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**Datasheet for the decision
of 14 November 2012**

Case Number: T 2181/08 - 3.3.04

Application Number: 01994219.2

Publication Number: 1351702

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A61K 38/18, C07K 14/705,
C07K 14/71, C07K 14/715,
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Language of the proceedings: EN

Title of invention:
TREM-1 splice variant for use in modifying immune responses

Applicant:
GenePrint Corporation

Headword:
TREM-1 splice variant/GENEPRINT

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

Keyword:
"Main and sole request - added matter (no); novelty, inventive
step, sufficiency of disclosure, clarity (yes)"

Decisions cited:
G 0005/83, T 0609/02, T 0986/02, T 0433/05

Catchword:
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Case Number: T 2181/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 14 November 2012

Appellant: GenePrint Corporation
(Applicant) 8027 Oakington Drive
Houston TX 77071 (US)

Representative: Vossius & Partner
P.O. Box 86 07 67
D-81634 München (DE)

Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 28 May 2008
refusing European patent application
No. 01994219.2 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Montrone
G. Alt

Summary of Facts and Submissions

- I. This appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse European patent application number 01 994 219 pursuant to Article 97(2) EPC.
- II. The decision under appeal dealt with a main and an auxiliary request.
- III. The following documents are referred to in this decision:
- D2 Bouchon A. et al., J. of Immunol., 2000, vol. 164, pages 4991-4995
- D3 Li P. et al., Biophysical J., 1999, vol. 77, pages 3394-3406
- D5 Exhibit A of applicants letter of 13 November 2012
- D6 Molecular Biology of the Cell, Alberts et al.; Garland Science, 4th edition, page 735
- D7 Gibot S. et al., J. Exp. Med., vol. 200, December 2004, pages 1419-1426
- IV. The examining division took the view that claims 1 to 14 of the main request related to subject-matter extending beyond the content of the application as filed (Article 123(2) EPC), lacked clarity (Article 84 EPC) and an inventive step (Article 56 EPC). The auxiliary request, consisting of claims 1 to 14 did not comply with the requirements of Article 123(2) EPC and

Article 56 EPC. In particular, the examining division found that the feature "functional equivalent" of claim 1 lacked clarity (Article 84 EPC) and that the subject-matter of claim 1 was not inventive (Article 56 EPC). The examining division considered document D2 as the closest prior art and defined the problem as the provision of compounds modulating the TREM-1 mediated immune response in an animal. Starting from D2, it was considered to be obvious for the skilled person to identify and use soluble parts of the TREM-1 receptor for modulating the immune response.

- V. With the statement of the grounds of appeal the appellant filed an amended main and auxiliary request and requested oral proceedings.

- VI. With the letter of 12 October 2012, the appellant filed a new main request and auxiliary requests 1 and 2 to replace the previous claim requests.

- VII. In a communication dated 30 October 2012 the board informed the appellant of its preliminary opinion that the subject-matter of claims 1, 3, 8 and 10 of the main request did not comply with the requirements of Article 123(2) EPC. In particular, the board observed that the application as filed appeared not to provide a basis for the feature "and/or TREM-1 sv" of claim 1, for the subject-matter of claim 3, for the feature "modulation" of claim 8 and for the feature "myeloid cell cytokine production" of claim 10. Further objections under Article 84 and 83 EPC were raised against the subject-matter of claims 1, 8 and 9.

VIII. In response to the board's communication the appellant filed evidence with its letter of 13 November 2012.

IX. During the oral proceedings which took place on 14 November 2012 appellant filed a new main request which replaced all previous requests.

Claims 1 and 6 of this sole request read:

"1. Use of a soluble polypeptide according to SEQ ID NO:2 or a fragment thereof, said fragment being a biological functional equivalent of SEQ ID NO: 2 for the manufacture of a medicament for decreasing the levels of TREM-1 ligand binding activity whereby an inflammatory response is decreased in an animal.

6. Use of an antibody that binds immunologically to the TREM-1 splice variant of SEQ ID NO: 2 but does not bind to TREM-1 for the manufacture of a medicament for increasing an inflammatory response in an animal."

The appellant submitted that all claims complied with the patentability requirements of the EPC. It requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 7 of the new main request filed during the oral proceedings.

Reasons for the Decision

Article 123(2) EPC

1. The subject-matter of the present set of claims has been amended to such an extent that the objections

pursuant to Article 123(2) EPC raised by the examining division in its decision no longer apply.

2. The board considers that the subject-matter of claim 1 is derivable from claims 12 to 14 in combination with paragraphs 9, 41 and 73 of the application as filed.
3. The subject-matter of claim 2 has its basis in claim 18 and paragraph 14 of the application as filed.
4. The subject-matter of claim 3 is derived from claim 15 of the application as filed in combination with paragraph 110 of that application whereas the subject-matter of claims 4 and 5 finds its basis on claims 16 and 19 of the application as filed.
5. The subject-matter of present claim 6 is derivable from the generic disclosure of paragraph 82 referring to the use of anti-TREM-1 sv antibodies for therapeutic applications in combination with the disclosure content of paragraphs 111 and 186 of the application as filed.
6. Finally, the subject-matter of present claim 7 is considered to be based on paragraph 31 of the application as filed.
7. Consequently, the board considers that the present set of claims complies with the requirements of Article 123(2) EPC.

Article 84 EPC

8. The subject-matter of present claims 1 to 7 relates to a second medical use drafted in the "Swiss-type" claim format as established by the decision G 5/83 of 5 December 1984. The subject-matter of claim 1 refers to the decreasing of an inflammatory response by the use of either a soluble polypeptide characterised by SEQIDNO:2 or a biological functional fragment thereof whereas claim 6 refers to an increase of an inflammatory response by using a TREM-1 splice variant (hereinafter "TREM-1 sv") specific antibody. Both claims relate to the treatment of a specified disease, namely an "inflammatory response". Although the term "inflammatory response" is rather the description of a pathological condition than a disease, the board considers that the skilled person - based on his or her common general knowledge - would in a straightforward manner have associated with it those diseases which are related to this condition and which can therefore be treated by either an increase or a decrease of it. Hence, the diseases to be treated are unambiguously defined by claims 1 and 6 which are therefore considered to be clear in this respect.
9. In the decision under appeal, the examining division held that the term "functional equivalent" in claim 1 of the main request lacked clarity. However, the definition in present claim 1 differs from that of claim 1 before the examining division in that the term "biological functional equivalent" is qualified as (i) "biological" and (ii) as being a fragment of SEQIDNO:2. In the board's view the skilled person would understand that this feature refers to (i) all fragments being

shorter than SEQIDNO:2 and (ii) which retain the functional biological property of SEQIDNO:2 itself, namely the ability to decrease the TREM-1 ligand binding activity by competing with the membrane bound TREM-1 for its natural ligand. Thus, claim 1 is clear in this respect.

10. The examining division had not raised any further objections of lack of clarity against the subject-matter of any of the dependent claims. Also the board has none. Hence, the subject-matter of claims 1 to 7 fulfils the requirements of Article 84 EPC.

Article 54 EPC

11. In the decision under appeal, the examining division had no objections as to lack of novelty. Also the board has none with regard to the subject-matter of present claims 1 to 7 when taking the disclosure of the prior art documents on file into account. The requirements of Article 54 EPC are therefore fulfilled.

Article 83 EPC

12. The soluble polypeptide according to SEQIDNO:2 of claim 1 is the naturally occurring splice variant of the membrane bound TREM-1 receptor and encodes a protein of 150 amino acids in length. This splice variant shares with TREM-1 the first 136 amino acids which are identical to the TREM-1 first 136 amino acids and encode an Ig-superfamily V type domain (see paragraphs 69, 70 and figure 4 of the application as

- filed) but has a unique stretch of 14 consecutive amino acids at its C-terminal end.
13. The invention as defined in claims 1 or 6 relates to the use of a specific soluble polypeptide according to SEQIDNO:2 or an antibody that binds TREM-1 sv of SEQIDNO:2 but does not bind to TREM-1 for the manufacture of a medicament for the treatment of an inflammatory response in an animal.
 14. The requirements of Article 83 EPC are only complied with if the patent application discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.
 15. In the case of claims to a second medical use such as those under consideration, this means that the disclosure content of the application should not only enable the skilled person to make the compounds to be used, but also that the application must disclose the suitability of the product to be manufactured for the claimed therapeutic effect, i.e. its suitability for the treatment of an inflammatory response because the therapeutic effect is considered as a functional technical feature of the claim (see T 609/02 of 27 October 2004 or T 0433/05 of 14 June 2007).
 16. In the board's view the skilled person is able to make the soluble polypeptide according to claim 1 by the provision of the sequence data of SEQIDNO: 2. Moreover, in view of the unique C-terminal end of SEQIDNO: 2 which is absent in TREM-1 (see point 12 above), the board is satisfied that the skilled person can develop

anti-TREM-1 sv antibodies which do not bind TREM-1 as referred to in claim 6.

17. As regards the suitability of the soluble polypeptides of claim 1 to achieve the claimed therapeutic effect, i.e. the decrease of an inflammatory response, the board observes the following. It is known from the prior art and the present application that TREM-1 triggers an inflammatory response upon stimulation with a ligand, such as LPS (see page 2, lines 17 to 25 of the application as filed and D2, abstract). Moreover, it is disclosed in the application that the polypeptide of SEQIDNO: 2, TREM-1 sv, functions as a competitive inhibitor for the ligand binding to membrane bound TREM-1 thereby decreasing an inflammatory response (see examples 11 to 13 of the application). This function depends on the presence of an identical ligand binding domain on TREM-1 and TREM-1 sv, i.e. a complete Ig-superfamily V type domain (see point 12 above and figure 4 of the application) which is known from common general knowledge to act in general as a functional ligand binding domain. Hence, the teaching of the present application makes it plausible that the therapeutic effect referred to in claim 1 has been achieved.

In addition, post-published experimental data filed by the appellant with the letter of 13 November 2012 further support the achievement of this therapeutic effect. These data show a decrease in the inflammatory response in an animal model for septic shock by administering TREM-1 sv or a peptide-sized fragment thereof (see document D5, and document D7, page 1419,

abstract, page 1420, left col., fourth paragraph, figures 4 and 5).

18. The achievement of the therapeutic effect referred to in claim 6, i.e. an increase of an inflammatory response by an antibody binding to TREM-1 sv, is considered to be plausible for the following reasons. TREM-1 sv is a natural soluble splice variant of the membrane-bound TREM-1 (see point 12 above). As such, it is considered to act as a natural competitive inhibitor of TREM-1 mediated inflammatory responses stimulated by the binding of its ligand in that it competes for the ligand binding with the membrane-bound TREM-1 (see point 17, supra). This competition results in a lower concentration of TREM-1 ligand available for binding to the membrane-bound TREM-1 receptor. However, the binding of an antibody to TREM-1 sv which does not itself bind to TREM-1, reduces the available amount of this natural inhibitor which can then no longer capture the TREM-1 ligand and thereby no longer prevent it from binding to TREM-1. As a consequence thereof an increase of any TREM-1 mediated inflammatory response occurs due to the then increased availability of its ligand.

19. The examining division has not raised any objections of lack of sufficiency of disclosure against the subject-matter of any of the dependent claims 2 to 5 and 7. The board has no reason to come to a different result. Hence, the subject-matter of the claims 1 to 7 is considered to comply with the requirements of Article 83 EPC.

Article 56 EPC

Closest prior art for the subject-matter of claim 1

20. The closest prior art is generally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most technical features in common, i.e. requiring the minimum of structural modifications. This is not different with respect to the claims currently under consideration, i.e. second medical use claims (see T 986/02 of 21 October 2004).

The subject-matter of claim 1 relates to the use of a soluble polypeptide for decreasing an inflammatory response mediated by the membrane-bound TREM-1 receptor by competing with this receptor for the binding of its natural ligand. Thus, the treatment is based on a competitive receptor inhibition.

21. Document D2 is used by the examining division and the appellant as the closest prior art. This document, however, discloses the use of an agonistic anti-TREM-1 antibody for **increasing** the TREM-1 mediated inflammatory response (see page 4991, abstract and col. 2, second paragraph, page 4993, col. 1, second paragraph to col. 2, third paragraph) and is therefore silent on any therapy based on a competitive inhibition.
22. Document D3 relates to the use of soluble receptors **as competitive inhibitors** of their corresponding membrane-bound receptors for the treatment of various diseases. These soluble receptors are either the result of proteolysis of their membrane-bound counterparts or are

produced by alternative splicing (see page 3394, abstract and col. 1, first paragraph and col. 2, second paragraph). Thus, the board considers that document D3 and not document D2 represents the closest prior art for the subject-matter of claim 1.

Problem to be solved

23. Neither inflammatory diseases in general nor TREM-1 or TREM-1 sv in particular are disclosed in document D3. Hence, the objective problem to be solved can be seen as the provision of an alternative receptor-based competitive inhibition therapy.

Solution

24. In the board's view, the above formulated problem is considered to be solved in view of the provision of SEQIDNO: 2 and for the reasons given in point 17 above.

Obviousness

25. The skilled person knows from document D2 that membrane bound TREM-1 triggers inflammatory responses upon stimulation with either an agonistic anti-TREM-1 antibody or LPS or both compounds (see page 4993, left col. second paragraph to right col., first paragraph, page 4994, left col., second paragraph to right col., first paragraph). He would have therefore considered TREM-1 as a target for a receptor-based competitive inhibition therapy. Document D3 suggests the use of soluble receptors, ligands, or their analogs to competitively inhibit the unwanted interaction between membrane-bound receptors and their ligands (see

page 3394, right col., second paragraph). Moreover, this document teaches that soluble forms of receptors are either the result of a proteolytic cleavage of the extracellular part of a membrane bound receptor or produced by an alternative splicing of the transcript encoding this receptor (see page 3394, left col., first paragraph). Therefore following the teaching of document D3, one way of solving the problem mentioned above as suggested to the skilled person would be either to use a proteolytically cleaved soluble TREM-1 molecule or to look for a natural soluble TREM-1 splice variant.

26. However, at the priority date of the present application there were no indications in the art that a natural splice variant of TREM-1 existed. Document D2 mentions a screen of GenBank with the complete open reading frame of TREM-1 to find and isolate further TREM-1 related sequences. This screen did not reveal any splice variant of TREM-1 (see D2, page 4991, right col., third paragraph).

27. Moreover, if the skilled person had followed the route to use a proteolytic cleavage product of TREM-1 as a soluble receptor, he would have arrived at a molecule which is significantly different from the soluble polypeptide characterised by SEQIDNO: 2 of present claim 1. The molecule encoded by SEQIDNO: 2, which is a natural splice variant of TREM-1 (see point 12, above), lacks a considerable portion of the extracellular domain of TREM-1 (amino acid position 138-205). This deleted portion comprises in TREM-1 inter alia three N-linked glycosylation sites (see paragraph 70 and figure 4 of the application as filed). The skilled

person at the relevant date was aware of the fact that glycosylation could be necessary in assisting proper protein folding (see document D6, page 735, fourth paragraph). In addition, the soluble polypeptide of claim 1 contains 14 unique amino acids at its C-terminal end which are absent in TREM-1.

28. Consequently, in view of the combined teaching of documents D3 and D2 the skilled person would not have provided a soluble polypeptide according to present claim 1. Moreover, even if he had been aware of a naturally occurring soluble TREM-1 sv, he would not have reasonably expected, in view of the significant structural differences between the extracellular portion of TREM-1 and the splice variant, that this molecule can bind the TREM-1 ligand and thus act as a functional competitive inhibitor.

29. Hence, the board considers the subject-matter of present claim 1 as not obvious in view of the combination of documents D2 and D3 which represent the most relevant documents on file for the assessment of an inventive step. The same applies to the subject-matter of claims 2 to 5 and 7 being dependent thereon. Consequently, the subject-matter of claims 1 to 7 fulfils the requirements of Article 56 EPC.

Closest prior art for the subject-matter of claim 6

30. The subject-matter of independent claim 6 relates to the use of an antibody binding to TREM-1 sv of SEQIDNO:2, but not TREM-1, to increase an inflammatory response. Document D2 discloses the use of an agonistic

anti-TREM-1 antibody, i.e one which increases the inflammatory response mediated by membrane-bound TREM-1 by stimulating it upon binding (see page 4993, left col. second paragraph to right col., first paragraph). Consequently, the board considers that document D2 is the closest prior art for the subject-matter of claim 6.

Problem to be solved

31. The objective problem to be solved is thus the provision of an alternative antibody capable of stimulating TREM-1 mediated inflammatory responses.

Solution

32. In the board's view, the above formulated problem is solved in view of the provision of an antibody binding specifically to TREM-1 sv, but not TREM-1, and for the reasons given in point 18 above.

Obviousness

33. The skilled person at the relevant date of the present application had no indication that TREM-1 sv, the natural splice variant of TREM-1, exists (see document D2, page 4991, right column, third paragraph and point 26 above). Therefore, he had even less indication that it has a C-terminal end which is as such unique and not present in the TREM-1 molecule. Hence, the skilled person was neither aware of any naturally existing TREM-1 competitive inhibitor nor that it was structurally so different that antibodies binding specifically to it could be raised. The provision of this antibody results in the removal of free TREM-1 sv

which can then no longer act as a natural competitive inhibitor for TREM-1 mediated inflammatory responses. As a consequence of this removal TREM-1 mediated inflammatory responses are increased. Hence, the provision of an antibody that binds specifically and selectively to a natural inhibitor of TREM-1 which increases TREM-1 mediated inflammation cannot be considered obvious in the light of document D2 alone or in combination with any other document on file.

34. Consequently, the subject-matter of independent claim 6 and claim 7, being dependent thereon, involves an inventive step and fulfils 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 department of first instance with the order to grant a patent on the basis of claims 1 to 7 of the request filed during the oral proceedings of 14 November 2012 and a description and figures yet to be adapted thereto.

The Registrar:

The Chairman:

P. Cremona

C. Rennie-Smith