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Datasheet for the decision of 15 September 2016

Case Number: T 1581/12 - 3.3.08

Application Number: 05077865.3

Publication Number: 1645631

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Language of the proceedings: EN

Title of invention:
Neisseria antigens and compositions

Patent Proprietor:
GlaxoSmithKline Biologicals S.A.

Opponent:
Wyeth et al.

Headword:
Outer membrane protein immunogen Neisseria/GLAXOSMITHKLINE

Relevant legal provisions:
EPC Art. 114(2), 123(2), 76(1), 52, 57, 83, 54, 56
RPBA Art. 13(1), 13(3), 12(4)

Keyword:

Main Request - admissibility (yes);
Main Request - meets all requirements of the EPC (yes)

Decisions cited:

G 0010/91, T 0301/87, T 1329/04, T 0898/05, T 0018/09, T 0583/09, T 1451/09, T 2134/10

Catchword:

Europäisches Patentamt
European Patent Office
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Case Number: T 1581/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 15 September 2016

Appellant I: (Patent Proprietor)	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89 1330 Rixensart (BE)
Representative:	Marshall, Cameron John Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Appellant II: (Opponent)	Wyeth et al. Five Giralda Farms Madison NJ 07940 (US)
Representative:	Dörries, Hans Ulrich df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 May 2012 concerning maintenance of the European Patent No. 1645631 in amended form.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent no. 1 645 631 was granted with 40 claims on the basis of European patent application no. 05 077 865.3 (hereinafter "*the application as filed*"), a divisional application of European patent application no. 99 922 752.3 originally published as International patent application WO 99/57280 (hereinafter "*the parent application*"). The opposition division considered the main request (claims as granted) and auxiliary requests 1 to 5 not to fulfil the requirements of Article 56 EPC. The patent was maintained on the basis of an auxiliary request 6 filed at the oral proceedings on 15 November 2011.

II. Appeals were lodged by the patent proprietor and the opponent (appellants I and II, respectively). In the statement setting out the grounds of appeal, appellant II filed new evidence. Both parties requested oral proceedings as an auxiliary measure.

III. Each of the appellants filed a reply to the respective statement of grounds of appeal. Appellant I filed new evidence and a new auxiliary request 6, the request upheld by the opposition division was renumbered as auxiliary request 7.

IV. Both parties filed further submissions with new evidence.

V. The parties were summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of procedure of the Boards of Appeal (RPBA), they were informed of the preliminary, non-binding opinion of the board on some of the issues of the case.

VI. Both parties replied to the communication of the board and filed further evidence. Appellant I filed new auxiliary requests 8 to 10.

VII. Oral proceedings were held on 15 September 2016. At these proceedings, appellant I made auxiliary request 9 its new main request and withdrew all other claim requests.

VIII. Claims 1, 4, 6, 8 and 9 of the **main request** read as follows:

"1. A protein comprising:

. amino acid sequence SEQ ID NO:4;
. an amino acid sequence comprising a fragment of 20 or more consecutive amino acids from SEQ ID NO:4, wherein said fragment comprises an epitope from SEQ ID NO:4;
. acid sequence SEQ ID NO:6;
. amino an amino acid sequence comprising a fragment of 20 or more consecutive amino acids from SEQ ID NO:6, wherein said fragment comprises an epitope from SEQ ID NO:6.

4. An antibody which specifically binds to amino acid sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:6.

6. A nucleic acid molecule which encodes a protein according to any one of claims 1 to 3.

8. A composition comprising a protein, a nucleic acid molecule, or an antibody according to any preceding claim.

9. A composition according to claim 8 being an immunogenic composition."

Claims 2-3, 5 and 7 were directed to preferred embodiments of claims 1, 4 and 6, respectively. Claims 10 and 11 were directed to a vector comprising the nucleotide sequence of a nucleic acid molecule of claims 6-7, and to a host cell transformed with such a vector. Claim 12 was directed to a process for producing the protein of claims 1-3 culturing the claimed host cell under conditions which induce protein expression.

IX. The following documents are cited in this decision:

D1: Printouts of the files 1997-11-17-NM_shotgun.dbs and 1997-12-15-NM.dbs from the website ftp://ftp.sanger.ac.uk/pub/pathogens/old_data/ and cover pages of this website;

D12: PSORT analysis of SEQ ID NOs: 4 and 6, and of "Contig295" 300mer;

D12a: document D12 in a coloured version;

D27: WO 96/29412 (publication date: 26 September 1996);

D82: A.P. Pugsley, Microbiol. Reviews, March 1993, Vol. 57, No. 1, pages 50 to 108.

X. The submissions of appellant I, insofar as they are relevant to the present decision, may be summarized as follows:

Admission of the main request

Claim 1 was limited in scope by introduction of dependent claims and deletion of subject-matter present in previous requests. The subject-matter of the main request had been in the proceedings from the beginning.

Article 76(1) EPC

The objection concerning "*partial DNA sequences*" was not raised at first instance and was late filed. The nucleic acid sequences SEQ ID NOs 3, 5 were described as "*partial DNA sequences*" in the examples of the patent and in the parent application. A selection according to the "*two-lists principle*", as established in the case law, involved a selection from two independent lists, each of them including several discrete members. The fragment lengths disclosed in the parent application were not discrete members of a list, the higher values always comprised all other lower values. Rather, it was a disclosure of a series of minimum fragment lengths along a range, wherein each value was linked to the preceding range and to the maximum length which depended on each particular sequence and was one amino acid shorter than the full-length sequence. The selection of a value within that range did not single out new subject-matter but only narrowed the claimed subject-matter. The "*two-lists principle*" did not apply to the present case because there were not two independent lists. In the parent application, the series of fragment lengths were disclosed for each SEQ ID NO. As in the case underlying decision T 2134/10 of 14 November 2013, the relevant feature (fragment length) was disclosed as applying to each sequence and the series of fragment lengths was treated as a range, not as a list of discrete members. Contrary to the present case, the fragments referred to in the decision T 583/09 of 13 December 2011 were

linked to a specific function. The requirement for the presence of an epitope merely limited the claimed subject-matter to one of the two groups originally disclosed in the parent application.

Articles 83 and 57 EPC

The term "*epitope*" was understood in the field as a part of a protein, polypeptide or peptide (antigen) binding to an antibody. Uses for products containing an epitope were known in the art (antibody production/ detection). In 1998, a skilled person was able to screen a (poly)peptide sequence for antibody binding epitopes without undue burden. Although further work was required for elucidating which epitopes contributed to immuno-protection, the mere identification of epitopes was a routine task. None of the claims were directed to the prevention of a disease, a vaccine or a diagnostic composition. The objection for lack of industrial applicability was not an original ground of opposition, it had not been admitted into the opposition procedure, and it was not agreed to introduce it into the appeal procedure.

Content, public availability and admission of document D1

Document D1 as originally filed with the notice of opposition did not contain the sequence "Contig295". This document contained only shotgun sequences (NM_shotgun.dbs file) but not the assembled sequences derived therefrom (NM.dbs file). A copy of document D1 containing all sequences was filed only shortly before oral proceedings in appeal. The sequence data shown in document D12 was retrieved in 2010, thus after the claimed priority date.

Article 54 EPC

The evidence on file did not demonstrate that the sequence "Contig295" was available to the public. The allegation that the two files referred to in document D1 were available from the FTP server of the Sanger Institute did not demonstrate that document D1 disclosed a nucleic acid sequence encoding an open reading frame (ORF) of sequence SEQ ID NO 4 or 6. According to the case law (T 18/09 of 21 October 2009), even if a nucleic acid sequence encoding any of sequences SEQ ID NO 4, 6 was comprised in the genome sequence data of document D1, these sequences were not anticipated because document D1 contained only a long list of arbitrarily named, unannotated single-stranded nucleic acid sequences with no information on coding potential, identification of start/end codons, etc.

Article 56 EPC
Closest state of the art and technical problem

The closest state of the art document D27 disclosed a 22kDa meningococcal outer membrane protein (OMP) useful as a human vaccine antigen. Starting therefrom, the technical problem to be solved was the provision of a highly conserved, immunologically accessible antigen at the surface of *Neisseria meningitidis* organisms.

Is the technical problem solved?

It was plausible from the disclosure of the patent that the claimed subject-matter solved the problem. According to the case law, only plausibility was required, not certainty. The sequences SEQ ID NO 4, 6 were highly conserved between meningococcus A and B.

They had a degree of identity (greater than 90%) similar to the degree reported for the OMP disclosed in document D27. In the patent, the leader sequences of SEQ ID NO 4, 6 were underlined and the lipo-box motif was easily recognizable at the end of the underlined sequences. A serine residue after this motif was known to target the lipoprotein to the outer membrane. The PSORT algorithm (used in the art for predicting protein localization) identified the lipoproteins of sequences SEQ ID NO 4, 6 as located in the outer membrane. Although lipoproteins in the outer membrane could theoretically be inward (periplasm) or outward (extracellular milieu) facing, evidence on file showed that lipoproteins having the features of sequences SEQ ID NO 4, 6 were always located towards the extracellular milieu. There was no evidence on file pointing in a different direction. Moreover, all claimed fragments had a minimum length of 20 amino acids and comprised an epitope of the lipoproteins of sequences SEQ ID NO 4, 6. Thus, they were all immunologically related to the whole lipoprotein and, by having an epitope, they had to be recognized on the surface-exposed lipoprotein. This applied also for fragments derived from the leader sequences which had also a minimum length of 20 residues.

Obviousness

Starting from document D27 and trying to solve the technical problem, a skilled person would not have looked at the raw data of document D1. Analysis of whole genomes was not routine in 1998 but a cutting-edge technology. Document D1 provided partial sequence data from a project in progress, a huge amount of raw genome sequence data of low quality derived only from shotgun sequences. Even if a skilled person would have

looked at these raw data, nothing in document D1 would have led him/her to sequence "Contig295" (document D12/ D12a), let alone to sequences SEQ ID NO 4, 6. Only with hindsight knowledge of the invention it was possible to arrive at the four pages of document D1 (out of over 1000 pages and more than 12000 ORFs identified by the program ORFfinder) containing the sequence "Contig295". Moreover, even if a skilled person would have taken all identified ORF sequences and selected those having an appropriate length (about 300 residues), the sequence "Contig295" would have been retrieved together with many other sequences. However, the sequence "Contig295" was 26 residues longer than sequences SEQ ID NO 4, 6 because the program ORFfinder identified a wrong ATG start codon. The identification of a wrong start codon resulted in the lipo-box motif being hidden. The identification of this motif required to retrieve first the sequence "Contig295" by manual analysis and then to move the ATG start codon to the appropriate point. There was no reason for a skilled person to carry out a manual analysis of potential failures (ORF sequences not directly identified as OMP). Such a manual analysis would require a massive amount of work, resembling to the "pipeline approach", not considered to be realistic in the decision T 18/09 (*supra*). The absence of a Shine-Dalgarno (SD) sequence appropriately located 5' to the ATG start codon in the sequence "Contig295" was no reason for a skilled person to look for alternative start codons. It was known in the art that SD sequences were not always required for translation. Moreover, the first GTG start codon was only one alternative among other possible start codons downstream (second ATG, second GTG) and upstream (ATG with a better located SD sequence), of the ATG start codon identified in sequence "Contig295". Again, hindsight knowledge of the invention was required for manually selecting the first

downstream GTG start codon and identifying thereby the hidden lipo-box motif. Furthermore, the present case was not a case of "*structural non-obviousness*", i.e. where the claimed subject-matter derived its non-obviousness merely from its structural novelty. Rather, the claimed proteins were characterized by their structure (sequence) and by a functional feature (accessible to the immune system).

XI. The submissions of appellant II, insofar as they are relevant to the present decision, may be summarized as follows:

Admission of the main request

The main request was late filed and *prima facie* did not overcome the objections raised against previous requests on file. Thus, it should not be admitted into the appeal.

Article 76(1) EPC

On pages 1205 and 1206 of the parent application, the sequences SEQ ID NO 2535, 2537 (SEQ ID NO 3, 5 in the patent, respectively) were identified as "*partial DNA sequences*". This was in line with the definition of the term "*partial*" on page 71 and the information on page 52 of the parent application, wherein these sequences were stated not to be complete and to "*encode less than the full-length wild-type protein*". The deletion of these passages in the patent conveyed the information that they encoded complete ORFs, an information not directly derivable from the parent application.

Claim 1 was directed to a combination of sequences SEQ ID NO 4, 6 with a fragment length of "*20 or more*

consecutive amino acids", and a selection of those fragments containing an epitope of these sequences. In the parent application, sequences SEQ ID NO 4, 6 were disclosed as members of a list of several hundreds of sequences. Likewise, the fragment length indicated in claim 1 was disclosed in the parent application within a list of a plethora of lengths to be selected "*depending on the particular sequence*". Nothing in the parent application could be seen as a basis for singling out the combination of claim 1. Claim 1 required a further selection of those fragments having a functional feature (epitope; accessible to the immune system). All this was not in line with the case law established by the Boards of Appeal with regard to the selection of combinations from two or more lists (see, *inter alia*, T 583/09 and T 2134/10, *supra*). Indeed, this was the reason given in T 583/09 (*supra*) for not allowing a combination of a specific SEQ ID NO with a fragment length, independently whether or not the fragment was characterized by a functional feature. In the present case the question whether the list of SEQ ID NOs and the list of fragment lengths were independent was irrelevant because the combination present in claim 1 resulted from a selection that was neither disclosed nor derivable from the parent application.

Articles 83 and 57 EPC

Diagnostic assays were mentioned only in paragraph [0175] of the patent and, although immuno-diagnostic assays were cited, no particular method was described. The use of the claimed proteins and fragments as diagnostic compositions was not sufficiently disclosed. Moreover, claim 1 comprised fragments derived from leader sequences that did not reach the outer membrane.

The patent did not disclose any use for these fragments. The sole uses enabled by the patent were throw-away uses, none of them providing an immediate concrete benefit as required for acknowledging industrial applicability.

Content, public availability and admission of document D1

The deficiencies of document D1 filed with the notice of opposition were not noticed during the opposition procedure. When they were noticed during the appeal procedure, a copy of the complete document was filed together with further evidence to support that the files referred to therein were publicly available and that the assembled sequence data in the file 1997-12-15-NM.dbs included the sequence "Contig295". The deficiencies in original document D1 were not relevant because the address of the FTP server of the Sanger Institute and the link to the relevant databases were provided. Evidence therefor was provided in the patentee's reply to the notice of appeal, wherein document D1 was identified as a print-out of two files, the shotgun and the assembled file, and correct sequence information was used for providing document D12/D12a, which included sequence "Contig295". According to the case law, when evaluating the public availability of Internet disclosures, the standard "*balance of probability*" had to be applied and not a "*proof beyond reasonable doubt ("up to the hilt")*" (cf. "*Notice from the European Patent Office*", OJ EPO 2009, page 456).

Article 54 EPC

By using routine, software-driven analysis, a skilled person would have extracted the claimed sequences from the databases provided by the FTP server of the Sanger Institute, as shown by document D1. The sequences "Contig" resulting from such extraction, in particular the sequence "Contig295", demonstrated that the genome sequencing data found in the Sanger website anticipated the claimed sequences.

Article 56 EPC
Closest state of the art and the technical problem

Starting from the closest state of the art document D27, the problem underlying the patent was the provision of a further surface-exposed and conserved antigen from *Neisseria* useful for production of a broad spectrum *Neisserial* vaccine.

Is the technical problem solved?

There was no evidence in the patent that this problem was solved. Reformulation of the technical problem in less ambitious terms with no reference to a vaccine, such as for instance the provision of a conserved OMP from *Neisseria*, was not permissible, because it was not directly derivable from the patent and the parent application. Indeed, even this technical problem was not actually solved.

The degree of sequence identity between sequence SEQ ID NO 4 from *N. meningitidis* and the corresponding sequence from *N. gonorrhoeae* was only 61.4%, thus lower than the sequence identity with other putative proteins disclosed in the parent application. The information provided by the patent was based only on theoretical assumptions, not on experimental evidence. The criteria

for identifying OMPs, based only on the presence of a leader sequence, was not reliable because a plethora of putative proteins, with and without leader sequences, were disclosed as OMPs in the parent application, and the presence of noise sequences (i.e. OMPs not having the desired immunological properties) among them had been acknowledged. Neither the identification of a protein as an OMP nor the presence of a lipo-box motif followed by a serine indicated that the lipoprotein, once expressed and located in the outer membrane, would be surface-exposed and accessible to the immune system. As shown in Figure 18 of document D82, such lipoprotein could also be located inward, facing the periplasm and thus not being immunologically accessible. This information could only be provided by experimental evidence based on serological studies, not provided by the patent. According to the case law (*inter alia*, T 1329/04 of 28 June 2005), this deficiency could not be overcome by post-published evidence. It was not plausible from the disclosure of the patent that the claimed subject-matter solved the technical problem.

The patent did not demonstrate that any of the claimed fragments was located in the outer membrane and accessible to the immune system. Moreover, the claimed subject-matter included fragments derived from the leader sequences underlined in sequences SEQ ID NO 4, 6. A leader sequence was known to be cleaved before reaching the membrane and thus, none of these fragments could ever be surface-exposed and accessible to the immune system. Accordingly, the problem as formulated above had not been solved over the whole breadth of the claims.

Obviousness

Starting from document D27 a skilled person would mine the genome sequence data provided in document D1 and arrive at the claimed subject-matter in an obvious manner. Large-scale mining and analysis of whole genomes was an established routine methodology in the field and did not represent an undue burden in 1998. Although the data from document D1 was assembled from shotgun sequences of a project not yet finished, a skilled person was aware that it provided valuable information and that any positive result had to be checked by other standard methods, such as PCR. The analysis of the data provided by document D1 would have been done by applying standard software programs and algorithms, such as those cited in the patent itself. As a first step, a skilled person would have identified all ORFs (ORFfinder program), selected those having an appropriate length, and retrieved thereby the sequence "Contig295" (document D12/D12a). The fact that other ORF sequences would also have been retrieved was irrelevant because they all were obvious alternatives identified by an obvious method. The selection of one of these ORF sequences did not render this specific sequence inventive, the less so in absence of any advantage or surprising effect associated therewith. Acknowledgement of an inventive step based only on the fact that the arbitrarily selected ORF sequence was unique would be a sign that the erroneous principle of *"structural non-obviousness"* had been applied.

The skilled person would have further analyzed the identified long ORF sequences for sequences encoding putative OMPs, for instance by using the standard PSORT algorithm known to predict the cellular location of proteins. Having in mind the technical problem, the skilled person would have also scanned these ORF sequences and looked for further clues, such as the

presence of a lipo-box motif - used in the art for identifying outer membrane lipoproteins. The identification of the lipo-box motif within the sequence "Contig295" was straightforward, regardless of the actual start codon within this sequence. The presence of a serine residue after the lipo-box motif in the sequence "Contig295" would have further indicated to the skilled person that the putative lipoprotein was targeted to the outer membrane. Moreover, the presence of the lipo-box motif within the sequence "Contig295" provided the skilled person with a clear hint for identifying the actual start codon within this sequence. Whilst according to the length criteria both, the first and second ATG codon, would have been identified as possible start codons, the location of the lipo-box motif within the sequence "Contig295" would have identified the first GTG codon as the actual start codon. Even though 91% of the start codons known in the art were ATG codons, 8% were known to be GTG. There was no reason to disregard the first GTG codon in the sequence "Contig295". Applying the PSORT algorithm to the resulting lipoprotein would have identified this lipoprotein as located in the outer membrane. The presence of a SD sequence at a correct distance was a further indication corroborating the relevance of the first GTG start codon. Contrary thereto, a SD sequence was not located at an appropriate distance for the first ATG start codon and was lacking at all for the second ATG start codon.

XII. Appellant I (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request (claims 1 to 12) filed on 15 September 2016 during the oral proceedings before the board.

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

Reasons for the Decision

Admission of documents cited in appeal proceedings

1. Documents D12a and D82 were filed by appellant II with the statement of grounds of appeal. Document D12a is a coloured version of document D12, a document that has been in the procedure since the beginning of the opposition. Document D82, a review published in a scientific journal, provides general information on the secretory pathway in Gram-negative bacteria, such as *Neisseria*, and represents the common general knowledge of a skilled person working in the field of microbiology. No objections have been raised by appellant I as regards the admission of these two documents into the appeal nor has the board any objection on its own. Thus, both documents are admitted into the appeal proceedings (Article 12(4) RPBA).

Admission of the main request

2. The main request was filed by appellant I in reply to the board's communication pursuant to Article 15(1) RPBA. The subject-matter of this request was already present in previous requests filed by appellant I with the statement of grounds of appeal. The main request differs from previous requests by the deletion of subject-matter and by the introduction of subject-matter from dependent claims into the independent claims. It does not introduce new subject-matter, add complexity or raise issues surprising the board or the other party. Therefore, the board, in exercise of its

discretion, decides to admit the main request into the appeal procedure (Article 114(2) EPC, Article 13(1),(3) RPBA).

Main request
Article 123(2) EPC

3. The sole sequences from *Neisseria meningitidis* disclosed in the application as filed are the nucleic acid sequences SEQ ID NO 3, 5 and the encoded putative amino acid sequences SEQ ID NO 4, 6 (cf. pages 30 and 31 of the application as filed). Fragments of proteins with these sequences are disclosed on page 3, paragraph [0011] of the application as filed, with reference to fragments of, *inter alia*, 20 consecutive amino acids or more. Claim 14 of the application as filed is directed to such fragments of the amino acid sequence SEQ ID NO 4. The functional properties (antigenic, immunogenic, use as vaccine and diagnostic reagent) referred to in the description apply to these nucleic acid sequences and to the encoded putative proteins. Claims 1 to 39 as originally filed are directed to these specific nucleic acids and encoded putative proteins and refer to the structural and functional properties referred to above. Thus, the main request fulfils the requirements of Article 123(2) EPC.

Article 76(1) EPC

4. The nucleotide sequences SEQ ID NO 3, 5 are disclosed in the parent application as SEQ ID NO 2535, 2537, respectively. According to appellant II, these nucleotide sequences are identified in the parent application as partial DNA sequences encoding less than the full-length proteins, whilst they are disclosed in the patent as nucleotide sequences encoding full-length

proteins (cf. point XI *supra*). This objection has not been raised during the procedure before the first instance and it is, therefore, considered to be late filed. No reasons have been provided to explain why it has not been or could not have been raised earlier. Its admission into the present proceedings is subject to the board's discretion (Article 12(4) RPBA).

5. The board considers this objection to be *prima facie* not relevant. Although sequences SEQ ID NO 2535, 2537 disclosed on pages 1205 and 1206 of the parent application are characterized as "*partial DNA sequences*", the amino sequences SEQ ID NO 2536, 2538 (SEQ ID NO 4, 6, respectively, in the patent) encoded by these nucleotide sequences are disclosed on the same pages of the parent application and are not designated as being only "*partial*" amino acid sequences. What is more important, the first 19 residues at the N-terminus of the amino acid sequences SEQ ID NO 2536, 2538 are underlined and, in line with the disclosure on page 53 of the parent application, they are thus identified as potential leader sequences. In the board's view, the skilled person is thus made aware that amino acid sequences SEQ ID NO 2536, 2538 are amino acid sequences of full-length proteins.

6. With reference to the case law of the Boards of Appeal concerning a selection from two lists, appellant II has argued that there is no basis in the parent application for a combination of the sequences SEQ ID NO 4, 6 and a length of "*20 or more consecutive amino acids*" for fragments derived from these amino acid sequences and comprising an epitope (cf. point XI *supra*).

7. The case law referred to by appellant II is exclusively concerned with a combination of specific members from

two, fully independent lists. In these decisions the competent boards come to the conclusion that, in the absence of a clear pointer to such a combination, it is not possible to associate one member of one list with another member of the other list. Such combination is considered to create new subject-matter. However, the present situation, with a list with amino acid sequences and a list with fragment lengths, is different. The disclosure of an amino acid sequence, although inherently, makes available all possible fragments of this sequence, starting from the shortest peptide with only two consecutive residues up to a peptide having the full-length of the amino acid sequence minus one residue. As stated by appellant I (cf. point X *supra*), the longer fragments always comprise all shorter fragments, and the full-length sequence comprises all possible fragments. Indeed, the values of the fragment length disclosed in the parent application would be understood by a skilled person to apply to each and every member of the list of disclosed amino acid sequences (SEQ ID NOs), wherein the upper length of these fragments varies "*depending on the particular sequence*" (cf. page 6, first full paragraph of the parent application). The board does not see that the list of fragment lengths is actually independent from the list of amino acid sequences disclosed in the parent application. The combination of the value "*20 or more consecutive amino acids*" with the amino acid sequences SEQ ID NOs 4, 6, therefore only limits the orignal disclosure in the parent application. This limitation does not provide any new information and does not create new subject-matter.

8. Likewise, the requirement that the claimed fragments comprise an epitope does not create new subject-matter but also amounts to a limitation concerning the

preferred fragments disclosed in the parent application (cf. page 6, first full paragraph, last sentence of the parent application). Indeed, the term "*epitope*" is understood in the here relevant technical field to define the ability of a peptide, polypeptide or protein to raise antibodies. There is no requirement in the claims that these epitopes have to be protective, neutralizing or that they must have any other property. It is also known in the art that peptides of 8-10 residues may already comprise a linear epitope and that even shorter peptides, when associated with appropriate carrier proteins (haptens), may also have this ability. Therefore, fragments of "*20 or more consecutive amino acids from SEQ ID NO 4 and 6*" may certainly comprise an epitope and no additional selection is required which would result in the combination of subject-matter not disclosed in the parent application.

9. Contrary to the present case, the protein fragments claimed in the case underlying the decision T 583/09 were always defined by a functional feature ("*wherein the fragment has the ability to: i) bind to hyaluronic acid; or ii) bind to extracellular matrix*") (cf. T 583/09, *supra*, page 3, lines 1-4 and page 10, point 4 of the Reasons). In that case this board, in a different composition, considered that there was no disclosure in the application as filed linking fragments of each one of the disclosed lengths with said functional feature. In the present case, no such functional feature is required for the claimed fragments and, therefore, the situations underlying both cases are different.

10. If at all, the present case seems to have some similarity to the case underlying decision T 2134/10 (*supra*). In that case this board, in a different

composition, acknowledged a basis in the application as filed for a combination of a specific amino acid sequence with a particular fragment length, wherein the fragments also comprised an antigenic epitope. This combination was considered not to be a combination of features belonging to different lists. A similar decision was taken for a combination of a specific amino acid sequence with a particular degree of identity. The board considered such a combination to be only "*a limitation ... among all the degrees specified*" (cf. T 2134/10, *supra*, page 13, point 11 of the Reasons).

11. Thus, the main request fulfils the requirements of Article 76(1) EPC.

Article 57 EPC

12. No objection under this article was raised in the notice of opposition. The opposition division considered opponent's (appellant II's) arguments in this respect not to be *prima facie* relevant (cf. page 29 of the decision under appeal). In the statement of grounds of appeal, appellant II raised an objection under Article 57 EPC (cf. page 47, point 5 of appellant II's grounds of appeal). The board, in its communication pursuant to Article 15(1) RPBA, expressed its doubts whether this ground of opposition had actually been admitted by the opposition division into the procedure. In its communication, the board further noted appellant I's reference to decision G 10/91 (OJ EPO 1993, page 420) and its disapproval to the introduction of this ground of opposition at this late stage of the proceedings (cf. page 14, point 32 of the board's communication).

13. None of the parties put forward any further arguments or comments on this issue, neither in writing nor at the oral proceedings. In view thereof, the board considers Article 57 EPC not to be a ground of opposition.

Article 83 EPC

14. Contrary to previous claim requests, the main request does not contain any claim directed to a vaccine or a diagnostic composition. There is no reference to a medicament or pharmaceutical composition, nor is there any requirement that the claimed subject-matter has to be effective for the prevention of a disease caused by *Neisseria*. Whilst the fragments defined in claim 1 are required to have an epitope, this epitope is not further qualified, i.e. it is not required to be protective, neutralizing or to have any other property. In view of the commonly accepted definition of epitope (cf. point 8 *supra*), the disclosure of the specific amino acid sequences SEQ ID NO 4, 6 - and fragments of 20 or more consecutive amino acids therefrom - provides sufficient information for a skilled person to arrive at the claimed subject-matter without undue burden. Thus, the requirements of Article 83 EPC are fulfilled.

Article 87 EPC

15. It has not been disputed that the nucleic acid sequences SEQ ID NO 3, 5 and the encoded putative amino acid sequences SEQ ID NO 4, 6 were first disclosed in the priority document US 103796 P filed on 9 October 1998 (cf. page 12 of appellant II's grounds of appeal). As the main request is only entitled to this priority date, any public disclosure before this date is prior art under Article 54(2) EPC.

Contents, public availability and admission of document D1

16. According to the list of documents presented in the notice of opposition, document D1, cited under Articles 54 and 56 EPC, is a printout "*of the files 1997-11-17-NM_shotgun.dbs and 1997-12-15-NM.dbs from the website ftp://ftp.sanger.ac.uk/pub/pathogens/nm/old_data/ along with the cover pages of this website*" (cf. page 3, point IV of the notice of opposition). In the first instance proceedings, the patent proprietor questioned the availability of document D1 before the priority date of the patent. Relying on the evidence on file, the opposition division decided that the FTP server of the Sanger Institute was available to the skilled person and that "*the sequence Contig295 was present in the file 1997-12-15-NM.dbs* [accessible through said server] *before the relevant date of the opposed patent*" (cf. page 19, points 1 and 2 in the decision under appeal).

17. In reply to the board's communication pursuant to Article 15(1) RPBA and at the oral proceedings before the board, appellant I raised a new issue concerning document D1. According to appellant I, document D1 as originally filed with the notice of opposition did only contain the print out of file 1997-11-17-NM_shotgun.dbs but not of file 1997-12-15-NM.dbs. Since sequence "Contig295", comprising the complementary sequence of SEQ ID NO 5, results from the assemblage of shotgun sequences of the NM_shotgun.dbs file and is only present in the NM.dbs file, the late filing of a complete copy of document D1 including a print out of the NM.dbs file should not be allowed and the document should not be admitted into the appeal procedure (cf. point X *supra*).

18. The notice of opposition contains information concerning the disclosure provided by document D1 with reference to the FTP server of the Sanger Institute, the name of the two files and the general content thereof, in particular the presence of sequence "Contig295" and the nucleic acid positions defining the complementary sequence of SEQ ID NO 5 (cf. page 8, point IX of the notice of opposition). Indeed, in reply thereto, the patent proprietor cited document D1 and, whilst arguing that the relevant sequences were not available to the public, it explicitly referred to the presence of the two files (cf. page 2, point 2 of the patent proprietor's letter dated 8 May 2009). Based on this information, the patent proprietor downloaded the file from the FTP server of the Sanger Institute - even though, admittedly, after the relevant priority date - and retrieved sequence "Contig295". In consequence, it provided document D12, a "*PSORT analysis of SEQ ID NOs: 4 and 6, and of "Contig295" 300 mer*" (cf. page 2, point 1.8 and page 5, point 3.3 of the patent proprietor's letter dated 8 May 2009). During the entire opposition procedure, neither the patent proprietor nor the opposition division noted any deficiency with regard to document D1, and certainly not the deficiency pointed out by appellant I in the appeal procedure. This is all the more surprising as sequence "Contig295" - comprised in the file 1997-12-15-NM.dbs - was indeed the most important evidence for all objections raised by opponent/appellant II under Articles 54 and 56 EPC and also for all arguments put forward by the patent proprietor/appellant I against these objections.

19. In the light thereof, the board considers appellant I's objection regarding the deficiencies in document D1 as late filed and *prima facie* not relevant. In the board's

view, the information in document D1 as originally provided in the notice of opposition without doubt allowed to retrieve the relevant sequence data which, although not actually present in the print out filed as document D1, was critical for the assessment of the objections raised under Articles 54 and 56 EPC. Moreover, in view of the arguments put forward by the parties and the evidence on file, the board, in line with the criteria established by the Boards of Appeal for Internet citations as also set out in the "*Notice from the European Patent Office*" referred to by appellant II (cf. OJ EPO 2009, page 456), does not see any reason to deviate from the decision of the opposition division as regards the public availability of the two sequence data files cited in document D1 and of the sequence "Contig295" comprised in the file 1997-12-15-NM.dbs. The disclosure, content and complete information, provided by document D1 are considered to be relevant prior art under Article 54(2) EPC.

Article 54 EPC

20. As stated in point 17 *supra*, document D1 provides the print outs of the files 1997-11-17-NM_shotgun.dbs and 1997-12-15-NM.dbs, accessible through the FTP server of the Sanger Institute. Whilst the NM_shotgun.dbs file contains nucleic acid sequence data from *Neisseria meningitis* serogroup A obtained by shotgun sequencing, the NM.dbs file contains the assembled nucleic acid sequence resulting from these shotgun sequence data. However, in none of these files, the nucleic acid sequences or subsequences thereof are indexed or annotated, they are fully uncharacterized without any identification of possible structural features, such as transcription start and stop codons, SD sequences, etc. Although it is not disputed that the nucleic acid

sequence data of the NM_shotgun.dbs file contains the sequence "Contig295", which itself comprises the complementary nucleic acid sequence of SEQ ID NO 5, neither of these two sequences are identified as such in this file. They are disclosed only as an integral part of the complete nucleic acid sequence data provided by this file.

21. In line with the established case law of the Boards of Appeal concerning this type of disclosures (cf. *inter alia*, T 301/87, OJ EPO 1990, page 335, points 5.7 and 6 of the Reasons; T 18/09 of 21 October 2009, points 10-15 of the Reasons; T 1451/09 of 4 February 2011, points 4-8 of the Reasons), the board does not consider document D1 to disclose the sequence SEQ ID NO 5 as an isolated nucleic acid sequence made available as such to the public. There is thus no reason for the board to deviate from the findings of the opposition division as regards this issue (cf. pages 19 and 20, points 3 and 4 of the decision under appeal). The main request fulfils the requirements of Article 54 EPC.

Article 56 EPC
Closest state of the art and the technical problem to be solved

22. The opposition division identified document D27 as the closest state of the art (cf. page 21, third paragraph of the decision under appeal). Document D27 refers to the importance of providing a "*highly conserved, immunologically accessible antigen at the surface of Neisseria meningitidis organisms*" (cf. *inter alia*, page 4, lines 29-34, page 5, lines 24-27). This document is cited in paragraph [0007] of the patent which explicitly refers to "*the provision of further sequences* [of] *secreted or surface-exposed proteins that are presumed targets for the immune system and*

which are not antigenically variable" as the technical problem underlying the invention. Although in the patent emphasis is laid in the production of vaccines against meningococcus, the disclosure of the patent is not limited thereto but contemplates other applications as well (cf. *inter alia*, paragraph [0027], last sentence, of the patent). The board agrees with the identification of document D27 as the closest state of the art and, starting therefrom, with the objective technical problem formulated in the above terms.

Is the technical problem solved?

23. The first 19 residues at the N-terminus of the putative amino acid sequences SEQ ID NO 4, 6 (encoded by the nucleic acid sequences SEQ ID NO 3, 5, respectively) are underlined in the patent (see paragraphs [243] and [245]) and are thereby identified as leader sequences (cf. page 24, paragraph [0198] of the patent). The three last residues within these leader sequences are followed by a cysteine residue and the resulting subsequence ("*LTAC*") can be directly identified by a skilled person as a well-known lipo-box motif. This lipo-box motif is immediately followed by a serine residue which is known in the field to be associated with a localization and/or transport of the lipoprotein to the outer membrane of the organism.

24. Whilst the localization of an OMP within the outer membrane may be facing outwards (extracellular space) or inwards (periplasm) the cell, only the former may be visible or accessible to the immune system and has thus the ability to raise an immune response. Appellant II argues, with reference to Figure 18 of document D82, that the presence of a leader sequence and a lipo-box motif followed by a serine residue is not enough for a

skilled person to be completely certain of the actual location of the lipoprotein within the outer membrane and thus of its ability to raise an immune response (cf. point XI *supra*). However, the presence of all the specific structural features listed in point 23 *supra*, are a reliable sign for a skilled person to identify this lipoprotein as a plausible candidate to solve the posed technical problem by having the desired properties, particularly in absence of any evidence to the contrary. With the information provided by the patent, there was no reason for a skilled person to doubt the assumptions made in the patent, sometimes referred to as *"educated guesses"* in the case law of the Boards of Appeal (cf. T 898/05 of 7 July 2006, points 21-27 of the Reasons), and which may be confirmed only later by post-published evidence (cf. T 1329/04, *supra*, point 12 of the Reasons). In addition, it might be questionable whether a 61.4% degree of identity between the amino acid sequences SEQ ID NO 4, 6 from *N. meningitidis* and *N. gonorrhoeae*, respectively, are considered to be highly conserved, but there is no doubt that 95.6% identity between the amino acid sequences SEQ ID NO 4, 6 from different strains of *N. meningitidis* fulfil this requirement.

25. Moreover, the fact that not all putative amino acid sequences identified as OMPs in the parent application are actually OMPs is not relevant, because not all sequences identified in the parent application have the above mentioned specific structural features characterizing the amino acid sequences SEQ ID NO 4, 6. It is the presence of all these specific structural features that render the assumptions made in the patent as regards sequences SEQ ID NO 4, 6 fully plausible.

26. With reference to the claimed fragments, appellant II has also questioned whether the technical problem is solved over the whole scope of the claims (cf. point XI *supra*). The board notes that the claimed fragments must all have a length of "*20 or more consecutive amino acids*" and comprise "*an epitope from SEQ ID NO: 4 or 6*" (cf. point VIII *supra*). These fragments are thus all directly derivable from the specific sequences SEQ ID NO 4, 6 which solve the technical problem, and, in line with the definition of the term *"epitope"*, they are all able to raise antibodies (cf. point 8 *supra*). Not all epitopes will necessarily always be surface-exposed and immunologically accessible when present in the wild-type lipoprotein located in the outer membrane of *Neisseria*. However, they may well be accessible under other specific or alternative conditions, in which these epitopes and related antibodies may find relevant applications, such as those disclosed in the patent itself (cf. *inter alia*, paragraph [0027] of the patent). Indeed, this is also the case for fragments derived from the leader sequences of SEQ ID NO 4, 6 for which the feature of a length of "*20 or more consecutive amino acids*" is enough to differentiate them from other fragments derived from known bacterial leader sequences described in the prior art. The fact that the leader sequence is processed and cleaved along transportation of the wild-type lipoprotein to the outer membrane does not exclude that, under different conditions, the epitopes within these sequences may be accessible to, and capable of binding, related antibodies and have also relevant applications (such as in the recombinant production of full-length lipoproteins; see claim 12).

27. Thus, the technical problem is solved by the claimed subject-matter over the whole scope of the claims.

Obviousness

28. Starting from document D27 with the motivation to look for alternative surface-exposed proteins, the skilled person would certainly have looked at the sequence data provided by document D1 and, in particular by the NM.dbs file containing the assembled nucleic acid sequences resulting from the shotgun sequencing data of the NM_shotgun.dbs file (cf. point 20 *supra*). Contrary to appellant I (cf. point X *supra*), the board is of the opinion that the quality of the sequence data would not have refrained the skilled person, defined in the field of biotechnology as a team of scientists (cf. "Case Law of the Boards of Appeal", 8th edition 2016, I.D.8.1.3, page 191), from using these data. The possibility of retrieving a positive result would have outweighed the risk of high effort and high expenditure of time referred to by appellant I. The skilled person, being aware of the nature and deficiencies of these data, would have checked and confirmed any possible relevant result by standard methods known in the art.

29. At the priority date of the patent, it was normal practice in the art to analyze this type of genome sequence data using standard software programs and algorithms available from different sources, including the providers of the data of document D1, the FTP server of the Sanger Institute. Even nowadays, the sheer size and amount of sequence information provided by genome sequencing studies, such as the project behind the data disclosed in document D1, precludes a straightforward manual analysis and requires, as an initial step, to analyze these sequencing data using such programs and algorithms (cf. paragraphs [0194] to [0198] of the patent). As a first step in this

analysis, it is also normal practice to identify possible translational start codons and thereby retrieve encoded putative ORFs, using standard programs such as the program ORFfinder from the National Center for Biotechnology Information (NCBI) (cf. paragraph [0197] of the patent).

30. The complementary sequence to the nucleic acid sequence SEQ ID NO 5 is found within a region of the sequence data of the NM.dbs file in which several possible start codons and encoded putative ORFs are identified. Document D12/D12a shows a schematic drawing of this region with encoded putative ORFs and a list of the positions of possible start and stop codons. Document D12/D12a also shows "Contig295", a nucleic acid sequence with start (ATG) and stop (TAA) codons at positions 10544 and 9642, respectively, encoding the fifth longest putative ORF (300 residues). This information, together with information on other regions and sequences, is retrieved when applying the program ORFfinder to the sequence data of document D1.

31. Although the length of encoded putative ORFs may be a standard criterion for discarding non-significant sequences, the considerations made for defining this criterion (such as average length of (lipo)proteins in a specific organism, average length of secreted and/or surface-exposed (lipo)proteins in general and/or in said organism, etc.) are to a certain extent subjective and open to interpretation of the skilled person. Only with hindsight, a skilled person would specifically select the sequence "Contig295" for a further detailed manual analysis, from all other possible encoded putative ORF sequences fulfilling the length criterion. This is all the more so in the absence of a straightforward identification of this specific

sequence as a sequence encoding an outer membrane, surface-exposed protein, for instance by application of the PSORT algorithm, an algorithm commonly used at the relevant date for prediction of protein localization sites (cf. paragraph [0198] of the patent).

32. In fact, for arriving at a subsequence within the sequence "Contig295" encoding a putative ORF with the specific amino acid sequence SEQ ID NO 6, it would have been necessary for a skilled person to look for alternative start codons different from the most frequently used ATG start codon (about 91% of all bacterial genes). Such GTG start codon has been found between a second ATG start codon and a second GTG start codon within the sequence "Contig295". Appellant II argues (cf. point XI *supra*) that the GTG start codon is not that unusual and is found in about 8% of the bacterial genes and that other codons such as the TTG and ATT codons are also used in bacterial genes, even though more rarely. The board is not impressed by this argument but considers that the interrogation of the sequence "Contig295" for other alternative start codons, and in particular for ones less frequently used, only seems obvious with a certain amount of hindsight.

33. Appellant II has argued that the identification of a SD sequence at an appropriate distance upstream from the first GTG start codon as well as the presence of a lipo-box motif downstream from this start codon are possible hints which would have led the skilled person into the right direction (cf. point XI *supra*). However, although the presence of a SD sequence is an important - if not the main - determinant for translation of bacterial genes, alternative mechanisms for initiation of translation without a SD sequence as well as the

presence of putative (non-functional, pseudo) SD sequences far downstream in the coding sequences of bacterial genes were also known in the art at the priority date. Moreover, the lipo-box motif within the sequence "Contig295" is not found immediately after the GTG start codon but at the end of the 19 amino acid residues long leader sequence (at positions 17-20 of sequence SEQ ID NO 6). A skilled person, in order to take into account all these features, would have to engage in an in-depth and fully detailed analysis of the sequence "Contig295". Such an analysis would not be routinely started by a skilled person without hindsight of the present invention.

34. Therefore, taking into account all the above considerations, the main 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 on the basis of the new main request (claims 1 to 12) filed during the oral proceedings and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated