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D E C I S I O N
of 19 September 1995

Case Number: T 0495/92 - 3.3.4

Application Number: 83109788.6

Publication Number: 0112976

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Novel DNA and Recombinant plasmid containing the same

Patentee:
THE CANCER INSTITUTE OF JAPANESE FOUNDATION FOR CANCER RESEARCH, et al

Opponent:
Boehringer Ingelheim GmbH

Headword:
Gln^{9} - interferon variant/CANCER INSTITUTE

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - (no)"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0495/92 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 19 September 1995

Appellant: (Opponent)
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Respondent: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office dated 1 April 1992 concerning maintenance of European patent No. 0 112 976 in amended form.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 0 112 976 was granted with the title "Novel DNA and recombinant plasmid containing the same", with six claims based on European application No. 83 109 788.6.

II. A notice of opposition was filed. Grounds were presented for the revocation of the patent in its entirety under Article 100(a) EPC (lack of inventive step) and Article 100(b) EPC (insufficiency of disclosure) .

Five documents were cited in support of the grounds for opposition:

(1): Gray et al., Nature, volume 295, pages 503 to 508, (1982)

(2): Devos et al., Nucl.Acids Res., volume 10, pages 2487 to 2501 (1982)

(3): Derynck et al., Nucl.Acids Res., volume 10, pages 3605 to 3615, (1982)

(4): Doolittle, "The proteins" , volume IV, H. Neurath et al., Ed., Academic Press pages 17, 18, 43, 44, (1979)

(5): Nishi et al., J. Biochem., volume 97, pages 153 to 159, (1985).

III. On 3 January 1992, the Respondent (Patentee) filed a new set of claims for the Contracting States GB, DE, FR, IT, CH, BE, NL and on 11 February 1992, a new set of claims for AT which corresponded to the set of claims for the other Contracting States.

IV. The Opposition Division maintained the patent in an amended form on the basis of these claims.
Claim 1 for all designated Contracting States but AT reads:

"A DNA sequence encoding Gln^9-interferon-gamma, said Gln^9-interferon-gamma having the following amino acid sequence:

CYS TYR CYS GLN ASP PRO TYR VAL GLN...(*wild type sequence of gamma interferon follows*)".

Claim 1 for the Contracting States AT relates to an Escherichia coli microorganism containing a recombinant DNA including said sequence.

V. The Appellant (Opponent) lodged an appeal against the decision of the Opposition Division, paying the appeal fee at the same time. The statement of grounds of appeal was submitted.

VI. Further submissions were received from both parties.

VII. A communication was sent by the Board according to Article 11(2) of the Rules of Procedure of the Boards of Appeal setting out the Board's preliminary position.

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

(a) It was known from documents (1) - (3) that variants of the wild-type interferon could be isolated. In view of this knowledge, any novel, specific interferon-gamma variant could only be acknowledged as inventive if endowed with unexpected properties.

(b) The two experiments provided by the Respondent in the course of examination to allegedly show that the claimed Gln^{9}-interferon-gamma variant had unexpected properties when compared with the wild-type interferon were not in any way conclusive, for the following reasons:

In both experiments, the biological activity of each interferon was defined as the average between three independent measurements which were so widely scattered that their combination within one average value had to be meaningless.

The difference between the biological activities at physiological temperatures of both Gln^{9}- and wild-type interferons was always very narrow. It could only be considered statistically significant if said biological activities had been derived from many more independent measurements than were done. The slightly better results found for the Gln^{9}-interferon were, thus, of no value.

If any conclusion relevant to inventive step was to be derived from Experiment 1, it was that Gln^{9}-interferon was more labile than wild-type interferon at low temperatures. In the same manner, the only clear-cut result brought by Experiment 2 was that Gln^{9}-interferon was 50% less activatable by trypsin in high concentration than wild-type interferon.

In Document (5) (to be considered an expert document), the Respondent himself admitted that the presence of Gln at position 9 might not affect the specificity of the wild-type.

IX. The Respondent replied as follows:

The scattering of the experimental values used to define biological activity occurred in the same manner for both interferons. It should, therefore, not be given too much importance.

The statistical findings of the Appellant could not be denied but should be put in the proper perspective which was that biological effects may exist and still not be prone to assessment with the help of mathematics.

Experiment 1 showed enhanced activity for the Gln^9-interferon at 37°C compared with 5°C. This result was certainly unexpected.

Experiment 2 showed a tendency for the Gln^9-interferon to be more activatable than the wild-type interferon at low concentrations of trypsin. This effect might not be derived from the teachings of (5), which did not deal with trypsin activation.

The low activation of Gln^9-interferon at high trypsin concentration had to be disregarded. It was probably due to the fact that such a high trypsin concentration is not physiological and, therefore, led to aberrant results.

X. The Appellant requested that the decision under appeal be set aside and that the European patent No. 0 112 976 be revoked.

XI. The Respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Inventive step (Article 56 EPC)

The closest prior art

2. Document (2) discloses the DNA encoding an interferon-gamma, which differs from the DNA already obtained in document (1) by the replacement of a Gln codon at position 420 with an Arg codon. It is not possible to deduce from the teachings of documents (1) and (2) which of the Gln-140- or Arg-140- interferon encoding DNAs is the wild-type and which is the variant.

3. On the other hand, document (3) describes both said DNAs and is the first document to unambiguously identify the Gln-140-interferon-gamma DNA of document (1) as the variant. In addition to disclosing the DNAs encoding the Gln-140- and Arg-140- interferons, document (3) also discloses the interferons (per se) and shows both of them to be indistinguishable from each other in terms of biological activity.

The technical problem

4. In the light of documents (2) or (3), the underlying technical problem can be defined as the provision of an alternative interferon gamma.

The solution

5. The solution is an interferon gamma variant as claimed which carries a glutamine instead of a lysine at position 9 on the molecule.

Assessment of inventive step

6. Document (3) discloses that it is possible to isolate variants of interferon-gamma, as well as a method for doing so. Thus the mere fact that a further gamma-interferon variant has been obtained by the Respondent cannot in itself be considered unexpected.

7. In the Board's view, the very specificity of the claimed Gln9-interferon variant cannot be indicative of inventive step either, because a variant necessarily has to carry a change in its sequence and there is no prejudice in the art against the position and type of change observed.

8. On the other hand, there does not seem to exist any reliable way to predict which specific change in the primary structure of a protein will lead to a change in biological activity. Thus, the isolation of the specific Gln9-interferon variant can be considered unexpected if said variant is shown to have altered biological properties.

9. Two experiments were submitted by the Respondent during examination procedure to provide evidence of the Gln^{9}-interferon gamma's unexpected properties. In both experiments, each biological activity tested is defined as the average between three independent measurements.

10. Experiment 1 discloses a comparison between the biological activities of the Gln^{9}- and the wild-type interferons under physiological conditions, i.e. after incubation for 24 hours at 37°C and shows that the Gln^{9}-interferon is 14% more active than the wild-type. It also provides evidence that the Gln^{9}-interferon is 50% more active at 37°C than at 5°C whereas the activity of the wild-type remains the same at both temperatures.

11. Experiment 2 is meant to compare the susceptibility of the Gln^{9}- and wild-type interferons to trypsin activation. Both interferons are incubated with various amounts of trypsin before their biological activities are tested. It is found that the Gln^{9}-interferon is 27%, 6.5% or 18% more active than the wild-type at trypsin concentrations of 1/100, 1/200 and 1/400. At a trypsin concentration of 1/50, the Gln^{9}-interferon is 51% less active than the wild-type interferon.

12. If recognition of inventive step is to be based on the results of a comparison of the average biological activities of the Gln^{9}- and wild-type interferons, these activities have to be intrinsically meaningful.

13. In Experiment 1, the values on which the average biological activity of the Gln^{9} and the wild-type interferons is based are as follows: Gln^{9}-: 248.3, 230.9, 284 U/ml; wild-type: 234.0, 233.8, 205.7 U/ml. Thus,in each case, two of the experimental values are practically identical whereas the third one is remarkably high (Gln9-interferon: 284) or remarkably low (wild-type: 205.7).

14. It is to be expected that independent experimental measurements of biological activity lead to different results. Biological assays are intrinsically variable because they involve live materials, the behaviour of which is hardly exactly reproducible. This inherent characteristic of biological assays can, however, be taken care of in a standard manner in order to produce significant biological data, which is to repeat the assays and to discard any "stray value" which may occur.

15. It is apparent from the way the average values have been calculated that the 14% increase in activity of the Gln^{9} over the wild-type interferon is solely based on the

experimental value for each interferon which obviously strays from the values otherwise obtained. The Board cannot accept the argument of the Respondent that because the scattering of the experimental values used to determine the average biological activities occurs in the same manner for both the wild-type and variant interferons, it should not be given any importance. In the Board's view, if stray values are not eliminated in the calculation of averages, these averages are objectionable and their comparison meaningless.

16. The statistical data carried out by the Appellant and accepted by the Respondent at oral proceedings indicate that many convergent measurements would be necessary to make a 14% difference statistically relevant. The Respondent himself recognizes in a post-published publication (Document (5)) that "the presence of Gln at position 9 might not affect the specificity of the wild-type".

17. The Respondent emphasizes that the Gln°-interferon appears to be 50% more active after 24 hours at 37°c than after 24 hours at 5°C. This result is, however, also obtained by comparing averages calculated from too few and too far-apart experimental values. Accordingly, by the same rationale as given above, the experiment does not show that the Gln°-interferon has altered, unexpected properties.

18. For these reasons, the Board is not convinced by the results of Experiment 1 with regard to an enhanced biological activity of the variant compared to the wild-type.

19. Experiment 2 purportedly shows the activation of both interferons by trypsin at low concentrations.

20. Some determinations of average biological activity are fairly homogeneous: for example, the biological activity of the wild-type interferon at a trypsin concentration of 1/200 (1240.6 U/ml) is calculated from three independent measurements which vary by 4.7% at the most (1271.8 and 1214.5 U/ml). Others, however, are widely scattered: the biological activity of the Gln^{9}-interferon at a trypsin concentration of 1/100 (887.7 U/ml) is calculated from three independent measurements which vary by as much as 39% (760.2 and 1059.3 U/ml), that of the wild-type interferon at a trypsin concentration of 1/400 (1309.2 U/ml) derives from measurements which vary by as much 56% (1004 and 1566 U/ml).

21. As in Experiment 1, the interpretation of the data did not involve the elimination of stray values. Moreover, too few repeats of each measurement were performed for the difference observed between average biological activities calculated therefrom to be significant.

22. Accordingly, the Board cannot find Experiment 2 any more conclusive than Experiment 1 as to the improved biological properties of the Gln9-interferon compared to the wild-type.

23. The Respondent has pointed out to the Board that there is a definite albeit small tendency for the Gln^{9}-interferon to show a better biological activity in the presence of trypsin at low concentrations. In his opinion, this effect should be acknowledged as unexpected even if the experiment was not sufficiently repeated that a statistical analysis could be performed. However, it is apparent from the results obtained that the more trypsin is added, the less active are the interferons (887, 1240 and 1553 U/ml at trypsin concentrations of 1/100, 1/200 and 1/400 respectively).

This observation is in direct contradiction with the knowledge that trypsin activates interferons. Thus, the biological meaning of the data is quite unclear and not conducive to drawing any conclusion as to the properties of the Gln^{9}-interferon.

24. Accordingly, the Board decides that inventive step may not be acknowledged to the subject-matter of any of the claims filed for the Contracting States GB, DE, FR, IT, CH, BE, NL. The same conclusion is equally reached for the set of claims filed for Austria.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

A. Townend U. Kinkeldey