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Datasheet for the decision of 1 March 2016

Case Number: T 1118/12 - 3.3.04

Application Number: 02806591.0

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Title of invention:
Glycoconjugate vaccines for use in immune-compromised populations

Applicant:
GlaxoSmithKline Biologicals SA

Headword:
Immune-compromised patient/GLAXOSMITHKLINE

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - (yes)
Inventive step - (no)

Decisions cited:
G 0002/88, T 0019/86, T 0893/90

Catchword:

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Case Number: T 1118/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 1 March 2016

Appellant: (Applicant)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Johnston, Caroline Louise GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 14 December 2011 refusing European patent application No. 02806591.0 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	M. Blasi

Summary of Facts and Submissions

I. The appeal of the applicant ("appellant") lies against the decision of the examining division refusing European patent application No. 02806591.0 entitled "Glycoconjugate vaccines for use in immune-compromised populations".

II. The following documents are cited in the present decision:

D1 Welch P.G. et al., J. Am. Soc. Nephrol. (1996), vol. 7, pages 247-253

D4 Fattom A. et al., American Chemical Society, Abstracts of Papers (at the National Meeting), April 2001, vol. 221, abstract BIOT45

D9 Johnson J. et al., Abstracts of the general meeting of the American Society for microbiology (1997), vol. 97, page 43, abstract B-87

D11 Kluytmans J. et al., Clinical Microbiology Reviews (1997), vol. 10, pages 505-520

D15 Creech C.B., 2nd, et al., Vaccine (2010), vol 28, pages 256-260

III. The examining division held that the vaccine used in document D4 was the same as the vaccine used in the application and that the feature "wherein said immune-compromised individual has nasal carriage of *S. aureus*" did not render the subject-matter of claim 1 novel over that disclosed in document D4. In particular, it held (see reasons, point 21) that "(...) it appears that at

least one third of the hemodialysis patients vaccinated with StaphVAX in the prior art carried S. aureus in their nasal cavity. The group of immune-compromised patients treated with StaphVAX is so large that it is beyond reasonable doubt (cf. GL. C-IV 9.6) that at least one patient carrying S. aureus has been vaccinated. Thus, a patient group or individual patients defined by being immune-compromised having nasal carriage of Staphylococcal bacteria was/were inherently vaccinated in the prior art."

IV. With the statement setting out the grounds of appeal the appellant re-submitted the claims on which the decision under appeal was based as auxiliary requests 1A, 2A, 3 and 4. In addition, an auxiliary request 5 was filed.

Claim 1 of auxiliary request 1A reads:

"1. A vaccine comprising a glycoconjugate of a Type 5 polysaccharide antigen of *S. aureus* and an immunocarrier, and a glycoconjugate of a Type 8 polysaccharide antigen of *S. aureus* and an immunocarrier, for use in protecting an immune-compromised individual from staphylococcal bacterial infection, wherein said immune-compromised individual has nasal carriage of *S. aureus*."

V. The appellant was summoned for oral proceedings and informed of the board's preliminary opinion in a communication pursuant to Article 15(1) RPBA. The board *inter alia* indicated that it considered that document D11 represented the closest prior art for the claimed subject-matter.

VI. In reply to the communication by the board, the appellant submitted further arguments and document D15.

VII. Oral proceedings before the board took place on 1 March 2016. During the oral proceedings the appellant withdrew auxiliary requests 2A, 3, 4, and 5. At the end of the oral proceedings the chairwoman announced the board's decision.

VIII. The appellant's arguments submitted in writing and during the oral proceedings may be summarised as follows:

Auxiliary request 1A (sole request)

Novelty (Article 54 EPC)

There was no indication in document D4 that the described conjugate vaccine was effective in a particular patient group consisting of immune-compromised patients having nasal carriage of *Staphylococcus aureus* (*S. aureus*). A certain efficacy was described solely in haemodialysis patients in general.

The nasal carriage-positive sub-group was also not identified in document D9 and there was no indication of whether the vaccine would be effective in such a sub-group.

Inventive step (Article 56 EPC)

The application concerned the use of a vaccine for the generation of an immune response in order to protect against *S. aureus* infection in an immune-compromised population. Document D4 represented the closest prior

art because it was directed to the same purpose as the invention and shared the greatest number of technical features with the claims. The only difference between the teaching of document D4 and the claimed subject-matter was the patient sub-group, i.e. immune-compromised individuals with nasal carriage of *S. aureus*.

Document D11 belonged to a different technical field. It was concerned with the carriage of *S. aureus* in the anterior nares. Document D11 disclosed the direct treatment of nasal carriage using topical antibiotics with the expectation that this would result in reduced bacteremia. The subject-matter of claim 1 differed from document D11 in that it related to the use of a vaccine. The protection achieved by the use of a vaccine could not have been achieved by topical administration of an antibiotic.

The problem to be solved was the provision of improved means for the protection of nasal carriage-positive, immune-compromised individuals from staphylococcal bacterial infection.

It was not obvious to combine the teaching of document D11 with the teaching of document D4 as these documents belonged to different technical fields. Document D11 disclosed the direct treatment of nasal carriage using topical antibiotics and mentioned several alternative ways of eliminating nasal carriage of *S. aureus*. The skilled person faced with the problem of reducing nasal carriage of *S. aureus* would not have seen vaccination as a good way of achieving this.

The skilled person might have been aware of documents D1 and D4 but in view of the encouraging

results from the treatment of nasal carriage in document D11 and the many possibilities for improvement within this area he was unlikely to change the focus, especially when the results in document D4 - a 26% reduction of bacteremia - were not particularly promising and document D1 showed no effect at all of vaccination on nasal carriage.

Even if the skilled person had combined the teaching of document D11 with that of document D4, there was no reason why the skilled person would have limited the vaccine treatment to the nasal carriage-positive sub-group. The skilled person was unaware of which patient group would have benefited from vaccination. The skilled person reading document D4 would not have expected more than the 26% reduction in *S. aureus* bacteremia disclosed therein.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of auxiliary request 1A filed with the statement of grounds of appeal.

Reasons for the Decision

Introduction

1. The present invention relates to the use of staphylococcal glycoconjugate vaccines in preventing *Staphylococcus aureus* (*S. aureus)* infection in immune-compromised individuals who have nasal carriage of *S. aureus*. *S. aureus* causes a wide spectrum of human diseases, the most important of which is bacteremia, *i.e.* an invasion of the bloodstream by *S. aureus*. Before the priority date of the application it was considered that nasal carriage of *S. aureus* played a key role in

the epidemiology and pathogenesis of infection (see document D11, a review article published in the year 1997, page 505, left hand column, first paragraph). Indeed, document D11 also discloses that the nasal carriage-positive patient group has a 6.3-fold higher risk of bacteremia (see page 512, left hand column, second paragraph). According to document D11 (see page 505, right hand column, first paragraph), "Approximately 20% of individuals almost always carry one type of *[S. aureus]* strain" (so-called "persistent carriers"). Roughly 60% of the population harbors *S. aureus* intermittently while 20% of the population never carries *S. aureus* (so-called "non-carriers")".

Auxiliary request 1A (sole request)

Novelty (Article 54 EPC)

2. Claim 1 of auxiliary request 1A is directed to a vaccine comprising glycoconjugates of capsular polysaccharide antigens of *S. aureus*, for use in protecting an immune-compromised individual from staphylococcal bacterial infection, "wherein said immune-compromised individual has nasal carriage of *S. aureus*" (see section II above for the complete wording of claim 1).

3. The examining division decided that the disclosure in document D4 anticipated the claimed subject-matter.

4. Document D4, an abstract published in April 2001, discloses the results of a clinical trial involving 1800 hemodialysis patients. In a double-blind, randomised, placebo-controlled trial, the efficacy of a bivalent *S. aureus* glycoconjugate vaccine that included capsular polysaccharide (CP) type 5 and 8 conjugated to a non-toxic recombinant exoprotein A from *Pseudomonas*

aeruginosa, termed Nabi® StaphVAX®, was evaluated. Ten months post-vaccination, 26 *S. aureus* bacteremias had occurred in the placebo group and 11 in the vaccinated group. This corresponded to a 57% reduction in the occurrence of bacteremia. Document D4 concludes "that StaphVAX® was well tolerated, and can significantly reduce the incidence of *S. aureus* bacteremia in this at-risk population through approximately 10 months post-vaccination." Document D4 is silent about nasal carriage of *S. aureus*.

5. It is undisputed that the compound and the treated disorder disclosed in document D4 fall under the definitions in present claim 1, and that the patients disclosed in document D4 are immune-compromised. The question is whether they also have nasal carriage of *S. aureus*.

6. The reasoning of the examining division in holding that document D4 also disclosed the feature "wherein said immune-compromised individual has nasal carriage of *S. aureus*" can be summarised as follows: It was known from document D11 that hemodialysis patients showed a mean nasal carriage rate of 51.5% (range from 30.1% to 84.4%). Therefore, at least one third of the hemodialysis patients vaccinated according to document D4 carried *S. aureus* in their nasal cavity. Since the group of vaccinated patients was so large it was beyond reasonable doubt that at least one patient carrying *S. aureus* in his or her nasal cavity had been vaccinated. The examining division concluded that "thus, a patient group or individual patients defined by being immune-compromised having nasal carriage of Staphylococcal bacteria was/were inherently vaccinated in the prior art."

7. The Enlarged Board of Appeal, when considering, in its decision G 2/88 (OJ EPO 1990, 93, corr. 469), claims directed to a new use of a known compound, commented on the interpretation of Article 54(2) EPC as follows (see reasons, point 10): "Article 54(2) EPC defines the state of the art as comprising "everything made available to the public by means of a written or oral description, by use, or in any other way." (...) the question of what has been made available to the public is one of fact in each case. (...) In the case of a "written description" which is open for inspection, what is made available in particular is the information content of the written description. (...) In each such case, however, a line must be drawn between what is in fact made available, and what remains hidden or otherwise has not been made available" (emphasis added).

Furthermore, it stated in point 10.1 that "under Article 54(2) EPC the question to be decided is what has been "made available" to the public: the question is not what may have been "inherent" in what was made available (by a prior written description, or in what has previously been used (prior use), for example) (...)".

8. For determining the information content - or disclosure - of a document, the boards have established certain principles to be observed. Thus, the information content of a document is what the skilled person derives directly and unambiguously, using common general knowledge, from the document as a whole, including features which for the skilled person are implicit in what is explicitly disclosed. In this context "implicit disclosure" means disclosure which any person skilled in the art would objectively consider as necessarily implied in the explicit content, e.g. in view of general scientific laws. In particular, the term "implicit

disclosure" should not be construed to mean matter that does not belong to the content of the technical information provided by a document but may be rendered obvious on the basis of that content (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, sections I.C.3.1 and I.C.3.3).

9. Given the examining division's reasoning that in view of the disclosure of document D11 "a patient group or individual patients defined by being immune-compromised having nasal carriage of Staphylococcal bacteria was/ were inherently vaccinated in the prior art" (see point 6 above), the question to be addressed in the light of the observations in points 7 and 8 above is, whether or not the skilled person would have directly and unambiguously derived this disclosure from document D4 when reading it with his common general knowledge about nasal carriage rates taught in document D11.

10. The board notes that the nasal carrier rates disclosed in document D11 were determined on the basis of reports of eight different studies on nasal carriage carried out between 1975 and 1991, while the study disclosed in document D4 was carried out in the year 2000.

11. In the board's judgement, the skilled person would not have considered that the nasal carriage rates disclosed in document D11 would necessarily also apply to the later study disclosed in document D4. This is so, firstly, because document D11 also discloses that the range of carriage rates reported is large, that older studies tended to find higher carriage rates and that changes in *S. aureus* nasal carriage may have occurred over the years (see paragraph bridging pages 505 and 506). Secondly, because the skilled person would have

also known that it could not be excluded that the patients of document D4 were treated topically to eliminate nasal carriage (see e.g. document D11, page 505, right hand column, first paragraph).

12. Hence, the board concludes from points 8 to 11 above that the skilled person would not have derived directly and unambiguously, using common general knowledge, from document D4 as a whole, the disclosure that nasal carriage-positive patients were vaccinated.

13. Lastly, also in view of the boards' established case law that the use of the same compound in the treatment of the same disease for a particular group of subjects can nevertheless represent a novel therapeutic application, provided it is carried out on a new group of subjects which has a distinct physiological or pathological status (see e.g. T 19/86, OJ EPO 1989, 24, reasons, point 8; and T 893/90, reasons, point 4.2), the board comes to the conclusion that the claimed subject-matter is novel. The patient group concerned is distinguished from the patient group of document D4 by both its physiological (nasal carriage) and pathological (higher risk of bacteremia) status.

14. In view of the observations in points 8 to 13 above the board thus concludes that the subject-matter of claims 1 to 10 is not anticipated by the disclosure of document D4.

15. Similar considerations likewise apply to document D9.

16. Therefore the board decides that auxiliary request 1A fulfils the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

Closest prior art

17. In accordance with established jurisprudence the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter 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 (see Case Law of the Boards of Appeal of the EPO, 7th edition 2013, section I.D.3.1).

18. The purpose of the claimed invention is the protection of *S. aureus* nasal carriage-positive, immune-compromised individuals from staphylococcal bacterial infection.

19. Document D11 discloses (see page 505, left hand column, first paragraph) that nasal carriage of *S. aureus* appears to play a key role in the epidemiology and pathogenesis of staphylococcal infection. It concludes (see page 511, left hand column, first paragraph) that "patients on hemodialysis have an increased *S. aureus* carriage rate and that most *S. aureus* infections in this setting are of endogenous origin". It also reports that "Several oral and topical antibiotics for the eradication of *S. aureus* nasal carriage in hemodialysis patients have been studied" (see page 514, right hand column, third paragraph), and that "elimination of nasal carriage with mupirocin in hemodialysis patients significantly reduces the *S. aureus* infection rates but carries a risk for the development of resistance" (see page 515, left hand column, first paragraph). The use of rifampin, an oral antibiotic, also led to a "significant reduction" of the *S. aureus* infection rate but was

accompanied by a "rapid emergence of rifampin-resistant strains" (see page 514, right hand column, third paragraph). It is undisputed that the skilled person knows that hemodialysis patients are immune-compromised (see also document D1, page 247, right hand column, third paragraph). The board thus concludes that document D11 relates to the protection of *S. aureus* nasal carriage-positive, immune-compromised individuals from staphylococcal bacterial infection and hence to the same purpose as the claimed invention.

20. The appellant submitted that document D4 was the closest prior art because it disclosed the same vaccine as claim 1.

21. The board is not persuaded by this argument. The boards have consistently held that a document could not qualify as the closest prior art to an invention merely because of similarity in the composition of the products; its suitability for the desired use of the invention also had to be described (see Case Law of the Boards of Appeal of the EPO, *supra*, section I.D.3.2). Thus, document D4 which discloses the same vaccine as defined in claim 1 (see point 5 above), but does not aim at the treatment of nasal carriage-positive, immune-compromised individuals (see point 18 above) is not an appropriate starting point for the assessment of inventive step. Therefore document D11 rather than document D4 is the closest prior art.

Technical problem and its solution

22. The subject-matter of claim 1 differs from the teaching of document D11 in that a vaccine instead of an antibiotic is used for the protection of *S. aureus* nasal carriage-positive, immune-compromised individuals from

staphylococcal bacterial infection. The use of a vaccine has the additional benefit that it also provides protection - via the immune response it induces - against *S. aureus* bacteremia which does not originate from nasal *S. aureus*. The board considers that the problem to be solved vis-à-vis document D11 can thus be formulated as the provision of improved means for the protection of nasal carriage-positive, immune-compromised individuals from staphylococcal bacterial infection. In view of the experimental results disclosed in the application, e.g. in Tables 5 and 6, the board is satisfied that the subject-matter of claim 1 solves the problem.

Obviousness

23. The question to be addressed is whether the skilled person, in the expectation of solving the problem, would have modified the teaching in the closest prior art document D11 in the light of other prior art teachings so as to arrive at the claimed invention.

24. As set out above in point 19, document D11 identifies the patient group of *S. aureus* nasal carriage-positive, immune-compromised individuals, and discloses that nasal carriage is associated with an increased risk of *S. aureus* bacteremia and that antibiotics significantly reduce the bacterial infection rate but also carry a risk of producing resistant strains. The skilled person looking for improved means for the protection of nasal carriage-positive, immune-compromised individuals from staphylococcal bacterial infection would also have been aware of document D4. As set out above in point 4, document D4 reports that a bivalent *S. aureus* glycoconjugate vaccine was well tolerated and could significantly reduce the incidence of *S. aureus*

bacteremia in hemodialysis patients for 10 months post-vaccination.

25. The skilled person would have recognised that the drawbacks associated with the use of antibiotics identified in document D11, i.e. the development of resistance, could be avoided by the use of a vaccine, and also that a vaccine induces a lasting immune response while the effect of the antibiotic is of short duration. Moreover, while the effect of the immune response induced by the vaccine is systemic, the effect of the antibiotic is local. The skilled person would thus have been motivated to use the vaccine of document D4 in nasal carriage-positive, immune-compromised individuals since its potential benefits would have been immediately obvious to him.

26. The skilled person had also no reason to assume that the vaccine of document D4 would not be effective in nasal carriage-positive patients. Document D4 had already established that the vaccine significantly reduced the incidence of *S. aureus* bacteremia in immune-compromised patients. Moreover, document D1, which relates to the safety and immunogenicity of an *S. aureus* type 5 capsular polysaccharide conjugate vaccine - i.e. a vaccine consisting of one component of the vaccine of document D4 - in patients on hemodialysis, had disclosed that "polysaccharide-based vaccines have been shown to result in the prevention of nasopharyngeal carriage and systemic infection of capsulated bacteria" (see document D1, page 251, right hand column, second paragraph).

27. The appellant submitted that the skilled person would not have considered document D4 at all because it related to a different technical field from document D11

and because there was no evidence that vaccination would have any effect on nasal carriage of *S. aureus*.

28. However, both document D4 and document D11 relate to the treatment of *S. aureus* bacteremia in immune-compromised patients. Moreover, the skilled person was not faced with the problem of reducing nasal carriage of *S. aureus,* but with the problem of protecting nasal carriage-positive, immune-compromised individuals from staphylococcal bacterial infection (see point 22 above). Therefore, and although nasal carriage is not an issue in the document, the skilled person had no reason to disregard document D4 right away.

29. The appellant further submitted that document D11 mentioned several alternative approaches to eliminating nasal carriage, including the local application of antibiotics, the use of systemic antibiotics or bacterial interference, i.e. active colonisation with a minimally pathogenic strain of *S. aureus,* and that this was a further reason for the skilled person not to turn to document D4.

30. The board is not convinced by this argument. Document D11 does indeed disclose alternative approaches to eliminate nasal carriage and reduce infection rates, but their drawbacks are also apparent from the document. For example, the use of antibiotics led to the development of resistant strains, and bacterial interference had not been pursued because it was compromised by serious *S. aureus* infections; even a fatal one had been reported. Consequently, in the board's view, the skilled person would rather have recognised from the disclosure in document D11 that an improvement was called for, and would therefore have turned to other documents, including document D4, for

the reasons given in point 25 above.

31. Finally, the appellant submitted that the mere 26% reduction in *S. aureus* bacteremia 12 months after vaccination, as reported in document D4, would not have encouraged the skilled person to use the vaccine, and that in the light of document D4 there was no reason why the skilled person would restrict immunisation to nasal carriage-positive individuals.

32. The board is not persuaded by this argument either. Document D4 reports that the vaccine can significantly reduce the incidence of *S. aureus* bacteremia in hemodialysis patients for 10 months post-vaccination. And indeed, after that time a 57% reduction in bacteremia was observed. D4 also reports that a population-based assessment suggested that vaccine efficacy was related to a minimum circulating antibody titer. Therefore the skilled person would not have been discouraged by the results seen 12 months after vaccination. On the contrary, he would have been encouraged by the results obtained at 10 months and would also have known that he needed to ensure a minimum circulating antibody titer, e.g. by repeating the vaccination, to prevent bacterial infections. The skilled person also knew from document D11 that the nasal carriage-positive patient group had a 6.3-fold higher risk of bacteremia (see page 512, left hand column, second paragraph). This would have motivated him to treat this patient group above all others.

33. The board concludes from the above that the subject-matter of claim 1 fails to meet the requirements of Article 56 EPC. Accordingly, auxiliary request 1A, which is the sole request on file and of which claim 1 is a part, is not allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated