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Datasheet for the decision of 14 October 2013

Case Number: T 0015/10 - 3.3.08

Application Number: 04022858.7

Publication Number: 1518936

IPC: C12Q1/68, C12N9/02

Language of the proceedings: EN

Title of invention:
Marker assisted selection of chicken against fishy taint

Patent Proprietor:
Lohmann Tierzucht GmbH

Opponent:
Hendrix Genetics B.V.

Headword:
Fishy taint/LOHMANN

Relevant legal provisions:
EPC Art. 53(b), 56

Keyword:
Exceptions to patentability - essentially biological process for the production of animals - Claim 14 (no)
Inventive step - (yes)

Decisions cited:
G 0002/07, G 0001/08, T 0003/90

Catchword:

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Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0015/10 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 14 October 2013

Appellant: (Opponent)	Hendrix Genetics B.V. Spoorstraat 69 P.O. Box 114 5830 AC Boxmeer (NL)
Representative:	Swinkels, B. Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Respondent: (Patent Proprietor)	Lohmann Tierzucht GmbH Am Seedeich 9-11 27454 Cuxhaven (DE)
Representative:	Wachenfeld, J. Vossius & Partner Siebertstrasse 4 81675 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 October 2009 rejecting the opposition filed against European patent No. 1518936 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman: M. Wieser
Members: T.J.H. Mennessier
C. Heath

Summary of Facts and Submissions

I. The opponent (appellant) lodged an appeal against the decision of the opposition division dated 14 October 2009, whereby the opposition filed against European patent No. 1 518 936, which had been granted on European patent application No. 04022858.7, was rejected.

II. The statement setting out the grounds of appeal was filed on 15 February 2010. The appellant argued that the claimed invention did not involve an inventive step. The patent proprietor (respondent) replied on 28 June 2010 by refuting the appellant's arguments. Oral proceedings were requested by the appellant only.

III. On 24 May 2013, the Board issued, as an annex to a summons to oral proceedings, a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) expressing its preliminary and non-binding views.

IV. On 24 September 2013, the appellant replied to the Board's communication by filing further submissions in support of its objection of lack of inventive step and of an objection raised against claim 14 under Article 53(b) EPC which was argued to be directed to an essentially biological process for producing animals in the sense of G 2/07 and G 1/08 (OJ EPO 2012, 130 and 206). The submissions were accompanied by a new document to be referred to as document D16. With the same letter, the appellant informed the Board that it will not attend the scheduled oral proceedings.

V. In a communication faxed on 8 October 2013 the Board informed the parties that the scheduled oral proceedings were cancelled.

VI. The set of claims as granted is the only claim request on file. It consists of 19 claims, of which claims 1 and 14 read as follows:

"1. A method of testing an avian for its predisposition for fishy taint in eggs comprising analyzing the nucleic acid of a sample comprising the gene encoding FMO3 or a corresponding mRNA for a nucleotide polymorphism which is linked to said predisposition, wherein a difference from the wild-type FMO3 sequence is indicative of fishy taint, said difference being the presence of a serine codon in a position corresponding to position 329 of chicken FMO3 as shown in SEQ ID NO: 25 or in a homologous position of other avian FMO3 (poly)peptides."

"14. A method for selecting an avian or part of an avian, including their semen or eggs, comprising the steps of:
(a) testing for a predisposition for fishy taint in eggs comprising the steps of the method of anyone of claims 1 to 13;
(b) selecting the avian based on the information derived from said testing; and
(c) optionally, using said information for further breeding considerations."

Claims 2 to 16 are dependent on claim 1.
Claim 17 is directed to the use of a nucleic acid molecule of the FMO3 gene for testing an avian for its predisposition for fishy taint on eggs characterised by the presence of a serine codon at position 329 of

chicken FMO3 or in a homologous position of other avian FMO3 (poly)peptides.

Claim 18 is directed to a primer suitable for use in detecting the polymorphism at nucleotide position 694 of SEQ ID NO:3.

Claim 19 is directed to a kit for the detection of animals having a predisposition for fishy taint in eggs, comprising the primer of claim 18 in one or more containers.

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

(D2) WO 01/23603 (published on 5 April 2001)

(D11) NCBI GeneBank Record with Accession Number AJ431390 (20 February 2002)

(D16) W. Bolton et al., Br. Poult. Sci., Vol. 17, 1976, pages 313-320

VIII. The submissions made by the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

Article 53(b) EPC

Claim 14 was directed to an essentially biological process for the production of animals within the meaning of Article 53(b) EPC which was not patentable in view of decisions G2/07 and G1/08 (see supra).

Article 56 EPC

The technical problem underlying the subject-matter of claim 1 in the light of document D2, which represented the closest state of the art, was the provision of a method for testing an avian for its predisposition for fishy taint in eggs based on an investigation of the avian FMO3 gene. The solution proposed in claim 1 was not inventive in view of the teaching of document D2 itself.

At the priority date it was known in the art that an elevated level of trimethylamine (TMA) was associated with a fishy odour in human excreta, in cow's milk and in chicken eggs. It was also known that mutations abolishing activity of the FMO3 polypeptide produced the fishy off-flavour in human excreta and cow's milk. It was postulated in document D2 that mutations in the chicken FMO3 gene could be associated with fish off-flavour of eggs produced by hens carrying such mutations. D2 provided a clear and unambiguous teaching how to test chicken for sequence differences with regard to the wild-type FMO3 sequence, in order to further investigate this association.

D2 described how to amplify exonic parts of the chicken FMO3 gene. The sequences obtained from hens that produced eggs with a fishy off-flavour and sequences from normal hens could be compared and sequence variants could be identified.

The tools which were to be used for testing an avian for a predisposition for fishy taint in eggs were commonly available to the skilled person at the priority date. In particular, the sequence of the gene encoding the chicken FMO3 polypeptide had been

published. Hens producing eggs with fishy taints were also available (see document D16).

By following the clear and unambiguous teaching of D2, the skilled person inevitably would have arrived at the identification of the mutation that was claimed for use in the method of claim 1.

Document D2 provided a clear incentive for the skilled person to investigate the avian FMO3 gene for a mutation causative of the defect. The patent itself also acknowledged that it was not surprising that markers associated with fishy taint appeared to reside in the FMO3 gene. The skilled person would not have had any particular reason to believe that this association would not apply to avians.

The skilled person did not need to use any information in hindsight and would have had a reasonable expectation of success to arrive at the claimed method.

Although it could not have been foreseen which particular mutation finally would be identified when following the teaching of D2, the fact that the FMO3 of hens producing eggs with fishy flavour was found to contain only a single amino acid difference in a highly conserved region excluded a choice from a multiplicity of possibilities. Thus, a one-way-street situation was created. The detection of the single mutation had to be considered as an additional effect which was inevitably achieved by the skilled person on the basis of obvious measures.

IX. The submissions made by the respondent, insofar as they are relevant to the present decision, may be summarised as follows:

Article 53(b) EPC

No comments were made by the respondent on this issue.

Article 56 EPC

It was not known to the skilled person that FMO3 plaid a role in the manifestation of fishy taint in avian eggs. Document D2 only contained a suggestion that FMO3 might be involved in fishy taint in avian eggs. No causative link had been established between a deficiency in the gene and the disorder.

A link had been established only between polymorphisms in the human and bovine FMO3 gene and the manifestation of fishy odour in human excreta and fishy smell in cow's milk. Based on taxonomic differences between avians and mammals and considering the differences in disease manifestation, the skilled person would not have expected that the teaching based on mammals could simply be transferred to avians

The fact that the phenotypic differences between mammals and avians were independent of the underlying genetic factor was only known since it had been shown by the present inventors.

The appellant's argument that despite the observed differences in phenotypic expression, the skilled person would not have had any problem to identify hens that carry the disease and would have selected these hens for genetic testing relied on hindsight.

The present invention did not represent a one-way-street-situation. If the skilled person had

disregarded the taxonomic differences between bovine and human on the one hand and avians on the other hand, then the most straight-forward approach would have been to analyse the chicken FMO3 gene for the presence and role of mutations also identified in human or bovine to be causative in disease manifestation. Consequently the skilled person would not necessarily have followed the approach shown in Example 3 of D2 to identify mutations and would not necessarily have arrived at the identification of the T329S mutation in chicken FMO3. More likely, it would have searched for corresponding mutations to the known causative mutations found in mammals. Thus, at least two different approaches were available.

Even if D2 were considered to provide an incentive to analyse the chicken FMO3 for causative mutations, it was not obvious from D2 that a mutation of threonine to serine at position 329 would solve the technical problem.

At the priority date, no sequence information was available regarding the chicken genome. It was not known on which chromosome the chicken FMO3 gene was localised. However, the inventors of the patent surprisingly found that the FMO3 gene was localised in chicken on chromosome 8. Finally, since the level of sequence identity between chicken and human is a mere 61% and between chicken and bovine 64%, the primers known from these other species were not suitable to simply amplify the chicken FMO3 gene. Consequently, a substantial amount of work and inventive effort was required in order to arrive at the method of claim 1.

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

XI. The respondent (patent proprietor) requested that the appeal be dismissed.

Reasons for the Decision

Cancellation of oral proceedings

1. The statement in the appellant's letter dated 24 September 2013 that it will not attend the oral proceedings scheduled on 24 October 2013 is interpreted by the Board as equivalent to a withdrawal of its request for oral proceedings (see decision T 3/90; OJ EPO 1992, 737). Therefore, as the respondent had not requested oral proceedings, oral proceedings were cancelled.

Article 53(b) EPC

2. The appellant has raised an objection under Article 53(b) EPC in its letter 24 September 2013 sent in reply to the Board's communication pursuant Rule 15(1) RPBA. The objection is raised against claim 14, which the appellant argued to be directed to an essentially biological process for the production of animals.

3. This objection has not been mentioned in the statement setting out the grounds of appeal, but the Board notes that the opposition was originally filed *inter alia* on the ground that the subject-matter of the patent was not patentable under Article 53(b) EPC (see point VI of the notice of opposition (Form EPO 2300.2).

4. The appellant has explained that it decided to raise the objection in view of the conclusion reached by the

Enlarged Board of Appeal in consolidated decisions G 2/07 and G 1/08 (see *supra*) with regard to the term "essentially biological" within the meaning of Article 53(b) EPC. These decisions have been issued on 9 December 2010, ie. after the date of filing of the statement of grounds.

5. Using the discretionary power conferred to it by Article 12(4) RPBA the Board, considering that this explanation justifies the late raising of the objection under Article 53(b) EPC in the appeal procedure, decides to admit the objection.

6. The appellant argues that it applies the conclusion reached by the Enlarged Board of appeal in decisions G 2/07 and G 1/08 (with regard to processes for the production in plants) to processes for the production of animals. It considers that the process of claim 14 qualified as a non-microbiological process for the production of animals that is excluded from patentability for being "essential biological" because it contains a step of crossing the whole genomes of animals and a step of selecting of animals.

7. The first question to be answered by the Board, before embarking on any further interpretation of the teaching of decisions G 2/07 and G 1/08, is whether claim 14 is actually directed to a process for the production of animals including a step of crossing the whole genomes of animals and a step of selecting of animals.

8. Claim 14, which is *expressis verbis* directed to a method for selecting an avian (or part of an avian), comprises two compulsory steps (a) and (b) which can be supplemented by a third step (c). Step (a) refers to testing the avian or part thereof for predisposition

for fishy taint in eggs. It is carried out using the method of claim 1 or claims dependent thereon. Step (b) concerns selecting the avian based on the conclusions drawn from the results of step (a) and step (c) concerns the use of these conclusions for further breeding considerations which may be breeding management considerations such as the propagation, culling and feeding of animals (see paragraph [0069] in the patent specification) or the exclusion of animals with a predisposition to produce eggs with fishy smell from breeding programs (see paragraph [0012] in the patent specification).

9. This analysis clearly shows that claim 14 is not at all directed to a method of production of animals, let alone to a method comprising a step of crossing the whole genomes of animals. It features a method which provides information useful to manage animals depending on their predisposition to produce eggs with fishy odour or to pass on to the offspring specific alleles or variants of a gene responsible for developing such a phenotype (see paragraph [0017] in the patent specification).

10. The appellant's argument is therefore not convincing and, consequently, claim 14 meets the requirements of Article 53(b) EPC.

Article 56 EPC

11. The appellant has objected that the subject-matter of all claims lacks an inventive step.

12. Claim 1 is directed to a method for testing an avian for fishy taint in eggs based on the analysis of the

gene encoding the flavin-containing monooxygenase 3 (FMO3).

13. Document D2 has been considered by the opposition division and the appellant to represent the closest state of the art as regards claim 1. This has not been disputed by the respondent in the appeal proceedings. The Board sees no reason to depart from this choice.

14. Document D2 essentially deals with a method for identifying mutations occurring in the bovine FMO3 polypeptide which could be associated with fishy off-flavor in cow's milk. A particular nonsense mutation (denoted R238X) in the bovine FMO3 gene, leading to the R238X substitution in the FMO3 polypeptide which is causative for this flavor, is identified. The possibility to extend the teaching of D2 to other mammals and poultry, such as hens and cocks, is mentioned on page page 6, lines 24 to 33 and is further described as a future aim to go for in Example 3 on pages 16 and 17, which, however, is not experimentally illustrated.

15. The technical problem underlying the patent in suit in the light of the disclosure in document D2 is defined as the provision of a method for testing an avian for its predisposition for fishy taint in eggs based on an investigation of the avian FMO3 gene. As a solution to this problem the patent proposes the method according to claim 1 relying on the determination of the presence of a serine codon at a position corresponding to amino acid at position 329 in the chicken FMO3 polypeptide or at an homologous position of other avian FMO3 polypeptides. In view of the experiments reported the technical problem is considered to be credibly solved.

16. The appellant has argued that the method of claim 1 is obvious in view of document D2 alone.

17. The question to be answered is whether a skilled person relying on the teaching of document D2 alone would have identified the T329S mutation in the evolutionary highly-conserved region containing the FMO-characteristic pentapeptide motif FATGY (see paragraph [100] in the patent specification) of the chicken FMO3 polypeptide and the corresponding change in exon 8 of the chicken FMO3 gene, and, thereby, would have arrived at the claimed subject-matter in an obvious way.

18. The only mutation causative for fishy off-flavor in cow's milk which is described in document D2 is the nonsense mutation R238X present in exon 6 of the bovine FMO3 gene (see page 12, lines 13 to 18). The experimental part of the document focuses on the identification of this particular mutation. There is no guidance available to the skilled person to identify other mutations, in particular not by looking at other exons of the bovine FMO3 gene.

19. Regarding the presence of a mutation in the FMO3 gene of any avian causative for fishy taint in eggs, document D2 provides only speculative information. It is indeed only postulated that "*mutations in the chicken FMO3 gene may be associated with fish off-flavour of eggs produced by hens carrying such mutations*" (see page 6, lines 24 to 25). A method for detecting a mutation in the FMO3 gene in any animal, be it a mammal or poultry (such as a hen or a cock),is mentioned on page 6 lines 26 to 37. Here, the skilled person is taught to obtain a nucleic sample from the tested animal and to determine therein the presence of

a nucleic sequence encoding a mutated FMO3 polypeptide. A further method is described on page 7 (see lines 1 to 10) which specifies that the nucleic acid sample obtained from the animal has to be contacted with a nucleic acid probe spanning "said mutation". Both methods are drafted in a way so that they rather appear to be designed for the determination of the nucleic acid sequence which codes for an already identified mutation in the FMO3 polypeptide than for the determination of a not yet identified mutation. Example 3 of document D2 (see pages 16 to 17) only generally and without any illustrative experimentation teaches (i) to obtain cDNAs coding for the chicken FMO3 polypeptide from RT-PCR products derived from liver mRNA using primers corresponding to expressed sequence tags available in a chicken EST database, (ii) to compare such sequences obtained from hens that have been shown to produce eggs with a fishy off-flavor with sequences obtained from normal hens and (iii) to identify sequence variants.

20. The postulate made on page 6 of document D2 (see point (18) above) is based on the hypothesis that the symptoms of fish-odor syndrome in avians parallel those in humans and bovine and originate from a similar genetic disorder. The Board considers this hypothesis to be critical as the disease manifestation in avians is quite different in the sense that fishy tainting is observed only under certain conditions (see paragraph [0013] in the patent specification). Consequently, the skilled person was merely left with some hope to identify a mutation causative for the fishy taint in avian eggs in the chicken FMO3 gene but he/she had no reasonable expectation of success, in particular not to identify the mutation referred on claim 1. The appellant has argued that the disclosure on page 16

line 38 to page 17 line 4 of document D2 provides a clear and unambiguous teaching how to test chicken for sequence differences with regard to the wild-type FMO3 sequence. This argument is not convincing in view of the above comments. The disclosure in example 3 is far too cursory and not supported by any experiments. There is not even a detailed disclosure how to amplify exonic parts of the chicken FMO3 gene. What is offered is only a schematic and undetailed invitation to perform a further search program. Whereas, as correctly noted by the appellant, the gene encoding the chicken (*Gallus gallus*) FMO3 polypeptide was known at the priority date (see document D11), the structural organisation of the chicken FMO3 gene was not known at that time. Only with hindsight, as a consequence of the structural differences between the chicken FMO3 gene and the human or bovine FMO3 gene highlighted in the patent (see paragraph [0013]) and emphasized by the respondent in its letter of 28 June 2010 (see page 6), the skilled person was provided with an essential technical information which was not at its hand at the priority date and which document D2 failed to provide. Furthermore, there is no pointer in document D2, which is silent in respect of that region, to look at the highly conserved region of FMO3 polypeptide containing the characteristic polypeptide motif FATGY.

21. The Board comes to the conclusion that the skilled person facing the objective technical problem to be solved (see point 16 *supra*), when starting from the disclosure of document D2, would not have arrived at the solution provided by claim 1 in an obvious way.

22. Therefore, the method according to claim 1 involves an inventive step. The same conclusion applies *de facto* to the subject-matter of dependent claims 2 to 16.

23. Claim 17 is directed to the use of a nucleic acid molecule of the FMO3 gene for testing an avian for its predisposition for fishy taint in eggs. The molecule is a probe or a primer capable of hybridizing under stringent conditions to a nucleic acid molecule containing the coding sequence polymorphism in position 694 of SEQ ID NO: 3, that leads to the amino acid change T329S. Therefore, the claimed use also involves an inventive step. The same conclusion applies to the primer of claim 18 which is suitable for use in detecting this polymorphism and to the kit of claim 19 which comprises the primer.

24. Therefore, the claim request as a whole involves an inventive step and thereby meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated