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Datasheet for the decision of 17 March 2011

Case Number: T 0878/09 - 3.3.04

Application Number: 92924777.3

Publication Number: 0616613

IPC: C07K 7/06

Language of the proceedings: EN

Title of invention:
Fragments of prion proteins

Patentee:
Protherics Medicines Development Limited

Opponents:
Prionics AG
CSL Behring GmbH
Caprion Pharmaceuticals, Inc.
Commissariat à l'Energie Atomique and Pasteur Sanofi Diagnostics

Headword:
Method for the detection of prion proteins/PROTHERICS

Relevant legal provisions:
EPC Art. 56, 83, 84, 123(2)(3)

Keyword:
"Main request: admissibility (yes); added matter, extension of scope (no); clarity, novelty, inventive step, sufficiency of disclosure (yes)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0878/09 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 17 March 2011

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 5 February 2009 revoking European patent No. 0616613 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
R. Gramaglia

Summary of Facts and Submissions

I. The European patent at issue has the number EP 616 613 and the title "Fragments of prion proteins".

II. This patent has been opposed by Opponents 01 to 04 pursuant to Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC) and lack of industrial applicability (Article 57 EPC), pursuant to Article 100(b) EPC on the ground of lack of sufficient disclosure (Article 83 EPC) and pursuant to Article 100(c) EPC on the ground of added subject-matter (Article 123(2) EPC).

III. In a decision dated 17 September 2003 the Opposition Division held that the claims of the only request before them did not meet the requirements of Article 123(2) and (3) EPC.

IV. The patent proprietor lodged an appeal against this decision becoming case number T 79/04. In its decision of 2 June 2006 the board held that the amended claims of the only request before it complied with the requirements of Articles 123(2) and (3) EPC and remitted the case to the department of first instance for further prosecution.

V. The opposition division held in its second decision of 5 February 2009 that the only request before it - corresponding to the request remitted by the board of appeal, auxiliary requests 1 to 3 having not been admitted - did not comply with the requirements of Article 83 EPC and therefore revoked the patent pursuant to Article 101(3)(b) EPC.

VI. The present appeal by the patent proprietor is against this second decision of the opposition division.

VII. With the statement of the grounds of appeal the appellant submitted a new main request and auxiliary requests 1 to 5 and with a letter dated 30 June 2010 it filed auxiliary requests 6 to 31.

VIII. With its letter dated 24 February 2011 the appellant withdrew all requests and filed a main and an auxiliary request corresponding to the previously filed auxiliary requests 26 and 27. The requests included not only claims but also amendments to the description shown on pages from the application as filed.

IX. The only claim of the main request read:

1. A method of detecting prion proteins in a bovine sample which comprises

incubating said sample with an antibody or antigen binding fragment thereof, which specifically binds to a synthetic polypeptide which has at least one antigenic site of a prion protein and is SEQ ID NO: 47: Gly-Gln-Gly-Gly-Ser-His-Ser-Gln-Trp-Asn-Lys-Pro-Ser-Lys-Pro-Lys-Thr-Asn-Met-Lys-His-Val-Gly-Cys

wherein said sample has been pretreated by predigestion with enzymes and by denaturation by strong alkali.

X. None of respondents I, II or IV filed written submissions on substantive or formal issues during the appeal proceedings.

XI. Respondent IV (Opponent 04) withdrew its opposition by a letter dated 26 October 2009.

XII. Oral proceedings took place on 17 March 2011. Only respondent III was represented. The appellant and respondents I and II had informed the board that they would not attend.

XIII. The appellant requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the main or the auxiliary request.

XIV. Respondent III requested that the appeal be dismissed.

XV. At the end of the oral proceedings the board announced its decision.

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

J9 J. Immunology, vol. 140, 1988, pages 1188-, Barry et al.

J10 J. Immunology, vol. 147, 1991, pages 3568-. Rogers et al.

J11 J. Mol. Recog. vol. 4, 1991, pages 85-, Di Martino, et al.

J27 J. Virol, vol. 65, 1991, pages 3667 - , Bolton, et al.

J28 J. Infect. Diseases, vol. 153, 1986, pages 848-, Barry et al.

XVII. The appellant's arguments submitted in writing and as far as they apply to the main request and answer the objections of respondent III (hereinafter "respondent") can be summarized as follows.

Admissibility of the main request

The reduction of the number of requests from 31 to 2, i.e. a main and an auxiliary request, simplified the matters under consideration and clarified the appellant's position regarding the patentability of the claimed invention.

The only claim of the main request was the same as claim 1 of the request remitted to the opposition division by the board of appeal after the first appeal proceedings, with the exception that the feature "or antibodies against prion proteins" had been deleted and the feature "wherein said sample has been pretreated by predigestion with enzymes and by denaturation by strong alkali" had been added. The opposition division had revoked the patent for lack of sufficiency of disclosure due to the presence of the first-mentioned feature and the respondent had objected to the absence of the second feature throughout the proceedings. Thus, the absence and presence, respectively, of the features could not surprise the respondent. Moreover, the new claim was formally allowable.

Therefore, the main request should be admitted.

Rule 80 EPC

The deletion of the feature "or antibodies against prion proteins" addressed the reason for refusing the main request in the decision under appeal for lack of sufficiency of disclosure.

The inclusion of the feature "wherein said sample has been pretreated by predigestion with enzymes and by denaturation by strong alkali" was occasioned by the respondent's objections under Articles 56 and 83 EPC.

Article 123(2) EPC

The feature "or antibodies against prion proteins" described an alternative way of detecting prion proteins and therefore its deletion did not add matter.

The feature "wherein said sample has been pretreated by predigestion with enzymes and by denaturation by strong alkali" had a basis on page 29, lines 19 to 23 of the application as filed.

Article 83 EPC

The relevant data with regard to the claimed subject-matter were those shown in Table II of the dot blot assay obtained with antibodies denoted with numbers 97 and 98. When evaluating these results it was important to consider the relationship between the results and not the results in isolation. Doing so showed in fact that antibodies which specifically bound to a synthetic polypeptide having SEQ ID NO: 47 were suited for the detection of prion proteins in bovine samples.

The experimental setting of the dot blot assay did not require the complete absence of antibody binding in the negative control sample. Therefore the detection of some reactivity was not an indication that the claimed method did not work.

Article 56 EPC

Document J11 disclosed that the N-terminal region of the proteinase-resistant core in the prion protein contained an epitope that was determinative for species-selectivity of antibodies raised thereto. The sequence of the ovine and the bovine prion proteins differed in this region by two residues. The synthetic peptide having SEQ ID No: 47 covered this region. Thus, the skilled person would not have expected that antibodies binding to the synthetic peptide derived from the ovine prion protein would react with the native bovine prion protein and would therefore not have used antibodies binding to the peptide having SEQ ID No: 47 for detecting prion proteins an a sample of bovine origin.

Hence, the subject-matter of claim 1 involved an inventive step.

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

Admissibility of the main request

Although the appellant reduced the number of requests to be dealt with at the oral proceedings from 31 to 2,

this did not simplify the proceedings, since for the respondent it was not sufficient to confine its preparation to only these two remaining requests. Rather it had to be prepared to deal with the withdrawn requests as well in case that the appellant suddenly choose to rely on one of these older requests during the oral proceedings.

Claim 1, i.e. the only claim of the main request contained the new feature "wherein said sample has been pretreated by predigestion with enzymes and by denaturation by strong alkali". The absence of this feature from claims relating to a method for the detection of prion proteins had been objected to by the respondent during the whole opposition and appeal proceedings. Thus, claims comprising this feature could have been filed earlier.

Moreover, claim 1 suffered prima facie from several formal deficiencies.

Consequently, the main request should not be admitted into the proceedings.

Rule 80 EPC

Many of the previous requests, for example also the one allowed after the first appeal, contained a dependent claim 3. This claim had never been attacked per se by any ground of opposition. Hence, there was no reason for its deletion which therefore contravened the requirements of Rule 80 EPC.

Article 84 EPC

The adapted description contained several passages calling in doubt the meaning of claim 1. Therefore, the claims did not comply with the requirements of Article 84 EPC.

Article 123(2) EPC

The method of detection as defined in claim 1 of the main request recited the feature "wherein said sample has been pretreated by predigestion with enzymes and by denaturation with strong alkali".

The passage on page 29, lines 19-23 disclosed this feature in relation to a method of discrimination.

According to the general understanding of the skilled person, a method of "discrimination" was different from a method of "detection". While a method of "detection" meant the identification of the presence of a specific analyte, a method of "discrimination" involved the identification of the presence of a specific analyte in the presence of at least one further analyte.

This difference in understanding was reflected by the fact that the application as filed contained two independent claims relating to each of the two methods.

Thus, the passage on page 29 was not a basis for the subject-matter of claim 1 and therefore this claim contravened the requirements of Article 123(2) EPC.

Article 83 EPC

The normal cellular prion protein (PrPc) was proteinase K-sensitive. Therefore, and this was also disclosed in the patent in paragraph [0013], the treatment of a sample with proteinase K should completely digest any PrPc contained therein. Hence, no antibody reactivity with the normal cellular prion protein should be measurable in the sample providing the negative control, after proteinase K treatment. However, the results of the dot blot assays disclosed in Table II for antibodies 97 and 98, i.e. antibodies according to claim 1, demonstrated that the expected result was not achieved. However, without a proper negative control, a meaningful interpretation of the results of the assay was not possible. Thus, the disclosure in the patent did not demonstrate that the claimed method was suited for specific detection of the infective form of the bovine prion protein.

Moreover, a feature of Claim 1 was that the "sample has been pretreated by predigestion with enzymes and by denaturation with strong alkali". However, enzmyes other than proteinase K for digestion and strong alkali compounds other than guanidine hydrochloride for denaturation were not disclosed in the patent. Therefore, the disclosure did not enable the claimed invention to be carried out over the whole breadth of the claim.

Hence, for these reasons the requirements of Article 83 EPC were not fulfilled.

Article 56 EPC

Each of documents J9, J10, J11, J27, J28 could be considered as the closest prior art document because they all taught that a region corresponding to that covered by the peptide with sequence SEQ ID No: 47 was antigenically relevant.

The problem underlying the invention was to provide an alternative method for the detection of prion proteins.

In view of this problem the skilled person would - by routine methods - have prepared synthetic peptides of this region from prion proteins of any species and would have raised antibodies against them. The skilled person would have routinely tested these antibodies for reactivity with native prion proteins from each and any species. The skilled person would thus have found in a straightforward manner antibodies binding specifically to a synthetic peptide having amino acid sequence SEQ ID No: 47 and also that they bound to the native bovine prion protein.

Consequently, the method of claim 1 did not involve an inventive step.

Reasons for the decision

1. The invention relates to a diagnostic assay for bovine spongiform encephalitis (BSE). The causative agent of BSE is an isoform of an endogenous cellular protein differing from said protein by its three-dimensional structure. The non-infectious normal cellular version

is denoted "PrP^C", the infectious form "PrP^{SC}". Both have a molecular weight of 33-35 kd after electrophoresis on an SDS-polyacrylamide gel. The two isoforms have different physical properties: PrP^C disappears during proteinase K digestion, while PrP^{SC} looses an amino-terminal peptide. The resulting proteinase-resistant core protein has a molecular mass of 27-30 kd after electrophoresis on an SDS-polyacrylamide gel and is known as PrP27-30.

Admissibility of the main request

2. Claim 1, the only claim of the present main request, was filed on 24 February 2011, i.e. less than a month before the oral proceedings. The claim is identical with claim 1 of the main request submitted with the statement of the grounds of appeal, with the difference that the feature "wherein said sample has been pretreated by predigestion with enzymes and by denaturation with strong alkali" has been introduced into the present claim.

3. However, and as remarked by the respondent itself, it has objected to the absence of this feature from a claim to a method for the detection of prion proteins throughout the opposition and appeal proceedings.

4. Therefore, the board on the one hand agrees with the respondent's view that the appellant could have filed claims containing the feature at issue at an earlier point in time. However, the board considers on the other hand that it can be safely assumed that the respondent had no difficulties in preparing arguments in relation to such a claim.

5. Consequently, although the main request was formally filed only shortly before the oral proceedings, in the board's view, the time between its filing and the oral proceedings was sufficient for the respondent to properly prepare its case with regard to the new request.

6. Moreover, the board could not - either prima facie or after closer consideration, see points 10 to 39 below - share the respondent's view as to the various formal deficiencies it alleged against the main request.

7. Finally, the board is not convinced by the respondent's argument that the appellant's strategy of filing a huge number of requests during the proceedings and of withdrawing most of them shortly before the oral proceedings, forced it to prepare to argue not only the two remaining requests, but also those which had been withdrawn in order to be prepared should the appellant choose to revert to those.

8. The reasons are that, firstly, this argument is not related to the main request per se, but rather to the absent requests or to the appellant's filing strategy. Secondly, the situation depicted by the respondent, i.e. reintroduction of one or more of the withdrawn requests, was at the time when the request for non-admission of the main request was filed not only hypothetical, but also unlikely to arise because the appellant had announced its absence at the oral proceedings.

9. Thus, in the circumstances of the present case, the board decided to admit the main request into the proceedings.

Rule 80 EPC

10. The main request as filed with the statement of grounds of appeal and also some of the auxiliary requests filed with this statement or later in the proceedings contained an independent claim 2 directed to a method of discriminating between PrP^{C} and PrP^{SC} and a claim 3 dependent on this claim reading: "A method as claimed in claim 2 wherein said synthetic peptide is linked to a carrier." These two claims are absent from the present main request.

11. The respondent argues that the deletion of claim 3 contravenes the requirements of Rule 80 EPC because no objection had ever been raised against claim 3 per se.

12. However, in its reply to the appellant's statement of the grounds of appeal dated of 11 August 2009, the respondent states on page 5 under the heading "Art. 83 EPC, Insufficiency of disclosure" in relation to the main request then on file:

"Present claims 2 and 3 are insufficiently disclosed contrary to Art. 83 EPC; a person skilled in the art would not be capable of carrying out the invention based on the disclosure of either the claims or the claims and the specification taken together."

That statement is followed by approximately five pages of reasoning as to why the requirements of Article 83 EPC were not fulfilled.

13. Thus, the deletion of claim 3 can certainly be considered as being occasioned by the objection of lack of sufficiency of disclosure which is a ground for opposition under Article 100 EPC.

14. No other objections pursuant to Rule 80 EPC were advanced by the respondent with regard to the present main request and also the board has no such objections.

15. Hence, the main request complies with the requirements of Rule 80 EPC.

Article 84 EPC

16. Article 84 EPC requires the claims to be clear. Moreover, it is established case law that the description and the drawings may be used to interpret the claims (see Case Law of the Boards of Appeal, 6th edition 2010, II.B.5.3.1, second and third paragraph). Thus, discrepancies between the description and the claims may result in claims with unclear meaning.

17. The respondent submits that the following discrepancies between the description and the claims obscure the meaning of claim 1. (References below are to pages of the description in the application as filed as amended by the appellant - see section VIII above.)

(i) On pages 12 to 15 and 32 to 34 the description refers to peptides other than that having the sequence

denoted as SEQ ID No: 47. The peptide with sequence SEQ ID No: 47 is disclosed on pages 15 and 33, but it is not highlighted in any way. Therefore, it is not clear whether claim 1 relates also to methods using antibodies binding to peptides having sequences other than SEQ ID No: 47. The impression that the invention relates to such other methods is reinforced by the first sentence on page 29, in particular by the expression (added as an amendment in the request) "as described herein": "We have found that antibodies raised against peptide sequences as described herein and subfragments may also be used to discriminate between PrP^{C} and PrP^{SC}". It is also reinforced by Example 1 (see page 30) which discloses the use of a peptide with the sequence shown in SEQ ID No: 41 for antibody production. It is stated that this is a "preferred" peptide. Moreover, the example is not labelled as, for example, a "comparative" or "illustrative" example.

(ii) The description refers on page 19 to positions "X" and "Y" in the formulae of the peptides. The sequence given as SEQ ID No: 47 does however not recite positions "X" and "Y", raising the question whether these positions may have to be added to the sequence of SEQ ID No: 47 as recited in the claim.

(iii) On page 29, lines 19 to 23 it is disclosed that "in some instances discrimination may be enhanced by pre-treatment of the sample, for example by pre-digestion or denaturation or combination of these treatment." Due to the word "may" it is not clear whether digestion and denaturation are mandatory features of the claimed method.

18. Claim 1 reads:

"A method of detecting prion proteins in a bovine sample which comprises incubating said sample with an antibody or antigen binding fragment thereof, which specifically binds to a synthetic polypeptide which has at least one antigenic site of a prion protein and is SEQ ID NO: 47: Gly-Gln-Gly-Gly-Ser-His-Ser-Gln-Trp-Asn-Lys-Pro-Ser-Lys-Pro-Lys-Thr-Asn-Met-Lys-His-Val-Gly-Cys wherein said sample has been pretreated by predigestion with enzymes and by denaturation by strong alkali."

19. The board considers that claim 1 is drafted in a way that leaves no room for an interpretation other than that mandatory features of the method are

(a) predigestion and denaturation ("said sample has been pretreated by predigestion with enzymes and by denaturation by strong alkali") and

(b) the use of an antibody which binds to a peptide having exactly the sequence of SEQ ID No: 47 ("which specifically binds to a synthetic polypeptide which has at least one antigenic site of a prion protein and is SEQ ID NO: 47").

Thus, since claim 1 is clear per se there is no need to consult the description or drawings for the interpretation of this claim.

20. By the same token, even if the claim was considered in the light of the description, the features at issue are so clearly stated in the claim, that even if there were

discrepancies between the description and the claims in this respect, they would not call in doubt the meaning of the claim.

21. Finally, in the board's view, there are no such discrepancies in the present case because it is unambiguously stated in the amended description what the "invention" is: "The invention therefore provides a method as claimed in claim 1" (see amended page 29, line 24).

22. This sentence makes it clear that the expression "as described herein" does not refer to subject-matter belonging to the "invention", but that it refers to subject-matter that is present in the description for illustrative purposes.

23. Thus, claim 1 is considered as clear. The respondent did not raise other objections pursuant to Article 84 EPC. Also the board has no such objections.

24. The requirements of Article 84 EPC are fulfilled.

Article 123(2) EPC

25. Article 123(2) EPC stipulates that the European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

The content of the application as filed is the subject-matter which the skilled person clearly and unambiguously derives from the disclosure in the application.

26. The subject-matter of amended claim 1 has the following features:

(a) It is a method for the detection of prion proteins in a sample.
(b) The sample is from bovine material.
(c) The sample is treated by digestion with enzymes and by denaturation with strong alkali.
d) The sample so treated is incubated with an antibody or an antigen-binding fragment thereof.
e) The antibody/fragment is one which specifically binds to a synthetic polypeptide which has an antigenic site of a prion protein and has the sequence shown in SEQ ID No: 47.

27. The following is described on pages 28 to 29 of the application as filed:

"Discrimination between natural Prp^{C} and PrP^{SC} is highly desired since PrP^{C} is found in normal subjects and both PrP^{C} and PrP^{SC} are found in a diseased subject."

"Accordingly, the invention provides a **method of discriminating** between PrP^{C} and PrP^{SC} in which a sample is contacted with a substance selected from peptide sequences according to the invention, preferably those relating to regions A, B and C, and significant subfragments thereof, antibodies raised against said sequences and sub-fragments and the presence or absence of PrP^{SC} is determined.

In some instances **discrimination** may be enhanced by pretreatment of the sample, for example by pre-

digestion with enzymes e.g. proteinase K, or denaturation by strong alkali e.g. 6M guanidine hydrochloride or by a combination of such treatments." (emphasis added).

28. The respondent submits that this passage describes a "method of discrimination" and not a "method of detection" as in claim 1. A "method of discrimination" is different from a "method of detection", because "detection" means the identification of the presence of a specific analyte, while "discrimination" means the identification of the presence of a specific analyte in the presence of at least one further analytes. Thus, the passage on page 29 is not a basis for the subject-matter of claim 1.

29. However, the board observes first that the determination of whether or not the provisions of Article 123(2) EPC are fulfilled requires the determination of "subject-matter". Since the same subject-matter may be described by different words - for example the same glass may be described as either "half full" or "half empty" - a difference in wording does not per se necessarily establish that the subject-matter defined by the words is different.

30. Second, the terms "of detection" and "of discrimination" are indications of the purpose of the method. It is conceivable that, where the subject-matter is a method defined by a number of steps and where the only difference in the definition of this method and another is the indication of the purpose to be achieved, then, due to this difference in the definition of the purpose, a different method may be

defined despite the identity of the definition of the steps. This is so because the skilled person might understand that the indicated steps of the method have to be carried out in such a way that the different purpose is achieved.

31. However, this is not the situation in the present case. Here the step of (i) the treatment of the sample with digesting enzymes results in the "digestion", i.e. removal, of in particular the normal cellular PrP^C protein, while the core of the infective prion protein, which is insensitive to enzymatic digestion, is retained and the step of (ii) denaturation with strong alkali serves to denature the remaining core in order to make it accessible to reaction with the antibody. Thus, the subsequent detection of the prion protein with the antibody mandatorily (under ideal circumstances; see however, points 44 to 50) occurs in the absence of further analytes.

32. Hence, in the present case the method disclosed on page 29 cannot be carried out in a way that matches the respondent's interpretation.

33. Therefore, although it is (maybe inappropriately) labelled as a "method of discrimination", the skilled person would nevertheless clearly and unambiguously derive from the passage on page 29 that the subject-matter disclosed in this passage is in fact a "method of detection".

34. Consequently, the passage on page 29 discloses a method having features (a), (c) and (d) as defined above.

35. Feature (b), i.e. the application of the method disclosed on page 29 in relation to a bovine sample is, for example, derivable from

(i) the first paragraph of the application as filed: "It is of particular interest to the design of immunodiagnostics, vaccines and other medical veterinary or scientific agents in relation to human bovine and ovine spongiform encephalopathies.

(ii) the examples in general because they disclose detection of prion proteins in samples of bovine material and

(iii) from, in particular, the disclosure in Table II reporting the detection of prion proteins in bovine brain material using antibodies binding to SEQ ID No: 47, i.e. antibodies labelled as "97" and "98".

36. Thus, Table II also discloses feature d) above, i.e. the use in the method disclosed on page 29 of antibodies or antigen binding fragments thereof which specifically bind to a synthetic polypeptide which has at least one antigenic site of a prion protein and is SEQ ID NO: 47.

37. Consequently, the board concludes that the skilled person would clearly and unambiguously derive the subject-matter of claim 1 from the application as filed.

38. The requirements of Article 123(2) EPC are fulfilled.

Article 123(3)

39. The respondent had no objections and also the board has no objections.

The requirements of Article 123(3) EPC are fulfilled.

Article 83 EPC

40. The claimed method comprises (i) treating a bovine sample by digestion with enzymes and by denaturation with strong alkali, (ii) incubating the sample so treated with an antibody which specifically binds to a polypeptide which has an antigenic site of a prion protein and has the sequence of SEQ ID No: 47, thereby (iii) detecting the presence or absence of prion proteins.

41. Paragraph [0108] of the patent discloses how samples are prepared. Digestion of the sample with proteinase K as an example of an "enzyme" and guanidine hydrochoride as an example of a strongly alkaline denaturating agent are disclosed in paragraphs [0110] and [0111]. The patent refers to methods of protein synthesis for example in paragraphs [0064] to [0069] and [0081]. Antibodies and their preparation are referred to in the patent in paragraphs [0071], [0074], [0083] and [0084]. Methods of detection of proteins with antibodies, i.e. immunoassays, are well-known to the skilled person. This is acknowledged in the patent in paragraph [0072]. Three different immunoassays are specifically disclosed in paragraphs [0109] to [0112] of the patent, in particular a dot blot assay.

42. The respondent argues however, that the skilled person is not taught by the disclosure in the patent how the detection of the absence or presence of prions is achieved with the claimed method and that therefore the invention should be considered as insufficiently disclosed.

43. The reasons are as follows:

43.1 Table II indicates the results of dot blot assays carried out with antibodies as defined in claim 1 and which are denoted in the Table with numbers "97" and "98".

43.2 The dot blot assays underlying the results presented in Table II have the following experimental setting:

For the determination of whether or not a particular sample contains infectious prion proteins, assays with three different samples are carried out: (i) with the brain material suspected to contain prion proteins (ii) with material known to contain prion proteins as a positive and (iii) with material known to contain only the normal cellular prion proteins as a negative control.

Before incubation with the antibody, each of the samples is treated in three different ways, i.e. it is either not treated, treated with proteinase K alone or treated with proteinase K and guanidine hydrochloride. Antibody-reactivity is indicated as "-", "+/-", "+", "++", "+++".

43.3 The respondent refers to paragraph [0113] of the patent where it is stated under the heading "Dot Blot Data": "When a protein sample is treated with proteinase K any PrPc should be completely digested. Therefore, in a sample containing only PrP^C, no PrP of any form will remain after proteinase K treatment."

43.4 However, according to Table II when the respective sample is probed with antibodies according to the invention, this promised result is not achieved, i.e. reactivity is detected in the negative control, which is "+" in the case of antibody 97 and +/- in the case of antibody 98.

43.5 The respondent concludes that if a protein is detected in the negative control sample, i.e. a sample where theoretically nothing should be detected, the test lacks a proper negative control. Without such a proper control the test results cannot be meaningfully interpreted and therefore the test cannot be considered as suitable to achieve the intended purpose, i.e. to detect prion proteins.

43.6 Furthermore, if there is reactivity in the negative control it is impossible to rely on any given signal which is caused by the antibodies, because it cannot be established whether or not the antibody signal comes from reactivity with a prion or another protein. Thus, the test certainly produces false positive results and can also for this reason not be considered as suitable to achieve the intended purpose.

44. However, as regards the respondent's view that the examples showed that a proper negative control was

absent, the board observes that the disclosure in the patent cannot be interpreted as requiring that the negative control is "completely" negative.

44.1 It is stated in the paragraph referred to by the respondent, i.e. paragraph [0113], that any PrP^{C} "should" and not "will" or "must" be digested.

44.2 Furthermore, in paragraph [0117] the results for antibodies 97 and 98 are qualified as "exactly as expected" despite the fact that some antibody-binding was detected in the proteinase K treated, negative control sample.

45. It is derivable, for example, from paragraph [0117] of the patent, explaining the rationale of the test setting, why in the framework of the assays presented in Table II a completely negative control is de facto not required.

"As mentioned previously, antibodies which recognise PrP^{SC} generally only recognise the protein in its denatured state. Infected and uninfected samples, as well as containing PrP^{SC} and/or PrP^{C} in their "native" states, will also contain both PrP forms in various stages of denaturation due to natural protein turnover within cells.

For this reason, antibodies would be expected to detect all three untreated samples. However proteinase K treatment will digest PrPC and any partially denatured PrPSC leading to a loss of antibody recognition in all samples (assuming the antibody only recognises denatured PrP). The addition of guanidine should

restore antibody recognition in material which had originally contained PrP^{SC}."

46. In the board's view, it follows from these explanations that in the context of the present test it is only decisive that the difference in the antibody reactivity between the control sample and the sample to be analysed is such that a positive sample can be unequivocally determined.

47. This is in fact the case with regard to the tests carried out with antibodies 97 and 98. In all of the untreated samples (the order of samples in the following is: sample to be analysed - negative control - positive control) the reactivity is high (antibody 97: +++, ++, +++; antibody 98: +++, ++, +++;). The reactivity is lower relative to the former reactivity in all the proteinase K-treated samples (antibody 97: +, +, ++; antibody 98: +, +/-, +/-). It is higher relative to the former reactivity in the sample to be analysed and the positive control (antibody 97: ++, +++; antibody 98: ++, +++) and the same in the negative control (antibody 97: +; antibody 98: +/-).

48. Thus, in summary, first, there is no indication in the patent that the absence of reactivity in the negative control is a mandatory requirement and, second, the experimental setting of the dot blot assay is such that such a requirement in fact does not arise. Therefore, the presence of antibody reactivity in the negative control of the dot blot assays with antibodies according to the invention, i.e. 97 and 98, is not an indication that the claimed method does not work.

49. Moreover, given that the test results for antibodies 97 and 98 are as expected, the board considers that the antibody reactivity in the negative control cannot be ascribed to an unspecific binding of the antibodies. Rather, under the circumstances of the present test, it is highly likely that proteinase K digestion was not complete and that the antibodies - correctly - bound to the remaining normal cellular prion protein. Thus, the board is not convinced that the test produces false positive results.

50. Hence, the board cannot come to the conclusion that the invention is not sufficiently disclosed for the reason that the disclosure in the patent fails to teach how the detection of the absence or presence of prions is achieved with the claimed method.

51. In a further line of argument the respondent submits that the patent gives only one example of an enzyme for digestion, i.e. proteinase K, and only one example of a strongly alkaline denaturing agent, i.e. guanidine hydrochloride, whereas the invention as defined in the claims refers in general to "predigestion with enzymes" and "denaturation by strong alkali". Therefore, the invention could not be carried out over the whole claimed breadth and also for that reason has to be considered as insufficiently disclosed.

52. The skilled person is aware that in the framework of the claimed method, the "digestion by enzymes" serves to remove the normal prion protein and those parts of the infective prion protein which are not resistant to enzymatic digestion leaving the digestion-resistant core of that protein. Thus, the skilled person

understands that the feature "digestion with enzymes" refers to enzymes for digestion of proteins. By the same token, the skilled person understands that, in the context of the present method, the treatment of denaturation by a strongly alkaline agent is for the denaturation of the protease-resistant core of the prion protein.

53. According to established case law the skilled person may use his/her common general knowledge to supplement the information contained in the application (Case Law of the Boards of appeal, 6th edition 2010, II.A.2, second paragraph).

54. On the basis of his/her common general knowledge the skilled person knows many protein digesting enzymes, i.e. proteinases, in particular of the type of proteinase K, which is, as is commonly known and also disclosed in the patent in paragraph [0113], an unspecific proteinase. Also many strongly alkaline denaturating agents other than guanidine hydrochloride are generally known.

55. Thus, the board cannot come to the conclusion that the invention cannot be carried out over the whole claimed breadth and that there is a lack of sufficiency of disclosure for that reason.

56. The requirements of Article 83 EPC are fulfilled.

Novelty

57. The respondent has not raised an objection and also the board has none.

The requirements of Article 54 EPC are fulfilled.

Inventive step

Closest prior art

58. According to the respondent each of documents J9, J10, J11, J27 and J28 could be considered as the closest prior art document because each of them teaches that generally the position in the different prion proteins corresponding to that covered by SEQ ID No: 47 is antigenically relevant.

59. It is established case law that the closest prior art document should be a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention. The commonality of technical features is a secondary criterion (Case Law of the Boards of appeal, 6th edition 2010, I.D.3.1 and 3.2).

60. Claim 1 relates to a method for the detection of prion proteins in a bovine sample.

61. With regard to the determination of the closest prior art document, the relevant technical features of the claimed method are (i) the treatment of the sample by predigestion with enzymes and by denaturation with

strong alkali and (ii) the incubation with an antibody which binds to a synthetic protein having SEQ ID No. 47.

62. With regard to these features the relevant content of documents J9, J10, J11, J27 and J28 is as follows.

62.1 Document J9 discloses the antibody-mediated detection of prion proteins in samples from scrapie-infected hamster brains. The antibodies, i.e. polyclonal antisera, are obtained by immunizing rabbits with, inter alia, a synthetic peptide denoted "P1" said in document J9 to correspond to residues 90 to 102 according to the translated PrP cDNA and genomic DNA hamster sequence (page 1189, "Preparation of synthetic peptides). Anti-P1 antisera react with peptide P1 (see page 1190, sentence spanning first and second column), with both of the 33-35kDa isoforms PrP^{SC} and PrP^{C} and with PrP27-30. The hamster brain-derived samples are either untreated or treated with proteinase K prior to incubation with antibodies (page 1190-1191, lines 1 to 7 of passage "Immunoblotting studies with the peptide antisera").

62.2 Document D28 contains a corresponding disclosure on page 850, second column and page 851, under heading "Shared polypeptide epitopes".

62.3 Document J11 discloses inter alia the detection of the mouse prion protein PrP27-30 and of a peptide P1 with antibodies raised against this peptide (see page 86, "Antisera production"; page 88, second column, first full paragraph; paragraph spanning pages 88 to 89). Peptide P1 is said to correspond to codons 89-107 of

the translated cDNA sequence of mouse PrP (page 86, first column, first paragraph).

62.4 Document J10 discloses the reactivity of eighteen monoclonal antibodies raised against hamster PrP27-30 with chimeric mouse-hamster prion proteins expressed in an vaccinia virus system (see page 3571, first paragraph of section "Epitope mapping of hamster specific mAB).

62.5 Document J27 discloses the reactivity of three monoclonal antibodies raised against hamster prion protein Sp33-37 (page 3668, "Production of MAbs) with hamster infective prion protein Sp33-37 (page 3669, first paragraph under "Species specificity of the MAbs") and with synthetic peptide A111-78 (page 3670, first column, second full paragraph).

63. In the board's view, given the relevant disclosures summarized above, among documents J9, J10, J11, J27 and J28 either document J9 or J28 may be considered as the closest prior art document because they both disclose subject-matter conceived for the same purpose as the invention - a method for the detection of a "naturally occurring" infective prion protein (in contrast to for example the detection of a chimeric prion protein in document J10)- and, because in addition the disclosed method has the most technical features in common with the claimed method, i.e.
(i) the antibodies used in the method react with a synthetic peptide derived from the part of the prion protein from which the synthetic peptide according to claim 1 is derived and (ii) the method involves proteinase K digestion.

Problem to be solved

64. In view of the closest prior art and the claimed invention, the problem underlying the invention may be seen in the provision of an alternative method for the detection of prion proteins in a sample.

Solution

65. The solution to this problem is the method according to claim 1. The patent contains in Table II data showing that the claimed methods achieves the intended effect (see point 47 and observations in points 44 to 46, 48 to 50). Thus, the board is satisfied that the patent contains evidence that the claimed method is a solution to the above formulated problem.

Obviousness

66. The method of claim 1 differs from that disclosed in the closest prior art document in that (a) it is for the detection of prion proteins in a bovine sample; (b) it includes pretreatment of the sample by denaturation by strong alkali; and (c) it includes the use of an antibody for detection of the prion protein which binds specifically to a synthetic polypeptide which has the sequence as shown in SEQ ID No: 47.

67. With regard to feature c) above the respondent argues that the skilled person knows that the hamster prion protein-derived peptide P1 disclosed in document J9 elicits antibodies reacting with the native hamster prion protein. He/she would therefore - by routine

methods - have prepared peptides corresponding to the P1 peptide of document J9 and derived from prion proteins of other species and would - again with routine methods - have tested them for reactivity against prion proteins of different species. He/she would thus have found in an obvious way that antibodies binding to a P1-corresponding peptide from the ovine prion protein, i.e. a peptide having the sequence of SEQ ID No: 47, reacted with the native bovine prion protein and therefore have used these antibodies to test for prion proteins in bovine samples.

68. It follows from the respondent's argument that feature c) could be regarded as obvious if it was at least both obvious (i) to prepare antibodies to peptides covering P1-corresponding regions, amongst them those binding to a peptide having SEQ ID No. 47 and (ii) to test all of them, i.e. including antibodies binding to a peptide having SEQ ID No: 47 against prion proteins of different species, among them the bovine prion protein.

69. Assuming that the skilled person had prepared antibodies binding to a peptide having SEQ ID No: 47, in the board's view, the skilled person would not have tested such antibodies for reactivity with the bovine prion protein for the following reason.

70. The synthetic peptide having the sequence of SEQ ID No: 47 is a subfragment of the ovine prion protein. Thus, the particular property of the antibodies used in the method for the detection of bovine prion proteins according to claim 1 is that they bind to a subfragment of the prion protein from sheep.

71. First it is noted that there is no teaching in the prior art that such antibodies even react with the native sheep prion protein. For this reason alone the skilled person would be reluctant to test these antibodies for reactivity with the prion protein of a different species.

72. Second, the sequence of SEQ ID No: 47 is GQGG**S**H**S**QWNKPSK whereas that of the bovine prion protein at the relevant position is GQGG**T**H**G**QWNKPSK. Thus, the relevant sequences of the ovine and bovine prion protein differ in two amino acid residues (highlighted above).

73. Although the overall identity between the two sequences is high and even if it is accepted - as argued by the respondent - that serine and threonine are structurally similar amino acids, in the board's view, the skilled person would have had good reasons to expect that antibodies recognizing a peptide having SEQ ID No: 47 which is derived from the ovine prion protein would not recognize the native bovine prion protein.

74. This is so because the skilled person knows from document J11 that the region in the prion protein covered by SEQ ID No: 47 comprises an epitope which confers species-selectivity to the antibodies raised against that part of the prion protein.

74.1 Document J11 discloses that an antiserum against the mouse prion protein-derived peptide P1 does not react with human native prion proteins (page 90, second column, first paragraph). At the relevant position the sequence of the mouse prion protein is GQGGGTHN**Q**WNKPSK,

whereas the sequence of the human prion protein is GQGGGTHN**S**WNKPSK. Thus, although the two amino acid sequences differ in only a single residue, antibody cross-reactivity is absent.

75. Thus, in the light of the teaching of document J11 the skilled person would not have attempted to test antibodies which bind specifically to a synthetic polypeptide which has the sequence as shown in SEQ ID No: 47 for reactivity with native bovine prion protein. Hence, the board comes to the conclusion that the skilled person would in this respect not have acted as suggested by the respondent.

76. Consequently, for that reason alone, feature (c) above, i.e. the use of an antibody for detection of the prion protein which binds specifically to a synthetic polypeptide which has the sequence as shown in SEQ ID No: 47, is not regarded as obvious.

77. Since this is so, first, it needs not be assessed whether or not it was obvious to provide antibodies binding specifically to a synthetic polypeptide which has the sequence as shown in SEQ ID No: 47 and second, the obviousness or non-obviousness of the further features by which the method differs from that of the closest prior art and the obviousness or non-obviousness of the combination of features need not be assessed either.

78. The subject-matter of claim 1 involves an inventive step and thus the requirements of Article 56 EPC are fulfilled.

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 the following documents:

   – Claim 1 of the Main Request filed with the letter dated 24 February 2011

   – Pages 1, 3, 4, 12, 15, 19-20, 22-30 and 32-34 of the description enclosed with the letter dated 24 February 2011

   – Pages 2, 13, 14, 31 and 35-61 of the Druckexemplar enclosed with the communication under Rule 51(4) EPC 1973 of 22 October 1997.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith