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Datasheet for the decision of 17 January 2018

Case Number: T 1311/13 - 3.3.08

Application Number: 00970414.9

Publication Number: 1224299

IPC: C12N15/57, C12N9/64, A61K38/48, C07K19/00, C12Q1/37, C12N15/62

Language of the proceedings: EN

Title of invention:
RECOMBINANT PROTEINS AND PEPTIDES FOR ENDOTOXIN BIOSENSORS, ENDOTOXIN REMOVAL, AND ANTI-MICROBIAL AND ANTI-ENDOTOXIN THERAPEUTICS

Patent Proprietor:
NATIONAL UNIVERSITY OF SINGAPORE

Opponent:
Ström & Gulliksson AB

Headword:
LPS binding peptides/ NATIONAL UNIVERSITY OF SINGAPORE

Relevant legal provisions:
EPC Art. 54, 56, 83, 108, 114(2), 123(2)
EPC R. 99(2), 101(1)
RPBA Art. 12(2), 13(1)

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It can be changed at any time and without notice.

Keyword:
Admissibility of the appeal (yes)
Admission of the main and first auxiliary requests (yes)
Admission of objection raised under Article 123(2) EPC (yes)
Main request - added subject-matter (yes)
First auxiliary request - added subject-matter (no)
Admission of objections raised under Articles 83 and 54 EPC (no)
First auxiliary request - inventive step (yes)

Decisions cited:
G 0009/91, J 0016/13, T 0021/81, T 0069/83, T 0432/88, T 0939/92, T 0967/97, T 0356/08, T 2048/10, T 2477/12

Catchword:

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Case Number: T 1311/13 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 17 January 2018

Appellant: (Opponent)	Ström & Gulliksson AB Box 4188 203 13 Malmö (SE)
Representative:	Roos, Rikard Ström & Gulliksson AB Studentgatan 1 P.O. Box 4188 203 13 Malmö (SE)
Respondent: (Patent Proprietor)	NATIONAL UNIVERSITY OF SINGAPORE 10 Kent Ridge Crescent Singapore 119260 (SG)
Representative:	Cripps, Joanna Elizabeth Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 April 2013 concerning maintenance of the European Patent No. 1224299 in amended form.**

Composition of the Board:

Chairman B. Stolz
Members: P. Julià
D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 224 299, based on European patent application No. 00 970 414.9 and published as International patent application WO 01/27289 (hereinafter "the patent application") was maintained in amended form on the basis of an auxiliary request 1 filed at the oral proceedings before the opposition division (Article 101(3)(a) EPC). The opposition division considered the main request (claims as granted) to contravene Article 100(c) EPC.

II. An appeal was lodged by the opponent (appellant) against the interlocutory decision of the opposition division. In the statement setting out the grounds of appeal, the appellant maintained all the objections raised under Articles 123(2), 83, 54 and 56 EPC in the opposition procedure.

III. In reply thereto, the patent proprietor (respondent) filed new auxiliary requests I to X and further arguments.

IV. The appellant filed a new submission in reply to the filing of new auxiliary requests.

V. Both parties requested oral proceedings as an auxiliary measure.

VI. The board summoned the parties to oral proceedings. In a communication annexed to the summons, the board expressed a provisional, non-binding opinion on the issues of the case.

VII. The appellant, without making any substantive submission, informed the board that it would attend the oral proceedings.

VIII. In a letter dated 5 January 2018, the respondent informed the board of its intention not to attend the oral proceedings and filed a new main request and new first and second auxiliary requests.

IX. Oral proceedings were held on 17 January 2018 in the presence of the appellant.

X. The claims of the main request are as follows:

"1. A method for preserving a sample from contamination by gram negative bacteria comprising adding a polypeptide selected from the group consisting of:

GFKLKGMARISCLPNGQWSNFPPKCIRECAMVSS (sushi-1 peptide);

GFKLKGKAKISCLPNGQWSNFPPKCIRECAMVSS (sushi-1Δ peptide);

HAEHKVKIGVEQKYGQFPQGTEVTYTCSGNYFLM (sushi-3 peptide);

HAEHKVKIKVKQKYGQFPQGTEVTYTCSGNYFLM (sushi-3Δ peptide);

RAEHKVKKIVKQLYGQFRQLTRVTRTCSRFLRRM (sushi-4 peptide);

HKVKKIVKQLYRAEHKVKKIVKQL (sushi-5 peptide);

MRKLVLALAKALAKVDKKNL (sushi-6-vg1 peptide);

LLNAVPHKATHAALKFLKEK (sushi-7-vg2 peptide);

GVSTTVLNIYRGIINLLQLNVKK (sushi-8-vg3 peptide); and

IYRGIINLIQLAVKKAQNVYQM (sushi-9-vg4 peptide),

to said sample in an amount effective for preventing the growth of said gram negative bacteria."

Claims 2 and 3 are directed to a method for purifying a sample and a method for detecting a gram negative bacteria or a lipopolysaccharide in a sample, respectively, comprising the use of the polypeptides of claim 1. Claims 4 to 7 are directed to particular embodiments of claim 3.

"8. The method according to any one of claims 3 to 7, wherein said sample comprises tissues or cells and said polypeptide comprises a member selected from the group consisting of:

SSCrFC-sushi-1-GFP

M R V L V L A L A V A L A V G D Q S N L G C P L L P S D S Q V Q E V R N P P D N P Q T I D Y S C S P G F K L K G M A R I S C L P N G Q W S N F P P K C I - GFP;

SSCrFC-sushi-3-GFP

M R V L V L A L A V A L A V G D Q S N L G C P D L D P V N H A E H K V K I G V E Q K Y G Q F P Q G T E V T Y T C S G N Y F L M G F D T L K C N P D G S W S G S Q P S C - GFP; and

SSCrFC-sushi-1,2,3-GFP

M R V L V L A L A V A L A V G D Q S N L G C P L L P S D S Q V Q E V R N P P D N P Q T I D Y S C S P G F K L K G M A R I S C L P N G Q W S N F P P K C I R E C A M V S S P E H G K V N A L S G D M I E G A T L R F S C D S P Y Y

L I G Q E T L T C Q G N G Q W N G Q I P Q C K N L V F C P D L D P V N H A E H K V K I G V E Q K Y G Q F P Q G T E V T Y T C S G N Y F L M G F D T L K C N P D G S W S G S Q P S C - GFP."

Claim 9 is directed to a polypeptide consisting of a lipopolysaccharide binding domain of Factor C protein which is selected from the group consisting of the polypeptides of claim 1. Claims 10 to 13 are directed to preferred embodiments of claim 9, claim 12 referring to the presence of a secretory signal sequence of a vitellogenin protein.

Claim 14 is directed to the use of a polypeptide selected from the group consisting of the polypeptides of claim 1 in the preparation of a medicament for treating sepsis caused by a gram negative bacterial infection. Claim 15 is directed to preferred embodiment of claim 14.

Claim 16 is directed to an isolated nucleic acid encoding the polypeptide according to any of claims 9 to 11. Claims 17 to 21 are directed to preferred embodiments of claim 16, wherein claim 17 refers to the presence of a nucleic acid encoding a secretory signal sequence of a vitellogenin protein, and claim 21 to nucleic acids encoding *inter alia* the polypeptides of claim 8 (SSCrFC-sushi-1-GFP, SSCrFC-sushi-3-GFP, and SSCrFC-sushi-1,2,3-GFP).

Claims 22 to 24 are directed to a method for producing an isolated polypeptide according to any one of claims 9 to 13 and preferred embodiments thereof.

XI. The first auxiliary request is identical to the main request except for the deletion of claims 8 and 21 and the renumbering of the claims accordingly.

XII. The following documents are cited in this decision:

(1): US 5,716,834 (publication date: 10 February 1998);

(5): J.L. Ding and M.A.A. Navas III, Molecular Marine Biology and Biotechnology, 1995, Vol. 4(1), pages 90 to 103;

(6): A.W.M. Pui *et al.*, J. Endotoxin Research, 1997, Vol. 4(6), pages 391 to 400;

(9): T. Muta *et al.*, J. Biol. Chem., 1991, Vol. 266(10), pages 6554 to 6561;

(10): Sequence of Limulus clotting factor C precursor, Uniprot website, Accession number P28175, Release 36, 15 July 1998.

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

Admissibility of the appeal

Arguments as to why the opposition division erred when assessing the objections raised under Articles 123(2), 83 and 54 EPC were included in the statement of grounds of appeal. The ground for opposition under Article 100(c)/123(2) EPC was not a fresh ground since it was already raised in the Notice of opposition, and arguments on the inconsistency of some claims and their lack of support in the patent application were put

forward at the oral proceedings before the opposition division. The appeal was substantiated and admissible.

Admission of the main and first auxiliary requests

These requests were filed shortly before the oral proceedings and were thus late filed. There was no opportunity to examine them in detail and to assess the arguments provided in the late filed submission accompanying their filing. The amendments introduced into these requests were not limited to deletion of subject-matter and/or of claims.

Main request
Admission of the objection raised under Article 123(2) EPC

Objections under Article 100(c) EPC/Article 123(2) EPC were raised in the Notice of opposition and were not a fresh case introduced only in appeal proceedings. Arguments addressing the lack of support of claims 8, 12, 13 and 17 to 24 were raised at the oral proceedings before the opposition division and the patent proprietor/respondent did not object to their discussion. Therefore, the ground of opposition and the objection raised under Article 123(2) EPC were part of the appeal proceedings.

Article 123(2) EPC

A first objection concerned all independent claims, in particular claim 9, as far as they were directed to isolated polypeptides as such, and not as sub-sequences of a full-length sequence as disclosed in the Sequence Listing of the patent application. The second objection concerned claims 8, 12, 13 and 17 to 24 which specified

the presence of additional sequence elements although they referred back to independent claims that were directed to isolated polypeptides of a defined amino acid sequence and length - excluding thereby the presence of additional elements. Whilst isolated polypeptides comprising other elements were contemplated in the patent application - as shown in the original claims of the patent application - there was no support for the unclear embodiments of claims 8, 12, 13 and 17 to 24. A third objection concerned claims 8 and 21 as far as they comprised the amino acid sequences of "SSCrFC-Sushi-1-GFP", "SSCrFC-Sushi-3-GFP", and "SSCrFC-Sushi-1,2,3-GFP". These sequences were neither disclosed in the Sequence Listing (SEQ ID NO: 1 to 4) nor anywhere else in the patent application.

First auxiliary request
Article 123(2) EPC

The deletion of claims 8 and 21 overcame the third objection raised under Article 123(2) EPC against the main request, but not the first and second objections.

Admission of the objections raised under Articles 83 and 54 EPC

A reference to earlier submissions, as in the case underlying decision T 432/88 of 15 June 1989, resulted in a mere assertion that the contested decision was incorrect but left the board and the other party to conjecture in what respect the decision under appeal was defective. However, the presentation of earlier arguments (that had already been addressed at the first instance proceedings) on which an objection was based, was admissible. In the present case, it was clear from

the statement of grounds of appeal that the decision under appeal as regards Articles 83 and 54 EPC was contested, and arguments were adequately submitted and put forward against the flawed conclusion of the opposition division regarding both articles.

Article 56 EPC

The closest state of the art, document (6), disclosed a N-terminal fragment of the recombinant Factor C (rFC) protein from *C. rotundicauda* containing the cysteine-rich region, the EGF-like domain and one or two sushi domains. This fragment (rFCEE) had LPS-binding activity, albeit lower than the full-length rFC protein. Starting from this prior art, the problem to be solved was the provision of alternative polypeptides with LPS-binding activity, including polypeptides with lower activity than the full-length rFC protein. Document (6) referred to the relevance of other domains for the LPS-binding activity, including downstream sushi domains. The selection of these sushi domains would have been obvious to a skilled person. The selection of the claimed sushi domains was not justified by any unknown advantageous effect because, as shown in Figure 3 of the patent, the claimed polypeptides had a lower LPS-binding activity than the full-length rFC protein. These polypeptides represented a mere arbitrary selection with no inventive merit (cf. decisions T 939/92, OJ EPO 1996, 309, and T 967/97 of 25 October 2001). Document (6) was by itself detrimental to inventive step. All the more so since the purification procedure disclosed in document (6) was identical to the one described in Example 12 of the patent. Therefore, the method carried out in document (6) resulted in a slurry that necessarily contained the claimed polypeptides. No inventive merit was required

to isolate and characterize these polypeptides by their amino acid sequence.

Moreover, starting from document (6), a skilled person would have turned its attention to document (1). This document disclosed truncated rFC fragments comprising the sushi-2 to 5, sushi-3 to 5, or sushi-5 domains (λ clone 21 lacked the N-terminal Cys-rich region and the EGF-like domain), and all these fragments had LPS-binding activity. Although these fragments comprised more amino acids than the claimed polypeptides, this difference did not result in any effect because both, the claimed polypeptides and those disclosed in document (1), had lower activity than the full-length FC protein. Thus, the claimed polypeptides lacked inventive step over the combination of documents (6) and (1).

Indeed, the combination of either document (6) or document (1) with other prior art documents on file, such as documents (5), (9) or (10), rendered the claimed polypeptides not inventive. These documents referred to the sushi domains of rFC proteins from horseshoe crabs, including *C. rotundicauda*. Document (10) indicated the position of the sushi-1, 2 and 3 domains (residues 142 to 195, 200 to 254 and 260 to 321, respectively), close to the position of the sushi-1, 2 and 3 domains identified in the rFC protein of the patent. Documents (6) and (1) disclosed rFC fragments similar to those disclosed in these documents and showed them to have LPS-binding activity. The isolation of shorter fragments was a routine procedure without inventive merit. The claimed polypeptides had a greatly diminished LPS-binding activity in comparison to the full-length rFC protein and thus, their selection was not inventive.

Claim 8 was directed to several peptides without reference to their LPS-binding activity. Document (9) disclosed the amino acid sequence of the rFC protein and identified the sequences of five putative sushi domains that were predicted to be sites for protein-protein interactions. Thus, it would have been obvious to isolate these domains and, according to the case law (cf. T 21/81, OJ EPO 1983, 15; and T 69/83, OJ EPO 1984, 357), the presence of an additional effect (LPS-binding activity) was a bonus effect because it was inherent to the isolated peptides.

XIV. The submissions made in writing by the respondent, insofar as relevant to the present decision, may be summarised as follows:

Admissibility of the appeal

The objections under Articles 54 and 83 EPC in the statement of grounds of appeal were not substantiated, and those under Article 123(2) EPC had not been raised in opposition proceedings and were thus not admissible. Lack of inventive step was the sole ground of appeal substantiated in line with Rule 99(2) EPC and Article 12(2) RPBA.

Admission of the main and the first auxiliary requests

These requests addressed issues raised for the first time by the board in the communication pursuant to Article 15(1) RPBA. The objection raised under Article 123(2) EPC by the board had been raised neither during opposition nor in appeal proceedings. The amendments introduced into these requests consisted of deletions of subject-matter within dependent claims,

and did not raise additional or new issues requiring further consideration.

Main request
Admission of the objection raised under Article 123(2) EPC

The objection raised under Article 123(2) EPC against claims 8, 12, 13 and 17 to 24 was a new objection, not raised in opposition. Although the opponent/appellant raised a similar objection at oral proceedings, this objection was raised under Article 83 EPC and confined only to claim 8. The introduction of this new ground of opposition was objected to by the patent proprietor/ respondent, as noted in the Minutes and in the decision under appeal. In the Notice of opposition, the subject matter of claim 8 was neither attacked under Article 123(2) EPC nor under Article 83 EPC; in fact, it was not opposed on any ground of opposition. In line with the case law (cf. G 9/91, OJ EPO 1993, 408, and T 356/08 of 7 July 2009), the introduction of this objection represented a fresh ground of opposition and, thus, was not admissible into the appeal proceedings.

Article 123(2) EPC

As regards the first objection, the sushi polypeptides listed in claim 9 were referred to throughout the patent application and their amino acid sequences were shown in Figure 11B of the patent application. Although claim 12 of the patent application did not use the term "consisting of" and the polypeptides as such were not claimed in the patent application, these polypeptides were nevertheless disclosed as such in the context of the invention. As regards the second objection, claims 8, 12, 13 and 17 to 24 were supported by a

combination of the original claims, in particular claims 10, 12, 13, 16, 32, 34, 39 to 45 and 49 of the patent application. If at all, this objection concerned Article 84 EPC, itself not a ground for opposition. As regards the third objection, the subject-matter of claim 8 was identical to that of claim 34 of the patent application. The amino acid sequences cited in claims 8 and 21 were derivable from the numbering given in Figure 10A and the sequence of SEQ ID NO: 4 in the Sequence Listing of the patent application. The sequences at the N/C-terminus corresponded to the vitellogenin secretory signal and to the green fluorescent protein (GFP), respectively. As noted in the patent application under the heading "Summary of the invention", the sequence of this signal was disclosed in US patent application No. 09/426,776 (US 6,733,997), filed on 26 October 1999, and was explicitly incorporated by reference in the granted patent. The entire US document was concerned with this secretory signal sequence and thus, this was not a situation where the skilled person was expected to search for or chose from many alternatives provided in the reference document. Accordingly, the skilled person would have had no difficulty in deriving all this information from the patent application.

First auxiliary request
Article 123(2) EPC

The deletion of claims 8 and 21 overcame the third objection raised under Article 123(2) EPC against the main request.

Admission of the objections raised under Articles 83 and 54 EPC

As regards Article 83 EPC, the arguments put forward against claim 2 repeated substantially *verbatim* those given in the Notice of opposition. The statement of grounds of appeal contained neither a reference to the reasons given in the decision under appeal nor any argument why these reasons were wrong. As regards the objection raised at the oral proceedings before the opposition division against the subject-matter of other dependent claims, the statement of grounds of appeal contained no reference to the decision under appeal nor any reason why this decision was wrong. As regards Article 54 EPC, the statement of grounds of appeal was also copied *verbatim* from the Notice of opposition and there was no reference to the reasons given by the opposition division for acknowledging novelty of the claims. The grounds of appeal with regard to Articles 83 and 54 EPC were thus not substantiated and therefore, not admissible.

Article 56 EPC

Starting from the closest state of the art, document (6), the problem to be solved was the provision of further FC polypeptides with LPS-binding activity. The claimed polypeptides, derived from the sushi domains and retaining a high LPS affinity represented a non-obvious solution. At the priority date, it was not known that the sushi domains of the FC protein were responsible for the LPS-binding activity. There was no motivation for a skilled person to consider these domains as a starting point in its search for LPS-binding activity, let alone to try even smaller domains of the FC protein, such an approach went against the teaching of document (6). The patent provided evidence of unexpected effects of the claimed polypeptides which combined a high LPS affinity with

high anti-endotoxin potency and antisepsis activity coupled with low or no cytotoxicity. Document (1) did not provide a motivation for the skilled person to arrive at the claimed polypeptides. The general disclosure of document (1) could not be interpreted in any specific way without the benefit of hindsight.

None of the prior art documents on file, such as documents (5) or (9), mentioned LPS-binding activity and thus, none of these documents provided a motivation to isolate peptides derived from the sushi domains with an expectation to bind LPS or to achieve any of the technical effects of the claimed polypeptides as disclosed in the patent. At the priority date, it was known that sushi domains were present in numerous proteins and these domains were predicted to provide sites for protein-protein interactions. However, there was no teaching that the sushi domain fold in general, let alone the particular sushi domains of the FC protein, was linked to LPS-binding. It was the domain structure of the whole FC protein which was thought to be important for LPS-binding, as stated in document (6) by the reference to "downstream sequences of Factor C [that] may co-operate directly or indirectly" to LPS binding.

According to the case law, a bonus effect was the result of a "one-way street" situation which a skilled person had necessarily to follow for solving the technical problem and which led to predictable advantages that remained obvious in spite of some other unexpected (bonus) effect. In the present case, sushi domains from other proteins were available to the skilled person and known to be involved in protein-protein interactions. However, no reasons had been given to explain why a skilled person would have

arrived at the claimed polypeptides using the FC protein from horseshoe crabs other than the (*C. rotundicauda*) crab used in the patent, and why the sushi domains had to be modified so as to arrive at the shorter polypeptides claimed. This situation was far from a one-way street situation.

XV. The appellant (opponent) requested to set aside the decision under appeal and to revoke the patent.

XVI. The respondent (patent proprietor) requested in writing to set aside the decision under appeal and to maintain the patent on the basis of the claims of the main request, or alternatively, upon the basis of one of the first or second auxiliary requests, all filed under cover of a letter dated 5 January 2018.

Reasons for the Decision

Admissibility of the appeal

1. In the communication pursuant to Article 15(1) RPBA (cf. point VI *supra*), the board informed the parties that, in its opinion, the respondent did not challenge the admissibility of the appeal but only some of the appellant's grounds of appeal. The board noted that the respondent's acknowledgement that the requirements of Article 108, third sentence, EPC were fulfilled for at least one ground of appeal, namely inventive step, was also an acknowledgement that the admissibility of the appeal was not contested, since there is no partial admissibility of an appeal (cf. "Case Law of the Boards of Appeal of the EPO", 8th edition 2016, IV.E.2.6.9, 1108). In the reply to the board's communication, the respondent has not contested the board's provisional

opinion as regards this issue and the board has thus no reason to deviate from said opinion. Therefore, the appeal is admissible under Article 108 EPC and Rules 99(2) and 101(1) EPC.

Admission of the main and first auxiliary requests

2. The main request and the first auxiliary request have been filed in reply to the board's communication pursuant to Article 15(1) RPBA shortly before the date of the scheduled oral proceedings.

3. The main request is identical to the main request filed with the appellant's statement of grounds of appeal except for the deletion of one amino acid sequence (SSCrFCES) in dependent claim 21. The main request filed with the statement of grounds of appeal was the request on the basis of which the opposition division decided to maintain the patent and was part of the proceedings from the beginning.

4. The first auxiliary request is identical to the main request filed in reply to the board's communication pursuant to Article 15(1) RPBA except for the deletion of claims 8 and 21 of the main request.

5. The deletion of subject-matter of dependent claim 21 in the main request and the deletion of dependent claims 8 and 21 in the first auxiliary request are amendments of the previous main request that intend to overcome an objection raised under Article 123(2) EPC by the board in its communication pursuant to Article 15(1) RPBA. These amendments are thus a direct reply to this communication and, by their nature, do not change the subject-matter of the appeal nor do they raise new issues in the appeal proceedings.

6. Thus, the board, exercising its discretion pursuant to Article 114(2) EPC, governed by the principles laid down in Article 13(1) RPBA, admits the main request and the first auxiliary request in the appeal proceedings.

Technical background

7. The patent describes the expression and secretion of functional endotoxin or lipopolysaccharide (LPS) binding domains of Factor C from the circulating amebocytes of the mangrove horseshoe crab *Carcinoscorpius rotundicauda* (CrFC). It discloses polypeptides of 20 to 34 amino acid residues in length derived from the CrFC short consensus repeats - also known as sushi domains; in particular amino acid sequences of the sushi-1, sushi-3, sushi-4, sushi-5, sushi-6-vg1, sushi-7-vg2, sushi-8-vg3, and sushi-9-vg4 polypeptides. The patent further discloses isolated nucleic acids encoding these polypeptides, a method for producing them recombinantly, and the use of these polypeptides for various purposes, such as for preserving a sample from contamination by gram negative bacteria, for purifying a sample by removal of endotoxin, for detecting gram negative bacteria or LPS in a sample, and for the preparation of a medicament for treating sepsis caused by a gram negative bacterial infection (cf. point X *supra*).

Main request
Admission of the objection raised under Article 123(2) EPC

8. In the statement of grounds of appeal, the appellant raised three objections under Article 123(2) EPC, the first against all independent claims, the second against dependent claims 8, 12, 13 and 17 to 24, and

the third against claims 8 and 21 (cf. point XIII *supra*). The arguments on which the first objection is based, were already put forward in the Notice of opposition and the admission of this objection in appeal proceedings is not contested by the respondent.

9. In point 2.2.1.4 of the decision under appeal, the opposition division referred to an objection raised under Article 123(2) EPC by the opponent/appellant against claim 10 as granted (corresponding to claim 8 of the main request) and, in analogy thereto, against granted claims 14, 15 and 21 to 28 (corresponding to claims 12, 13 and 17 to 24 of the main request). Point 3.3 of the "Minutes of the oral proceedings before the opposition division" (hereinafter "the Minutes") refers to this objection and does not report any protest from the patent proprietor/respondent to the introduction of this objection into the opposition proceedings. None of the parties contested the Minutes. Thus, the board sees no reason for not admitting the second objection into the appeal proceedings.

10. The second and third objections raised under Article 123(2) EPC in the statement of grounds of appeal are directed against claims that had been discussed under the same ground of opposition in the opposition procedure. However, whilst the arguments on which the second objection is based are clearly found in both the decision under appeal and the Minutes, this is not the case for the arguments on which the third objection is based. Nevertheless, the subject matter at the basis of the second objection, namely the presence of "additional parts" (cf. first sentence of point 3.3 of the Minutes), is also at the basis of the third objection, namely the presence of the secretory signal sequence (21 residues) and the "additional" amino acids

of the corresponding sushi domains in the polypeptides of claims 8 and 21.

11. In view thereof, the objections raised under Article 123(2) EPC do not introduce a fresh ground of opposition in the appeal proceedings, and all three objections are admitted.

Article 123(2) EPC

12. The first objection was raised against all independent claims, in particular claim 9. The appellant argued that the patent application did not disclose the specific peptide sequences listed in these claims.

13. Under the heading "Summary of the invention", the patent application refers to a functional LPS-binding domain (spanning 333 amino acids) of *C. rotundicauda* Factor C protein (SSCrFCES) and portions/fragments thereof (cf. page 3, lines 23 to 30), 34-mer synthetic sushi peptides, such as the sushi-1 (S1) and sushi-3 (S3) peptides, as well as fusion constructs (cf. page 4, line 23 to page 5, line 31; in particular, page 4, lines 27 to page 5, line 2). Likewise, under the heading "Brief description of the drawings", reference is made to the LPS-binding domain of SSCrFCES, synthetic sushi peptides, such as those of 34 amino acids in length shown in Figure 11B, and fusion constructs (cf. *inter alia*, page 6, line 30 to page 7, line 14 for Figures 3(A) and 3(E); page 9, lines 10 to 15 for Figures 10(a) and 10(b), and Figures 11(a) and 11(B)). The examples of the patent application refer to the LPS-binding domain of SSCrFCES, synthetic sushi peptides, and several SSCrFCsushi-GPF fusion proteins (cf. *inter alia*, page 21, Example 3; page 29, lines 28 to 30). The disclosure of the patent application as a

whole, and in particular the amino acid sequences of the sushi peptides shown in Figure 11B of the patent application, provide a formal basis for the specific amino acid sequences of the isolated polypeptides of claim 9 and for all other independent claims of the main request.

14. The second objection was raised against dependent claims 8, 12, 13 and 17 to 24. The appellant argued that although the independent claims of the main request referred to isolated polypeptides of specific lengths and sequences, the polypeptides of the dependent claims comprised "additional elements". The patent application did however not provide a basis for the subject matter of the dependent claims.

15. Claim 10 of the patent application is directed to an isolated polypeptide comprising a LPS-binding domain of a FC protein that may be selected from those given in claim 12 which include *inter alia* the sushi-1, sushi-2 and sushi-3 domains as well as the sushi-1, sushi-2 and sushi-3 peptides. The isolated polypeptide may also comprise "additional elements", such as a specific (vitellogenin) secretory signal sequence (claim 13), a reporter protein or an affinity tag (claim 16). Likewise, claim 37 of the patent application is directed to an isolated nucleic acid encoding the polypeptide of claim 10, and dependent claims 38 to 40 contemplate the presence of "additional elements". Claims 44, 45 and 49 of the patent application are directed to a method for producing an isolated LPS-binding protein using an isolated nucleic acid. The board considers these claims to directly and unambiguously disclose the subject matter of claims 12, 13, 17 to 20, and 22 to 24 of the main request. Appellant's objection arising from an alleged lack of

clarity - due to the use of the term "consisting" in the independent claims instead of "comprising" - is not an issue within the scope of the appeal since Article 84 EPC is not a ground for opposition and this wording was in the claims as granted.

16. The appellant argued furthermore, that the specific amino acid sequences shown in claims 8 and 21 were neither disclosed in the claims nor in the sequence listing of the patent application.

16.1 Claims 8 and 21 define fusion polypeptides containing a secretory signal sequence (the first 21 residues), a sushi (sushi-1, sushi-3, or sushi-1,2,3) domain from the *C. rotundicauda* FC protein, and a GFP protein (for which no amino acid sequence is shown).

Figures 10 and 28 of the patent application schematically show fragments (SSCrFCES) and fusion proteins (cf. page 9, lines 10 to 13; page 12, lines 13 to 20). With reference to SEQ ID NO: 4, Figure 10A indicates the start/end amino acids of several CrFC21 domains. Figure 10B refers to the FC fragments in pAc5/ssCrFCES-V5-His, pAc5.1/sssushi-1,2,3-EFGP, pAc5.1/sssushi-1-EFGP, and pAc5.1/sssushi-3-EFGP, but does not disclose any amino acid sequence. None of these constructs is exemplified in the patent application.

The first 21 residues of all the sequences of the polypeptides shown in claims 8 and 21 are identical, and the subsequences starting at position 22 of the first, second and third polypeptide of claim 8 (identical to the second, third and fourth polypeptide sequences of claim 21) correspond to: i) a sushi-1 domain consisting of residues 142 to 196 of SEQ ID

NO: 4, ii) a sushi-3 domain consisting of residues 260 to 321 of SEQ ID NO: 4, and iii) a sushi-1,2,3 domain conisting of residues 142 to 321 of SEQ ID NO: 4 (cf. also Figure 10A).

The start/end residues of the sushi-1, sushi-3 and sushi-1,2,3 domains encoded by the vector constructs shown in Figure 10B are not indicated, only the start/ end residues of subsequences (residues 171 to 204 of SEQ ID NO: 4 for sushi-1 peptide; residues 268 to 301 of SEQ ID NO: 4 for sushi-3 peptide, even though in Figure 10B it is wrongly annotated as residues 288 to 301 of SEQ ID NO: 4). These start/end residues are however different from those indicated in Figure 10A. Yet other start/end residues characterizing the sushi domains are indicated on page 15, lines 1 to 11, and in Figure 28 of the patent application, namely residues 29 to 201 for sushi-1, residues 264 to 330 for sushi-3, and residues 29 to 330 for sushi-1,2,3. Reference is also made to the functional relevance of residues 60 to 70 in the sushi-1 domain, residues 170 to 185 in the sushi-2 domain, and residues 270 to 280 in the sushi-3 domain (cf. page 15, lines 6 to 9).

16.2 The facts of the present case differ substantially from, and cannot be compared to, those of the case underlying decision T 2048/10 of 21 July 2015 (cf. points 4 and 5 of the Reasons). In said case, the indication of the start/end residues of a fragment or subsequence in a Figure of the patent application was sufficient for acknowledging direct and unambiguous disclosure of this fragment or subsequence as such. In the present case, however, the reference in Figure 10A of the patent application to the start/end residues of the sushi domains is not the sole disclosure of these domains and there is a considerable degree of ambiguity

in the characterization of the respective start/end residues (*supra*). The board concludes therefore that the specific amino acid sequences from residue 22 onwards of the polypeptides of claims 8 and 21 are not directly and unambiguously derivable from the patent application.

16.3 Moreover, the patent application does not disclose the first 21 amino acid residues of these polypeptides which, as stated above, are identical in all the amino acid sequences of claims 8 and 21. There is no reference to this sequence in Figures 10(A) and 10(B) or Figure 28, nor in the description of these figures under the heading "Brief description of the drawings". Although there is a reference to "a novel secretory signal" on page 3, line 28 to page 4, line 2 of the patent application, the sequence of this secretory signal is disclosed only in US Patent Application No. 09/426,776, which is based on the provisional US patent application No. 60/106,402. This US patent application is also cited in Example 1 describing SSCrFCES expression in stable cell lines of Drosophila (cf. page 18, lines 13 to 15). Although a reference to a US patent application may fulfil - under certain circumstances - the conditions required by the case law for acknowledging a direct and unambiguous disclosure (cf. *inter alia*, J 16/13 of 22 May 2014, points 14 to 20 of the Reasons; T 2477/12 of 12 November 2015; and "Case Law", *supra*, II.E.1.1.2, 402), it is questionable whether the general reference to a US patent application, which in the present case is based on a provisional US patent application, suffices as a basis for the disclosure of the specific first 21 amino acid residues of the polypeptides shown in claims 8 and 21 and a combination of these residues directly fused with the sequence of the sushi domains as in claims 8 and

21. In this context, it is worth noting again that there is no signal sequence shown in the constructs of Figure 10B and there is no information on the actual components/elements defining the pAc5.1 constructs shown in this Figure.

16.4 In view of these considerations, the board concludes that the patent application does not directly and unambiguously disclose the specific amino acid sequences of the (fusion) polypeptides shown in claims 8 and 21 of the main request.

17. Thus, the main request contravenes Article 123(2) EPC.

First auxiliary request
Article 123(2) EPC

18. The first auxiliary request is identical to the main request except for the deletion of claims 8 and 21 (cf. point XI *supra*). The deletion of these claims overcomes the third objection raised under Article 123(2) EPC against the main request. The other two objections raised under this article against the main request, and maintained by the appellant against the first auxiliary request, are not successful (cf. points 13 and 15 *supra*) and thus, the first auxiliary request does not contravene Article 123(2) EPC.

Admission of objections raised under Articles 83 and 54 EPC

19. In the communication pursuant to Article 15(1) RPBA, the board drew the parties' attention to the case law concerning the substantiation of grounds of appeal (cf. "Case Law", *supra*, IV.E.3.2.1.h) and IV.E.3.2.1.i), 1122; and related IV.E.2.6.3.b), 1098; IV.E.2.6.4.a),

1102; IV.E.2.6.6, 1107, on admissibility of the appeal).

As stated in this case law, a mere reference to a party's earlier submissions and/or the *verbatim* repetition of the arguments presented in these submissions ("grounds by cut-and-paste"), including those submissions or arguments put forward at the oral proceedings before the opposition division, but without actually dealing with, or entering into a discussion of, the reasons given in the decision under appeal by the opposition division for arriving at its decision, is not enough to substantiate a ground of appeal.

20. The board informed the parties that, in view of the reasons given by the opposition division in relation to Articles 83 and 54 EPC (cf. pages 7 to 10, points 2.3.5 and 2.3.6 of the decision under appeal) and of the parties' submissions on these articles in appeal, the board was of the provisional opinion that the grounds of appeal on Articles 83 and 54 EPC were not sufficiently substantiated.

In its communication, the board further indicated that, if a discussion on these objections arose at the scheduled oral proceedings, the first issue to be discussed was their admissibility into the appeal. At the oral proceedings before the board, the appellant referred to its written submissions and did not put forward any further argument or reason that could have led the board to deviate from its provisional opinion as expressed in its communication. Thus, the grounds of appeal under Articles 83 and 54 EPC are considered not to be substantiated and therefore, not admitted into the appeal proceedings.

Article 56 EPC

21. The board agrees with the opposition division that document (6) represents the closest state of the art (cf. page 13, point 2.3.7.3 of the decision under appeal). Document (6) refers to the presence of proteins capable of LPS binding and neutralization in the circulating amebocytes of horseshoe crabs (cf. paragraph bridging pages 391 and 392) and describes the production of recombinant Factor C from *C. rotundicauda* (CrFC21/rFC21) and of a 762 amino acid fragment (CrFC21EE/rFC21EE) thereof comprising the cysteine-rich region, the EGF-like domain and one or two sushi domains with a "slightly reduced endotoxin-binding capacity" (cf. page 392, left-hand column, second paragraph, and right-hand column, first paragraph; paragraph bridging pages 394 and 395; page 396, right-column, first paragraph; and page 397, left-hand column, first paragraph). Document (6) refers also to "the potential of genetically engineered rFC for the detection and removal of endotoxin in the pharmaceutical industry, and protection against Gram-negative bacteria endotoxemia" (cf. page 392, left-hand column, last sentence of the second paragraph).

22. Starting from document (6), the opposition division defined the objective technical problem as the provision of alternative Factor C polypeptides with LPS-binding activity (cf. page 14, first paragraph of the decision under appeal). This formulation of the technical problem has not been contested by the parties and the board agrees with it. The claimed polypeptides, in particular those of claim 8, are the solution proposed by the patent.

23. Examples 2 and 3 of the patent show the polypeptides of claim 8 to have LPS binding activity (albeit lower than the full-length Factor C protein) and thus, to solve the technical problem as formulated above.

24. The appellant argued that, in view of the low LPS-binding activity, the polypeptides shown in Example 3, and Figures 3B to 3E of the patent, did not represent true alternatives to the CrFC21EE/rFC21EE fragment disclosed in document (6). The board, however, shares the respondent's view that Example 4 and Table 3 of the patent show the claimed polypeptides to retain an unexpectedly high affinity for LPS-binding allowing thereby the detection of the Gram-negative bacterial endotoxin and providing a significant endotoxin-neutralizing activity (anti-endotoxin potency). Moreover, contrary to the appellant, the board considers that the selection of these polypeptides is not an arbitrary selection because, as stated by the respondent and the opposition division in the decision under appeal (cf. page 15, lines 5 to 7 from the bottom), other advantageous properties (cheaper production costs, easier handling, low cytotoxicity) are associated with these polypeptides.

25. Whilst document (6) refers to the "reduction in intensity of binding of rFCEE to lipid A as compared to that of rFC" and, in this context, mentions the "downstream sushi domains" of the Factor C protein, this citation is found within a general reference stating that "further downstream sequences of Factor C", in general, "may co-operate directly or indirectly, via protein-protein interaction" (cf. page 395, right-hand column, first paragraph). This reference does not hint at or suggest that an isolated sushi domain or a polypeptide consisting of a small number of them, let

alone fragments thereof, such as the claimed polypeptides, may have LPS binding ability. On the contrary, in the board's view, this reference teaches away from such expectation and, if at all, leads the skilled person towards longer rFC fragments. Moreover, although, as argued by the appellant, the method for producing rFC protein and/or rFCEE fragment described in document (6) is identical to the method disclosed in Example 12 of the patent, none of these methods results in the production of the claimed polypeptides. There is no evidence on file - nor has any been provided by the appellant at the oral proceedings before the board - of a slurry that contains any of the claimed polypeptides in any of the steps carried out in these methods. There is neither evidence on file showing the degradation or cleavage of the rFC protein and/or rFCEE fragment to shorter fragments in any of these methods, nor a reference to any degradation or cleavage of these products in either document (6) or in Example 12 of the patent. Indeed, none of them refers to a slurry containing whatever polypeptides other than the rFC protein and/or the rFCEE fragment. Thus, the board considers the claimed polypeptides not to be obvious from the disclosure of document (6) alone.

26. Furthermore, the claimed polypeptides are not obvious from a combination of the disclosure of document (6) with any of the prior art documents on file, in particular, documents (1), (5), (9) or (10) (cf. point XIII *supra*).

26.1 Document (1), originating from two of the three authors of document (6), discloses a cDNA encoding the full-length Factor C protein from *C. rotundicauda* (CrFC 26, Figure 6, 1083 residues; SEQ ID NO: 1 and 2; cf. column 5, lines 20 to 42) and several cDNAs encoding fragments

derived from this protein (cf. column 5, first paragraph, and Figure 3), the longest fragment having 1019 residues (CrFC 21, Figure 8; SEQ ID NO: 3 and 4; cf. column 5, lines 49 to 57). Figure 11 shows an alignment of the two cDNA sequences and the encoded putative proteins (cf. column 6, lines 4 to 21; column 14, Example 6). Document (1) identifies "five short consensus repeats" (the five sushi domains: residues 206 to 259, 263 to 318, 324 to 385, 640 to 698 and 758 to 812) in the CrFC 26 sequence (cf. column 15, first paragraph) but discloses no biological function or activity associated with these domains. Although document (1) states that the disclosed proteins have "the same enzymatic activity as Factor C protein in assays for Gram negative bacterial endotoxin" (cf. column 2, second paragraph) and further refers to "biologically functional equivalents" as "nucleic acid sequences and polypeptides exhibiting the same or similar biological activity as the particular nucleic acid sequences and polypeptides described herein" (cf. column 16, second paragraph; column 2 and 3, last full paragraphs), the sole polypeptides for which a biological activity (endotoxin binding assay) is disclosed are the two forms (single and double-chain) of Factor C (pro)enzyme purified from the amebocytes of *C. rotundicauda* (cf. column 21, line 36 to column 26, first paragraph). There is no information in document (1) on the biological activity of the polypeptides encoded by the various cDNAs shown in Figure 3, and there is no indication or suggestion that all these polypeptides may have a biological activity. Indeed, the section of document (1) concerned with "biologically functional equivalents" does not refer to these polypeptides at all but only to muteins, derivatives, fragments and portions in general without characterizing or defining the essential residues and/

or domains necessary for retaining the desired biological activity. In view thereof, the board does not consider the disclosure of document (1) to provide additional technical information that would allow a skilled person starting from document (6) to arrive at the claimed polypeptides in an obvious manner.

26.2 Document (5), the scientific publication corresponding to document (1), describes only part of the results shown in document (1). Thus, as stated above for document (1), the disclosure of document (5) in combination with that of document (6), does not lead a skilled person to the claimed polypeptides in an obvious manner.

26.3 Document (10), an excerpt from the UNIPROT databank, discloses the amino acid sequence (1019 residues) of the Limulus clotting Factor C precursor and identifies several domains within this sequence, including four short consensus repeats (SCR) or sushi domains (sushi-1, 2, 3 and 4; residues 142 to 195, 200 to 254, 260 to 321, and 576 to 634, respectively). There is however no indication of any biological function or activity associated with these domains, let alone with fragments or subsequences therefrom. As for bibliographic data, document (10) refers to a single scientific publication which is document (9) in the present proceedings.

26.4 Document (9) discloses the amino acid sequence of the Factor C protein from amebocytes of *Tachypleus tridentatus* (horseshoe crab) and identifies five putative sushi domains (residues 117 to 170, 174 to 229, 235 to 296, 551 to 609, and 615 to 723; cf. page 6556, Figure 2 and page 6558, Figures 7 and 8) which, based on studies of proteins with homologous domains,

are predicted to be sites for interactions with proteins of the mammalian complement system (cf. page 6557, left-hand column, second paragraph). None of these domains has been isolated and, in the board's view, a skilled person would not be motivated to isolate them, let alone fragments or sub-sequences therefrom, based on this general statement. Moreover, the amino acid sequences of the putative sushi domains identified in document (9) do not correspond to the sequences of the polypeptides of claim 8 which represent fragments and/or combinations of several of these domains. The sushi-1 peptide of claim 8 corresponds to amino acids 146 to 179 of the sequence shown in Figure 2 of document (9) and includes several residues of the sushi-1 domain and a few residues of the sushi-2 domain (cf. Figure 6 of document (9)). In addition, the claimed sushi-1 peptide differs from the amino acid sequence shown in Figure 2 of document (9) at three positions (V152M, S165N, and K176M). The sushi-3 peptide of claim 8 corresponds to amino acids 243 to 276 of the sequence shown in Figure 2 of document (9). It represents thus a sub-fragment of this sushi domain but with one substitution (Q247K). None of the other sequences of claim 8 is present within the sequence shown in Figure 2 of document (9). It is thus not obvious for a skilled person to arrive at the specific amino acid sequences of the polypeptides of claim 8 based on the disclosure of document (9) alone or in combination with document (6).

26.5 In conclusion, the combination of document (6) with any of documents (1), (5), (9) or (10), or with other, less relevant prior art on file, would not have led the skilled person to the claimed polypeptides and thereby to the claimed subject-matter of the first auxiliary request in an obvious way.

27. Thus, the first auxiliary request fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with the following claims and a description to be adapted:

Claims:

Nos. 1 to 22 of the first auxiliary request filed under cover of a letter dated 5 January 2018.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated