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Datasheet for the decision of 30 July 2015

Case Number: T 1032/12 - 3.3.08

Application Number: 99960372.3

Publication Number: 1129190

IPC: C12N15/12, C12N5/10, C07K14/475, C07K16/22, A61K38/18

Language of the proceedings: EN

Title of invention:
HUMAN TSLP DNA AND POLYPEPTIDES

Patent Proprietor:
Immunex Corporation

Opponents:
Schering Corporation
Baldock, Sharon Claire

Headword:
Human TSLP/IMMUNEX CORPORATION

Relevant legal provisions:
EPC Art. 123(2), 54(3), 56
RPBA Art. 12(4), 13(1)

Keyword:
Main request - requirements of the EPC met (yes)

Decisions cited:
G 0001/03, T 0583/09

Catchword:

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Case Number: T 1032/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 30 July 2015

Appellant: (Patent Proprietor)	Immunex Corporation One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
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Appellant: (Opponent 2)	Baldock, Sharon Claire Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Representative:	Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 6 March 2012 concerning maintenance of the European Patent No. 1129190 in amended form.**

Composition of the Board:

Chairman	M. Wieser
Members:	B. Stolz
	J. Geschwind

Summary of Facts and Submissions

I. Appeals against the decision of the opposition division, whereby European patent No. 1129190 was maintained in amended form, were filed by the patent proprietor (appellant I), opponent I (appellant II) and opponent II (appellant III).

II. The opposition division decided that the main request (claims as granted), auxiliary request 1 and auxiliary request 2 before it lacked novelty (Article 54 EPC). Auxiliary request 3 was found to meet all requirements of the EPC.

III. With its grounds of appeal, appellant I submitted a main request (claims as granted) and auxiliary requests 1 to 5. With its observations on the grounds of appeal submitted by appellants II and III, appellant I filed 25 additional auxiliary requests.

IV. Appellants I and II filed new documents with their grounds of appeal and in response to the other parties' grounds of appeal.

V. The appellants were summoned to oral proceedings. A communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to the summons, informed them of the preliminary non-binding opinion of the board on some of the issues of the appeal proceedings.

VI. With its response to the board's communication, appellant I submitted a new main request and 5 auxiliary requests, and withdrew all previous requests.

VII. Appellant III informed the board that it would not be represented at the oral proceedings.

VIII. Oral proceedings were held on 30 July 2015, in the absence of appellant III. At the oral proceedings, appellant I filed a new main request and withdrew all previous requests.

IX. Claim 1 of the main request reads:

"1. An isolated antibody that binds to a purified TSLP polypeptide selected from the group consisting of:

a) the TSLP polypeptide of SEQ ID NO:2;

b) a fragment of the polypeptide of (a), from amino acid 29 to amino acid 159, and amino acid 35 to amino acid 159 of SEQ ID NO: 2;

c) a TSLP polypeptide comprising the amino acid sequence of SEQ ID NO:2; and

d) a TSLP polypeptide comprising an amino acid sequence that is at least 95%identical to the amino acid sequence presented in SEQ ID NO:2."

Dependent claims 2 and 3 define specific embodiments of the polypeptides of claim 1, claims 4 and 5 define a fusion protein and a composition, respectively, comprising the claimed polypeptides.

X. The following documents are referred to in this decision:

C5: DATABASE EMBL-EBI Accession No.: AA889581,"EST; Homo sapiens cDNA clone IMAGE: 1407260",

published: 6 April 1998, republished: 6 January 1999;

C6: Ray R.J. et al., "Characterization of thymic stromal-derived lymphopoietin (TSLP) in murine B cell development in vitro", Eur. J. Immunol., 26 , pages 10-16, January 1996;

C7: Friend S.L. et al., "A thymic stromal cell line supports in vitro development of surface IgM and B cells and produces a novel growth factor affecting B and T lineage cells", Exp. Hematology, (3), pages 321-328, March 1994;

C8: WO 00/17362 A2 (Bazan J) Published: 30 March 2000, Filing Date: 20 September 1999;

C9: US 09/157,749 (Bazan J) Filing Date: 21 September 1998;

C21: Amino acid sequence alignment between SEQ ID NO:1 of C8 and SEQ ID NO:2 of the opposed patent;

C40: Instructions to Authors, European Journal of Immunology, Vol. 26(1), pages A7-A9, January 1996, (revised December 1995).

XI. The arguments of appellant I, as far as relevant for this decision, are summarized as follows:

Admissibility of the main request

Claims 1 to 5 of the main request corresponded to claims 7 to 9, 12 and 13 of the auxiliary request I filed with the grounds of appeal. No new issues arose and the procedure was not delayed.

Article 123(2) EPC

Item d) of claim 1 was unambiguously disclosed and did not result from the combination of features from two lists. SEQ ID NO 2 was disclosed as the preferred sequence in the application as filed, e.g. on page 9, last paragraph and on page 12, last full paragraph of the application as filed. Therefore, the polypeptide presented in SEQ ID NO 2 could not be regarded as selected from a "list" of polypeptides. Variants comprising amino acid sequences with different degrees of identity to the preferred polypeptide were disclosed on page 14.

The polypeptides of items a) to d) of claim 1 represented different, i.e., alternative, embodiments of the TSLP polypeptide, which were all directly and unambiguously disclosed.

As to the objection against "purified" proteins, pages 30-32 of the application as filed comprised an entire section relating to the "Purification" and the "Isolation and and Purification" of the polypeptides and polypeptide fragments of the present invention. On page 32, last paragraph, it was also proposed to test the "purified" polypeptides of the invention for TSLP receptor binding. Further basis could be found on page 13, lines 23-26, and page 6 (first paragraph).

Article 54(3) EPC

The objection that claim 1 d) encompassed protein fragments disclosed in document C8 (and C9) had been raised for the first time at the oral proceedings before the board. The polypeptides encompassed by item

d) of claim 1 had to have 95% sequence identity with the full-length amino acid sequence represented by Seq ID NO:2. The proteins of C8 and C9 had less than 95% identity.

Article 56 EPC

Document C5 merely disclosed an unannotated EST sequence encoding an incomplete sequence. Document C6 disclosed a murine protein called TSLP and its activity on B cells. It contained a statement that a cDNA encoding a soluble protein with biological activity indistinguishable from IL-7 had been cloned but it did not provide any structural information at all. The skilled person could therefore not arrive at the claimed subject matter in an obvious way.

XII. The arguments of appellant II, as far as relevant for this decision, are summarized as follows:

Admissibility

The main request was the first request filed during the entire procedure without claims to antibodies. Such a request could have been filed earlier. A request restricted to polypeptides shifted the focus of the discussion completely. Moreover, claim 1 d) lacked novelty which rendered the request unallowable.

Article 123(2) EPC

The polypeptide of claim 1 d) was defined by two features which were not disclosed in combination but had been selected from two independent lists. On pages 12 and 13, the patent application disclosed several polypeptides as preferred polypeptides. The polypeptide

of Seq ID NO 2 was selected from this list and combined with the feature of 95% identity which was selected from a list of degrees of identity to the preferred polypeptide disclosed on page 14.

Article 54(3) EPC

According to paragraphs [0018] and [0053] of the patent, the invention encompassed polypeptides and fragments thereof. Thus, a polypeptide according to claim 1 d) could be shorter than the full-length molecule defined by Seq ID NO: 2. For the determination of the degree of sequence identity of such fragments, standard programs could be used, for instance GAP which, according to paragraph [0055], set no penalty for end gaps. Under such circumstances, the protein disclosed as Seq ID NO: 2 in document C8 had more than 95% identity with the polypeptide of the patent.

Article 56 EPC

In the absence of a functional limitation, claim 1 d) lacked inventive step because it encompassed non-functional sequence variants. Such variants did not solve any technical problem and, accordingly, did not involve an inventive step.

XIII. The arguments of appellant III, as far as relevant for this decision, are summarized as follows:

Article 123(2) EPC

Item d) of claim 1 related to a polypeptide defined by a combination of features which could not be derived from the application as filed. The two features were selected from two independent lists. Several sequence

variants were disclosed on pages 14 to 17 and multiple possible sequence identities on page 14. Moreover, claim 1 encompassed a group of polypeptides which was not apparent as a group from the application as filed. Finally, the claim lacked basis insofar as it related to a group of purified polypeptides.

Article 56 EPC

Claim 1 lacked an inventive step in view of document C5 disclosing an incomplete EST. The problem to be solved consisted in identifying the amino acid sequence encoded by the full-length nucleotide sequence which was partially disclosed in document C5. This did not require inventive skills. As an alternative,, starting from document C6 as the closest prior art, the problem to be solved consisted in finding a human molecule capable of stimulating lymphocytes. This problem was not plausibly solved because the claimed human protein had only 43% sequence identity with the mouse protein.

XIV. Appellant I requests that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed at the oral proceedings on 30 July 2015

XV. Appellants II and III request that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

1. Claims 1 to 5 of the main request correspond to claims 7 to 9, 12 and 13 of auxiliary request 1 filed with the grounds of appeal, and to claims 7 to 9, 12 and 13 as granted. The remaining claims of auxiliary request 1

(and of the claims as granted, respectively) have been deleted. Thus, no new issues arise.

In the decision under appeal, the opposition division held a request allowable which contained claims to antibodies. There was, therefore, no reason for appellant I to file a request without claims to antibodies in opposition proceedings.

Since claims 1 to 5 of the present main request were part of auxiliary request 1 already filed with the grounds of appeal, the board, exercising its discretion under Article 114(2) EPC, governed by the principles laid down in Articles 12(4) and 13(1) RPBA, decides to admit the main request into the procedure.

Article 123(2) EPC

2. Appellants II and III objected to the combination of features in claim 1 d). Appellant II submitted that the patent specification at paragraphs [0018, 0053 and 0055] disclosed that the invention encompassed isolated polypeptides and fragments of various lengths. Hence, the term "preferred polypeptides" encompassed a list of possible polypeptides.

3. According to page 14, under the header "*Variants*", "*Variants may exhibit amino acid sequences that are at least 80% identical. Also contemplated are embodiments in which a polypeptide or fragment comprises an amino acid sequence that is at least 90% identical, at least 95% identical, ..., at least 99.9% identical to the preferred polypeptide or fragment.*"

On page 9, under the heading "*Preferred sequences*" it is stated that "*The particularly preferred nucleotide*

sequence of the invention is SEQ ID NO:1, as set forth above", and "*The sequence of amino acids encoded by the DNA of SEQ ID NO:1 is SEQ ID NO:2.*"

According to page 12, "*Particularly preferred polypeptides comprise the amino acid sequence of SEQ ID NO:2 with particularly preferred fragments comprising amino acids 29 to 159 (the mature polypeptide sequence) of Seq ID NO:2.*"

4. Thus, the protein of SEQ ID NO:2 is singled out as the particularly preferred polypeptide, and when reference to fragments as the preferred sequences is made, they are always labelled as "*particularly preferred fragments*". The above mentioned reference on page 14 of the description to "*the preferred polypeptide*" is therefore a reference to the polypeptide of SEQ ID NO: 2.

5. It is this specific mention of the full-length molecule as the particularly preferred molecule that distinguishes the present case from the case underlying decision T 583/09 of 13 December 2011, referred to by appellant II, where different molecules were presented as equivalent alternatives.

6. Therefore, the board decides that claim 1 d) and the entire main request meet the requirements of Article 123(2) EPC.

Articles 123(3) EPC and 84 EPC

7. As claims 1 to 5 correspond to claims 7 to 9, 12 and 13 as granted, no objections under these articles arise.

Article 54(3) EPC

8. The subject matter of claim 1 d) is *"a TSLP polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence presented in SEQ ID NO:2"*. Exactly this subject matter is also disclosed in the priority application of the patent in suit (cf. pages 10 to 12, 14 and 15 of priority application US 60/108452, filed on 13 November 1998).

9. Appellant II argued that claim 1 d) lacked novelty in view of the polypeptide disclosed as SEQ ID NO:2 in document C8.

10. The filing date of document C8 is 20 September 1999. It claims priority from document US 09/157749 (document C9), filed on 21 September 1998. SEQ ID NO:2 of document C8 differs from SEQ ID NO:3 of document C9 by a single amino acid at position 61 (Arg in document C9, Xaa in document C8). This difference is due to the fact that the corresponding nucleic acid sequence of document C8 (SEQ ID NO:1) discloses the codon cgn at the respective position. Since all four possible variants of the codon cgn encode Arg, document C8 validly claims priority rights for SEQ ID NO:2 from document C9.

11. SEQ ID NO:2 of document C8 defines a polypeptide which differs from SEQ ID NO:2 of the opposed patent at the N and C-termini and by 5 amino acids at positions 59 to 63 (cf. document C21). The parties did not contest that the sequence identity of SEQ ID NO:2 of document C8 to the full-length sequence of the polypeptide presented in SEQ ID NO:2 of the patent is 87.4% (cf. point 2.4 of appellant III's submission of 10 December 2012).

12. Appellant II submitted that the language used in claim 1 d) did not require sequence comparison over the full-length of the polypeptide defined by SEQ ID NO: 2. It referred to several paragraphs in the description of the patent showing that the term *"variants"* encompassed shorter fragments and that standard settings could be used for sequence comparisons, including the setting of no penalty for end gaps ([0018, 0053, and 0055]). If one were to take into account only the overlapping part of the two sequences, the calculated sequence identity between SEQ ID NO:2 of the patent and SEQ ID NO:2 of document C8 was 97%.

13. The board does not agree with appellant II's interpretation of the subject-matter of claim 1 d), which is a TSLP polypeptide comprising an amino acid sequence that is at least 95% identical to **the** amino acid sequence presented in SEQ ID NO:2. This amino acid sequence is the full-length sequence from residue 1 to 159 as represented in SEQ ID NO:2.

14. This interpretation is further confirmed by the structure of claim 1, which distinguishes between polypeptides consisting of or comprising the amino acid sequence of SEQ ID NO: 2 (items a) and c)), and polypeptides consisting of fragments of SEQ ID NO:2 of a specified length (item b)). Likewise, the description provides a chapter on polypeptides and fragments thereof (cf. paragraphs [0045 - 0066]): "*The polypeptides of the invention include full-length proteins encoded by the nucleic acid sequences set forth above*" (paragraph [0045]). "*Particularly preferred polypeptides comprise the amino acid sequence of SEQ ID NO:2 with particularly preferred fragments comprising amino acids 29 to 159 (the mature polypeptide sequence) of SEQ ID NO:2*" (paragraph

[0045]). Furthermore, "*the polypeptide of SEQ ID NO:2 includes an N-terminal hydrophobic region that functions as a signal peptide*" (paragraph [0046]).

15. In view of the fact that the patent (description and claims) consistently distinguishes between the full-length protein presented in Seq ID NO:2 and fragments thereof, the board concludes that the reference in claim 1 to "*at least 95% sequence identity to **the** amino acid sequence presented in SEQ ID NO:2*" (emphasis added) has to be understood as requiring 95% sequence identity over the full-length of SEQ ID NO:2. It follows that the degree of sequence identity of SEQ ID NO:2 of the patent to SEQ ID NO:2 of document C8 is 87% (cf. document C21).

16. The subject-matter of claim 1 d) is therefore novel over the disclosure in document C8. Consequently the main request meets the requirements of Article 54 EPC.

Article 56 EPC

17. In the written procedure, appellant III raised inventive step objections using any one of documents C5 to C7 as closest state of the art.

18. Document C5 discloses a nucleic acid sequence which, in fact, is a partial nucleic acid sequence of hTSLP. Due to the absence of any information about homologies or functions of the disclosed sequence, this document is not suitable as the closest state of the art.

19. Document C7 discloses an activity found in conditioned media of a particular murine thymic stromal cell line. The conditioned medium affects proliferation of murine B cells and has a co-stimulatory effect on thymocyte

proliferation (cf. Figure 3). The isolation of a cDNA encoding a soluble protein with biological activity indistinguishable from IL-7 depleted conditioned medium is mentioned in a "*Note added in proof*", but no sequence information is given.

20. Document C6, a follow up on the work published in document C7, describes the effects of isolated mouse TSLP, on the proliferation and differentiation of B cell precursors. It does also not disclose any sequence information, but since it is the only one of the three documents disclosing a stimulatory effect of an isolated molecule, it is considered to represent the closest state of the art.

21. The technical problem to be solved is the provision of a new molecule for (co-)inducing T cell proliferation.

22. As a solution to this problem, the patent provides the polypeptide of claim 1.

23. As demonstrated by Example 8, the polypeptide defined by SEQ ID NO:2, when applied in combination with IL-7, has an effect on T cell proliferation. Thus, the problem is convincingly solved by this embodiment of the invention.

24. However, Appellant II argued that claim 1 d) also encompassed non-functional TSLP variants which did not solve the underlying technical problem.

25. If a claim comprises non-working embodiments, but there is a large number of conceivable alternatives and the specification contains sufficient information on the relevant criteria for finding appropriate alternatives over the claimed range with reasonable effort, the

inclusion of non-working embodiments is of no harm (cf. point 2.5.2. of decision G 1/03 (OJ 2004, 413)). In the present case, Example 8 provides sufficient instructions to identify the functional variants.

26. The board comes to the conclusion that the solution provided by claim 1 solves the underlying technical problem over its entire scope.

27. It remains to be established whether the claimed solution involves an inventive step.

28. Document C6, focusing on B cell stimulation, provides neither structural nor functional guidance to the claimed solution.

29. Appellant III argued that the authors of document C6, by publishing the results of their research work, implicitly agreed to make any research material freely available to the public.

30. This argument is contradicted by the contents of document C40, which shows that the instructions to authors in force at the time of publication of document C6 did not require that the research material be made available to the public.

31. Therefore, even if the skilled person, starting from the disclosure in document C6, would have looked for the human ortholog of the mouse TSLP, in the absence of any sequence information and unless with hindsight, it would not have considered document C5 at all.

32. None of the further documents on file provides any structural or functional information that would have

led the skilled person to combine this information with that of document C6.

The skilled person, trying to solve the above mentioned technical problem would therefore not have arrived at the solution provided by claim 1 in an obvious way.

33. The main request involves an inventive step and meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of claims 1 to 5 of the new main request filed at the oral proceedings and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated

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Case Number: T 1032/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
# of correcting an error in the decision
of 30 July 2015

Appellant: (Patent Proprietor)	Immunex Corporation One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
Representative:	Dörries, Hans Ulrich df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Appellant: (Opponent 1)	Schering Corporation 2000 Galloping Hill Road Kenilworth, N.J. 07033-0530 (US)
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Appellant: (Opponent 2)	Baldock, Sharon Claire Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Representative:	Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on**

6 March 2012 concerning maintenance of the European Patent No. 1129190 in amended form.

Composition of the Board:

Chairman	M. Wieser
Members:	B. Stolz
	J. Geschwind

In application of Rule 140 EPC, the decision of the Technical Board of Appeal dated 30 July 2015 is hereby corrected as follows:

On page 2 of the decision, the wording of item IX is corrected to read as follows:

IX. Claims 1 and 2 of the main request read:

"1. A purified TSLP polypeptide selected from the group consisting of:

a) the TSLP polypeptide of SEQ ID NO:2;

b) a fragment of the polypeptide of (a), from amino acid 29 to amino acid 159, and amino acid 35 to amino acid 159 of SEQ ID NO: 2;

c) a TSLP polypeptide comprising the amino acid sequence of SEQ ID NO:2; and

d) a TSLP polypeptide comprising an amino acid sequence that is at least 95%identical to the amino acid sequence presented in SEQ ID NO:2.

2. The TSLP polypeptide of SEQ ID NO:2."

Dependent claim 3 defines specific embodiments of the polypeptides of claims 1 and 2, claims 4 and 5 define a fusion protein and a composition, respectively, comprising the claimed polypeptides.

The Registrar: The Chairman

A. Wolinski M. Wieser

Decision electronically authenticated