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DECISION
of 28 June 2005

Case Number: T 1329/04 - 3.3.8
Application Number: 94907259.9
Publication Number: 0678101
IPC: C12N 15/11
Language of the proceedings: EN

Title of invention:
Growth differentiation factor-9

Applicant:
THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Headword:
Factor-9/JOHN HOPKINS

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main and auxiliary requests - inventive step (no) - no plausible solution of technical problem is provided"

Decisions cited:
T 0939/92, T 0182/03

Catchword:
The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve.
Case Number: T 1329/04 - 3.3.8

DE C I S I O N  
of the Technical Board of Appeal 3.3.8  
of 28 June 2005  

Appellant: THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE  
720 Rutland Avenue  
Baltimore, MD 21205 (US)  

Representative: Lee, Nicholas John  
Kilburn & Strode  
20 Red Lion Street  
London WC1R 4PJ (GB)  

Decision under appeal: Decision of the Examining Division of the European Patent Office posted 5 August 2004 refusing European application No. 94907259.9 pursuant to Article 97(1) EPC.  

Composition of the Board:  
Chairman: L. Galligani  
Members: F. L. Davison-Brunel  
M. B. Günzel
Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division dated 5 August 2004 refusing the European patent application No. 94 907 259.9 published under the international application No. WO 94/15966 with the title "Growth Differentiation Factor-9" claiming priority from US 08/003303 of 12 January 1993. The decision was based on the main request and auxiliary requests 1 to 3 then on file.

Claim 1 of the main request read as follows:

"1. A polynucleotide encoding a polypeptide having GDF-9 activity selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of SEQ ID NO:3;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO:4;

(c) a polynucleotide which is an RNA sequence corresponding to the polynucleotide of (a) or (b);

(d) a polynucleotide encoding a fragment of the polypeptide encoded by any one of (a) to (c); and

(e) a polynucleotide which hybridises under stringent conditions with the polynucleotide of any one of (a) to (d)."

The main request was found to contravene the requirements of Articles 56, 57, 83 and 84 EPC.
The examining division took document (3) as closest prior art and defined the problem to be solved as being the provision of a putative further member of the TGF-ß super family of protein and/or nucleic acid encoding sequences. The examining division held, in particular, that the mouse GDF-9 cDNA (SEQ ID NO: 3) as well as the protein sequence (SEQ ID NO: 4) did not involve an inventive step because the cloning of a sequence of a putative new member of a gene family based on conserved sequence motifs would be achieved as a matter of routine and also, because the minimal characterisation given, i.e. the tissue specificity of GDF-9 expression was not sufficient to elucidate its physiological function or putative involvement in pathologies or to provide any surprising effect in view of the prior art. The many speculations about the function of GDF-9 which had been made on the basis of tissue distribution were found to be obvious. Finally, the examining division, in this context, refused to take into account the teachings of post-published documents showing that GDF-9 was a growth differentiation factor because the application per se did not provide any evidence in this respect. The same objections were considered to apply to auxiliary requests 1 to 3 which were found to contravene the requirements of Articles 56, 57, 84 EPC.

II. Following the filing of the appeal, the examining division did not rectify its decision and remitted the case to the board of appeal (Article 109 EPC). Pursuant to Article 11(1)of the Rules of Procedure of the Boards of Appeal, the board sent a communication indicating its preliminary, non-binding opinion.
III. In reply thereto, the appellant filed on 26 May 2005 a further submission together with a new main request and two new auxiliary requests to replace the corresponding previous requests on file. The main request was then withdrawn during oral proceedings before the board which took place on 28 June 2005. The first and second auxiliary request filed on 26 May 2005 were then taken as main and auxiliary requests, respectively. Claim 1 of the new main request read as follows:

"1. A polynucleotide encoding a polypeptide [-] selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of SEQ ID NO:3;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO:4;

(c) a polynucleotide which is an RNA sequence corresponding to the polynucleotide of (a) or (b);

(d) a polynucleotide encoding a fragment of the polypeptide encoded by any one of (a) to (c), which fragment causes growth and differentiation of oocytes; and

(e) a polynucleotide which hybridises under stringent conditions with the polynucleotide of any one of (a) to (d) and encodes a polypeptide which causes growth and differentiation of oocytes." (the differences with claim 1 refused by the examining division are shown in bold).
Claims 2 to 5 related to further features of the polynucleotide of claim 1. Claims 6 to 8, 9 to 11 were respectively directed to a vector/host cells including/transformed by, the polynucleotide of earlier claims. Claims 12 and 13, 14 to 16 respectively related to the polypeptide encoded by the polynucleotide of any one of claims 1 to 5 and to antibodies specific to that polypeptide.

Claim 1 of the auxiliary request corresponded to claim 1 (a) to (c) of the main request.

IV. The documents mentioned in the present decision are the following:


V. The appellant's submissions in writing and during oral proceedings regarding inventive step may be summarized as follows:
Document (3) was the closest prior art. It disclosed the identification of a novel member (GDF-1) of the transforming growth factor-β family (TGF-β). The GDF-1 cDNA was isolated by screening a cDNA library constructed from mouse embryos with oligonucleotides selected on the basis of the amino acid sequences of conserved regions amongst members of the superfamily. The GDF-1 polypeptide was shown to have all of the structural characteristics of members of the family and, thus, was acknowledged as belonging to it.

The problem to be solved could be defined as providing a new growth differentiation factor of the TGF-β family.

The solution provided was the polynucleotide SEQ ID NO: 3 encoding the polypeptide SEQ ID NO: 4 (GDF-9; claim 1).

Although being slightly different from the cloning method disclosed in document (3), the method used to isolate GDF-9 cDNA needed not be taken into account when assessing inventive step. Inventive step was to be acknowledged on the basis of the unexpected structural properties of GDF-9. Its sequence was only very weakly conserved (no more than 34% homology with known members of the TGF-β family) and, furthermore, it contained only six cysteine residues instead of the seven cysteine residues which were a key characterising feature shared by all members of the family. A further distinguishing property was that GDF-9 expression was restricted to ovarian tissue whereas GDF-1 expression had been shown to occur not only in brain but also in
ovary and adrenal gland (document (2), passage bridging pages 4250 and 4251).

The present case was, in fact, analogous to that dealt with in decision T 182/03 of 23 June 2004 where inventive step was acknowledged to a nucleic acid encoding human cAMP-specific phosphodiesterase (PDEIVB) of SEQ ID NO: 2, on the basis of the unique structural features of the enzyme and of its restricted pattern of expression. The then competent board had accepted post-published evidence that a drug had been developed on the basis of the enzyme's structural properties as supportive of inventive step.

In the present case, the appellant had also filed numerous post-published documents as further evidence of the role of GDF-9 as a growth differentiation factor. Admittedly, this evidence served to support the description in the application as filed of presumed functions of GDF-9, rather than to support any kind of technical evidence that GDF-9 would be capable of performing any one of these. Yet, predictions should be permitted because of the "first to file" approach of the European patent system which forced the applicant to cover all subject-matter connected to the invention. Furthermore, in accordance with the case law (T 939/92 OJ EPO 1996, 309, point 2.6.2 of the decision), reasonable predictions of relations between chemical structure and biological activity could be taken into account while assessing inventive step. Thus, the combination of the predictions regarding the functions of GDF-9 - as the post-published documents corroborated - with the disclosure of the structural properties specific to GDF-9 was sufficient evidence for a
surprising effect to be acknowledged, which warranted recognition of inventive step.

VI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the first or second auxiliary requests, to be taken as main and auxiliary requests, filed on 26 May 2005.

Reasons for the Decision

Main and auxiliary requests

Article 56 EPC; inventive step of the subject-matter of claim 1(a), i.e. a polynucleotide having the nucleic acid sequence of SEQ ID NO:3 and claim 1(b), i.e. a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO:4.

1. The closest prior art is document (3), a study in the field of cell differentiation. In its introductory part, it provides a list of polypeptide factors which play critical roles in regulating differentiation processes during embryogenesis. These factors are regrouped in a superfamily, the TGF-β superfamily, on the basis of their functional and structural relationships to the transforming growth factor-β which itself has influence on a wide variety of differentiation processes such as adipogenesis, myogenesis etc.. The structural features common to the family members are discussed on page 1035, right-hand column, last paragraph to page 1037, left-hand column, first paragraph. They reside in the C-terminal domain which starts with a cluster of basic residues. Seven cysteine residues are conserved with their characteristic invariant spacing (16/16 members
of the family; Fig.3A). Furthermore, there exists amino acid sequence homology between the TGF-β family members in the regions starting with the first conserved cysteine residue and extending to the C-terminal end (Fig. 3B).

2. The aim of the work described in document (3) is to isolate a further member of the TGF-β family. A cDNA library is constructed and screened with oligonucleotides selected on the basis of the amino acid sequences of conserved regions amongst known members of the family. A positive recombinant clone is obtained which carries a cDNA encoding a 357 amino acids long protein designated GDF-1. A comparison (cf. page 1035, right-hand column) of the GDF-1 122 amino acids long C-terminal domain with that of known members of the TGF-β family shows the presence of the cluster of basic residues at the beginning of the domain, of the seven cysteine residues with their characteristic spacing as well as of many of the other highly conserved amino acids. In addition, GDF-1 is 52% homologous to a previously identified member of the family: Vg-1 (page 1037, left-hand column). On page 1038 (right-hand column), it is mentioned that:

"An elucidation of the specific role(s) played by GDF-1 during embryogenesis and/or adult animals awaits characterization of the temporal and spatial patterns of GDF-1 mRNA expression and the functional activities of GDF-1 protein both in vitro and in vivo." Yet, it is concluded on the basis of the structural analysis that "the predicted sequence of GDF-1 clearly identifies it as a new member of this superfamily." (cf. page 1038, left-hand column).
3. It follows from the overall information given in document (3) that, while the TGF-β superfamily was initially identified by comparing the sequences of factors having a common role (their involvement in differentiation), once an unambiguous consensus sequence had been defined, the skilled person was prepared to accept that a polypeptide belonged to the TGF-β family if it exhibited this consensus sequence, even in the absence of any evidence as to its role.

4. Starting from document (3), the problem to be solved can be defined as isolating a further member of the TGF-β superfamily.

5. The solution provided is the polynucleotide of SEQ ID NO:3 encoding the polypeptide of SEQ ID NO:4, denoted GDF-9 (claim 1(a) and (b)).

6. Whether or not the problem as defined in point 4 above has been plausibly solved, i.e. whether or not it is plausible that the molecule as defined in point 5 above constitutes a further member of the TGF-β superfamily needs to be investigated.

7. In the application as filed (pages 10 and 11), GDF-9 is described as a 441 amino acids long protein having a C-terminal domain preceded by a putative tetrabasic proteolytic processing site. Yet, it does not exhibit the most striking structural feature which serves to establish whether or not a polypeptide belongs to the TGF-β family: namely the presence of the seven cysteine residues with their characteristic spacing; in fact, only six cysteine residues are present (cf. page 11, lines 3 to 9). The common general knowledge regarding
cysteine residues is that because of their ability to form S-S bridges, they play a fundamental role in the tertiary structure of proteins, which tertiary structure is to a very large extent responsible for functional activity. Accordingly, any change in the TGF-β characterising pattern of seven cysteine residues and their invariant spacing would be expected to have significant repercussions on the function of any TGF-β family member. In the same manner, a molecule which does not exhibit the "seven cysteine residues pattern" cannot clearly and unambiguously be considered a member of the TGF-β family, unless further evidence is available to that effect.

8. Furthermore, as already mentioned above, members of the TGF-β superfamily share sequence homology. In the part of the application as filed describing the prior art related to the invention (page 2), it is disclosed that subgroups in the family had been defined according to the percentage of homology between members, the members of a given subgroup being from 70% to 90% homologous. Here, GDF-9 is very far from fulfilling this criteria as its sequence is stated to be significantly divergent from those of other family members (cf. page 28), the maximal percentage of homology which was observed being 34% with the bone morphogenetic protein, BMP-4. This implies that GDF-9 cannot be attributed to any subgroup and, thus, must at best be considered as the first member of a yet unidentified subgroup. This finding and that in point 7 lead to the conclusion that, contrary to GDF-1 in document (3), GDF-9 cannot be clearly and unambiguously identified as a member of the TGF-β superfamily by only using a "structural approach".
9. Of course, the situation could most probably be looked at differently if it had been demonstrated in the application as filed that GDF-9 played a role similar to that of the transforming factor-β (as was the case for all of the factors which initially served to define the superfamily). Yet, there is no evidence at all in this respect. In fact, the application only discloses that expression of GDF-9 is localised in ovarian tissues, which per se is useful but insufficient information in relation to any function the molecule might have.

10. As already pointed out above (cf. point 8), in the application (page 28), it is admitted that "..., the sequence of GDF-9 is significantly diverged from those of other family members". Yet, functions of members of the TGF-β superfamily previously isolated from ovarian follicular fluid (inhibins) or shown to inhibit ovarian cancer (MIS) are recited, and tentatively and presumptively attributed to GDF-9. Further putative roles are also suggested for GDF-9 which cover some of the effects observed with TGF-β (paragraphs bridging pages 8 and 9). At oral proceedings, it was argued that speculations of this kind should be permitted because of the "first to file approach" of the European patent system which forced the applicant to cover any and all subject-matter connected with its invention. The board is unable to endorse this reasoning. On the contrary, in a first-to-file system the (earlier) filing date of the application, not the date at which the invention was made determines to whom of several persons having made an invention independently of each other, the right to a European patent belongs (cf. Article 60(2) EPC). Hence, it is particularly important in such a
system that the application allows to conclude that the invention had been made, i.e. that a problem had indeed been solved, not merely put forward at the filing date of the application. Therefore, the issue here is rather how much weight can be given to speculations in the application in the framework of assessing inventive step, which assessment requires that facts be established before starting the relevant reasoning. In the board's judgment, enumerating any and all putative functions of a given compound is not the same as providing technical evidence as regard a specific one.

11. Accordingly, as a significant structural feature fails to be identical in TGF-9 and the members of the TGF-β superfamily, and no functional characterisation of TGF-9 is forthcoming in the application, it is concluded that the application does not sufficiently identify this factor as a member of this family i.e. that there is not enough evidence in the application to make at least plausible that a solution was found to the problem which was purportedly solved.

12. The appellant filed post-published evidence (e.g. document (4) and Exhibit E) establishing that GDF-9 was indeed a growth differentiation factor. This cannot be regarded as supportive of an evidence which would have been given in the application as filed since there was not any. The said post-published documents are indeed the first disclosures going beyond speculation. For this reason, the post-published evidence may not be considered at all. Indeed, to do otherwise would imply that the recognition of a claimed subject-matter as a solution to a particular problem could vary as time went by. Here, for example, had the issue been examined
before the publication date of the earliest relevant post-published document, GDF-9 would not have been seen as a plausible solution to the problem of finding a new member of the TGF-β superfamily and inventive step would have had to be denied whereas, when examined thereafter, GDF-9 would have to be acknowledged as one such member. This approach would be in contradiction with the principle that inventive step, as all other criteria for patentability, must be ascertained as from the effective date of the patent. The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve.

13. The appellant cited two decisions in support of its case. In T 182/03 (supra), inventive step was acknowledged to human cAMP-phosphodiesterase on the basis of its unexpected properties, it being structurally divergent from other phosphodiesterases and its expression being restricted to specific tissues. In this earlier case, however, the question of whether or not the enzyme was a solution to the problem to be solved - which has to be positively answered before any other criteria are taken into consideration - did not arise. Thus, the rationale underlying said decision has no bearing on the present case.
14. Decision T 939/92 (supra) was cited insofar as it held that it was possible to take into account predictions of relations between chemical structure and biological activity when assessing inventive step. That is indeed what is stated in point 2.6.2 of the decision, the sentence however continues to "... but ... there is a limit beyond which no such prediction can be validly made." In the board's judgment, the present case goes beyond the acceptable limit in the sense of that decision because the chemical structure of GDF-9 is not that for which the predicted biological function would be expected (see points 7 and 8, supra).

15. For the above reasons, the main request is refused for lack of inventive step of the subject-matter of claim 1 (a) and (b). As the same subject-matter is found in claim 1 of the auxiliary request, the said request is also refused for the same reasons.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:     The Chairman:

A. Wolinski     L. Galligani