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D E C I S I O N
of 17 July 1997

Case Number: T 0475/93 - 3.3.4

Application Number: 85904699.7

Publication Number: 0189481

IPC: C07H 21/04

Language of the proceedings: EN

Title of invention:
Insulin-like Growth factor II

Patentee:
Chiron Corporation

Opponent:
US Surgical Corp.

Headword:
IGF-II/CHIRON

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no: reasonable expectation of success)"

Decisions cited:
T 0001/81, T 0296/93

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0475/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 17 July 1997

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 23 March 1993 revoking European patent No. 0 189 481 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
W. Moser

Summary of Facts and Submissions

I. European patent No. 0 189 481, based on European patent application No. 85 904 699.7 and claiming priority from US 630557 dated 13 July 1984, was granted on 23 January 1991.

II. A notice of opposition was filed by the Respondent (Opponent). Revocation of the patent in its entirety was requested on the grounds of lack inventive step (Article 56 EPC) and because the elucidation of the DNA sequence encoding IGF-II was a mere discovery excluded from patentability (Article 52(2)a EPC).

III. The Opposition Division revoked the patent. The decision was based on claims 1 to 6 as granted. Claim 1 as granted read as follows:

"1. A DNA molecule comprising a nucleotide sequence encoding insulin-like growth factor II (IGF-II) said IGF-II-encoding nucleotide sequence comprising:

5'-GCT TAC CGC CCC AGT GAG ACC CTG TGC
GGC GGG GAG CTG GTG GAC ACC CTC CAG TTC
GTC TGT GGG GAC CGC GGC TTC TAC TTC AGC
AGG CCC GCA AGC CGT GTG AGC CGT CGC AGC
CGT GGC ATC GTT GAG GAG TGC TGT TTC CGC
AGC TGT GAC CTG GCC CTC CTG GAG ACG TAC
TGT GCT ACC CCC GCC AAG TCC GAG -3'."

Claim 2 related to a specific embodiment of claim 1, while claims 3 and 4 to 6 covered a nucleotide probe and cells containing the DNA molecule of claim 1, respectively.

IV. While the opposition division disagreed that the DNA molecule of claim 1 was a discovery pursuant to Article 52(2)a EPC, it came to the conclusion that this DNA encoding IGF-II lacked an inventive step over documents

(1) Jansen et al., Nature, vol. 306, pages 609 to 611 (1983)

and

(3) Rutter et al., Insulin-like Growth Factors/Somatomedins, Proc. Symp. 1982 (published 1983), pages 629 to 640, Walter de Gruyter and Co., Berlin-New York.

Further documents referred to in the present decision are:

(4) Gray et al., Nature, Vol. 303, pages 722 to 725 (1983)

(5) Rinderknecht et al., FEBS Letters, vol. 89, pages 283 to 286 (1978)

(7) Jansen et al., Rep. Ross. Conf. Pediatr. Res., vol. 89, pages 12 to 19 (1985)

(9) Woods et al., Proc. Natl. Acad. Sci. USA, vol. 79, pages 5661 to 5665 (1982)

(10) Affidavit of Dr. Rall dated 11 April 1994

V. The Appellant (Patentee) lodged an appeal against this decision, paid the appeal fee and filed a statement of Grounds of Appeal.

VI. Oral proceedings were held on 17 July 1997. The subject-matter discussed was patentability of the claims as granted.

VII. In support of the inventive step of the claimed DNA, the Appellant essentially submitted in writing and at the oral proceedings the following arguments:

- The view taken by the opposition division that the cloning strategy for arriving at the DNA of claim 1 was obvious and hence the claimed DNA was also obvious, was legally not correct. Rather, the correct assessment of the patentability of product claim 1 should have been made without reference to a particular process (decision T 01/81, OJ 1981, 439, headnote).

- There was no evidence to suggest that at the priority date of the patent in suit a person of ordinary skill in the art would have been able to utilise routine cloning methods, such as the method disclosed in document (1) involving low degeneracy probes, in order to arrive at the claimed DNA encoding IGF-II. (In points 14 to 18 of the "Reasons", more detailed arguments put forward by the Appellant are dealt with by the Board).

- The affidavits of Dr. Rall (document (10)) and Prof. Bell showed that all routine methods which had been tried in an attempt to isolate a cDNA clone coding for IGF-II had been unsuccessful. In particular, all the screening methods involving low to moderate degeneracy (32- to 64-fold degeneracy) oligonucleotide probes failed. These

negative results did not lie with the screened libraries made from liver and thus they could not be worse than the Woods' library referred to in document (1) also made from liver.

- In view of these failures the inventors had to turn to screening methods involving highly degenerate probes and a single positive IGF-II clone was identified with one highly degenerate probe (256-fold degeneracy). However, the likelihood of success in cloning genes using highly degenerate oligonucleotide probes was low and highly unpredictable (see affidavits of Dr. Truett and Prof. Struhl)

VIII. The Respondent essentially submitted the following arguments in writing and at the oral proceedings:

- The conclusions reached by the Opposition Division were correct in every respect.

- Isolation of a cDNA encoding IGF-II was an obvious goal before the priority date of the patent in suit. The human liver cDNA bank disclosed by document (1) was the first obvious bank to be screened in order to pick up the cDNA coding for IGF-II, as document (1) taught that liver was a major site of production of both IGF-I and IGF-II. Document (1) also disclosed the screening method involving oligonucleotide probes for isolation of the desired cDNA. Therefore the skilled person would have inevitably arrived at the claimed DNA by merely applying the teachings of document (1) to the screening of the cDNA encoding IGF-II.

IX. The Appellant requested that the decision under appeal be set aside and that the patent be maintained unamended.

The Respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. As to the question of whether the elucidation of the DNA sequence encoding IGF-II was a mere discovery excluded from patentability (Article 52(2)a EPC), the Opposition Division came to the conclusion that this was not the case and the Respondent expressed agreement to this conclusion (see paragraph VIII supra). The Board also has no reason for questioning the conclusion the Opposition Division arrived at.

3. The only point at issue in the present case is the inventive step (Article 56 EPC).

Document (3) represents the closest prior art for the claimed subject-matter. It is concerned with proteins belonging to the "insulin gene family" (IGF), comprising insulin, IGF-I, IGF-II and relaxin. Under the heading "IGF genes" (see page 639), it is stated that the known amino acid sequences of IGF-I and IGF-II can be used to predict possible oligonucleotides which could be synthesized as probes for screening.

4. Concerning the closest prior art document, the Appellant argued that document (5), reporting the correct amino acid sequence of IGF-II, should be preferred to document (3), comprising an IGF-II's wrong amino acid sequence, which would not lead the skilled

person to the claimed cDNA. In the Board's view, however, document (5) is not concerned with DNAs, unlike document (3) which even suggests a possible way for arriving at the gene coding for IGF-II. Thus, document (3) deals with the same problem as the patent in suit, namely the problem of looking for the gene encoding IGF-II and conveys on the skilled person the incentive to look for the desired DNA. Whether or not the amino acid sequence disclosed in document (3) is correct, is less important because amino acid sequence information about IGF-II had been available to the skilled person since 1978 from other sources, for instance from the documents referred to in the patent in suit on page 5, second paragraph, which documents also include document (5). Therefore, the skilled person had not necessarily to rely on the amino acid sequence of Figure 1 of document (3). On the contrary, for the reasons emphasized in point 17 infra, the skilled person would not rely at all on these amino acid sequences.

5. In the light of document (3), the technical problem to be solved is the provision of the DNA encoding IGF-II for the production of human IGF-II in recombinant host organisms.

6. This problem is solved by the subject-matter of claim 1 of the patent in suit. In view of the detailed information contained in the specification of the patent, in particular Figure 1, the Board is satisfied that the above-stated technical problem has been solved.

7. The key question in the present case is whether the skilled person, starting from document (3) and applying means and methods available before the priority date of the patent in suit for identifying by screening and cloning the desired gene, would have readily expected

to succeed in arriving at the claimed subject-matter. Although it was obvious, in the light of document (3), to try cloning the gene encoding IGF-II, since the document gave an explicit suggestion to do so, it was not necessarily true that the skilled person would have had any reasonable expectation of success when embarking on this task (see eg decision T 296/93, OJ EPO 1995, 627).

8. The Board agrees with the Appellant's submission that the correct assessment of the patentability of product claim 1 should be made without reference to a particular process, because the patentability of a process has no necessary influence on the patentability of a product (decision T 01/81, OJ 1981, 439). Yet, unlike the situation dealt with in decision T 01/81 (above), the point at issue here is not whether any possible process claims (in the present case, the screening methods of the prior art which are not on file), would be **per se** patentable and whether they would confer patentability on the claimed product, in the present case the DNA. Thus, the only way of assessing the inventive step of the claimed DNA must consist in establishing whether or not this particular product is derivable in an obvious manner from the prior art.

9. An inventive step for the claimed sequence may follow from the selection of this sequence among a great many other possible allelic DNA sequences, if said selection brings about an unexpected advantageous effect, eg as in the instance a higher expression is achieved with the claimed DNA than with any other allelic DNA. However, the Appellant has not even provided any evidence showing that in the present case such a selection occurs, let alone any evidence of the unexpected advantageous effect.

10. In the technical circumstances given in the light of the disclosure in document (3), the only blockage that could have prevented the skilled person to try cloning the gene encoding IGF-II could have been a possible low expectation of being successful. Accordingly, the inventive step of the claimed DNA can only be supported by this low expectation of success by the skilled person, once the screening methods available before the priority date of the patent in suit were put into practice in an attempt to isolate from a library a gene encoding IGF-II. The Board observes that the Appellant takes the same approach to the inventive step as the Board when arguing that the claimed DNA is inventive because the skilled person had no reasonable expectation to succeed in isolating the gene encoding IGF-II by using highly degenerate probes (see paragraph VII supra).

11. Before embarking on the cloning of a DNA encoding IGF-II, the skilled person would have considered carefully which screening method offered the best chances of success. The simplest approach referred to in broad lines on page 639 of document (3) was to use chemically synthesized DNA probes which were designed on the basis of the partial or complete amino acid sequence of a given gene product. This cloning technique was illustrated in document (1), a piece of prior art disclosing the isolation of the cDNA encoding IGF-I by screening 60,000 transformants of an adult human liver Woods' cDNA library with a probe of low degeneracy, namely an 8-fold degenerate tetradecamer oligonucleotide designed on the basis of amino acids 58-62 of IGF-I (Glu-Met-Tyr-Cys-Ala) and achieving 5 clones showing unambiguous hybridisation (see page 609, the paragraph bridging left-hand and right-hand columns after the abstract).

As the library of choice to be screened, the skilled person would have turned to the Wood's cDNA library derived from human adult liver suggested by document (1) for the successful isolation of a cDNA encoding IGF-I. This is because it was known from document (1) (see abstract) that the liver was the site of production of both IGF-I and IGF-II. Thus, the fact that there were cDNAs of the closely related IGF-I in this library was **a very good** technical information that imparted a high degree of confidence to the skilled person wishing to find the IGF-II cDNA. At all event, before screening, care had to be taken that the Woods' library used to pick up the gene encoding IGF-II had at least the same complexity than the one utilized to isolate the DNA coding for IGF-I. This is because the skilled person believed that the mRNA frequency for IGF-II in the cell used to make the Woods' library was comparable with the mRNA frequency for IGF-I, albeit low (see point 13 infra).

In summary, at least on paper, the skilled person would have been in a position to design a simple protocol for isolating the gene encoding IGF-II in the light of the successfully applied technique for the isolation of the IGF-I gene disclosed in document (1).

12. For picking up the gene coding for IGF-II, the skilled person had to replace in this protocol the 8-fold degenerate tetradecamer oligonucleotide designed on the basis of IGF-I's amino acid information with a probe designed on the basis of IGF-II's amino acid sequence. In view of assessing the inventive step, it has to be established whether the skilled person would have readily expected to succeed or not in isolating the DNA coding for the IGF-II protein. The Board is convinced that the cloning of the IGF-II DNA by using the technique of document (1) did not require to overcome additional difficulties in comparison with the cloning

of the DNA encoding IGF-I. Difficulties that could have arisen when trying to put into practice the approach described above (point 11) were, for instance, a lower mRNA frequency for IGF-II than for IGF-I in the human adult liver cell from which the cDNA library was made or the necessity of designing probes with higher degeneracy. In the framework of the "reasonable expectation" approach there might be concerns of that kind known to the skilled person. In the present case, however, the Board sees none.

13. The Appellant, however, argued that a person of ordinary skill in the art would not have arrived at the claimed DNA encoding IGF-II by utilising the cloning method disclosed in document (1) involving low degeneracy probes. In points 14 to 18 infra, the Board takes position in respect of each ground brought forward by the Appellant in support of the above proposition.

14. It is first argued that the level of IGF-II cDNA in the Woods' library was low and thus the library might not have comprised the IGF-II transcript at all or might have comprised the transcript looked for at so low a level that it could not have been detected. Further, the genetic content of a library could have changed over time. While it is conceded that the frequency in the Woods' library of the DNA encoding IGF-I is low (5 unambiguous positives/ 60,000 transformants screened: see point 11), the conclusion cannot be drawn, on the basis of the evidence on file, that the human adult liver cell on which the Woods' cDNA library of document (1) is based, produces considerably less IGF-II than IGF-I. Since the skilled person assumed that liver cells expressed somehow comparable levels of IGF-I and IGF-II (see document (1), abstract) and because protein expression levels reflected mRNA frequency (see document (4), page 722, end of left-hand

column), he/she had no reason to believe that the Woods' library contained less cDNA encoding IGF-II than cDNA encoding IGF-I. Thus, contrary to the Appellant's view, the fact that there were IGF-I cDNAs in this library imparted a reasonable degree of confidence to the skilled person that IGF-II cDNA would also be there.

15. Further, as to the possibility that IGF-II cDNAs could not have been present at all or only in infinitesimal concentration in the Woods' library because, inter alia, the genomic content of a library could have changed over time, the skilled person would not have regarded as likely a library's selective depletion over time only of IGF-II cDNA but not IGF-I cDNA, or vice versa. This is because, as seen above, mRNA frequencies for IGF-I and IGF-II were believed to be comparable. Thus, one had to expect that either both DNAs encoding IGF-I and IGF-II were present or none. In any case, if a skilled person unable to isolate the cDNA coding for IGF-I upon reproducing the teaching of document (1), for example as a test experiment, established that the Woods' library has changed to a considerable extent, then a new Woods' library could have been prepared following the teaching of document (9).

16. In a second line of argument it has been submitted that it was much more difficult to clone the gene encoding IGF-II than that encoding IGF-I. A probe with a much higher level of degeneracy was needed to isolate the DNA encoding IGF-II. This was because the existence of one internal methionine in IGF-I enabled the authors of document (1) to design a pool of oligonucleotide probes having a degeneracy of only 8-fold, while IGF-II did not contain any internal methionine or tryptophan, both encoded by only one possible codon. The Board's consideration to this is the following: the choice by the authors of the patent in suit of a highly

degenerate probe was not motivated by the absence of an internal methionine or tryptophan, both encoded by only one possible codon in the IGF-II amino acid sequence, but rather by their desire to "kill two birds with one stone", ie to pick up in one screening both genes coding for IGF-I and IGF-II (see page 2, lines 17 to 23 of the application as filed).

17. The Appellant further maintained that no DNA sequence encoding IGF-II would have been picked up if the skilled person used oligonucleotide probes designed on the basis of the erroneous amino acid sequence of IGF-II disclosed in Figure 1 of document (3). This figure, however, merely serves to emphasize the general structural similarities which exist between proinsulin, IGF-I and IGF-II. It is stated in the legend to Figure 1 that "The analogous structures of IGF I and II are presented above", but it is not even indicated which is IGF-I and which is IGF-II. Doubts also arise as to whether the sequence stops at or continues after RRSR (above)/RAPQT (below). To clarify the matter the skilled person had to consult another document such as document (5), from which it could have been seen not only which was IGF-I and which was IGF-II, but also that IGF-II stopped at RRSR and continued at GIV: this was not clear at all from Figure 1 of document (3). Of course, in view of these unclarities affecting Figure 1, the skilled person would have refrained from designing any oligonucleotide probe on the basis of document (3), especially because many other documents, for instance those referred to in the patent in suit on page 5, second paragraph, comprised unambiguous amino acid information about IGF-II.

18. In a further line of argument, the Appellant disagrees with the proposition that the technique involving low degeneracy probes of document (1) would have inevitably led to the claimed DNA encoding IGF-II. Document (7)

showed that it was possible to pick up a variant with an additional cytosine base at position 22 or a splice variant (see page 14 and Figure 1). Thus, depending on the technique used for isolating the gene, a variant different from the claimed one could have been obtained. The Board observes that the variant referred to in Figure 1 of document (7) comprises an additional cytosine base at position 22 **outside the coding region**, while the coding region thereof is indistinguishable from the claimed DNA sequence. Thus, selection of this allele cannot depend on the oligonucleotide probe designed on the basis of the amino acid sequence spanning the coding sequence utilized for picking it up. Further, while it is true that the authors of document (7) isolate a splice variant, they also obtain a DNA whose coding region is identical to the claimed one. Therefore, the conclusion cannot be drawn that, depending on the technique used for isolating the gene, a variant different from the claimed one could have been obtained.

19. The Board has to conclude that the facts discussed in points 14 to 18 supra would not have lowered the skilled person's expectation of success in isolating the DNA coding for the IGF-II protein by applying the technique disclosed in document (1).

20. Finally, the Board has to deal with the affidavits of Dr. Rall and Prof. Bell illustrating the series of failures experienced by researchers attempting to isolate the DNAs coding for IGF-I or IGF-II proteins by applying the technique based on oligonucleotide probes of low degeneracy. They had to turn to screening methods involving highly degenerate probes, the outcome of which was highly unpredictable.

21. A decisive experimental fact in support of this assertion would have been, in the Board's view, a clear demonstration by these affidavits that the screening of a **Woods' library** with probes of low degeneracy inevitably leads to failure, even if this contradicts the teaching of document (1). However, no such test has been performed by Dr. Rall and Prof. Bell, whose experiments show that screening "house" libraries with low degeneracy probes does not lead to success. The technique applied by Dr. Rall and Prof. Bell indeed differs from the one disclosed in document (1) by a fundamental feature, namely the library to be screened. These researchers screened in their experiments "house" libraries although document (1) recommended the use of a Woods' cDNA library as the library of choice to be screened (see point 11 supra). But it has been admitted by Dr. Rall himself that the choice of the right cDNA library was critical for success in cloning the gene looked for (see document (10), paragraph 32: "We had to combine the **right library** with the right probe under the right hybridization and wash conditions to achieve the success we attained." (emphasis added)).

22. The Appellant's view that these "house" libraries were not worse than the Woods' library referred to in document (1) because both were made from liver, is contradicted by affidavit (10). According to this document, the highly degenerate "effective probe" was tried on a "house" library made by Dr. Hallewell and no positive could be found (see paragraph 29). But when the same "effective probe" was tried on a Woods' library, eight positive could be found (paragraphs 30 and 31). This implies that the "house" library was a poor one for the gene looked for in comparison with the available Woods' library.

23. Further, Dr. Rall's and Prof. Bell's failure to isolate the gene encoding IGF-I by using low degeneracy probes could not be ascribed to the hybridization/wash conditions, since the latter were substantially the same as the ones employed for the "successful isolation" (compare paragraphs 19 and 24 of document (10)).

24. Finally, the Board observes that Dr. Rall and Prof. Bell used the "house" libraries at a complexity of 60,000, while the library complexity was reduced to 9,600 when they finally turned to the Wood's library. This seems to be an acknowledgment that the Woods' library was expected to be much richer for the gene looked for than the "house" libraries.

25. In summary, the experimental findings of Dr. Rall and Prof. Bell reported in the affidavit (10) do not conflict with the conclusion arrived at by the Board in point 12 supra that the skilled person would have readily expected to succeed in isolating the DNA coding for the IGF-II protein by using the technique of document (1).

26. For these reasons, in the Board's judgement, the subject-matter of claims 1 to 6 does not involve an inventive step as required by Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

D. Spigarelli U. Kinkeldey

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