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Datasheet for the decision of 29 June 2011

Case Number: T 0578/06 - 3.3.04

Application Number: 97918523.8

Publication Number: 1007070

IPC: A61K 38/00

Language of the proceedings: EN

Title of invention:
Prolonging survival of transplanted pancreatic cells

Applicant:
IPSEN PHARMA

Headword:
Pancreatic cells/IPSEN

Relevant legal provisions:
EPC Art. 54(1)(2)(5), 56, 83, 123(2)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Novelty, inventive step, sufficiency of disclosure - yes"
"Added matter - no"

Decisions cited:
G 0002/08, T 0002/81, T 0383/88, T 0270/90, T 0160/92, T 0939/92, T 0893/02, T 1329/04, T 0082/07, T 0716/08

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0578/06 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 29 June 2011

Appellant: IPSEN PHARMA
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 27 September 2005 refusing European application No. 97918523.8 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: B. Claes
G. Alt

Summary of Facts and Submissions

I. European patent application 97918523.8 is based on international patent application PCT/US97/05722 which was published as WO97/37675 (which will be referred to in the present decision as the "application" or the "application as published"). The application has the title: *"Prolonging survival of transplanted pancreatic cells".*

II. The examining division refused the application based on the ground that the subject-matter of the claims before it lacked inventive step (Article 56 EPC).

III. The appellant (applicant) lodged an appeal against the decision and filed a main request with the statement of grounds of appeal which was identical to the request on which the decision of the examining division was based. In addition the appellant filed four further documents. Claim 1 of the main request read:

"1. Use of somatostatin or a somatostatin agonist in the formulation of a pharmaceutical formulation or preparation for the treatment of a human patient in receipt of transplanted isolated pancreatic islet cells, wherein the pharmaceutical composition is administered until the transplanted cells have become established and fully functional, whereby the functional life of the isolated transplanted pancreatic islet cells is extended relative to untreated transplanted isolated pancreatic islet cells."

Claims 2 to 12 all concerned embodiments dependent on claim 1.

IV. The following documents are referred to in the present decision:

D10: Gores *et al.* (1993), The Lancet, Vol. 341, pages 19-21.

D11: Zambre *at al.* (1999), Biochem. Pharmacol., Vol. 57, pages 1159-1164.

D12: Björk *et al.* (1998), Diabetes Care, Vol. 21, pages 427-430.

Dl3: Grill and Björklund (2001), Diabetes, vol. 50 (S1), pages 122-124.

D14: Hiramatsu *et al.* (2000), Metabolism, Vol. 49, No. 5, pages 657-661.

D16: Keller (1990), J. Autoimmun., Vol. 3, No. 3, pages 321-327, Pubmed Abstract.

V. In point 13 of its decision the examining division reasons its decision on Article 56 EPC. It decided the case based on the following considerations:

– The examining division agreed with the appellant that document (Dl0) represented the closest prior art for the assessment of inventive step. The technical problem was to provide a means for prolonging the survival of transplanted pancreatic islet cells. The solution that was proposed by the application was the use of somatostatin.

– The examining division noted that the application did not illustrate the use of somatostatin by way of experimental data showing the effect of an improvement in the survival of transplanted cells.

– The examining division considered furthermore that post-published documents (D11) and (D12), which disclosed that somatostatin induced a ß-cell rest in insulin production of islets *in vitro* did not prove an improved survival upon transplantation, because survival of transplanted cells might not depend only on their insulin production. The examining division considered that other tests were needed, such as the survival of cells (even *in vitro*) during a certain period of time when challenged by an immune attack in the presence of somatostatin. However, the applicant had not been able to carry out such straightforward experiments.

– The examining division considered that it was the applicant, in *ex parte* proceedings, who bore the burden of proof for the facts in his favour and considered that it was not credible that the technical problem had been solved by using any of the claimed compounds. Consequently, the requirements of Article 56 EPC were not met.

– Finally, the examining division added that, provided the applicant had been able to show that the effect of prolonging the survival of transplanted isolated islet cells by the use of somatostatin or its agonists had been shown, the application might possibly have been recognised as making an inventive contribution to the art.

VI. The appellant has argued essentially as follows during the appeal proceedings:

– According to the case law of the boards of appeal in order to demonstrate that the application provides a credible solution to the stated problem, the applicant had to prove his allegation to the standard of the balance of probabilities (*cf.* decisions T 270/90 and T 939/92).

– Document (D10) represented the closest prior art and disclosed that the administration of a new immunosuppressant (15-deoxyspergualin) in the ten days following transplantation to a patient extended the life of transplanted islet cells. The administration of an immunosuppressant had, however, a number of associated drawbacks, such as an increased susceptibility to infection and risk of cancer. The technical problem to be solved by the present invention was therefore the provision of an improved method for prolonging the survival of transplanted isolated islet cells in a patient.

– The administration of somatostatin or its analogs to a transplanted patient induced a ß-cell rest in the transplanted islet cells which resulted, firstly, in the inhibition of the glucose-induced endocrine function of those cells whereby the production of insulin, glucagons and other autoantigens was quite significantly reduced and the rendering of the transplanted cells less liable to attack by the host immune system and, secondly, in a reduced energy requirement of the

transplanted cells. These two actions of somatostatin administration extended the functional life of transplanted islet cells as compared to non-treated transplanted cells. The argument was also supported by the teachings in post-published documents (D11) to (D14).

– The evidence presented discharged the appellant's burden of proof with regard to the credibility of the proposed solution. It demonstrated to the standard of the balance of probabilities that the claimed use of somatostatin or an analog thereof was a credible solution to the problem of prolonging the survival of transplanted isolated islet cells as compared to these cells when untreated.

– There was no teaching in any of the prior art documents that motivated the skilled person to use somatostatin to extend the functional life of transplanted isolated pancreatic islet cells. There was no mention in the prior art of somatostatin in relation to islet transplantation. Moreover, there was no teaching in the prior art that the induction of a quiescent state extended the functional life of transplanted isolated pancreatic islet cells, nor that this state could be induced in transplanted islet cells using somatostatin or an analog thereof.

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed with the statement of the grounds of appeal dated 7 February 2006. The appellant

further requested the appointment of oral proceedings if the board did not intend to order the grant of a patent on the main request.

Reasons for the Decision

1. The appeal is admissible.

Procedural matter

2. The examining division did not rectify its decision pursuant to Article 109(1) EPC and consequently remitted the case to the board of appeal under Article 109(2) EPC.

3. The appellant requested the appointment of oral proceedings if the board did not intend to order the grant of a patent on the main request. In view of the outcome of the present appeal, see below, this request needs not to be considered by the board. Indeed the board considered that the case could be decided on the basis of the grounds and facts on file including those already dealt with at first instance. There is therefore no need to hear the appellant further. Accordingly, oral proceedings have not been summoned.

Articles 54, 83 and 123(2) EPC

4. The examining division has acknowledged that the claimed subject-matter meets the requirements of Articles 54 and 123(2) EPC. Apart from those under Article 56 EPC (see below) no objections have been formulated during the first instance proceedings based

on any further substantive requirements for patentability against the claimed subject-matter. The board also sees no reasons for deviating from the examining division's opinion in respect of the above referred to requirements.

Inventive step

5. The pivotal point to be decided in this appeal is whether or not the subject-matter of claim 1 involves an inventive step.

Closest prior art

6. For 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. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.

7. The claimed invention concerns "the use of somatostatin or a somatostatin agonist in the formulation of a pharmaceutical formulation or preparation for the treatment of a human patient in receipt of transplanted isolated pancreatic islet cells, wherein the pharmaceutical composition is administered until the transplanted cells have become established and fully

functional, whereby the functional life of the isolated transplanted pancreatic islet cells is extended relative to untreated transplanted isolated pancreatic islet cells".

8. Both the appellant and the examining division considered the closest prior art to be represented by document (D10). Document (D10) discloses the administration of a new immunosuppressant (15-deoxyspergualin) to human patients receiving pancreatic islet transplantation to protect the islet cells from host immune assault, thereby sustaining the function of the cells (see abstract). In fact, document (D10) is the sole document cited in the examination proceedings which addresses the effect of extending the functional life of transplanted pancreatic islet cells. The board therefore concurs with the appellant and the examining division that document (D10) represents the closest prior art.

9. The board also largely concurs with the examining division's formulation of the problem to be solved by the claimed invention. Based on the technical teaching in document (D10), and in the absence of any argument for or evidence of an improvement over the teaching in that document, the problem to be solved by the claimed invention is the provision of an alternative means to prolong the functional survival of transplanted pancreatic islet cells in human patients.

Is the problem solved?

10. In the decision under appeal the examining division reasoned (see point 13 of the decision) that the

formulated technical problem had not been shown to be solved by the claimed invention and, consequently, that the requirements of Article 56 EPC were not met (see section V, above). It was argued in essence that the patent application as filed did not comprise experimental data showing the claimed effect. Furthermore, the experimental results in post-published documents (D11) and (D12) did not reflect those of the required test experiments. The examining division concluded that, since in *ex parte* proceedings it was the applicant who bore the burden of proof for the facts in his favour, it was not credible that the formulated technical problem had been solved.

11. The application as filed summarises the invention by stating that "[t]*he present invention relates to a method of prolonging the survival of tranplanted pancreatic cells in a patient*" (page 1, lines 20 to 22). Most of the description relates to somatostatin and its agonists as such, to the synthesis of the latter and to somatostatin receptor binding assays, but it also contains a final part entitled "Survival of Transplanted Pancreatic cells" (page 17, line 19 ff.) which deals, albeit in a theoretical manner, with syngeneic islet transplantation in rats and human ß-islet xenografts in non-immunocompetent mice and which discloses an experimental methodology to test the ability of somatostatin receptor binding compounds to extend the functional life of transplanted pancreatic islet cells. On the basis of this disclosure the board notes that the application explicitly addresses the effect(s) claimed.

12. The examining division based its negative decision on the fact that neither the application as filed nor post-published documents "illustrated" the use of somatostatin by way of experimental data showing the claimed effect. In relation to the latter, the examining division considered that other tests were needed which the applicant had not been able to carry out. The board notes that neither in its decision nor during the prosecution of the application has the examining division produced arguments which could discredit the plausibility of the claimed invention. Also the board sees no reasons to doubt the usefulness of somatostatin to attain the claimed effect.

13. The board notes that the EPC requires no experimental proof for patentability and considers that the disclosure of experimental data or results in the application as filed and/or post-published evidence is not always required to establish that the claimed subject-matter solves the objective technical problem. This is in particular true in the absence of any formulated substantiated doubt as is the case here.

14. The boards of appeal have indeed dealt with cases where, in the context of the assessment of inventive step, there could only be an invention if the application made it at least plausible that its teaching did indeed solve the problem it purported to solve and in which to establish plausibility the disclosure of experimental results in a patent application, or, under certain circumstances, by post-published evidence, was considered necessary (see decision T 716/08 of 19 August 2010, points 14 to 16 for a summary of the case law).

15. The board re-emphasises in this context however that this case law considers the establishment of plausibility only relevant when examining inventive step if the case at hand allows the substantiation of doubts about the suitability of the claimed invention to solve the technical problem addressed and when it is thus far from straightforward that the claimed invention solves the formulated problem. This is all the more clear from decisions where an inventive step was in fact denied because the formulated problem was not considered to have been solved. By way of example the board refers to the following two decisions:

15.1 In T 893/02 of 26 May 2004 the board agreed in point 12 of the reasons for the decision with the appellants that the technical effect of inducing immunoprotection against melanoma would "probably not be expected" by the skilled person since the prior art taught that gp75 was not a protein present at the surface of melanoma cells and that anti-gp75 auto-antibodies are only very rarely found in the sera of melanoma patients.

15.2 In T 1329/04 of 28 June 2005 the same board, albeit in a different composition, dealt with the situation where allegedly a new member (GDF-9) of the TGF-ß superfamily had been described. However, the board noted in point 7 of the reasons for the decision that GDF-9 as disclosed did not exhibit the most striking structural feature which served to establish whether or not a polypeptide belonged to the TGF-ß superfamily: namely the presence of seven cysteine residues with their characteristic spacing. Any change in the TGF-ß characterising pattern of cysteins and their invariant spacing was expected to

have significant repercussions on the function of any TGF-ß family member. In point 8 of the reasons for the decision the board noted moreover that GDF-9 was also far from fulfilling the homology criterion as its sequence was stated to be significantly divergent from those of other family members. The board concluded (see point 8) that these findings lead to the conclusion that GDF-9 could "not be clearly and unambiguously identified" as a member of the TGF-ß superfamily by only using a "structural approach".

16. In the present case, the appellant has argued, based mainly on the disclosure in post-published document (D11), that the administration of somatostatin or its analogs to a transplanted patient induced a ß-cell rest in the transplanted islet cells which resulted in the inhibition of the glucose-induced endocrine function of those cells, thereby rendering the transplanted cells less liable to an attack by the host immune system. Furthermore, the administration of somatostatin or its analogs to a transplanted patient resulted in a reduced energy requirement of the transplanted islet cells. Both the above actions of somatostatin administration extended the functional life of transplanted islet cells as compared to non-treated transplanted cells.

17. The board has established in point 12 above that it has no reason to doubt the usefulness of somatostain for the claimed effect. Under these circumstances, post-published evidence may be taken into account. Document (D11) concludes indeed on page 1163, that the use of somatostatin analogs could be envisaged in cases where a decrease in ß-cell function could contribute to reduce antigen expression and thus diminish an immune

assault against these cells as was the case following islet transplantation. Furthermore, post-published documents (D13) and (D14) demonstrate that the treatment of a recipient of an islet graft with a compound that blocks glucose-induced insulin secretion (diazoxide) improves the islet cell transplant function, by preventing desensitisation of the cells upon transplantation (see (D13) page 123, right-hand column line 26 to page 124, left-hand column, line 6 and (D14), page 657, left-hand column, line 35 to page 657, right hand column, line 7). A compound shown to be capable of blocking glucose-induced insulin secretion *in vitro* was somatostatin (see (D13) page 122, right-hand column, lines 22 to 25). Further evidence that somatostatin (analogs) can mimic the effects of diazoxide *in vivo* comes from post-published document (D12) which discloses that both diazoxide and octreotide, being a somatostatin analog, are capable of inducing ß-cell rest (see page 429, right hand column, lines 14 to 16.

18. The board accepts that the data referred to in this post-published literature do not constitute an explicit proof of the claimed effects. Nevertheless, they at the least constitute proof that the claimed effects are plausible. In this context also the argument of the examining division that survival of transplanted islet cells might not only depend on their insulin production cannot weaken the finding on plausibility.

19. In view of the above considerations, the board considers that it is plausible that the technical problem is solved by the claimed subject-matter.

20. In the present case, the examining division further considered, as a basis for requiring experimental proof that it was credible that the formulated technical problem had been solved by using any of the claimed compounds, that it was the applicant, in *ex parte* proceedings, who bore the burden of proof for the facts in his favour.

21. It is an accepted principle in proceedings before the European Patent Office that he who raises an objection has the burden of proof for it, i.e. evidence, facts or any other sort of substantiation must be provided to support the objection. In the board's view it follows firstly that in examination proceedings, as far as issues relating to patentability requirements are concerned, the burden of proof cannot lie initially with the applicant. It follows, secondly, that if an examining division raises an objection, it must appropriately be substantiated. In the present case, the examining division failed to provide such substantiation (see point 12 above). Thus, the board is not convinced by the examining division's argument in point 20, above, which is, in the context of the present case, understood to mean that in *ex parte* proceedings the burden of proof is on the appellant even without a substantiated objection by the examining division.

22. In fact, the examining division's proposition as referred to in point 20, above, seems to originate from the EPO publication "Case Law of the Boards of Appeal of the European Patent Office" and is still present in its 6th Edition (English version) published in 2010 in the paragraph bridging pages 564 and 565. The board

notes however that the cited passage exemplifies the proposition by reference to cases holding that a document cited by an examining division does not form part of the state of the art (decision T 160/92 OJ EPO 1995, 35), that the conditions laid down in Article 123 EPC have been met (decision T 383/88 of 1 December 1992), or that a limitation of the claims is admissible (decision T 2/81, OJ EPO 1982, 394). Furthermore, the passage continues by observing, in the context of sufficiency of disclosure, that the applicant is obliged to provide evidence of the skilled person's relevant knowledge if there is reason to believe the disclosure may not cover all the subject-matter claimed (decision T 82/07 of 23 January 2008). The board notes that all the procedural situations referred to in this passage are those where, in response to a substantiated objection from the examining division, the applicant was required to support his/her contention. Consequently, also the passage (apparently) relied on by the examining division does not support its view that in *ex parte* proceedings the applicant has the burden of proof for facts in his favour. It therefore appears that the proposition cited by the examining division has been taken out of its context.

23. In view of the above considerations the board is satisfied that the claimed invention should be considered to solve the formulated technical problem in accordance with the requirements developed in the case law of the boards of appeal.

Obviousness

24. The examining division stated in the reasons for its decision that, provided the applicant had been able to show that the effect of prolonging the survival of transplanted isolated islet cells by the use of somatostatin or its agonists, the application might possibly have been recognised as making an inventive contribution to the art. The board takes from this that the fact that the formulated technical problem had allegedly not been proved to be solved was the only reason for the examining division to refuse the application. In view of this positive votum of the examining division and in absence of any reason for deciding differently, the board therefore accepts that the invention as claimed involves an inventive step as required by Article 56 EPC.

Article 54(5) EPC

25. With reference to the feature "wherein the pharmaceutical composition is administered until the transplanted cells have become established and fully functional" in claim 1, the board is satisfied that the claimed subject-matter complies with the requirements of Article 54(5) EPC in view of the findings in decision G 2/08 of the Enlarged Board of Appeal (OJ EP 2010, 456).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first with the order to grant a patent on the basis of claims 1 to 12 of the main request filed with the statement of the grounds of appeal dated 7 February 2006 and a description to be adapted thereto.

The Registrar The Chairman

P. Cremona C. Rennie-Smith