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Datasheet for the decision of 26 January 2016

Case Number:	T 2488/12 - 3.3.08
Application Number:	06802307.6
Publication Number:	1916903
IPC:	A23C9/12, C12N15/74, C12Q1/68, C12N1/21
Language of the proceedings:	EN

Title of invention:
USE OF CRISPR ASSOCIATED GENES (CAS)

Patent Proprietor:
DuPont Nutrition Biosciences ApS

Opponents:
Dutch Dairy Ingredients B.V.
Chr. Hansen A/S

Headword:
Cas genes/DUPONT NUTRITION BIOSCIENCES

Relevant legal provisions:
EPC Art. 114(2), 83
RPBA Art. 13(1)

Keyword:
Main request and Auxiliary requests 1-5 - sufficiency of disclosure (no)
Auxiliary requests 6 and 7 not admitted

Decisions cited:

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Catchword:

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Case Number: T 2488/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 26 January 2016

Appellant: (Patent Proprietor)	DuPont Nutrition Biosciences ApS Langebrogade 1 Postboks 17 1001 Copenhagen K. (DK)
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Appellant: (Opponent 2)	Chr. Hansen A/S Boege Alle 10-12 2970 Hoersholm (DK)
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Representative:	ten Haaft, Petrus Johannes Fredrik Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 31 October 2012 concerning maintenance of the European Patent No. 1916903 in amended form.**

Composition of the Board:

Chairman	M. Wieser
Members:	B. Stolz
	J. Geschwind

Summary of Facts and Submissions

I. The patent proprietor (appellant I) and opponent 2 (appellant II) each filed an appeal against the decision of the opposition division, whereby European patent No. 1916903 was maintained in amended form.

II. The opposition division has decided that the main request (claims as granted) and auxiliary requests 1 to 30 did not meet the requirements of Article 83 EPC. Auxiliary request 31 was not admitted into the proceedings. Auxiliary request 32 was found to meet the requirements of the EPC.

III. With its grounds of appeal, appellant I filed auxiliary requests 1 to 7. Auxiliary requests 1 to 5 and 7 correspond to auxiliary requests 1 to 5 and 32, respectively, underlying the decision under appeal. Auxiliary request 6 was new in the procedure. Moreover, it resubmitted document D32 which had been filed but not admitted into the opposition proceedings, and submitted two new declarations, D33 and D34.

IV. With its grounds of appeal, appellant II submitted new documents D35 to D37.

V. All parties, including opponent 1 (respondent), made further submissions in response to the two statements of grounds of appeal. The respondent submitted document D38. Appellant I filed a new auxiliary request 8, and submitted new documents D39 to D41, D44 and D45. Appellant II submitted new documents D42 and D43. With letter dated 30 September 2013, appellant I withdrew its auxiliary request 6 and renumbered auxiliary requests 7 and 8 as auxiliary requests 6 and 7.

VI. The parties were summoned to oral proceedings. A communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to the summons, informed them of the preliminary non-binding opinion of the board on some of the issues of the appeal proceedings.

VII. With further submissions, appellant II submitted new document D46.

VIII. Oral proceedings were held on 26 January 2016. In the course of these proceedings, appellant I filed new auxiliary requests 6 and 7, and renumbered previous auxiliary requests 6 and 7 as auxiliary requests 8 and 9. Later in the proceedings auxiliary requests 8 and 9 were withdrawn.

IX. The main request (claims as granted) and auxiliary requests 1 to 5 consist of 32 claims each. Claims 1 and 31 of all these requests read as follows:

"1. Use of one or more cas (CRISPR associated) genes or proteins for modulating resistance in a bacteria against a target nucleic acid or a transcription product thereof."

"31. A method for modulating the resistance of a bacteria comprising at least one or more cas genes or proteins and two or more CRISPR repeats against a target nucleic acid or a transcription product thereof comprising modifying the one or more cas genes or proteins in the cell."

X. The following documents are referred to in this decision:

D11: Barrangou et al. (2007), Science, 315, 1709-1712;

D30: Sapranauskas et al. (2011), Nucleic Acid Research, 1-8;

D32: Brouns et al. (2008), Science, 321, 960-964;

D33: 1st Declaration Dr. Romero;

D34: Declaration Dr. Moineau;

D35: Deveau et al. (2010), Annu. Rev. Microbiol., 64, 475-93;

D42: Almendros et al. (2012), PLoS One, 7(11): e50797;

D46: Barrangou R. (2015), Genome Biology, 16: 247.

XI. The arguments of appellant I, as far as relevant for this decision, can be summarized as follows:

Admissibility of documents

The opposition division did not exercise its discretion correctly and should have admitted document D32 into the proceedings. Objections based on an alleged necessity for taking into account protospacer associated motifs (PAM) were not mentioned in the communication of the opposition division attached to the summons to oral proceedings. They were for the first time raised by opponent 2 only two weeks before oral proceedings and were based on document D30 which related to the use of the CRISPR/cas system of S. thermophilus. Document D32 had been filed as early as possible to show that not all CRISPR/cas systems were

PAM dependent and was prima facie relevant for the examination of this issue.

Should the board follow its argument with regard to the admissibility of document D32, appellant I had no objections to the admissibility of any document submitted during the appeal procedure.

Article 83 EPC

The teaching of the patent was repeatable and allowed the skilled person to increase resistance in a bacterium. A reasonable amount of trial and error was permissible. Paragraphs [0013, 0014, 0124, 0186, 0187 and 0224] taught the importance of functional CRISPR/cas, paragraph [0187] the use of functional combinations for achieving resistance. Example 5 taught the selection of a complete, functional CRISPR/cas unit, thus avoiding any problems related to the issue of PAM motifs. Document D30 showed that the transfer of a complete unit from S. thermophilus to E. coli rendered the latter resistant. Example 6 described the exchange of spacer sequences between two bacterial strains comprising the same CRIPSPR/cas system. Document D32, in particular at page 6 of the "Supporting online material", disclosed that randomly selected spacer sequences could be inserted into the CRISPR/cas system of E. coli. Figure 2 of document D46 showed that some CRISPR/cas systems required a PAM motif whereas others did not. The type I system to which the E. coli system belonged had degenerate PAM motifs which were thus less important. Document D42 did not mention document D32 and disclosed that the PAM motifs merely affected the efficiency of the resistance mechanism. The bacterial strains mentioned in documents D33 and D34 belonged to the type III system which was

PAM independent. Example 11 of the patent taught the selection of suitable spacers and CRISPR/cas units. Paragraph [0422] of the patent taught the skilled person how to modify the cas genes.

Admissibility of auxiliary requests 6 and 7

The requests were filed in direct response to the board's opinion about sufficiency of the main request as expressed at the oral proceedings. Up to this point in time, appellant I was convinced that the requests already on file addressed the board's concerns as expressed in the communication attached to the summons to oral proceedings.

XII. The arguments of appellant II, as far as relevant for this decision, can be summarized as follows:

Admissibility of documents

The opposition division, when deciding not to admit document D32, has exercised its discretion correctly. The document did not address the issue raised on the basis of document D30, because it concerned a different CRISPR/cas system. Documents D33 and D34 should not be admitted for the same reasons. Should any of these documents be admitted, appellant II's subsequently submitted documents should also be admitted.

Article 83 EPC

Example 5 was a hypothetical example and in this case, the burden of proof that it could be readily performed shifted to the patent proprietor. All examples of the patent were based on the use of S. thermophilus. According to paragraph [0601] of Example 1, any spacer

sequence could be selected. According to document D30, PAM motifs were, however, important for the selection of spacer sequences in S. thermophilus. Yet, the patent made no mention of PAM sequences. Document D46 disclosed different classes of CRISPR/cas systems, the majority thereof requiring PAM motifs for binding to an invading nucleic acid. Document D42 showed that the CRISPR/cas system of E. coli was also PAM dependent. Documents D33 and D34 only confirmed that type III systems were PAM independent but these represented only a minority of CRISPR/cas systems. Document D11 showed that only some cas genes played a role in conferring resistance while the knock-out of others did not affect resistance. Thus, not all cas genes could be used to modulate resistance.

Admissibility of auxiliary requests 6 and 7

New requests could only be admitted, if they were filed in reaction to a new procedural situation. This was not the case. In its submissions of 18 July 2012, appellant II had already pointed out that all elements of a functional CRISPR/cas spacer system were required to increase resistance. In opposition proceedings, appellant I has already presented an auxiliary request comprising the combination of features now present in claim 1 of auxiliary requests 6 and 7. This auxiliary request, however, has not been maintained in the appeal procedure and was reintroduced only at the oral proceedings after a negative opinion about appellant I's main request. The requests should not be admitted.

XIII. The arguments of the respondent, as far as relevant for this decision, can be summarized as follows:

Admissibility of documents

The opposition division, when not admitting document D32, has exercised its discretion correctly. The documents submitted in the appeal procedure, at least the scientific publications, could be admitted.

Article 83 EPC

Claim 1 was not limited to the modulation of resistance to phage infections but included resistance to any target nucleic acid. There was, however, no teaching how the system could be used against non-phage nucleic acids. The most frequent CRISPR/cas systems were the type I system which includes E. coli and the type II system which includes S. thermophilus. Both were PAM dependent. Example 11 provided only an analysis of the S. thermophilus CRISPR/cas system but did not teach how to modulate resistance. Examples 2 and 3 of the patent described the insertion of spacer elements into a cell, but did not mention the importance of PAM motifs on the invading nucleic acid. Example 5 was silent about the importance of properly selected spacer elements. The teaching of the patent was therefore insufficient across the full scope of the claims.

XIV. Appellant I requested that the decision under appeal be set aside and the patent be maintained as granted, in the alternative that the patent be maintained on the basis of any of auxiliary requests 1 to 5 filed with the statement setting out the grounds of appeal or auxiliary requests 6 or 7 filed at the oral proceedings.

XV. Appellant II requested that the decision under appeal be set aside and the patent be revoked.

XVI. The respondent requested that appellant I's (patent proprietor's) appeal be dismissed.

Reasons for the Decision

Main request and auxiliary requests 1 to 5

Admissibility of documents

1. Appellant I requested that document D32 be admitted into the procedure. The document had already been filed in the opposition procedure, but had not been admitted. Appellant I argued that the opposition division improperly exercised the discretion given to it under Artikel 114(2) EPC.

2. In the opposition proceedings, the patent proprietor (appellant I) had filed document D30 in response to a communication of the opposition division and in order to support its position that Example 5 of the opposed patent could indeed be performed. This submission was made on 26 July 2012, two months before the oral proceedings.

3. Document D30 discloses the cloning of the S. thermophilus CRISPR3/Cas locus in E. coli thereby rendering E. coli resistant against phage infection. The CRISPR locus integrates short nucleic acid sequences, called spacers, which match sequences present in invading genetic elements. The spacers are used to recognise invading genetic elements. Document D30 shows that the interference mechanism is sequence specific and also dependent on the presence of a sequence element (proto-spacer associated motif, PAM)

located in close proximity to the proto-spacer sequence of the invading genetic element.

4. In a submission, made on 18 September 2012 and thus only 10 days before oral proceedings, opponent 2 (appellant II) raised a new objection based on the disclosure of document D30. It argued that the PAM motifs were important for the selection of suitable spacer sequences. The patent, however, made no mention of them and therefore insufficiently disclosed the claimed subject matter.

5. At the oral proceedings before the opposition division, the patent proprietor submitted document D32 and requested that it be admitted into the procedure. It argued that the document was filed in response to the late filed objection of opponent 2 concerning the importance of PAM motifs (cf. page 2 of the minutes of the oral proceedings).

6. The opposition division reasoned that document D32 "*did not rebut the conclusions that could be drawn from the yet later* [published] *document D30*" and decided not to admit it (cf. page 1 of the decision under appeal).

7. According to established case law of the boards of appeal, if the way in which a department of first instance has exercised its discretion on a procedural matter is challenged in an appeal, it is not the function of a board of appeal to review all the facts and circumstances of the case as if it were in the place of the department of first instance, and to decide whether or not it would have exercised such discretion in the same way as the department of first instance. A board of appeal should only overrule the way in which a department of first instance has

exercised its discretion if the board concludes it has done so according to the wrong principles, or without taking into account the right principles, or in an unreasonable way (T 640/91, OJ 1994, 918; see also T 182/88, OJ 1990, 287; T 986/93, OJ 1996, 215; T 237/96 and G 7/93, OJ 1994, 775). When considering the admissibility of late filed documents in opposition proceedings, important factors are the relevance of a document for the outcome of the case, the reasons why it was submitted late and not at an earlier stage of the proceedings and the consequences thereof on procedural economy.

8. In the present case, document D32 was filed in response to an argument raised by opponent II for the first time only ten days before oral proceedings. Under these circumstances the board accepts appellant I's submission that the document could not have been filed earlier.

9. Document D32 discloses the insertion of spacer sequences matching sequences in four essential genes of phage lambda into the E. coli CRISPR/cas system in order to render E. coli resistant to infection by this phage. In the view of appellant I, this document demonstrates that for the creation of resistance in E. coli no attention has to be paid to PAM motifs within the phage lambda genome.

10. Claim 1 is neither restricted to the use of particular cas genes nor to the modulation of resistance in particular bacteria.

Document D30 allowed the skilled person to conclude that for the modulation of resistance by the CRISPR/cas system of S. thermophilus suitable spacer elements had

to be located close to PAM motifs in the target sequence. Document D32 was, however, not filed to rebut this conclusion, but to demonstrate that, when using the CRISPR/cas system of E. coli, the selection of spacer elements was not limited by a requirement for PAM motifs in the vicinity of a target sequence, and that therefore conclusions drawn on the basis of document D30 could not be generalized but were limited to the CRISPR/cas system of S. thermophilus.

11. Document D32 was thus prima facie highly relevant for the examination of the late filed objection.

12. Consequently, in the specific situation of the present case, the board takes the view that the opposition division has not correctly exercised its discretion and decides to admit document D32 into the proceedings.

13. The parties, including appellant I as a consequence of the board's decision with regard to document D32, had no objections to the admission of the documents submitted in the appeal procedure (D33 to D46). The board sees no reason to raise an objection of its own and admits these documents into the procedure.

Article 83 EPC

14. Claim 1 is directed to the use of one or more cas genes for modulating resistance in a bacterium against a target nucleic acid. Claim 31 is directed to a method for modulating the resistance of a bacterium comprising modifying the one or more cas genes or proteins in the cell.

15. It is not contested that the term "modulating" comprises both, decreasing as well as increasing

resistance (cf. page 54, lines 10-12 of the patent application published as WO 2007/025097).

16. The first issue to be assessed is whether the patent sufficiently discloses the use of cas genes for increasing the resistance in a bacterium against a target nucleic acid.

17. The patent discloses that cas genes or proteins are required for achieving immunity against target nucleic acids or transcription products thereof (paragraph [0012]). It also refers to properties of the CRISPR repeat cas gene system, such as the association of specific cas genes with specific CRISPR repeats (functional pairs) (paragraphs [0013], [0014], [00124], [0186], [0193]), methods for identifying functional pairs (paragraphs [0034] and [0224]), and the use of the system for the modulation of resistance (paragraphs [0017], [0018], [0130], [0187], [0223]). In essence, the patent teaches that functional combinations of specific CRISPR repeat sequences and specific cas genes arranged in a particular way are needed for the improvement of resistance against a target nucleic acid.

18. Hypothetical example 5 consists of a single sentence which reads as follows: "*A whole CRISPR repeat cas combination is inserted into a cell - such as a recipient cell - to provide immunity against incoming nucleic acid*".

19. There was agreement between the parties that the insertion of "a whole CRISPR repeat cas combination" comprising also spacer sequences already present in such a combination could provide immunity to a bacterium. Likewise, resistance of bacteria comprising

a functional CRISPR/spacer/cas system could be increased by exposing the bacteria to a new infecting entity such as a bacteriophage.

20. Appellant II and the respondent however strongly disputed that randomly selected spacer sequences could be inserted into an existing CRISPR repeat cas combination as taught in paragraphs [0430-0433] in order to increase resistance.

21. Based on documents D30, D35, D42 and D46, they argued that target sequences to be used as spacer elements in a CRISPR/cas system could not be randomly selected from target nucleic acid sequences because in the majority of CRISPR/cas systems cas proteins recognized and bound to a particular sequence motif (protospacer associated motif, PAM) on an infecting/target nucleic acid. This motif had to be located at a specific distance from the spacer sequence, either upstream or downstream, and the skilled person had to take this into account when selecting spacer elements. The patent however was completely silent on this issue. Therefore its teaching in respect of the insertion of new spacer elements was insufficient.

22. Referring to declarations D33, D34 and to documents D32 and D46, appellant I argued that not all cas proteins involved in binding to a target sequence required the presence of a PAM motif. Therefore, even if some systems depended on PAM motifs, the skilled person was left with a sufficiently large number of alternative CRISPR/cas systems such that the teaching of the patent was sufficient to carry out the invention without undue burden.

23. The question whether the PAM motif is indeed important and the teaching of the patent insufficient in the absence of any mention of it can be left unanswered in view of the following considerations:

24. According to the wording of claim 1, the achievement of the technical effect of increasing resistance in a bacterium against a target nucleic acid is not limited to the use of complete CRISPR/spacer/cas systems or the insertion of randomly or specifically selected spacer elements into existing CRISPR/cas systems. The claim covers any use of cas genes or proteins for increasing resistance in a bacterium, including for instance the use of modified cas genes (cf. in this context claim 31, item VIII, above).

25. It is not put into question that a skilled person can readily modify bacterial genes. However, the patent does not contain any teaching which modifications would be suitable for increasing resistance according to claim 1. Although a reasonable amount of trial and error is permissible when it comes to sufficiency of disclosure, e.g. in an unexplored field or where there are many technical difficulties, the skilled person has to have at his disposal, either in the specification or on the basis of common general knowledge, adequate information leading necessarily and directly towards success through the evaluation of initial failures. In the present case, there is no such information at all and the skilled person has to perform a research project in order to identify suitably modified cas genes. Likewise, in respect of any further uses of cas genes or proteins, the patent provides no guidance at all.

26. Therefore, the patent does not sufficiently disclose the invention across the entire breadth of claim 1. The same applies to claim 31.

27. The main request and auxiliary requests 1 to 5 do not meet the requirements of Article 83 EPC.

Admissibility of auxiliary requests 6 and 7

28. Admissibility of late filed requests is at the board's discretion (Article 114(2) EPC). With regard to any amendment to a party's case after it has filed its grounds of appeal or reply, this is governed by the principles laid down in Article 13(1) of the Rules of Procedure of the Boards of Appeal (RPBA).

29. Auxiliary requests 6 and 7 were filed at the oral proceedings before the board after an extensive discussion of the main request with regard to the requirements of Article 83 EPC. This is a very late stage at which to seek to introduce claim requests into the proceedings.

30. Claim 1 of both new auxiliary requests defines the use of the one or more cas genes or proteins by a combination of features of claims 1 and 11 of the main request. A similar request with an identical claim 1 had been filed on 30 November 2011 and presented as auxiliary request 6 in opposition proceedings. The opposition division decided that it did not meet the requirements of Article 83 EPC (cf. page 5 of the decision under appeal).

31. Appellant I did not maintain such a claim request, neither in the statement setting out its grounds of appeal nor in any of its subsequent written

submissions. Appellant II and the respondent could therefore assume that appellant I did not intend to pursue this matter further.

32. Auxiliary requests 6 and 7 contain subject matter which, up to the afternoon of the oral proceedings before the board, had not formed part of appellant I's case. The admission of these requests would lead to procedural delays and run contrary to procedural economy. Moreover, appellant I's argument that, until the board had expressed its opinion about the main request and auxiliary requests 1 to 5, it was convinced that the requests already on file met the requirements of Article 83 EPC, cannot convince the board, as this subjective assessment should not have prevented appellant I from filing adequate fallback positions in the form of auxiliary requests at the earliest possible time in the procedure. Hence, the board decides not to admit auxiliary requests 6 and 7 into the proceedings.

33. Since the main request and auxiliary requests 1 to 5 are not allowable and auxiliary requests 6 and 7 are not admitted into the procedure, the patent is revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated