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Datasheet for the decision of 8 May 2012

Case Number: T 1254/07 - 3.3.04

Application Number: 95933880.7

Publication Number: 783520

IPC: C07K 14/31, C07K 16/12, A61K 39/085, A61K 39/40

Language of the proceedings: EN

Title of invention:
Broadly reactive opsonic antibodies reactive with common staphylococcal antigens

Patentee:
HENRY M. JACKSON FOUNDATION FOR THE ADVANCEMENT OF MILITARY MEDICINE

Opponent:
Inhibitex Inc

Headword:
Antibodies/JACKSON FOUNDATION

Relevant legal provisions:
EPC Art. 56

Keyword:
"All requests - inventive step (no)"

Decisions cited:
T 0188/09

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1254/07 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 8 May 2012

Appellant: (Patent Proprietor)	HENRY M. JACKSON FOUNDATION FOR THE ADVANCEMENT OF MILITARY MEDICINE 1401 Rockville Pike Suite 600 Rockville, MD 20852 (US)
Representative:	Sheard, Andrew Gregory Patent Attorney P.O. Box 521 Berkhamsted, Herts. HP4 1YP (GB)
Respondent: (Opponent)	Inhibitex Inc 8995 Westside Parkway Alpharetta, Georgia 30004 (US)
Representative:	Armitage, Ian Mewburn Ellis LLP 33 Gutter Lane London EC2V 8AS (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 25 May 2007 revoking European patent No. 783520 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: B. Claes
R. Gramaglia

Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division to revoke European patent No. 0 783 520 with the title "*Broadly reactive opsonic antibodies reactive with common staphylococcal antigens*" which was granted on the basis of European patent application 95933880.7, published as WO 96/09321.

II. Claim 1 of the main request before the opposition division filed on 4 March 2005 read:

"1. An isolated surface protein of a coagulase-negative staphylococcus, wherein the protein induces antibodies that are **opsonic and** broadly reactive against staphylococci." (emphasis added by the board)

Claim 1 of the first auxiliary request before the opposition division filed on 8 March 2007 read:

"1. An isolated surface protein of a coagulase-negative staphylococcus, wherein the protein **binds to opsonic antibodies against Staphylococcus epidermidis and** induces antibodies that are broadly reactive against staphylococci." (emphasis added by the board)

Claim 1 of the second auxiliary request before the opposition division filed on 8 March 2007, which claim was identical to claim 1 as granted, read:

"1. An isolated surface protein of a coagulase-negative staphylococcus, wherein the protein induces antibodies that are broadly reactive against staphylococci."

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

(D1): WO 93/19373

(D21): Ichiman *et al.* (1987), J. Appl. Bacteriol., Vol. 63, pages 165-169.

(D32): Ichiman & Yoshida (1981), J. Appl. Bacteriol., Vol. 51, pages 229-241.

(D33): Ichiman (1984), J. Appl. Bacteriol., Vol. 56, pages 311-316.

(D51): Baldassari *et al.* (1996), Infect. Immun., Vol. 64, pages 3410-3415.

IV. The opposition division decided that the main request met the requirements of Article 123(2) EPC, that all the requests complied with the requirements of Articles 83 and 100(b) EPC, but that the claimed subject-matter of all the requests before it lacked inventive step (Article 56 EPC).

V. With the statement of the grounds of appeal, the appellant filed a **third auxiliary request** wherein claim 1 was identical to claim 1 of the main request filed on 4 March 2005.

VI. The board summoned the parties to oral proceedings to be held on 8 May 2012. Subsequently, the respondent announced it would not attend the oral proceedings and the appellant withdrew its request for oral proceedings.

VII. Oral proceedings were duly held in the absence of the parties.

VIII. The appellant's arguments as far as they are relevant for the present decision can be summarised as follows:

– The invention was based on the insight that antigens from coagulase-negative staphylococci, in particularly from *Staphylococcus epidermidis*, which were able to induce antibodies that were broadly reactive and opsonic, were, surprisingly, surface proteins. Previous work, for example the serotyping scheme of Ichiman and Yoshida referred to in paragraphs [0136] to [0138] of the patent and equally disclosed in documents (D21), (D32) and (D33), had rather yielded antibodies to the polysaccharide capsule of staphylococci. It was not obvious to the skilled person from document (Dl), taken either alone or in combination with any other document, that protein antigens could be responsible for the effect. In fact, it would not be expected that protein antigens were responsible.

– The impugned decision was based on an *ex post facto* analysis, which impermissibly made use of knowledge of the invention as disclosed in the patent in suit. None of the inferences in the decision were contained in document (D1). Document (D1) disclosed that the antigen was a mixture of components and did not suggest that proteins could give rise to antibodies that were broadly reactive and opsonic. The decision did not exclude the possibility that there were antigens other than protein antigens that were responsible, such as

for instance peptidoglycans or polysaccharides. Although the serotyping scheme of Ichiman and Yoshida (see above) was indeed based on serospecific polysaccharide antigens, there were also polysaccharide antigens which were common across serotypes such as for example the polysaccharide predominantly containing N-acetyl glucosamine that was a major component of the extracellular slime produced by *S. epidermidis* as disclosed in post-published document (D51) (see page 3412, right column, first complete paragraph).

– It was more likely for a bacterial antigen that gave rise to broadly reactive and opsonic antibodies to be something other than a protein because the molecular selective mutational pressure upon exposure of bacteria to the human immune system was more likely to result in more poorly conserved surface proteins among staphylococci as compared to surface polysaccharides or peptidoglycans.

IX. The respondent's arguments as far as they are relevant for the present decision can be summarised as follows:

– Claim 1 of all requests lacked inventive step (Article 56 EPC) based on the disclosure in document (D1).

– Antisera raised against strain Hay, whether whole cells or TCA extract immunisation, exhibited the opsonic activity across the three *Streptococcus epidermidis* serotypes I, II and III, as set out in the examples in both document (D1) and the patent

in suit. However, both whole cells and TCA extracts contained cell wall polysaccharides which were known to be highly immunogenic and indeed to give rise to the serotyping observed by the Ichiman and Yoshida and referred to in paragraphs [0136] to [0138] of the patent. Therefore, the antisera would certainly contain opsonising antibodies induced by polysaccharide antigens.

– The conclusion in the patent, with reference to the Ichiman and Yoshida research papers referred to in paragraphs [0136] to [0138] of the patent, that the capsular material from the *S. epidermidis* serotypes only induced "homologous" protective antibodies, i.e. they did not protect across the serotypes, but only to the serotype that had raised the antibodies and that therefore the observed cross-serotype opsonic antibody activity had to be due to a surface protein, was not tenable. Document (D33) for instance disclosed numerous examples where the reaction was "polyvalent", i.e. across two, or even all three, serotypes. Therefore, the very basis for the assumption that the opsonising and cross-protective antibodies must derive from a surface protein, rather than a surface polysaccharide, was flawed.

– As a consequence it was necessary that the patent in suit demonstrated that the isolated surface protein which was claimed could induce antibodies that were opsonic and were broadly reactive, which the patent failed to to. Therefore it had not been demonstrated that the problem had been solved

(irrespective of whether it would be obvious to solve it) and hence the claimed subject matter lacked inventive step.

X. The appellant (patentee) requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of one of the following claim requests:
a. The main request filed on 4 March 2005;
b. The first auxiliary request filed on 8 March 2007;
c. The second auxiliary request filed on 8 March 2007;
d. The third auxiliary request filed with the Statement of Grounds of Appeal.

The respondent (opponent) requested in writing that the appeal be dismissed.

Reasons for the Decision

Main request - claim 1 - inventive step (Article 56 EPC)

1. The pivotal point to be decided in this appeal is whether or not the subject-matter of claim 1 of the main request involves an inventive step (Article 56 EPC).

Closest prior art

2. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with the established

case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.

3. The opposition division considered for assessment of inventive step the disclosure in document (D1) to represent the closest prior art. The appellant has not contested this and also the board sees no reason to disagree.

4. International patent application document (D1) is from the same inventor as the patent in suit and their disclosures largely overlap. It relates to immunoglobulin and isolated antigen which can be used to prevent, diagnose and treat *Staphylococcus* infections (see page 1 "Field of the Invention", lines 1 to 4). The document, in particular and as acknowledged by the appellant, discloses that broadly reactive and opsonic antibodies can be generated from coagulase-negative staphylococci such as *Staphylocuccus epidermidis*, in particular *S. epidermidis* Hay (ATCC 55133).

5. All thirteen examples of document (D1) are in essence identical to examples 1 to 10 and 12 to 14 of the patent in suit. In particular, example 5 in document (D1) concludes that "[t]*hus, it can be concluded that anti-staphylococcal antibodies were directed against key staphylococcal antigens which could provide both specific protection against S. epidermidis and broad*

protection against other Staphylococcus serotypes and species." (see page 38, lines 5 to 9). It is continued on page 38 of document (D1), in example 6, that "[a]*s shown in Figures 5 and 6, both the TCA treated and whole cell preparations induced an antibody response with very high opsonic activity against all three serotypes.* [...] *These data show that antibodies to S. epidermidis capsular antigens are important for immunity and that one or more antigens may be antigenically similar between different serotypes.*" (see lines 18 to 28).

6. Document (D1) discloses further as a particular embodiment of the invention "isolated" antigen (see page 24, line 11, ff.) being preferably a "*single purified antigen or a small number of purified antigens which may be proteins, polysaccharides, glycoproteins, or synthetic molecules. Methods of macromolecular purification include filtration, fractionation, precipitation, chromatography, affinity chromatography, HPLC, FPLC, electrophoresis, and any other suitable separation technique. Methods for the purification of proteins are well-known in the art*." (see page 24, lines 20 to 28). The document subsequently continues that preferably TCA extracts of whole *S. epidermidis* Hay (ATCC 55133) could be used and makes reference to a number of protein purification methods known in the art (see page 24, line 29 to page 30, line 5).

The problem to be solved

7. The patent in suit adds to the technical disclosure of document (D1) its relevant example 15 which "*determines the total protein composition of the various serotypes*

of S. epidermidis and identifies proteins reactive with opsonic rabbit antisera" (see paragraph [0135] of the patent in suit). The opsonic rabbit antisera referred to were the antisera also obtained and disclosed in document (D1). By means of two dimensional electrophoresis followed by either silver staining or electroblotting (Western transfer), i.e. standard techniques available to the skilled person at the relevant date of the patent in suit (see paragraphs [0142] to [0145] of the patent in suit) the inventor was able to identify in whole bacterial cell TCA extracts a protein having a molecular weight of about 45-50,000 daltons, as identified by a spot in Figure 13 of the patent, which was found to react strongly to the antisera (see paragraph [0146] of the patent in suit). On the basis of the fact that the reacting protein could be extracted from whole cell bacteria by TCA, it was concluded that it constituted "*most likely*" a *S. epidermidis* surface protein important for phagocytosis and immunity (see paragraph [0147] of the patent in suit, in particular line 53).

8. The subject-matter of claim 1 of the main request concerns an isolated surface protein of a coagulase-negative staphylococcus which induces antibodies that are opsonic and broadly reactive against staphylococci and is the result of the inventor's inferences from the experimental data provided in example 15 of the patent in suit (see point 7, above), i.e. a generalisation of the protein as defined by the indicated spot in Figure 13 of the patent.

9. Starting from the closest prior art disclosed in document (D1), the technical contribution of the

claimed invention therefore addresses the objective technical problem of identifying, or actually providing, a **concrete** entity reactive with the antisera containing the broadly reactive and opsonic antibody generated from coagulase-negative staphylococci such as *Staphylococcus epidermidis*.

10. It is established case law that the objective technical problem, i.e. the objective technical problem which is taken into account for the problem and solution approach, is a problem for which it is at least plausible that it is solved by the invention. The board is in fact satisfied that the disclosure of example 15 would make it indeed plausible that the claimed subject-matter solves the formulated problem.

11. It has however been argued at length by the respondent that the subject-matter of claim 1 does *not* in fact solve the above objective technical problem, without however arguing that the problem was wrongly formulated. For this reason, the respondent asserts that the claimed invention lacked inventive step. However, the board notes that in the present case the consequence of a finding that the claimed subject-matter in fact does not plausibly solve the formulated technical problem would be a reformulation of the problem to one which is less ambitious and then plausibly solved (see e.g. decision T 188/09 of 21 July 2011, points 18 to 22).

12. In the present case, the respondent's argument would lead to the reformulated objective technical problem of identifying, or actually providing, a **putative** entity reactive with the antisera containing the broadly reactive and opsonic antibody generated from coagulase-

negative staphylococci such as *Staphylococcus epidermidis*.

13. The board considers however that its conclusion as to obviousness set out below applies to both the specific and the general formulation of the objective technical problem. Consequently, an in-depth analysis of the respondent's argumentation as to why the specific problem is not solved would be of no relevance for the outcome of the present case.

Obviousness

14. The board acknowledges that document (D1), representing the closest prior art, is not conclusive as to the chemical nature of the antigen to be identified. Rather it considers in example 6 that it concerns "*epidermidis capsular antigens*" and that "*one or more antigens may be antigenically similar between different serotypes*" (see point 5, above). On the other hand the document discloses that the antigen "*may be comprised of proteins, polysaccharides, lipids, glycoproteins, or any other suitably antigenic material.* [...] *Most preferably, isolated antigen contains proteins and glycoproteins*." (see page 24, lines 14 to 20). These passages in document (D1) therefore unambiguously draw the skilled person's attention to the possibility that the antigenic entity of interest is a protein.

15. Document (D1) itself discloses a variety of isolation methods for identifying the antigen for the antibodies described in document (D1) (see point 7, above). The board notes that in this respect the patent does not describe any particular difficulties that had been

encountered applying the technology of the prior art to the disclosed process for identification of the claimed subject matter and that the appellant has also not argued along this line. In fact, the methods disclosed in example 15 of the patent in suit, i.e. two dimensional electrophoresis followed by either silver staining or electroblotting (Western transfer) were routine technologies at the relevant date of the patent (see point 6, above).

16. Accordingly, in the board's judgement, the disclosure in document (D1) itself suggests to the skilled person the route to take by means of routine experimentation known in the art to identify the antigenic entity of the invention and also renders it obvious to the skilled person to consider the possibility of identifying a surface protein as now claimed, i.e. to conduct identification experimentation for the antigen being a protein.

17. The above deals with the main arguments of the appellant. It has however also been argued, based on the consideration that the molecular selective mutational pressure upon exposure of bacteria to the human immune system was more likely to result in more poorly conserved surface proteins among staphylococci as compared to surface polysaccharides or peptidoglycans, that "*it would actually be more likely for a bacterial antigen that gave rise to broadly reactive and opsonic antibodies to be something other than a protein*" (see section VIII, above). The board is satisfied however that the skilled person having knowledge of the disclosure in document (D1) would not view the appellant's considerations, although

conceivable, as sufficiently persuasive as to abandon any identification experimentation for proteins when endeavouring to find a solution for the technical problem to be solved.

18. Accordingly, the disclosure in document (D1) combined with routine experimentation renders the subject-matter of claim 1 obvious to the skilled person. Accordingly, it lacks inventive step (Article 56 EPC).

19. The board notes that both parties have argued that the opposition division in the substantiation of the decision relating to Article 56 EPC had erred in reasoning. In view of the above considerations, findings and outcome however, the board considers it not necessary to review the correctness of the impugned decision in this respect.

Auxiliary requests - claim 1 - inventive step (Article 56 EPC)

20. The appellant has not argued why the subject-matter of claim 1 of each of the auxiliary requests would provide extra technical features beyond those of the subject-matter of claim 1 of the main request so as to support inventive step. The board considers that the conclusion in point 16, above, applies *mutatis mutandis* to the subject-matter of claim 1 of each of the three auxiliary requests. Accordingly the subject-matter of these claims lacks inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar | The Chairman

B. Atienza Vivancos | C. Rennie-Smith