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Datasheet for the decision of 18 February 2016

Case Number: T 1113/12 - 3.3.04

Application Number: 03776426.3

Publication Number: 1551444

IPC: A61K38/19

Language of the proceedings: EN

Title of invention:
Method for treatment of demyelinating central nervous system disease using GM-CSF

Applicant:
Hunter, Samuel F.

Headword:
Use of GM-CSF and a type 1 interferon for treating multiple sclerosis/HUNTER

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)
RPBA Art. 13(1), 13(3)

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

Decisions cited:
G 0005/83, T 1021/11

Catchword:

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Case Number: T 1113/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 18 February 2016

Appellant: (Applicant)	Hunter, Samuel F. 908 High Point Red Road Franklin, TN 37069 (US)
Representative:	Wallis, Naomi Rachel Greaves Brewster LLP Copa House Station Road Cheddar BS27 3AH (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 29 November 2011 refusing European patent application No. 03776426.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal was lodged by the applicant (hereinafter "the appellant") against the decision of the examining division to refuse European patent application No. 03776426. The application was filed as an international application, published as WO 2004/035086 (hereinafter "the application") and has the title "*Method for treatment of demyelinating central nervous system disease*".

II. In its decision the examining division dealt with a single request. It took the view that the requirements of Article 123(2) EPC were met for the claims under consideration but that the subject-matter of claims 1, 3, 8 and 10 lacked novelty (Article 54 EPC) over the disclosure of document D3 (see section VII below).

III. With the statement of grounds of appeal, the appellant submitted a main request and four auxiliary requests. The main request corresponded to that underlying the decision under appeal.

IV. Two further auxiliary requests were filed by letter dated 20 January 2016.

V. In a communication pursuant to Article 15(1) RPBA, the board informed the appellant of it's preliminary opinion that none of the pending requests on file appeared to fulfil the requirements of the EPC.

VI. In reply to the board's communication, the appellant withdrew the pending main request and auxiliary requests 1 to 5 and made auxiliary request 6 its new main request. It further submitted five auxiliary requests.

VII. Oral proceedings before the board were held on 18 February 2016. During the oral proceedings the appellant submitted a new main request. At the end of the oral proceedings the chairwoman announced the board's decision.

Claims 1 to 8 of the main request read:

"1. A therapeutically active amount of a granulocyte-macrophage colony stimulating factor for use in the treatment of multiple sclerosis wherein said use is in combination with a type 1 interferon.

2. The therapeutically active amount of a granulocyte-macrophage colony stimulating factor for use according to claim 1, wherein said type 1 interferon is interferon-β-la.

3. The therapeutically active amount of a granulocyte-macrophage colony stimulating factor for use according to claim 1 or claim 2, wherein said granulocyte-macrophage colony stimulating factor is for administration to a subject in an amount of from 50 to 250 micrograms.

4. The therapeutically active amount of a granulocyte-macrophage colony stimulating factor for use according to any of claims 1-3, wherein multiple sclerosis has at least one manifestation selected from acute, chronic, single episode, recurrent episode, progressive, progressive-relapsing, relapsing-progressive, and unremitting.

5. Use of a therapeutically active amount of a granulocyte-macrophage colony stimulating factor in the manufacture of a medicament for use in the treatment of

multiple sclerosis wherein said use is in combination with a type 1 interferon.

6. Use according to claim 5, wherein said type 1 interferon is interferon-β-1a.

7. Use according to claims 5 or claim 6, wherein said granulocyte-macrophage colony stimulating factor is for administration to a subject in an amount of from 50 to 250 micrograms.

8. Use according to any of claims 5-7, wherein multiple sclerosis has at least one manifestation selected from acute, chronic, single episode, recurrent episode, progressive, progressive-relapsing, relapsing-progressive, and unremitting."

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

D3: WO 02/13862

D4: Bartholomé E.J., et. al., Acta Neurologica Belgica, vol. 99, no. 1, 1999, pp. 44-52

D7: McQualter J.L., et. al., J. Exp. Med., vol. 194, no. 7, 2001, pp. 873-881

D8: Smith M.E., et. al., J. Neuroscience Res., vol. 54, no. 1, 1998, pp. 68-78

IX. The appellant's arguments may be summarised as follows:

Amendments (Article 123(2) EPC)

The subject-matter of claims 1 to 8 was disclosed in the application as filed and therefore complied with the requirements of Article 123(2) EPC.

Sufficiency of disclosure (Article 83 EPC)

The application disclosed a clinical study treating multiple sclerosis (MS) in patients by a combination of granulocyte-macrophage colony stimulating factor (GM-CSF) and interferon-β-1a (IFN-β-1a). The patients showed a stabilisation of the disease and an improvement of disability parameters. The suitability of the claimed combination for the treatment of MS was thus credible.

Novelty (Article 54 EPC)

None of the available prior art documents disclosed the use of GM-CSF and a type 1 IFN in the treatment of MS. The claimed invention was thus novel.

Inventive step (Article 56 EPC)

The IFN-β-1a monotherapy of MS disclosed in document D4 represented the closest prior art. The subject-matter of claims 1 and 5 differed therefrom in that it used a combination of GM-CSF and a type 1 IFN. This treatment resulted in improved disability parameters of the MS patients. The technical problem to be solved was thus the provision of an improved treatment of MS patients. The solution, *i.e.* the use of a combination of GM-CSF and a type 1 IFN, was not obvious from the teaching of document D4, either alone or in combination with any of

the other available prior art documents, since the prior art suggested that GM-CSF rather worsened MS and the skilled person would therefore not have used it. The claimed invention was thus inventive.

X. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division with the order to grant a European patent on the basis of the main request filed at oral proceedings and a description and figures adapted thereto.

Reasons for the Decision

Main request

Admission

1. The main request now under consideration was filed during the oral proceedings. The amendments made in this request are straightforward, do not raise new issues and neither increased the complexity of the appeal case nor required a postponement of the oral proceedings. Consequently, the board admitted the request into the proceedings (Article 13(1) and (3) RPBA).

Amendments (Article 123(2) EPC)

2. The subject-matter of claims 1 and 5 can be derived from the disclosure in claims 15 and 20 as filed which reads: "*A method of treating multiple sclerosis comprising: administering to the subject a composition comprising a therapeutically active amount of a granulocyte-macrophage colony stimulating factor or colony stimulating factor-like ligand*" and "*the method of claim*

15 wherein said composition includes a type 1 interferon-congener". That the "*type 1 interferon-congener*" of claim 20 as filed is a type 1 interferon can be derived from page 10, line 11 of the application as filed reading "*type 1 interferons (largely interferon alpha and beta congeners)*".

3. The subject-matter of claims 2 and 6 is supported by the disclosure on page 10, lines 12 and 13 of the application as filed which reads: "*The most preferred immunomodulator is interferon-beta-1a*".

4. The subject-matter of claims 3 and 7 reflects the disclosure in claim 22 as filed which reads: "*The method of claim 15, wherein said granulocyte-macrophage colony stimulating factor or colony stimulating factor-like ligand is administered to the subject in an amount of from about 50 to about 250 micrograms*".

5. The subject-matter of claims 4 and 8 is disclosed in claim 14 as filed which reads: "*The method of claim 1, wherein said disease* [demyelinating central nervous system diseases] *has at least one of the following manifestations: acute, chronic, single episode, recurrent episode, progressive, progressive-relapsing, relapsing-progressive, and unremitting*". That multiple sclerosis (MS) is a demyelinating disease of the central nervous system can be derived from the disclosure on page 1, lines 7 and 8 of the application as filed reading: "*The present invention relates to the treatment of demyelinating central nervous system diseases, including multiple sclerosis*".

6. The board therefore concludes that the subject-matter of claims 1 to 8 has a basis in the application as filed and meets the requirements of Article 123(2) EPC.

Clarity, support (Article 84 EPC)

7. Claims 1 and 5 are directed to the use of a combination of granulocyte-macrophage colony stimulating factor (GM-CSF) and type 1 interferons (type 1 IFNs) in the treatment of MS.

8. The application discloses that the compounds GM-CSF and type 1 IFNs, and MS as the disease to be treated, are known at the priority date of the application and have a defined meaning (see page 1, line 18 to page 2, line 11, page 2, lines 15 to 17 and page 6, lines 12 to 19 of the application). The subject-matter of claims 1 and 5 is thus clear and supported by the application, and allows the skilled person to distinguish the compounds that belong to the combination of agents for use in the claimed treatment from those that do not. The board also has no objections regarding the clarity of the subject-matter of claims 2 to 4 and 6 to 8.

9. Accordingly, the board is satisfied that the subject-matter of claims 1 to 8 meets the requirements of Article 84 EPC.

Sufficiency of disclosure (Article 83 EPC)

10. Independent claims 1 and 5 are directed to a second medical use drafted either in the form pursuant to Article 54(5) EPC or in the "Swiss-type" form instituted by decision G 5/83 (OJ EPO 1985, 64). The board has no objections to the presence of claims drafted in the "Swiss-type" format and according to the provisions of

Article 54(5) EPC in a single set of claims (see decision T 1021/11, points 34 to 49 of the reasons).

11. The application discloses that GM-CSF and type 1 IFNs are generally known in the art (see point 8 above). The skilled person is thus able to treat MS patients by a combination of these two agents based on the information disclosed in the application.

12. It is also established case law in relation to claims directed to a medical use that, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed medical use at the relevant date (see Case Law of the Boards of Appeal of the EPO, 7th edition, II.C.6.2, first and second paragraphs).

13. Regarding the suitability of GM-CSF and type 1 IFNs for treating MS, the application provides evidence in the form of data from a clinical study with five human MS patients, four of whom showed a stabilisation of the disease and an improvement in certain disability parameters when treated by a combination of GM-CSF and IFN-β-1a (see the example starting on page 12, line 15 to page 14, line 20 and figures 1 to 5).

14. Also, the prior art discloses that type 1 IFNs, such as interferon-α and interferon-β (IFN-β), are known to exert beneficial immunomodulatory effects in the treatment of MS patients (see e.g. document D4, abstract, page 44, column 2, third paragraph to page 45, column 1, first paragraph and table I).

15. The board therefore concludes, in view of the evidence disclosed in the application and in the prior art, that

it is credible that the use of the combination of GM-CSF and a type 1 IFN is suitable for the treatment of MS.

16. Thus, the subject-matter of independent claims 1 and 5 fulfils the requirements of Article 83 EPC. The same applies to the subject-matter of their dependent claims 2 to 4 and 6 to 8.

Novelty (Article 54 EPC)

17. The board observes that the use of GM-CSF in a composition with other unknown ingredients in the treatment of MS is no longer an embodiment of the subject-matter of independent claims 1 and 5, contrary to the subject-matter of the corresponding claims 1 and 8 of the request underlying the decision under appeal. The present claims 1 and 5 are now directed to the treatment of MS by a composition comprising at least the combination of GM-CSF and type 1 IFNs.

18. Document D3 was the sole prior art document considered by the examining division in the decision under appeal, to anticipate a composition comprising GM-CSF for use in the treatment of MS. It discloses *inter alia* the use of a chimeric protein in combination with GM-CSF for the treatment of B-cell pathologies, such as MS. The chimeric protein comprises at least a portion of a V_H or V_L region and at least a portion of an immunoglobulin constant region (see document D3, page 8, line 26 to page 9, line 9, claims 34 in combination with claims 43, 44 and 51). The board therefore considers that the chimeric protein of document D3 is in fact an antibody or a fragment thereof which is structurally and functionally different from type 1 IFNs.

19. The board therefore concludes that the subject-matter of independent claims 1 and 5 is novel. This conclusion also applies to the subject-matter of their dependent claims 2 to 4 and 6 to 8.

20. Hence, the subject-matter of claims 1 to 8 meets the requirements of Article 54 EPC.

Inventive step (Article 56 EPC) - claims 1 and 5

Closest prior art

21. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art.

22. The examining division and the appellant agreed that the disclosure of document D4 represented the closest prior art for the subject-matter of claims 1 and 5, and the board sees no reason to differ.

23. Document D4 reports that clinical studies have demonstrated the beneficial effects of IFN-β, which is a type 1 IFN, in the treatment of MS (see page 44, column 1, first and second paragraph). This treatment of MS by IFN-β thus represents the closest prior art.

Technical problem and solution

24. The subject-matter of claim 1 differs from the closest prior art treatment in that it uses a combination of GM-CSF and a type 1 IFN for treating MS patients, thus improving their disability parameters. In view of the

closest prior art and in view of the effects achieved by the combination of GM-CSF and a type 1 IFN, the technical problem to be solved is formulated as the provision of an improved treatment for MS patients.

25. The board is satisfied that this problem is solved by the subject-matter of claims 1 and 5 in view of the improved disability parameters reported in the application (see point 13 above).

Obviousness

26. It remains to be assessed whether or not the skilled person, starting from the use of IFN-β for the treatment of MS in document D4 and faced with the technical problem defined in point 24 above, would be motivated to modify the teaching of the closest prior art either in the light of the teaching of document D4 alone or in combination with that of other prior art documents.

27. The active principle underlying the therapeutic effect of IFN-β in the treatment of MS according to document D4 is the persistent inhibition of interleukin-12 synthesis in dendritic cells (DCs) impairing the DC's ability to activate T-cells, which are thought to be the major pathogenic effectors (see page 49, column 1, last line to column 2, last paragraph). Document D4 does not contemplate means to further improve the efficacy of IFN-β in the treatment of MS, e.g. by combining it with another agent. In particular, it does not suggest the combining with GM-CSF.

28. Accordingly, the board concludes that document D4 on its own provides no hint to use a combination of IFN-β and GM-CSF to achieve an improved treatment of MS.

29. Nor is a pointer motivating the skilled person to combine IFN-β with GM-CSF for the treatment of MS derivable from any of the other available prior art documents.

30. On the contrary, document D7 discloses that GM-CSF maintains a chronic inflammation in the brain of mice suffering from experimental autoimmune encephalomyelitis, which serves as an animal model for MS in humans (see abstract). Inflammatory processes in the brain could be successfully treated by an antibody directed against GM-CSF (see figure 7).

31. Document D8 reports that GM-CSF activates macrophages and microglia cells in the brain of patients affected by MS (see abstract and page 75, column, 2 first paragraph). In particular the latter cells are proposed as one of the main effectors fostering MS progression by promoting brain injury through myelin phagocytosis and free radical production (see page 76, column 2, third paragraph).

32. In the board's view, the skilled person would derive from the teaching of documents D7 and D8 that GM-CSF worsens MS rather than having a beneficial therapeutic effect, and would therefore avoid using it to treat the disease.

33. In summary, the board concludes that the subject-matter of claims 1 and 5 was not obvious to the skilled person from the state of the art. The same reasoning also applies to the subject-matter of their dependent claims 2 to 4 and 6 to 8.

34. Hence, the subject-matter of claims 1 to 8 fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

- The decision under appeal is set aside.

- The case is remitted to the examining division with the order to grant a patent on the basis of the claims of the main request as filed at the oral proceedings and a description and figures to be adapted thereto.

The Registrar: The Chairwoman:

A. Wolinski G. Alt

Decision electronically authenticated