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Datasheet for the decision of 26 February 2013

Case Number: T 2101/09 - 3.3.08

Application Number: 98915305.1

Publication Number: 972041

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Novel human delta3 compositions and therapeutic and diagnostic uses therefor

Patent Proprietor:
MILLENNIUM PHARMACEUTICALS, INC.

Opponent:
REGENERON PHARMACEUTICALS, INC.

Headword:
Human Delta3 - Notch/MILLENNIUM

Relevant legal provisions:
EPC Art. 123(3), 84, 83, 57, 54, 56
EPC R. 80
RPBA Art. 12(4), 13(1)

Keyword:
"Admissibility of Main Request (yes) and of new documents (no)"
"Main Request - amendments occasioned by opposition grounds (yes); extension of protection (no), clarity (yes), sufficiency of discloure and industrial applicability (yes), novelty and inventive step (yes)"

Decisions cited:
T 0019/90, T 0079/96, T 0190/99, T 1084/00, T 0189/01, T 1466/05, T 0030/09

Catchword:
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Case Number: T 2101/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 26 February 2013

Appellant: (Opponent 1)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 August 2009 concerning maintenance of European patent No. 972041 in amended form.

Composition of the Board:

Chairman: M. Wieser
Members: P. Julià
J. Geschwind

Summary of Facts and Submissions

I. European patent No. 0 972 041 is based on European patent application No. 98 915 305.1, published as International patent application WO 98/45434 (hereinafter "*the application as filed*"), and was granted with 34 claims. Claims 1, 13 and 21 read as follows:

"1. An isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleotide sequence which is at least 75% identical to the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3, the cDNA insert of the plasmid deposited with the ATCC as Accession Number 98348, or a complement thereof; ..."

"13. An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence which is at least 75% homologous to the amino acid sequence of SEQ ID N:2; ..."

"21. An antibody or antibody fragment that selectively binds to the polypeptide of claims 13, 17, 18 or 19."

Claim 1 contained paragraphs (b) to (g) defining further nucleic acid molecules related to SEQ ID NO: 1 or SEQ ID NO: 3 or to the cDNA insert of the deposited plasmid. Claim 13 contained paragraphs (b) to (e) defining further polypeptides related to SEQ ID NO: 2.

II. Two oppositions were filed against the patent on the grounds of Articles 100(a),(b) and (c) EPC. One opposition was withdrawn on 1 July 2008. The opposition division considered the Main Request and Auxiliary Requests 1 to 3 (filed with letter of 6 January 2009) not to fulfil the requirements of Article 84 EPC. The patent was maintained on the basis of an Auxiliary Request 4 filed on 3 March 2009 at oral proceedings before the opposition division.

III. A notice of appeal and a statement setting out the Grounds of Appeal were filed by the remaining sole opponent (appellant), which maintained all grounds of opposition (Articles 100(a),(b) and (c) EPC) and raised further objections under Article 84 EPC. The appellant also filed documents D17 to D24.

IV. The patentee (respondent) replied to the appellant's statement of grounds of appeal.

V. In a communication dated 5 October 2012 issued pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the board informed the parties of its preliminary, non-binding opinion on some issues of the appeal proceedings.

VI. On 21 December 2012, the respondent replied to the board's communication and filed a Main Request, identical to the Auxiliary Request 4 maintained by the opposition division, and new Auxiliary Requests 1 to 6.

VII. With letter dated 25 January 2013, the appellant replied to the board's communication and to the respondent's submissions and filed document D25.

VIII. Oral proceedings took place on 26 February 2013. At these proceedings, the respondent withdrew all requests except for its previous Auxiliary Request 6 that was made its Main Request.

IX. The **Main Request** contained 9 claims. Claims 1, 5 and 6 read as follows:

"1. An isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule whose nucleotide sequence is at least 95% identical to the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3, the cDNA insert of the plasmid deposited with the ATCC as Accession Number 98348, or a complement thereof;
b) a nucleic acid molecule which encodes a polypeptide which has the amino acid sequence of SEQ ID NO:2 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as Accession Number 98348."

"5. An isolated polypeptide whose amino acid sequence is at least 95% identical to the amino acid sequence of SEQ ID NO:2."

"6. An antibody or antibody fragment that is specifically reactive with the polypeptide of claim 5."

Claim 2 referred to a preferred embodiment of claim 1. Claims 3 and 4 were directed, respectively, to a vector comprising an isolated nucleic of claim 1 and to a host

cell comprising said vector. Claims 7 to 9 referred to preferred embodiments of claim 6.

X. The documents cited in the present decision are:

D2: WO 97/01571 (publication date: 16 January 1997);

D3: B. Bettenhausen et al., Development, 1995, Vol. 121, pages 2407 to 2418;

D19(a): WO 98/51799 (publication date: 19 November 1998);

D19(b): English translation of document D19(a);

D25: Decision issued on 6 July 2012 by the opposition division in the opposition proceedings against European patent EP 1 004 669 based on European patent application No. 98 919 575.5.

XI. The appellant's arguments may be summarized as follows:

Admissibility of documents D19 and D25

D19 concerned the human Delta3 (hDelta3) protein disclosed in the patent-in-suit. D25 showed that the interpretation of the term "*specifically*" in the context of antibodies, established in decision T 189/01 of 15 June 2004, was followed by first instance departments, such as in the opposition proceedings concerning D19. Both documents were highly relevant.

Main request
Rule 80 EPC

Several amendments merely aimed at tidying-up the claims, such as the reference to identity rather than to homology in claim 5. If the wording "*specifically reactive*" in claim 6 had the same meaning than that of "*selectively binding*" in granted claim 21, the amendment was superfluous.

Articles 123(3) and 84 EPC

There was no unequivocal generally accepted meaning in the art for the term "*specifically*" which was thus ambiguous and open to interpretation. According to the case law, the terms in the claims had to be given the broadest technically sensible meaning (cf. T 79/96 of 20 October 1998). The term "*specifically*" when applied to antibodies described, at a general level, the nature of an antibody-epitope interaction rather than the narrower concept of exclusive binding to a single target protein. In the present case, the term in its broadest interpretation did not exclude antibodies cross-reactive with the hDelta3 protein and with other Delta proteins, such as the human Delta1 (hDelta1) protein.

Whereas the wording "*selectively binding*" in granted claim 21 excluded antibodies cross-reactive with related (hDelta1) proteins, the wording "*specifically reactive*" was broader and did not exclude cross-reactive antibodies. The term "*reactive*" was broader than "*binding*"; the former included the latter. The term "*selectively*" defined the ability of an

antibody to selectively bind to a particular target rather than to other targets. This ability was not required by the term "*specifically*". In decision T 189/01 (*supra*), the board decided that the notion of antibody specificity did not exclude cross-reactive antibodies. Decision T 1084/00 of 11 April 2003 was not relevant since it did not concern an antibody/antigen interaction but a different (hybridisation) interaction. There was no disclosure in the patent-in-suit of an antibody reacting with the hDelta3 protein but not with other Delta (hDelta1) proteins. The general references in the patent, such as the one to the use of specific antibodies for immunoaffinity purification, were not a basis for interpreting the term "*specifically*".

Articles 83 and 57 EPC

Claim 6 did not exclude cross-reacting antibodies. These antibodies were not exemplified by the patent-in-suit, were difficult to obtain and required intensive labour and non-routine equipment. In decision T 1466/05 of 27 July 2007, the board emphasized the need to provide guidance in regard to epitopes that allowed for an antibody to bind a particular protein and how to select antibodies that were not cross-reactive. There was no teaching in the patent-in-suit of a screening process leading to antibodies reactive with hDelta3 protein but not with other Delta proteins. No epitopes unique to the hDelta3 protein were disclosed and it was not described how to screen anti-hDelta3 antibodies from other cross-reactive antibodies. Undue burden was required to arrive at these antibodies, the more so, since claim 6 was not limited to antibodies specifically reactive

with a polypeptide of sequence SEQ ID NO: 2 but rather with all polypeptides having a sequence being at least 95% identical thereto. Thus, claim 6 comprised antibodies raised against new epitopes that were not present in the hDelta3 protein and for which the patent-in-suit failed to disclose any use.

Article 54 EPC

Since claim 6 comprised cross-reactive antibodies, antibodies binding to epitopes that were highly conserved in all Delta proteins, such as those shown in Figure 2 of the patent-in-suit, anticipated the subject-matter of the claim. D2 disclosed antibodies raised against such epitopes in the hDelta1 protein.

Article 56 EPC

The closest prior art D2 disclosed the isolation and characterization of the hDelta1 protein. The alleged technical problem, namely to provide a human Delta gene encoding a further functionally active human Delta protein, was not solved over the entire scope of the claims.

Claims 1 and 5 were not limited to the hDelta3 sequences disclosed in the patent-in-suit but comprised molecules having at least 95% identity thereto. In absence of any functional feature, such as the ability to bind to a Notch polypeptide, these claims comprised subject-matter unrelated to hDelta3 (stop-codons, frame-shifts, insertions, deletions, etc. resulting in small, truncated polypeptides or inactive polypeptides with different properties and effects) which did not

solve the technical problem. Likewise, claim 6 comprised antibodies reacting with epitopes not present in the hDelta3 protein and thus, unrelated thereto.

Moreover, starting from D2, it was obvious to arrive at the claimed subject-matter. The presence of two Delta proteins in *Xenopus* was known in the art and in D3 the presence of a second mouse Delta protein was indicated. The skilled person was motivated to follow the indications of D2 and to look for further human Delta proteins. Methods and means, such as probes derived from regions of high homology and common to all Delta proteins, PCR conditions, source libraries, etc., were available from D2. In view of this prior art, there was a reasonable expectation of success to arrive at the claimed subject-matter. Although the Delta3 gene was not identified in the human library used in D2 for isolating the hDelta1 gene, there was no reason to believe that it was not present in that library or in any other human library mentioned in D2 as possible starting material. Although a different library and different methods were used in the patent-in-suit, there was no evidence on file to support the existence of technical difficulties when isolating the hDelta3 gene.

XII. The respondent's arguments may be summarized as follows:

Admissibility of documents D19 and D25

D19 was late-filed and not more relevant than other prior art on file. D25 provided an interpretation of the findings of the board in decision T 189/01 (*supra*). However, the decision itself was already on file.

Main request
Rule 80 EPC

The wording of granted claim 21 ("*selectively binds*") was objected under Article 123(2) EPC and replaced by the wording "*specifically reactive*" present in the application as filed. The replacement of homology by identity degree addressed objections raised under Articles 123(3) and 84 EPC.

Article 123(3) and 84 EPC

According to the case law, a claim had to be construed by a mind willing to understand (cf. T 190/99 of 6 March 2001). The sole technical sensible interpretation of the wording "*specifically reactive*" in claim 6 was that the antibodies were able to bind only to hDelta3 protein but not to other Delta proteins. In fact, this was the meaning given to the term "*specifically*" in the entire patent-in-suit, as for instance in the reference to the immunoaffinity purification of the hDelta3 protein in paragraph [0147]. The present case was different from the one underlying decision T 189/01 (*supra*), since claim 6 explicitly referred to antibodies reacting with a polypeptide, not to epitopes thereof. In the present case the contested term had a clear meaning that excluded cross-reactive antibodies. The wording "*specifically reactive*" in claim 6 had the same meaning as the wording "*selectively binding*" in granted claim 21. The same meaning was also given to the term "*specifically*" in decision T 1084/00 (*supra*), although in the context of nucleic acid hybridization.

Articles 83 and 57 EPC

An objection for lack of sufficiency could only be successful if there were serious doubts substantiated by verifiable facts (cf. T 19/90, OJ EPO 1990, page 476), which was presently not the case. The subject-matter of the claims was a reasonable generalization of the hDelta3 sequences disclosed in the patent. In view of the biological activities cited in paragraph [0056] of the patent, which were not limited to the binding to a Notch protein, it was plausible that the group of molecules claimed shared these activities, or at least some of them, with hDelta3. The subject-matter of claim 6 was directed to antibodies specifically reacting with the hDelta3 protein. Standard methods for antibody production were known in the art and the disclosure of the hDelta3 protein allowed the development of standard screening methods for isolating antibodies with the desired specificity and properties. No evidence was on file to support the presence of technical difficulties when carrying out these standard methods. The present situation was different from the one underlying decision T 1466/05 (*supra*) which relied only on a deposited hybridoma that produced a monoclonal antibody with particular specificity and properties.

Article 54 EPC

Claim 6 did not cover cross-reactive antibodies. Thus, antibodies which reacted with other Delta proteins, such as the antibodies disclosed in D2 reacting with hDelta1, laid outside the scope of claim 6.

Article 56 EPC

The closest prior art D2 was concerned with hDelta1. Starting therefrom, the technical problem to be solved was the provision of a further human Delta gene and protein with effects and properties different from those of hDelta1. The problem was solved by the provision of the hDelta3 protein which had a low (50%) identity to hDelta1 and had distinctly different properties (tissue distribution, biological activity, etc.). It was plausible that the group of molecules claimed shared all or at least some of the properties cited in paragraph [0056] of the patent. All these molecules represented closely related solutions to the technical problem, which was thus solved over the entire scope of the claims.

None of the prior art documents on file provided a motivation to look for a further human Delta protein. The reference to a second mouse Delta homologue in D3 was ambiguous and without technical support. A second mouse Delta homologue was not mentioned in other publications of the authors of D3 or in any other contemporaneous publication, such as D2. At the priority date of the patent-in-suit, two Delta genes had been identified only in *Xenopus* but not in any mammalian.

Document D2 disclosed standard cloning methods and libraries, but not the specific library and method used in the patent-in-suit. The emphasis put in D2 on the importance of Delta and Notch proteins in neural and fetal tissues conducted the skilled person in a

different direction. Following the approach suggested there, as carried out in Example 8 of D2 by using a human fetal brain plasmid library, led to the identification of hDelta1 only. In the absence of any indication, there was no motivation for the skilled person and definitely no reasonable expectation of success, to look for a second human Delta gene with properties different from those of hDelta1 by using the method and library of D2. Only with hindsight the skilled person would have considered to use the different library and method disclosed in the patent-in-suit.

XIII. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

XIV. The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 9 of the new Main Request filed at the oral proceedings before the board.

Reasons for the Decision

Admissibility of the Main Request

1. The Main Request was filed as Auxiliary Request 6 in direct reply to the board's communication under Article 15(1) RPBA. The subject-matter of claims 1 to 9 is already contained in the claims that have been found allowable by the opposition division, i.e. Auxiliary Request 4 in opposition procedure, so that no new

objections that were not already on file can be raised against it. Therefore, the board, exercising its discretion under Article 13(1) RPBA, decides to admit the Main Request into the appeal proceedings.

Admissibility of documents D19 and D25

2. D19 is a post-published document filed with appellant's Grounds of Appeal. No reasons have been given why it was filed at this stage of the proceedings and not at an earlier stage. The document has been cited in the context of Article 56 EPC. However, for an analysis under this article, *prima facie*, it is not more relevant than other prior art on file, like documents D2 or D3. Thus, the board, exercising its discretion under Article 12(4) RPBA, does not admit D19 into the appeal proceedings.

3. D25, a decision of the first instance to revoke a patent granted on the basis of D19, was filed in response to the board's communication under Article 15(1) RPBA. This document has been cited in the context of Articles 123(3) and 84 EPC with regard to the interpretation of the term "*specifically recognizes*", allegedly made in accordance with the findings of the decision T 189/01 (*supra*). This decision has been cited in the Grounds of Appeal and it is already in the procedure. The interpretation of a decision of the Boards of Appeal by a first instance department is *prima facie* not considered to be more relevant than the findings in the decision itself. Thus, the board, exercising its discretion under Article 13(1) RPBA, does not admit D25 into the appeal proceedings.

Rule 80 EPC

4. The replacement of the wording "*selectively binds to*" by "*specifically reactive with*" in claim 6 overcomes an objection raised under Article 123(2) EPC against granted claim 21. The fact that it raises new issues under Articles 123(3) and 84 EPC is not relevant under Rule 80 EPC. The replacement of homology by identity in claim 5 addresses objections raised under Articles 123(3) and 84 EPC. The requirements of Rule 80 EPC are thus fulfilled.

Articles 123(2),(3) and 84 EPC

5. No objections have been raised under Article 123(2) EPC, and the board does not see any basis for such an objection. The requirements of Article 123(2) EPC are fulfilled.

6. The wording "*specifically reactive with*" in claim 6 has been objected under Articles 84 and 123(3) EPC (cf. Section XI *supra*).

7. Contrary to the term "*interact*" for which a definition is given in paragraph [0069] of the patent-in-suit, there is no definition for the term "*reactive*" in the patent. Although "*reactive with*" may include "*binding to*", in the field of immunology and in the context of an antibody/antigen reaction, this wording is understood by a skilled person as referring to the binding of these two molecules. The more so if this reactivity is required to be specific, excluding thereby non-specific reactions between both molecules.

8. There has been much discussion about the proper interpretation of the terms "*selectively*" and "*specifically*". Although, in the communication under Article 15(1) RPBA, the board prompted the parties to provide evidence of the common general knowledge for these terms (dictionary, encyclopaedia, etc.), none has been provided and there is no piece of prior art on file defining the precise meaning of these terms in the field and context mentioned above. Nevertheless, from the usual language in patents and patent applications related to this field, the board, in the present case, considers itself entitled to make the following observations:

8.1 First, whereas it is known in the field that an antibody always binds to an epitope, claim 6 requires the antibody to be "*specifically reactive with*" the polypeptide of claim 5. From this wording and the interpretation made of the term "*reactive*" (cf. point 7 *supra*), the board understands the claimed antibodies to be limited to those that bind only to those epitopes of the polypeptide of claim 5 that are specific for this polypeptide, independently of whether or not they are identified and/or characterized in the patent-in-suit. In the light thereof, the board fails to see any difference between the wording of claim 6 and that of granted claim 21 which requires that the claimed antibody "*selectively binds to*" related polypeptides.

8.2 Second, in order for the claimed antibodies to be "*specifically reactive with*" or "*selectively binding to*" the polypeptide of claim 5, they must bind to epitopes that are not present in other polypeptides, in particular, not in those polypeptides which are more

closely related and/or structurally similar to the polypeptide of claim 5, since - by their sequence identity and functional conformational folding - they may have the highest probability to have identical or similar epitopes. In the present case, the polypeptide of claim 5 is the hDelta3 protein and the structurally closest proteins are other members of the Delta family. Thus, the claimed antibodies are reactive with those epitopes of the hDelta3 protein that discriminate the hDelta3 protein from other structurally related proteins such as those cited in Table 1 of the patent. The board, being aware that the case law of the Boards of Appeal on this point is not strictly homogenous (see for instance decision T 189/01, *supra*), is nevertheless convinced that, in the present case, this is a technically sensible interpretation of the term "*specifically*" which is in line with other decisions of the Boards (cf. *inter alia*, T 30/09 of 4 May 2012, in particular points 12 to 18 of the Reasons).

8.3 Third, although it cannot be excluded with absolute certainty that one of the epitopes that discriminate the hDelta3 protein from structurally related proteins will be present in other unrelated proteins, antibodies raised against these epitopes are not "*specifically reactive with*" the hDelta3 protein and thus, not within the scope of claim 6. This is the technically sensible interpretation given to similar claims in patents and patent applications in the field of antibody technology.

8.4 The above interpretation is also in line with the findings of decision T 1084/00 (*supra*) wherein, although in the context of nucleic acid hybridization, the term "*specifically*" is given a similar meaning.

Moreover, although the antibodies of claim 6 are not exemplified in the patent-in-suit, the references given therein are also in line with this interpretation, such as for instance the reference to immunoaffinity purification (cf. *inter alia*, page 21, lines 37 to 40, page 25, line 26 of the patent-in-suit).

9. In view of the above considerations, in the light of the evidence on file and the arguments presented by the parties, the board considers that the objection raised under Article 84 EPC against the subject-matter of claim 6 must fail.

10. Likewise, the board considers that both, claim 6 and granted claim 21, do not cover cross-reactive antibodies. In the light thereof and taking into account that claim 6 is directed to an antibody that "*specifically reacts with*" a polypeptide whose amino acid sequence is at least 95% identical to the amino acid sequence of SEQ ID NO: 2, whereas granted claim 21 requires that the antibody "*selectively binds to*" a polypeptide comprising an amino acid sequence which is at least 75% homologous to the amino acid sequence of SEQ ID NO: 2, the board considers claim 6 to fulfil the requirements of Article 123(3) EPC as it does not extend the protection conferred by the patent as granted.

Articles 83 and 57 EPC

11. No objections have been raised under these articles against subject-matter directed to the nucleic acid sequences SEQ ID NO: 1 or 3, the amino acid sequence SEQ ID NO: 2, or the cDNA insert of the plasmid deposited with the ATCC. No submissions have been made arguing for the presence of technical difficulties to obtain sequences with at least 95% identity to those of SEQ ID NO: 1 or 3 or amino acid sequences with at least 95% identity to that of SEQ ID NO: 2.

12. Appellant's objection is based on the argument that, within the claimed group of nucleic acid molecules and polypeptides having sequences that are not identical to the specific sequences of SEQ ID NOs 1, 2 and 3 but which are only at least 95% identical thereto, there are molecules completely unrelated to hDelta3 with properties different from those of the hDelta3 (cf. Section XI *supra*). These molecules might lack any technical effect and thus any industrial applicability.

13. It is common practice in the field of biotechnology that claims in patents/patent applications related to a novel and inventive (nucleic acid, amino acid) sequence are not required to be limited to a very specific sequence but may also embrace molecules having a certain degree of homology and/or identity to this specific sequence. The degree of homology/identity accepted depends on the relevant prior art and the particular circumstances of each individual case. This practice allows patentees/applicants to protect their inventions against arbitrary modifications of the specific sequences. The reference to at least 95%

identity in claims 1 and 5 is in line with this practice. Moreover, the wording of these claims ("... *whose ... sequence is at least 95% identical to the ... sequence...*"; underlined by the board) requires a degree of identity over the full-length of the sequence and not over short, arbitrary fragments thereof.

14. In some cases, it might be necessary to further limit the scope of a claim referring to such group of molecules either by increasing the degree of identity and/or homology or by requiring the indication of further technical properties, such a specific activity, effect, etc. None of these additional limitations is present in claims 1 and 5. In particular, there is no limitation to polypeptides - or to nucleic acid molecules encoding them - that specifically bind to a Notch polypeptide.

15. Paragraph [0056] of the patent-in-suit refers to the biological activities that may be, directly or indirectly, performed by hDelta3. The ability to bind a Notch polypeptide is only one among several other activities. The use of nucleic acid molecules is not limited to the production of the encoded polypeptides but may also be related to their ability to hybridize to the specific nucleic acid sequences disclosed in the patent (cloning, detection, diagnostic probes, etc.). Likewise, polypeptides may also be used as possible inhibitors or as antigens for the production of antibodies, etc.

16. In view of the close structural (at least 95%) identity of the group of molecules of claims 1 and 5 and their low degree of identity to the closest structurally

related molecules, i.e. other human delta proteins (cf. page 8, Table 1 of the patent; Maximum 54% identity), there are no serious doubts (let alone substantiated by verifiable facts; cf. T 19/90, *supra*) that they can be used in at least one of the several biological activities contemplated in paragraph [0056] of the patent-in-suit.

17. As for the antibodies of claim 6, the interpretation of the feature "*specifically reactive with*" made in points 8 to 10 *supra* is relevant. Since these antibodies must necessarily have the ability to discriminate the hDelta3 protein from other known Delta proteins, there are no doubts that such antibodies have an industrial application. Although the patent does not disclose any specific examples of these antibodies, there are standard techniques well-known in the art and cited in the patent-in-suit, that allow their production. The disclosure of the amino acid sequence SEQ ID NO: 2 of the hDelta3 protein with the characterization of its domains, in particular, the extracellular (amino acid 1 to 529), the transmembrane (amino acid 530 to 553) and the intracellular (amino acid 554 to 685) domains as well as regions thereof which have a low homology to those of other known Delta proteins (cf. Figure 2 of the patent-in-suit), allows the selection of suitable candidate epitopes. Likewise, the fact that the hDelta3 protein and other known Delta proteins are available to the skilled person allows the development of appropriate screening methods without undue burden. The present situation is not comparable with that of decision T 1466/05 (*supra*) where the antibody specifically discriminated between the same organic

compound in two different states, namely peptide-linked pyridinoline and free pyridinoline.

18. Thus, the Main Request is considered to fulfil the requirements of Articles 83 and 57 EPC.

Article 54 EPC

19. Appellant's submissions with regard to lack of novelty are based on the argument that claim 6 comprises cross-reactive antibodies (cf. Section XI *supra*). However, in line with the observations made in points 8 to 10 *supra*, these cross-reactive antibodies are not considered to fall within the scope of this claim. Thus, the objection is considered not to be relevant and the Main Request is considered to fulfil the requirements of Article 54 EPC.

Article 56 EPC

20. The closest prior art document D2 discloses the cloning, identification and characterization of the Delta1 gene and protein, including nucleic acid sequences and the encoded putative amino acid sequence of hDelta1 (cf. page 76, Example 8 and Figures 12 to 14 of D2). D2 refers to the use of the nucleic acid sequences for the identification and isolation of additional genes encoding Delta proteins (cf. *inter alia*, page 14, lines 14 to 19, page 16, line 28 to page 17, line 6 of D2).

21. Starting from this closest prior art, the technical problem to be solved is the provision of a further human Delta gene and protein. As a solution to this problem the patent proposes the subject-mater of claims

1 and 5. In view of the observations made in points 13 to 17 *supra*, the technical problem is solved over the entire breadth of the claims.

22. The appellant argues that the mention of the presence of a second mouse Delta homologue in document D3 would have prompted a skilled person to look for a second human Delta homologue (cf. Section XI *supra*). However, the reference to a second mouse Delta homologue in D3 contains some ambiguity, since it is made in the context of other proteins that bind to Notch proteins, namely the Jagged and Serrate homologues (cf. page 2416, right-hand column in D3). The source of this reference is a personal communication from which a skilled person cannot derive any precise technical information on the features characterizing this second mouse Delta homologue and what may differentiate it from other Notch binding proteins. Even more important, none of the other publications of the author of the personal communication in D3 on file, and no other contemporaneous document, refers to this second mouse Delta homologue. Thus, although there was already a disclosure of a second Delta protein in *Xenopus* (cf. paragraph [0010] of the patent-in-suit), there was no clear and unambiguous indication of such a second Delta protein in a mammal. Under these circumstances, the reference in D3 is not considered to prompt a skilled person to look for a second human Delta homologue with a reasonable expectation of success.

23. Likewise, the references in D2 cited by the appellant are of a general character and directed to the identification of variants related to the disclosed Delta1 protein or to further Delta1 homologues of other

species. The references to sources of (vertebrate) cells, genomic and cDNA libraries, etc. are all of a general character (cf. *inter alia*, page 13, Section 5.1 of D2). Indeed, D2 emphasizes the importance of Delta and Notch proteins in fetal and neural tissues, thereby instructing the skilled person to use fetal or embryonic neural cDNA libraries. A human fetal brain plasmid library is used in Example 8 of D2 and results in the detection and identification of, only and exclusively, hDelta1 (cf. page 76 of D2). In view of the disclosure in the prior art at the priority date of the patent-in-suit, there were no obvious reasons for a skilled person to look for further human Delta homologues in the library used in Example 8 of D2, and certainly not to look for a human Delta homologue having a degree of identity as low as of only 50% to the hDelta1 protein. In the absence of any clear hint in the prior art, which is not derivable from D2 or D3, the skilled person only with hindsight would have started such undertaking.

24. As correctly stated by the opposition division (cf. page 9, last paragraph to page 10 of the decision under appeal), there is no indication in the prior art that would have directed a skilled person, trying to solve the problem underlying the patent-in-suit (cf. point 21 *supra*), to the specific human cDNA microvascular endothelial cell (HMVEC) library used in Example 5 of the patent-in-suit, let alone to the initial HMVEC treatment (pool of four differently treated samples), high throughput random sequencing and screening followed in that Example (cf. page 37, Example 5 of the patent). There was certainly no reasonable expectation of success to identify and isolate a second human Delta

homologue with the properties of the hDelta3 disclosed in the patent-in-suit.

25. The board does not see any reason to deviate from the findings of the opposition division as regards Article 56 EPC and considers the Main Request to fulfil the requirements of Article 56 EPC.

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 instance with the order to maintain the patent on the basis of claims 1 to 9 of the new Main Request filed during the oral proceedings and the description to be adapted thereto.

The Registrar: The Chairman:

A. Wolisnki M. Wieser