several related members of a class did not automatically make the discovery of a hitherto unknown member of the class obvious. It was not acceptable to attribute to the skilled person a *per se* "forever occupied" attitude towards "furthering" an already (perhaps?) "satisfied" or "closed" class of compounds (such as a protein family). Due to the absence of any mention in D4 that there might exist still another member of the IL-17 cytokine family, the person skilled in the art could have attempted to try to seek further members of the IL-17 cytokine family, but in the absence of an incentive he/she would not have done so. Thus, already for this reason it would not have been obvious to try to provide further members of the IL-17 cytokine family, let alone IL-174.

Moreover, even if in the light of document D2 there was a motivation to seek further IL-17 family members, the

skilled person would have had no reasonable expectation that any further members existed, and that they could be found applying the "wet-biology" approach suggested in D2. Concerning a computer-assisted approach, D4 did not provide any guidance, let alone teaching, as to how to search for further members of the IL-17 cytokine family in publicly available sequence databases. In any case, these databases did not contain even a partial sequence for human IL-174, let alone the complete nucleotide sequence encoding the IL-174 polypeptide disclosed in the application.

Even if it was assumed that, at the filing date, a human IL-174 nucleotide sequence was present in an available database, it was not likely that a skilled person would have found it using the teaching of document D4. This document described seven domains (domains I to VII) shared by all or some of the IL-17 family members. However, IL-174 failed to meet the criteria of high sequence identity with domains I to VII, and showed no sequence identity at all in domains V and VI.

Thus, for the identification of IL-174, the inventors had to design a new screening approach which combined wet-lab and *in silico* methods and overcame the difficulties derived from the restricted expression pattern of IL-174, without having any guidance from the prior art. Therefore, the claimed subject-matter involved an inventive step.

Article 57 EPC

It was stated in the application that the claimed polypeptides exhibited significant sequence similarity to the cytokine designated CTLA-8 (IL-17), which functioned in controlling physiology, development and differentiation of mammalian cells, eg cells of a mammalian immune system. Thus, as disclosed on page 9, lines 18 to 23 of the application, one could plausibly assume that the polypeptides of the invention were capable of mediating various physiological responses which would lead to biological or physiological responses in target cells, eg those responses characteristic of cytokine signaling. Document D5, which was cited as post-published evidence, confirmed that the IL-174 polypeptide was involved in immune response and induced a set of cytokine genes. Thus, the circumstances of the present case were different from those underlying decision T 604/04 of 16 March 2006.

XIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 15 filed during the oral proceedings.

Reasons for the Decision

Amended claims – Formal issues

Articles 123(2) and 84 EPC

1. The application discloses various interleukin-17 related cytokines and polynucleotides encoding them, in

particular a human cytokine designated IL-174 and a polynucleotide encoding the IL-174 polypeptide.

2. Amended claims 1 and 2 (cf. section X *supra*) have a basis in page 3, lines 36 and 37 of the application as filed, read in connection with the passage on page 4, lines 9 and 10 in the light of Table 3 and SEQ ID NO: 13 of the Sequence Listing. From the information provided in SEQ ID NO: 13, a person skilled in the art can unmistakably identify the mature IL-174 polypeptide as corresponding to the amino acid residues numbered from 1 to 145, whereas the amino acid residues numbered from -16 to -1 represent a signal sequence. It is also apparent from SEQ ID NO: 13 that the sequence encoding the mature IL-174 polypeptide disclosed in the application corresponds to the nucleotides numbered 67 to 501 (cf. numeric identifier <222>).

3. Amended claim 3 has a basis in the statements on page 3, lines 36 and 37 read in connection with the passage on page 4, lines 5 and 6 of the application as filed, as well as in original claim 3 b) i). Amended claim 4 is based on claim 3 b) iii) and on the passage in page 3, lines 36 and 37 read in connection with the statements in page 4, lines 8 and 9 of the application as filed. A basis for amended claim 5 is found in page 35, lines 25ff. Amended claim 6 is based on claim 8 as originally filed as well as on the passage from page 37, line 6 to page 38, line 35.

4. The method of amended claim 7 is disclosed in page 4, lines 22 to 24 and in page 34, lines 31 to 33 of the application as filed, and amended claim 8 has a basis in the statements on page 5, lines 35 and 36, read in

connection with the passage in page 6, lines 6 and 7 of the application as filed, as well as in original claim 11 B) a). The basis for claim 9 is found in page 32, lines 20 to 25, and in claim 3 b) i) as originally filed. Claims 10 to 12 and 14 have a basis in original claim 12, and a basis for claim 13 is found in page 6, lines 35 to 37 of the application as filed. The method of amended claim 15 is disclosed in page 6, lines 35 and 36 and in page 7, lines 1 to 4 of the application as filed.

5. The requirement of Article 123(2) EPC is, thus, fulfilled. Since no deficiencies concerning clarity and conciseness of the claims are apparent, also the requirements of Article 84 EPC are considered to be met.

Article 83 EPC - Sufficiency of disclosure

6. The application provides the amino acid sequence of the mature IL-174 polypeptide and a nucleotide sequence encoding it (cf. SEQ ID NOs: 13 and 14). In the absence of evidence to the contrary, there is no reason to doubt that a person skilled in the art at the filing date would be able, on the basis of the sequence information provided in the application supplemented by his/her common general knowledge, to obtain further polynucleotides comprising a sequence which encodes the mature IL-174 polypeptide, as well as expression vectors containing a nucleotide sequence that encodes this polypeptide. Methods for cultivating host cells transformed with a recombinant expression vector, and suitable conditions to produce polypeptides encoded by nucleotide sequences contained in an expression vector were well known in the art, and there is no

circumstantial evidence on file indicating that they may not be applicable to the production of the IL-174 polypeptide. Thus, sufficiency of disclosure is acknowledged.

Article 82 - Unity of invention

7. In the decision under appeal, the examining division raised an objection of lack of unity of invention against claim 1 as then on file, which was directed to nucleotide sequences encoding three different interleukin-17 related cytokines (SEQ ID NOs: 14, 15 and 18). Since the claims have now been restricted to subject-matter related to a single polypeptide - the mature IL-174 polypeptide comprised within SEQ ID NO: 14 - and to nucleic acid sequences encoding this polypeptide, the board is satisfied that the claimed subject-matter relates to one invention only, as required by Article 82 EPC.

Substantive issues

Articles 87 and 54(2) EPC - Entitlement to priority and relevant state of the art

8. In the decision under appeal, the examining division found that, with regard to IL-174, only the murine sequences, ie. the nucleic acid sequence of SEQ ID NO: 15 and the encoded amino acid sequence of SEQ ID NO: 16, were disclosed in the priority document for the present application. Consequently, the priority claimed in the application was not considered to be valid in respect of subject-matter relating to, *inter alia*, SEQ ID NOs: 13 and 14 corresponding to human

IL-174. This finding has not been disputed by the appellant and the board sees no reason to disagree with the view of the examining division.

9. Since the amended claims on file are now limited to subject-matter relating to SEQ ID NOs: 13 and 14, it follows from the above that the effective date in the context of determining the state of the art relevant to the assessment of novelty and inventive step is the filing date, ie. 10 January 2000. Hence, the relevant state of the art comprises not only the content of the documents D1 to D3 cited in the decision under appeal, but also the content of document D4 (see Section XI *supra*), which was cited in the International Search Report established for the present application.

Article 54 EPC - Novelty

10. The examining division did not raise any objection of lack of novelty in respect of subject-matter relating to SEQ ID NOs: 13 and 14. Having regard to the prior art documents presently on file, the board is convinced that the requirements of Article 54 EPC are fulfilled.

Article 56 EPC - Inventive step

11. Even though the examining division and the appellant itself regarded document D1 and/or document D2 as representing the closest prior art, the board considers that document D4 offers a better starting point for the assessment of inventive step applying the problem-solution approach, because this document reflects more closely the relevant state of the art at the filing date of the application.

12. Whilst D2, a document published in 1995, describes the first member of the IL-17 cytokine family (CTLA-8, later renamed as IL-17 or IL-17A), and document D1 - published four years later - reports on the isolation of two further members of this family (IL-17B and IL-17C), document D4, published only one month before the date of filing of the present application, provides not only the amino acid sequence of the family member described first (IL-17), but also the amino acid sequence of IL-20 - later renamed as IL-17B - and of two new members of the family, designated IL-21 and IL-22.

13. Moreover, document D4 describes the regions of identity between the amino acid sequences of four members of the IL-17 cytokine family known at the time and identifies several domains conserved among these members (cf. Figure 3A, B, C, and page 12, lines 4ff). It is stated in D4 that all four polypeptides exhibited a high degree of sequence identity in several conserved domains (cf. page 12, lines 14 to 33; and Figures 3A to C) and that, in addition, IL-21 and IL-22 showed further conserved domains compared with IL-17 and IL-20. As preferred polypeptides, the mature forms of the IL-21 and IL-22 polypeptides are mentioned (cf. page 40, lines 35 and 36).

14. Starting from document D4 as the closest prior art, the technical problem to be solved can be defined as the isolation of a further polypeptide of the IL-17 cytokine family, and a nucleotide sequence encoding the polypeptide.

15. In the present case, the mere formulation of this problem is not considered to contribute to an inventive step, because furthering the existing state of knowledge belongs to the routine tasks with which a person skilled in the art is constantly occupied (see, for example, T 195/84, OJ EPO 1986, 121; T 886/02 of 7 December 2006 and T 956/03 of 19 July 2006, not published in the OJ).

16. The problem indicated above has plausibly been solved by a IL-174 polypeptide as defined in claim 8 and a polynucleotide as defined in claim 1.

17. Thus, in view of the reasons given by the examining division for the refusal (cf. Section III *supra*), the question to be decided in the present case is whether, having regard to the state of the art at the filing date, the solution proposed in the claims was obvious to a person skilled in the art.

18. Like the examining division, the board considers that, in view of the fact that several members of the IL-17 family isolated from mouse or human cells had already been described, it was obvious to a skilled person to try to isolate further members of this family. The board is not convinced by the appellant's argument that the skilled person would not be motivated to seek for an already (perhaps) "satisfied" or "closed" protein family. No evidence has been filed by the appellant for an indication or suggestion in the prior to the effect that all members of the IL-17 cytokine family had already been identified. In the absence of such a suggestion, the board believes that a person skilled in the art, who may be defined as a molecular biologist

working in the field of medical or pharmaceutical biotechnology, not only could, but, in view of the medical relevance of cytokines, also **would** try to isolate further members of the IL-17 family.

19. The decisive question in the framework of assessing inventive step is, thus, whether or not the skilled person, in view of the information provided in D4 supplemented by further prior art documents on file and/or the common general knowledge, would have reasonably expected to isolate polynucleotides encoding a new member of the IL-17 cytokine family, in particular the mature polypeptide comprised within SEQ ID NO: 14 and a polynucleotide encoding this polypeptide.

20. The board is convinced that a person skilled in the art embarking on the search for a new member of the IL-family would have known that the immunoscreening approach suggested generally in document D2 was not only time-consuming, but, having regard to the fact that the members of the family have very low overall similarity at the level of primary structure, also not straightforward and with uncertain results.

21. As for the *in vitro* or *in silico* screening of DNA libraries or databases - the approach indicated by the examining division -, the board accepts that, at the filing date of the present application, DNA databases as well as technical means for searching such databases were available in the art, and that the knowledge required to conduct searches was part of the common general knowledge of the skilled person. However, in view of the circumstances of the present case, a

reasonable expectation of success in identifying the specific IL-17-related polypeptide described in the application cannot, in the board's view, be assumed objectively.

22. Having regard to the teaching of D4 concerning the domains of homology between the known members of the IL-17 cytokine family (cf. pages 12 and 13 of D4), a person skilled in the art would have assumed that further unknown members of this family would also have presented very similar domains, and would have designed his/her screening strategy accordingly. However, it is apparent from a comparison between, on the one hand, the domains of homology on pages 12 and 13 of document D4 and, on the other hand, the corresponding domains in the amino acid sequence of IL-174 (cf. SEQ ID NO:14) that, even though the IL-174 polypeptide shows features which allow to ascribe it to the IL-17 family, in particular the characteristic spacing of cysteine residues, significant differences exist in the amino acid sequence of the particular domains described in D4, up to the complete absence of some of these domains in the IL-174 polypeptide. This fact neither was known nor could have been foreseen by the skilled person at the filing date, and only was revealed after the identification of the IL-174 sequence by the inventors. Thus, a screening strategy designed on the basis of the domain information provided in D4 would, most probably, have failed to "fish out" the IL-174 sequence. Under these circumstances, a reasonable expectation of success as required by the case law of the Boards of Appeal of the EPO to deny an inventive step cannot be assumed.

23. Contrary to the view of the examining division, the board judges that, in the present case, an inventive step cannot be denied on the grounds that the invention consists merely in selecting one (further) IL-17 related polypeptide out of several polypeptides of this family. To assume a selection in the present case presupposes that, at the filing date, IL-174 was part of the state of the art, from which the inventors, in expectation of a particular technical effect, selected this particular polypeptide. This was, however, not the case, since IL-174 was described for the first time in the present application.

24. Thus, for the reasons given above the board concludes that, having regard to the state of the art on file, the claimed subject-matter involves an inventive step within the meaning of Article 56 EPC.

Article 57 EPC - Industrial applicability

25. The board is convinced that the requirements of Article 57 EPC are fulfilled. The sequence information provided in the application with respect to the presence in IL-174 of the characteristic cysteine spacing of the IL-17 cytokine family makes it plausible that this polypeptide may belong to this family and have biological activities similar to those of the other family members known at the filing date, in particular CTLA-8. This is confirmed by post-published evidence filed by the appellant. In document D5, it is stated that the *in vitro* findings for the IL-17E polypeptide, which is identical to the mature sequence comprised within SEQ ID NO:14, suggest that this polypeptide is directly involved in T_H2-associated

allergic inflammation (cf. page 1270, last sentence of the first paragraph).

26. Summarising the above, the board concludes that the requirements of the EPC are met.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remanded back to the first instance with the order to grant a patent according to the main request with claims 1 - 15 as submitted in the oral proceedings, and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani