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D E C I S I O N
of 25 May 1998

Case Number: T 0027/93 - 3.3.4

Application Number: 84301377.2

Publication Number: 0121338

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Biosynthetically produced human nerve growth factor, process for producing it, compositions containing it, DNA sequence encoding it, vectors containing the sequence and host cells transformed thereby

Patentee:
Genentech, inc.

Opponent:
Synthex (U.S.A.) Inc.

Headword:
Human nerve growth factor/GENENTECH, INC.

Relevant legal provisions:
EPC Art. 83

Keyword:
"Main request: sufficiency of disclosure (yes)"

Decisions cited:
-

Catchword:

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0027/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 25 May 1998

Respondent: (Opponent 01)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 12 November 1992 concerning maintenance of European patent No. 0 121 338 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
W. Moser

Summary of facts and submissions

I. European patent No. 0 121 338 with the title "Biosynthetically produced nerve growth factor, process for producing it, compositions containing it, DNA sequence encoding it, vectors containing the sequence and host cells transformed thereby" was granted with 13 claims for all designated Contracting States except Austria and with 11 claims for the designated Contracting State Austria, on the basis of European patent application No. 84 301 377.2.

As regards the claims for all designated Contracting States except Austria of the patent in suit as granted, claim 1 read as follows:

"1. A polypeptide of the amino acid sequence ... (amino acid sequence follows) ... and having the properties of human β-NGF."

Dependent claim 2 related to a further embodiment of the polypeptide of claim 1 and dependent claims 3 and 4 related to pharmaceutical preparations containing it. Dependent claims 5 to 8 related to a DNA isolate, an expression vector and a host cell carrying/expressing the DNA sequence encoding the polypeptide. Claims 9 to 13 were addressed to processes for production of the polypeptide and pharmaceutical preparations thereof.

Corresponding method claims were filed for the designated Contracting State Austria.

II. A notice of opposition was filed requesting the revocation of the patent under Article 100(a) EPC (lack of novelty and inventive step) and under Article 100(b) EPC (insufficiency of disclosure).

III. The Appellant filed a new main request and three auxiliary requests for consideration by the Opposition Division. As regards all designated Contracting States except Austria, the main request was the claim request as granted except for the dependency of claims 7 and 8 which was corrected to be on claims 6 and 7 rather than on claims 5 and 6, respectively. As regard the designated Contracting State Austria, the main request was the claim request as granted. The auxiliary requests are irrelevant in view of the "Reasons for the decision".

IV. By an interlocutory decision within the meaning of Article 106(3) EPC, the Opposition Division maintained the patent in amended form according to Article 102(3) EPC on the basis of the third auxiliary request and of a correspondingly amended description.

Novelty and inventive step were acknowledged to the claims of the main request. It was, however, decided that the subject-matter of claim 1 of this request was not disclosed in an enabling manner since the patent specification did not provide any information on how to isolate human β-NGF from E. coli in a biologically active form.

V. The Appellant (Patentee) filed an appeal, paid the appeal fee and submitted the grounds for the appeal together with a main request identical to that refused by the Opposition Division and three further auxiliary requests.

VI. The Respondent (Opponent) filed an appeal which was subsequently withdrawn.

VII. A communication was sent according to Article 11(2) of the Rules of Procedure of the Boards of Appeal, setting out the Board's provisional, non-binding opinion.

VIII. The Appellant filed a further submission together with three declarations from scientific experts.

IX. Oral proceedings took place on 25 May 1998.

X. The following documents on file will be considered in this decision:

(3): Goldstein, L.D. et al., Neurochemical Res., vol. 3, 1978, pages 175 to 183

(34): Declaration of Dr F. Collins dated 15 June 1990 filed by the Respondent with letter dated 3 July 1990

(54): Sutter, A. et al., The J. of Biol. Chem., vol. 254, No. 13, 1979, pages 5972 to 5982

(74): Declaration of Dr F. Collins dated 30 January 1992, filed by the Respondent with letter dated 7 February 1992

(143): Declaration of Dr K. Nicholics dated 12 March 1993, filed by the Appellant with letter dated 19 March 1993

(154): Declaration of Dr M. Sadick dated 29 December 1997 filed by the Appellant with letter dated 13 January 1998

(155): Excerpts from an internal Genetech Inc. report by Mr Wai-Pan Chan, 1993 filed by the Appellant with letter dated 30 December 1997.

XI. The submissions in writing and during oral proceedings by the Appellant can be summarized as follows:

- Documents (34) and (74) were reports on the experiments submitted to the Opposition Division by the Respondent as evidence that human recombinant β-NGF (rhNGF) produced from E. coli had no biological activity. These experiments were flawed because the expression systems used were different from the expression system taught by the patent in suit and also because the assay for biological activity had been carried out in a way which essentially precluded that rhNGF would be found to be active (i.e. in the presence of urea). Nonetheless the graph showed a low level of specific activity when increasing amounts of rhNGF were added in the nerve cells growth assay, proving that in spite of unsuitable experimental conditions, rhNGF was biologically active.

- Excerpts of an internal Genentech, Inc. report by Mr Wai-Pan Chan (document (155)) described a protocol which enabled the purification of rhNGF. This report provided evidence that rhNGF bioactivity could be detected at every step in the purification process, including in the cell lysate supernatant before any purification had taken place. This protocol could have been carried out by the person skilled in the art at the filing date of the patent in suit. In particular, the growing of a sufficient amount of E. coli cells from which to start the purification would have been achieved following current laboratory practice, and the radio receptor assay used to show the presence of rhNGF in a suspension of the cells' pellet was readily available (documents (54) and (143)). No undue burden was involved.

- The experiments carried out by the Appellant (document (143)) showed biologically active rhNGF to be the outcome of a multi-step purification process starting with the supernatant of an E. coli cell culture and involving anion exchange, cation exchange chromatographies and RP-HPLC. At the filing date of the patent in suit, it was well within the competence of the skilled person to devise and carry out such a process.

- Some post-published documents mentioned difficulties in obtaining rhNGF in sufficient quantities for clinical trials or general research. The non-availability of a product for such uses could not necessarily be assumed to be due to difficulties in producing it. And besides, it was well established that for patent purposes the actual quantity was unimportant so long as the product was produced at all. Finally the fact that bioactive rhNGF was produced in eucaryotic cells in later years did not imply that it could not be made in E. coli.

XII. The submissions in writing by the Respondent can be summarized as follows:

- The Respondent had not been able to obtain biologically active human rhNGF by following the teachings of the patent in suit as evidenced by the results obtained in documents (34) and (74). Neither the expression system nor the conditions for the assay which were chosen in these two experimental reports would have been likely to affect the biological activity of the expressed polypeptide.

- The experiment by the Appellant (document (143)) showing that biologically active rhNGF could be produced from E. coli was carried out following a method different from that taught in the patent in suit, which would not have been within the competence of the skilled person at the filing date. It thus was not a suitable basis on which to acknowledge sufficiency of disclosure.

- As the detailed description in the Example of the patent in suit relating to E. coli did not enable the skilled person to produce bioactive rhNGF, it was not credible that the series of very general statements which had also been made in relation to possible other host cells such as mammalian cells would be sufficient to support sufficiency of disclosure.

XIII. The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the following requests:

(a)- claims 1 to 13 filed on 19 March 1993 as main request, or

(b)- claims 1 to 7 filed on 19 March 1993 as first auxiliary request, or

(c)- claims 1 to 7 filed on 19 March 1993 as second auxiliary request, or

(d)- claims 1 to 5 filed on 19 March 1993 as third auxiliary request.

The Respondent requested that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.

Main request

Sufficiency of disclosure

2. The Opposition Division decided that the subject-matter of claim 1, which relates to a polypeptide with a defined amino-acid sequence and having the properties of human β-NGF, had not been sufficiently disclosed. Thus, the fulfilment of the requirements of Article 83 EPC is at issue.

3. The isolation of vectors carrying the coding sequence for human β-NGF and potentially suitable for the expression of said sequence in E. coli is described in detail in the specification (paragraphs C5 to C7) of the patent in suit, which also discloses the expression therefrom of a polypeptide of the expected molecular weight for human β-NGF. This polypeptide is characterized by its ability to react with rabbit anti-mouse β-NGF antibodies in a Western blot, which ability is also a property shared by human β-NGF (document (3)). There is no disclosure that rhNGF possesses any of the other biological properties of natural human β-NGF.

4. According to the wording of claim 1 ("A polypeptide ... having the properties of β-NGF"), the polypeptide produced in E. coli has more than one biological property of natural human β-NGF. Sufficiency of disclosure can be acknowledged if the E. coli produced polypeptide possesses two biological features of natural human β-NGF. Additionally, as the specification of the patent in suit (page 9, lines 3 to 5) discloses

that the rhNGF is to be used for the treatment of subjects suffering from nerve damage, this further feature should be the biological activity of natural human β-NGF.

5. The biological activity of E. coli-produced rhNGF was tested in documents (34) and (74) which are experimental reports submitted by the Respondent to the Opposition Division. The recombinant E. coli cells are grown, lysed and centrifuged. An immunological assay carried out with rabbit anti mouse β-NGF antibody shows that rhNGF is exclusively present in the cell pellet resulting from the centrifugation. RhNGF is then solubilized from this pellet in a buffer containing 8M urea and tested for biological activity using the nerve growth stimulation assay. The results are recorded in a graph where the increase in optical density due to neural growth is plotted against the amount of rhNGF added in the assay.

6. The Appellant provided a statistical analysis (document (154)) of the graph shown in document (74) which led him to conclude that there was a significant amount of bacterially produced rhNGF bioactivity in at least the two higher concentrations tested.

7. In the Board's judgment, while the statistical analysis of data such as in document (74) may suggest the biological phenomenon which could be responsible for the results observed, an unambiguous proof of the existence of this biological phenomenon resides in unambiguous results obtained by biological methods. This opinion is at least partly shared by the author of document (154), who concludes the statistical analysis contained therein by the statement: "And ... it follows that had Dr Collins tested higher concentrations of sample, an increase in bioactivity could have been

observed ...". Accordingly, the Board concludes that documents (34) and (74) do not sufficiently prove that the claimed rhNGF has biological activity.

8. However, at the appeal stage, the Appellant provided excerpts of an internal report by Mr Wai-Pan Chan disclosing the protocol used in 1993 in the Appellant's firm to purify rhNGF from transformed E. coli. According to this report, it is possible to show the presence of bioactive rhNGF in the E. coli cell paste suspension prior to any purification by the NGF radio receptor assay. The experiment is done starting from 1.6 kg of cell paste. The cell paste suspension is shown to contain 6 ng/ml of rhNGF. From these data, it can be concluded that rhNGF is synthesized by E. coli in bioactive form.

9. Asked by the Board during oral proceedings whether it would have constituted an undue burden for the skilled person at the filing date to grow such an amount of E. coli cells as necessary to obtain a measurable quantity of human β-NGF, the scientific expert of the Appellant answered "no". There is no counter-evidence on file that it would indeed have constituted an undue burden. Furthermore, documents (54) and (143) show that the NGF radio receptor assay was already available in 1979. Thus, it is concluded that at the priority date the skilled person would have had the ability and knowledge necessary to produce without undue burden, a polypeptide according to claim 1 with the immunological properties and biological activity of human β-NGF by a process as claimed in claim 9 in a host cell as described in claim 8.

10. The Appellant submitted further experimental evidence (document (143)) that biologically active rhNGF could be purified from the supernatant of lysed E. coli cells

by a multi-step process involving anion and cation exchange chromatographies as well as RP-HPLC. The question of whether at the priority date this protocol could have been carried out with undue burden by the skilled person willing to assess the presence of biologically active rhNGF in E. coli need not be answered in view of the findings in paragraphs 8 and 9, above.

11. Sufficiency of disclosure with regard to the subject-matter of the other claims of the main request was never put into question. The requirements of Article 83 EPC are fulfilled.

Novelty and Inventive Step

12. These two issues were already dealt with by the Opposition Division which concluded that the main request fulfilled both these requirements. The Board agrees with the conclusions reached by the Opposition Division in respect of novelty and inventive step of the claims of the main request.

Conclusion

Since the subject-matter of the granted claims 1 to 11 for the designated Contracting State Austria also meets the requirements of Article 83, 54 and 56 EPC, the patent in suit can be maintained with the claims 1 to 13 for all designated Contracting States except Austria, filed on 19 March 1993 as main request, and the claims 1 to 11 for the designated Contracting States Austria as granted.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent as amended in the following version:

   description: pages 2 to 9 as granted, and

   claims: 1 to 13 for all designated Contracting States except Austria filed on 19 March 1993 as main request, and 1 to 11 for the designated Contracting State Austria as granted.

   drawings: Figures 1 to 8 as granted.

The Registrar: The Chairwoman:

D. Spigarelli U. Kinkeldey